The Recent Evolution of the Application of Single-Cell Analysis in Kidney Diseases: A bibliometric analysis

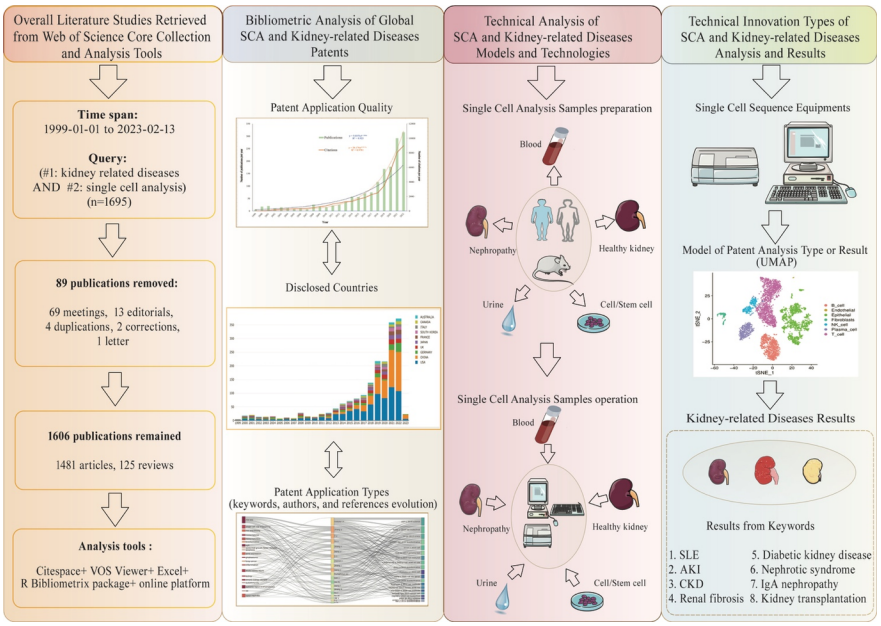
Marady Hun[1], Huai Wen[1], Min Wen[1], Qiuwei Tian[1], Zisai Wang[1], Phanna Han[2], Tharith Wun[3], Tin Som[1], Boren Preap[2], Mingyi Zhao[1], and Qingnan He[1]

[1]Central South University Third Xiangya Hospital
[2]The Second Xiangya Hospital of Central South University
[3]Xiangya Hospital Central South University

June 8, 2023

Abstract

Abstract There is increasing interest in employing Single-Cell Analysis (SCA) technologies to improve the efficiency of renal disease diagnosis and treatment. Nevertheless, comprehensive studies summarizing and analyzing research trends in the field are lacking. There is increasing interest in employing Single-Cell Analysis (SCA) technologies to improve the efficiency of renal disease diagnosis and treatment. Nevertheless, comprehensive studies summarizing and analyzing research trends in the field are lacking. This article discusses the use of bibliometric analysis to evaluate the progress and potential of Single-Cell Analysis (SCA) technologies in the field of kidney disease. The study identified 1,606 articles and reviews published between 1999 and 2023, involving 11,737 authors from 2,317 institutions across 67 countries or regions. The major contributors to SCA in kidney disease were highlighted, including top authors, institutes, countries, and journals. Research hotspots included molecular and pathological aspects, with disease-, molecular-, and pathological-related keywords such as expression, EGFR, gene-expression, activation, gene, cell, protein, mechanism, mutation, inflammation, resistance, apoptosis, and T-cell. Key kidney-related disease keywords included SLE, AKI, CKD, renal fibrosis, diabetic kidney disease, nephrotic syndrome, IgA nephropathy, and kidney transplantation. The authors note that the field of SCA in kidney-related disease research is rapidly growing, with the potential for further expansion. SCA technologies could provide novel diagnostic, therapeutic, and prognostic approaches and support routine clinical diagnosis and individualized treatment.



Graphical Abstract: Flow diagram of the included publications, methods, and results of bibliometric analysis

The Recent Evolution of the Application of Single-Cell Analysis in Kidney Diseases: A bibliometric analysis

Marady Hun[1], Huai Wen[1], Min Wen[1], Qiuwei Tian[1], Zisai Wang[1], Phanna Han[2], Tharith Vun[3], Tin Som[4], Boren Preap[5], Mingyi Zhao[1*] and Qingnan He[1*]

[1]Department of Pediatrics, The Third Xiangya Hospital, Central South University, Changsha, China

[2]Department of Ophthalmology, The Second Xiangya Hospital, Central South University, Changsha, China

[3]Department of General Surgery, Xiangya Hospital, Central South University, Changsha, China

[4]Department of Gynecology and Obstetrics, The Third Xiangya Hospital, Central South University, Changsha, China

[5]Department of Gynecology and Obstetrics, The Second Xiangya Hospital, Central South University, Changsha, China

*Correspondence to:

Qingnan He

Department of Pediatrics, The Third Xiangya Hospital, Central South University, Changsha, China

heqn2629@csu.edu.cn

Mingyi Zhao

Department of Pediatrics, The Third Xiangya Hospital, Central South University, Changsha, China

zhao_mingyi@csu.edu.cn

Abstract

There is increasing interest in employing Single-Cell Analysis (SCA) technologies to improve the efficiency of renal disease diagnosis and treatment. Nevertheless, comprehensive studies summarizing and analyzing research trends in the field are lacking. There is increasing interest in employing Single-Cell Analysis (SCA) technologies to improve the efficiency of renal disease diagnosis and treatment. Nevertheless, comprehensive studies summarizing and analyzing research trends in the field are lacking. This article discusses the use of bibliometric analysis to evaluate the progress and potential of Single-Cell Analysis (SCA) technologies in the field of kidney disease. The study identified 1,606 articles and reviews published between 1999 and 2023, involving 11,737 authors from 2,317 institutions across 67 countries or regions. The major contributors to SCA in kidney disease were highlighted, including top authors, institutes, countries, and journals. Research hotspots included molecular and pathological aspects, with disease-, molecular-, and pathological-related keywords such as expression, EGFR, gene-expression, activation, gene, cell, protein, mechanism, mutation, inflammation, resistance, apoptosis, and T-cell. Key kidney-related disease keywords included SLE, AKI, CKD, renal fibrosis, diabetic kidney disease, nephrotic syndrome, IgA nephropathy, and kidney transplantation. The authors note that the field of SCA in kidney-related disease research is rapidly growing, with the potential for further expansion. SCA technologies could provide novel diagnostic, therapeutic, and prognostic approaches and support routine clinical diagnosis and individualized treatment.

Keywords: kidney disease, single cell analysis, scRNA-seq, bibliometric study

INTRODUCTION

Kidney-related diseases, also known as renal diseases, are a major health concern, affecting millions of individuals worldwide[1-3]. Some common kidney-related diseases include chronic kidney disease (CKD)[4], acute kidney injury (AKI)[5], systemic lupus erythematosus (SLE)[6, 7], lupus nephritis (LN)[8], nephrotic syndrome (NS)[9-11], IgA nephropathy (IgAN)[12, 13], renal fibrosis[14], kidney transplantation[15], diabetic kidney disease (DKD)[16], and glomerulonephritis[12] (**Graphical Abstract**). These diseases can have serious and far-reaching impacts on a person's health and quality of life[1, 4]. Moreover, they can lead to a range of serious health complications. Some of the most common complications of kidney disease include kidney failure, high blood pressure, cardiovascular disease, anaemia, nerve damage, and osteoporosis, among others[4, 17-19]. There are various causes of kidney-related diseases including diabetes, high blood pressure, infections, autoimmune disorder, genetic disorders, immune system dysfunction etc[6-8, 10, 11, 20]. Currently reporting hundreds of loci associated with kidney-related characteristics such as glomerular filtration rate (GFR), albuminuria, hypertension, electrolyte and metabolite levels have been identified through genome-wide association studies (GWAS). Yet these powerful large-scale mapping techniques have not always been translated into a more comprehensive concept of the disease or into the discovery of therapeutic options[21, 22]. Therefore, there is an urgent need for scientists all over the world to develop safe, powerful, novel and efficient methods or technologies for finding the root causes of various types of kidney diseases[21, 23-25].

Single-cell analysis (SCA) technologies is a powerful technique that has been paralleled by revolutionary new approaches to profile genetic, epigenetic, spatial, proteomic and lineage-specific information in individual cells[26, 27]. Single-cell RNA sequencing (scRNA-seq) is one of SCA's most widespread single-cell sequencing techniques, with a panel of technologies for ultra-sensitive, highly multiplexed or combinatorial sequencing[28, 29]. To improve the understanding of normal and disease models, scRNA-seq has been applied to various models including humans, animals and plants. Human health is a particular focus, with many scRNA-seq methods focused on learning about development, immunology, diabetes, microbiology, SARS-CoV-2, cancer, renal, vascular, neurobiology, and clinical diagnostics[2, 24, 26, 29, 30].

In kidney-related diseases, SCA has become a powerful tool for investigating the complex cellular and molecular mechanisms as well as the genetic, epigenetic and proteomic profiles of individual cells involved in kidney disease[2, 31-33]. By investigating individual cells within the kidney, investigators can obtain new insights into disease pathogenesis and target potential therapeutics[14, 19, 32, 34]. Furthermore, SCA is used for studying various cell types, including glomerulus and tubule epithelium cells, interstitium cells, immune cells, and endothelial cells[35, 36]. Through the analysis of these cells at the single-cell level, researchers can identify the specific cell types involved in the development and progression of kidney disease, as well

as the molecular pathways and signalling networks that are dysregulated[32, 37, 38]. According to Kidney Diseases: Improving Global Outcomes (KDIGO), the monogenic mutation rate for children with chronic kidney disease stages G3b-G5 is about 30% to 50% and 10% to 30% for adults with stages G3b-G5[39]. Despite its potential for first-line diagnostics in certain clinical disciplines, exome sequencing has not been proven to be beneficial in the majority of constitutional disorders of adults and children with chronic kidney disease, which affects more than one out of ten people worldwide[40, 41]. In recent years, it has become evident that this group of patients may represent up to 16% of newly diagnosed end-stage renal disease (ESRD) patients, and that traditional diagnostic approaches are often inappropriate or contraindicated in the diagnosis of these patients[41]. It is difficult to identify the pathophysiological mechanisms behind kidney disease because of the fact that two genetic and environmental risk factors are implicated[39, 41, 42]. Overall, single-cell analysis is a powerful tool which could transform our understanding of kidney disease, resulting in more effective treatments and improved patient outcomes. Therefore, in recent years, there has been rapidly increasing high-quality evaluation of the progression of SCA in association with kidney disease research through numerous published studies.

Bibliometrics is a scientific field that studies the library and data-processing sciences by analyzing bibliographic records based on a range of quantification measures. While such surveys inform readers of current and aggregated information, to our knowledge there is a shortage of statistical data describing the evolution of scientific publications on SCA in kidney diseases over time, thus providing scientists, physicians, policy-makers, politicians and others with a comprehensive view of scholarly science communications in the field. The objective of this research is to apply bibliometric techniques to establish a twenty-year longitudinal view (1999 to 2022) (while the report in 2023 does not have enough information) of the trend of the academic evidence on SCA in kidney diseases by focusing on a specific topic, assessing the overall quality of the research, analyzing the main areas of research and predicting the future direction of scientific research.

METHODS

Data Sources and Search Strategies

The Web of Science Core Collection (WoSCC) was used to conduct a literature retrieval on SCA in kidney-related diseases over the past 22 years (from January 1, 1999, to February 13, 2023). The query formulation was established as [TS= (Single cell analysis) AND TS= (kidney-related diseases)]. As a target dataset for analysis, we selected a dataset derived from WoSCC. We selected the WoSCC topic retrieval as a way to more accurately capture a topic as the WoSCC topic extraction can be regarded as a model for keyword retrieval via words in the title, abstract, author keywords, and keyword plus. Moreover, we applied MeSH and the current method of SCA technology (Spatial-ATAC-seq[24, 25, 43, 44]) to extract all search samples. A review of the literature has been conducted on the following topics: The entire search formula of the [TS= (Single cell analysis) AND TS= (kidney-related diseases)] was detailed in (**Graphical Abstract and Supplementary Table 1**). For the inclusion studies, we collected the following information: number of publications and citations, titles, year of publication, countries, affiliations, authors, journals, keywords, and references of each publication.

Data Analysis

For the analysis and visualisation of data, it is necessary to have the most suitable software and an online platform in order to do so. WoSCC was used to collect and export bibliographic records and citation references for all publications in .txt format, which were then imported into CiteSpace 6.1R6, 64-bit basic (Drexel University, Philadelphia, PA, USA), VOSviewer 1.6.17 (Leiden University, The Netherlands), and Microsoft Excel 2019.

The open-source Java application CiteSpace, developed by Dr. Chaomei Chen[45], has been widely applied to visualize and analyze trends and developments in academic literature[46]. CiteSpace relies primarily on data from the WoSCC. By utilizing CiteSpace, we were able to cluster, keyword, and reference burst analyze SCA in kidney-related diseases. The VOSviewer software tool (https://www.vosviewer.com/) establishes and visualizes bibliometric networks in an easy and effective manner[47]. By analyzing the data obtained

from the WoSCC, we were able to create networks based on co-authorship, citation-based, and co-occurrence. Using the co-citation networks that were investigated, the countries, institutions, and authors that collaborated as well as the journals that cited each other were examined. In order to analyze keyword occurrences across publications, co-occurrence networks were used. In addition to the publication counts indicated by these patterns, thresholds (minimum number of documents and maximum link strength) were also displayed separately. The circle size of an item was based on its publication count, whereas the line width was based on its link strength. An article's total link strength reflects how closely it cooperates, with the same colour indicating close cooperation. R language-based Bibliometrics package (4.1.0 package) was employed to perform the country scientific analysis, Production, three field plots (co-cited references, authors, keywords), author impact (H-index), WordCloud, Collaboration Network, Affiliations' Production over Time, Countries' Production over Time, Factorial Analysis (topic dendrogram) and thematic evolution analysis[48] (**Graphical Abstract**).

RESULTS and DISCUSSION

Research Hotspot of the Publication and Citation Trends

Our WoSCC search strategy yielded a total of 1695 studies. For the present study, 1606 studies (1481 articles and 125 reviews) in English were identified after excluding 89 articles, including meetings (n=69), letters (n=1), editorials (n=13), corrections (n=2), and duplicate records (n=4). There was a significant increase in the number of global publications in the field, from 6 publications in 1999 to 316 publications in 2021 and 21 publications in 2023 (there was only a 2-month period of publication in 2023). The specific search formula and the sample of publications are shown in **Graphical Abstract and Supplementary Table 1** . It is evident from **Figure 1A and Supplementary Table 1** that the number of SCA-related kidney disease publications increased rapidly each year between 1999 and 2023, with a slight decrease in 2007**.** While the number of publications increased steadily, the most significant increase was observed from 2018 to the present. 2023 data were incomplete. There was a significant correlation, with an R^2 coefficient of 0.923, between the number of publication years and the number of publications. Consequently, the total number of citations for the recovered articles was SCA in kidney disease (n= 43058). Annual citations showed a strong upward trend, continuously increasing from 1 in 1999 to 8,973 in 2022, with a significant sudden and rapid growth from 5,567 in 2020 to 8,045 in 2021, with a correlation coefficient of R^2=0.9781. The interesting integrated evolution in the year 2018 demonstrated the forcefully increasing attention in the international arena on SCA for dealing with kidney-related diseases. A few recent bibliometric studies of SCA regarding improving the field of gene expression[49], food products related to protein[50], and immune cells and their application of DNA damage repair in cancer immunotherapy[51] found a major evolution trend in annual publications around 2015-recent, suggesting that there have been rapid developments on SCA in the last decade.

Annual Publications of Active Countries and Institutions

Several institutions and countries contributed to the publications on SCA in kidney-related diseases published worldwide between 1999 and 2023 as shown in **Figure 1B, Figure 2 (A, B), and Supplementary Table 3 (A, B).** A total of sixty-seven countries and regions across the world published articles in this field, with the United States having the most published articles (683 articles, 37.65% of all articles), followed by China (499, 27.51%), Italy (157, 8.65%), Germany (100, 5.51%) and Spain (95, 5.24%). In terms of citations, the United States had the highest number (24,511 citations), followed by China (6,359 citations), Italy (5,257 citations), Germany (3,894 citations) and Spain (3,472 citations), with the rest totalling over 3,000. Using these findings, we can see that the United States (683 articles, 2,4511 citations, 0.65 centralities, and a total of 296 total links) and China (499 articles, 6,359 citations, 0.11 centralities, 149 total link strength) accounted for the top two leading countries when it came to how many citations there were in other countries as well as the number of links to other countries (**Supplementary Table 3A, Figure 1B, and 2A**).

In the past 22 years, 2,317 articles have been published about SCA use in kidney-related diseases by institutions worldwide. It is estimated that out of 2,317 institutions that appeared at least 10 times in the

study, 75 met the threshold for meeting the threshold calculation (Figure 2D and 3B). Almost all the top 10 productive institutions came from the United States (6 institutions), except Shanghai Jiao Tong University, Fudan University, Chinese Academy of Sciences, and Sun Yat-Sen University from China. The leading university in terms of publication was Harvard Medical School (51 articles), followed by Nanjing Medical University (24 articles), Shanghai Jiao Tong University (22 articles), Michigan State University (40 articles), Shanghai Jiao Tong University (35 articles), and Fudan University (34 articles). There is also evidence that Harvard Medical School (total link strength = 49 times) collaborates most frequently with other institutions. Next in line are Michigan State University (40 times), Johns Hopkins University (30 times) and Stanford University (24 times), suggesting their leading role in SCA in kidney-related diseases (**Supplementary Table 3B, Figure 2B**). Together, the publication and citation numbers indicate that research on SCA in kidney-related diseases is still in the high-speed evolution stage, causing significant interest.

Analysis of Journals, Authors, Co-authorship, and Co-cited references

Only 68 of the 633 productive journals that appeared at least 5 times met the threshold (**Figure 2C**). **Supplementary Table 4**shows 25.4% of all SCA-kidney disease publications are published in the top 10 most productive journals and co-cited journals. Frontiers in Immunology had the highest number of published articles in the top 5 journals, followed by Scientific Reports (40 articles), Plos One (35 articles), JCI Insight (35 articles), and Nature Communications (23 articles). According to the H-index of the top 5 productive journals, Plos One had the largest number of impact measures (19 H-index), followed by Proceedings of the National Academy of Sciences of the United States of America (PNAS) (15), Scientific Reports (15), JCI Insight (15), Journal of the American Society of Nephrology (JASN) (12) and Nature Communications (12). A noteworthy point is that among these highest H-index scores above, many are related to nephrology. The most co-cited journals among the 6176 were Nature (2,327 citations, 50,277 link strength), PNAS (2,224 citations, 49,608 link strength), and Cell (1,839 citations, 39,630 link strength). The largest number of co-citations were found in JASN (1,258 citations, 34,220 total link strength) and Science (1,633 citations, 36,586 total link strength). SCA might have some influence over a central role and balance on the publication of this study based on the number of citations and articles, total link strength, and H-index above, which can be analysed as shown in **Supplementary Table 4** , suggesting that there is a high volume of high-impact papers in this field.

Based on an alluvial flow map (every 10 items were set), **Figure 2D** shows the relationship between countries, institutions and journals. As a result of the top 2 countries linked to the top 10 institutions, it appears that the United States is associated with at least 10 relevant institutions (Harvard Medical School, Michigan State University, Shanghai Jiao Tong University, Fudan University, Sun Yat-Sen University, University of Pennsylvania, University of Washington, Stanford University, the University of California Los Angeles, and the University of California San Francisco). Eight universities targeted by China are contained/connected with those institutions (Harvard Medical School, Michigan State University, Shanghai Jiao Tong University, Fudan University, Sun Yat-Sen University, University of Washington, the University of California Los Angeles, and the University of California San Francisco). Harvard Medical School is affiliated with ten targeted countries and associated with four relevant journals (JCI Insight, Nature Communications, Scientific Reports, and Kidney International). As part of the collaboration, Michigan State University established close ties with 9 targeted countries (except France) and 5 targeted publishers (JCI Insight, PNAS, JASN, Scientific Reports, and Kidney International). The University of Pennsylvania is affiliated with 9 targeted countries (except China) and connected with 5 targeted journals (JCI Insight, PNAS, JASN, Frontiers in Immunology, and Nature Communications). The University of California San Francisco is connected from all 10 targeted countries and connected with 4 targeted journals (JCI Insight, PNAS, Frontiers in Immunology, and Nature Communications). Stanford University is connected to 8 targeted countries (except Japan and China) and connected with 5 targeted journals (JCI Insight, PNAS, Frontiers in Immunology, Plos One, and Nature Communications). It is interesting to note that most of the collaborations within the Chinese or American institutions took place inside the respective institutions of the two countries (**Figure 2D**).

Supplementary Table 5 presents the top ten productive and co-cited authors in the field of SCA in kid-

ney diseases. In total, 11,737 authors have published articles in SCA related to kidney diseases. However, Humphreys, Benjamin D (12 articles, 435 citations, and 19 total link strength) and Susztak, Katalin (10 articles, 264 citations, and 69 total link strength) have been the most prolific and active. Among all 72,050 citations, Trapnell, C (135 citations and 1,604 total link strength) and Wu, Haojia (120 citations and 2,619 total link strength) were the most prolific co-cited authors. Moreover, Wu, Haojia was the author with the highest number of citations, having a high 6th rank in publication, and a H-index of 8[37, 52-58]. A collaborative network of authors under Humphreys, Benjamin D Prof (Correspondent author from Division of Nephrology, Department of Medicine, Washington University, St. Louis, MO, USA) with a primary focus on kidney-related diseases research (Humphreys, Benjamin D Prof, top 1 and 3 in the number of publications, respectively) is the third-biggest collaboration network of authors. As far as collaboration and active teamwork are concerned, the second-largest collaboration network and the most active teamwork are collaborations with Putterman, Chaim Prof (Correspondent author from the Division of Rheumatology and Department of Microbiology and Immunology at Albert Einstein College of Medicine in Bronx, New York, USA). It is Zhang, Yu; Liu, Zhihong, etc. that have the most collaborations and active teamwork, while some of them focus on SCA cancer research (**Supplementary Table 5; Figure 3B-C**). Overall, Humphreys, Benjamin D[23, 37, 52-71] Prof and Putterman, Chaim Prof[72-74] are the authors with the greatest collaborative network, active teamwork, and connections to other authors in kidney diseases associated with SCA. What is more, prof Humphreys, Benjamin D is not only one of the leading contributive and active team in the SCA-related kidney research field but Wu Haojia who also come from prof Humphreys, Benjamin D's team is the main focus and active in SCA-related kidney research[37, 52-58]. Moreover, this team has established a single-cell-related database, named KIT:*http://humphreyslab.com/SingleCell/*. With KIT, users can query gene expression across single-cell datasets for the mouse kidney and human kidney-like organs. InDrop, DropSeq, or 10X Chromium platforms are used to create libraries. Spatial transcriptomes from healthy adult kidney epithelial cells, rejected kidney allograft biopsy tissue, healthy adult kidney tissue, kidney-like organs, fetal kidneys, diabetes-prone kidneys, and human kidney snRNA/ATAC-seq tissues and organs are included. Overall, although most scholars were from different countries (**Supplementary Table 3A**), and the cooperation was mostly confined to the research team, the research on SCA in kidney-related diseases was not a very good link for co-partnership among authors, while researchers from the USA stood the core country research. So, researchers from different countries should reinforce collaboration and partake in beneficial terraces to achieve more significant progress and improve the clinical translation of research, as well as the exchange of technological innovation among scientists working on different aspects between SCA and kidney-related diseases.

The top 20 co-cited references related to SCA in kidney-related diseases are listed in **Table 1** . Among all 72.050 cited references, Andrew Butler et al[75]. (2018, 68 citations, 241 total link strength), Tim Stuart et al[76]. (2019, 65 citations, 265 total link strength) and Evan Z Macosko et al.[77] (2015, 39 citations, 181 total link strength) were the most selected prolific co-cited references related to SCA-method with kidney diseases. And Park Jh et al.[36] (2018, 60 citations, 271 total link strength), Arazi A et al.[78] (2019, 56 citations, 241 total link strength), and Evan Der et al.[73] (2019, 38 citations, 169 total link strength) were the most prolific co-cited references related to SCA in kidney diseases. Interestingly, most of the top 20 co-cited references and the top 8 publications focused on the methods' main usage in SCA-related kidney diseases[75-77, 79-83]. Other top 12 publications were focused on the main usage of the SCA methods revealing molecular characterization, states, heterogeneity, as well as gene, cellular responses and expression etc from basic research to clinical approach in kidney diseases[36, 55, 57, 61, 72, 73, 78, 84-89]. 18 publications were articles and 1 other was brief communication[83] which was reported by Qiu Xj et al. concentrated on using monocle 2, they investigated the development of blood and discovered that mutations in genes encoding key lineage transcription factors diver cells to alternative fates. Moreover, most of their impact factors are more than 10, except JCI Insight (IF=9.496), and 8 co-cited references (40%) are from Nature, JASN, Science, Cell, PNAS, Genome Biology, and Immunity.

Additionally, "bursts" refer to references appearing over a period of time and reflecting the popular topics during that period. The top 25 co-cited references with the strongest citation bursts are shown in**Figure**

3A . The findings indicated that the first instance of a citation burst occurred in 2015, and the most recent instance of a reference with a citation burst was recorded in 2020. The highest burst strength for SCA in kidney-related diseases was from Stuart T et al. [76] (2019, 11.51 strength), Macosko EZ et al. [77] (2015, 11.24 strength) and Dobin A et al.[90] (2013, 10.75 strength). Moreover, T Nehar-Belaid D al. [85] (2020), Wu Hj et al.[55] (2019), Arazi A et al. [78](2019) and Der E et al. [73] (2019) received more attention in recent years. Interestingly, among the top 25 co-cited references, only 7 co-cited references (20%) focus on SCA-related kidney research[55, 73, 78, 85, 89, 91, 92], that started from 2015 to 2019, but in 2019 is the main burst co-cited references, suggesting that the field of SCA in kidney-related disease research domain is recent rapidly growing, and its domain is likely to expand in the next decade.

Notably, we discovered numerous potentially unique characteristics of SCA in kidney-related diseases. Notably, we identified important keywords from relationships between the top 20 co-cited references, authors and keywords evolution of SCA in kidney-related diseases (**Figure 3D**), including "inflammation", "acute kidney injury", "kidney", "chronic kidney disease", "autoimmunity", "systemic lupus erythematosus", "SLE", and "lupus nephritis". They were almost closely connected with the top 10 authors and co-cited references (**Supplementary Table 5; Table 1,2**). As shown by a relatively rapid translation of basic research to clinical research on SCA and kidney-related diseases, the research on these topics has a good connection between basic and clinical studies, suggesting a favourable development pattern on SCA in kidney disease research.

Analysis of Keywords

A total of 7,879 keywords were obtained, and after set as the 10 occurrence times of a keyword, 265 keywords appeared in **Figure 4A** by using VOSviewer. As shown in **Figure 4A** , all of the keywords could be divided into the following five big groups: cluster 1 (blue nodes focus on the role of SCA (RNA-seq) in mechanism or clinical applications for finding some gene-expression, pathway or repair in kidney-related diseases (in vivo) including inflammation, apoptosis, diabetic nephropathy, AKI, renal fibrosis, etc.), cluster 2 (yellow nodes focus on the use or function of SCA tools (RNA transcription, Chip-seq, genomic analysis, etc.) for potential mechanism finding gene-expression or binding in protein, RNA/DNA, RNA-polymerase, escherichia coli, and nucleoid-associated protein, etc.), cluster 3 (red nodes focus on the role, use of SCA in finding marker, activation, therapy (chemotherapy, resistance), mechanism others diseases including lung cancer, glioma, prostate cancer, colorectal cancer, etc.), cluster 4 (purple nodes focus on SCA-related material preparation or use including cell activation, flow cytometry, membrane, electropermeabilization etc.), and cluster 5 (blue nodes focus on the mechanism, pathogenesis, clinical applications from SCA in kidney-related diseases (autoimmune diseases or rheumatoid arthritis) including IgA nephropathy, SLE, etc.) Furthermore, the top 25 co-occurrence keywords related to SCA in kidney-related diseases and the main 10 collected keywords related to kidney diseases are shown in**Table 2** . Among the top 25 keywords, suggesting that expression was the most frequent keyword (374 occurrences, 593 total link strength), followed by RNA-seq (181 occurrences, 316 total link strength), and egfr (159 occurrences, 211 total link strength). Among the top 10 keywords related to kidney diseases, SLE was the most attractive disease, followed by AKI, CKD, renal fibrosis, diabetic kidney disease (DKD), nephrotic syndrome, IgA nephropathy, kidney transplantation, etc (**Graphical Abstract, Table 2**). Overall, Realising the allocation and growth of distinct research hotspots in this field is possible. Subsequently, based on the results in the timeline viewer analysis of clustering, we defined the research hotspots and growth frontiers in the field of SCA in kidney-related diseases.

The early stage (1999-2006) of inquiry on SCA in kidney-related disease was mostly focused on "egfr", "DNA damage", "cytokines" and "apoptosis", "autoimmunity", as shown by the thematic evolution analysis of the author's keywords based on publication year. These findings indicate that knowledge of SCA and kidney-related diseases was not well-understood at this stage. In the platform stage (2007-2013), the challenge developmental evolution of kidney-related diseases (lupus nephritis, SLE, inflammation, and autoimmunity) has steadily developed toward "chronic kidney disease", a breakthrough from 2008 to 2013. The years 2014 and 2019 is the main stage in the developmental evolution of using SCA in kidney-related disease research "RNA-seq", "glomerulosclerosis", "EGFR", and "systemic lupus erythematosus". The terms in the usage

or the growth of new SCA-related tools (chip-seq, RNA-seq, etc.) in "systemic lupus erythematosus" and "autoimmune diseases" have captured the interest of academics throughout the course of the last three years. (**Figure 4B**).

The top 25 co-cited keywords with the strongest citation bursts based on Citespace are shown in **Figure 4C** . The highest burst strength relevant to kidney-related diseases was from systemic lupus erythematosus (1999) and injury (2017). Moreover, injury (2017), single-cell RNA seq (2020), and package (2021) received more attention in recent years (**Figure 4C**).

Word clouds of author keywords were shown in **Figure 4D** . Author keywords were able to provide us with more valuable information. The current authors focus on the usage of the SCA methods (RNA-seq, transcriptome, single-cell RNA seq) in potential mechanisms or clinical applications kidney related diseases (CKD, AKI, lupus nephritis, diabetic kidney disease, IgA nephropathy, kidney transplantation, etc.)

We also applied the R package to analyze the Factorial Analysis by using the author's keywords method with Multiple correspondence analysis (MCA) to construct a topic dendrogram of this field. All author's keywords were classified into two clusters in blue and red (**Figure 4E**). The words in the red clusters were mainly focused on SCA and its potential mix usage in kidney diseases. As a result, we suggested that SCA methods may mix with other methods or use multimodal "bioinformatics" or "machine learning" to identify "genomics", "biomarkers" or "proteomics" in kidney-related diseases "e.g: lupus nephritis, etc." The blue cluster focuses on the significance of SCA in "precision medicine" utilizing its methods or other multimodal "RNA-seq", "Chip-seq", "single-cell analysis", etc. to identify "biomarkers", "prognosis", "targeted therapy", "EGFR", "gene-expression", "immune-response", and so on in kidney-related diseases "SLE", "AKI", "CKD", "DKD", "IgA nephropathy", etc. as well as cancers and Covid-19 (**Figure 4E**).

MAJOR APPLICATIONS of SINGLE-CELL ANALYSIS in KIDNEY DISEASES

Cell Landscapes for Renal Microenvironment (RME)

Over the past few decades, kidney disease has evolved fundamentally. Kidney diseases are now recognized as more than genetic disorders. They include a variety of renal and non-renal cells and their complex interactions with kidney disease. Genetic mutations in the kidney are now recognized as necessary, but not sufficient, for kidney disease development and progression[2]. An extremely complex ecosystem surrounds the renal microenvironment (RME), including immune cells, kidney-associated fibroblasts, endothelial cells, mesangial cells, tubule cells, proximal tubule cells, distal tubule cells, the loop of Henle cells, podocytes, and a variety of other types of cells that reside in the tissues[36, 38, 52, 93]. In renal disease mechanisms, these cells once thought to be bystanders in nephrogenesis play a critical role. RME cellular composition and function vary widely depending on the nephrogenesis organ, kidney-associated cells' intrinsic characteristics, and patient characteristics[31, 44, 94] (**Figure 5 and Table 3**).

To build large single-cell atlases or Human Cell Atlas[34], Lotfollahi M et al. have assembled single-cell datasets from different single-cell methods/technologies/platforms or multiple methods covering tissues, organs, developmental stages and conditions. Their strategy maps query datasets onto a reference called single-cell architectural surgery (scArches) using deep learning[95] (**Figure 6B**). In the Human Cell Atlas (*https://data.humancellatlas.org*), the Human Developmental Cell Atlas (HDCA) initiative is dedicated to creating a comprehensive reference map of cells during development. Human development, congenital and childhood disorders, and the cellular basis of ageing, cancer, renal disease, and regenerative medicine will be greatly enhanced by examining normal organogenesis, mutations, environmental factors, and infectious agents[96]. Using the HDCA, SCA can identify both known and unknown transcription factors that contribute to nephron development (normal or abnormal organogenesis, mutations, environmental, and infectious factors)[97-99]. Moreover, SCA can provide or detect a useful resource in the emerging landscape of spatial profiling technologies in 2D and 3D counterparts for understanding the cell-specific transcriptional responses from initial kidney disease to therapy by using animal or human models as well as renal biopsy, urine and blood[33, 43, 52, 57, 64, 78, 97, 100-108].

As shown in our study we extracted or summarized the top 46 major achievement articles on SCA in kidney-related diseases (IF[?]10) about cell landscapes (**Table 3**). The initial two articles published by Lu Y et al. [109, 110] in 2017 focused on podocytes and mesangial cells. Out of 58 endothelium-associated genes, 18 encode proteins, of which eleven (Angpt2, Anxa5, Axl, Ecm1, Eng, Fn1, Mfge8, Msn, Nrp1, Serpine2, and Sparc) were upregulated, while two (Apoe and Fgf1) were downregulated. Based on the mesangial cell essential gene list, 173 genes were specifically expressed[109]. An absence of 30 of 92 podocyte genes caused either cytoskeletal injury (FGFR1, AIF1L, HAUS8, RAB3B, LPIN2, GOLIM4, CERS6, ARHGEF18, ARPC1A, SRGAP1, ITGB5, ILDR2, MPP5, DNAJC11, SEPT10, MOCS2, FNBP1L, and TMOD3) or significant downregulation of CD2AP (FGFR1, AOX1, AIF1L, HAUS8)[110]. In 2018, Park J et al[36]. found that the analysis of cell trajectory and lineage tracing in vivo revealed that Notch signals govern transitions between intercalated cells and principal cells. During metabolic acidosis in mouse and human kidney diseases, the fate of the cells changed towards a principal cell trajectory. The phenotypic manifestation and differentiated cell type of inherited kidney diseases are influenced by distinct genetic mutations. Zimmerman KA et al.[111] have used healthy renal tissue from rats, pigs, and humans in order to identify a signature of gene expression in kidney resident macrophages of immune cells across species. Recently, as reported by He B et al.[112] that use both human and mouse kidneys for the identification of all four glomerular cell types (podocytes, glomerular endothelial cells, mesangial cells (MCs), and parietal epithelial cells (PECs)) as well as macula densa cells. Pdgfrb-expressing glomerulus-associated cells include bona fide intraglomerular MCs with functional phagocytosis. An atlas of murine diabetic kidney disease and its treatment has been generated by Wu H et al.[52] as a resource for understanding the cell-specific transcriptional responses to DKD and its treatment (**Figure 6A**).

Overall, kidney diseases are no longer viewed exclusively as a genetic disorder, but as a complex interplay between various renal and non-renal cells within the renal microenvironment. As part of the Human Developmental Cell Atlas initiative, a comprehensive map of cell development will be created, which will assist in understanding normal organogenesis, mutations, environmental factors, and infectious agents. A single-cell profiling technique can investigate cell-specific transcriptional responses in animal and human models, renal biopsies, urine samples, and blood samples, providing a deeper understanding of kidney disease and potential treatments. RME's extensive cellular atlas has been transformed by SCA's powerful capabilities, bringing new perspectives to clinical applications in various kidney diseases. Additionally, RME's cellular composition and communication are promising targets for kidney disease therapies and precision medicine advancements. SCA technologies have been implemented more widely in clinical practice as a result of advancements in technology and wider application.

TheSingle-Cell Analysis Identifies Cell and Gene Expression/Marker.

In cell type-specific gene regulatory regions, kidney-related genetic variants alter gene transcript levels to modulate disease risk[21]. SCA studies have begun dissecting the genetic determinants of kidney cell types and are showing remarkable correlations with established molecular mechanisms, confirming earlier findings and this revolutionary method. SCA reveals the astonishing diversity of immune cells in normal kidneys and provides new insight into renal cell plasticity. New insight into kidney physiology mechanisms and biomarkers for disease and therapy can be gained from characterizing kidney disease mechanisms[33, 113, 114].

In SLE, Arazi A et al.[78] human kidney tissue, urine, and blood LNs from SLE patients (n=24) were compared to healthy kidneys (n=10), revealing that 21 leukocyte subsets demonstrated both pro-inflammatory responses and inflammation-resolving responses, with most cells showing type 1 interferon response genes. CXCR4 and CX3CR1 were found to have widespread expression, indicating a central role. The immune cells found in urine were strongly correlated with those in the kidney, suggesting that urine could be a suitable alternative to kidney biopsy. Similarly, in another study by Nehar-Belaid et al.[85] human peripheral blood mononuclear cells (PBMC) were used to analyze SLE children (n=33), healthy children (n=11), adult SLE (n=8), and adult healthy (n=6). The researchers found that in children with SLE, interferon-stimulated genes (ISGs) were expressed more than in healthy controls, with the high ISG expression signature (ISG^{hi})

predominantly derived from 8/20 PBMC subpopulations, which were associated with high levels of disease activity. Furthermore, human kidney and skin tissue LNs (n=21) vs healthy kidneys (n=3) were analyzed in Fluidigm C1-seq and SMART-Seq and identified tubular cells with a fibrotic signature and a high IFN response score as one of the key causes of treatment failure[73]. Interestingly, the scholars used different patient samples, treatments, and methods to achieve different results, all of which were published in Nature Immunology in 2019 (**Table 3**).

In parallel, Goel R et al.[115] proposed from basic research that deleting the IFN-λ receptor significantly reduced immune cell activation and skin and kidney damage in lupus mice. In response to IFN-λ stimulation, IFN-λ activated keratinocytes and mesangial cells to produce chemokines, with only mouse neutrophils and human B cells upregulating ISGs. However, with larger samples, Perez RK et al[33]. used human PBMCs from SLE patients (n=162) and controls (n=99) and conducted multiplexed scRNA-seq, 10X Genomics Chromium, and snATAC-seq, finding that among the patients, type 1 interferon-stimulated genes (ISGs) were expressed in monocytes, and naive CD4+ T cells were reduced while repertoire-restricted cytotoxic CD8+ T cells were expanded. The patients were stratified into two molecular subtypes based on their cell type-specific expression features (**Figure 6C**). Deng Y et al.[116] also identified ISG expression features in leukocyte clusters and delineated ISG regulation pathways in SLE and LN patients, with ISG expression possibly regulated by transcription factors PLSCR1, TCF4, IRF9, and STAT1. Granulocytes may be targeted as early as possible in ISGs to prevent overwhelming activation of downstream pathways, and SLE and Lupus nephritis may benefit from Avacopan, a C5aR antagonist for intervention. In general, interferon-stimulated genes (ISGs) have been identified by SCA technology as a recent hotspot gene expression/marker for SLE findings (**Table 3**).

Recently, several high-quality studies have shed light on kidney disease and fibrosis. Doke T et al.[117] identified DACH1 as a renal disease risk gene using a multimethod approach and discovered that kidney tubule cells with profibrotic-inflammatory properties secrete CXCL1, which recruits basophils with CXCR2+ by expressing cytokines and chemokines associated with immune cell recruitment[118]. Similarly, in mice and humans, Kuppe C et al.[104] identified NKD2 as a myofibroblast-specific therapeutic target in human kidney fibrosis using genetic fate-tracing, single-cell RNA sequencing, ATAC sequencing, and spatial transcriptomics experiments. In the nephrotic syndrome, Sidhom EH et al.[119] found that GDC-0879 treatment restored GPX4, an enzyme that protects against PUFA-mediated lipid peroxidation, in podocyte cells. GPX4 and Braf/Mapk pathway gene expression patterns in kidney disease tissue also demonstrated broader human disease relevance. Kim SR et al.[120] mainly concentrated on proximal, distal tubular, and endothelial cells in renal artery stenosis (RAS), and they discovered that senolytic strategies have been developed to delay chronic ischemic renal injury by delaying p16 (Cdkn2a), p19 (Cdkn2d), and p21 (Cdkn1a) dysregulated senescence. Finally, Yoshiharu M et al.[64] used snRNA-seq, snATAC-seq, and 10X Genomics Chromium to study rare autosomal dominant polycystic kidney disease (ADPKD) and found that proinflammatory and profibrogenic signalling pathways are activated in the collecting duct by proinflammatory fibroblasts and proximal tubular cells. They also identified and validated a putative distal enhancer that regulates GPRC5A expression in cells lining the collecting duct. These cells are more likely to express transcription factors TEAD, CREB, and retinoic acid receptors. Overall, recent studies have revealed valuable insights into renal fibrosis molecular mechanisms and identified genes like DACH1 and NKD2 as potential therapeutic targets. A promising advance in kidney disease treatment is the restoration of the GPX4 enzyme by GDC-0879 treatment in podocyte cells. Senolytic strategies delay chronic ischemic renal injury in RAS and activate proinflammatory and profibrogenic signalling pathways in ADPKD. Understanding these complex kidney diseases may help develop novel therapeutic strategies.

The Single-Cell Analysis Identifies Transient Cell Types and Other Novel Cells

For CKD and AKI, De Chiara L et al.[121] revealed that maintaining residual kidney function early after AKI through YAP1-driven tubular cell polyploidization could prevent AKI-CKD transition without affecting AKI fatality. Additionally, Chung JJ et al.[122] found that podocytes were acutely activated by the Hippo pathway after nephrotoxic immune injury, which appeared type-specific and injury-specific, and YAP or TAZ

deletion resulted in more severe and prolonged proteinuria in response to injury. Li H et al.[123] also reported that ischemia-induced injury induces diverse injury states in proximal tubular cells, including an early state with enhanced lipid metabolism and during the initial stages of IRI, lipid metabolism is transiently activated, and PLIN2+ lipid droplets are present. While Rudman-Melnick V et al.[124] found that AKI stages and renal cell types show altered gene expression patterns, with several novel genes (Ahnak, Sh3bgrl3, and Col18a1) not previously examined in kidney pathologies including kidney injury molecule-1 (Kim1), lipocalin 2 (Lcn2), and keratin 8 (Krt8). Sox4 and Cd24a show a pronounced nephrogenic signature after AKI. Similarly, Kirita Y et al.[61] suggested that the failed-repair proximal tubule cell (FR-PTC) state may be a therapeutic target. In addition, Conway B et al.[125] reported that during injury and repair of the kidney, monocytes recruited early on adopt a proinflammatory, profibrotic phenotype expressing Arg1, and later transition to become Ccr21 macrophages, while a novel Mmp121 macrophage subset is involved in the repair. Furthermore, Hinze C et al.[126] used human kidney models and revealed that high-depth single-cell gene expression data in human kidneys with AKI identified novel injury-associated cell states in major cell types of the tubular epithelium, characterized by transcriptome patterns linked to oxidative stress, hypoxia, interferon response, and epithelial-to-mesenchymal transition, with differences in the transcriptome primarily driven by cell type-specific abundance of these injury subtypes rather than individual molecular responses. Altogether, studies of potential single-cell analysis have revealed some rare/novel cell types involved in kidney diseases such as AKI and CKD. In addition to YAP1-driven polyploidization of tubular cells, Hippo pathway-mediated podocyte activation, altered gene expression patterns in different renal cell types and stages of acute kidney injury, and identification of novel injury-associated cell states in major tubular epithelium cell types. During injury and repair, different macrophage subsets play different roles, and the failed-repair state of proximal tubule cells may be a therapeutic target. Human kidneys with acute kidney injury may be more effectively treated if high-depth gene expression data are collected on single cells.

In several recent studies in renal tumours mostly focused on immune cells, Young MD et al.[89] found that one population of ascending vasa recta cells expressed VEGF-signalling receptors KDR, FLT1, and FLT4, while the other cluster tE2 exhibited lymphangiogenic VEGFC and FLT1, and high levels of ACKR1, a marker of venular endothelium promoting tissue migration of immune cells, indicating a complex VEGF signalling circuit within RCC tissue. Moreover, Krishna C et al.[127] supposed that the immune microenvironment and TCR clonotype dynamics of multiregional clear cell renal cell carcinoma (ccRCC) samples are dissected by single-cell analysis. ccRCC response and resistance to immune checkpoint blockade (ICB) are linked to CD8+ tissue-resident T cells and tumour-associated macrophages (TAM). Similarly, Li R et al[128]. identified six conserved meta-programs that distinguish tumour cells from normal cells and found one high-enriched at tumour-normal interfaces that co-localized with IL1β-expressing macrophages, which offers a potential therapeutic target. On the other hand, TREM2/APOE/C1Q-positive macrophage infiltration was identified as a potential biomarker for the recurrence of ccRCC as well as a therapeutic target reported by Obradovic A et al.[129] (**Figure 6D**). Overall, recent studies on renal tumours have identified complex signalling circuits involving VEGF receptors and lymphangiogenic factors in RCC tissue. In addition, they have identified potential biomarkers and therapeutic targets, including CD8+ T cells, TAMs, IL1β-expressing macrophages, and TREM2/APOE/C1Q-positive macrophage infiltration. Interestingly, immune cell-related TAMs are a hotspot and active domain of renal tumour research. These findings suggest that a better understanding of the immune microenvironment in RCC may lead to improved therapies for this type of cancer (**Table 3**).

The

Integration of Single-Cell Applications with Other Techniques/Methods in Kidney Diseases

Although we know the major potential and powerful applications of the single-cell analysis technology[34, 130], there are still many other significant multi-methods, multi-models and multi-omics aspects that facilitate scholars to easily explore the much more complicated kidney diseases research domain and deserve more attention and exploration, such as the combination or integration application between SCA techniques and CRISPR screening[131-133], other multi-omics platforms[130, 134-136], nanotechnology[107, 137-139], stem cell/exosomes[53, 58, 107, 134, 140-145], Genome-wide association studies (GWAS)[21, 105, 146-151],

machine-learning[95, 135, 152, 153], as well as the mendelian randomization approach (MRA)[117, 148, 154], and so on. The combination or integration of various single-cell technologies and other techniques, methods or models allows for a more comprehensive understanding of pathophysiological mechanisms and biological processes behind kidney disease to obtain or improve new or traditional diagnostic/treatment approaches. Interestingly, the more authors use the multi-methods, multi-techniques or advanced/recent hotspot models, the better or high-quality journals that they published, moreover what they discover tends to be more complex, new basic/clinical findings or new hotspot/keywords research for the next scholars.

For instance, Doke T et al.[117] performed GWAS, MRA, SCA, and MetaXcan to identify DACH1 as a kidney disease risk gene that contributes to fibrosis. Treacy NJ et al. [107]mainly conducted SCA, stem cell(hiPSC), and nanomedicine techniques (hiPSC-derived kidney organoids) and found that embedding hiPSC-derived kidney organoids within fully synthetic peptide-based hydrogels is a promising approach to producing viable replacement organs from hiPSCs. Comparably, Wang G et al.[134] carried out typically SCA (spatial dynamic metabolomics) and stem cell(hiPSC), suggesting that kidney development may replace glycolysis with fatty acid oxidation. HiPSC-derived kidney organoids have immature metabolic phenotypes that can be improved by supplementing them with butyrate to enhance tubular epithelial differentiation (**Figure 7A**). On the other hand, Puelles VG et al.[108] combined the current SCA technologies and optical techniques to build in-depth 3D quantitative endpoints based on a comprehensive analysis of intact glomeruli in murine crescent nephritis, revealing the morphologic and cellular evolution of tubular crescents (**Figure 7C**). However, all existing technologies, methods, and models have basically built-in trade-offs between the time required, the cost needed, challenges, considerations, as well as technical performance[155] (**Table 3**).

Advanced Translation of Single-Cell Analysis Findings to Renal Clinical Properties

SCA technologies have been found to be useful in a number of different areas, including the prediction of clinical properties in oncologic[156-158], neurologic[159, 160], cardiac[161] therapy, as well as the potential developmental road of CAR-T[162-165], cell therapy[160, 163, 164], gene therapy[166], biological therapy[167], immunotherapy[156, 168], predicting drug response[169], and chemotherapy[170] etc. By understanding disease at the cellular and tissue level with the Human Cell Atlas, investigators can develop powerful disease diagnostics, identify new drug targets, predict their efficacy, toxicity and resistance mechanisms, and create novel therapies[34, 171]. Although the descriptions of HCA, RME and GWAS provided by SCA technologies are valuable and informative, the next step is to understand how these organizational patterns are formed and their function and clinical hallmarks. In order to answer these questions, annotations, additional data, and well-controlled perturbations must be integrated with SCA profiling technologies. For example below:

For the diagnosis tool, as previous mentions, by combining SCA technology with different models and techniques, we have identified interferon-stimulated genes (ISGs) as a recent hotspot gene expression/marker for SLE[33, 73, 78, 85, 115, 116]. From these basic findings, Avacopan, an inhibitor of C5aR, may benefit patients with SLE and LN after the identification of ISG expression features in leucocyte clusters[116]. Profiling urine cells in subjects with focal segmental glomerulosclerosis (FSGS) can aid in the diagnosis and prognosis of nephrotic syndrome, as well as the development of personalized therapies by identifying molecular pathways in immune cells and podocytes[172]. Similarly, urine proteomics can be a noninvasive way to monitor active intrarenal biologic pathways in lupus nephritis (LN) and the findings implicate IL-16 as a potential target and biomarker for LN[173]. However, GPRC5A serves as a marker for cyst-lining collecting duct cells in Autosomal dominant polycystic kidney disease (ADPKD), and its expression is regulated by a distal enhancer containing binding motifs for NF-kappaB, TEAD, CREB, and retinoic acid receptors, providing potential for developing novel diagnostic and therapeutic strategies[64]. Skin biopsies may serve as a valuable tool for the management of lupus nephritis, allowing for repeat biopsies and the use of scRNA-seq to gain insights into its pathogenesis[72, 73]. Otherwise, another study emphasized the importance of the fibrotic kidney local microenvironment (KLM) in progressive CKD and suggested that targeting HGF/c-met signalling in different cell types within KLM may be a promising therapeutic approach[174]. The snRNA-seq analysis of human diabetic kidney samples reveals that Na(+)/K(+)-ATPase, mineralocorticoid

receptor, and WNK1 expression are altered in the thick ascending limb, late distal convoluted tubule, and principal cells, along with decreased NEDD4L expression and paracellular calcium and magnesium reabsorption. Also, glomerular cells, proximal convoluted tubule, distal convoluted tubule, and principal cells have strong angiogenic signatures, indicating that the diabetic kidney responds early to potassium secretion and angiogenic signalling[175] (**Table 3**).

For the prediction of therapeutic response, several investigators show that tumour-associated macrophages (TAM) may be a potential prognostic/therapeutic target for renal tumours[127-129]. By using human/mouse models in kidney fibrosis, Kuppe C et al.[104] revealed that NKD2 is specifically targeted to the myofibroblasts in the kidneys of patients with kidney fibrosis. Furthermore, when YAP or TAZ were deleted, podocytes activated the Hippo pathway in response to nephrotoxic immune injury, resulting in more severe and prolonged proteinuria[122]. And DACH1 was identified as a kidney disease risk gene[117]. And for diabetic kidney disease, ACE inhibitors and SGLT2 inhibitors elicit varying gene expression and pathway activation responses in different cell types, highlighting the importance of understanding cell type-specific responses to develop effective treatments in mice[52]. On the other hand, in animal models, the study suggests that targeting S100A8/A9 signalling with small-molecule inhibitors may be a promising therapeutic strategy for treating AKI, as S100a9(hi) Ly6c(hi) infiltrated macrophages play a key role in mediating kidney inflammation and blocking this pathway has been shown to improve renal function, reduce mortality, and ameliorate kidney injury and fibrosis[176]. Similarly, two early-phase populations with dysregulated lipid and amino acid metabolism were identified in Sci-RNA-seq3. In the chronic phase, lipid metabolism was defective, but in the very early phase of ischemia-induced injury, it was transiently activated. By crosstalk between epithelial and stromal cells, perilipin 2 was recognized as an intracellular lipid droplet marker[123]. Study results revealed differentials between effector and memory B cells by analyzing data from single-cell transcriptomes, DNA methylomes, and chromatin accessibility profiles of B cells from SLE patients and healthy controls. Resting naïve cells already exhibited the SLE molecular signature dominated by AP-1 and EGR transcription factors, which in synergy with T-BET shaped the epigenome of expanded SLE effector B cell subsets, defining the molecular basis for pathogenic B cell dysfunction[164]. In summary, these findings provide significant evidence that advanced technologies can be utilized to improve our understanding of kidney diseases and develop personalized approaches from diagnosis to treatment both in clinical and laboratory settings (**Table 3**).

Prospects of Single-cell Analysis for Kidney Disease

Bibliographic analysis has many functions, but one of the most crucial is to provide an indication of the dynamics associated with the development of a specific field[177]. Using these indicators, researchers can predict whether or not their research ideas will grow or decline in the future. Based on an analysis of the temporal evolution of countries, institutions, authors, journals, references, and keywords over time, we discussed the prospects of SCA technologies and kidney disease in terms of their potential relationship. SCA technologies are shifting from diagnosis to precise treatment-centred study alongside the global burden of kidney disease relevant to technological and clinical development.

For Human Cell Atlases in medicine to live up to their potential of being transformative, significant challenges need to be overcome-technical, practical, and fundamental and these have to be overcome for this potential to materialize**[34]** . By integrating transcriptome, epigenome, and proteome profiles, as well as their current behaviour and differentiation potential, multi-omics approaches provide a holistic understanding of cells[130, 134, 135]. The importance of future studies integrating spatial transcriptomics with kidney disease research will be critical to defining the cell types and changes that take place during this process[44, 114, 155, 178, 179] (**Figure 7B**). Single Cell ProtEomics (SCoPE2) is a second-generation method derived from the combination of Single Cell ProtEomics by Mass Spectrometry (SCoPE-MS) and Single Cell ProtEomics by Mass Spectrometry (SCoPE-MS). It allows the analysis of any primary tissue or cell culture that can be processed as a suspension of single cells. This protocol can also be adapted for other small samples, such as biopsies. RNA-Seq can also be performed on single cells using similar methods to prepare single-cell suspensions. However, some preparation methods may negatively impact cell protein surfaces. The SCoPE2 protocol

emphasizes ultrasensitive analysis and analyzes individual cells in small samples, such as biopsies**[180, 181]** . Single-cell architectural surgery (ScArches) is a decentralized, iterative, and efficient approach to building reference data from query datasets, using deep learning. The method utilizes transfer learning and parameter optimization to improve the contextualization of existing datasets with existing references. Additionally, it allows the imputation of missing modalities and generalizes to multimodal reference mapping. A reference cell atlas can be constructed, updated, shared, and efficiently utilized using scArches by facilitating collaborative projects[95] (**Figure 6B**). Some kidney-related diseases, including SLE, CKD, diabetic kidney disease, IgA nephropathy and nephrotic syndrome, are difficult to cure completely and often require long-term or lifelong medication, which severely affects patients' quality of life. While the integration of SCA and CAR-T therapy has shown excellent results in clinical trials for these diseases, and we hope to bring more effective treatments to patients in the near future[164, 165, 182, 183]. Together, we are confident that these integrated strategies will allow us to better explore how clinically relevant findings relate to the development of kidney disease. In parallel with the increasing utility of methods and the deepening of single-cell techniques to address critical research questions, new directions in renal clinical research will be discussed (**Table 3**).

Challenges of Single-cell Analysis for Kidney Disease

Although our bibliometric analysis of variable SCA technologies has provided a brief overview of recent advancements in their application to renal clinical hallmarks. However, several challenges remain that hinder their further use in practice. Firstly, it is inherently noisy since this data is derived from scRNA-seq in eukaryotic cells that exhibit burst-like stochastic transcription[184-186]. Even though many computational techniques have been invented to minimise the influence of these noise factors[186, 187]. Failure to detect a transcript from a particular gene in a cell at a specific point in time can be ambiguous and may not necessarily indicate gene inactivity. Having a complete view of the cellular transcriptome has helped overcome this limitation, and pathway analysis and gene-set enrichment indicate greater accuracy than single gene expression[188, 189]. Secondly, transcriptome data alone is not sufficient to establish genotype-phenotype correlations, whereas they need to work in concert with other techniques in order to improve the main results, such as machine learning, genome-wide association studies (GWAS), and multi-omics[117, 135, 190]. Thirdly, Although the cost per cell has decreased considerably, the cost per sample remains very high. Currently, SCA technologies remain challenging to be routinely used in renal clinical settings[27, 29, 191, 192]. However, recent innovation in SCoPE2 technology has allowed for a substantial increase in quantitative accuracy and throughput. In addition, it has reduced costs and time spent on hands-on preparation by introducing automated and miniaturized sample preparation. Yet it is not widely practised in the renal clinic[180, 181]. Fourth, the major challenge of single-cell RNA sequencing is the loss of histological information resulting from the preparation of individual cells and nuclear suspensions from tissues. Nevertheless, factors such as tissue digestion and preservation can alter gene expression and cell representation in trajectory analysis. Spatial transcriptomics, including barcoded array-based capture and in situ sequencing, has emerged as a breakthrough in studying the whole organism's architecture at the molecular level. This will revolutionize how we understand tissues/organs/organisms, their composition, complexity, interactions, and functions[94, 193]. Finally, samples can be affected by batch effects when processed on different days, sex, and aging. However, multiple correction methods exist that must be applied judiciously to avoid masking true biological differences[194, 195].

Limitations And Strengths

SCA is promising for kidney disease applications, but clinical implementation remains challenging. Firstly, for our own study used a comprehensive retrieval strategy to search data from WoSCC, but limitations such as fewer studies about SCA-related cancer and potential deviations in the machine algorithms used, suggest the need for more bibliometric data updates to further clarify scientific trends and hotspots in SCA-related kidney disease research, particularly for recent power-published and potentially high-impact studies. According to our knowledge, this is the first study to use the bibliometric approach to systematically assess trends in the advancement of renal-related diseases using a recent analysis of emerging global research trends in SCA research.

CONCLUSIONS

According to our current knowledge, SCA bibliometric analysis in kidney disease still lacks significant evidence. This work presents a bibliometric analysis of SCA application usage in kidney disease over the last decade. In summary, the main findings of this research were as follows:

1. During the period from 1 January 1999 to 13 February 2023, 1606 articles and reviews were published directly or indirectly related to SCA in kidney disease. 11,737 authors from 2,317 institutions in 67 countries or regions investigated SCA's role in kidney diseases.
2. Major authors, institutes, countries, and journals contributed to the rapid development of SCA in kidney disease. (1) The majority of publications were published in the United States and China. SCA-related kidney disease publications were most prevalent in the United States, with Harvard Medical School (United States) being the most active institution. (2) The author who has contributed the most papers on SCA in kidney disease is Humphreys, Benjamin D (Corresponding author), followed by Trapnell, Cole, who had the most co-citations in his papers. (3) It is also worth noting that most papers on SCA in kidney diseases have been published in Frontiers in Immunology, whereas Nature is the journal that has been co-cited the most.
3. We found the hotspot in SCA technologies and kidney-related diseases research as follows: (1) SCA technologies-related keywords included RNA-seq, transcriptome, single-cell, chip-seq, single-cell RNA sequencing, histone-like nucleoid structuring protein (H-NS), and genome-wide association. (2) Disease-, molecular-, and pathological-related keywords included expression, EGFR, gene-expression, activation, gene, cell, protein, mechanism, mutation, inflammation, resistance, apoptosis, and T-cell. (3) Kidney-related disease keywords are SLE, AKI, CKD, renal fibrosis, diabetic kidney disease, nephrotic syndrome, IgA nephropathy, and kidney transplantation.

Overall, there is rapid growth in the field of SCA in kidney-related disease research, and it is likely that this field of research will expand in the coming decades. Despite this, most clinical SCA studies are still in their exploratory stages, mostly aimed at revisiting and improving diagnosis and therapeutic marker identification. Researchers will be able to create novel diagnostic, therapeutic and prognostic ideas and methodologies that will help them establish novel diagnostic, therapeutic and prognostic approaches to kidney diseases based on the findings of these comprehensive analyses. SCA technologies may also be applied in the future to support other main technologies or models that will help routine clinical diagnoses and personalize medicine, providing a promising or hopeful future for this technology.

Contributors

1. Hunan innovative province construction project (Grant no. 2019SK2211)
2. Key research and development project of Hunan Province (Grant no. 2020SK2089)
3. The Natural Science Foundation of Hunan province (Grant no. 2020JJ4833)
4. The Natural Science Foundation of Hunan province (Grant no. 2019SK2211)
5. The Natural Science Foundation of Hunan province (Grant no. XY040019)
6. Hunan Province Key Field R&D Program (Grant no. 2020SK2097)
7. Horizontal Project (Grant no. KY080269)
8. Horizontal Project (Grant no. KY080262)
9. Horizontal Project (Grant no. XY080323)
10. Horizontal Project (Grant no. XY080324)

Disclosure statement: All authors have declared no conflicts of interest.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Author Contributions

Marady Hun had the idea for the study. Huai Wen, Marady Hun, Qiuwei Tian, Zisai Wang, and Tharith

Vun selected studies for inclusion and abstracted data. Marady Hun, Tin Som, and Phanna Han did the statistical analyses. Marady Hun, Boren Preap, Min Wen, and Huai Wen interpreted the data. Marady Hun wrote the first draft. Mingyi Zhao and Qingnan He critically revised the paper for important intellectual content. All authors have read and approved the content of the manuscript.

Patient consent for publication: Not required.

Ethical approval: All data for this study were obtained from existing publications and Ethical approval was not required for this research.

Data availability statement: All data generated or analyzed during this study are included in this published article and its supplementary information files.

REFERENCES

[1] Collaboration GCKD. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet (London, England). (2020).395(10225):709-33 doi: 10.1016/s0140-6736(20)30045-3

[2] Bishop NC, Burton JO, Graham-Brown MPM, Stensel DJ, Viana JL and Watson EL. Exercise and chronic kidney disease: potential mechanisms underlying the physiological benefits. Nat Rev Nephrol. (2023) doi: 10.1038/s41581-022-00675-9

[3] Murray R, Zimmerman T, Agarwal A, Palevsky P, Quaggin S, Rosas S, et al. Kidney-Related Research in the United States: A Position Statement From the National Kidney Foundation and the American Society of Nephrology. American journal of kidney diseases : the official journal of the National Kidney Foundation. (2021).78(2):161-7 doi: 10.1053/j.ajkd.2021.04.006

[4] Kalantar-Zadeh K, Jafar TH, Nitsch D, Neuen BL and Perkovic V. Chronic kidney disease. Lancet. (2021).398(10302):786-802 doi: 10.1016/S0140-6736(21)00519-5

[5] Kellum J, Romagnani P, Ashuntantang G, Ronco C, Zarbock A and Anders H. Acute kidney injury. Nature reviews. Disease primers. (2021).7(1):52 doi: 10.1038/s41572-021-00284-z

[6] Durcan L, O'Dwyer T and Petri M. Management strategies and future directions for systemic lupus erythematosus in adults. Lancet. (2019).393(10188):2332-43 doi: 10.1016/S0140-6736(19)30237-5

[7] Dorner T and Furie R. Novel paradigms in systemic lupus erythematosus. Lancet. (2019).393(10188):2344-58 doi: 10.1016/S0140-6736(19)30546-X

[8] Anders HJ, Saxena R, Zhao MH, Parodis I, Salmon JE and Mohan C. Lupus nephritis. Nat Rev Dis Primers. (2020).6(1):7 doi: 10.1038/s41572-019-0141-9

[9] Kopp JB, Anders HJ, Susztak K, Podesta MA, Remuzzi G, Hildebrandt F, et al. Podocytopathies. Nat Rev Dis Primers. (2020).6(1):68 doi: 10.1038/s41572-020-0196-7

[10] Noone DG, Iijima K and Parekh R. Idiopathic nephrotic syndrome in children. Lancet. (2018).392(10141):61-74 doi: 10.1016/S0140-6736(18)30536-1

[11] Boyer O, Schaefer F, Haffner D, Bockenhauer D, Holtta T, Berody S, et al. Management of congenital nephrotic syndrome: consensus recommendations of the ERKNet-ESPN Working Group. Nat Rev Nephrol. (2021).17(4):277-89 doi: 10.1038/s41581-020-00384-1

[12] Kidney Disease: Improving Global Outcomes Glomerular Diseases Work G. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. (2021).100(4S):S1-S276 doi: 10.1016/j.kint.2021.05.021

[13] Sethi S, De Vriese AS and Fervenza FC. Acute glomerulonephritis. Lancet. (2022).399(10335):1646-63 doi: 10.1016/S0140-6736(22)00461-5

[14] Li L, Fu H and Liu Y. The fibrogenic niche in kidney fibrosis: components and mechanisms. Nat Rev Nephrol. (2022).18(9):545-57 doi: 10.1038/s41581-022-00590-z

[15] Bertaina A, Grimm PC, Weinberg K, Parkman R, Kristovich KM, Barbarito G, et al. Sequential Stem Cell-Kidney Transplantation in Schimke Immuno-osseous Dysplasia. N Engl J Med. (2022).386(24):2295-302 doi: 10.1056/NEJMoa2117028

[16] DeFronzo RA, Reeves WB and Awad AS. Pathophysiology of diabetic kidney disease: impact of SGLT2 inhibitors. Nat Rev Nephrol. (2021).17(5):319-34 doi: 10.1038/s41581-021-00393-8

[17] Matsushita K, Ballew SH, Wang AY, Kalyesubula R, Schaeffner E and Agarwal R. Epidemiology and risk of cardiovascular disease in populations with chronic kidney disease. Nat Rev Nephrol. (2022).18(11):696-707 doi: 10.1038/s41581-022-00616-6

[18] Beldhuis IE, Lam CSP, Testani JM, Voors AA, Van Spall HGC, Ter Maaten JM, et al. Evidence-Based Medical Therapy in Patients With Heart Failure With Reduced Ejection Fraction and Chronic Kidney Disease. Circulation. (2022).145(9):693-712 doi: 10.1161/circulationaha.121.052792

[19] Haarhaus M and Evenepoel P. Differentiating the causes of adynamic bone in advanced chronic kidney disease informs osteoporosis treatment. Kidney Int. (2021).100(3):546-58 doi: 10.1016/j.kint.2021.04.043

[20] Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Perrone RD, Koch G, et al. Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease. N Engl J Med. (2017).377(20):1930-42 doi: 10.1056/NEJMoa1710030

[21] Sullivan KM and Susztak K. Unravelling the complex genetics of common kidney diseases: from variants to mechanisms. Nat Rev Nephrol. (2020).16(11):628-40 doi: 10.1038/s41581-020-0298-1

[22] Saez-Rodriguez J, Rinschen MM, Floege J and Kramann R. Big science and big data in nephrology. Kidney Int. (2019).95(6):1326-37 doi: 10.1016/j.kint.2018.11.048

[23] Humphreys B. Mapping kidney cellular complexity. Science (New York, N.Y.). (2018).360(6390):709-10 doi: 10.1126/science.aat7271

[24] Deng Y, Bartosovic M, Ma S, Zhang D, Kukanja P, Xiao Y, et al. Spatial profiling of chromatin accessibility in mouse and human tissues. Nature. (2022).609(7926):375-83 doi: 10.1038/s41586-022-05094-1

[25] Deng Y, Bartosovic M, Kukanja P, Zhang D, Liu Y, Su G, et al. Spatial-CUT&Tag: Spatially resolved chromatin modification profiling at the cellular level. Science (New York, N.Y.). (2022).375(6581):681-6 doi: 10.1126/science.abg7216

[26] Stuart T and Satija R. Integrative single-cell analysis. Nat Rev Genet. (2019).20(5):257-72 doi: 10.1038/s41576-019-0093-7

[27] Ziegenhain C, Vieth B, Parekh S, Reinius B, Guillaumet-Adkins A, Smets M, et al. Comparative Analysis of Single-Cell RNA Sequencing Methods. Mol Cell. (2017).65(4):631-43 e4 doi: 10.1016/j.molcel.2017.01.023

[28] Vistain LF and Tay S. Single-Cell Proteomics. Trends Biochem Sci. (2021).46(8):661-72 doi: 10.1016/j.tibs.2021.01.013

[29] Jovic D, Liang X, Zeng H, Lin L, Xu F and Luo Y. Single-cell RNA sequencing technologies and applications: A brief overview. Clin Transl Med. (2022).12(3):e694 doi: 10.1002/ctm2.694

[30] Haniffa M, Taylor D, Linnarsson S, Aronow B, Bader G, Barker R, et al. A roadmap for the Human Developmental Cell Atlas. Nature. (2021).597(7875):196-205 doi: 10.1038/s41586-021-03620-1

[31] Hinze C, Karaiskos N, Boltengagen A, Walentin K, Redo K, Himmerkus N, et al. Kidney Single-cell Transcriptomes Predict Spatial Corticomedullary Gene Expression and Tissue Osmolality Gradients. J Am Soc Nephrol. (2021).32(2):291-306 doi: 10.1681/ASN.2020070930

[32] Desanti De Oliveira B, Xu K, Shen T, Callahan M, Kiryluk K, D'Agati V, et al. Molecular nephrology: types of acute tubular injury. Nature reviews. Nephrology. (2019).15(10):599-612 doi: 10.1038/s41581-019-0184-x

[33] Perez RK, Gordon MG, Subramaniam M, Kim MC, Hartoularos GC, Targ S, et al. Single-cell RNA-seq reveals cell type-specific molecular and genetic associations to lupus. Science. (2022).376(6589):eabf1970 doi: 10.1126/science.abf1970

[34] Rood JE, Maartens A, Hupalowska A, Teichmann SA and Regev A. Impact of the Human Cell Atlas on medicine. Nat Med. (2022).28(12):2486-96 doi: 10.1038/s41591-022-02104-7

[35] Stewart B, Ferdinand J, Young M, Mitchell T, Loudon K, Riding A, et al. Spatiotemporal immune zonation of the human kidney. Science (New York, N.Y.). (2019).365(6460):1461-6 doi: 10.1126/science.aat5031

[36] Park J, Shrestha R, Qiu C, Kondo A, Huang S, Werth M, et al. Single-cell transcriptomics of the mouse kidney reveals potential cellular targets of kidney disease. Science (New York, N.Y.). (2018).360(6390):758-63 doi: 10.1126/science.aar2131

[37] Wu H and Humphreys B. The promise of single-cell RNA sequencing for kidney disease investigation. Kidney international. (2017).92(6):1334-42 doi: 10.1016/j.kint.2017.06.033

[38] Taylor D, Aronow B, Tan K, Bernt K, Salomonis N, Greene C, et al. The Pediatric Cell Atlas: Defining the Growth Phase of Human Development at Single-Cell Resolution. Developmental cell. (2019).49(1):10-29 doi: 10.1016/j.devcel.2019.03.001

[39] KDIGO CP. Genetics in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. (2022).101(6):1126-41 doi: 10.1016/j.kint.2022.03.019

[40] Meng L, Pammi M, Saronwala A, Magoulas P, Ghazi A, Vetrini F, et al. Use of Exome Sequencing for Infants in Intensive Care Units: Ascertainment of Severe Single-Gene Disorders and Effect on Medical Management. JAMA pediatrics. (2017).171(12):e173438 doi: 10.1001/jamapediatrics.2017.3438

[41] Groopman EE, Marasa M, Cameron-Christie S, Petrovski S, Aggarwal VS, Milo-Rasouly H, et al. Diagnostic Utility of Exome Sequencing for Kidney Disease. N Engl J Med. (2019).380(2):142-51 doi: 10.1056/NEJMoa1806891

[42] Rasouly HM, Groopman EE, Heyman-Kantor R, Fasel DA, Mitrotti A, Westland R, et al. The Burden of Candidate Pathogenic Variants for Kidney and Genitourinary Disorders Emerging From Exome Sequencing. Ann Intern Med. (2019).170(1):11-21 doi: 10.7326/M18-1241

[43] Moffitt JR, Lundberg E and Heyn H. The emerging landscape of spatial profiling technologies. Nat Rev Genet. (2022).23(12):741-59 doi: 10.1038/s41576-022-00515-3

[44] Dixon EE, Wu H, Sulvaran-Guel E, Guo J and Humphreys BD. Spatially resolved transcriptomics and the kidney: many opportunities. Kidney Int. (2022).102(3):482-91 doi: 10.1016/j.kint.2022.06.011

[45] Chen C. Searching for intellectual turning points: progressive knowledge domain visualization. Proc Natl Acad Sci U S A. (2004).101 Suppl 1(Suppl 1):5303-10 doi: 10.1073/pnas.0307513100

[46] Synnestvedt MB, Chen C and Holmes JH. CiteSpace II: visualization and knowledge discovery in bibliographic databases. AMIA Annu Symp Proc. (2005).2005:724-8 doi:

[47] van Eck NJ and Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics. (2010).84(2):523-38 doi: 10.1007/s11192-009-0146-3

[48] Aria M and Cuccurullo C. bibliometrix: An R-tool for comprehensive science mapping analysis. Journal of Informetrics. (2017).11(4):959-75 doi: 10.1016/j.joi.2017.08.007

[49] Luo L, Gribskov M and Wang S. Bibliometric review of ATAC-Seq and its application in gene expression. Brief Bioinform. (2022).23(3) doi: 10.1093/bib/bbac061

[50] Ribeiro GO, Rodrigues LAP, Dos Santos TBS, Alves JPS, Oliveira RS, Nery TBR, et al. Innovations and developments in single cell protein: Bibliometric review and patents analysis. Front Microbiol. (2022).13:1093464 doi: 10.3389/fmicb.2022.1093464

[51] Zhao Y, Xiao Y, Hu Z, Wang J, Xu Z, Mo Y, et al. Bibliometric analysis of single-cell sequencing researches on immune cells and their application of DNA damage repair in cancer immunotherapy. Front Oncol. (2023).13:1067305 doi: 10.3389/fonc.2023.1067305

[52] Wu H, Gonzalez Villalobos R, Yao X, Reilly D, Chen T, Rankin M, et al. Mapping the single-cell transcriptomic response of murine diabetic kidney disease to therapies. Cell Metab. (2022).34(7):1064-78 e6 doi: 10.1016/j.cmet.2022.05.010

[53] Wu H and Humphreys BD. Single Cell Sequencing and Kidney Organoids Generated from Pluripotent Stem Cells. Clin J Am Soc Nephrol. (2020).15(4):550-6 doi: 10.2215/CJN.07470619

[54] Wu H and Humphreys BD. Immune cell heterogeneity in a mouse model of diabetic kidney disease. Kidney Int. (2022).102(6):1215-6 doi: 10.1016/j.kint.2022.09.007

[55] Wu H, Kirita Y, Donnelly EL and Humphreys BD. Advantages of Single-Nucleus over Single-Cell RNA Sequencing of Adult Kidney: Rare Cell Types and Novel Cell States Revealed in Fibrosis. J Am Soc Nephrol. (2019).30(1):23-32 doi: 10.1681/ASN.2018090912

[56] Wu H, Lai CF, Chang-Panesso M and Humphreys BD. Proximal Tubule Translational Profiling during Kidney Fibrosis Reveals Proinflammatory and Long Noncoding RNA Expression Patterns with Sexual Dimorphism. J Am Soc Nephrol. (2020).31(1):23-38 doi: 10.1681/ASN.2019040337

[57] Wu H, Malone AF, Donnelly EL, Kirita Y, Uchimura K, Ramakrishnan SM, et al. Single-Cell Transcriptomics of a Human Kidney Allograft Biopsy Specimen Defines a Diverse Inflammatory Response. J Am Soc Nephrol. (2018).29(8):2069-80 doi: 10.1681/ASN.2018020125

[58] Wu H, Uchimura K, Donnelly EL, Kirita Y, Morris SA and Humphreys BD. Comparative Analysis and Refinement of Human PSC-Derived Kidney Organoid Differentiation with Single-Cell Transcriptomics. Cell Stem Cell. (2018).23(6):869-81 e8 doi: 10.1016/j.stem.2018.10.010

[59] Malone AF, Wu H and Humphreys BD. Bringing Renal Biopsy Interpretation Into the Molecular Age With Single-Cell RNA Sequencing. Semin Nephrol. (2018).38(1):31-9 doi: 10.1016/j.semnephrol.2017.09.005

[60] Schmidt IM, Colona MR, Kestenbaum BR, Alexopoulos LG, Palsson R, Srivastava A, et al. Cadherin-11, Sparc-related modular calcium binding protein-2, and Pigment epithelium-derived factor are promising non-invasive biomarkers of kidney fibrosis. Kidney Int. (2021).100(3):672-83 doi: 10.1016/j.kint.2021.04.037

[61] Kirita Y, Wu H, Uchimura K, Wilson PC and Humphreys BD. Cell profiling of mouse acute kidney injury reveals conserved cellular responses to injury. Proc Natl Acad Sci U S A. (2020).117(27):15874-83 doi: 10.1073/pnas.2005477117

[62] Ngo D, Wen D, Gao Y, Keyes MJ, Drury ER, Katz DH, et al. Circulating testican-2 is a podocyte-derived marker of kidney health. Proceedings of the National Academy of Sciences. (2020).117(40):25026-35 doi: 10.1073/pnas.2009606117

[63] E Oh, Wu H, Muto Y, Donnelly EL, Machado FG, Fan LX, et al. A conditionally immortalized Gli1-positive kidney mesenchymal cell line models myofibroblast transition. Am J Physiol Renal Physiol. (2019).316(1):F63-F75 doi: 10.1152/ajprenal.00460.2018

[64] Muto Y, Dixon EE, Yoshimura Y, Wu H, Omachi K, Ledru N, et al. Defining cellular complexity in human autosomal dominant polycystic kidney disease by multimodal single cell analysis. Nat Commun. (2022).13(1):6497 doi: 10.1038/s41467-022-34255-z

[65] Nam SA, Seo E, Kim JW, Kim HW, Kim HL, Kim K, et al. Graft immaturity and safety concerns in transplanted human kidney organoids. Exp Mol Med. (2019).51(11):1-13 doi: 10.1038/s12276-019-0336-x

[66] Malone AF, Wu H, Fronick C, Fulton R, Gaut JP and Humphreys BD. Harnessing Expressed Single Nucleotide Variation and Single Cell RNA Sequencing To Define Immune Cell Chimerism in the Rejecting Kidney Transplant. J Am Soc Nephrol. (2020).31(9):1977-86 doi: 10.1681/ASN.2020030326

[67] Humphreys B. Mechanisms of Renal Fibrosis. Annual review of physiology. (2018).80:309-26 doi: 10.1146/annurev-physiol-022516-034227

[68] Gatti S, Bruno S, Deregibus MC, Sordi A, Cantaluppi V, Tetta C, et al. Microvesicles derived from human adult mesenchymal stem cells protect against ischaemia-reperfusion-induced acute and chronic kidney injury. Nephrology Dialysis Transplantation. (2011).26(5):1474-83 doi: 10.1093/ndt/gfr015

[69] Wilson PC, Muto Y, Wu H, Karihaloo A, Waikar SS and Humphreys BD. Multimodal single cell sequencing implicates chromatin accessibility and genetic background in diabetic kidney disease progression. Nat Commun. (2022).13(1):5253 doi: 10.1038/s41467-022-32972-z

[70] Little MH and Humphreys BD. Regrow or Repair: An Update on Potential Regenerative Therapies for the Kidney. J Am Soc Nephrol. (2022).33(1):15-32 doi: 10.1681/ASN.2021081073

[71] Dixon EE, Wu H, Muto Y, Wilson PC and Humphreys BD. Spatially Resolved Transcriptomic Analysis of Acute Kidney Injury in a Female Murine Model. J Am Soc Nephrol. (2022).33(2):279-89 doi: 10.1681/ASN.2021081150

[72] Der E, Ranabothu S, Suryawanshi H, Akat KM, Clancy R, Morozov P, et al. Single cell RNA sequencing to dissect the molecular heterogeneity in lupus nephritis. JCI Insight. (2017).2(9) doi: 10.1172/jci.insight.93009

[73] Der E, Suryawanshi H, Morozov P, Kustagi M, Goilav B, Ranabothu S, et al. Tubular cell and keratinocyte single-cell transcriptomics applied to lupus nephritis reveal type I IFN and fibrosis relevant pathways. Nat Immunol. (2019).20(7):915-27 doi: 10.1038/s41590-019-0386-1

[74] Der E, Suryawanshi H, Buyon J, Tuschl T and Putterman C. Single-cell RNA sequencing for the study of lupus nephritis. Lupus Sci Med. (2019).6(1):e000329 doi: 10.1136/lupus-2019-000329

[75] Butler A, Hoffman P, Smibert P, Papalexi E and Satija R. Integrating single-cell transcriptomic data across different conditions, technologies, and species. Nat Biotechnol. (2018).36(5):411-20 doi: 10.1038/nbt.4096

[76] Stuart T, Butler A, Hoffman P, Hafemeister C, Papalexi E, Mauck WM, 3rd, et al. Comprehensive Integration of Single-Cell Data. Cell. (2019).177(7):1888-902 e21 doi: 10.1016/j.cell.2019.05.031

[77] Macosko EZ, Basu A, Satija R, Nemesh J, Shekhar K, Goldman M, et al. Highly Parallel Genome-wide Expression Profiling of Individual Cells Using Nanoliter Droplets. Cell. (2015).161(5):1202-14 doi: 10.1016/j.cell.2015.05.002

[78] Arazi A, Rao DA, Berthier CC, Davidson A, Liu Y, Hoover PJ, et al. The immune cell landscape in kidneys of patients with lupus nephritis. Nat Immunol. (2019).20(7):902-14 doi: 10.1038/s41590-019-0398-x

[79] Korsunsky I, Millard N, Fan J, Slowikowski K, Zhang F, Wei K, et al. Fast, sensitive and accurate integration of single-cell data with Harmony. Nat Methods. (2019).16(12):1289-96 doi: 10.1038/s41592-019-0619-0

[80] Wolf FA, Angerer P and Theis FJ. SCANPY: large-scale single-cell gene expression data analysis. Genome Biol. (2018).19(1):15 doi: 10.1186/s13059-017-1382-0

[81] Zhou Y, Zhou B, Pache L, Chang M, Khodabakhshi AH, Tanaseichuk O, et al. Metascape provides a biologist-oriented resource for the analysis of systems-level datasets. Nat Commun. (2019).10(1):1523 doi:

10.1038/s41467-019-09234-6

[82] Becht E, McInnes L, Healy J, Dutertre CA, Kwok IWH, Ng LG, et al. Dimensionality reduction for visualizing single-cell data using UMAP. Nat Biotechnol. (2018) doi: 10.1038/nbt.4314

[83] Qiu X, Mao Q, Tang Y, Wang L, Chawla R, Pliner HA, et al. Reversed graph embedding resolves complex single-cell trajectories. Nat Methods. (2017).14(10):979-82 doi: 10.1038/nmeth.4402

[84] Young M, Mitchell T, Vieira Braga F, Tran M, Stewart B, Ferdinand J, et al. Single-cell transcriptomes from human kidneys reveal the cellular identity of renal tumors. Science (New York, N.Y.). (2018).361(6402):594-9 doi: 10.1126/science.aat1699

[85] Nehar-Belaid D, Hong S, Marches R, Chen G, Bolisetty M, Baisch J, et al. Mapping systemic lupus erythematosus heterogeneity at the single-cell level. Nature Immunology. (2020).21(9):1094-106 doi: 10.1038/s41590-020-0743-0

[86] Fu J, Akat KM, Sun Z, Zhang W, Schlondorff D, Liu Z, et al. Single-Cell RNA Profiling of Glomerular Cells Shows Dynamic Changes in Experimental Diabetic Kidney Disease. J Am Soc Nephrol. (2019).30(4):533-45 doi: 10.1681/ASN.2018090896

[87] Jenks SA, Cashman KS, Zumaquero E, Marigorta UM, Patel AV, Wang X, et al. Distinct Effector B Cells Induced by Unregulated Toll-like Receptor 7 Contribute to Pathogenic Responses in Systemic Lupus Erythematosus. Immunity. (2018).49(4):725-39 e6 doi: 10.1016/j.immuni.2018.08.015

[88] Gerhardt LMS, Liu J, Koppitch K, Cippa PE and McMahon AP. Single-nuclear transcriptomics reveals diversity of proximal tubule cell states in a dynamic response to acute kidney injury. Proc Natl Acad Sci U S A. (2021).118(27) doi: 10.1073/pnas.2026684118

[89] Young MD, Mitchell TJ, Vieira Braga FA, Tran MGB, Stewart BJ, Ferdinand JR, et al. Single-cell transcriptomes from human kidneys reveal the cellular identity of renal tumors. Science. (2018).361(6402):594-9 doi: 10.1126/science.aat1699

[90] Dobin A, Davis C, Schlesinger F, Drenkow J, Zaleski C, Jha S, et al. STAR: ultrafast universal RNA-seq aligner. Bioinformatics (Oxford, England). (2013).29(1):15-21 doi: 10.1093/bioinformatics/bts635

[91] Lee JW, Chou CL and Knepper MA. Deep Sequencing in Microdissected Renal Tubules Identifies Nephron Segment-Specific Transcriptomes. J Am Soc Nephrol. (2015).26(11):2669-77 doi: 10.1681/ASN.2014111067

[92] Kang H, Ahn S, Choi P, Ko Y, Han S, Chinga F, et al. Defective fatty acid oxidation in renal tubular epithelial cells has a key role in kidney fibrosis development. Nature medicine. (2015).21(1):37-46 doi: 10.1038/nm.3762

[93] Karaiskos N, Rahmatollahi M, Boltengagen A, Liu H, Hoehne M, Rinschen M, et al. A Single-Cell Transcriptome Atlas of the Mouse Glomerulus. J Am Soc Nephrol. (2018).29(8):2060-8 doi: 10.1681/ASN.2018030238

[94] Efremova M, Vento-Tormo R, Park JE, Teichmann SA and James KR. Immunology in the Era of Single-Cell Technologies. Annu Rev Immunol. (2020).38:727-57 doi: 10.1146/annurev-immunol-090419-020340

[95] Lotfollahi M, Naghipourfar M, Luecken MD, Khajavi M, Buttner M, Wagenstetter M, et al. Mapping single-cell data to reference atlases by transfer learning. Nat Biotechnol. (2022).40(1):121-30 doi: 10.1038/s41587-021-01001-7

[96] Schreibing F and Kramann R. Mapping the human kidney using single-cell genomics. Nat Rev Nephrol. (2022).18(6):347-60 doi: 10.1038/s41581-022-00553-4

[97] Camp J, Wollny D and Treutlein B. Single-cell genomics to guide human stem cell and tissue engineering. Nature methods. (2018).15(9):661-7 doi: 10.1038/s41592-018-0113-0

[98] Aldridge S and Teichmann S. Single cell transcriptomics comes of age. Nature communications. (2020).11(1):4307 doi: 10.1038/s41467-020-18158-5

[99] Fink E, Sona S, Tran U, Desprez P, Bradley M, Qiu H, et al. Single-cell and spatial mapping Identify cell types and signaling Networks in the human ureter. Developmental cell. (2022).57(15):1899-916.e6 doi: 10.1016/j.devcel.2022.07.004

[100] Rao DA, Arazi A, Wofsy D and Diamond B. Design and application of single-cell RNA sequencing to study kidney immune cells in lupus nephritis. Nat Rev Nephrol. (2020).16(4):238-50 doi: 10.1038/s41581-019-0232-6

[101] Tipton CM, Fucile CF, Darce J, Chida A, Ichikawa T, Gregoretti I, et al. Diversity, cellular origin and autoreactivity of antibody-secreting cell population expansions in acute systemic lupus erythematosus. Nat Immunol. (2015).16(7):755-65 doi: 10.1038/ni.3175

[102] Mistry P, Nakabo S, O'Neil L, Goel RR, Jiang K, Carmona-Rivera C, et al. Transcriptomic, epigenetic, and functional analyses implicate neutrophil diversity in the pathogenesis of systemic lupus erythematosus. Proc Natl Acad Sci U S A. (2019).116(50):25222-8 doi: 10.1073/pnas.1908576116

[103] Stanley S, Vanarsa K, Soliman S, Habazi D, Pedroza C, Gidley G, et al. Comprehensive aptamer-based screening identifies a spectrum of urinary biomarkers of lupus nephritis across ethnicities. Nat Commun. (2020).11(1):2197 doi: 10.1038/s41467-020-15986-3

[104] Kuppe C, Ibrahim MM, Kranz J, Zhang X, Ziegler S, Perales-Paton J, et al. Decoding myofibroblast origins in human kidney fibrosis. Nature. (2021).589(7841):281-6 doi: 10.1038/s41586-020-2941-1

[105] Qiu C, Huang S, Park J, Park Y, Ko YA, Seasock MJ, et al. Renal compartment-specific genetic variation analyses identify new pathways in chronic kidney disease. Nat Med. (2018).24(11):1721-31 doi: 10.1038/s41591-018-0194-4

[106] Liu H, Doke T, Guo D, Sheng X, Ma Z, Park J, et al. Epigenomic and transcriptomic analyses define core cell types, genes and targetable mechanisms for kidney disease. Nat Genet. (2022).54(7):950-62 doi: 10.1038/s41588-022-01097-w

[107] Treacy NJ, Clerkin S, Davis JL, Kennedy C, Miller AF, Saiani A, et al. Growth and differentiation of human induced pluripotent stem cell (hiPSC)-derived kidney organoids using fully synthetic peptide hydrogels. Bioact Mater. (2023).21:142-56 doi: 10.1016/j.bioactmat.2022.08.003

[108] Puelles VG, Fleck D, Ortz L, Papadouri S, Strieder T, Bohner AMC, et al. Novel 3D analysis using optical tissue clearing documents the evolution of murine rapidly progressive glomerulonephritis. Kidney Int. (2019).96(2):505-16 doi: 10.1016/j.kint.2019.02.034

[109] Lu Y, Ye Y, Yang Q and Shi S. Single-cell RNA-sequence analysis of mouse glomerular mesangial cells uncovers mesangial cell essential genes. Kidney Int. (2017).92(2):504-13 doi: 10.1016/j.kint.2017.01.016

[110] Lu Y, Ye Y, Bao W, Yang Q, Wang J, Liu Z, et al. Genome-wide identification of genes essential for podocyte cytoskeletons based on single-cell RNA sequencing. Kidney Int. (2017).92(5):1119-29 doi: 10.1016/j.kint.2017.04.022

[111] Zimmerman KA, Bentley MR, Lever JM, Li Z, Crossman DK, Song CJ, et al. Single-Cell RNA Sequencing Identifies Candidate Renal Resident Macrophage Gene Expression Signatures across Species. J Am Soc Nephrol. (2019).30(5):767-81 doi: 10.1681/ASN.2018090931

[112] He B, Chen P, Zambrano S, Dabaghie D, Hu Y, Moller-Hackbarth K, et al. Single-cell RNA sequencing reveals the mesangial identity and species diversity of glomerular cell transcriptomes. Nat Commun. (2021).12(1):2141 doi: 10.1038/s41467-021-22331-9

[113] Papalexi E and Satija R. Single-cell RNA sequencing to explore immune cell heterogeneity. Nature reviews. Immunology. (2018).18(1):35-45 doi: 10.1038/nri.2017.76

[114] Balzer MS, Rohacs T and Susztak K. How Many Cell Types Are in the Kidney and What Do They Do? Annu Rev Physiol. (2022).84:507-31 doi: 10.1146/annurev-physiol-052521-121841

[115] Goel RR, Wang X, O'Neil LJ, Nakabo S, Hasneen K, Gupta S, et al. Interferon lambda promotes immune dysregulation and tissue inflammation in TLR7-induced lupus. Proc Natl Acad Sci U S A. (2020).117(10):5409-19 doi: 10.1073/pnas.1916897117

[116] Deng Y, Zheng Y, Li D, Hong Q, Zhang M, Li Q, et al. Expression characteristics of interferon-stimulated genes and possible regulatory mechanisms in lupus patients using transcriptomics analyses. EBioMedicine. (2021).70:103477 doi: 10.1016/j.ebiom.2021.103477

[117] Doke T, Huang S, Qiu C, Liu H, Guan Y, Hu H, et al. Transcriptome-wide association analysis identifies DACH1 as a kidney disease risk gene that contributes to fibrosis. J Clin Invest. (2021).131(10) doi: 10.1172/JCI141801

[118] Doke T, Abedini A, Aldridge DL, Yang YW, Park J, Hernandez CM, et al. Single-cell analysis identifies the interaction of altered renal tubules with basophils orchestrating kidney fibrosis. Nat Immunol. (2022).23(6):947-59 doi: 10.1038/s41590-022-01200-7

[119] Sidhom EH, Kim C, Kost-Alimova M, Ting MT, Keller K, Avila-Pacheco J, et al. Targeting a Braf/Mapk pathway rescues podocyte lipid peroxidation in CoQ-deficiency kidney disease. J Clin Invest. (2021).131(5) doi: 10.1172/JCI141380

[120] Kim SR, Puranik AS, Jiang K, Chen X, Zhu XY, Taylor I, et al. Progressive Cellular Senescence Mediates Renal Dysfunction in Ischemic Nephropathy. J Am Soc Nephrol. (2021).32(8):1987-2004 doi: 10.1681/ASN.2020091373

[121] De Chiara L, Conte C, Semeraro R, Diaz-Bulnes P, Angelotti ML, Mazzinghi B, et al. Tubular cell polyploidy protects from lethal acute kidney injury but promotes consequent chronic kidney disease. Nat Commun. (2022).13(1):5805 doi: 10.1038/s41467-022-33110-5

[122] Chung JJ, Goldstein L, Chen YJ, Lee J, Webster JD, Roose-Girma M, et al. Single-Cell Transcriptome Profiling of the Kidney Glomerulus Identifies Key Cell Types and Reactions to Injury. J Am Soc Nephrol. (2020).31(10):2341-54 doi: 10.1681/ASN.2020020220

[123] Li H, Dixon EE, Wu H and Humphreys BD. Comprehensive single-cell transcriptional profiling defines shared and unique epithelial injury responses during kidney fibrosis. Cell Metab. (2022).34(12):1977-98 e9 doi: 10.1016/j.cmet.2022.09.026

[124] Rudman-Melnick V, Adam M, Potter A, Chokshi SM, Ma Q, Drake KA, et al. Single-Cell Profiling of AKI in a Murine Model Reveals Novel Transcriptional Signatures, Profibrotic Phenotype, and Epithelial-to-Stromal Crosstalk. J Am Soc Nephrol. (2020).31(12):2793-814 doi: 10.1681/ASN.2020010052

[125] Conway BR, O'Sullivan ED, Cairns C, O'Sullivan J, Simpson DJ, Salzano A, et al. Kidney Single-Cell Atlas Reveals Myeloid Heterogeneity in Progression and Regression of Kidney Disease. J Am Soc Nephrol. (2020).31(12):2833-54 doi: 10.1681/ASN.2020060806

[126] Hinze C, Kocks C, Leiz J, Karaiskos N, Boltengagen A, Cao S, et al. Single-cell transcriptomics reveals common epithelial response patterns in human acute kidney injury. Genome Med. (2022).14(1):103 doi: 10.1186/s13073-022-01108-9

[127] Krishna C, DiNatale RG, Kuo F, Srivastava RM, Vuong L, Chowell D, et al. Single-cell sequencing links multiregional immune landscapes and tissue-resident T cells in ccRCC to tumor topology and therapy efficacy. Cancer Cell. (2021).39(5):662-77 e6 doi: 10.1016/j.ccell.2021.03.007

[128] Li R, Ferdinand JR, Loudon KW, Bowyer GS, Laidlaw S, Muyas F, et al. Mapping single-cell transcriptomes in the intra-tumoral and associated territories of kidney cancer. Cancer Cell. (2022).40(12):1583-99 e10 doi: 10.1016/j.ccell.2022.11.001

[129] Obradovic A, Chowdhury N, Haake SM, Ager C, Wang V, Vlahos L, et al. Single-cell protein activity analysis identifies recurrence-associated renal tumor macrophages. Cell. (2021).184(11):2988-3005 e16 doi: 10.1016/j.cell.2021.04.038

[130] Miao Z, Humphreys BD, McMahon AP and Kim J. Multi-omics integration in the age of million single-cell data. Nat Rev Nephrol. (2021).17(11):710-24 doi: 10.1038/s41581-021-00463-x

[131] Shi H, Doench JG and Chi H. CRISPR screens for functional interrogation of immunity. Nat Rev Immunol. (2022) doi: 10.1038/s41577-022-00802-4

[132] Datlinger P, Rendeiro AF, Schmidl C, Krausgruber T, Traxler P, Klughammer J, et al. Pooled CRISPR screening with single-cell transcriptome readout. Nat Methods. (2017).14(3):297-301 doi: 10.1038/nmeth.4177

[133] McKenna A, Findlay GM, Gagnon JA, Horwitz MS, Schier AF and Shendure J. Whole-organism lineage tracing by combinatorial and cumulative genome editing. Science. (2016).353(6298):aaf7907 doi: 10.1126/science.aaf7907

[134] Wang G, Heijs B, Kostidis S, Rietjens RGJ, Koning M, Yuan L, et al. Spatial dynamic metabolomics identifies metabolic cell fate trajectories in human kidney differentiation. Cell Stem Cell. (2022).29(11):1580-93 e7 doi: 10.1016/j.stem.2022.10.008

[135] Eddy S, Mariani LH and Kretzler M. Integrated multi-omics approaches to improve classification of chronic kidney disease. Nat Rev Nephrol. (2020).16(11):657-68 doi: 10.1038/s41581-020-0286-5

[136] Tomaszewski M, Morris AP, Howson JMM, Franceschini N, Eales JM, Xu X, et al. Kidney omics in hypertension: from statistical associations to biological mechanisms and clinical applications. Kidney Int. (2022).102(3):492-505 doi: 10.1016/j.kint.2022.04.045

[137] Garalde DR, Snell EA, Jachimowicz D, Sipos B, Lloyd JH, Bruce M, et al. Highly parallel direct RNA sequencing on an array of nanopores. Nat Methods. (2018).15(3):201-6 doi: 10.1038/nmeth.4577

[138] Workman RE, Tang AD, Tang PS, Jain M, Tyson JR, Razaghi R, et al. Nanopore native RNA sequencing of a human poly(A) transcriptome. Nat Methods. (2019).16(12):1297-305 doi: 10.1038/s41592-019-0617-2

[139] Soneson C, Yao Y, Bratus-Neuenschwander A, Patrignani A, Robinson MD and Hussain S. A comprehensive examination of Nanopore native RNA sequencing for characterization of complex transcriptomes. Nat Commun. (2019).10(1):3359 doi: 10.1038/s41467-019-11272-z

[140] Luo T, Chen SY, Qiu ZX, Miao YR, Ding Y, Pan XY, et al. Transcriptomic Features in a Single Extracellular Vesicle via Single-Cell RNA Sequencing. Small Methods. (2022).6(11):e2200881 doi: 10.1002/smtd.202200881

[141] Jansen J, van den Berge BT, van den Broek M, Maas RJ, Daviran D, Willemsen B, et al. Human pluripotent stem cell-derived kidney organoids for personalized congenital and idiopathic nephrotic syndrome modeling. Development. (2022).149(9) doi: 10.1242/dev.200198

[142] Chuang HC, Chen MH, Chen YM, Ciou YR, Hsueh CH, Tsai CY, et al. Induction of Interferon-gamma and Tissue Inflammation by Overexpression of Eosinophil Cationic Protein in T Cells and Exosomes. Arthritis Rheumatol. (2022).74(1):92-104 doi: 10.1002/art.41920

[143] Chuang HC, Chen MH, Chen YM, Yang HY, Ciou YR, Hsueh CH, et al. BPI overexpression suppresses Treg differentiation and induces exosome-mediated inflammation in systemic lupus erythematosus. Theranostics. (2021).11(20):9953-66 doi: 10.7150/thno.63743

[144] Peired A, Antonelli G, Angelotti M, Allinovi M, Guzzi F, Sisti A, et al. Acute kidney injury promotes development of papillary renal cell adenoma and carcinoma from renal progenitor cells. Science translational medicine. (2020).12(536) doi: 10.1126/scitranslmed.aaw6003

[145] Little MH, Howden SE, Lawlor KT and Vanslambrouck JM. Determining lineage relationships in kidney development and disease. Nat Rev Nephrol. (2022).18(1):8-21 doi: 10.1038/s41581-021-00485-5

[146] Yin X, Kim K, Suetsugu H, Bang SY, Wen L, Koido M, et al. Biological insights into systemic lupus erythematosus through an immune cell-specific transcriptome-wide association study. Ann Rheum Dis. (2022).81(9):1273-80 doi: 10.1136/annrheumdis-2022-222345

[147] Sheng X, Guan Y, Ma Z, Wu J, Liu H, Qiu C, et al. Mapping the genetic architecture of human traits to cell types in the kidney identifies mechanisms of disease and potential treatments. Nat Genet. (2021).53(9):1322-33 doi: 10.1038/s41588-021-00909-9

[148] Li Y, Haug S, Schlosser P, Teumer A, Tin A, Pattaro C, et al. Integration of GWAS Summary Statistics and Gene Expression Reveals Target Cell Types Underlying Kidney Function Traits. J Am Soc Nephrol. (2020).31(10):2326-40 doi: 10.1681/ASN.2020010051

[149] Gillies CE, Putler R, Menon R, Otto E, Yasutake K, Nair V, et al. An eQTL Landscape of Kidney Tissue in Human Nephrotic Syndrome. Am J Hum Genet. (2018).103(2):232-44 doi: 10.1016/j.ajhg.2018.07.004

[150] Ko YA, Yi H, Qiu C, Huang S, Park J, Ledo N, et al. Genetic-Variation-Driven Gene-Expression Changes Highlight Genes with Important Functions for Kidney Disease. Am J Hum Genet. (2017).100(6):940-53 doi: 10.1016/j.ajhg.2017.05.004

[151] Wainberg M, Sinnott-Armstrong N, Mancuso N, Barbeira A, Knowles D, Golan D, et al. Opportunities and challenges for transcriptome-wide association studies. Nature genetics. (2019).51(4):592-9 doi: 10.1038/s41588-019-0385-z

[152] Sealfon R, Mariani L, Avila-Casado C, Nair V, Menon R, Funk J, et al. Molecular Characterization of Membranous Nephropathy. J Am Soc Nephrol. (2022).33(6):1208-21 doi: 10.1681/ASN.2021060784

[153] Dangi A, Natesh NR, Husain I, Ji Z, Barisoni L, Kwun J, et al. Single cell transcriptomics of mouse kidney transplants reveals a myeloid cell pathway for transplant rejection. JCI Insight. (2020).5(20) doi: 10.1172/jci.insight.141321

[154] Yazar S, Alquicira-Hernandez J, Wing K, Senabouth A, Gordon MG, Andersen S, et al. Single-cell eQTL mapping identifies cell type-specific genetic control of autoimmune disease. Science. (2022).376(6589):eabf3041 doi: 10.1126/science.abf3041

[155] Elhanani O, Ben-Uri R and Keren L. Spatial profiling technologies illuminate the tumor microenvironment. Cancer Cell. (2023).41(3):404-20 doi: 10.1016/j.ccell.2023.01.010

[156] Gohil SH, Iorgulescu JB, Braun DA, Keskin DB and Livak KJ. Applying high-dimensional single-cell technologies to the analysis of cancer immunotherapy. Nat Rev Clin Oncol. (2021).18(4):244-56 doi: 10.1038/s41571-020-00449-x

[157] Li PH, Kong XY, He YZ, Liu Y, Peng X, Li ZH, et al. Recent developments in application of single-cell RNA sequencing in the tumour immune microenvironment and cancer therapy. Mil Med Res. (2022).9(1):52 doi: 10.1186/s40779-022-00414-y

[158] Nolan E, Lindeman GJ and Visvader JE. Deciphering breast cancer: from biology to the clinic. Cell. (2023).186(8):1708-28 doi: 10.1016/j.cell.2023.01.040

[159] Shalita R and Amit I. The industrial genomic revolution: A new era in neuroimmunology. Neuron. (2022).110(21):3429-43 doi: 10.1016/j.neuron.2022.09.030

[160] Temple S. Advancing cell therapy for neurodegenerative diseases. Cell stem cell. (2023) doi: 10.1016/j.stem.2023.03.017

[161] Steffens S, Nahrendorf M and Madonna R. Immune cells in cardiac homeostasis and disease: emerging insights from novel technologies. Eur Heart J. (2022).43(16):1533-41 doi: 10.1093/eurheartj/ehab842

[162] Ramakrishna S and Shah NN. Using single-cell analysis to predict CAR T cell outcomes. Nat Med. (2020).26(12):1813-4 doi: 10.1038/s41591-020-01157-w

[163] Gottschlich A, Thomas M, Grunmeier R, Lesch S, Rohrbacher L, Igl V, et al. Single-cell transcriptomic atlas-guided development of CAR-T cells for the treatment of acute myeloid leukemia. Nat Biotechnol. (2023) doi: 10.1038/s41587-023-01684-0

[164] Scharer CD, Blalock EL, Mi T, Barwick BG, Jenks SA, Deguchi T, et al. Epigenetic programming underpins B cell dysfunction in human SLE. Nat Immunol. (2019).20(8):1071-82 doi: 10.1038/s41590-019-0419-9

[165] Mackensen A, Muller F, Mougiakakos D, Boltz S, Wilhelm A, Aigner M, et al. Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus. Nat Med. (2022).28(10):2124-32 doi: 10.1038/s41591-022-02017-5

[166] Abouleisa R, Salama A, Ou Q, Tang X, Solanki M, Guo Y, et al. Transient Cell Cycle Induction in Cardiomyocytes to Treat Subacute Ischemic Heart Failure. Circulation. (2022).145(17):1339-55 doi: 10.1161/circulationaha.121.057641

[167] Vgontzas A and Renthal W. Predicting erenumab adverse events with single-cell genomics. Lancet. (2020).396(10244):95-6 doi: 10.1016/S0140-6736(19)32952-6

[168] Wu J, Zeng D, Zhi S, Ye Z, Qiu W, Huang N, et al. Single-cell analysis of a tumor-derived exosome signature correlates with prognosis and immunotherapy response. J Transl Med. (2021).19(1):381 doi: 10.1186/s12967-021-03053-4

[169] Wu Z, Lawrence PJ, Ma A, Zhu J, Xu D and Ma Q. Single-Cell Techniques and Deep Learning in Predicting Drug Response. Trends Pharmacol Sci. (2020).41(12):1050-65 doi: 10.1016/j.tips.2020.10.004

[170] Lee SHR, Yang W, Gocho Y, John A, Rowland L, Smart B, et al. Pharmacotypes across the genomic landscape of pediatric acute lymphoblastic leukemia and impact on treatment response. Nat Med. (2023).29(1):170-9 doi: 10.1038/s41591-022-02112-7

[171] Yofe I, Dahan R and Amit I. Single-cell genomic approaches for developing the next generation of immunotherapies. Nat Med. (2020).26(2):171-7 doi: 10.1038/s41591-019-0736-4

[172] Latt KZ, Heymann J, Jessee JH, Rosenberg AZ, Berthier CC, Arazi A, et al. Urine Single-Cell RNA Sequencing in Focal Segmental Glomerulosclerosis Reveals Inflammatory Signatures. Kidney Int Rep. (2022).7(2):289-304 doi: 10.1016/j.ekir.2021.11.005

[173] Fava A, Rao DA, Mohan C, Zhang T, Rosenberg A, Fenaroli P, et al. Urine Proteomics and Renal Single-Cell Transcriptomics Implicate Interleukin-16 in Lupus Nephritis. Arthritis Rheumatol. (2022).74(5):829-39 doi: 10.1002/art.42023

[174] Fu H, Gui Y, Liu S, Wang Y, Bastacky SI, Qiao Y, et al. The hepatocyte growth factor/c-met pathway is a key determinant of the fibrotic kidney local microenvironment. iScience. (2021).24(10):103112 doi: 10.1016/j.isci.2021.103112

[175] Wilson PC, Wu H, Kirita Y, Uchimura K, Ledru N, Rennke HG, et al. The single-cell transcriptomic landscape of early human diabetic nephropathy. Proc Natl Acad Sci U S A. (2019).116(39):19619-25 doi: 10.1073/pnas.1908706116

[176] Yao W, Chen Y, Li Z, Ji J, You A, Jin S, et al. Single Cell RNA Sequencing Identifies a Unique Inflammatory Macrophage Subset as a Druggable Target for Alleviating Acute Kidney Injury. Adv Sci (Weinh). (2022).9(12):e2103675 doi: 10.1002/advs.202103675

[177] Nguyen VT, Kravets AG and Duong TQH. Predicting Research Trend Based on Bibliometric Analysis and Paper Ranking Algorithm[J]. Journal 2021(Issue).

[178] Park J, Kim J, Lewy T, Rice CM, Elemento O, Rendeiro AF, et al. Spatial omics technologies at multimodal and single cell/subcellular level. Genome Biol. (2022).23(1):256 doi: 10.1186/s13059-022-02824-6

[179] Davis-Marcisak EF, Deshpande A, Stein-O'Brien GL, Ho WJ, Laheru D, Jaffee EM, et al. From bench to bedside: Single-cell analysis for cancer immunotherapy. Cancer Cell. (2021).39(8):1062-80 doi: 10.1016/j.ccell.2021.07.004

[180] Specht H, Emmott E, Petelski AA, Huffman RG, Perlman DH, Serra M, et al. Single-cell proteomic and transcriptomic analysis of macrophage heterogeneity using SCoPE2. Genome Biol. (2021).22(1):50 doi: 10.1186/s13059-021-02267-5

[181] Petelski AA, Emmott E, Leduc A, Huffman RG, Specht H, Perlman DH, et al. Multiplexed single-cell proteomics using SCoPE2. Nat Protoc. (2021).16(12):5398-425 doi: 10.1038/s41596-021-00616-z

[182] Santamaria-Alza Y and Vasquez G. Are chimeric antigen receptor T cells (CAR-T cells) the future in immunotherapy for autoimmune diseases? Inflamm Res. (2021).70(6):651-63 doi: 10.1007/s00011-021-01470-1

[183] Su M, Zhao C and Luo S. Therapeutic potential of chimeric antigen receptor based therapies in autoimmune diseases. Autoimmun Rev. (2022).21(1):102931 doi: 10.1016/j.autrev.2021.102931

[184] Carter B and Zhao K. The epigenetic basis of cellular heterogeneity. Nat Rev Genet. (2021).22(4):235-50 doi: 10.1038/s41576-020-00300-0

[185] Rodriguez J, Ren G, Day CR, Zhao K, Chow CC and Larson DR. Intrinsic Dynamics of a Human Gene Reveal the Basis of Expression Heterogeneity. Cell. (2019).176(1-2):213-26 e18 doi: 10.1016/j.cell.2018.11.026

[186] Bai Y, Baddoo M, Flemington E, Nakhoul H and Liu Y. Screen technical noise in single cell RNA sequencing data. Genomics. (2020).112(1):346-55 doi: 10.1016/j.ygeno.2019.02.014

[187] Li R and Quon G. scBFA: modeling detection patterns to mitigate technical noise in large-scale single-cell genomics data. Genome biology. (2019).20(1):193 doi: 10.1186/s13059-019-1806-0

[188] Reinius B and Sandberg R. Random monoallelic expression of autosomal genes: stochastic transcription and allele-level regulation. Nature reviews. Genetics. (2015).16(11):653-64 doi: 10.1038/nrg3888

[189] Dar R, Razooky B, Singh A, Trimeloni T, McCollum J, Cox C, et al. Transcriptional burst frequency and burst size are equally modulated across the human genome. Proceedings of the National Academy of Sciences of the United States of America. (2012).109(43):17454-9 doi: 10.1073/pnas.1213530109

[190] Sealfon RSG, Mariani LH, Kretzler M and Troyanskaya OG. Machine learning, the kidney, and genotype-phenotype analysis. Kidney Int. (2020).97(6):1141-9 doi: 10.1016/j.kint.2020.02.028

[191] Bode D, Cull AH, Rubio-Lara JA and Kent DG. Exploiting Single-Cell Tools in Gene and Cell Therapy. Front Immunol. (2021).12:702636 doi: 10.3389/fimmu.2021.702636

[192] Heather J and Chain B. The sequence of sequencers: The history of sequencing DNA. Genomics. (2016).107(1):1-8 doi: 10.1016/j.ygeno.2015.11.003

[193] Longo SK, Guo MG, Ji AL and Khavari PA. Integrating single-cell and spatial transcriptomics to elucidate intercellular tissue dynamics. Nat Rev Genet. (2021).22(10):627-44 doi: 10.1038/s41576-021-00370-8

[194] Tran HTN, Ang KS, Chevrier M, Zhang X, Lee NYS, Goh M, et al. A benchmark of batch-effect correction methods for single-cell RNA sequencing data. Genome Biol. (2020).21(1):12 doi: 10.1186/s13059-019-1850-9

[195] Huang Z, Chen B, Liu X, Li H, Xie L, Gao Y, et al. Effects of sex and aging on the immune cell landscape as assessed by single-cell transcriptomic analysis. Proc Natl Acad Sci U S A. (2021).118(33) doi: 10.1073/pnas.2023216118

[196] Villani AC, Satija R, Reynolds G, Sarkizova S, Shekhar K, Fletcher J, et al. Single-cell RNA-seq reveals new types of human blood dendritic cells, monocytes, and progenitors. Science. (2017).356(6335) doi: 10.1126/science.aah4573

[197] Stewart BJ, Ferdinand JR and Clatworthy MR. Using single-cell technologies to map the human immune system - implications for nephrology. Nat Rev Nephrol. (2020).16(2):112-28 doi: 10.1038/s41581-019-0227-3

[198] Chen L, Lee JW, Chou CL, Nair AV, Battistone MA, Paunescu TG, et al. Transcriptomes of major renal collecting duct cell types in mouse identified by single-cell RNA-seq. Proc Natl Acad Sci U S A. (2017).114(46):E9989-E98 doi: 10.1073/pnas.1710964114

[199] Liao J, Yu Z, Chen Y, Bao M, Zou C, Zhang H, et al. Single-cell RNA sequencing of human kidney. Sci Data. (2020).7(1):4 doi: 10.1038/s41597-019-0351-8

[200] Lake BB, Chen S, Hoshi M, Plongthongkum N, Salamon D, Knoten A, et al. A single-nucleus RNA-sequencing pipeline to decipher the molecular anatomy and pathophysiology of human kidneys. Nat Commun. (2019).10(1):2832 doi: 10.1038/s41467-019-10861-2

[201] Legouis D, Ricksten SE, Faivre A, Verissimo T, Gariani K, Verney C, et al. Altered proximal tubular cell glucose metabolism during acute kidney injury is associated with mortality. Nat Metab. (2020).2(8):732-43 doi: 10.1038/s42255-020-0238-1

[202] Abedini A, Zhu YO, Chatterjee S, Halasz G, Devalaraja-Narashimha K, Shrestha R, et al. Urinary Single-Cell Profiling Captures the Cellular Diversity of the Kidney. Journal of the American Society of Nephrology. (2021).32(3):614-27 doi: 10.1681/asn.2020050757

[203] Schuh MP, Alkhudairy L, Potter A, Potter SS, Chetal K, Thakkar K, et al. The Rhesus Macaque Serves As a Model for Human Lateral Branch Nephrogenesis. J Am Soc Nephrol. (2021).32(5):1097-112 doi: 10.1681/ASN.2020101459

[204] Zambrano S, He L, Kano T, Sun Y, Charrin E, Lal M, et al. Molecular insights into the early stage of glomerular injury in IgA nephropathy using single-cell RNA sequencing. Kidney Int. (2022).101(4):752-65 doi: 10.1016/j.kint.2021.12.011

[205] Zheng Y, Lu P, Deng Y, Wen L, Wang Y, Ma X, et al. Single-Cell Transcriptomics Reveal Immune Mechanisms of the Onset and Progression of IgA Nephropathy. Cell Rep. (2020).33(12):108525 doi: 10.1016/j.celrep.2020.108525

[206] Subramanian A, Sidhom EH, Emani M, Vernon K, Sahakian N, Zhou Y, et al. Single cell census of human kidney organoids shows reproducibility and diminished off-target cells after transplantation. Nat Commun. (2019).10(1):5462 doi: 10.1038/s41467-019-13382-0

Figure legends

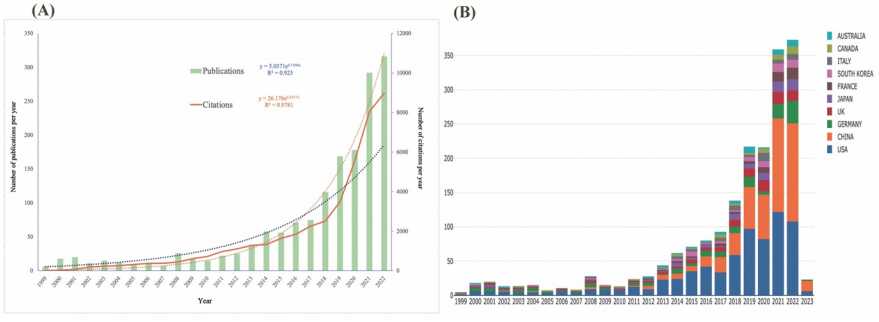


Figure 1: The annual publication between countries and institutions trends over past 22 years. (A) The annual publication, and annual citation. (B) The annual publication in the top 10 countries.

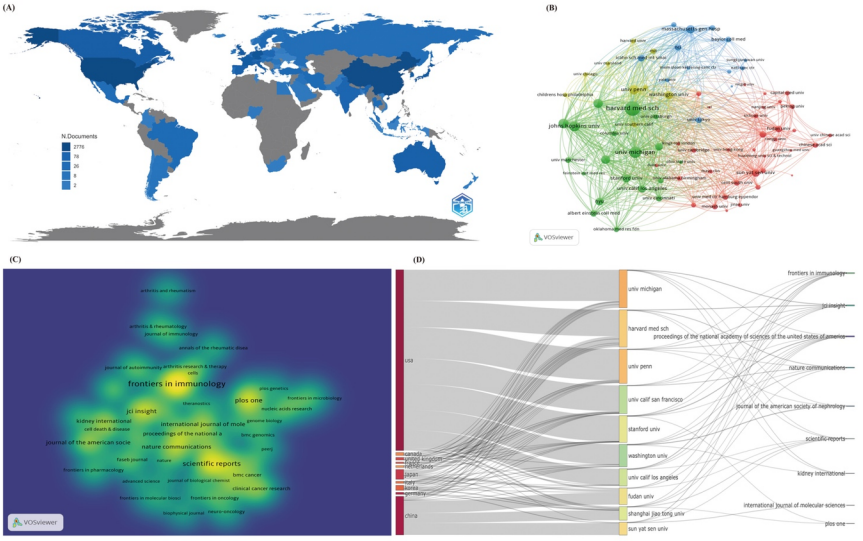


Figure 2: Countries, institutions and journals related to SCA in kidney disease published worldwide. (A) Network map of the country distribution based on R. (B) The chronological order of institutions produced the articles based on VOS viewer. (C) Journal density map based on VOS viewer. (D) The relationship of the countries, institutions, and journals produced articles based on an alluvial flow map based on R.

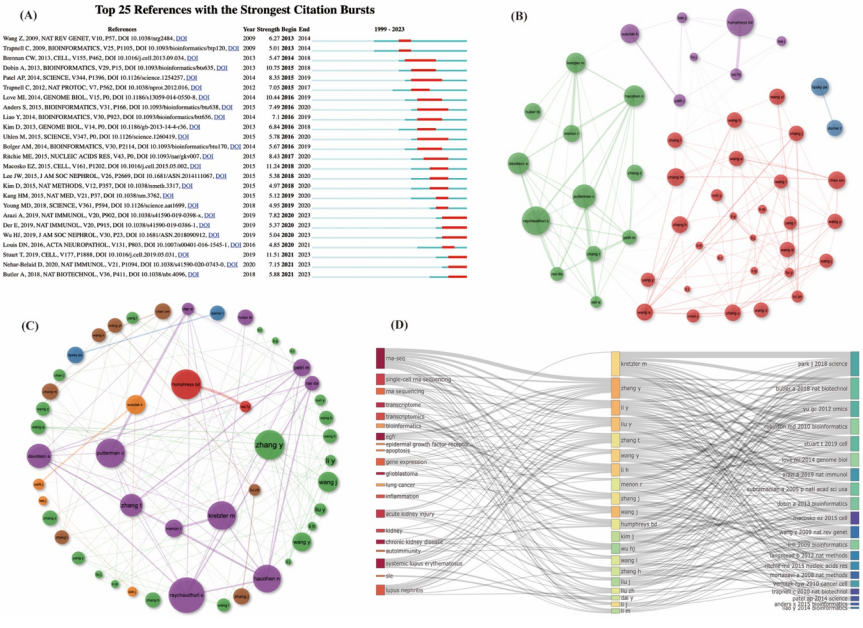


Figure 3: Analysis of authors, references, and keywords involved in SCA in kidney disease. (A) Top 25 references with the strongest citation bursts based on CiteSpace. (B-C) Collaboration network of authors based on R. (D) The relationship of the top 20 co-cited references, authors, and keywords evolution based on an alluvial flow map by R.

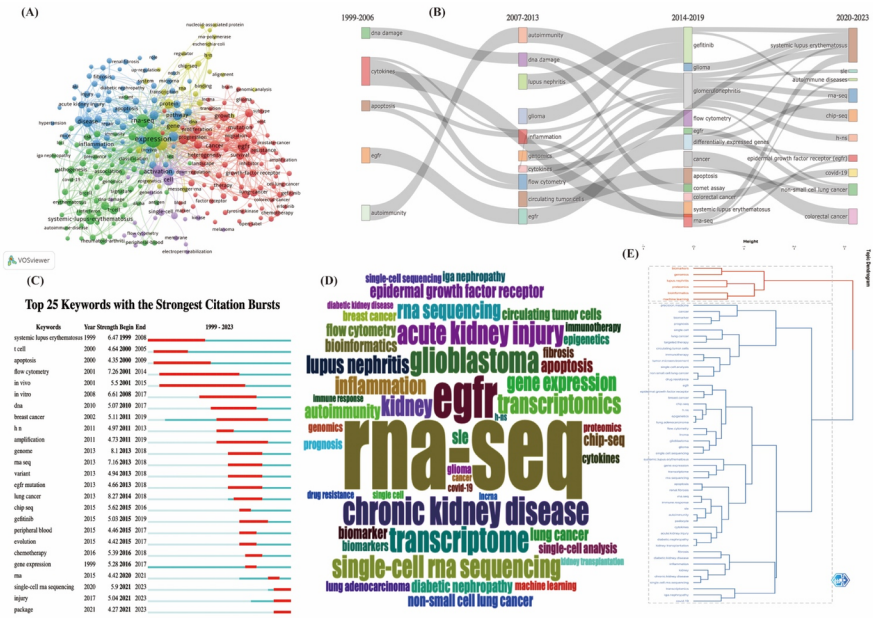


Figure 4: Keyword-related mapping in studies on SCA in kidney disease. (A)Visualization based on keyword co-occurrence relationship based on VOS viewer. In this network map, keywords with close relationships are assigned to one cluster with the same colour. All the keywords could be divided into five clusters: cluster 1 (green nodes), cluster 2 (blue nodes), cluster 3 (yellow nodes), cluster 4 (red nodes), and cluster 5 (purple nodes). (B) Major keywords evolution based on R. (C) Top 25 keywords with the strongest bursts by CiteSpace. (D) Visualization based on cloudword for top 50 keyword co-occurrences. (E) Topic dendrogram of factorial.

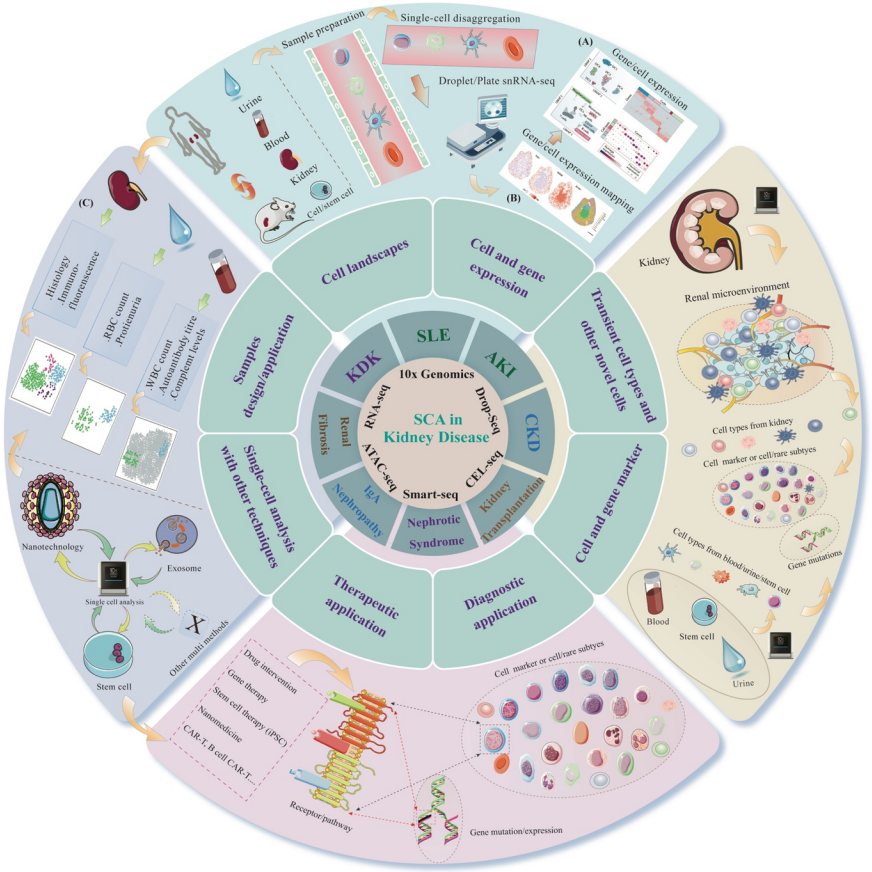


Figure 5 Major applications of single-cell analysis in kidney disease. (A) Mapping immune cells in peripheral blood. Single-cell RNA sequencing (scRNA-seq) has been used to identify new or novel subsets of cells in peripheral blood. For example, plate-based scRNA-seq of sorted myeloid populations has been used to identify a novel subset of dendritic cells (DCs)[196, 197]. Copyright 2017, American Association for the Advancement of Science (AAAS) and Copyright 2020, Springer Nature Limited. (B) Schematic representation of tissue processing, library generation, and sequencing for next-generation sequencing-based spatially resolved transcriptomics with expression profiles for representative segment-specific genes (Podxl, Slc22a6, and Slc12a1) and an example of cell-type mapping in a female sham kidney from 10X Genomics Visium[44]. Copyright 2022, Elsevier Inc. (C) Towards a cellular classification of renal immunopathology. Current clinical data evaluate metrics of immune activation and tissue injury in kidney, urine and blood[100]. Copyright 2020, Springer Nature Limited.

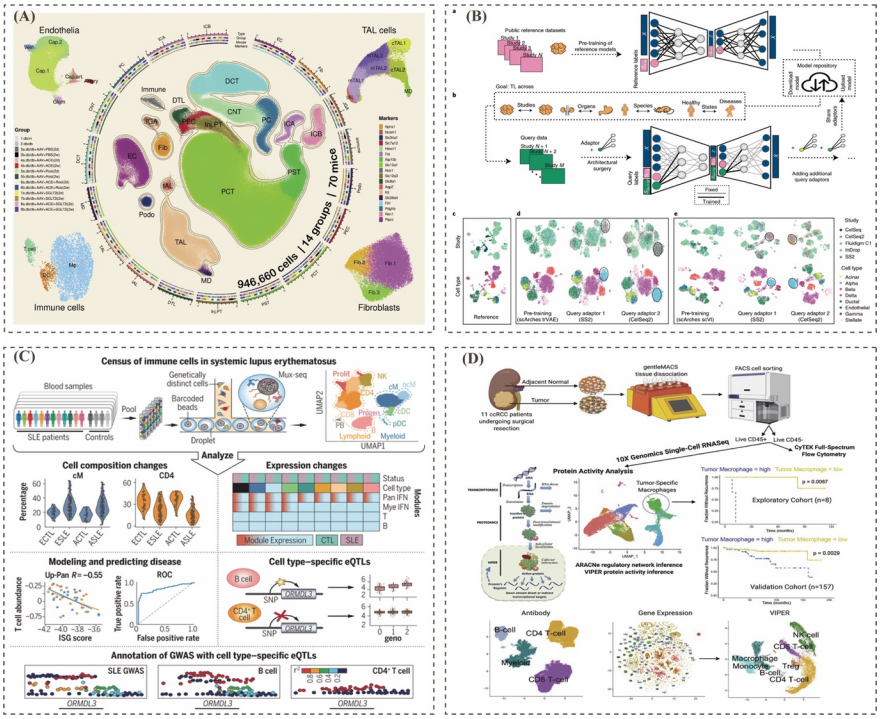


Figure 6: (A) Single-cell atlas of drug treatments in a mouse model of DKD. A total of 946,660 high-quality cells from 70 mouse kidneys in 14 different groups are projected by uniform manifold approximation and projection (UMAP) plot[52]. Copyright 2022, CellPress. (B) The scArches approach allows iterative integration of query and references single cells[95]. Copyright 2022, Springer Nature Limited. (C) Detection of cellular and genetic correlates of SLE. Genetic multiplexing enabled single-cell profiling of hundreds of individuals with and without SLE. These profiles revealed that SLE patients exhibit changes in cell composition and cell type-specific gene expression, which were used to model disease status and severity. Additionally, cell type-specific cis-eQTL maps were produced and used to annotate and contextualize genetic loci associated with SLE[33]. Copyright 2022, American Association for the Advancement of Science (AAAS). (D) The process of single-cell protein activity analysis identifies recurrence-associated renal tumour macrophages[129]. Copyright 2022, CellPress.

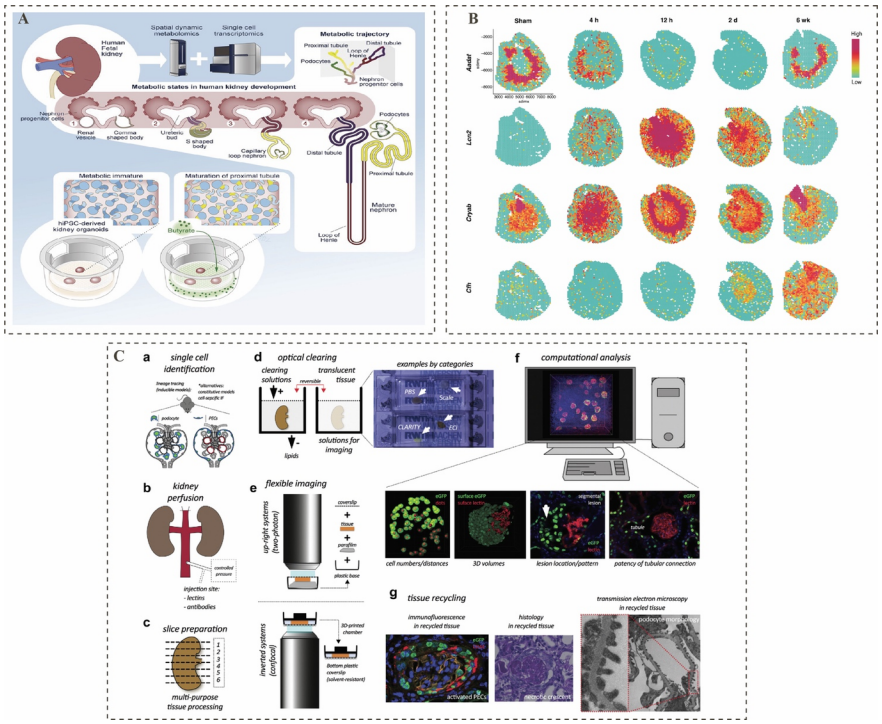


Figure 7: (A) The approach of spatial dynamic metabolomics identifies metabolic cell fate trajectories in human kidney differentiation[134]. Copyright 2022, CellPress. (B) Representative gene expression across a time course (sham, 4 hours, 12 hours, 2 days, and 6 weeks) of bilateral ischemia-reperfusion injury in female C57BL6/J mice, demonstrating changes in expression (low [teal] to high [magenta]) and localization of differentially expressed injury genes, including Aadat, Lcn2, Cryab, and Cfh[44]. Copyright 2022, Elsevier Inc. (C) A new pipeline for 3-dimensional morphometrics validated in kidney tissue. (a) Cell-specific identification; (b) kidney perfusion via aorta cannulation; (c) slice preparation using a physical slicer for multi-purpose tissue processing; (d) reversible optical clearing; (e) flexible in-house built chambers compatible with multiple microscopy systems; (f) comprehensive computational analyses, where the white arrow shows a segmental lesion; and (g) tissue recycling for subsequent immunofluorescence (IF), classical histology, and transmission electron microscopy. ECi, ethyl cinnamate[108]. Copyright 2019, Elsevier Inc.

TABLE 1 | Top 20 co-cited references related to SCA in kidney disease.

Rank	Title	Journal IF_{2021}	First author (reference)	Paper's main focus	Publication time	Reference type	Total citation	Total li strengtl
1	Integrating single-cell transcriptomic data across different conditions, technologies, and species	Nature Biotechnology (IF=68.164)	Andrew Butler[75]	SCA Method	2018	Article/Analysis	68	241
2	Comprehensive Integration of Single-Cell Data.	Cell (IF=66.85)	Tim Stuart[76]	SCA Method	2019	Article/Resource	65	265
3	Single-cell transcriptomics of the mouse kidney reveals potential cellular targets of kidney disease.	Science (IF=63.832)	Jihwan Park[36]	SCA+ kidney diseases	2018	Article	60	271
4	The immune cell landscape in kidneys of patients with lupus nephritis.	Nature Immunology (IF=31.25)	Arnon Arazi[78]	SCA+ lupus nephritis	2019	Article	56	241

Rank	Title	Journal IF_{2021}	First author (reference)	Paper's main focus	Publication time	Reference type	Total citation	Total li strengtl
5	Highly Parallel Genome-wide Expression Profiling of Individual Cells Using Nanoliter Droplets.	Cell (IF=66.85)	Evan Z Macosko[77]	SCA Method	2015	Article/Resour	39	181
6	Tubular cell and keratinocyte single-cell transcriptomics applied to lupus nephritis reveal type I IFN and fibrosis relevant pathways.	Nature Immunology (IF=31.25)	Evan Der[73]	SCA+ lupus nephritis	2019	Article	38	169

Rank	Title	Journal IF_{2021}	First author (reference)	Paper's main focus	Publication time	Reference type	Total citation	Total li strengtl
7	Single-Cell Transcriptomics of a Human Kidney Allograft Biopsy Specimen Defines a Diverse Inflammatory Response.	JASN (IF=14.981)	Haojia Wu[57]	SCA+ kidney transplantation	2018	Article	35	150
8	Advantages of Single-Nucleus over Single-Cell RNA Sequencing of Adult Kidney: Rare Cell Types and Novel Cell States Revealed in Fibrosis.	JASN (IF=14.981)	Haojia Wu[55]	SCA+ inflamed fibrotic kidney disease	2019	Article	35	151

Rank	Title	Journal IF_{2021}	First author (reference)	Paper's main focus	Publication time	Reference type	Total citation	Total li strengtl
9	Cell profiling of mouse acute kidney injury reveals conserved cellular responses to injury.	PNAS (IF=12.779)	Yuhei Kirita[61]	SCA +acute kidney injury	2020	Article	28	97
10	Single-cell transcriptomes from human kidneys reveal the cellular identity of renal tumors.	Science (IF=63.832)	Matthew D Young[84]	SCA+ renal tumor	2018	Article	28	160
11	Single cell RNA sequencing to dissect the molecular heterogeneity in lupus nephritis.	JCI Insight (IF=9.496)	Evan Der[72]	SCA+ lupus nephritis	2017	Article	26	145

Rank	Title	Journal IF_{2021}	First author (reference)	Paper's main focus	Publication time	Reference type	Total citation	Total li strengtl
12	Mapping systemic lupus erythematosus heterogeneity at the single-cell level.	Nature Immunology (IF=31.25)	Djamel Nehar-Belaid[85]	SCA+ SLE	2020	Article	26	93
13	Dimensionality reduction for visualizing single-cell data using UMAP.	Nature Immunology (IF=31.25)	Etienne Becht[82]	SCA Method	2019	Article/Analysis	24	93
14	Fast, sensitive and accurate integration of single-cell data with Harmony.	Nature Methods (IF=47.99)	Ilya Korsunsky[79]	SCA Method	2019	Article/Analysis	23	91
15	Single-Cell RNA Profiling of Glomerular Cells Shows Dynamic Changes in Experimental Diabetic Kidney Disease.	JASN (IF=14.981)	Jia Fu[86]	SCA +diabetic kidney disease	2019	Article	20	102

Rank	Title	Journal IF_{2021}	First author (reference)	Paper's main focus	Publication time	Reference type	Total citation	Total li strengtl
16	SCANPY: large-scale single-cell gene expression data analysis.	Genome Biology (IF=18.01)	F Alexander Wolf[80]	SCA Method	2018	Article	20	91
17	Distinct Effector B Cells Induced by Unregulated Toll-like Receptor 7 Contribute to Pathogenic Responses in Systemic Lupus Erythematosus.	Immunity (IF=43.474)	Scott A Jenks[87]	SCA+ SLE	2018	Article	20	76
18	Reversed graph embedding resolves complex single-cell trajectories.	Nature Methods (IF=47.99)	Xiaojie Qiu[83]	SCA Method	2017	brief communications	19	117

Rank	Title	Journal IF_{2021}	First author (reference)	Paper's main focus	Publication time	Reference type	Total citation	Total li strengt
19	Metascape provides a biologist-oriented resource for the analysis of systems-level datasets.	Nature Communications (IF= 17.694)	Yingyao Zhou[81]	SCA Method	2019	Article	16	53
20	Single-nuclear transcriptomics reveals diversity of proximal tubule cell states in a dynamic response to acute kidney injury.	PNAS (IF=12.779)	Louisa M S Gerhardt[88]	SCA +acute kidney injury	2021	Article	13	271

PNAS, Proceedings of the national academy of Sciences of the United States of America; JASN, Journal of the American Society of Nephrology

TABLE 2 | Top 25 co-occurrence keywords and top 10 keyword-related to kidney disease for SCA in kidney disease

Rank	Top 25 keywords	Occurrences	Total link strength	Rank	Top 10 keyword-related to kidney disea
1	expression	374	593	1	SLE
2	RNA-seq	181	316		systemic lupus erythematosus
3	EGFR	159	309		systemic-lupus-erythematosus
4	gene-expression	152	211		lupus
5	activation	144	283		lupus nephritis
6	cancer	118	257	2	acute kidney injury
7	gene	115	205		acute-renal-failure
8	cell	114	209		AKI
9	systemic-lupus-erythematosus	104	118		ischemia-reperfusion injury

Rank	Top 25 keywords	Occurrences	Total link strength	Rank	Top 10 keyword-related to kidney disea
10	disease	101	157		nephriti
11	growth	96	191	3	chronic kidney disease
12	protein	87	147		chronic kidney-disease
13	identification	86	150	4	renal fibrosis
14	mechanism	81	144		fibrosis
15	pathway	78	175	5	diabetic kidney disease
16	mutation	76	150		diabetic nephropathy
17	inflammation	74	127		diabetic-nephropathy
18	receptor	73	165	6	focal segmental glomerulosclerosis
19	inhibition	61	134		nephrotic syndrome
20	resistance	60	125	7	IgA nephropathy
21	apoptosis	60	123	8	kidney transplantation
22	differentiation	60	118	9	autoimmune-disease
23	T-cell	60	82		rheumatoid-arthriti
24	glioblastoma	55	122	10	kidney
25	transcriptome	54	111		kidney-disease

RNA-seq, RNA-sequence; EGFR, epidermal growth factor receptor; SLE, systemic lupus erythematosus; AKI, acute kidney injury

Table 3 Summary of top major achievement articles on SCA in kidney-related diseases (IF[?]10)

Disease types	**Journal (year)**	**Sample type and number of samples**	**Single-cell analysis method type**	**Cell type focused**	**Main findings**	**Author (Reference)**
Cell landscape in kidneys	Kidney International (2017)	Healthy mouse kidney (NA)	Fluidigm C1	Mesangial cells	Mesangial cell function can be dissected by identifying and analysing genes expressed in every single cell.	Lu Y et al.[109]
	Kidney International (2017)	Healthy mouse kidneys (n=20)	Fluidigm C1	Podocytes	A large number of proteins related to the cytoskeleton are encoded by essential genes specific to podocytes.	Lu Y et al.[110]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	PNAS (2017)	Healthy mouse kidney (NA)	Fluidigm C1 and SMART-seq	Renal duct cells	A better understanding of physiological regulation and pathophysiology in the renal collecting duct can be achieved by identifying gene expression patterns among the three types of cells.	Chen L et al.[198]
	JASN (2019)	Healthy mouse, rat, pig, and human kidney tissue (NA)	10 × Genomics Chromium & Fluidigm C1	Immune cells	Finding a signature of gene expression across species in kidney resident macrophages.	Zimmerman K et al.[111]
	JASN (2018)	Healthy mouse kidneys (n=8)	Drop-seq	Mesangial cells, endothelial cells, and podocytes	They have discovered novel markers for all types of glomerular cells and have found that both endothelial cells and podocytes have a diversity of transcriptional profiles.	Karaiskos N et al.[93]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	Nature Communications (2021)	Normal human biopsy kidney (n=8) and wt adult male C57BL/6J mice (n=16)	Smart-seq2 and 10X Genomics Chromium	Mesangial (MCs) and glomerular parietal epithelial cells (PECs)	Identification of all four glomerular cell types (podocytes, glomerular endothelial cells, mesangial cells (MCs), and parietal epithelial cells (PECs)) as well as macula densa cells. Pdgfrb-expressing glomerulus-associated cells include bona fide intra-glomerular MCs with functional phagocytosis.	He B et al.[112]
	JASN (2021)	Mouse kidney, wild-type male mouse kidneys (n=2, C57Bl/6N)	Illumina HiSeq 4000 seq and Dropseq	Tubule cells	With single-cell transcriptomics from dissociated kidneys, osmotically regulated genes can be quantified and physiological phenotypes predicted.	Hinze C et al.[31]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	Scientific data (2020)	Normal human kidneys (n=3)	10X Genomics Chromium	Renal tubular cells	The transcriptomic map of the human kidney classifies collecting duct cells into two subtypes and proximal tubule cells into three subtypes.	Liao J et al.[199]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	Nature Communications (2019)	Human kidneys, (NA)	snDrop-seq	Proximal tubule cells	They provided insight into potential targeted therapies by delineating common and rare cell type-specific expression of genes associated with chronic kidney disease, diabetes and hypertension. These include the expression of a mechanosensory ion channel associated with hypertension in mesangial cells and the identification of cell populations in the proximal tubule that are defined by pathogenic expression signatures.	Lake B et al.[200]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	Science (2018)	Mouse kidneys healthy vs diseased mouse models (NA)	Drop-seq and 10X Genomics Chromium	20 different cell types in mouse kidneys	1) the analysis of cell trajectory and lineage tracing in vivo revealed that Notch signals govern transitions between intercalated cells and principal cells. 2) During metabolic acidosis in mouse and human kidney diseases, the fate of the cells changed towards a principal cell trajectory. 3) The phenotypic manifestation and differentiated cell type of inherited kidney diseases are influenced by distinct genetic mutations.	Park J et al.[36]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	JASN (2018)	Healthy adult kidney (n=1)	DropSeq and InDrops	Epithelial, endothelial, immune and stromal cells	1) In independent transplant biopsy samples, both nonclassical CD16+ and classical CD16- groups expressed dendritic cell maturation markers. 2) Novel proinflammatory responses to rejection were identified by comparing healthy kidney epithelial transcriptomes with biopsy specimens. 3) Endothelial cells were subdivided into three groups: resting cells, activated endothelial cells, and a group expressing antibodies that internalize Ig and activate Fc receptors.	Wu H et al,[57]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	Cell stem cell (2022)	Human fetal kidneys (n=3) (13 weeks, 16 weeks, and 18 weeks of gestation)	Spatial dynamic metabolomics	Proximal tubular cells	During differentiation from the renal vesicle to the proximal tubules, isotopic labeling revealed a shift from glycolysis to fatty acid β-oxidation, and hiPSC-derived kidney organoids have immature metabolic phenotypes that can be enhanced by butyrate supplementation to improve tubular epithelial differentiation.	Wang G et al.[134]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
SLE	Nature Immunology (2019)	Human kidney tissue, urine and blood LN (n=24) vs healthy kidney (n=10)	CEL-Seq2 and 10X Genomics Chromium	Immune cells	1) 21 leukocyte subsets active in immune cells (myeloid cells, T cells, NK cells and B cells) that demonstrated both pro-inflammatory responses and inflammation-resolving responses. 2) type 1 interferon response genes in most cells. 3) CXCR4 and CX3CR1 have widespread expression, suggesting a central role. 4) In urine, immune cells are strongly correlated with those in the kidney, suggesting that urine could simulate kidney biopsy.	Arazi A et al.[78]
	Nature Immunology (2019)	Human kidney and skin tissue LN (n=21) vs healthy kidneys (n=3)	Fluidigm C1 /SMART-Seq	Tubular cells and skin keratinocytes	As one of the key factors contributing to treatment failure, they have identified a high IFN response score and fibrotic signature in tubular cells.	Der E et al.[73]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	Nature Immunology (2019)	Human peripheral blood mononuclear cells (PBMC), SLE children (n=33), healthy children (n=11), adult SLE (n=8), adult healthy (n = 6)	10X Genomics Chromium	Monocytes, CD4+ and CD8+ T cells, natural killer cells, dendritic cells, B cells, and plasma cells.	In children with SLE, interferon-stimulated genes (ISGs) were expressed more than in healthy controls, the high ISG expression signature (ISG^{hi}) are predominantly derived from 8/20 PBMC subpopulations, and ISG-enriched subpopulations are associated with high levels of disease activity.	Nehar-Belaid et al.[85]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	PNAS (2019)	Healthy blood donors (NA), mouse spleen (NA)	10X Genomics Chromium	human whole blood cells, immune cells and mesangial cells	1) Deleting the IFN-λ receptor resulted in significantly reduced immune cell activation and reduced skin and kidney damage in lupus mice. 2) In response to IFN-λ stimulation, IFN-λ activated keratinocytes and mesangial cells to produce chemokines, and only mouse neutrophils and human B cells upregulated ISGs.	Goel R et al.[115]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	PNAS (2019)	Human peripheral blood, SLE patients (n = 3)	10X Genomics Chromium	Immune cells	In SLE patients, low-density granulocytes (LDGs) play a significant role in determining the type 1 IFN signature, and there are two sub-populations of LDGs that have been identified in SLE: immature and intermediate mature LDGs. And the latter outcome is strongly associated with the pathology of organs resulting from SLE as well as the presence and severity of coronary artery disease.	Mistry P et al.[102]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	EBioMedicine (2021)	Human peripheral blood, SLE (n=5) vs healthy controls (n=3)	10X Genomics Chromium	Monocytes, B cells, dendritic cells, and granulocytes	1) Identification of ISG expression features in leucocyte clusters and delineation of ISG regulation pathways in SLE and LN patients. 2) ISG expression may be regulated by transcription factors PLSCR1, TCF4, IRF9, and STAT1. To prevent an overwhelming activation of downstream pathways, granulocytes may be targeted as early as possible in ISGs. 3) SLE and lupus nephritis may benefit from the use of Avacopan, a C5aR antagonist.	Deng Y et al.[116]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	Arthritis & Rheumatology (2022)	Human kidneys and urine (n=30)	CEL-Seq2	Urinary proteins and immune cells	Urinary proteomics could revolutionize diagnosis and management of lupus nephritis by monitoring active intrarenal biologic pathways, implicate IL-16 in lupus nephritis pathogenesis, and identify IL-16 as a potentially therapeutic biomarker.	Fava A et al.[173]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	Science (2022)	Human PBMCs, SLEs (n=162) vs controls (n=99)	Multiplexed scRNA-seq, 10X Genomics Chromium, and snATAC-seq	Immune cells	Among the patients, type 1 interferon-stimulated genes (ISGs) were expressed in monocytes, naive CD4+ T cells were reduced, and repertoire-restricted cytotoxic CD8+ T cells were expanded. Patients were stratified into two molecular subtypes based on their cell type-specific expression features.	Perez R et al.[33]

Disease types	**Journal (year)**	**Sample type and number of samples**	**Single-cell analysis method type**	**Cell type focused**	**Main findings**	**Author (Reference)**
AKI	Advanced Science (2022)	Mouse kidney, blood, and spleen (n=6)	10X Genomics Chromium	Kidney resident macrophages (KRMs) and monocyte-derived infiltrated macrophages (IMs)	As evidenced by better kidney function and lower mortality, small molecule inhibitors targeting the S100a8/a9 signalling system have demonstrated renoprotective effects. It also reduced inflammation, improved renal injury, and reduced renal fibrosis in a unilateral IRI model.	Yao W et al.[176]
	Nature Metabolism (2020)	Mouse kidneys, IRI (n=8)	HiSeq 4000 platform and 10X Genomics Chromium	Proximal tubular cells	AKI is associated with impaired gluconeogenesis in the proximal tubule cells of the kidney.	Legouis D et al.[201]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	JASN (2020)	Mouse kidneys, Swiss-Webster, 4-week-old male mice (n=3–6 per group)	Illumina HiSeq 2500	Proximal tubular cells	AKI stages and renal cell types show altered gene expression patterns. Several novel genes (Ahnak, Sh3bgrl3, and Col18a1) have not been examined previously in kidney pathologies, including kidney injury molecule-1 (Kim1), lipocalin 2 (Lcn2), and keratin 8 (Krt8). Sox4 and Cd24a show a pronounced nephrogenic signature after AKI.	Rudman-Melnick V et al.[124]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	Genome Medicine (2022)	Human kidneys, AKI (n=8) vs control patients* (n=4).	Illumina HiSeq 4000 seq and 10X Genomics Chromium	Tubular epithelial cells	Comprehensive resources were provided for examining the cell type-specific transcriptomic responses associated with critical illness-associated acute kidney injury in humans, concluding that recurrent disease-associated signatures and individual heterogeneity can be noted.	Hinze C et al.[126]
	PNAS (2020)	Mouse kidney, IRI (n=3) vs control (n=3)	NovaSeq 6000 (Illumina) and 10X Genomics Chromium	Proximal tubule cells	The failed-repair proximal tubule cell (FR-PTC) state may be a therapeutic target.	Kirita Y et al.[61]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	JASN (2020)	Mouse kidney (NA)	10X Genomics Chromium and SMART-seq2	Myeloid cells	The study found that during injury and repair of the kidney, monocytes recruited early on adopt a proinflammatory, profibrotic phenotype expressing Arg1, and later transition to become Ccr21 macrophages, while a novel Mmp121 macrophage subset is involved in repair.	Conway B et al.[125]

Disease types	**Journal (year)**	**Sample type and number of samples**	**Single-cell analysis method type**	**Cell type focused**	**Main findings**	**Author (Reference)**
DKD	Nature Communications (2022)	Human kidneys, heathy control (n= 6) vs DKD (n = 7)	10X Genomics Chromium, snRNA-seq, and snATAC-seq	Proximal tubule cells	1) Using allele-specific chromatin accessibility (ASCA), the researchers suspect genetic background influences kidney function, altering DKD progression. 2) The proximal tubule responds differently to external stimuli depending on genetic background and metabolic memory.	Wilson P et al.[69]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	Cell Metabolism (2022)	Mouse kidneys (n=70)	10X Genomics Chromium	Podocytes, proximal tubule cells, distal tubule cells, endothelial cells, and immune cells	1) Different cell types respond differently to therapeutic interventions in murine diabetic kidney disease. 2) ACE inhibitors and (sodium-glucose cotransporter-2 inhibitors) SGLT2 inhibitors altered gene expression patterns and pathway activation in different cell types, like podocytes, proximal tubule cells, distal tubule cells, and endothelial cells. 3) The development of effective diabetic kidney disease treatments requires understanding cell type-specific responses to therapies.	Wu H et al.[52]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	JASN (2019)	streptozotocin-induced diabetic endothelial nitric oxide synthase (eNOS)–deficient (eNOS2/2) mice and control eNOS2/2 mice (NA)	Fluidigm C1 and Illumina NextSeq 500	Glomerular Cells and immune cells	The heterogeneity of the responses of the glomerular cells in experimental diabetic kidney disease and the changes in the type of glomerular cells.	Fu J et al.[86]
	PNAS (2019)	Human kidney DKD (n=3) vs healthy kidney (n=3)	snRNA-seq and 10X Genomics Chromium	Podocytes, mesangial, endothelial, leukocytes, proximal tubules	1) All the thick ascending limbs in diabetics, as well as the distal convoluted tubule, exhibit increased potassium secretion and decreased paracellular calcium and magnesium absorption. 2) Convoluted tubules, proximal convoluted tubules, and principal cells have strong angiogenic signatures.	Wilson P et al.[175]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	JASN (2021)	24-hour urine samples (n=17) from Diabetic nephropathy (n=5)	10X Genomics Chromium	Podocytes, proximal tubules, loop of Henle and collecting duct cells, macrophages, and lymphocytes	1) The major types of kidney cells and leukocytes can be found in the urine. 2) Cells of the urinary tract have a similar gene expression pattern to those of the kidneys.	Abedini A et al.[202]
CKD	Nature Communications (2022)	Mouse kidneys, Pax8/WT (n = 30) and Pax8/SAV1ko mice (n = 16)	10X Genomics Chromium	Tubular cells	Maintain residual kidney function early after AKI through YAP1-driven tubular cells polyploidization. Targeting tubular cells polyploidization after the early AKI phase is one way to prevent AKI-CKD transition without affecting AKI fatality.	De Chiara L et al.[121]
	The Journal of Clinical Investigation (2021)	Mouse kidneys, WT (n = 6), Dach1 HZ (n = 6).	ChIP-qPCR and 10X Genomics Chromium	Tubular cells	DACH1 was identified as a kidney disease risk gene.	Doke T et al.[117]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	JASN (2020)	Healthy mice (NA) vs nephrotoxic serum nephritis, diabetes, doxorubicin toxicity, and CD2AP deficiency (n=4 different disease models, from different disease models)	10X Genomics Chromium	Glomerular cells	Podocytes were acutely activated by the Hippo pathway after nephrotoxic immune injury, which appeared type-specific and injury-specific. YAP or TAZ deletion results in more severe and prolonged proteinuria in response to injury.	Chung J et al.[122]
	JASN (2021)	Four fetal rhesus kidneys	scRNA-Seq and snRNA-Seq	Comparation between rhesus and human cells	A model of human-like lateral branch nephrogenesis based on the Rhesus macaque, allowing molecular studies of late gestation nephrogenesis.	Schuh M et al.[203]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
Kidney fibrosis	Nature Immunology (2022)	Mouse kidneys, 6 sham (n=6) and UUO wild-type (WT) mice (n=2). Human kidneys, CKD (n=6) vs healthy controls (n = 6)	10X Genomics Chromium	Immune cells and tubule cells	The expression of cytokines and chemokines associated with immune cell recruitment identifies a subset of kidney tubule cells with a profibrotic-inflammatory phenotype. Profibrotic tubules secrete CXCL1 which recruits basophils with CXCR2+.	Doke T et al.[118]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	Nature (2021)	Human kidneys, CKD (n=13) vs non-CKD (n=7); Mouse kidneys (NA)	Smart-Seq2, spatial transcriptomics, and ATAC–seq	Epithelial, endothelial, haematopoietic cells and resident mesenchymal cells	NKD2 was identified as a myofibroblast-specific therapeutic target in human kidney fibrosis, using genetic fate-tracing, time-course single-cell RNA sequencing and ATAC sequencing experiments in mice, as well as spatial transcriptomics in human kidney fibrosis.	Kuppe C et al.[104]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
Kidney fibrosis/AKI	Cell Metabolism (2022)	Mouse kidneys, fibrogenesis and IRI (n=24) vs hearlthy (n=11)	sci-RNA-seq3 and NovaSeq 6000	Epithelial, endothelial, immune, and stromal cells	Ischemia-induced injury induces diverse injury states in proximal tubular cells, including an early state with enhanced lipid metabolism. During the initial stages of IRI, lipid metabolism is transiently activated, and PLIN2+ lipid droplets are present.	Li H et al.[123]
IgAN	Kidney International (2022)	Mouse kidneys, gddY (n=5) and ddY (contro, n=5) (cells from 1 mouse failed in quality control)	SMARTseq2	Mesangial cell-derived Slit3 potentially activating Robo-receptors in podocyte/endothelial cells.	A new understanding of IgAN-associated glomerulopathy's molecular pathogenesis was provided by the validation of key cell-cell crosstalk pathways and the Slit-Robo signaling axis through cell culture models.	Zambrano S et al.[204]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	Cell reports (2020)	Human kidney and blood, IgAN kidney (n=13) and blood (n=5) vs healthy kidney (n=6) and peripheral blood mononuclear cells (n=5)	STRT-seq	Mesangial, intercalated and principal cells, PBMCs	1) CD8+ T cells exhibit downregulation of cytotoxic marker genes in peripheral blood monocytes. 2) EMT and fibrosis signatures are seen in a transition cell type with intercalated and principal cell markers. 3) Mesangial cells expressing IgAN show upregulation of JCHAIN, which is critical for dimerization and transepithelial transport of IgA.	Zheng Y et al.[205]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
Renal tumor	Science (2018)	Human kidney (fetal, pediatric and adult) Wilms' tumor (n=3), clear cell (ccRCC; n=3) and papillary renal cell carcinoma (pRCC; n=1) vs healthy fetal (n=2), pediatric (n=3), adolescent (n=2), and adult kidneys (n=5), ureters (n=4)	10X Genomics Chromium	Tumor cells, immune cells, epithelial cells, and proximal tubular cells	The study found that one population of ascending vasa recta cells expressed VEGF-signalling receptors KDR, FLT1, and FLT4, while the other cluster tE2 exhibited lymphangio-genic VEGFC and FLT1, and high levels of ACKR1, a marker of venular endothelium promoting tissue migration of immune cells, indicating a complex VEGF signalling circuit within RCC tissue.	Young M et al.[89]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	Cancer cells (2021)	Human kidney tumor regions, lymph node, normal kidney, and peripheral blood (n=29)	scRNA-seq and TCR-seq	Immune cells	The immune microenvironment and TCR clonotype dynamics of multiregional clear cell renal cell carcinoma (ccRCC) samples are dissected by single-cell analysis. ccRCC response and resistance to immune checkpoint blockade (ICB) are linked to CD8+ tissue-resident T cells and tumour-associated macrophages (TAM).	Krishna C et al.[127]

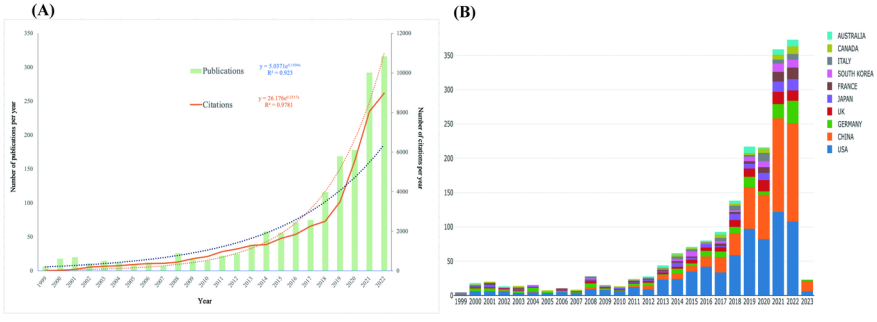
Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
	Cancer cells (2022)	Human kidney tumors, Tissues were sampled from multiple regions of the tumor core, the tumor-normal interface, normal surrounding tissues, and peripheral blood. (n=12)	10x Genomics Visium spatial Transcriptomics, TCR-seq	Immune cells, stromal cells and lineage-trace myeloid cells	They identified six conserved meta-programs that distinguish tumor cells from normal cells, and found one high-enriched at tumor-normal interfaces that co-localized with IL1β-expressing macrophages, which offers a potential therapeutic target.	Li R et al.[128]
	Cell (2021)	Human kidneys, clear cell renal carcinoma, ccRCC (n=11, tumor+ adjacent normal)	10X Genomics Chromium	Immune cells	They identified TREM2/APOE/C1Q-positive macrophage infiltration as a potential prognostic biomarker for ccRCC recurrence, as well as a potential therapeutic target for this disease.	Obradovic A et al.[129]

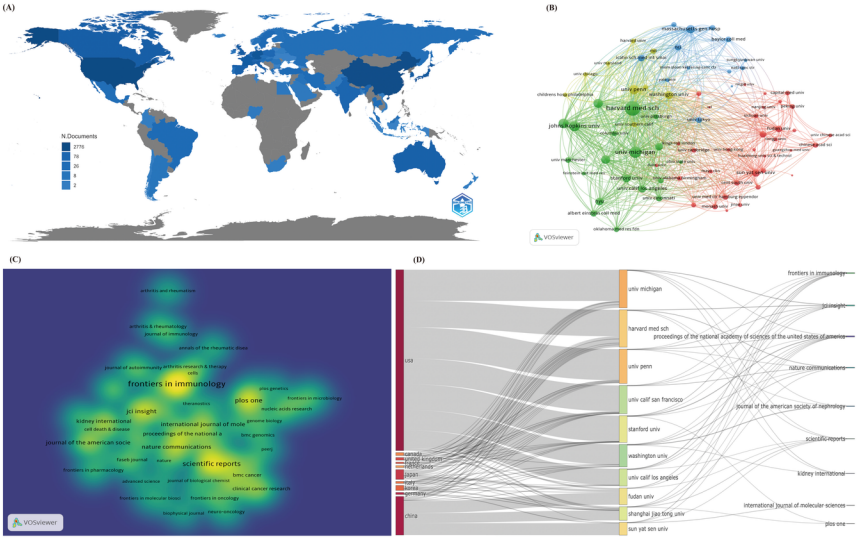
Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
kidney transplantation	JASN (2020)	Human kidneys, kidney transplant biopsy (n=5)	Illumina HiSeq platform and 10X Genomics Chromium	Immune cells	They demonstrate that donor macrophages and T cells may persist for years after transplantation and that donor macrophages exhibit distinct transcriptional profiles.	Malone AF et al.[66]
	Nature Communications (2019)	Human kidneys, human iPSC (n=4)	10X Genomics Chromium	Immune cells	Identifies the source of variability in iPSC-derived kidney organoids, highlights their reproducibility, and demonstrates a reduction in off-target cells after transplantation.	Subramanian A et al.[206]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
Nephrotic syndrome	The Journal of Clinical Investigation (2021)	Mouse kidneys, 5-month-old $Pdss2^{kd/kd}$ mice (KDKD) (n=3) and age-matched control mice (CTRL (n=3)	Illumina HiSeq 2000/HiSeq 2500	Podocyte cells.	The GDC-0879 treatment restored Gpx4, an enzyme that protects against PUFA-mediated lipid peroxidation. Gpx4 and Braf/Mapk pathway gene expression patterns in kidney disease tissue demonstrate broader human disease relevance.	Sidhom E et al.[119]
Renal artery stenosis (RAS)	JASN (2021)	Mouse kidneys, (NA), samples are up to date (weeks) (sham-vehicle, sham-AP, RAS-vehicle, and RAS-AP mice; n=6–8 each)	Illumina HiSeq 2500 and 10X Genomics Chromium	Proximal, distal tubular, and endothelial cells	Senolytic strategies have been developed to delay chronic ischemic renal injury by delaying p16 (Cdkn2a), p19 (Cdkn2d), and p21 (Cdkn1a) dysregulated senescence.	Kim S et al.[120]

Disease types	Journal (year)	Sample type and number of samples	Single-cell analysis method type	Cell type focused	Main findings	Author (Reference)
Autosomal dominant polycystic kidney disease (ADPKD)	Nature Communications (2022)	Human kidneys, ADPKD (n=8) vs healthy kidney (n=5)	snRNA-seq, snATAC-seq, and 10X Genomics Chromium	Proximal tubule cells	1) Proinflammatory and profibrogenic signaling pathways are activated in the collecting duct by proinflammatory fibroblasts and proximal tubular cells. 2) Using GPRC5A, cells lining the collecting duct are more likely to express transcription factors TEAD, CREB and retinoic acid receptors. 3) Identify and validate the putative distal enhancer that regulates GPRC5A expression.	Yoshiharu M et al.[64]

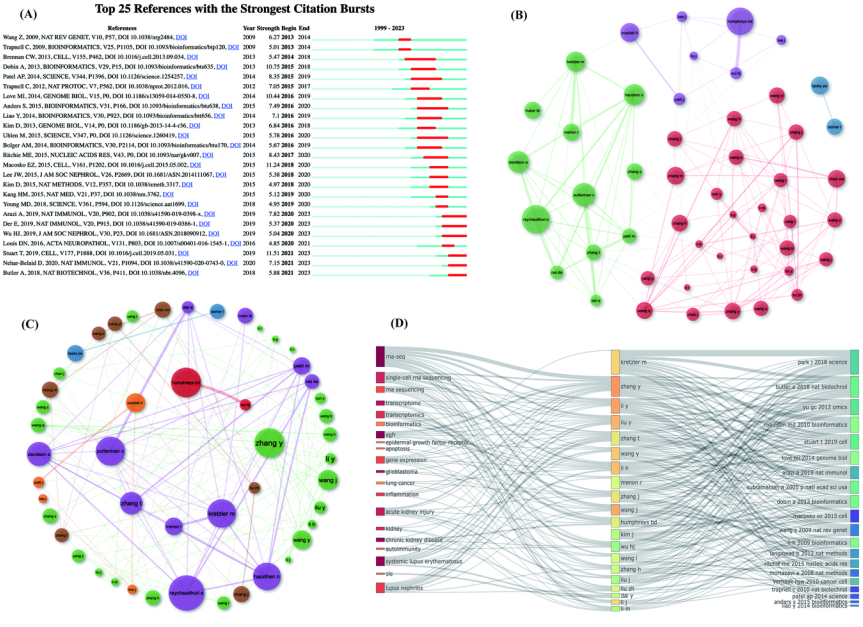
NA, Not Available, * Control kidney tissues were obtained post-mortem or after nephrectomy from individuals without AKI.

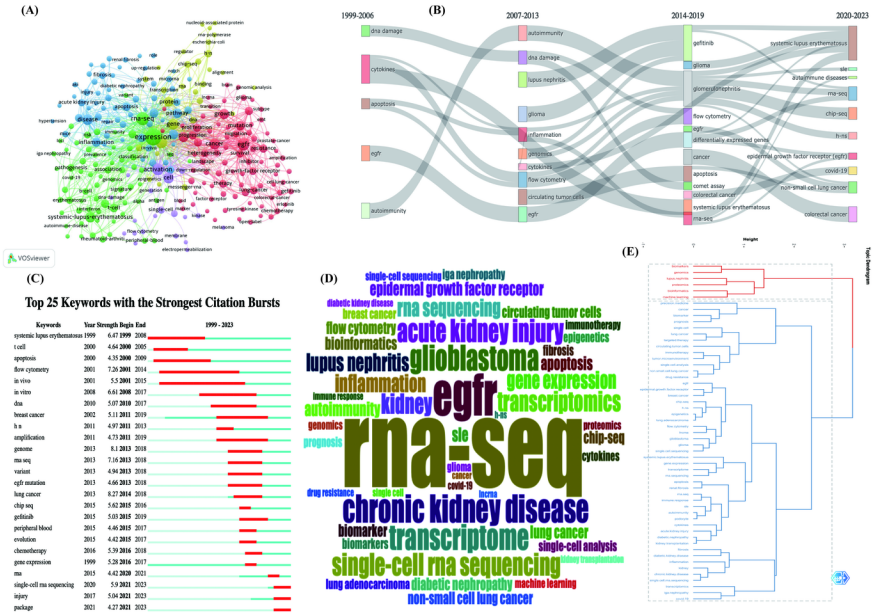




(A) Top 25 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	1999 - 2023
Wang Z, 2009, NAT REV GENET, V10, P57, DOI 10.1038/nrg2484, DOI	2009	6.27	2013	2014	
Trapnell C, 2009, BIOINFORMATICS, V25, P1105, DOI 10.1093/bioinformatics/btp120, DOI	2009	5.01	2013	2014	
Brennan CW, 2013, CELL, V155, P462, DOI 10.1016/j.cell.2013.09.034, DOI	2013	5.47	2014	2018	
Dobin A, 2013, BIOINFORMATICS, V29, P15, DOI 10.1093/bioinformatics/bts635, DOI	2013	10.75	2015	2018	
Patel AP, 2014, SCIENCE, V344, P1396, DOI 10.1126/science.1254257, DOI	2014	8.35	2015	2019	
Trapnell C, 2012, NAT PROTOC, V7, P562, DOI 10.1038/nprot.2012.016, DOI	2012	7.05	2015	2017	
Love MI, 2014, GENOME BIOL, V15, P0, DOI 10.1186/s13059-014-0550-8, DOI	2014	10.44	2016	2019	
Anders S, 2015, BIOINFORMATICS, V31, P166, DOI 10.1093/bioinformatics/btu638, DOI	2015	7.49	2016	2020	
Liao Y, 2014, BIOINFORMATICS, V30, P923, DOI 10.1093/bioinformatics/btt656, DOI	2014	7.1	2016	2019	
Kim D, 2013, GENOME BIOL, V14, P0, DOI 10.1186/gb-2013-14-4-r36, DOI	2013	6.84	2016	2018	
Uhlen M, 2015, SCIENCE, V347, P0, DOI 10.1126/science.1260419, DOI	2015	5.78	2016	2020	
Bolger AM, 2014, BIOINFORMATICS, V30, P2114, DOI 10.1093/bioinformatics/btu170, DOI	2014	5.67	2016	2019	
Ritchie ME, 2015, NUCLEIC ACIDS RES, V43, P0, DOI 10.1093/nar/gkv007, DOI	2015	8.43	2017	2020	
Macosko EZ, 2015, CELL, V161, P1202, DOI 10.1016/j.cell.2015.05.002, DOI	2015	11.24	2018	2020	
Lee JW, 2015, J AM SOC NEPHROL, V26, P2069, DOI 10.1681/ASN.2014111067, DOI	2015	5.38	2018	2020	
Kim D, 2015, NAT METHODS, V12, P357, DOI 10.1038/nmeth.3317, DOI	2015	4.97	2018	2020	
Kang HM, 2015, NAT MED, V21, P37, DOI 10.1038/nm.3762, DOI	2015	5.12	2019	2020	
Yoong MD, 2018, SCIENCE, V361, P594, DOI 10.1126/science.aat1699, DOI	2018	4.95	2019	2020	
Arazi A, 2019, NAT IMMUNOL, V20, P902, DOI 10.1038/s41590-019-0398-z, DOI	2019	7.82	2020	2023	
Der E, 2019, NAT IMMUNOL, V20, P915, DOI 10.1038/s41590-019-0386-1, DOI	2019	5.37	2020	2023	
Wu HJ, 2019, J AM SOC NEPHROL, V30, P23, DOI 10.1681/ASN.2018090912, DOI	2019	5.04	2020	2023	
Louis DN, 2016, ACTA NEUROPATHOL, V131, P803, DOI 10.1007/s00401-016-1545-1, DOI	2016	4.85	2020	2021	
Stuart T, 2019, CELL, V177, P1888, DOI 10.1016/j.cell.2019.05.031, DOI	2019	11.51	2021	2023	
Nehar-Belaid D, 2020, NAT IMMUNOL, V21, P1094, DOI 10.1038/s41590-020-0743-0, DOI	2020	7.15	2021	2023	
Butler A, 2018, NAT BIOTECHNOL, V36, P411, DOI 10.1038/nbt.4096, DOI	2018	5.80	2021	2023	





Keywords	Year	Strength	Begin	End	1999 - 2023
systemic lupus erythematosus	1999	6.47	1999	2008	
t cell	2000	4.64	2000	2005	
apoptosis	2000	4.35	2000	2009	
flow cytometry	2001	7.26	2001	2014	
in vivo	2001	5.2	2001	2015	
in vitro	2008	6.61	2008	2017	
dna	2010	5.07	2010	2017	
breast cancer	2002	5.11	2011	2019	
h n	2011	4.97	2011	2013	
amplification	2011	4.73	2011	2019	
genome	2013	8.1	2013	2018	
rna seq	2013	7.16	2013	2018	
variant	2013	4.94	2013	2018	
egfr mutation	2013	4.66	2013	2018	
lung cancer	2013	8.27	2014	2018	
chip seq	2015	5.62	2015	2016	
gefitinib	2015	5.03	2015	2019	
peripheral blood	2015	4.46	2015	2017	
evolution	2015	4.42	2015	2017	
chemotherapy	2016	5.39	2016	2018	
gene expression	1999	5.20	2016	2017	
rna	2015	4.42	2020	2021	
single-cell rna sequencing	2020	5.9	2021	2023	
injury	2017	5.04	2021	2023	
package	2021	4.27	2021	2023