PLOS Science Wednesday: Hi reddit, my name is Daniel and I organized the Dicty World Race, which compared the motility and chemotaxis in engineered cell lines, as described in our PLOS ONE study – Ask Me Anything!

PLOSScienceWednesday [1] and r/Science AMAs[1]

[1]Affiliation not available

April 17, 2023

Abstract

Hi reddit, my name is Daniel Irimia and I am an Associate Professor in the Surgery Department at Massachusetts General Hospital and Harvard Medical School, and a Senior Investigator at Shriners Burns Hospital in Boston. My research focuses on designing novel technologies for measuring the activities of white blood cells from patients, towards better ways to predict, diagnose, monitor, and treat inflammation, infections, and sepsis. In 2016, I received the "Pioneers of Miniaturization" prize from the Chemical and Biological Microsystems Society, for pioneering work on microfluidic technologies for measuring human neutrophil activities and applications to human diseases. I am the organizer of the recent Dicty World Race, an unorthodox approach aimed at encouraging biologists to employ emerging microfluidic technologies to make high precision measurements of cell migration for biological and medical research applications. The results and learning from this experiment were recently published as an article titled "A Worldwide Competition to Compare the Speed and Chemotactic Accuracy of Neutrophil-Like Cells" in PLOS ONE. The race enabled a large-scale comparison of motility and chemotaxis in the engineered cell lines, allowing exploration of a diverse set of strategies for enhancing chemotactic performance. We found that there are tradeoffs between cell speed and chemotactic accuracy in maze-like environments and that the winning cells were not the fastest cell type, but excelled in finding the shortest paths through the maze. These findings could eventually help us develop better therapies against infections and chronic inflammation. Don't forget to follow me on Twitter @D__Irimia. I will be answering your questions at 1pm ET – Ask Me Anything!

the WINNOWER

REDDIT

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PLOSSCIENCEWEDNESDAY R/SCIENCE

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Hi Professor Irmia,

Thanks for doing this AMA!

Forgive me but a lot of what you have written has gone quite above my head. From what I can tell you 'raced' various types of cell around a specific maze-like environment, and determined that it's not necessarily the fastest cell that won. This sounds very cool but I'm not sure what impact this might have on, say, medical applications. I'd guess possibly faster delivery of drugs and medical treatments?

Could you expand a little on what impacts this research might have in the 'real world'? Finding impact for bleeding edge research is something that I have an interest in from a previous job.

OldBoltonian

There are two aspects of this race that are important to emphasize. First, there is the technological advance that enabled this race in the first place. The measurements we could make today are the most precise among the various assays available. The technology could be applied to medical problems, like the study we are doing right now on the motility of human neutrophils for diagnosing sepsis. If you are interested, you could read more about this in one other PLOS One paper we have published recently. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0114509.

Second, there is the impact on biology. What we learned from this competition teaches us about long-term strategies to control cell migration, which could ultimately have medical applications. For example, in measuring neutrophils from patients with sepsis, we find that these neutrophils are moving

significantly slower and are less accurate at moving towards targets (e.g. microbes). If we had a way to correct these deficiencies, we could have better medicines for treating patients with sepsis. Right now there is no medicine of this kind. Among the reasons for this situation, our insufficient knowledge of the mechanisms of cell migration. Our work aims at improving that and obviously, this is going to take a longer time before any medical benefit emerges.

Hi, Dr. Irimia.

I have to say your AMA woke me up this morning more than my usual cup of coffee; it's totally in my wheelhouse. Up until 3 years ago, I worked in a lab at Brigham & Women's elucidating the contribution of glycoproteins to stem cell and lymphocyte trafficking and extravasation. I also collaborated with an MGH lab studying chemorepulsion/fugetaxis of T cells in the presence of HIV gp120 and typical chemoattractants. Anyways, my questions:

1) Why Dicty and HL60 cells? Has anyone tried other cell types through your maze?

2) I noticed most teams in your paper employed strategies that manipulated intracellular mechanisms. Has anyone tried manipulations of the extracellular surface (eg increased expression or enhancement of integrins, selectins, chemokine receptors, etc)?

3) Does your race only allow for chemoattraction? Would it be possible to employ chemorepulsion?

4) How does one join the race? I think my old PI and collaborator would be interested. At the very least they would be interested in your microfluidics expertise.

MeloYelo

Hi MeloYelo, wonderful to hear from people that are dedicated to research in the field of cell migration! 1) The choice of Dicty and HL60 was mostly based on practical concerns: these two cell types are most common in labs that study cell motility. We would race any other cell type if we get the request. We tried lymphocytes - you could read our recent paper and watch some cool movies in the supplemental material - no login required - http://pubs.rsc.org/en/Content/ArticleLanding/2015/IB/c5ib00146c#!divAbstract. We also have experience with dendritic cells and monocytes. We have a lot of experience with cancer cells moving through the mazes. 2) There was one attempt to manipulate the integrins. Unfortunately, not enough cells were available at the day of the race. I hope we will get to test these cells during the next race, when more of the work will happen in the labs that sign up for the race, to minimize the chances for this issue happening again. 3. The race tests for several migration patterns. On the particular topic of chemorepulsion, you will find more ideas from our recent paper that deals with neutrophils and lymphocytes moving towards and away from chemokines. I am more inclined to say that the "attraction" and "repulsion" classifications are a consequence of the limitations of current technologies to probe cell migration and when one employs more sophisticated tools a whole range of possibilities emerges, which challenge the traditional views of what is an attractant or a repellent for cells. http://www.nature.com/articles/ncomms5787 4. Please visit our website and sign up for news about the race, or sign up to be a participant. The next race will take place in May and will be more fun if more people join: http://www.dictyworldrace.com/

Could you please elaborate on the types of therapies that could be used to treat chronic inflammation? Chronic inflammation anywhere in the body? Or more specific? Thanks!

everytingirie865

At this time, the discussion about therapies is more at the concept level. The fundamental idea is that by controlling cell migration we could control inflammation. This could work because most of the cells participating in inflammation aka white blood cells reside in the blood most of the time, and move into the tissues only when an inflammation trigger is turned on. Thus, reducing the number of cells, e.g. neutrophils, from entering a tissue could have an impact on inflammation. The most important thing for this strategy to work in practice is that the control has to be very precise. Blocking all neutrophils from entering a tissue would leave the door open for microbes to enter/grow into tissues and will lead to significant problems with infections. Thus, tools to allow us to measure the effect of various

interventions with high precision are very important towards this goal.

I'm currently studying Epidemiology, and I know that many diseases, especially bacterial and fungal infections, can cause incredibly painful cases of inflammation in the affected area(s). When said inflammation occurs due to a severe infection, what kind (or kinds) of treatment(s) would be the most useful to clear both the inflammation and the localized infected area?

Mastercodex199

The type of treatment would depend on the particular infection. Painful inflammation is usually caused by large numbers of white blood cells accumulating in a tissue in a short time. Thus, reducing the number of white blood cells and at the same time stimulating their microbe killing abilities could be helpful. Are you thinking about any infection in particular?

This is a very cool idea! Can you talk a little about the different strategies the teams used and how they accomplished these enhancements to the cell lines?

divvyflax

The different strategies are summarized in a table and discussed extensively in the paper. Thus, I would invite you to take a look at Table 1: http://dx.doi.org/10.1371/journal.pone.0154491.t001 and the specific trajectories of cells through mazes that are also available through a link from the paper: https://figshare.com/s/ebf97b9cf877696dc20a. Any favorite strategy you would want to discuss more?

How do subtly different substrates affect which cells are the fastest? I would think that there are some things that could be done even to fluids within the body that would facilitate better cell motility, have you done investigation into how platelet count or other differences in the fluid surrounding the cells affects motility?

StupidName2010

This is a great question! For human neutrophils, some substrates, like glycoprotein E-selectin, could help cells move fast because they replicate molecules that cells would encounter on the walls of the blood vessels. For Dicty, it may not matter. These cells live in soil usually and are rather resilient to the nature of the substrate they are moving on.

Yes, we have a recent study that looked at the effect of interactions between platelets and neutrophils. You could read more about this in the Journal of Leukocyte Biology: http://www.jleukbio.org/content/early/2016/09/12/jlb.1TA1115-517RR.abstract

Thank you for this unorthodox project, I would never have considered this as a way when looking to measure cell motility. I had to reread the submission several times to make sure I wasnt misinterpreting it.

What were some of the initial thoughts that went through your head when developing the hypothesis and experiment? And were there any kind of competition among associates in the lab about "racing" different cell types?

EnigmaticShark

One thought was that the microfluidic mazes enable unprecedented precision of the measurements of cell migration, by the range of parameters to be quantified and reduction of noise from stochastic cell behavior. Thus, the race could serve as a demonstration and capture differences between cells not available through traditional tools. Another thought was that we do not really know today what molecular circuits are responsible for the speed and accuracy during migration. We know some of the key molecules, but the complex connections between the more than 100 molecular types are still up for debate. Together, a large number of modifications of these circuits and a large number of quantitative measurements could help us reverse engineer these circuits. This remains the goal for the

next iterations of the race. We have run a few races already for other cell types (e.g. cancer cells) and will continue to increase the number of cell types by engaging an increasing number of scientists in these efforts.

Could your research lead to earlier detection of common infections and thus result in the need for reduced medication to halt the infection, or will it lead to better medication?

Or both?

How do you feel about today's medical practice of throwing antibiotics at people for everything?

Thanks for your time!

Start_button

It is the "fight" between our white blood cells and microbes, which ultimately keeps our tissue sterile. Antibiotics act on one side, killing or impairing microbes, and making white blood cell's job easier. There is also the side of white blood cells. If we could stimulate the white blood cells to be better "microbe killers" that will also have benefits. Our research has shown that at least in some patients, the white blood cells (in particular the neutrophils) are impaired - they move slower and are less accurate - see: https://figshare.com/articles/_Spontaneous_Neutrophil_Migration_Patterns_during_Sepsis_after_Major_Burns_/1265814 Thus, better medications are possible. Unfortunately, we do not have these now. Hopefully, we will have these just in time, when the antibiotic resistance is becomeing a significant problem.

What role do you believe cannabinoid's, such as THC and CBD, will play in the medical field as more research is done with it? Do you believe that cannabinoids are the potential answer to cancer, or an answer to many other disease/disorders? I'm interested in the research conducted with cannabinoids and cancerous cells, and would love to learn more, except I don't believe there's too much research pertaining to this area.

ajuan3

Neutrophils have cannabinoid receptors and a small number of studies have reported that neutrophil motility is reduced by the binding of cannabinoids to the CB(1) and CB(2) receptors. Most of the research has been performed in the context of inflammation, to test the potential of cannabinoids as anti-inflammatory compounds. It remains to be determined the impact of cannabinoids on these and other diseases. I agree with you that more research is needed in this area. There are only a few biomedical labs that do this type of research. The requirements for compliance with the strict rules and regulations that govern the use of cannabinoid compounds is an important factor limiting the number of research labs working with cannabinoids. It is unclear at this time if cannabinoids are the "answer to cancer" or if they have any potential in that direction.

Hi Daniel! Thank you very much for doing this AMA! I have a close relative that suffers chronic myeloid leukemia and I know its an uncontrolled growth in quantity of white blood cells. I was wondering what kind of improvement your research could do to the detection and treatment of leukemia being chronic or acute? Is it possible to develop new miracle drugs like imatinib to other bone marrow cancers?

keyser_soze23

I am sorry to hear about your close relative. This is a terrible disease.

Some therapies are possible with a focus on controlling leukemic cell migration, although I do not know of any specific efforts. Such therapies may control the infiltration of various tissues by leukemic cells and thus prevent some complications. Such therapies may not be sufficient by themselves, but in combinations with other interventions may be helpful.

What made you decide on this maze design? Have different maze designs been considered?

This is a very interesting project; thank you for sharing through this AMA.

Johnsonschlager

We designed the mazes based on the experience we have to assays for neutrophil migration. We started with a simple orthogonal maze, like the one you could see in the supplemental material to one other paper from our group: http://pubs.rsc.org/en/Content/ArticleLanding/2015/IB/c5ib00146c#!divAbstract We then realized that this would not be challenging enough for the Dicty and neutrophil cells. We made these mazes more challenging by adding dead end channels and blocking some of the paths, and including some wider spaces where cells have little mechanical guidance. You could learn more about how neutrophils interact with various channels by watching our movies on YouTube: https://www.youtube.com/watch?v=zz1E5UB9wbI&list=PLaQa1Eq_GBD2EEgzpMQVOK_4uGos14Q2N .