ACS AMA: I am Wilfredo "Freddy" Colon, Ph.D., a professor at Rensselaer Polytechnic Institute who researches the biology and pathology of misfolding proteins. Ask me anything about prions or brain-affecting protein-based diseases.

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

[1]Affiliation not available

April 17, 2023

Abstract

Hi Reddit! I'm Dr. Wilfredo Colon. Call me Freddy. I'm a Professor and the Chair in the Department of Chemistry and Chemical Biology, Rensselaer Polytechnic Institute (http://rpi.edu) in Troy, NY. I research the biological and pathological roles of protein hyperstability in protein function, misfolding and amyloid formation. Proteins in our bodies are marginally stable, allowing us to repair and replace older proteins with new identical ones. As we age, our bodies become less efficient at this degradation process, and proteins can misfold and aggregate, leading to problems associated with aging (e.g., Alzheimer's, Parkinson's, cancers). Hyperstable protein aggregates are too stable to degrade, interfering with cellular function and are thought to contribute to complications with aging and disease. A long-term goal of my research is to understand the role of protein hyperstability in biological adaptation, aging, and diseases. To that end, I've developed methods for discovering and analyzing protein hyperstability in biological fluids or tissue. I am a first-generation Hispanic college student who went into science in academia. I've had various roles over the years including a National Science Foundation (www.nsf.gov) program director, a director of education and outreach programs, and my current role as a professor. I got a B.S. in chemistry from the University of Puerto Rico at Mayagüez (www.uprm.edu/) and a Ph.D. in chemistry from Texas A&M University (www.tamu.edu). I am an ACS Expert, an AAAS Fellow, and I've been honored to receive a Presidential Early Career Award in Science and Engineering. **Hi everyone. This hour went by too fast. Thank you for your questions and interest on this topic. I had a great time and wish I had been able to answer more of your questions. I apologize if I did not get to your question. Perhaps I could come back in the near future for another session. -acs affiliation correction and style edits

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AMERCHEMSOCIETYAMA R/SCIENCE

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Thanks for spending time with us today, could you briefly discuss tau and amyloid beta prion-like properties and their role in Alzheimer's and if this is comparable to CJD?

PHealthy

Aggregates of A-beta and Tau proteins are widely believed to play a pathological role in Alzheimer’s disease. Just about all proteins that form amyloid can catalyze other proteins of the same kind to form amyloid. That is, Tau amyloid can induce other Tau proteins to form amyloid, and A-beta amyoid can induce other A-beta proteins to form amyloid. In this sense, it has a prion-like property. However, these amyloids and all others I know of lack a critical prion property that is present in CJD, scrapie, mad cow disease, etc – they are not remarkably stable like the infectious PrP prion, and therefore they would be degraded before they could do any damage (assuming they could even make it through the brain-blood barrier). (WC)

Hi Dr. Freddy, as regular people. what are some of the things that WE SHOULD DEFINITELY know about your field?

quibblefish

Proteins play a critical role in health and disease. Just about every disease (excluding infections) involves one or more malfunctioning protein(s). A key to life and health is our body’s ability to repair and remove defective proteins. This protein quality control system works great when we are young, but becomes less effective as we age. That is why most protein misfolding/aggregation diseases (including Alzheimer’s, Parkinson’s, type II diabetes, many cancers, etc) are aging related. The presence of misfolded/aggregated protein that is hyperstable during/after middle age years may be particularly

dangerous, as it will make it more likely that these abnormal species will accumulate in the body, thereby increasing the risk of disease.

Good day Doctor and thank you for providing your insight.

1: To my understanding the prions that brought us Mad Cow Disease act by misfolding existing proteins in our brains seemingly instantaneously. Has there been any work to determine how this occurs?

2: Strange as it may be, it also seems that this mechanism could potentially be harnessed to quickly effect other proteins in humans as a cure for different ailments. Is there any ongoing research in this area?

AkMoDo

Reply: 1. Much work has been done. The conversion process is not instantaneously upon infection, as it may take many years for disease to occur. Although the molecular mechanism is still being debated, what is clear is that the misfolded prion has the ability to catalyze the conformational change on other prions that are normally folded. Reply: On your second question, I would say "yes", but I think we are far from being there. One day, perhaps we may be able to design a "good prion" that can go in and take out a toxic protein/prion by inducing it to adopt the benign conformation. (WC)

Here's to old RPI! (Materials undergrad at RPI here).

I ask this of most researchers I meet, what do you believe is the Holy Grail or most important future discovery in your field? And what is being done today to work towards it?

Zaiush

Greetings! There are several. Here is one: To be able to keep our body's protein quality control system working at youth performance for decades longer - if you don't mind living in good health past 100 years. :-)

Hey Dr Colon, I got my BS in biology myself and hope to continue education in healthcare. One thing I remembered about prions was that in Alzheimer's patients, the symptoms are in response to an accumulation of misfolded proteins in the brain with no way to "drain" these proteins away. Is there work underway that will hopefully solve this problem in the future? Are there medicines in development that can be used to degrade these misfolded proteins to a level that reduces symptoms? Thank you so much for your time and good luck with your research!

PhillipThatBlunt

Alzheimer's is an extremely complicated disease, but protein aggregation appears to be a key and likely pathological "player". What is less clear is whether the accumulation of certain type of amyloid/aggregates or the smaller misfolded A-beta/tau protein species are the main "toxic agent" in AD. There is indeed much research and effort to target aggregates and misfolded species as a therapeutic approach to AD, but the brain-blood barrier issue makes it so much harder. (WC)

Do you think that the ban on donating blood based on the creutzfeldt jakob or mad cow epidemic of the UK and Europe is still appropriate and relevant today? If yes, why and what would make that change? If no, what changed and do you expect this public policy to be reviewed?

For instance from North America, the HEMA-Quebec guidelines state:

You will be permanently disqualified as a blood donor if:

You spent a cumulative total of three months or more in the United Kingdom between January 1, 1980, and December 31, 1996.
You spent a cumulative total of three months or more in France between January 1, 1980, and December 31, 1996.
You have spent a cumulative total of five years or more in Western Europe (outside of France and the United Kingdom) between January 1,
You spent a cumulative total of six months or more in Saudi Arabia between January 1, 1980, and December 31, 1996.
You have received a blood transfusion (whole blood, red blood cells, platelets or plasma) in France, the United Kingdom or another country
versolitaire

Very interesting question. I think the ban was appropriate because the incubation period or prion disease could be decades, and there was no clear knowledge of how much the disease may spread. I personally think the current risk is very low, but I don't know if it is low enough to change policy. As we

learn more about the prion disease mechanism(s) and develop more sensitive ways to detect pathogenic prions, I’m sure public policy will be impacted. (WC)

Hi, Doctor. I unfortunately witnessed one grandparent succumb to Alzheimer's and another to "traditional" dementia. What is the current understanding of preventative measures that my parents, and ultimately I could take to avoid similar fates? I've heard that obesity is thought to be a contributing factor- what is the current understanding of the role that may play?

username_redacted

I don’t know of anything we can do that is proven to reduce the risk of AD. There are still genetic, epigenetic, and environmental factors that need to be discovered to better understand the risk factors involved. However, if it turns out to be true (as it appears to be the case) that the accumulation of amyloid/aggregates/misfolded proteins plays a role in the onset and progression of AD, then anything we can do to reduce metabolic stress in our system to allow our protein quality control system to work as best as possible, may decrease risk or progression of any aging-related misfolding disease. In the case of AD, it progresses slowly, and therefore delaying its onset or progression would bring major benefits. (WC)

Hi, thank you for doing this AMA. Protein folding is a really interesting topic that affects us all, despite its lack of coverage in general bio courses at university. I have a couple questions:

I used to run Folding@Home, though truth be told I didn't keep up with the results. How much of a wave did that make in the field, and what realistic benefit has it created?

Also, forgive my ignorance if this sounds silly to you, but do you think it'll be possible to unfold the fibers that prions form at some point in the future, and reintroduce the correct conformation? What hypothetical treatments do you imagine future humans will use to treat prion-related diseases, and other protein-aggregating brain diseases in general?

Thank you!

ImpeachJohnV

Not sure about the first question, but on your second question, I think its plausible, but the extreme stability of prion fibers make it unlikely that they will be easy to unravel. A more likely treatment in my opinion is to figure out which region of the misfolded prion is responsible for converting other proteins into pathogenic prion and target that region with a small molecule drug. (WC)

Thank you for doing this AMA. My wife and I are both US veterans who were stationed on US air bases in Germany between 1985 and 1990. Because of this we, and our three children, are both disqualified from donating blood. American Red Cross source The concerns stated are that vCJD can be transferred via transfusion.

This doesn't make sense to me because by the American Red Cross standards entire generations of Europeans could never donate blood.

In your opinion is this policy of disqualification overkill or is it justified? Should my family and I be concerned about someday developing vCJD?

catharticwhoosh

I think the ban was appropriate because the incubation period or prion disease could be decades, and there was no clear knowledge of how much the disease may spread. I personally think the current risk is very low, but I don’t know if it is low enough to change policy. As we learn more about the prion disease mechanism(s) and develop more sensitive ways to detect pathogenic prions in the blood, I’m sure public policy will be impacted. The risk of developing vCJD is so low that it is not worth worrying about it - especially since worrying won't help anyway.

I unfortunately know of this stuff personally. My wife is diagnosed with CJD. I have done what research I can and have a doctor who has actually seen this before, and what I read is not good.

My question is whether or not there are any ongoing clinical research trials at the moment. All that I find are ones that are closed and done (with negative results) or ones that are just collecting data at the moment (San Francisco).

Thanks.

mfarokl

I am sorry for your wife and your family. I don't know of any ongoing trial. I hope one day there will be an effective treatment for this horrible disease. It's a great challenge for biomedical research.

Can cannibalism really cause prion diseases? I recall watching a documentary about a tribe that practices cannibalism and a prion disease had run rampant in their population. How exactly can dead, ingested material turn into prions? Does it have anything to with a dead body's inability to maintain properly folded structures?

Zapfaced

yes. I don't recommend it:-) The disease Kuru was caused by the eating of brain post-mortem. Basically, the prion was already in the brain and was transmitted to mostly women and children. The disease basically went away once the tribe stopped practicing cannibalism. (WC)

Hi Freddy, thank you for doing the AMA! Do you think a prion disease could infect (is that the right word?) a very large percentage of the population without detection?

SavingMyWit

I doubt it because prions are very rare. The only way I see it happening is if the prion would have such a long incubation time on EVERYONE so that many were infected before someone showed symptoms and actions taken - extremely unlikely in my opinion. (WC)

Is there any prospect of a test for the prions which are responsible for mad cow disease (specifically cjd). There is supposedly millions of people in the UK who were exposed to these and at the time there were scare stories that we would have mass outbreaks of CJD on a very long timescale.

http://www.nbcnews.com/id/41406612/ns/health-infectious_diseases/

Spoonshape

Nothing reliable to my knowledge (WC)

Hello Doctor,

I'm currently an aeronautical engineering undergrad at RPI, and hope to see you around campus this upcoming semester. My only question is are we any closer to understanding the preventative measures that could go into treating Alzheimer's disease? Thanks.

dbursch30

I don’t know of anything we can do that is proven to reduce the risk of AD. There are still genetic, epigenetic, and environmental factors that need to be discovered to better understand the risk factors involved. However, if it turns out to be true (as it appears to be the case) that the accumulation of amyloid/aggregates/misfolded proteins plays a role in the onset and progression of AD, then anything we can do to reduce metabolic stress in our system to allow our protein quality control system to work as best as possible, may decrease risk or progression of any aging-related misfolding disease. In the case of AD, it progresses slowly, and therefore delaying its onset or progression would bring major benefits. Hope to see you around at RPI (WC)

I have read that almost half of all patients suffering from Alzheimers may in fact be suffering from Cruetzfeld-Jacobs aka. mad cow disease, however since it can easily contaminate, and since you cannot test of it until after a victim has passed, it goes unnoticed. I have read that the FDA has no guidelines for determining if cows and chickens have prion diseases that are being passed to humans, how accurate do you think that statement is about those ill with Alzheimers, could it be prion disease wrongly diagnosed, and how big of an issue do you think contracting prion disease from eating meat is?

banglainey

I don't think the statement is accurate. The pathological features of AD and CJD are very different. I still

eat meat occasionally, but the more I think about why it may not be good for me as I age, the more I want to become vegetarian, even though the risk of prion disease is extremely low.

If somebody has a bad prion, is there a way to cure him? Are there any drugs or anti-bodies that react differently to correct and wrongly folded proteins?

hawkwings

Unfortunately, there is no cure for prion diseases. (WC)

My grandma died of CJD. IS there any way to tell if it is genetic and whether me or my family is at risk?

Greg_Olden

It is possible to determine if its genetic due to a mutation on the prion gene. I suggest you discuss with family doctor.

Hey there, Freddy! Thank you for your time here.

I was curious about the nature of amyloids -in your work, have you seen any epigenetic factors (physical/mental trauma, for instance) that can majorly influence their formation?

Trentious

This question is outside the scope of my research so I have not seen this; perhaps someone else has. However, if I had to answer it, I would say "yes". Amyloids require not only a protein sequence that is able to access a stable amyloid structure, but the environmental conditions to do so. It is very plausible that epigenetic factors may influence amyloid formation by directly modifying a protein and enhancing its amyloidogenicity, or indirectly by modifying a secondary protein that then interacts and enhances amyloid formation of another protein. (WC)

Thanks for doing this Freddy! I was wondering if you could speak about the association between proteins like tau and head trauma. I am thinking particularly about the case of CTE. How can physical forces (i.e. head trauma) alter protein folding?

afuzzyhaze

Great question, but no one has an answer for it. If I had to guess, I would say that because proteins play a key role in brain structure and function, any brain trauma has the potential for causing damage long-term. Damaged proteins must be repaired or removed. If the brain can't do this well, bad things are likely to happen.

Hi Freddy, thanks for doing this!

What is the likelihood of human transmission to other humans for prion diseases? For example kuru involved eating the brains of others to get infected, and mad cow also involved ingestion of infected meat (and jumped the species barrier) but whats the likelihood (if possible at all?) For humans to transmit prions to each other in day to day life, or via blood transfusions etc?

LilyRex

I would say plausible and certainly possible from the biophysics standpoint. But in practice it seems highly unlikely and there is no precedent.

Thank you for doing this AMA! I had no idea I had any questions about this stuff until I saw the post!

Where do prions actually come from? What are they made of? And what role do they play in the onset of later-in-life diseases? Are there any developing treatments that look particularly promising?

My girlfriend also had a question. She has been working with the elderly for the past six months and took a class on Alzheimer's and learned how the patients can lose sight of certain colors on the spectrum. Her question is, Are any of the misfolded proteins the cause for this change in sight, and if so, what is happening? Is it a physical change or a change in the way the receptors respond to light?

McLovin804

It appears that pathogenic prion formation is a very rare occurance. Prions are made of a specific protein that misfolds and aggregates into a extremely degradation-resistant structure that is able to induce other correctly folded proteins of its kind to misfold.There are no treatment for prion diseases, but fortunately they are rare.

Hey Dr. Freddy, would you argue that prions are undoubtedly the most horrifying microscopic entities known to man? They remind me of Midas.

keyclackwarrior

Can't disagree.

Is there any truth to the article that states oral surgery is a major factor in the spread of prions? It seems the tools used are not cleaned in a way that would kill prions.

Book8

I don't believe it because prions are so extremely rare.

Are there any evidence (or studies) about the effects of prolonged marijuana usage on the misfolded protein accumulation speed in our brain?

Thanks a lot for spending the day answering questions!

radyokafa

Not to my knowledge.

How prevalent is mad cow disease now?

dadoffive

very rare