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REDDIT

PLOS Science Wednesday: Hi reddit, we're Hui-Chen Lu, Yousuf Ali, Hunter Allen and we found that people with the NMNAT2 protein had greater resistance to cognitive decline – Ask Us Anything!

PLOSSCIENCEWEDNESDAY R/SCIENCE

Hi Reddit,
My name is Hui-Chen Lu and I am a Professor at Indiana University Bloomington. My research focuses on how neural circuits wire up during development and how to keep neurons healthy despite various insults and with aging. The majority of neurons in the brains are born prenatally and have to stay healthy throughout our lifespan.
My name is Yousuf Ali and I am an assistant scientist in Dr. Lu's lab. My research focuses on understanding the underlying mechanisms that disrupt cellular homeostasis and serve as a basis of disease in different proteinopathies, specifically Alzheimer's disease and tauopathies.
My name is Hunter Allen and I am a research assistant in the lab of Dr. Hui-Chen Lu at Indiana University Bloomington. I currently head-up operation of our multi-photon microscope as well manage lab IT functions and assist with technical and computing activities such as Matlab, Python, and other programming for data analysis.
My name is Hugo Bellen and I am a Professor at Baylor College of Medicine and a HHMI Investigator. Our research interests include neuronal communication/maintenance and development of scientific tools allowing large scale and efficient scientific discoveries.
We recently published a paper titled "NMNAT2: HSP90 Complex Mediates Proteostasis in Proteinopathies" in PLOS Biology.
NMNAT2, or nicotinamide mononucleotide adenylyl transferase 2, is becoming recognized as a key neuronal maintenance factor. By examining NMNAT2 levels in brains donated by more than 500 elderly people whose cognitive function was tested annually before death, we found higher levels of NMNAT2 in people who had greater resistance to cognitive decline. People with lower NMNAT2 were more likely to suffer from dementia, suggesting that the protein helps preserve neurons related to learning and memory.
NMNAT2 exerts both an enzyme function to protect neurons from stress caused by over-excitation, and a 'chaperone' function to combat the misfolded proteins produced in the brain during aging. Many neurodegenerative disorders are caused by accumulation of "misfolded" proteins that "clump up" in the brain in forms often referred to as "plaques," or "tangles." Using mouse and cell culture models, we found that NMNAT2 act as a molecular chaperone and binds to misfolded proteins to prevent or repair the errors that cause these clumps. Interestingly, its enzymatic function is required to defend against excitotoxicity. Our work here suggests that NMNAT2 uses both its chaperone and enzymatic functions to combat different neuronal insults in a context-dependent manner.
We will be answering your questions at 1pm ET -- Ask Us Anything!

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Do you have any ultra up-to-date practical advice (for detection or prevention) for people in their 20's, 30's, 40's or 50's worrying about old age dementia/Alzheimer's, generally or based on your findings? (I.e., what advice do you yourself follow?)

beorn

Hui-Chen, Yousuf, and Hunter: The need of biomarkers to detect at AD at an early age (hopefully, when disease progression can be slowed or stopped) is an obvious one. Currently a lot of scientific research is ongoing to identify AD biomarkers. The Alzheimer's Association website (http://www.alz.org/research/science/alzheimers_prevention_and_risk.asp) has a good discussion on lifestyle changes and other approaches to decrease AD risk. Because of our preliminary finding that caffeine increases NMNAT2 levels and the epidemiological association between moderate caffeine intact and lower dementia risk, we are all drinking coffee and tea.

Do you have any ultra up-to-date practical advice (for detection or prevention) for people in their 20's, 30's, 40's or 50's worrying about old age dementia/Alzheimer's, generally or based on your findings? (I.e., what advice do you yourself follow?)

beorn

Hui-Chen, Yousuf, and Hunter: "Is it possible to reduce the risk for dementia in later life through

preventative measures?" is a question we all like to ask. The answers to this question are complex and vary quite a bit depending on one's genetics and living environment. Epidemiological studies incorporating a large number of subjects and following them for many years are necessary to uncover this. What we found regarding NMNAT2 is just a beginning. This study points to the importance of neuronal maintenance factors. House-keeping function has not been actively studied despite the fact that majority of neurons in our brains are born before birth and have to stay functional till the end of our life. More efforts on finding out how neurons maintain their health despite all the stresses they are subjected to during aging are needed to find ways to reduce the dementia risk later in life.

There is strong evidence suggesting that caffeine intake via 2-3 cups coffee containing 95–200 mg caffeine or several cups of tea per day reduce the risk of dementia. Our preliminary and unpublished studies find that treating adult mice with caffeine (equivalent to about 3 cups of coffee for a human) can increase NMNAT2 protein levels in the brain. Together, these results suggest that caffeine's beneficial affects on dementia may be by increasing NMNAT2 levels.

Despite the potential cognitive benefits, not everyone can take coffee or tea, especially elderly or people with a history of cardiovascular or high blood pressure problems. We are actively searching for small molecules that modulate NMNAT2 levels either upward or down.

For more details on the benefits of caffeine in reducing dementia, please check into the following links: https://www.washingtonpost.com/national/health-science/caffeine-consumption-in-older-women-seems-to-reduce-risk-of-dementia/2016/10/03/7ae7513c-8714-11e6-92c2-14b64f3d453f_story.html?utm_term=.c300f9fee348 https://www.alzdiscovery.org/cognitive-vitality/ratings/coffee-and-caffeine https://www.alzheimers.org.uk/site/scripts/documents_info.php?documentID=2211&pageNumber=9 https://scholar.google.com/scholar?q=caffeine+AND+dementia&hl=en&as_sdt=0&as_vis=1&oi=scholart&sa=X&ved=0ahUKEwiuuvaAlOLQAhUi_IMKHRU2C1MQgQMIGjAA

So, which cells produce NMNAT2, how can you introduce it into a person therapeutically, and the levels found, were they detected on a sliding scale of strength / concentration levels, if yes, what was the optimum levels ? Nice easy questions to start with. Congrats on your research to date.

OutRunTerminator

Hui-Chen, Yousuf, and Hunter: Based on our studies using mice, we have demonstrated that cortical neurons produce NMNAT2. However, we cannot rule out the possibility that other cells may also express NMNAT2. Several possible strategies can be explored to introduce NMNAT2 into a person. For examples, gene therapy viral vector carrying NMNAT2 or small molecules that increase NMNAT2 levels or stability. Of course, this will require rather extensive drug-discovery efforts. Using human tissue samples acquired from Oregon Brain Bank, we found that NMNAT2 levels in the NDAN group (control subjects who had no dementia but with plaques and tangles similar to Alzheimer's patients) are about 60% of normal levels. In AD groups, the average NMNAT2 level is 30% of control. Based on this finding, we hypothesize that restoring NMNAT2 levels to >60% will be sufficient to protect from dementia.

I understand that the samples of the 500 patients were taken after their death, but were there any lifestyle choices related the higher levels of NMNAT2? Areas where the lived related to pollution? Or would it take more than 500 test points?

Oh.. and thanks for making science fiction real.

PizzaReel

Hui-Chen, Yousuf, and Hunter: All of the subjects in the study lived within a relatively small geographic area, and it isn't possible for us to draw a correlation with air quality or other external factors.

There are so many people doing so much basic research on proteins, especially in neurobiology.

1. Why study this protein? Was it luck, broad spectrum analysis, or is there substantial literature and you guys were the first ones to connect two dots?
2. What types of protein interactions does NMNAT2 do to be neuroprotective? Is it Glutamatergic, GABAergic, calcium related, etc.?
3. How easy is it to purify?
4. Where are NMNAT2 producing neurons located, and is the protein present during development?

Ubiquitous, Mb, Hb, Fb, etc./neural tube, X-somite stage, fetal, etc.?

5. Any correlations with other well-characterized proteins?
6. Next big step you can actually tell me about? (Spare me the bs pls)

Thanks!

SextiusMaximus

Hui-Chen, Yousuf, and Hunter:

- 1) NMNATs have been shown to be neuroprotective by many different groups in different model systems, ranging from Drosophila to mouse models of neurological disorders. A wide range of published work has already established NMNAT2 as an important neuronal protein. Our earlier work has shown that NMNAT2 levels decline quite early in a mouse model of tauopathy, prior to the onset of any behavioral deficits and brain degeneration. Also, we were amazed to observe an improvement in brain degeneration in these mice, when we genetically increased the levels of this protein in diseased neurons. In our recent work, we wanted to understand the mechanisms by which this protective protein was offering such robust improvements.
- 2) In this paper, we discovered a novel chaperone function of NMNAT2 that allows it to reduce aggregated proteins that are likely causes to neuronal death and dysfunction in many of these brain diseases. To function as a chaperone that can refold these proteins, NMNAT2 needs to interact with HSP90. Without this interaction it cannot act to refold these toxic proteins. We are certain that NMNAT2 is present in both glutamatergic neurons and gabaergic neurons based on our unpublished data, whereby loss of this protein can affect both these types of neurons. We also know that NMNAT2 functions in an activity-dependent manner, where its levels can increase when we treat neurons with forskolin that increases cAMP. At the same time, increasing activity in neurons that lack NMNAT2 promotes cell death, showing a requirement of this protein to buffer excitotoxicity in neurons.
- 3) NMNAT2 is a difficult protein to purify from bacteria. Despite its small size, the stability of the protein is very weak and it easily precipitates during the purification process. Currently, we are exploring alternative ways to purify this protein.
- 4) NMNAT2 appears to be present in both excitatory and inhibitory neurons from an early developmental stage in the mouse brain (unpublished data). From preliminary observations, we do not detect any NMNAT2 in neuronal precursors or progenitors but start detecting it in mature neurons, post differentiation. However, others have also shown its levels to increase in neurons as they mature. In the peripheral neurons, NMNAT2 appears to be very important during development and lack of the protein cause neurite outgrowth deficits. NMNAT2 knock out mice die at birth as a result of collapsed diaphragm from denervation.
- 5) We see a strong correlation of NMNAT2 levels with well-characterized presynaptic proteins such as RIM1 alpha and synaptophysin. We are exploring the underlying basis of this correlation.
- 6) Our next big step is understanding how this protein is regulated. We have a manuscript in revision that outlines essential pathways that regulate the abundance of neuronal NMNAT2. We also are studying why this protein is so important for maintaining the integrity of neurons. We are essentially approaching this question through unbiased mass spectrometric approach to identify the protein interactions of NMNAT2. Although increasing NMNAT2 can be therapeutic in proteinopathies such as tauopathies, we have to understand the functions of this protein in neurons especially since it is extremely labile and has a very short half life.

What are the implications of this for my life? How do I decrease my risk of getting dementia later on in life?

mgmfa

Hui-Chen, Yousuf, and Hunter: Epidemiological studies suggest that drinking 2-3 cups of coffee per day decrease your risk for dementia. This may increase NMNAT2 levels based on an ongoing study, that we hope to publish soon. Other well accepted ways to decrease dementia include: Eat a healthy diet, quit smoking, regular exercise, maintain normal body weight, treat high blood pressure, and keep socially engaged.

Is there any relationship between NMNAT2 levels and other risk factors or protective factors for dementia?

Are known risk and protective factors independent or are some of them explained by on an effect on NMNAT2?

leaffall

Hui-Chen, Yousuf, and Hunter: Part of a previous answer might address your question.

There is strong evidence suggesting that caffeine intake via 2-3 cups coffee containing 95–200 mg caffeine or several cups of tea per day reduce the risk of dementia. Our preliminary and unpublished studies find that treating adult mice with caffeine (equivalent to about 3 cups of coffee for a human) can increase NMNAT2 protein levels in the brain. Together, these results suggest that caffeine's beneficial affects on dementia may be by increasing NMNAT2 levels.

Does introducing the enzyme in a person's organism help it retroactively regain neurological stability as the enzyme repairs neurons, improving people already suffering from neurodegeneration associated problems, or does the enzyme merely mitigates damage of future misfolded neurons?

Thanks!

Joltie

Hui-Chen, Yousuf, and Hunter: We don't have answer for this question, especially with regards to humans. In our mouse studies, NMNAT2 can reduce toxic tau species after the decline of NMNAT2 levels and toxic Tau presence. However, the stage we tested in these mice is pre-symptomatic. Based on the negative outcomes from clinical trials using therapeutic interventions to reduce A beta plaques at later stages of AD, it is generally believed that treating early is the key.

So is NMNAT2 part of the standard panel from 23andMe yet?

SWaspMale

Hui-Chen, Yousuf, and Hunter: We wish we had the answer for you. So far, no genetic variant has been identified that affects NMNAT2 levels. Active studies are ongoing.

Our family history is riddled with dementia (noticeably affecting women more than men) but it seems random, skipping generations left and right. Is there any pattern in which this is hereditary passed on, genetically or epi?

AIWsyndrome

Hui-Chen, Yousuf, and Hunter: As you may have guessed, we have no answer for you. It is complicated. You may want to engage a medical geneticist to conduct DNA analysis/sequencing to check into this if your family tree is rather large. Women are more prone to dementia in general.

What can i eat to get higher NMNAT2 levels in my brain?

trumpisnowpresident

Hui-Chen, Yousuf, and Hunter: We would recommend more coffee or tea! :)

For those of us in pharma, what, if any, are the possibilities of using small molecule drugs or biologics to enhance the function of NMNAT2? You write that NMAT2 has the shortest half-life among mammalian NMNATs - is there a particular enzyme that degrades NMNAT2 that could be targeted?

Ratsofat

Hui-Chen, Yousuf, and Hunter: I appreciate your interest and please help us to identify the modulators. Yes, NMNAT2 has rather short half-life. It would be great to increase its stability and potentially provide more neuroprotection. However, the labile nature of NMNAT2 may be critical for its endogenous function. Thus, this may be more complicated than one would like.

(Are these types of questions allowed here? If not, please remove)

Why did you decide to publish in PLoS One? A paper of this caliber could have probably faired well in higher IF journals.

I see you have quite a few grants from different institutions. What's your advice for getting funded so well?

baileycoraline

Hui-Chen, Yousuf, and Hunter: This study was published in PloS Biology (not PLoS One), which is a moderately high impact journal (IF>8). What really matters to us is to deliver our scientific discovery to the public and we believe in open access, the spirit of PLoS journals. One can spend (waste) a lot of time trying to get one's findings into the highest impact factor journals. Getting published in high impact journals is often a random process, determined by editors chasing the next "hot" topic, and is not necessarily a judge of the quality, impact, or significance of the work. The list of funding is the sum of all authors and thus is pretty extensive. The most expensive studies are the human studies. Very general advice to be successful in obtaining funding is to have a solid hypothesis for important questions, clear feasibility of the project, and a track record for getting tasks done with scientific rigors.

Do you know why certain people have higher levels of this protein? Is it a genetic variant? Or is it a correlation of another process rather than a causative factor in dementia?

Zoeismine

Hui-Chen, Yousuf, and Hunter: We wish we had the answer for you. So far, no genetic variant has been identified that affects NMNAT2 levels. Active studies are ongoing.

Is there a correlation found in different blood types?

arieous

Hui-Chen, Yousuf, and Hunter: Dementia is a complicated aging related disease. NMNAT2 level changes can be caused by a variety of factors. So far, we have not seen a clear correlation of NMNAT2 levels with different blood types.

If this protein directly acts as a chaperone protein which helps against the mis-folding, can we use this directly as a therapeutic agent?

If not, what are potential therapeutic outcomes of this research?

MonteDoa

Hui-Chen, Yousuf, and Hunter: Thanks for a great question! In our recent work, we have shown that this protein works in misfolding protein aggregates, which are typical of many neurological disorders such as AD, PD, HD etc. The fact that this protein is already present at high levels in neurons positions it to serve as a first line of defense in these diseases collectively termed proteinopathies. At the same time, we and others have shown an important neuronal maintenance function of NMNAT2 and the two functions of the protein, enzyme and chaperone, are mutually exclusive and are utilized in a context-dependent manner. Hence, increasing the overall abundance of the protein can be therapeutically relevant. In essence, molecules that upregulate the protein can target both the enzyme and the chaperone functions of the protein and can be applicable in a variety of disorders.

Is it ever practical to collaborate directly with cognitive psychologists as you conduct biological research such as this, or is your research conducted mostly independently from the research of other related disciplines? If so, how does collaboration take place, broadly speaking?

(If not, sorry!)

I ask as an undergrad that is considering pursuing the study of cognition and that loves to learn from any subject, but is unsure about where his place should be as a researcher.

jasomayo

Hui-Chen, Yousuf, and Hunter: We definitely would like to collaborate with cognitive psychologists to explore further. Our study is just the beginning and there is definitely a lot to work on after this. Effective collaboration usually takes place when two or more laboratories find common interests and

have expertise in different and complementary disciplines. Of course, research funding has to be available to sponsor the research activity and frequent open discussions among all the researchers involved are also key to a successful collaboration.

Has there been any attempt to use CRISPR and "paste" the gene responsible for encoding NMNAT2 into an animal model for any neurodegenerative diseases? Also thanks for your contributions to the field.

Psilystudent

Hui-Chen, Yousuf, and Hunter: Thanks for recognizing our efforts. The NMNAT2 gene itself is normal in the tauopathy mouse model we examined. The reduction of NMNAT2 levels is likely to be transcriptional and may caused by reduced CREB activity as we have demonstrated in our previous publication. https://www.ncbi.nlm.nih.gov/pubmed/22027994

Hi, do you know how the protein interacts with apoe status? Does it afford a lower risk of cognitive decline in apoe e4 carriers or even lower risk in apoe e2 carriers?

apricotpajamas

Hui-Chen, Yousuf, and Hunter: We have explored this and found no relationship between NMNAT2 levels and Apo e genotypes with RNAseq data. However, we have not examined the protein-protein interactions.

Congratulations on your findings! I am curious if you observed any relationship between levels of NMNAT2 and Dopamine or Serotonin? I ask because both neurotransmitter are critical in cognitive function and abnormalities in neuronal concentration can lead to reduced cognitive abilities or in some cases, generation of reactive oxygen species which can accelerate the rate of neurodegeneration. Did you also observe an elevated levels of NADH in some of these samples right (NAD+ functions to promote cell survival if I remember correctly)

Also have you had a chance to look at Anthony DiAntonio's research regarding using NMNAT enzymes and reversing the JNK pathway to regenerate mechanically lesioned nerves? Really fun stuff.

Congrats on your success and happy sciencing! Cheers!

zeeuqsze

Hui-Chen, Yousuf, and Hunter: Thanks! Dr. DiAntonio and his group have made great contributions to NMNATs field. We have examined the impacts of serotonin and dopamine signaling on NMNAT2 levels in our preliminary studies using pharmacological reagents. So far, we have not observed any significant changes.

Is it possible to introduce NMNAT2 to people who have low levels of it, especially those who are presenting early signs of Alzheimer's or even help in rehabilitation of stroke patients?

rescure

Hui-Chen, Yousuf, and Hunter: We and others are actively working on this, so stay tuned!

I would like to know if there are any promising external applications that can help stave off brain degeneration, regardless of the protein you are given at birth, such as foods/supplements like hericium erinaceus (Lion's Mane) and fish oil. Aside from and in addition to cardiovascular exercise. Thank you very much for your work. Brain health is a new field of science I have recently grown extremely interested in.

jhunta

Hui-Chen, Yousuf, and Hunter: The effect of natural compounds on NMNAT2 levels has yet to be determined. We hope that our work will encourage other scientists to take on this investigation.

Is there a specific kind of decline this is related to such Alzheimers, Dementia, or whatever the name

for the getting old one is?

TheInsaneWombat

Hui-Chen, Yousuf, and Hunter: Our focus was on dementia and Alzheimer's diseases, however, previous micro-array studies also indicated a decrease in NMNAT2 levels in brains of patients with Parkinson's disease, Huntington's disease, and fronto-temporal dementia.

This has parallels to the Sinclair lab work on NAD+ precursors, sirtuin signalling, and aging. Do you think that your work may suggest further work with NAD+ precursors (niacin, nicotinamide riboside etc) or CD38 and Parp-1 inhibitors (major NAD+ consumers) inhibitors for dementia prevention?

BTW, it very important to get at least the RDA for niacin (F: 14 mg, M: 16 mg), as lower levels are associated with faster decline: Morris et al. 2004. Dietary niacin and the risk of incident Alzheimer's disease and of cognitive decline. Journal of Neurology, Neurosurgery & Psychiatry, 75(8), pp.1093-1099.

Sanpaku

Hui-Chen, Yousuf, and Hunter: Dr. Sinclair's work on the role of NAD in aging helps us appreciate the importance of NAD in the normal aging process. With respect to NMNAT2, we show that both the enzyme and chaperone function of this protein performs essential neuroprotective functions in a context-dependent manner. For example, the NAD synthesis activity of NMNAT2 is required to reduce excitotoxicity in developing cortical neurons, while its chaperone function is critical to deal with protein stress.

Thanks for doing this AMA. Your patient data on NMNAT2 is interesting, however my concern is related to the mechanism by which NMNAT2 is operating. HSP90 interacts with *almost* every cytosolic protein- in fact, a pubmed search reveals over 9000 HSP90 related publications-suggesting YourFavoriteProtein:HSP90 complexes may provide less or no real mechanistic insight. There are hundreds of low to medium impact publications that basically show HSP90 affects almost every pathway the lead authors are investigating. Thus HSPs may have more of a global rather than any specific role.

pighalf

Hui-Chen, Yousuf, and Hunter: Two cell-free assays we used to examine HSP90:NMNAT2 interactions employed recombinant proteins and tested the importance of this complex formation. We found that HSP90 is required for NMNAT2's refoldase activity to reduce citrate synthase aggregates. NMNAT2's ATPase activity is only present when HSP90 binds to it. Thus, the interaction between NMNAT2 and HSP90 is specific for these actions. We certainly appreciate the large numbers of HSP90 partners. However, we found that HSP90:NMNAT2 interactions mainly occur when there are protein aggregates. For example, in wildtype brains, immunoprecipitation using HSP90 antibody doesn't pull down much NMNAT2. In contrast, in tauopathy brains, a lot of NMNAT2 was pulled down by HSP90 antibody. These observations led us to hypothesize that HSP90 interacts with different protein partners depending on its task. NMNAT2's recruitment of HSP90 may reduce HSP90's inhibition on HSF transcription or its other actions.

Do you have any reason why it lowers risk? Does it have any effect on plaques/tangles?

age_of_rationalism

Hui-Chen, Yousuf, and Hunter: Based on the human data, NMNAT2 levels are negatively correlated with plaque and tangle pathology. In addition, we found that NMNAT2 associated with the portion of the brain proteins that contained these aggregated proteins.

Hi! Thanks for doing an AMA. I got excited because I'm studying AD at my Uni, have personal attachments to the disease, and you articulated your research very well/simply.

1. We learn about the well known things like beta amyloid, tau, and some of their mediators like advanced glycation end products, but where do you see your findings, specifically regarding NMNAT2, directing future Alzheimer's research?
2. How does the amount of NMNAT2 vary person to person? (I.e. Is it genetic differences?)

3. Are there lifestyle choices than can raise/lower the amount of NMNAT2?
4. Theoretically, would it be possible to exogenously add or induce increased production of NMNAT2 in vivo while someone is still alive?
5. And lastly, similar to my first question. What are the implications of your study to the Alz community (non-academically)?

Thank you again for your time. It's very exciting to come across topics learned from school.

HarambeDied4Us

Hui-Chen, Yousuf, and Hunter: These are excellent questions. I believe the answers to your questions are in our responses above. Reply if you need something clarified, and we'll do our best to help.

Thank you for this AMA and congratulations for your findings !

- Do you know which transcription factor and gene are responsible for the synthesis of NMNAT2 ?
- Have you tried DNA amplification or overexpression ? Would there be negative effects when amplifying/overexpressing NMNAT2 ?
- What will be the next step in your research concerning NMNAT2 ?

Wishing you success !

CoffeeLaxative

Hui-Chen, Yousuf, and Hunter:

- 1) Our previous work has shown a role of cyclic AMP/CREB transcription factor in regulating NMNAT2 transcription.
- 2) In adult wild-type mice, NMNAT2 overexpression in the brain does not cause any obvious negative effects.
- 3) We hope to understand the endogenous role of NMNAT2 in healthy neurons.

So if we say, that the stuff you fund out is awesome, how can it be used in medical terms? Would you be able to put it inside of drinks and other food, so you can drink Dementia away?

RayFritschairadar

Hui-Chen, Yousuf, and Hunter: Thanks for giving us "Awesome" note. All we can suggest (based on epidemiological studies) at this moment is drinking 2-3 cups of coffee per day if there is no risk for you to consume that much caffeine.

How do you see these findings change the way we understand and treat aging and memory retention in the future?

derekzimm

Hui-Chen, Yousuf, and Hunter: Our study points to the potential importance of neuronal maintenance factors. Until recently, house-keeping functions have not been actively studied, despite the fact that the majority of neurons in our brains are born before birth and have to stay functional till the end of our life. More efforts on finding out how neurons maintain their health despite all the stresses they are subjected to during aging are needed to find ways to reduce neurodegeneration and the risk for dementia later in life. Neurons often have very long and thin processes connected to their pre- or post-synaptic partners. Proteins synthesized in the cell body will need to be transmitted far distances, to where synaptic connections are located. Neurotransmitter release, occurring in under a millisecond upon the arrival of an action potential to the terminal involves a massive number of proteins changing their conformations. Keeping right balance in protein homeostasis in various parts of the neuron is a constant challenge. The accumulation of misformed/misfolded proteins during aging will undoubtedly impair neuronal function and may lead to reduced memory retention.

Are there any genetic markers for this protein? That is, can people be genetic screened for the presence of this protein?

gatz

Hui-Chen, Yousuf, and Hunter: Not yet. It is not clear whether there is genetic component for NMNAT2 levels.

When will I be able to go into a CRISPR-CAS9 clinic and get them to add this to my DNA?

RedErin

Hui-Chen, Yousuf, and Hunter: Genetic lack of this gene is lethal (at least in mice), so you shouldn't need to add it.

I'm in my first year of pharmacy school so we are going through various enzymes and their functions. NAT is an enzyme involved in Amino Acid conjugation, and I guess my question is NMNAT have the same function as a regular old NAT enzyme? Thanks!

cmg0047

Hui-Chen, Yousuf, and Hunter: The protein we are studying here is NMNAT, which are essential enzymes that catalyze the condensation of ATP to nicotinamide mononucleotide to produce NAD or nicotinamide adenine dinucleotide. NAD is an essential cofactor for many biological processes. The enzyme you mention NAT are N-Acyltransferases, responsible for conjugating acetyl groups to the N-terminal of proteins, regulating the functions of these proteins. NMNAT2 is not the same as these enzymes.

I read in a scientific paper about protein folding that protein mis-folding can actually lead to neuro-degenerative diseases. Does this protein have any sort of relation with that?

CincinnatusNovus

Hui-Chen, Yousuf, and Hunter: Protein aggregation has been linked to many neurodegenerative brain diseases such as Alzheimer's disease (plaques and tangles), Parkinson's Disease (alpha synuclein aggregation), Huntington's Disease (huntingtin protein aggregation). These aggregates serve as pathological hallmarks of each of these diseases. Our work shows that NMNAT2 can function as a protective protein, called a chaperone, which can bind to such aggregated toxic proteins and allow them to be refolded. At the same time, NMNAT2 can also bind to such proteins that are prone to aggregate and prevent this aggregation process. Hence, as a chaperone, NMNAT2 can reduce protein aggregation burden and protect neurons from dying from such proteotoxicity.

Could this information be used to prevent cognitive decline, or do we use it to find out who is at risk?

madpoontang

Hui-Chen, Yousuf, and Hunter: The identification of NMNAT2 as a key neuronal maintenance factor in preserving cognitive function qualifies NMNAT2 as a viable target for therapeutic intervention.

What do you think about the P7C3 class of NAMPT modulators that Calico (Google/Alphabet) own? Do you think they have an advantage over selectively modulating various NMNATs?

CLICK_BILE

Hui-Chen, Yousuf, and Hunter: Thanks for a great question. Google's venture biotech company, Calico, in collaboration with its pharmaceutical partner AbbVie, has acquired the rights to a class of drugs labeled "P7C3". These drugs can increase cellular NAD levels by acting upstream of NMNAT2 (http://sage.buckinstitute.org/breaking-nad/). This drug selectively binds to and activates NAMPT, an enzyme upstream of NMNATs and increases the levels of NMN, which is a substrate for NMNATs, which convert NMN to NAD. However, if NMNAT2 is reduced, increasing NMN by P7C3 may be insufficient to increase NAD in where is needed.

With respect to NMNAT2, we show that its chaperone function may protect against proteinopathies, such as AD. In this regard, even if P7C3 increases NAD levels, this may not be effective in clearing the aggregated proteins responsible for neuronal stress and ultimate demise.

How would one determine if they have this protein?

Is artificial administration of this protein potentially useful as a preventative measure? A cure?

MeltedTwix

Hui-Chen, Yousuf, and Hunter: As this protein is necessary for maintaining healthy neurons, all human have this gene. Our study indicated that reduction in levels of this protein is correlated with dementia outcome.

Has this protein been found as a result of data mining or were there prior accidental findings that let to this result? If so, for what reason was it thought to have a predictive link? Thanks

NoodleScience3

Hui-Chen, Yousuf, and Hunter: NMNATs have been shown to be neuroprotective by many different groups in different model systems, ranging from Drosophila to mouse models of neurological disorders. A wide range of published work has already established NMNAT2 as an important neuronal protein. Our earlier work has shown that NMNAT2 levels decline quite early in a mouse model of tauopathy, prior to the onset of any behavioral deficits and brain degeneration. Also, we were amazed to observe an improvement in brain degeneration in these mice, when we genetically increased the levels of this protein in diseased neurons. In our recent work, we wanted to understand the mechanisms by which this protective protein was offering such robust improvements.

Is there a genetic component to the NMNAT2 protein that could be identified by a 23&Me or Promethease type situation?

seraph582

Hui-Chen, Yousuf, and Hunter: So far, no NMNAT2 mutations/polymorphisms has been identified as a risk factor for dementia. It remains to be answered why NMNAT2 levels are heterogeneous in human population.

Has this protein been looked at in rodent models of neurodegeneration? If so, what was found compared to WT rodents

grabthembythe

Hui-Chen, Yousuf, and Hunter: We have two publications looking at NMNAT2's effect in rodent models of neurodegeneration.