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Science AMA Series: We are researchers Elizabeth Blackburn (cell biologist) and Elissa Epel (health psychologist). We have been studying the relationships between telomeres/telomerase with psychological and behavioral factors, and with disease.

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Hello Drs. Blackburn and Epel, and thank you for doing this AMA.

The big questions in aging research are typically: 1) *why do we age?* and 2) *can we do anything about it?*

In this context, I have always had a hard time getting too excited about telomeres.

In humans, multiple studies have tried to link telomere length to aging, mortality and other similar outcomes. While some studies have found minor associations, many have not. Similarly, telomere length at birth varies dramatically across haplotypes, without any seemingly strong association to longevity. You and others have described how a variety of environmental and genetic insults an lead to telomere shortening, but these very same insults often wreak havoc on other pathways commonly associated with aging as well (metabolism, circadian rhythm etc.).

And when it comes to “targeting” telomere length, I think the evidence and biological rationale that this may work is equally equivocal. While some animal models have shown that telomerase activation (gene therapy, transgenics etc.) can extend lifespan, it is unclear that this has any translational path forward. There just seem to be too many questions about how to do it: gene therapy with an oncogene (the telomerase subunits) is likely to scare clinicians, what would the endpoints of any such clinical trial be, what cell types have to be transduced and at what efficiency to see a benefit etc. Similarly, telomerase inhibitors (i.e. Imetelstat) have really struggled to put up results in the clinic.

So with all of this in mind, I’d love to return to those first two questions (why do we age and what can we do about it):

- In the next ten years, what are the critical experiments and readouts that you would want to see to be able to say that telomere shortening is a key driver of normal aging in humans?
- If you think that telomere shortening is a key driver of aging, do you think there is a path forward for therapeutically slowing or reversing the process in humans?

SirT6

(Liz) First, let's address mortality. There are some important studies to address your question that people may not be aware of. I think you'll find these interesting: Some updates on the connection between telomeres and mortality: Rode et al Rode et al (2015) J Natl Cancer Inst. PMID: 25862531 DOI: 10.1093/jnci/djv074

studied over 64,000 people and found telomere shortness predicted increased subsequent mortality on follow up for a median of 7 years, after the average telomere length in leukocytes was measured. To cite their abstract: "Decreasing telomere length deciles were associated with increasing all-cause mortality (P(trend) = 2*10(-15)). The multivariable-adjusted hazard ratio of all-cause mortality was 1.40 (95% confidence interval [CI] = 1.25 to 1.57) for individuals in the shortest vs the longest decile. Results were similar for cancer mortality and cardiovascular mortality."

Whooley and colleagues PLoS One on October 26, 2016 http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0160748

found that, in middle-aged/elderly heart disease patients (608 men and women with stable cardiovascular disease), the rate of telomere change over a 5 year period predicted mortality, during the subsequent 4 years. Change in telomere length was inversely predictive of all-cause mortality. Controlling for multiple other factors that can affect mortality, the researchers found that those who experienced telomere shortening were 32% more likely to die during the subsequent four years than those whose telomeres stayed the same, and those who experienced telomere lengthening were 56% less likely to die. I'll try to get back to your other questions.

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SirT6

I understand your frustration about the lack of causal studies in humans. Telomere length is challenging to study experimentally, because laboratory animal models are not usually relevant to humans. This is because humans have such long lifespans compared with most animal models. Telomere shortening is not the cause of rodent death and lifespan limitation, whereas converging evidence in humans indicates that it is is one pathway contributing to both earlier diseases, and naturally relatedly, to earlier mortality in humans. Telomere shortening contributes to cellular senescence pathways, and generation and persistence of senescence cells do tie in to aging in experimental mice model systems, but it is not caused by telomeres shortening in mice, whereas it is in human cells. However, the good news is that to help here, we have ever-increasing human genetics research (Mendelian randomization studies - please see my other answers elsewhere in this Reddit conversation). Such studies are increasingly helping to clarify what is the magnitude of telomere shortening role in humans. See Codd et al 2013 as an excellent example (Codd et al, 2013) Identification of seven loci affecting mean telomere length and their association with disease. Nat Genet. PMID: 23535734 PMCID: PMC4006270 DOI: 10.1038/ng.2528

If poor sleep, diet and stress are associated with shorter telemeres, is that because they cause them to shorten or does having short telemeres cause the stress and poor diet and sleep?

rainbowsloth72

(Elissa). Good question! There are many observational studies on the links between telomere length with these lifestyle factors, and this leaves open the possibility that people with short telomeres may be more vulnerable to these poor lifestyle habits. We cannot rule out that possibility. While not impossible, it is however hard to see mechanistically why having short telomeres would lead to poor health behaviors. It is more likely that offspring could inherit BOTH short telomeres and a load of other vulnerabilities to poor health and health behaviors, and so the two would be correlated (but not in a causal way). These are important questions that can be answered in the future with large longitudinal cohorts that have genetics, telomere length, and health. In terms of whether lifestyle is having an effect on telomeres, there are a growing number of intervention studies showing effects of lifestyle and/or stress reduction on short term changes in telomerase or telomere length. Thus the weight of current evidence suggests the arrow is from behavior to telomeres. But we should not rule out the other possibility as it could be somewhat bidirectional. (And i want to add that depression may be a more bidirectional story, looks like short telomeres can precede depression)

Do you think that some people have an implicit recognition of telomere length that results in an explicit predictive feeling of life expectancy? That is, are they the older adults that have feelings or a strong sense that their time is coming (so to speak)? (In the absence of other disease processes of course)

And has telomere length and suicidal ideation ever been studied? I certainly do not mean to downplay other factors contributing to this, but this follows from the idea that implicit recognition of telomere length could then drives conscious states and perceptions.

Thanks so much for doing this Q and A!!

taliquest

(Elissa) This is a very interesting question and I am sorry I don't know the answer. It has not been studied but i suppose it could be: One could measure TL, ask people their explicit beliefs about life expectancy and TL (and I don't know how you'd measure implicit beliefs about TL but there are social psych methods for that). The big problem with studying a question like this is that at least in people

over 50 there can be all sorts of health correlates with short telomeres (obesity, poor lifestyle, hypertension) and those would shape beliefs about TL and about life expectancy. Too many confounds.

Hello Dr. Blackburn and Dr. Epel,

Could you please briefly expand on the role of telomerase/telomeres on the vitality of the organism as a whole versus an individual cell?

royfresh

(Liz) The clinical human genetics of rare Mendelian mutations in humans (now studied in hundreds of individuals) in known telomere maintenance genes have been very helpful here to answer your question for humans. In short, having sufficient telomere maintenance is vital for humans. And in more detail: If a person has the misfortune to inherit a rare mutation causing half the telomerase level / reduced telomere maintenance, this is the list of the ranges of clinical outcomes (which are often seen clustered in in an individual patient, and their family members with the same mutation):

Early death

Cancers (hematologic, squamous cell, gut): account for 10% of deaths in these patients

Immune loss (major mortality reason is through succumbing to infections)

Pulmonary fibrosis

Liver Cirrhosis

Diabetes risk high

Neuropsychychiatric conditions

Cardiovascular conditions

Osteoporosis

These occur even if you inherit only one copy of such a mutated gene (with the same gene from the other parent being normal). Furthermore, their overly short telomeres get inherited from one generation to the next - grandparents to parent to child - getting abnormally shorter with each generation, and the diseases and conditions correspondingly worsening with the generations. Such (fortunately rare, but highly informative) human mutations in patients have been documented in well-studied genes whose products are known to be largely or completely dedicated to telomere functions For the aficionados, here is the list of known genes in which this has been clearly documented in humans: Telomerase genes: hTERC, hTERT, DKC1,NOP10, NHP2, WRAP53 or Telomere protein genes: TINF2, RTEL1, POT1, CTC1, TPP1

PhD student from across the road from Salk here (Sanford Consortium for Regenerative Medicine). I have two questions: what is know (or what do Drs. Blackburn and Epel speculate) about how autophagy affects telomere maintenance or vise versa? Second, what are your thoughts on Belmonte's recent paper about short, cyclic whole organism induction of Yamanaka factors (http://www.cell.com/cell/pdf/S0092-8674(16)31664-6.pdf) ? How do you think this work contributes to future aging research? Thanks for doing this AMA!

crushinrussian

(Liz) Good and interesting question but out of the scope of this particular Reddit conversation. (Hope that this very fascinating approach you refer to will become a topic of its own Reddit conversation)

Thanks for doing this AMA. What did you learn about communicating science to the public in the course of writing and promoting The Telomere Effect?

wesman9010

This is a great question. It is most definitely challenging and a strain but so important for scientists to be sharing with the public. The public is interested in knowing a fuller story than the soundbites they get in media. We feel strongly about communicating the helpful messages of research to the public, and often that means moving forward once enough converging data form different approaches and studies have accumulated. Of course there is a strain in that because we rarely have certainty, can rarely convey all of the complexity, the nuances and the disclaimers in writing to the general public. But it's important to do the best we can as honestly as we can. So we have written a book for the general public about telomere biology in humans, and how we can act on that knowledge accumulated over the past few decades. It is called The Telomere Effect. While explaining the science we also are always trying to point out correlation vs. causal evidence when we can. We hope our our scientific specialist colleagues will forgive us for at-times, simple statements, and for things we will end up being wrong on. (From Elissa & Liz)

Can you predict (with some probability) how long I will live based on my average telomere length? Can an insurance company base my rates on it?

Harry_Covair

(Liz) Please see my reply to Sirt6. Sorry I don't have the knowledge to give an answer regarding your insurance question.

Can you predict (with some probability) how long I will live based on my average telomere length? Can an insurance company base my rates on it?

Harry_Covair

(Elissa) The studies of telomere length predicting mortality is, as you know, based on statistical probability, usually with small effects in large samples (Telomere length is a reliable predictor of diseases of aging, as shown by meta-analyses, thus a good predictor of healthspan but not so much of lifespan). So for an individual, I believe it would not carry meaningful predictive power unless someone was extremely short in telomere length. Now on to the insurance question! (I have thought about this with concern for some time) With the increase in personal telomere testing, it is possible that it may eventually be used as a routine biomarker in healthcare, and then it is possible that insurance companies would become interested in it. This is unlikely since it is a weak predictor of actual longevity (lifespan vs diseasespan). Here's the troubling part: If insurance companies DO end up using telomere length, this would be discriminatory, because telomeres tend to be shorter in people with lower education or extreme poverty.

I'm seeing a lot more information out there surrounding the relationship between diet and telomere length, particularly glucose and fasting. Have you done any research on the effect(s) of a grain/sugar-free diet and telomere length, or the effect(s) of fasting, whether it be intermittent or otherwise? Thanks,

fascinating stuff!

rusHmatic

(Elissa) I agree this is a very interesting area, and still largely living in the correlational realm. However, you point out great ideas that are feasible for human intervention studies. These are important questions that could be addressed with well designed trials (starting with small proof of concept studies that determine the necessary parameters --dose and duration). I am going to make some methodological comments in case they are helpful to anyone considering interventions. One thing to be concerned about is duration of change: How long does it take for a diet change to lad to telomere length change, is the change dynamic, how long does the change last for? When studied in short periods of months or years, telomere length may oscillate. We've seen hints in that weight loss might lead to acute shortening and then lengthening. So this is a complicated area with few benchmarks/standards. In future studies I would recommend measuring telomere length in both buccal cells and blood cells (granulocytes and PBMCs) because then we at least can look at change in cell types not just mixed cells.

What are your thoughts on nutraceuticals (like TA-65) which increase telomerase activity? Should I be taking them to protect myself from telomere errosion? Are they maybe better suited for an older population?

QueenofDrogo

(Elissa) I don't have a good answer, because there are too few trials in humans. The main consideration is that increasing telomerase too much could potentially put one at risk for certain cancers. It would be more reassuring to see studies on long term use (more than a year), because cancer can develop slowly over years. It will also be important and very helpful to have studies on these supplements performed by researchers with no relationships to the companies selling these (i.e., no conflicts of interest).

Do you think immune stem cell aging may be the limiting factor for human aging?

(See http://www.nature.com/nrm/journal/v8/n9/full/nrm2241.html)

jbsinger

Immune aging is clearly one of the important pathways in aging in humans, but it is hard to say what's the limiting factor

Hello,

This question is unrelated to the topic, but I figured that you would know how to answer :)

I am a freshman in university who loves genetics and loves research, but finding and applying to labs has proven to be a pretty daunting task. Can you offer any tips on applying to labs and maximizing my chances of receiving an offer to help with their research?

Thanks for the help,

selectyour

Getting a foot in the door can be hard. I am not a basic scientist so take this with a grain of salt: Choose a lab who's work you are most interested in, read some of the papers. Send a very tailored cover letter,

show your knowledge with at least a few sentences, to show you are invested in the area (or method). Try to meet some students currently in the lab to learn about it. Try to get an informational interview with the lab supervisor or head of lab.

Have you identified evidence/signals for further study of activities or environmental factors that protect telomere length? Particularly what were the most promising of these factors?

AA_2011

(Elissa) The epidemiological literature shows many correlations with behavioral factors and stress, and there is an emerging body of intervention studies that suggest improvements over at least several months may help with telomere maintenance (either higher telomerase or telomere stability). There is a lot of potential knowledge to be gained by adding measures of telomere length in different cells types, over time, to already planned intervention studies that will follow people over years. We still don't know if short term changes are maintained, and if changes in telomere stability actually translate into improvements in health or healthspan because we need intervention studies with long term follow up. Liz earlier mentioned above, Mary Whooley's 2016 study where telomere lengthening over 5 years reduced odds of mortality. This is very interesting, but observational. There are many important questions yet to be answered and intervention studies offer a great way to indirectly understand/infer causal pathways in humans. (Also, see my points about methodology of interventions to RusHmatic above)

What are some of the neurological effects caused shortend telomeres you've observed ? And any corollaries with psychological disorders?

Zealousneutrophil

(Liz) Yes, there are associations. Here are a few examples: 1. This genetic study suggests causality Genes and Alzheimers (Zhan et al, 2015) Telomere Length Shortening and Alzheimer Disease—A Mendelian Randomization Study Yiqiang Zhan, MD1; Ci Song, PhD1; Robert Karlsson, PhD1; et al JAMA Neurol. 2015;72(10):1202-1203. doi:10.1001/jamaneurol.2015.1513 To cite the authors' abstract: "In summary, our study provided evidence for a causal relationship between TL and AD. Further elucidation of this association could provide insights into the physiological roles of telomeres in AD pathogenesis." 2. Please see this very interesting paper from Sharon Savage and collaborators in patients with inherited telomere disorders caused by mutations in a telomerase or telomere maintenance gene: Neuropsychiatric Conditions among Patients with Dyskeratosis Congenita: A Link with Telomere Biology? Psychosomatics. 2012 May; 53(3): 230–235. PMCID: PMC3348420 NIHMSID: NIHMS327890 3. depression has been linked to short telomeres, with most of the data indicating that there is a "dose response" in the direction of depression duration and severity being linked to shorter telomeres. Verhoeven et al Major depressive disorder and accelerated cellular aging: results from a large psychiatric cohort study. Molecular Psychiatry (2014) 19, 895–901; doi:10.1038/mp.2013.151; published online 12 November 2013

Is there a real possibility of reducing telomere degradation in the near future?

GreenMonster81

(Elissa) In terms of lifestyle pathways, see my comments above. In terms of pharmaceuticals, the field is in an early stage.

Is there a philosophical concern with the pursuit of extending natural life beyond what our planet can support? Class distinctions - the wealthy get to live while the poor die young?

ieswideopen

(Elissa) Yes. We don't have the levers for extreme longevity but if we did, it would put too much burden on the environment. We do know what extends healthspan, the years of living disease free (which in turn can extend lifespan toward one hundred) and this would reduce medical costs, human suffering (and likely the burden on the environment) and this is should be our goal.

What are the prevailing theories as to the main mechanism by which experiential stress downregulates telomerase gene expression? (How might stress hormones lead to long term modulation of telomerase gene expression?)

PS - I use your papers and Youtube videos in my genetics class. Thank you both for your personality-rich contributions.

High_Point_Genetics

(Elissa) Sounds like you know this but Rita Effros at UCLA (Choi et al, 2008, Brain Behavior and Immunity) has done some of the only in vitro mechanistic work in this area. She has found that cortisol exposure dampens telomerase activity in PBMCs. This area is ripe for in vitro work to further examine mechanisms (kinetics, is there an increase then decrease in telomerase) and other pathways (other types of stress hormones, growth factors, changes in oxidative stress, etc). Wish we knew more here!