DOWNLOAD PDF TELOMERES AND SENESCENCE MARIA BLASCO AND MIKE KHAN

Chapter 1 : The Molecular Biology of Cancer : Michael Khan :

Telomeres and Senescence: Maria Blasco & Mike Khan (Spanish National Cancer Center, Madrid; University of Warwick). Genetic Instability, Chromosomes, and Repair: Stella Pelengaris & Mike Khan (both University of Warwick).

In most cells, the number of telomeric repeats is reduced with each cell division. If telomeres are ever completely lost, the exposed chromosome ends are recognized as damaged DNA, activating a DNA damage response that can eventually lead to senescence or apoptosis. The rare cell that escapes these fates risks developing chromosomal aberrations or genomic instability and becoming cancerous 1. Her career took off as well, and her work has been at the leading edge of the field ever since. I think I always had a love for science generally, even as a child. I had a chemistry set growing up, and I loved to play with it. When I was in University, the topics that interested me most were cancer and aging. She worked on the bacteriophage DNA polymerase Phi29 and on the end-replication problem, which concerns how you copy DNA at the very end of a linear strand. The genes that make up the mammalian telomerase had not yet been identified, so there was a lot of room for discovery in the field. My project was to try to isolate one of the telomerase genes and then make a knockout mouse lacking telomerase activity. I had to take a course on mouse embryology. Was being in Cold Spring Harborâ€"in a different countryâ€"a big change for you, as well? Professionally, yes it was. Most of the people there were postdocs, and it was a competitive environmentâ€"everyone wanted to succeed, to get a job as an independent researcher somewhere. You had the feeling that you were in a place that was making a big impact, where you could learn many things, and that, if you were successful, it would help you in the rest of your career. What things did you learn there that you think have served you best? I think an important thing I learned is that European scientists lack a little bit of the self-confidence that American scientists have. Americans have a different attitude toward science and toward their careers; they set their goals much higher. You need to have the confidence to ask vital questions. I had always planned on coming back to Spain. I had some job offers in the US, but in the end I got a very good position in Madrid, so I decided to start my independent career there. I got a civil service position at the Spanish National Biotechnology Center. For a position like that, you take an exam, and if you pass then you can be hired by the government as a civil servant. My department had plenty of money, so I had a lot of space, the ability to hire people, and so on. It was very easy to get a lot done in a short time. I did enjoy my time in the States, and of course I go back every few years for meetings and so on, and I hope I will someday get to go back for a sabbatical. But I think it was a good decision to return to Spain. I have done the research I wanted to do, and I also wanted to give back to my country. I was recruited here by the director of CNIO, when they were just building the center. Mice overexpressing telomerase TERT age more slowly than normal mice. My laboratory has always focused on trying to understand the role of telomeres and telomerase in cancer and aging. Our main tools in our work have been various mouse models. First we studied a telomerase-deficient mouse, which showed us both that telomere loss can cause aging and also that telomeres act primarily as a tumor-suppressing mechanism. In other studies we showed that short telomeres could interfere with the normal repair of lesions in the genome. We also generated telomerase-overexpressing mice, through which we demonstrated one of the most significant contributions my laboratory has made: That was really the first time it was shown that telomerase has anti-aging activity in a mammal. And, of course, we have also been using mice to try to understand the role of telomerase in cancer. If you delay this telomere shortening, you can delay aging. On the other hand, if you accelerate telomere shortening, you can accelerate aging. This is particularly relevant at the level of the stem cell because stem cells with dysfunctional telomeres are not able to mobilize into tissues. Induced pluripotency is a technology that allows you to convert a differentiated cell back into an embryonic stem cellâ€"like state. It would be interesting to find out which factors are important for this rejuvenation of the telomeres because they could be important targets in cancer and aging. Telomeres green cap the ends of chromosomes blue. We started by being interested in DNA repair proteins that are also bound

to telomeresâ€”Ku and DNA-Pk, for exampleâ€”and later we became interested in activities that are important for the epigenetic regulation of telomere length. More recently we have been interested in understanding the role of telomere-binding proteins called shelterins. I think one of the things that we are most excited about right now is the anti-aging activity of telomerase. Your work has to be both original and relevant to the field.

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Chapter 2 : Aging, telomeres, and atherosclerosis | Cardiovascular Research | Oxford Academic

Aksinya Derevyanko, Kurt Whittemore, Ralph P. Schneider, VerÃ³nica JimÃ©nez, FÃ tima Bosch and Maria A. Blasco, Gene therapy with the TRF1 telomere gene rescues decreased TRF1 levels with aging and prolongs mouse health span, Aging Cell, 16, 6, (), ().

Advanced Search Abstract Although the level and pace of population aging display high geographical variability, virtually all countries have been experiencing growth in their elderly population, particularly in developed nations. Because aging is a major risk factor for atherosclerosis and associated disease, it is of up most importance to unravel the molecular mechanisms involved in vascular aging. Telomeres are specialized DNA-protein structures located at the ends of eukaryotic chromosomes whose length is progressively reduced in most somatic cells during aging. It is accepted that telomere exhaustion contributes to organismal ageing at least by impairing cell proliferation and viability. An emerging question is whether telomere erosion contributes to atherosclerosis. Here we discuss recent advances on the molecular control of telomere length in vascular cells, as well as animal and human studies that address the role of telomeres in vascular pathobiology. Although the interrelationships between telomere length and cardiovascular disease appear obvious, a chief question that remains unanswered is whether telomere ablation is cause of vascular injury or a surrogate phenomenon. Telomere biology Telomeres are specialized DNA-protein complexes located at both ends of eukaryotic chromosomes. Functional telomeres are required to prevent the recognition of chromosomal ends as double-stranded DNA breaks, thus preserving genome integrity and stability [1,2]. As depicted in Fig. The synthesis of telomeric DNA requires the activity of specialized telomere-associated proteins i. Schematic showing telomeres black circles at both ends of chromosomes. Enlargement of the telomere showing the human telomeric DNA tandem repeat sequence, the telomeric RNA component Terc , the catalytic telomerase reverse transcriptase TERT subunit, and additional telomerase-associated proteins. B Telomere attrition occurs progressively in somatic cells with each mitotic cycle during normal aging and passage in culture, due in part to low or absent telomerase activity. In contrast, high telomerase activity in germ and tumor cells allows the maintenance of telomere integrity and an extended proliferative capacity. Accelerated telomere erosion is a characteristic of several human premature aging syndromes i. Telomere protection depends on several factors, including the precise composition of telomere-associated proteins, the level of telomerase activity, and telomere length itself [1,2]. Cells with sufficiently long telomeres do not require telomerase activity, but lack of telomerase activity in cells with critically short telomeres leads to chromosomal fusions, replicative senescence, and apoptosis Fig. Telomerase expression and activity and telomere length are regulated in a tissue-specific and developmental manner in several species, including humans [3â€”6]. In general, these parameters are greater during embryonic development and become low or undetectable after birth, although significant differences in adult tissues have been reported. Notably, human premature aging syndromes i. Progressive telomere shortening in cell culture and during aging of the whole organism is a characteristic of most adult somatic cells, which exhibit low or absent telomerase activity [8â€”10].

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Chapter 3 : How do telomeres relate to aging? - Quora

Get this from a library! The molecular biology of cancer. [Stella Pelengaris; Michael Khan; MarÃ-a A Blasco;] -- This comprehensive text provides a detailed overview of the molecular mechanisms underpinning the development of cancer and its treatment.

February 20, Telomeres and aging: Telomeres are short DNA segments located at the end of all chromosomes. They are synthesized by an enzyme called telomerase [1]. Telomeres have become a subject of interest in the fight against aging since a correlation was found between telomere shortening and biological aging. This shortening happens during cell division, but many other factors can accelerate the process gender, stress, smoking, drinking, obesityâ€¦ Telomeres seem to be at the heart of the fight against aging, given the close bond between the two. Telomere length then becomes an interesting lead to elaborate therapies and solutions to fight against aging. As of now, no therapy has proven its efficiency to fight telomere shortening and lengthen the human lifespan, but a few studies have been conducted and there are methods to gain a longer lifespan and a better health by targeting telomeres. An anti-aging gene therapy targeting telomerase Experiments were conducted on mice by Spanish researchers in order to lengthen the mice healthspan and lifespan as they aged [3]. The goal of the experiment was to treat adult mice 1 year old and aged mice 2 years old by injecting them with an adeno-associated virus AAV that can synthesize mice telomerase through the TERT protein telomerase reverse transcriptase. Their lifespan and general health were then compared to those of healthy mice of the same age. In fact, the ability to synthesize telomeres in excess triggers an excess of cell divisions, and might even make them last indefinitely, which would create immortal cells, that would become malignant tumors when the immortal cells began to proliferate. Those results tell us that this telomerase therapy allows to push back the limits of a mouse lifespan and healthspan. It could be an efficient anti-aging therapy on mice, and potentially on other mammals and even humans in the future. Lifestyle changes to fight telomere shortening and aging Although no therapy was proven to work on humans, some behaviors and lifestyle changes can prevent telomere shortening. According to a study by Massod A. Shammas, from the Cancer Institute in Boston, many proofs tend to confirm that lifestyle affects health and lifespan, and directly affect telomere length [4] Here are a few factors that can effect health and lifespan according to that study, and the beneficial habits that can favour longer telomeres: Excess weight and obesity favour shorter telomeres Excess weight and obesity trigger an increase in oxidative stress, because of an unregulated adipocytokine production, and due to the production of oxidative agents in adipose tissue. Oxidative stress can cause DNA damage, and is very much likely to trigger telomere shortening, which induces a shorter lifespan by 8,8 years [4]. A diet can be changed as well: Thanks to experiments on rats, it was proven that caloric restriction can reduce oxidative stress and thus DNA damage. Eating antioxidant-rich foods can prevent telomere shortening According to a study, food rich in omega-3 type fatty acids which are antioxidants is associated to slower telomere shortening: After 5 years, a correlation was found between higher levels of those fatty acids and longer telomeres. The higher the antioxidant intake is, the less telomere shortening can be observed [4]. At last, eating fiber can be more recommended than fat and proteins. Still with experiments on rats, a positive correlation was found between long telomeres and a fiber-rich diet. Smoking increases telomere shortening and aging: Smoking a pack of cigarettes on a daily basis is linked to the loss of about 25,7 to 27,7 bp base pairs of telomeres a year, due to the considerable increase in oxidative stress caused by tobacco. Over 40 years, this equals to 7,4 years of lifespan loss. This is why smoking less matters, and stopping also helps limit telomeric DNA loss and slow down aging, or opting for an anti-oxidative therapy to reduce oxidative stress [4]. Stress has a direct effect on telomere length: Stress releases hormones that block the anti-oxidant proteins in the body, which leads to a higher oxidative stress that in turn induces telomere shortening and lower telomerase activity. Stress could be responsible for as much as a 10 year loss in life expectancy. This is why it is paramount to pay attention to external sources of stress and to lifestyle habits in order to fight against aging

[4]. There are anti-aging therapies, efficient on mammals, that directly affect telomeres. It is also possible to preserve your telomeres with lifestyle changes. Although no gene therapy has scientifically proven its efficiency on humans yet, there seems to be promising leads and we can only wait for real scientific studies and preclinical trials in order to adapt them. However, other causes of aging remain to be tackled before we can get to comprehensive anti-aging therapies.

Chapter 4 : Geroscience Interviews Michael Fossel on the Subject of Telomeres and Aging â€“ Fight Aging

Last week we heard the theoretical side of Dr. Michael Fossel's mission to bring aging to its knees, and why his chosen point of attack was on the grand orchestrator of the body's repair processes.

Geroscience recently published a long two part discussion with Michael Fossel. He is among the more prominent advocates for treating aging as a medical condition from the past few decades, and has written a couple of books on the topic. Rather he sees it as a convenient point of intervention that might at least partially reverse many of the epigenetic changes that occur with aging. Epigenetic decorations to DNA adjust the pace at which specific proteins are produced from their genetic blueprints. Cellular machinery is controlled by the amounts of various proteins that are present in the cell: The internal activity of a cell is a highly dynamic feedback loop running from protein production to protein activity to epigenetic change to protein production again, with thousands of proteins participating and interacting with one another. It is enormously complex, and patterns of epigenetic markers are constantly changing in response to the circumstances a cell finds itself in. Some of these changes are reactions to the rising levels of metabolic waste and molecular damage that cause aging, and can in and of themselves be either helpful or cause further harm. A number of factions within the research community are interested in trying force a reversal of age-related epigenetic changes: The fact that stem cell therapies can work even when the delivered cells die, and the only outcome is signaling that alters native cell behavior for some period of time, demonstrates that there are gains to be obtained in this sort of approach. It is nonetheless not really rejuvenation. It is instead something more akin to revving up a damaged engine - with all of the obvious downsides even if goals are achieved in the short-term. Thinking of telomere erosion as a cause of aging and acting accordingly is, I think, the wrong path, however. Average telomere length in a tissue is a function of a the rate at which somatic cells divide, losing a little of their telomere length each time until they self-destruct or become senescent , and b the rate at which the stem cells supporting that tissue provide fresh somatic cells with long telomeres. So average telomere length is clearly secondary to declining stem cell activity, and it is well known that stem cell populations decline and falter with age. An interview in the key of telomere with Dr. Michael Fossel When a lot of people look it aging, they view it in a very simplistic way: I have a beautiful picture of a Duesenberg , and the car looks absolutely gorgeous - spot free, runs smoothly. If compare that to my five-year-old car, mine is in much worse shape. But the reason the Duesenberg looks fantastic is that five generations of absolute fanatics took care of it. What happens with humans is that our rate of turnover comes down with age. But if you measure the rate of turnover in, for example, microglial cells with age, you find that the more senescent a cell is, the slower all of these turnover processes are - the rate of capture, the transmembrane translation , the rate of degradation. Instead, as the rate of turnover goes down, the percentage of denatured molecules goes up. This is true throughout the entire human body. Everything that you think of as aging or age-related disease is a dynamic process, and all of those processes slow with age. The mechanism of aging is a cascade of changes. Well, it occurs because the neurons die. Why does that happen? Well, because of the beta amyloid, and the tau tangles, and the changes in mitochondria and the oxidative damage. And why did that happen? Because the telomeres were shortened and now the pattern of epigenetic expression is playing a different tune. Why did that happen? Well, because the cell divided. Then it gets messier and brings you back to clinical medicine. For example, we know that the rate of microglial cell senescence - that is, microglial cell divisions - goes up in patients with closed head injury and infection. So is that why you find that some patients are people with viral infection, bacterial infection, fungal infection, closed head injury? I think the more effective point of intervention has to do with changing the pattern of gene expression. But rather than going after gene by gene by gene, rather than approaching an orchestra instrument by instrument, I would rather go to the conductor and say, "Play this tune. That was when we showed in the lab that when you reset the telomere length in individual human cells like fibroblasts , you reset the pattern of gene expression, and then they act like young cells. There, the answer is the year , when

someone showed that you could grow young human skin cells. And likewise you can do the same thing with endothelial cells , vascular structures, bone, and a number of other tissues. It is suggestive and intriguing, though. There are at least four ways, probably five, that we can reset telomeres in patients. The problem is that we need techniques that allow us to actually do that. Then Maria Blasco did the same thing with gene therapy. And the viral vector she used has been used in humans already, so we can actually do this now. There are a couple of odd variables. But it also depends on how fast your cells divide. So if this happens every time your cells divide, the more rapidly they divide, the less they have the telomerase. I actually see this as an advantage in several ways. I think of it as three different zones a cell can be in. If you have long telomeres, you repair DNA really quickly. Most cancers maintain their telomeres just long enough that they remain unstable from a genetic standpoint, but not long enough that they can repair. So if I give you telomerase, I want to make sure that I either give you a lot, enough to get through that risk zone, or none at all.

Chapter 5 : The molecular biology of cancer (eBook,) [www.nxgvision.com]

1. Author(s): Pelengaris,Stella; Khan,Michael; Blasco,MarÃ-a A(MarÃ-a Antonia) Title(s): The molecular biology of cancer/ edited by Stella Pelengaris and Michael Khan ; with contributions from Maria Blasco.

Email Print Like to share? Last week we heard the theoretical side of Dr. This week he goes into the practical details: What can we treat with such a therapy? And just how long could we live in the end, anyway? That was when we showed in the lab that when you reset the telomere length in individual human cells like fibroblasts, you reset the pattern of gene expression, and then they act like young cells. There, the answer is the year , when someone showed that you could grow young human skin cells. I used to joke back then that I could strip off your skin and give you a whole new one, reset your telomeres and then graft it all back again. And likewise you can do the same thing with endothelial cells, vascular structures, bone, and a number of other tissues. It is suggestive and intriguing, though. There are at least four ways, probably five, that we can reset telomeres in patients. The problem is that we need techniques that allow us to actually do that. Ronald DePinho at Harvard did some really nice work seven years ago where he showed that you could reset aging in a number of ways, including on behavioral measures. Then Maria Blasco, a collaborator in Spain, did the same thing with gene therapy. And the viral vector she used has been used in humans already, so we can actually do this now. How will that work in practice? Is telomerase therapy something patients will only need to do once? Well, there are a couple of odd variables. But it also depends on how fast your cells divide. So if this happens every time your cells divide, the more rapidly they divide, the less they have the telomerase. I actually see this as an advantage in several ways. I think of it as three different zones a cell can be in. If you have long telomeres, you repair DNA really quickly. Most cancers maintain their telomeres just long enough that they remain unstable from a genetic standpoint, but not long enough that they can repair. So if I give you telomerase, I want to make sure that I either give you a lot, enough to get through that risk zone, or none at all. Back twenty years ago, one of the first longevity companies, Geron, basically had three groups of patents: The only one they kept was telomerase inhibition for cancer treatment, and yet here they are twenty years later and still without a product. Well, nobody ever claimed myocardial infarctions starts in the myocardiumâ€”it starts in the primary arteries. Do you expect telomerase therapy to work well on certain diseases of aging, but not on others? The much bigger target is vascular aging. In almost every community in the developed worldâ€”and a lot of the undeveloped world, tooâ€”the major cause of death is arterial aging. The point is, you have options. They die of complications related to it. But we suspect that we can essentially treat all human age-related disease in a way that has never occurred in human history, and after the dementias, the next target is vascular aging. How would this affect healthcare costs? But what if we could actually lower it, rather than raise it? And I think we can do that. Even if people are living quite a bit longer? Yeah, I think so. So I think we can do a much better job than we do now. I think back on the old days, when I would gather progeric kids from around the world and camp in front of the White House, and dealing with that disease is expensive. These kids can die of all sorts of things. You mention yearsâ€”is that how far you think telomerase therapies could extend human lifespan? One question is, how far back can we reset the pattern of gene expression? And how effectively have you repaired the damage? Even in young cells, you probably every now and then inherit a mutation, and that adds up. The question is, how damn good? How far back can we reset it? I sometimes use the figure of just to raise eyebrows. I suppose I could say years or years. Yes, it would, but what is the time to re-treatment? One year, twenty years, two years?

Chapter 6 : MarÃ-a Blasco: Keeping a cap on cancer and aging

I can recommend you to read Michael Fossels book "the telomerase revolution", Ed Parks book "telomere timebombs", and/or watch some videos on well respected scientist in the field, such as: Michael Fossel, Aubrey de grey, Bill Andrews, Ed Park, Maria Blasco or Liz Parish.

There is all-but-universal and equally unwarranted assumption that both aging and age-related diseases are genetic. The reality is that both aging and age-related diseases are not genetic, they are epigenetic. To get at the difference, albeit in a slightly different context, consider the difference between a skin cell and a nerve cell. These cells have the same genes, but very different gene expression. The difference between a skin cell and a nerve cell is not genetic, but epigenetic. Same genes, different gene expression. The same is true of aging cells. The difference between a typical young cell and a typical old cell is not genes, but gene expression. The two cells â€" for example, a young skin cell and an old skin cell â€" have the same genes, but very different patterns of gene expression. To use the analogy of a symphony orchestra, both young cells and old cells have the same orchestral instruments violins, oboes, etc. This alteration in gene expression underlies all age-related diseases. In fact, there are literally hundreds perhaps thousands of such changes, all of which are not, by themselves, causes of disease or aging, but are the results of changes in telomere length. Aging â€" and age-related diseases â€" are not the result of one gene, nor the result of the change of expression in one gene, but rather the result of wholesale and subtle changes of expression in many genes, acting in concert. To harp back to the orchestra: Nor are do such epigenetic changes stop there. As the telomere influences the expression of a few local genes, these in turn influence the expression of more distant genes, which in turn influence genes on other chromosomes. Moreover, there are interactional effects between such genes: These trials my employ an effective intervention for one particular gene or gene product, but they ignore the expression of other genes and ignore the complex interactions of multiple genes, all of which are undergoing changes in gene expression as the cells age. Such human trials remove one tree and then wonder why the forest is still there. Moreover, as we will see, even when you restrict your focus to a particular gene, the problem is not the product itself, but the rate at which it turns over. To stretch our tree and forest analogy, even if you restrict your view to one particular tree, you find that it keeps regrowing. The problem comes back to the telomere. To account for the broad changes, you need to account for ALL the gene changes and account for the turnover rates as gene expression changes. Trying to treat disease is much like trying to treat hundreds of dynamic processes all at once. You can try aiming at all the processes with hundreds of drugs, you can even try to find a drug that will increase the turnover rates of all these hundreds of processes with hundreds of drugs, one-by-one and with interactive side effects. The upshot is plain, however. We could focus one-by-one on each of thousands of individual genes, we could focus one-by-one on each of dozens of different regulatory processes, and for each of these thousand genes or dozen processes attempt to develop one-by-one! Or, we can simply reset gene expression by addressing the change in telomere lengths.

Chapter 7 : Terraternal : Products : Telomere Guard - mg, capsules

Despite this suggestive evidence from genetically manipulated mice, it still remains to be demonstrated whether the telomere shortening in stem cells occurs during physiological aging, and whether stem cells with critically short telomeres undergo senescence or apoptosis in vivo.

Aging of the skin. Principles of Geriatric Medicine and Gerontology, 3rd ed. McGraw-Hill, New York, , Telomeres and Telomerase in Aging, Disease, and Cancer. Springer Publishing Maria A Blasco. Volume 3 Number 10 October 4: Yaar M, Gilchrest BA. Telomerase expression restores dermal integrity to to in vitro-aged fibroblasts in a reconsituted skin model. Exp Cell Res Skin reconstitution from early passage 20 population doublings cells with longer telomeres deomonstrated good adhesion, complex dermal-epidermal interdigitiation, and good resistance to sheer strees. There were no microbullae or splitting between the two layers. There results were equivalent to results observed clinically in young skin. Late-passage 85 population doubling human dermal cells that had short telomeres showed poor dermal-epidermal adhesion, simplified interdigiations, and a high sensitivity to sheer strees ther was extensive splitting and blistering microbullae along this junction. These results are equivalent to results observed clinically in older skin. For a detailed account of the effects of aging in cardiovascular, orthopedic, immune, endocrine, nervous systems and more, and their relationship to telomere shortening and cellular senescence, see: Cells, Aging and Human Disease. Oxford University Press 7. Faragher1, David Kipling2, How might replicative senescence contribute to human ageing? BioEssays Volume 20, Issue 12, pages â€”, December 8. Harley, Lui, Blasco, et al. Rejuvenation Research, Volume 14, Number Page 10, paragraph 4: However, we speculate this effect is explained by cell dynamics and the fact that telomerase preferentially lengthens the shortest telomeres. Aging Cell Volume 10, Issue 4, pages â€”, Yokoo, Furumoto, et al. Age-dependent telomere shortening is slowed down by enrichment of intracellular vitamin C via suppression of oxidative stress. BJ fibroblasts display high antioxidant capacity and slow telomere shortening independent of hTERT transfection. Free Radic Biol Med Saretzki G, von Zglinicki T. Replicative aging, telomeres, and oxidative stress. Ann N Y Acad Sci The FDA has not tested or approved the products sold here.

Chapter 8 : Part 5: Fight aging with telomere therapy - Work for human longevity

The contribution that telomeres and telomeraseâ€"the enzyme that maintains telomere length in cellsâ€"make to preventing cancer and aging () is the research passion of Dr. MarÃ-a Blasco at the Spanish National Cancer Research Center (CNIO) in Madrid.

Blasco is co-founder of Life Length, a biotechnology company that commercializes measurement of telomere length for different applications. The author s declared that no grants were involved in supporting this work. This is an open access article distributed under the terms of the Creative Commons Attribution Licence , which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Telomeres and telomerase as therapeutic targets to prevent and treat age-related diseases [version 1; referees: FResearch , 5 F Faculty Rev: A proper telomere structure prevents chromosome ends from being recognized as DNA strand breaks, thus preventing illegitimate homologous recombination between telomeres as well as chromosome end-to-end fusions 1. Finally, RAP1 is recruited to telomeres by TRF2, but can also bind throughout chromosome arms to regulate transcription, playing an important role in protection from obesity and metabolic syndrome in mice 3 â€" 5. Interestingly, all shelterins except RAP1 are essential for life 6 â€" 8 , owing to the fact that RAP1 is the only shelterin dispensable for telomere protection 3 , 9 , Telomeres are proposed to be further stabilized by the formation of a protective T-loop lariat structure. Thus, the T-loop sequesters the ends of chromosomes and provides a mechanism to prevent the full activation of a DNA damage response typically observed at most types of DNA ends Thus, chromosomes progressively shorten from both ends upon repeated cell division, a process which in the context of the organism contributes to progressive telomere shortening with aging in all cell types where it has been studied When telomeres reach a critically short length they are detected by the DNA repair systems as DNA damage and elicit cell cycle arrest and cell death responses Indeed, overexpression of telomerase is sufficient to counteract telomere attrition and to indefinitely extend the replicative lifespan of primary cells in culture in the absence of genomic instability, transforming them into cancerous cells 20 â€" However, high telomerase expression is normally restricted to early stages of embryonic development i. Thus, adult mammalian tissues including adult stem cell compartments do not express sufficient amounts of telomerase to maintain telomere length throughout organismal lifespan. Consequently, telomere shortening occurs along with physiological aging in humans and mice and this process is proposed to underlie aging and age-associated diseases as well as organismal longevity 25 , Holoenzyme assembly is thought to occur in the Cajal bodies 29 , and subsequently TCAB1 and TPP1 are required for proper trafficking of telomerase to telomeres. Moreover, the discovery of a long non-coding telomeric repeat-containing RNA, TERRA 30 , 31 , which has been proposed to regulate various aspects of telomere function, adds yet another level of complexity to telomere regulation 32 , Another crucial issue in telomere stability and maintenance is the replication of telomeric DNA, for which a myriad of proteins are required. The helicase BLM contributes to telomere stability by resolving late replication structures 39 , whereas FEN1 and RTEL1 function in Okazaki fragment processing 40 and T-loop disassembly during replication 41 , respectively. We recently published an in-depth review on the role of these proteins in telomere replication including the consequences for telomere maintenance if their function is impaired In this review, we will discuss the role of telomeres in the origin of age-associated diseases and organismal longevity, as well as the potential use of telomerase as a therapeutic target to delay aging and to prevent and treat age-related diseases. Telomeres as hallmarks of aging and longevity Aging is a multifactorial process that results in a progressive functional decline at cellular, tissue, and organismal levels. During recent years, a number of molecular pathways have been identified as main molecular causes of aging, including telomere attrition, cellular senescence, genomic instability, stem cell exhaustion, mitochondrial dysfunction, and epigenetic alterations, among others Interestingly, telomere attrition is considered a primary cause of aging, as it can trigger all the above-mentioned hallmarks of aging, although the degree to which it is a principal cause

of aging is under active investigation Critical telomere shortening elicits the induction of cellular senescence or the permanent inability of cells to further divide, which in turn has been proposed to be at the origin of different disease states 17 , In addition, telomere attrition in the stem cell compartments results in the exhaustion of their tissue- and self-renewal capacity, thus also leading to age-related pathologies 44 , Indeed, when this telomere exhaustion occurs prematurely owing to germline mutations in telomere maintenance genes i. Finally, short telomeres can trigger epigenetic changes at telomeric as well as subtelomeric chromatin In this regard, epigenetic regulation of telomeres has been described in processes that involve de-differentiation and loss of cellular identity such as during tumorigenesis 54 , as well as during the induction of pluripotency In particular, loss of heterochromatic marks at telomeres results in telomere elongation and increased telomere recombination Of note, in addition to the persistent DNA damage response elicited by critically short telomeres, it recently became evident that a large proportion of DNA damage in stress-induced senescence resides in telomeres. Importantly, this DNA damage is independent of telomere length and accumulates with aging in primates and mice, suggesting that stress-induced and telomere length-independent senescence may contribute to the aging process too 56 , In addition to being considered a primary molecular cause of aging, telomere shortening with time has been proposed to be a biomarker of biological aging, with a potential prognostic value for many different age-associated diseases, including cardiovascular failure 58 â€” Interestingly, telomere length has also been proposed as a marker of longevity. A study longitudinally following telomere length throughout the lifespan of individual zebra finches demonstrated that telomere length at day 25 after birth is a strong predictor of individual lifespan in this species In mice, a similar longitudinal follow up of telomere length throughout lifespan showed the rate of increase of short telomeres with time but not average telomere length or the rate of telomere shortening was predictive of individual lifespan A similar scenario was found in dogs, where telomere shortening has been described to be fold faster than in humans These findings suggest that it is the ability of different species to maintain telomeres rather than average telomere length per se that may be determinant of species longevity. This idea is further supported by longitudinal studies in free-living birds. In particular, in Seychelles warblers, telomeres shorten throughout life and higher rates of telomere shortening predict mortality Similarly, survival in jackdaws can be predicted by nestling telomere shortening but not by absolute telomere length Additional and independent evidence that the ability to maintain telomeres may determine mouse longevity came from the description of an age-specific metabolic signature predictive of chronological age in wild-type mice In particular, when this signature was used to predict the age of either telomerase-deficient or TERT-overexpressing mice, it predicted older or younger ages than their chronological age, respectively, in agreement with shorter telomeres and shorter lifespan in the telomerase-deficient mice, and longer telomeres and extended lifespan in the TERT-overexpressing mice 72 , thus suggesting that telomere length is a determinant of aging in wild-type mice. In humans, a large number of cross sectional epidemiological studies confirmed telomere shortening with aging in humans 16 , Recently published data from the GERA cohort Genetic Epidemiology Research on Adult Health and Aging , which comprises more than , individuals, further confirmed this correlation and also showed that telomere length correlates positively with survival in subjects older than 75, i. This is in agreement with a previous report showing that telomere length positively correlates with better median survival in individuals who are 60 years of age or older However, contradictory reports exist which do not support the correlation between average telomere length and the prediction of remaining years of life in the old and oldest 76 , In this regard, lessons from other species mice, birds show the importance of determining not only average telomere length but also longitudinal changes in telomere length as well as changes in the abundance of short telomeres. Thus, future epidemiological studies should take individual telomeres and their change over time into account i. In this regard, methods that can quantify the presence of short telomeres, like the high-throughput quantitative telomere fluorescence in situ hybridization FISH technique 58 or single telomere length analysis STELA 78 will be important for establishing telomere shortening as a biomarker of human aging. Intrinsic and environmental instigators of telomere length As mentioned above, there are

differences in the pace of telomere shortening across species, which indeed may contribute to explaining their different longevities, at least in part. The average telomere shortening in human blood cells occurs at a rate of 31â€”72 base pairs per year 79 , 80 while mouse telomeres shorten around a hundred times faster than that This indicates that, in addition to the intrinsic end replication problem, there are other factors contributing to telomere attrition. In particular, oxidative damage may severely impact on telomere length. Cells exposed to oxidative stress conditions e. H2O2, chronic hyperoxia display accelerated telomere shortening and reduced replicative lifespans, whereas antioxidant treatment has the opposite effect In humans, the choice of lifestyle can influence telomere shortening. As an example, smoking, an unhealthy diet e. Moreover, accelerated telomere shortening in leukocytes has been associated with psychological stress. In particular, patients with depression disorders have shorter telomeres compared to healthy individuals 88 , and this telomere erosion is found in all lymphocyte subpopulations of the adaptive immune system Stress provoked by physical abuse of children has been also associated with telomere shortening Furthermore, there is a wealth of studies investigating telomere length in major depressive disorder MDD , a severe illness which shows signs of premature aging 60 , 91 , In particular, it has been described that telomere length in MDD subjects corresponds to a year increase in biological age 93 compared to healthy subjects. In line with this, increased abundance of short telomeres in patients with bipolar II disorder has also been described to correspond to a year older biological age, again in agreement with increased risk for developing different diseases in these patients Interestingly, shorter telomeres are also associated with cognitive impairment in the elderly In contrast to the detrimental factors causing accelerated telomere shortening, certain life habits e. In addition to these various intrinsic and environmental factors, telomere length is also dictated by a genetic component. Earlier twin and family studies and a recent meta-analysis comprising nearly 20, subjects demonstrate that telomere length is highly heritable 79 , 99 â€” Whether the inheritance of telomere length correlates more strongly with paternal or maternal telomere length, however, is still debated Interestingly, in another twin study Christensen and colleagues reported that the perceived age in twins older than 70 years of age is a robust biomarker of aging which strongly correlates with telomere length. Moreover, within twin pairs, the twin with greater telomere length tends to look younger and live longer Genetic models to understand the causal role of telomeres in disease and longevity Firm experimental demonstration that critical telomere shortening is causative of aging was first achieved by generating mice deficient for telomerase. Mice deficient for TERC have progressively shorter telomeres over generations, leading to chromosome instability, developmental defects, premature aging phenotypes, and ultimately mouse infertility and premature death â€” These mice show a decreased median and maximum lifespan already at the first generation , and this decreased longevity and associated aging pathologies are anticipated with each mouse generation, thus demonstrating that telomere length in mice is causal of aging and longevity. Importantly, restoration of TERC expression in mice with inherited critically short telomeres is sufficient to prevent the phenotypes associated with short telomeres in these mice, including aplastic anemia, intestinal atrophy, and infertility, among others , In agreement with these pioneer studies, genetic ablation of TERT was shown to have similar consequences on organismal aging and lifespan , In line with these findings, lack of telomerase in lower vertebrates such as the zebrafish also causes premature aging which can be rescued by either telomerase restoration or inhibition of p53, which signals telomere damage Together, these findings demonstrate that short telomeres are causative of aging and that premature aging specifically induced by telomerase deficiency and short telomeres can be rescued by telomerase re-expression. In line with mouse studies, a number of human syndromes were later described to be caused by germ line mutations in telomerase and shelterin genes, the so-called telomere syndromes As in the telomerase-deficient mouse model, the diseases associated with telomerase mutations are anticipated with increasing generations and involve a loss of the ability of tissues to regenerate, resulting in skin abnormalities, aplastic anemia, or pulmonary fibrosis 46 , These analogies between humans and mice highlight that telomere length as a genetic determinant of disease and longevity is a molecular mechanism conserved in these species. However, definitive genetic demonstration that telomere length is also causative of physiological aging in

normal individuals first came from telomerase overexpression studies in mice. In particular, mice with increased transgenic telomerase expression throughout their lifespans were able to maintain longer telomeres with aging, showed decreased molecular i. This study demonstrated for the first time in any organism the anti-aging activity of telomerase. Importantly, these findings led to the idea that potential therapeutic strategies based on transiently increased telomerase expression could also delay age-associated pathologies and increase longevity. This was first achieved by delivering TERT using non-integrative gene therapy vectors adeno-associated vectors [AAVs] into middle-aged and old mice, which resulted in transiently increased TERT expression in the majority of mouse tissues. Importantly, a single treatment with these vectors resulted in elongated telomeres in a range of organs, delayed age-associated pathologies, and significantly extended median and maximal lifespan in both age groups Moreover, these mice did not show increased cancer; instead, as seen in other age-related conditions, cancer was also delayed Thus telomere-based gene therapies using non-integrative vectors may represent a new therapeutic strategy to transiently activate TERT for the prevention or treatment of many different age-related pathologies see below. Telomeres and Telomerase as therapeutic targets A substantial number of companies are now aiming to harness the knowledge that has been generated, unveiling the molecular mechanisms of aging in order to develop a new class of drugs to prevent and treat the major age-related diseases In this regard, telomerase overexpression studies in mice have been proof of principle that just modifying a single hallmark of aging, i. Indeed, the use of telomerase activation in delaying aging-associated conditions has spurred the interest of commercial enterprises. For instance, the low-potency telomerase activator TA a bio-active compound isolated from the herb Astragalus membranaceus has been shown to lead to a mild increase in telomere length in mice , zebra finches , and humans , and to improve several aging-related parameters in mice and humans , , although no increase in longevity has been reported in longitudinal mouse studies On the other hand, other natural compounds like sex hormones have been found to activate TERT at the transcriptional level â€” In this regard, androgen therapy has been applied as a first-line treatment in aplastic anemia for decades with mixed success and without a clear understanding of the mechanism that underlies remission in some patients but not in others , A recent study in mice which develop full-blown aplastic anemia provoked by short telomeres showed that androgen therapy rescues telomere attrition and subsequent death from aplastic anemia , indicating that telomerase activation may indeed be a treatment option for diseases associated with flawed telomere maintenance i. However, potential off-target effects of compounds that activate TERT at a transcriptional level should be a concern. In particular, TA has been shown to activate TERT through activation of mitogenic pathways that lead to the activation of the oncogene c-myc , and thus may drive cancer.

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Chapter 9 : - NLM Catalog Result

Telomere length shortening in the process of replication and accumulation of DNA damage causes cell senescence in various tissues and on the other hand, short telomere length is considered as one of the main factors in the replicative senescence.

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