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Telomerase gene therapy: a novel approach to combat aging

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Telomeres are repetitive DNA sequences located at the very ends of our chromosomes. Together with specific proteins, they form a cap like structure that prevents the cells from sensing the linear chromosome ends as ‘damaged’. Like a burning fuse, telomeres progressively shorten with every cell division and, depending on cell type, initiate either apoptosis or trigger a permanent proliferative arrest, termed cellular senescence, once a critical length is reached. It is thought that this cell division countdown timer developed as a tumour suppressing mechanism to prevent precancerous cells from proliferating indefinitely. While we currently do not know how efficient this tumour suppressing mechanism is in humans, numerous studies using mouse models have demonstrated that critically short and dysfunctional telomeres indeed present a powerful barrier to cancer growth (Artandi & DePinho, 2010).

Unfortunately, this tumour suppressing mechanism also comes at a cost. As we age, telomeres in most of our tissues progressively become

shorter and therefore likely contribute to the failure of our organs and tissues observed in old age. Supporting this are data demonstrating that healthy lifespan is positively correlated with longer telomeres in humans, and patients suffering from age-related diseases and premature aging syndromes display shorter telomeres compared to healthy individuals (Zhu et al, 2011). Furthermore, cells with damaged telomeres accumulate in some tissues of aging mice and nonhuman primates, supporting the model that telomere shortening and the resulting senescence response promotes aging in mammals (Fumagalli et al, 2012; Herbig et al, 2006; Hewitt et al, 2012). Indeed, preventing the accumulation of senescent cells in aging mice significantly improves healthspan, demonstrating that cellular senescence, regardless of its induction, is a cause of aging associated disorders (Baker et al, 2011).

> *»Telomerase is a reverse transcriptase that adds new telomeric repeats preferentially to critically short telomeres and, thereby, prevents them from triggering apoptosis or cellular senescence.«*

Certain cells within our tissues have the ability to stabilize telomere lengths more efficiently than others. Stem and progenitor cells can slow telomere erosion by expression of a ribonucleoprotein complex called telomerase. Telomerase is a reverse transcriptase that adds new telomeric repeats preferentially to critically short telomeres and, thereby, prevents them from triggering apoptosis or cellular senescence. In contrast to stem cells which constitutively express low levels of telomerase, normal somatic human cells repress telomerase expression shortly before birth. Consequently telomeres shorten in most of our cells throughout life. While the relatively low levels of telomerase activity in stem cells are not sufficient to completely prevent telomere erosion with advancing age, these levels are sufficient to delay aging substantially. Partial or complete loss of telomerase function dramatically accelerates aging in mice and promotes aging associated disorders in humans. Therefore, the presence of active telomerase in stem cells, and potentially in other cells, is vital for longevity and good health. A question that has therefore intrigued researchers for many years is whether it is possible to slow aging and improve health span by re-activating telomerase in all of our cells.

Constitutive expression of telomerase, unfortunately, is a characteristic of almost all cancer cells. It is therefore no surprise that transgenic animals overexpressing the catalytic subunit of mouse telomerase (mTERT), develop cancers earlier in life, thereby masking the potential beneficial lifespan extending properties of telomerase (Gonzalez-Suarez et al, 2001). A significant breakthrough came several years ago when Maria Blasco's group demonstrated that constitutive telomerase expression in mice, engineered to be also highly cancer resistant, dramatically extended median lifespan and reduced aging associated disorders (Tomas-Loba et al, 2008). While these studies demonstrated for the first time that telomerase has anti-aging and rejuvenating properties, this approach for improving health and extending lifespan is not feasible in humans since we are clearly not cancer resistant. However, what if one could activate telomerase expression temporarily, just enough to extend critically short telomeres in ‘old’ cells? This would prevent precancerous cells from proliferating continuously, but might give normal cells a temporary boost to maintain tissue function for a few more years. Similarly, aging-associated disorders, including diabetes, atherosclerosis, cardiovascular disease and cognitive impairment, all which have been associated with shortened telomere lengths (Zhu et al, 2011), could

potentially be ameliorated using such an approach.

In this issue of *EMBO Molecular Medicine*, Bernardes de Jesus and colleagues bring us one step closer to this goal (Bernardes de Jesus et al, 2012). The authors took advantage of the fact that recombinant adeno-associated viruses (rAAV), vectors used in gene therapy, only integrate into the host genome at very low rates (Li et al, 2011). mTERT expressed from such vectors should not promote cancer growth, since the episomal vector would be lost in rapidly dividing cells such as cancer cells. Using an AAV serotype of high tropism and capable of crossing the blood–brain-barrier (AAV9), the authors injected recombinant AAV9-mTERT virus in a single treatment via tail vein into normal adult mice, 1 and 2 years of age. Over-expression of mTERT could be readily detected in liver, kidney, lung, heart, brain and muscle, demonstrating that the virus transduced cells in a wide range of tissues. Remarkably, despite the broad expression of mTERT, these animals did not display a higher cancer incidence compared to control mice. This suggests that, at least in the short-lived mouse, a gene therapy approach to deliver telomerase to individual cells in tissue is safe. Animals injected with AAV9-mTERT were healthier compared to their control littermates and displayed a reduction in disabling conditions associated with physiological aging such as osteoporosis and insulin resistance, while significantly improving metabolic functions, cognitive skills, and physical performances. These rejuvenating changes were associated with an overall increase in telomere lengths and a reduction of short telomeres, demonstrating that telomerase counteracted telomere erosion in a variety of tissues (Fig 1). Median lifespan was extended by up to 24% in the 1-year-old treated group, and by up to 13% in animals injected at 2 years of age. This study therefore demonstrates that telomerase expression using gene therapy is a viable approach for improving healthspan and extending lifespan without increasing cancer incidence, even in organisms that are much more susceptible to cancer development than humans.

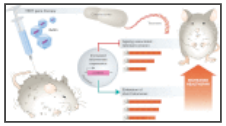

Figure 1

Promoting healthspan in mice using a telomerase gene therapy

»Animals injected with AAV9-mTERT were healthier compared to their control littermates and displayed a reduction in disabling conditions associated with physiological aging…«

Given that mice have much longer telomeres compared to humans, it may seem surprising that telomere erosion could contribute to aging and aging associated disorders in this short-lived animal. However, telomeres do erode with advancing age in mice, including in stem cell compartments (Flores et al, 2008), suggesting that telomere shortening and dysfunction also limits growth of mouse cells and consequently contributes to aging. In support of this, Bernardes de Jesus et al demonstrate that a mutant form of mTERT incapable of extending telomeres was unable to provide any of the rejuvenating and lifespan extending effects of catalytically active TERT. Thus, these studies also provide additional evidence that telomere erosion contributes to the functional decline of tissues in the mouse.

While these studies provide a proof-of-principle that telomerase gene therapy is a feasible and generally safe approach to improve healthspan and treat disorders associated with short telomeres, a clinical application in humans is likely still some time away. Low levels of integration of rAAV vectors into genomic DNA have been observed, raising the possibility that rare integration events of constitutively overexpressed TERT into genomes of long lived species might eventually promote cancer growth. Even if these vectors do not integrate and instead are maintained episomally, expression of TERT in cells of early and subtle neoplastic lesions could potentially provide these cells with enough proliferative potential to proceed to more advanced cancer stages. Further studies in long lived mammals should reveal the safety of this approach in extending healthspan also in humans. Furthermore, as with other gene therapeutic approaches, targeting the virus to specific cells in the body remains an obstacle. Also uncertain is specifically which cells should be targeted using a telomerase gene therapy. Stem and progenitor cells would be obvious candidates as these cells not only lose telomeres with advancing age, but also appear to be integral to preserving tissue damaged by age. This is an exciting and promising study as it demonstrates that we are getting closer towards developing therapies to treat certain aging associated disorders. Before we line up for treatment, however, the results and techniques need to be extended to specific cell populations and longer lived species, so that the potential of this novel approach to extend healthspan and treat diseases associated with short telomeres in humans can be fully realized.

Acknowledgments

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The authors declare that they have no conflict of interest.

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