Aging by Telomere Loss Can Be Reversed

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Recently in *Nature*, Jaskelioff et al. (2010) demonstrated that multiple aging phenotypes in a mouse model of accelerated telomere loss can be reversed within 4 weeks of reactivating telomerase. This raises the major question of whether physiological aging, likely caused by a combination of molecular defects, may also be reversible.

Accumulation of short/damaged telomeres with increasing age is considered one of the main sources of aging-associated DNA damage responsible for the loss of regenerative potential in tissues and during systemic organismal aging (Harley et al., 1990; Flores et al., 2005). Mounting evidence suggests that telomerase is a longevity gene that functions by counteracting telomere attrition. Thus, telomerase-deficient mice age prematurely, and telomerase overexpression results in extended longevity in mice (Tomas-Loba et al., 2008). Moreover, human mutations in telomerase components produce premature adult stem cell dysfunction and decreased longevity (Mitchell et al., 1999).

Previous work had shown that restoration of telomerase activity in mouse zygotes with critically short telomeres, owing to a deficiency in the telomerase RNA component (*Terc*), rescues critically short telomeres and chromosomal instability in the resulting mice (Samper et al., 2001). Restoration of telomerase activity in zygotes also prevented the wide range of degenerative pathologies that would otherwise appear in telomerase-deficient mice with critically short telomeres, including bone marrow aplasia, intestinal atrophy, male germ line depletion, and adult stem cell dysfunction (Samper et al., 2001; Siegl-Cachedenier et al., 2007), and resulted in a normal organismal life-span (Siegl-Cachedenier et al., 2007). Together, all the above findings indicate that aging provoked by critical telomere shortening can be prevented or delayed by telomerase reactivation. From these grounds, reversion of aging caused by telomere loss was the next frontier. A recent study in *Nature* takes an important step forward from these previous findings by using a new mouse model for telomerase deficiency, designed to permit telomerase reactivation in adult mice after telomere-induced aging phenotypes have been established (Jaskelioff et al., 2010). Specifically, DePinho and colleagues generated a knockin allele encoding a 4-OH tamoxifen (4-OHT)-inducible mouse telomerase (TERT-ER) under the control of the TERT endogenous promoter. In the absence of tamoxifen, these mice exhibit premature appearance of aging pathologies and reduction in survival (Figure 1). These mice phenocopy previously described *Terc*-deficient mice, which highlights that elongation of short telomeres by telomerase is the main mechanism by which telomerase protects from aging pathologies. Importantly, 4 weeks of tamoxifen treatment to induce TERT re-expression in adult TERT-ER mice with clear signs of premature aging was sufficient to extend their telomeres and rescue telomeric DNA damage signaling and associated checkpoint responses. Dramatically, tamoxifen-induced TERT re-expression also led to resumption of proliferation in quiescent cultured cells and eliminated the degenerative phenotypes across multiple organs, including testis, spleen, and intestines (Figure 1). Reactivation of telomerase also ameliorated the decreased survival of TERT-ER mice. These findings represent an important advance in the aging field, as they show that aging induced by telomere loss can be reversed in a broad range of tissues and cell types, including neuronal function.

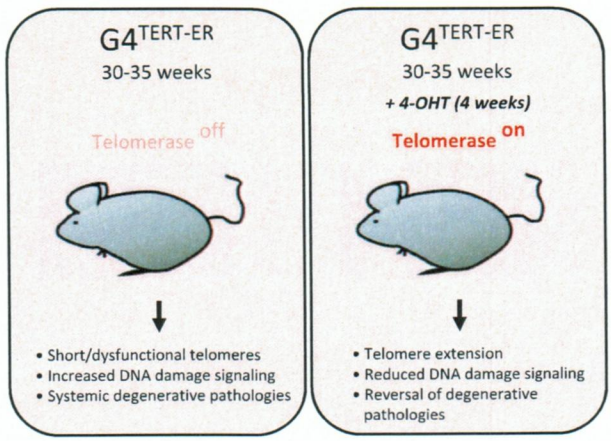

Figure 1. Antiaging Effects of Telomerase
Schematic showing the major findings of Jaskelioff et al. (2010). Telomerase reactivation in late generation telomerase-deficient mice ($G4^{TERT-ER}$) could revert some of the aging phenotypes observed, demonstrating the regenerative potential capacity of different tissues.

Looking to the future, the next key question is to what extent natural, physiological aging is caused by the presence of critically short telomeres and, consequently, to what extent telomere restoration will be able to reverse physiological aging. In this regard, other recent findings support the idea that telomere shortening does impact natural mouse aging. On one hand, despite the long-standing belief that mouse aging was not linked to telomere shortening given that

mice are born with very long telomeres—much longer than human telomeres—mouse telomeres do suffer extensive shortening associated with aging (Flores et al., 2008). In particular, while mouse cells maintain relatively long telomeres during their first year of life, there is a dramatic loss of telomeric sequences at 2 years of age, even in various stem cell populations, and this change is concomitant with the loss of regenerative capacity associated with mouse aging. In addition, telomerase-deficient mice from the first generation (G1*Terc*$^{-/-}$) exhibit a significant decrease in median and maximum longevity and a higher incidence of age-related pathologies and stem cell dysfunction compared with wild-type mice (Flores et al., 2005; Garcia-Cao et al., 2006), indicating that, as in humans, telomerase activity is rate limiting for natural mouse longevity and aging. These results suggest that strategies aimed to increase telomerase activity may delay natural mouse aging. Further supporting this notion, it was recently shown that overexpression of TERT in the context of mice engineered to be cancer resistant owe to increase expression of tumor suppressor genes (Sp53/Sp16/SARF/TgTERT mice) was sufficient to decrease telomere damage with age, delay aging, and increase median longevity by 40% (Tomas-Loba et al., 2008). However, it remains to be seen whether telomerase reactivation late in life would be sufficient to delay natural mouse aging and extend mouse longevity without increasing cancer incidence.

In summary, these proof-of-principle studies using genetically modified mice are likely to encourage the development of targeted therapeutic strategies based on reactivation of telomerase function. Indeed, small molecule telomerase activators have been reported recently and have demonstrated some preliminary health-span beneficial effects in humans (Harley et al., 2010). Identifying drugable targets and candidate activators clearly opens a new window for the treatment of age-associated degenerative diseases.

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HGPS-Derived iPSCs For The Ages

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In this issue of *Cell Stem Cell*, Zhang et al. (2011) generate patient-derived iPSCs for one of the major premature aging diseases, Hutchinson-Gilford Progeria Syndrome (HGPS). These cells are a much-needed new tool to study HGPS, and their use may lead to novel insights into mechanisms of aging.

Some problems in biology are more difficult to study than others. Human aging is certainly one of them. Most conclusions regarding molecular mechanism of human aging rely on mere correlation, and direct experimental testing is generally not feasible. One approach to dissect the molecular basis of human aging is to study naturally occurring premature aging disorders. One of the most dramatic and prominent of such diseases is Hutchinson-Gilford Progeria Syndrome (HGPS). Zhang et al. (2011) now report the generation of induced pluripotent stem cells (iPSCs) from HGPS cells, providing a powerful new tool to unravel the molecular and physiological mechanisms of premature and normal aging.

HGPS is a truly remarkable disease in many ways. To start with, it affects an unusually wide spectrum of tissues and leads to the development of highly diverse symptoms ranging from depletion of subcutaneous fat to loss of hair and tendon contractures. The diversity of affected tissues pointed early on to stem cell defects as a likely disease mechanism. Most relevant in patients are vascular defects and recurring strokes, which invariably are fatal in patients in their mid- to late teens (Hennekam, 2006). The disease is exceedingly rare