Aging by Telomere Loss Can Be Reversed

Bruno Bernardes de Jesus[1] and Maria A. Blasco[1,*]
[1]Telomeres and Telomerase Group, Molecular Oncology Program, Spanish National Cancer Centre (CNIO), Melchor Fernández Almagro 3, Madrid E-28029, Spain
*Correspondence: mblasco@cnio.es
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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.

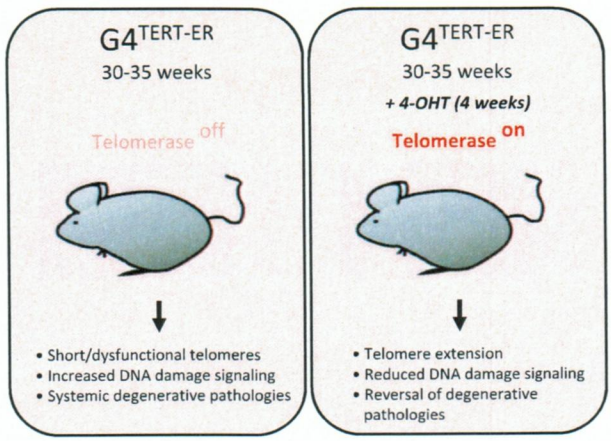

Figure 1. Antiaging Effects of Telomerase
Schematic showing the major findings of Jaskelioff et al. (2010). Telomerase reactivation in late generation telomerase-deficient mice ($G4^{TERT-ER}$) could revert some of the aging phenotypes observed, demonstrating the regenerative potential capacity of different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