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Review

The role of telomeres and telomerase in stem cell aging

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ABSTRACT

Stem cells regenerate our bodies. In a similar manner to match ignition, stem cell "ignition" has to be precisely tuned to avoid uncontrolled proliferation as may occur in tumors or, inversely, the lack of proliferation as happens in degenerative disorders. During the last years it has become evident that telomeres and telomerase are main components of the stem cell "ignition" mechanism, providing a way to restrain cancer and delay aging.

> "My grandmother said that each of us is born with a box of matches inside us but we can't strike them all by ourselves ... Each person has to discover what will set off the explosive flare of a match in order to live, since the combustion that occurs when one of them is ignited is what nourishes the soul. If there's nothing to trigger the explosion, our box of matches becomes damp, and then we will never be able to light any of them. Of course, it's important to light the matches one at a time. If a powerful emotion should ignite them all at once they would produce a splendor so dazzling that it would illuminate far beyond what we can normally see; and then a brilliant tunnel would appear before our eyes, revealing the path we forgot at birth..." (Like Water For Chocolate, Laura Esquivel, 1989)".

As matches nourish the soul in Laura Esquiveĺs novel, stem cells nourish our bodies. In a similar manner that match ignition, stem cell "ignition" has to be precisely tuned to avoid uncontrolled proliferation as may occur in tumors or, inversely the lack of proliferation responses as happen in degenerative disorders. During the last years it has become evident that telomeres and telomerase are main components of the stem cell "ignition" mechanism, providing a way to restrain cancer and delay aging.

1. Maintaining telomere homeostasis

Telomeres safeguard the chromosome ends from DNA repair and degradation activities. To accomplish this protective task a proper telomere structure and length is required. Telomere structure is provided by binding of shelterin to telomeric repeats. Shelterin encompasses six telomere-binding proteins with essential roles in telomere protection and telomere length regulation [1,2]. Telomere length is established by the outcome of two opposing forces: on one side telomere erosion generated during cell division by the end-replication problem, exonucleases, and oxidative activities; on the other side telomere elongation by telomerase and recombination-based processes known as alternative lengthening of telomeres or ALT. Depending on cell type and developmental status one force and mechanism dominates over the others. During the early cell cycles of mouse development telomeres lengthen by a mechanism involving sister-chromatid exchange and recombination [3]. At the blastocyst stage, telomeres are elongated by telomerase although telomere recombination activities are still present, at least in embryonic stem (ES) cells cultured in vitro [4]. In adults, telomerase maintains telomere length in young tissues, but its activity decays later on life likely contributing to a general telomere shortening [5]. Interestingly, mouse telomeres shorten at two different rates during the course of life, slightly until middle age (1-year-old) and more rapidly late in life [5]. Such biphasic phase of telomere shortening parallels the decline in tissue homeostasis observed during ageing, modest in middle-years but abruptly at old ages [6]. A correlation between telomere length and ageing symptoms suggests a positive role of telomere integrity

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in tissue fitness. It is unknown which events speed up the pace of telomere shortening late in life although the observed reduction in telomerase activity likely contributes to the acceleration in telomere erosion [5]. Whether telomerase activity decays with age due to an increase in stochastic molecular damage during aging or by the action of a temporal regulatory mechanism is a prominent question for future research.

2. Telomere length, telomerase and healthy life

The correlation between telomere length, telomerase activity and healthy life has been investigated in humans. Telomere length positively correlates with years of healthy life [7] and longevity in Ashkenazi centenarians [8]. Importantly, a common hTERT haplotype associated with longer telomere length is found in Ashkenazi centenarians and their offspring, indicating that TERT may function as a genetic agent in life-span determination [8]. Telomerase activity also increases in adult men that adhere to a healthy diet and perform regular exercise, conditions that led to reductions in physiological distress [9]. Conversely, in chronically stressed individuals telomerase activity diminishes leading to acceleration in telomere shortening [10]. Increased telomere shortening due to mutations in the main components of the telomerase complex, TERT, TERC and dyskerin, are found in patients with several degenerative disorders highlighting the importance of maintaining adequate telomere reserves for living a healthy life [11]. In the case of dyskeratosis congenita (DKC), a dominant degenerative disorder characterized by mutations in TERT and TERC, the disease displays features of "genetic anticipation" that is increasing severity and an earlier onset in successive generations [11]. Such disease anticipation phenotype may be explained by an earlier exhaustion of telomere reserves with each succeeding generation. An instrumental role for telomere integrity in preserving organ functionality rather than telomerase levels is illustrated in a mouse model in which short telomeres cause degenerative defects even when telomerase is wild-type [12,13], as well as by the recently generated mouse models for various shelterin components [14,15] which also show severe adult stem cell dysfunction.

3. Telomere shortening and stem cell aging

The aging process concurs with a reduction in the regenerative capacity of various tissues, a decline in stem cell functionality and a drop in telomere reserve. It is generally accepted that stem cell functionality limits organ homeostasis, which in turn limits organismal longevity. It is also known in humans and mice that telomeres shorten with age in stem cell compartments [5,16–18]. But whether the rates of telomere shortening during physiological aging influence stem cell functionality is a remaining question not yet completely answered. An approximation to the former question can be obtained using mice that lack telomerase activity. By successive intercrossing of mice that are deficient in telomerase activity (*Terc*$^{-/-}$ mice), it is possible to obtain sets of mice that only differ in their telomere length, thus providing a model system to analyze how telomere attrition affect the behavior of different tissue stem cells.

In the case of skin, epidermal stem cells (ESCs) from mice with critically-short telomeres (G_3 *Terc*$^{-/-}$ mice) have been compared with ESCs from mice that possess long telomeres (G_1 *Terc*$^{-/-}$ mice). Surprisingly, the number of G_3 *Terc*$^{-/-}$ ESCs exceeds the number of G_1 *Terc*$^{-/-}$ ESCs [19]. Such accumulation of G_3 *Terc*$^{-/-}$ ESCs could be explained by the presence of critically-short telomeres in ESCs which impairs their ability to respond to stimuli with the consequence of a blunted proliferation response, defects that may underlie the premature skin aging phenotype observed in these mice [19]. When skin from wild-type mice of different ages is analyzed a related retention of ESC numbers throughout aging is observed [20]. Despite similar ESC numbers in young and old-mice, aged skin suffers from a general reduction on epidermal proliferation and loss of epidermal integrity suggesting that ESCs functionality declines with advanced age [20].

In the case of the bone marrow, the presence of short telomeres in G_3 *Terc*$^{-/-}$ long-term reconstituting hematopoietic stem cells (LT-HSCs) reduces their ability to repopulate irradiated mice. Such decline in regenerative function is exacerbated in old G_3 *Terc*$^{-/-}$ HSCs, even though the HSC pool expands with age in these mice [21]. A direct function of telomere shortening *per se* (and not telomerase activity) in limiting proliferation is illustrated by a decrease in the number and growth of colony-forming units (cfu) formed in vitro in G_3 *Terc*$^{-/-}$ compared to G_1 *Terc*$^{-/-}$ bone marrow cell suspensions [22]. Similarly to ESC in skin, the increased frequency of LT-HSCs in old mice may reflect an accumulation of defective LT-HSCs during aging [23]. Indeed, the vast majority of LT-HSCs from old wild-type mice stain for phosphorylation of histone H2AX, a marker of the DNA-damage-response, indicating that DNA damage accumulates in stem cells with age [21].

Similar conclusions can be derived from studies in the gut where crypt apoptotic bodies increased progressively in each successive generation of G_1 to G_3 *Terc*$^{-/-}$ [22]. Finally, the deleterious effect of telomere shortening is not limited to high turnover tissues since the adult brain of late-generation telomerase-deficient mouse shows a reduction in its neural stem cells (NSC) proliferation and differentiation capacities [17,24].

4. Sensing telomere damage in stem cell populations

The tumor suppressor protein p53 is a major sensor of cellular stress, including telomere damage. Upon extreme telomere shortening in late-generation telomerase-deficient mice, p53 is activated in skin and gut leading to a proliferation arrest and an apoptosis response, respectively [22,25]. Interestingly, the majority of p53-positive cells accumulate within the stem/progenitor compartments in both tissues, suggesting that p53 is activated in stem/progenitor cells in the presence of short telomeres [25,22]. Increased levels of nuclear p53 are also detected in adult NSCs derived from late-generation telomerase-deficient mice [24].

To address the contribution of p53 activation in mediating stem cell functionality defects triggered by short telomeres, several groups have generated late-generation telomerase-deficient mice in a p53 null background. In pioneering experiments, Chin et al. demonstrated that the absence of p53 rescues the germ cell depletion associated with telomere dysfunction in late-generation *mTerc*$^{-/-}$ mice, suggesting that p53 senses telomere damage in stem/progenitor cell populations and leads to massive germ cell apoptosis [26]. More recently, we showed that p53 ablation rescues the mitogen induced hair and skin growth responses, at the same time that it corrects epidermal stem cell (ESC) activation in telomere-dysfunctional mice [25]. Ferrón et al. determined that p53 deletion not only rescues neural stem cell proliferation defects but also differentiation defects of adult neural progenitors with dysfunctional telomeres [17]. Finally, Begus-Nahrmann et al. have shown that the lack of p53 impairs the depletion of intestinal stem cells leading to an increase of chromosomal instability in basal crypts and premature intestinal failure of aging mice with short telomeres [27]. Therefore, the middle-term effect of p53 deletion in mice with short-term telomeres depends in the tissue, beneficial in testis, skin and brain, and detrimental in gut. Yet, since p53 deletion in late generation telomerase deficient mice ultimately leads to accelerated tumor formation, the overall data suggest that such p53-dependent checkpoint acting on stem cells in these mice col-

lectively serves as an ahead-of-time crucial first barrier against tumor progression.

5. "Live fast, die young" vs. "Live slow, die old and, with help, very old"

Unfortunately many talented human beings have fallen victim to the philosophy "live fast, die young". In the case of famous pop and rock stars a recent study reports that their chances of premature death double the ones of the rest of the population [28]. Although not reaching anxiety levels, depression and drug use sometimes present in this "high-risk" profession, common modern lifestyles tend to bring high levels of psychological and physiological stress. How stress influences our cells at the molecular level is unknown, but telomerase activity and telomere length may be potential mediators. Higher levels of perceived psychological stress in humans concurs with low levels of telomerase activity and shorter telomeres [10]. Risk of cardiovascular diseases and higher mortality rates are also associated with short telomeres [29,30]. In the telomerase knockout model, a progressive reduction in life span parallels a progressive reduction in telomere length as generations without *Terc* increases [22,31]. Collectively, these data suggest that telomerase and telomere length are rate-limiting for human and mice life-span.

To avoid the exhaustion of telomere reserves and to test the influence of telomere-maintenance mechanisms in life-span, telomerase has been constitutively expressed in several transgenic mice. Initial studies showed that forced-expression of telomerase moderately expands maximum life-span but at the cost of slightly higher rates of tumor formation early in life [32]. More recent studies from our group have prevented the telomerase protumorigenic activities by overexpressing Tert, the catalytic component of telomerase, in a tumor-resistant genetic background [33]. In mice with extra-Tert and extra copies of the tumor suppressors genes p53, Ink4a and ARF, the potential of telomerase in delaying aging was unmasked with the final outcome of an increase in median life expectancy up to 40% compared to controls [33]. It is important to remark that the life-span expansion is not due to cancer protection because when longevity was compared considering only those mice that do not succumb by tumors the difference in life expectancy between the quadruplet transgenics and controls was maintained [33]. In agreement with the beneficial longevity effect, the number of degenerative pathologies decreases at old ages in these compound mice. In addition, telomere reserves in stem cell compartments and proliferation potential of stem cells are better preserved, which could explain at the molecular level the antiaging effect of telomerase. Interestingly, a modest increase in Ink4a/Arf/p53 genes under their natural regulation and during the entire life of the mouse also has a positive effect on telomere and stem cell preservation [33].

Considering the above results, we propose a simplified model of life extension in which the time-point of tissue homeostasis failure is determined by the pace of stem cell division and the number of stem cell divisions permitted before stem cell telomeres become critically-short (see Fig. 1). Given that tumor suppressors restrain the proliferation of adult stem cells as well as may prevent accumulation of stem cells with DNA damage [34], stem cells carrying extra tumor-suppressor would present a lower rate of stem cell division, thus prolonging tissue homeostasis by "living slow". On top of that, telomerase would further extend life-span by maintaining telomeres above their critically-short length and therefore increasing the permissible number of stem cell divisions. Besides telomerase other factors may determine stem cell division at old ages since Tert forced-expression, although produces immortal cells, does not produce immortal mammals.

6. Delaying ageing avoiding telomere loss

According to the model presented in Fig. 1, treatments that help to maintain telomere length would produce beneficial effects in life-extension. One way to preserve telomere integrity would be elongating telomeres by activating telomerase; another non-exclusive way would be inhibiting telomere attrition indirectly by slowing-down the rate of stem cell division.

Natural interventions and drugs can activate telomerase. Specifically, physical activity, healthy diet and stress management augments telomerase activity in middle-age men and old women [9,35]. In addition, chemical telomere activators have been shown to act in vitro and experiments in vivo are underway [36]. Furthermore, moderate increases in the expression of genes involved in growth arrest, i.e., p21, in stem cells could be a plausible option to lower the rate of stem cell division and consequently delay exhaustion of telomere reserves. Indeed, small molecules that target the Mdm2-p53 interaction, elevating p21 levels, have already been characterized, showing in vivo activity [37]. Interestingly, reduction in bone thickness, one of the hallmarks of aging, is ameliorated in mutant mice with a partial reduction in Mdm2 activity, which supports a beneficial effect for long-term tissue homeostasis in disrupting Mdm2-p53 interactions [38].

7. The longest telomeres as a marker for adult stem cells

The main causes of telomere shortening are oxidative activities at the telomeres and the incomplete replication of telomeric DNA during cell division, the so-called "end-replication problem", attrition mechanisms that can be counteracted by the enzyme telomerase. In adults, telomerase is only expressed in germ cells, stem cells and some progenitor cells [39]. Furthermore, stem cells divide very infrequently and reside in specific microenvironments or niches that are protected from oxidative damage and other damaging agents [40], suggesting a low rate of telomere erosion throughout their life-time. A prediction from these observations is that those cells with the longest telomeres within a given tissue may correspond to the most primitive stem cell population.

We have recently generated topographic telomere length maps in tissue sections to examine the former prediction. Telomere maps performed in skin, small intestine, brain, cornea and testis sections show gradients of telomere length, with the longest telomeres generally marking the most primitive adult stem cell compartments and the shortest telomeres in the more differentiated compartments within a given tissue [5]. Other authors have confirmed some of these findings studying the gut and reported similar results in lingual epithelium [18,41]. Since telomere cell hierarchies are general features of almost all adult organs, identification of the longest telomeres may be useful in identifying new stem cell compartments. Indeed, we have recently defined a stem cell niche in the pituitary by combining telomere length measurements with other expression markers [42].

The correct identification and characterization of stem cell niches in healthy and disease conditions could lead to new clinical applications. In particular, stem cells have gained importance as the population of cells that tumors arise from, the so-called "cancer stem cells" [43]. The ability to identify this population will enable to monitor their behavior in response to different stimuli or therapeutic treatments, as well as to study the molecular changes within stem cells that lead to tumorigenesis.

8. Telomerase, telomeres, and pluripotency

Mouse and human Embryonic stem (ES) cells are pluripotent, proliferate indefinitely and bear very long telomeres owe to high

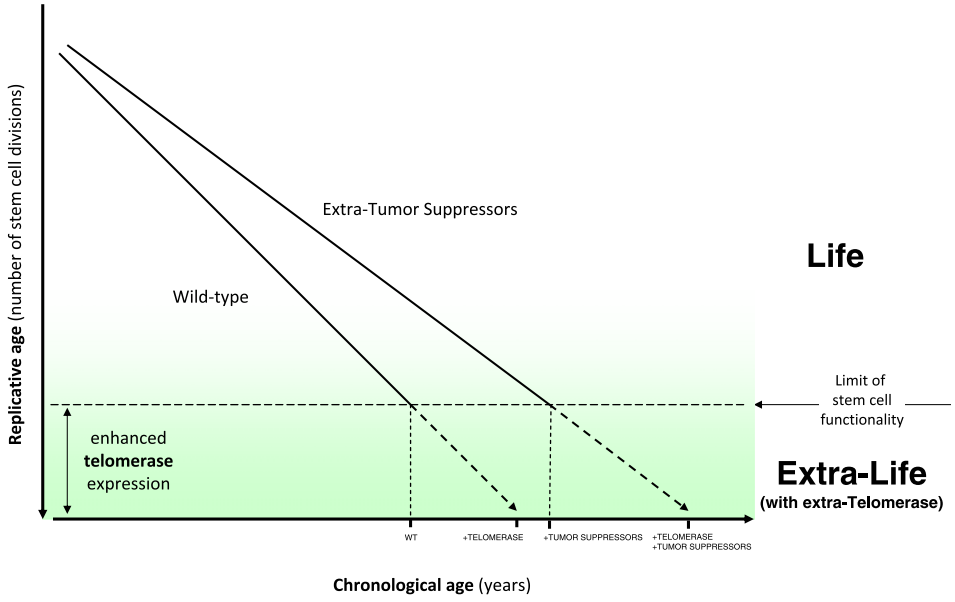

Fig. 1. Extra telomerase and extra tumor suppressors increase the life span of mice.

telomerase activity [44–46]. Indeed, high TERT expression is considered one of the landmarks of the pluripotent state. ES-like pluripotent stem cells have been recently generated from differentiated cells (i.e., MEFs) by using defined factors giving rise the so-called induced pluripotent stem (iPS) cells, which are considered functional equivalents of ES cells and also have high TERT expression [47–54]. Like ES cells, iPS cells are able to contribute to embryonic mouse development and to the mouse germline as well as share similar genome-wide epigenetic profiles [47,48,52,55,56]. We recently showed that iPS telomeres increase in length during and post nuclear reprogramming until reaching ES cell hyper-long telomeres, concomitant with a low density of trimethylated histones H3K9 and H4K20 at telomeric chromatin and an increased abundance of telomere transcripts, the so-called TERRA [56]. Importantly, telomere lengthening was not observed in iPS cells derived from first generation telomerase-deficient MEFs indicating that presence of hyper-long telomeres in iPS cells was not due to a selection of cells with very long telomeres already present at in parental MEFs population but, instead, it was due to an active telomere elongation by telomerase during and post nuclear reprogramming [56]. Importantly, we observed that the reprogramming efficiency of cells derived from increasing generations of telomerase deficient mice is drastically reduced, and this defect is corrected after telomerase reintroduction [56]. The fact that cells with short telomeres are not subject to nuclear reprogramming suggests the existence of some "reprogramming barriers" aborting the reprogramming of suboptimal parental cells bearing dysfunctional telomeres. In this regard, reprogramming in the face of pre-existing but tolerated DNA damage is aborted by the activation of the p53-dependent DNA damage response (DDR) and apoptosis. In particular, during reprogramming iPS cells increase their intolerance to the different types of DNA damage and p53 is critical to avoid generation of iPS cells from suboptimal parental cells [57]. Finally, given that certain reprogramming factors promote in vivo tumorigenesis, it is tempting to propose that the DDR observed in cultures of p53 deficient cells might be equivalent to the oncogene-induced DDR that takes place during malignant transformation. For the two scenarios, nuclear reprogramming and transformation, p53 is critical for controlling the dissemination of damaged cells.

Our results highlight the importance of telomere biology in the generation and in the functionality of iPS cells, and they have important implications for the clinical translation of iPS cells technologies, particularly so in those patients afflicted with the so called "telopathies".

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