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Extending the Models of Tumor Suppression and Telomere Integrity Interaction: Focusing on the Bone Marrow

Fernando Pires Hartwig*

Postgraduate Program in Epidemiology, Federal University of Pelotas Oncology Research Group; Technology Development Center (Biotechnology Unit), Federal University of Pelotas, Brazil

Abstract

Telomeres have been receiving attention given their roles in cancer and aging. Germline genetic variants that result in accelerated telomere dysfunction are often associated with bone marrow diseases, with bone marrow failure being the main cause of death for dyskeratosis congenita. It is well-established that telomere dysfunction activates tumor suppression pathways, thus limiting cell viability. Hartwig and Collares recently reviewed the literature on the differential roles of senescence and apoptosis in detecting telomere dysfunction, proposing biological models regarding tissue renewal impairment and cancer. Based on this paper, the present commentary extends the hypothesis to levels of telomerase activity/telomere integrity others than down-regulated, thus adding to the understanding of the effects of the interactions of senescence and apoptosis. Given the relevance of the bone marrow for the clinical manifestation of telomere syndromes, this commentary focuses on the implications of the proposed extensions for bone marrow impairments, suggesting a hematopoietic stem cell-based model according to which environmental factors plausibly add an extra degree of complexity to the effects of the interactions between telomere biology and tumor suppression responses on the balance between hematopoietic stem cell impairment and hematological malignancies in both telomere syndromes and physiological aging.

Keywords: Telomere dysfunction; Senescence; Apoptosis; Telomere syndromes; HSCs impairment; Hematological malignancies

Abbreviations: ASC: Adult Stem Cell; HSC: Hematopoietic Stem Cell; DC: Dyskeratosis Congenita; AML: Acute Myeloid Leukemia

Introduction

According to the World Health Organization, the age structure of most populations worldwide is changing, with an increase in the over 60 years-old group in almost every country. Such demographic change resulted in aging-related diseases as among the most prevalent causes of morbidity and mortality in the world, raising great interest in their study. In parallel with this, the discovery of the ribonucleoprotein telomerase was published in 1987 [1], and its role as a key aspect of aging and aging-related diseases have been extensively studied and is, currently, a well-established concept, which importance was recognized with the Nobel Prize in 2009 in Medicine and Physiology [2]. Telomerase activity is limited to a few cell types [3,4], including adult stem cells (ASCs), which are of great relevance for aging-related diseases. Telomerase activity promotes telomere (5' TTAGGG 3' DNA *tandem* repeats associated with six proteins called shelterin) [5] elongation through *de novo* DNA synthesis by reverse transcription, which is essential to allow a cell to continue to proliferate for several mitotic rounds (considering the end-replication problem) and the fact that critically shortened telomeres elicited DNA damage responses that results in cell cycle arrest or cell death [6]. A field where telomere biology is of great importance is cancer, since telomere dysfunction is associated with genetic instability and telomerase activity is estimated to be expressed in 85-90% of all human cancers, where it has a major contribution in cell immortalization [7]. In the context of ASCs, telomerase activity is sufficient only to delay telomere shortening along replicative rounds [8]. As a consequence, ASCs eventually reach a critical telomere length state, which culminates with loss of tissue self-renewal capacity and associated impairments [9].

Considering that telomere length limits ASC proliferation, it is intuitive that high-turnover tissues are the most affected by telomere dysfunction, featuring among the most common clinical manifestations caused by genetic profiles associated with premature telomere shortening. Importantly, the main cause of death for dyskeratosis congenital (DC) patients – a telomere syndrome – is bone marrow failure, and DC patients are prone to hematopoietic stem cell (HSC)-related disorders, including aplastic anemia and hematological cancers [10,11]. Given the roles of DNA damage response in sensing telomere dysfunction, the interplay between tumor suppression capacity and telomerase activity/telomere length in aging and aging-related diseases (including cancer and tissue self-renewal failure) has been investigated, and biological models for such interactions being proposed. Although other key studies will be considered here, this manuscript is mainly based on a recent publication that proposed biological models for the effects of the interaction between tumor suppression and telomere length in DC regarding cancer and ASC failure [12]. This manuscript was the first (in the best of my knowledge) to include the different effects of apoptosis and senescence into a biological model of a human telomere dysfunction-related disease, which provides an extensible framework to include such effects in other telomere length contexts. Moreover, the implications of the model are directly applicable to HSCs (as well be discussed shortly).

In a key study, mice over expressing both TERT (the catalytic subunit of telomerase, which expression is one of the main physiological rate-limiting factors for telomerase activity) in the epithelia and tumor suppressors (p53, p16 and p19ARF) showed that telomerase activity

***Corresponding author:** Fernando Pires Hartwig, Postgraduate Program in Epidemiology, Federal University of Pelotas; Oncology Research Group, Technology Development Center (Biotechnology Unit), Federal University of Pelotas, Brazil, Tel: (5553) 81347172; E-mail: fernandophartwig@gmail.com

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increases median lifespan and delays tissue self-renewal failure, considering either all or only cancer-free animals [13]. Interestingly, the results of this study also support the notion that increased tumor suppression in a wild-type telomerase background also has effects in the same direction (by looking at figure 4 of a review of the same research group [14], such effect can be calculated, resulting in increases of 11.3% and 8.7% for overall and cancer-free survival, respectively. This has been considered to occur by restraining ASCs proliferation and preventing accumulation of DNA damaged-ASCs (which is in accordance to the roles of both age-dependent DNA damage accumulation as a physiological limiting factor for HSC function [15] and tumor suppression responses in sensing telomere dysfunction and DNA damaging stresses) [16,17], resulting in the elaboration of stem cell-based models for longevity based on telomerase activity and tumor suppression capacity [17]. Such findings can be used to extend the model described in the commented paper, as shown in Figure 1A. According to this model, cancer risk and ASC failure are not necessarily (qualitatively) opposites. However, this model fails to consider one critical piece of experimental evidence, which showed that deletion of the *Cdkn1a* locus in telomere-deficient mice extended mice lifespan, rescued intestinal progenitor cells proliferation and improved the HSC repopulation and self-renewal capacities, without increasing cancer risk [18]. This, in combination with other studies (well-reviewed elsewhere [19]), evidenced that senescence and apoptosis are redundant regarding tumor suppression activated by telomere dysfunction, while senescence is the major determinant of loss of regenerative capacities due to short

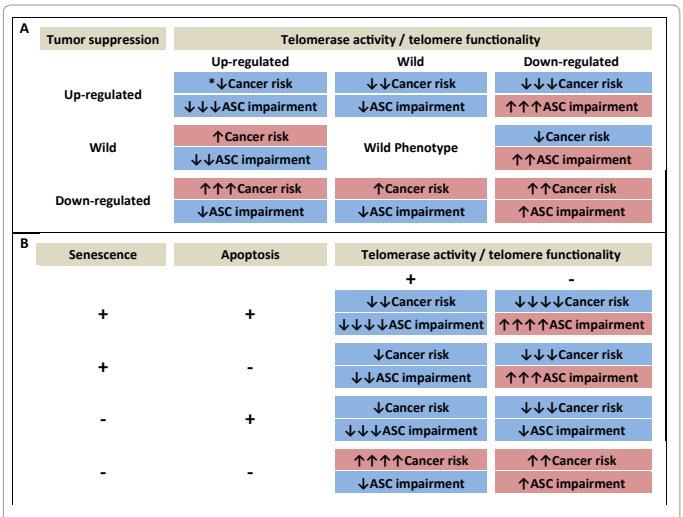

Figure 1: A schematic representation of the effects of the interactions between tumor suppression and telomerase activity/telomere functionality on cancer risk and ASC impairment. In both panels, the increase (↑) or decrease (↓) of outcome risk is compared to an "intermediate" condition (A: "Wild Phenotype"; B: A hypothetical intermediary condition regarding apoptosis, senescence and telomerase activity / telomere functionality, analogous to A). Importantly, both of these panels do not consider factors other than the ones depicted. (A) The effects of all possible combinations of tumor suppression (without distinguishing apoptosis and senescence) and telomere biology, obtained mainly by combining the commented paper and the SUPER-M mice study into a single model. (B). Similar to A, but depicting the distinct effects of senescence and apoptosis. In both models, an effect modification of the tumor suppression mechanisms according to telomere length regarding the outcomes of interest is clearly illustrated. *The arrows do not represent a fixed quantitative effect, but a rather illustrative representation of risk (for example: ↓↓ is not intended to necessarily represent twice the effect of ↓). Moreover, considering that all groups are compared to the same reference, some of them may have the same number of arrows in the same direction for the same outcome, but this is not necessarily the intended interpretation of this figure since the validity of such equality is of difficult estimation.

telomeres. Considering the differential responses of apoptosis and senescence caused by telomere dysfunction, the model of the interaction between tumor suppression and telomerase activity/telomere length can be extended as shown in Figure 1B, which represents a better extension of the model presented in the Figure 1 of the commented manuscript. Although it may look unexpected to consider telomerase activity/telomere length as a protective factor against cancer in all but in the least tumor suppression -capable group, it is important to note that the model includes only telomerase activity/telomere length and senescence/apoptosis as causative or protective factors regarding cancer and ASC failure. So, given the sufficiency of either senescence or apoptosis to sense telomere dysfunction and the delay of telomere shortening due to up-regulated telomerase, having one of these two tumor suppression pathways enhanced (even if the other is down-regulated) is, in this theoretical setting, a sufficient anti-tumor barrier.

Evidently, this model fails to take into account the broad range of cancer-associated environmental factors that an individual is exposed to in a real setting, and there is experimental evidence that support the notion that such factors may interfere with the interactions between tumor suppression pathways and telomere biology. Comparing two studies using *Terc*-null mice showed that *Trp53*$^{P/P}$ animals (homozygous to a R172P amino acid substitution which ablates p53 apoptotic function while maintaining its ability to induce senescence) are not competent at suppressing DMBA-induced skin cancers [20], while wild-type *Trp53* mice are [21]. This difference has been attributed to a possible need of having both apoptosis and senescence to suppress carcinomas [19], and that such explanation would be coherent with the finding that somatic p53 restoration in mice elicits apoptosis in T-cell lymphomas and senescence in sarcomas [22]. Although this is a possible explanation, the authors of the latter paper acknowledged the possibility that the senescence phenotype in sarcomas could be a consequence of p53 restoration on tumor vasculature or other stromal components. Moreover, this paper did not aimed at dissecting the roles of apoptosis and senescence with high accuracy (e.g., by making use of mutant animals). Still in the context on lymphomas, it has been shown that early generation *Eμ-myc*/*Terc*$^{-/-}$ mice (with telomeres functional) depends on apoptosis (evaluated by transplanting HSC of these animals overexpressing the antiapoptotic *Bcl2* gene) to suppress Burkitt lymphoma, while senescence acts as a tumor suppression mechanism in late-generation *Eμ-myc*/*Terc*$^{-/-}$ mice [23]. In another study, *Trp53*$^{P/P}$ mice showed susceptibility to lymphomas not significantly different than *Trp53*$^{P/+}$ animals (while *Trp53*$^{P/P}$/*Terc*$^{+/-}$ and *Trp53*$^{P/+}$/*Terc*$^{+/-}$ genotypes conferred susceptibility, and *Trp53*$^{P/P}$/*Terc*$^{-/-}$ and *Trp53*$^{P/+}$/*Terc*$^{-/-}$ genotypes conferred resistance) [24]. A third study in this context investigated the effects of the R172P mutation in *Eμ-myc* mice, indicating that senescence in *Eμ-myc*/*Trp53*$^{P/P}$ and *Eμ-myc*/*Trp53*$^{P/+}$ animals is capable of delaying lymphomagenesis compared to *Eμ-myc*/*Trp53*$^{+/-}$ mice, but suffer from lymphomas at a much earlier age than *Eμ-myc*/*Trp53*$^{+/+}$ animals [25]. These results, combined with the critical finding that *Cdkn1a* locus deletion in *Terc*$^{-/-}$ late-generation mice does not increase tumorigenesis neither chromosomal instability [18], are coherent with the notion that, although senescence acts as an important tumor suppression mechanism (especially regarding telomere dysfunction-dependent tumorigenesis), there are some stresses that are better sensed by the apoptotic pathway (in these studies, DMBA exposure and *Eμ-myc* expression). Importantly, this possibility does not necessarily exclude the ideas that both apoptosis and senescence might be required to efficiently suppress carcinomas and that induction of apoptosis and senescence depends on tumor type, but is an important consideration given that some common cancer-associated

environmental exposures could be efficiently sensed by apoptosis but not (or poorly) sensible by senescence, indicating that environmental exposures (which include any external of behavior-related factor) may interfere with the interactions between tumor suppression responses and telomere length in cancer and ASC impairment. Although none of these studies focused specifically on acute myeloid leukemia (AML) or myelodisplasia (the most commonly reported manifestations of hematological malignancies in telomere syndromes), the conclusions drawn based on such evidence are likely to apply to these cancer types, considering that cancer in telomere syndrome patients are more likely to occur in high-turnover tissues in general (given their common underlying cause – premature telomere dysfunction). It is also important to consider that the more recently proposed myeloid-based model for hematopoiesis suggests a greater degree of similarity between myeloid and lymphoid lineages than previously anticipated by the classic model [26]. In addition, is has been shown that SNPs in the p53 pathway are associated with AML in case-control studies [27,28], and experimental evidence shows that disabling p53 and activating a mutant form of the KRAS ($KRAS^{G12D}$, a common mutation in AML) promotes AML by allowing self-renewal of aberrant myeloid progenitor cells, which become leukemia-initiating cells [29].

The briefly discussed evidence could be better understood if contextualized in an example, which will focus on HSCs. In telomere syndromes, HSC-related diseases are among the main causes of morbidity and mortality [10]. This is, basically, a combination of the high cell turnover in the bone marrow (which is, thus, very sensible to telomere dysfunction-caused HSC exhaustion) and the clinical importance of hematological diseases that are commonly observed in telomere syndromes, including aplastic anemia, myelodysplasia, AML and bone marrow failure [30]. This characteristic of increased risk of both HSC-exhaustion diseases and malignancies in patients with telomere syndromes is in accordance with the models proposed in the commented manuscript and with the knowledge that AML is a common complication of aplastic anemia. Given that, although DC patients (as well as telomere syndrome cases in general) are known to be cancer-prone, the majority of DC patients' deaths are attributable to degenerative impairments (while cancer mortality accounts for a minor portion of deaths) [31], it is plausible to infer that, in the majority of cases, telomere dysfunction in telomere syndromes results in loss of cell viability (especially in high-turnover tissues as the hematopoietic compartment) as a result of being sensed by tumor suppression mechanisms or by resulting in genomic instability that leads to cell crisis. Combining these studies and focusing on HSC, a model according to which the balance between HSC-failure impairments and hematological cancers in patients with cryptic DC (where phenotypes such as aplastic anemia, mielodysplasia and AML are more commonly observed [11], although the model applies to other forms of telomere syndromes as well) is a consequence of apoptotic and senescence capacities and exposure to environmental factors that do not elicit senescence (Figure 2). According to this model, senescence capacity is a key factor in determining the severity of HSC-failure impairments and, as a consequence, whether or not an individual will be at risk of developing cancer. However, irrespectively (or with reduced importance) of the senescence capacity, an individual with reduced apoptotic function and highly exposed to environmental risk factors could develop a cancer even earlier than any sign of degenerative phenotypes. This model also illustrates the notion that the extra tumor suppression potential of apoptosis is more clearly observed in individuals with functional telomeres: in healthy (regarding telomere syndromes) or young people (regarding the general population), the cancer-associated stresses

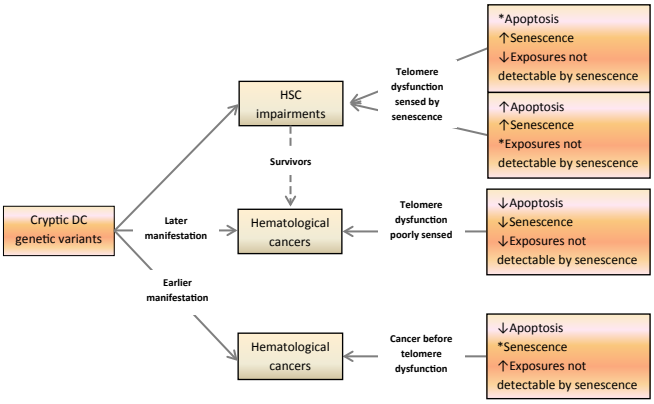

Figure 2: This scheme illustrates a simplistic model for the interaction between environmental factors and tumor suppression responses regarding HSC failure and hematological cancers in cryptic DC (and possibly other telomere syndromes). The explanation of the model can be found in the text. *Indicates that, in the correspondent situation, the marked factor has less prominent effects. For example, the effects of environmental exposures poorly detectable by senescence are smaller in individuals with competent apoptosis than in individuals with reduced apoptotic function.

are (at least partially) better sensed by apoptosis, while senescence has more modest effects as a tumor suppression mechanism. In telomere syndrome cases or in the elderly, senescence will sense telomere dysfunction (and perhaps other physiological markers of aging, which are prominent in these individuals), diluting (because it complements at a level of redundancy) the overall effect of apoptosis as a tumor suppression mechanism. Interestingly, a logical extension of this model is in accordance with one of the intriguing implications of the commented paper: a telomere syndrome case with efficient apoptosis and reduced senescence would be less prone to HSC-failure with slight increases in cancer (comparing with a case of both tumor suppression pathways highly efficient), which can be (at least partially) counterbalanced by surveillance and healthy habits. Moreover, both models are expected to apply to the understanding of similar phenotypes in sage-dependent telomere shortening in the general population [32], which is an important contribution given the current trends in the age-structures in most countries.

It is out of the expectations of this commentary manuscript to quantify and establish complete and fully-accurate models of the interactions between tumor suppression and telomere dysfunction regarding hematological phenotypes. The goal was to extend the model presented in a recent publication to include telomerase activity/telomere functionality situations not considered there based on qualified experimental evidence, as well as propose a more realistic model (including environmental factors) for the variability in clinical manifestations of telomere-related phenotypes, focusing on HSCs. In Figure 2, for example, rather than a complete causal model, it would be better interpreted as associations that would be expected to be found in a case-control study of telomere syndrome cases that share the same genetic profile (regarding telomere length/integrity) but have different clinical presentations. This is left as an implication and perspective of this manuscript. Another perspective is to identify which environmental factors affect HSC (or its early progeny), since ASC are protected by their niche, in addition to present relatively low mitotic rates [33]. In this context, the most studied factor is radiation (since it is a possible complication of radiotherapy that can be easily anticipated) [34,35], but other factors as oxidized low-density lipoprotein [36] and a wide

variety of DNA-damaging agents [37] have been evidenced to affect HSC. This perspective also includes investigating such HSC-affecting factors regarding the validity and relevance of the notion that some HSC-affecting exposures are efficiently sensed by apoptosis but not by senescence. Identifying these exposures would favor the development of interventional strategies to reduce the early accumulation of damage in HSCs, which would be beneficial to delay both cancer and HSC-failure impairments.

Conclusion

The final perspective is to stimulate the study of the interactions between tumor suppression (separating senescence and apoptosis) and telomere dysfunction at the epidemiological level, in both telomere syndrome cases and the elderly population, which is essential to refine biological models (such as the ones proposed here) with data that is more directly relevant to health interventions at the population and individual levels, which could be achieved by reducing the exposure to environmental factors that affect HSC and identifying high-risk individuals by genetic screening and allocating them to specific health programs.

References

1. Greider CW, Blackburn EH (1987) The telomere terminal transferase of Tetrahymena is a ribonucleoprotein enzyme with two kinds of primer specificity. Cell 51: 887-898.
2. Abbott A (2009) Chromosome protection scoops Nobel. Nature 461: 706-707.
3. Kim NW, Piatyszek MA, Prowse KR, Harley CB, West MD, et al. (1994) Specific association of human telomerase activity with immortal cells and cancer. Science 266: 2011-2015.
4. Wright WE, Piatyszek MA, Rainey WE, Byrd W, Shay JW (1996) Telomerase activity in human germline and embryonic tissues and cells. Dev Genet 18: 173-179.
5. de Lange T (2005) Shelterin: the protein complex that shapes and safeguards human telomeres. Genes Dev 19: 2100-2110.
6. Blackburn EH (2005) Telomeres and telomerase: their mechanisms of action and the effects of altering their functions. FEBS Lett 579: 859-862.
7. Shay JW, Bacchetti S (1997) A survey of telomerase activity in human cancer. Eur J Cancer 33: 787-791.
8. Flores I, Benetti R, Blasco MA (2006) Telomerase regulation and stem cell behaviour. Curr Opin Cell Biol 18: 254-260.
9. Mason PJ, Bessler M (2011) The genetics of dyskeratosis congenita. Cancer Genet 204: 635-645.
10. Bessler M, Wilson DB, Mason PJ (2010) Dyskeratosis congenita. FEBS Lett 584: 3831-3838.
11. Dokal I (2011) Dyskeratosis congenita. Hematology Am Soc Hematol Educ Program 2011: 480-486.
12. Hartwig FP, Collares T (2013) Telomere dysfunction and tumor suppression responses in dyskeratosis congenita: Balancing cancer and tissue renewal impairment. Ageing Res Rev 12: 642-652.
13. Tomás-Loba A, Flores I, Fernández-Marcos PJ, Cayuela ML, Maraver A, et al. (2008) Telomerase reverse transcriptase delays aging in cancer-resistant mice. Cell 135: 609-622.
14. Donate LE, Blasco MA (2011) Telomeres in cancer and ageing. Philos Trans R Soc Lond B Biol Sci 366: 76-84.
15. Rossi DJ, Bryder D, Seita J, Nussenzweig A, Hoeijmakers J, et al. (2007) Deficiencies in DNA damage repair limit the function of haematopoietic stem cells with age. Nature 447: 725-729.
16. He S, Nakada D, Morrison SJ (2009) Mechanisms of stem cell self-renewal. Annu Rev Cell Dev Biol 25: 377-406.
17. Flores I, Blasco MA (2010) The role of telomeres and telomerase in stem cell aging. FEBS Lett 584: 3826-3830.
18. Choudhury AR, Ju Z, Djojosubroto MW, Schienke A, Lechel A, et al. (2007) Cdkn1a deletion improves stem cell function and lifespan of mice with dysfunctional telomeres without accelerating cancer formation. Nat Genet 39: 99-105.
19. Deng Y, Chan SS, Chang S (2008) Telomere dysfunction and tumour suppression: the senescence connection. Nat Rev Cancer 8: 450-458.
20. Cosme-Blanco W, Shen MF, Lazar AJ, Pathak S, Lozano G, et al. (2007) Telomere dysfunction suppresses spontaneous tumorigenesis in vivo by initiating p53-dependent cellular senescence. EMBO Rep 8: 497-503.
21. González-Suárez E, Samper E, Flores JM, Blasco MA (2000) Telomerase-deficient mice with short telomeres are resistant to skin tumorigenesis. Nat Genet 26: 114-117.
22. Ventura A, Kirsch DG, McLaughlin ME, Tuveson DA, Grimm J, et al. (2007) Restoration of p53 function leads to tumour regression in vivo. Nature 445: 661-665.
23. Feldser DM, Greider CW (2007) Short telomeres limit tumor progression in vivo by inducing senescence. Cancer Cell 11: 461-469.
24. Liu G, Parant JM, Lang G, Chau P, Chavez-Reyes A, et al. (2004) Chromosome stability, in the absence of apoptosis, is critical for suppression of tumorigenesis in Trp53 mutant mice. Nat Genet 36: 63-68.
25. Post SM, Quintás-Cardama A, Terzian T, Smith C, Eischen CM, et al. (2010) p53-dependent senescence delays Emu-myc-induced B-cell lymphomagenesis. Oncogene 29: 1260-1269.
26. Kawamoto H, Wada H, Katsura Y (2010) A revised scheme for developmental pathways of hematopoietic cells: the myeloid-based model. Int Immunol 22: 65-70.
27. Xiong X, Wang M, Wang L, Liu J, Zhao X, et al. (2009) Risk of MDM2 SNP309 alone or in combination with the p53 codon 72 polymorphism in acute myeloid leukemia. Leuk Res 33: 1454-1458.
28. Ebid GT, Sedhom IA, El-Gammal MM, Moneer MM (2012) MDM2 T309G has a synergistic effect with P21 ser31arg single nucleotide polymorphisms on the risk of acute myeloid leukemia. Asian Pac J Cancer Prev 13: 4315-4320.
29. Zhao Z, Zuber J, Diaz-Flores E, Lintault L, Kogan SC, et al. (2010) p53 loss promotes acute myeloid leukemia by enabling aberrant self-renewal. Genes Dev 24: 1389-1402.
30. Armanios M, Blackburn EH (2012) The telomere syndromes. Nat Rev Genet 13: 693-704.
31. Alter BP, Giri N, Savage SA, Rosenberg PS (2009) Cancer in dyskeratosis congenita. Blood 113: 6549-6557.
32. Aubert G, Baerlocher GM, Vulto I, Poon SS, Lansdorp PM (2012) Collapse of telomere homeostasis in hematopoietic cells caused by heterozygous mutations in telomerase genes. PLoS Genet 8: e1002696.
33. Morrison SJ, Spradling AC (2008) Stem cells and niches: mechanisms that promote stem cell maintenance throughout life. Cell 132: 598-611.
34. de Laval B, Pawlikowska P, Petit-Cocault L, Bilhou-Nabera C, Aubin-Houzelstein G, et al. (2013) Thrombopoietin-increased DNA-PK-dependent DNA repair limits hematopoietic stem and progenitor cell mutagenesis in response to DNA damage. Cell Stem Cell 12: 37-48.
35. Chua HL, Plett PA, Sampson CH, Joshi M, Tabbey R, et al. (2012) Long-term hematopoietic stem cell damage in a murine model of the hematopoietic syndrome of the acute radiation syndrome. Health Phys 103: 356-366.
36. Zhang XP, Zhang GH, Wang YY, Liu J, Wei Q, et al. (2013) Oxidized low-density lipoprotein induces hematopoietic stem cell senescence. Cell Biol Int .
37. Guo F, Li J, Du W, Zhang S, O'Connor M, et al. (2013) mTOR regulates DNA damage response through NF-kB-mediated FANCD2 pathway in hematopoietic cells. Leukemia.