Clinical Perspective

Telomere Length and Skin Cancer

Jiali Han, PhD

Abstract

Telomere length in peripheral blood lymphocytes has emerged as a potential biomarker of aging and risk of age-related diseases such as cancers. However, telomere shortening is implicated in several aspects of tumorigenesis, including senescence, apoptosis, and genomic instability. Because of the distinct proliferative features of different cells, telomere length may play roles in both suppressing and facilitating carcinogenesis. Understanding this heterogeneity is key for the development of targeted cancer-preventative and -therapeutic interventions. We use skin cancer as one example to elucidate that distinct genetic constitutions among different types of cells and tissues evoke different DNA damage responses against telomere shortening and malignant transformation.

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Key Words: *telomere length, telomere shortening, skin cancer, melanoma, basal cell carcinoma (BCC), squamous cell carcinoma (SCC)*

Introduction

There are three major types of cells in the epidermis (melanocytes, basal keratinocytes, and squamous keratinocytes), giving rise to melanoma, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC), respectively. Melanocytes, which reside on the basal layer of the epidermis, exhibit less apoptotic activity and less differentiation than keratinocytes.[1] Melanocyte proliferation can lead to oncogene-induced senescence, which gives rise to melanocytic nevi, benign tumors commonly referred to as moles. On the other hand, squamous keratinocytes on the surface of the epidermis undergo continual cycles of proliferation and apoptosis throughout a lifetime. Basal cells are less susceptible to apoptosis than squamous keratinocytes[1] and have a lower tendency to enter senescence than melanocytes. The continuing division of basal cells results in further telomere shortening with a concurrent increase in genomic instability. Telomere shortening is implicated in several aspects of tumorigenesis, including senescence, apoptosis, and genomic instability. Because of the distinct proliferative features of these skin cells, telomere length may play different etiological roles in these three types of skin cancer.

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Skin Cancer

Cancer of the skin (non-melanoma and melanoma skin cancers combined) is the most common form of cancer, accounting for more than 50% of all cancers. Most of the more than 1 million cases of skin cancer diagnosed yearly in the United States are considered to be sun-related.[2] Melanoma, the most serious type of skin cancer, accounts for about 4% of skin cancer cases, but it causes about 75% of skin cancer deaths. The number of new cases of melanoma in the US is rising dramatically.[2] The American Cancer Society estimates that there were about 62,480 invasive melanoma cases diagnosed in 2008 and that melanoma accounted for most (about 8,420) of the 11,200 deaths due to skin cancer.[2]

Although the mortality rate associated with non-melanoma skin cancer (SCC and BCC) is low, the very large and ever-increasing incidence translates into considerable morbidity and substantial resources necessary to treat over 1 million lesions each year. SCC is the second most common type of skin cancer. About 16% of diagnosed skin cancers are SCC. It involves the malignant transformation and proliferation of squamous (flat, scaly) cells, which are the most abundant type of cell in the epidermis. About 200,000 cases are diagnosed every year. SCC requires early treatment to prevent metastasis. Although BCC doesn't typically metastasize, the lesions can eventually cause morbidity and/or disfigurement.

As skin cancer is increasingly becoming a more serious public health problem in the US and globally, research on genetic susceptibility to skin cancer is critical in identifying high-risk groups and providing individualized preventive strategies. However, skin cancers have been relatively understudied compared to other common cancers. UV exposure has been shown to contribute to the development of both melanoma and non-melanoma skin cancer.[3-6] Melanoma is consistently associated with intermittent UV exposure, whereas non-melanoma skin cancer, especially SCC, is more closely associated with cumulative UV exposure. In terms of host constitutional factors, nevus count and light hair color (especially red hair color) are more strongly associated with melanoma compared to non-melanoma skin cancer. Genetically, somatic mutation patterns differ greatly between melanoma and non-melanoma skin cancer, such as BRAF in melanoma and TP53 in SCC and PTEN in BCC. Most of the

genetic components that contribute to the risk of developing sporadic skin cancer remain unknown.

Telomere Shortening in Skin Tissue

Skin tissue undergoes continual cycles of proliferation and replacement throughout a lifetime. Such cycles of renewal are prominent under UV-induced damage. The total lifetime number of sunburns and exposure to UV are strongly associated with skin cancer risk. With an increased number of renewal cycles leading to an increased number of mitotic divisions, it follows that erosion of telomeres may be accelerated in skin tissue. UVB irradiation shortens telomeres and induces telomerase activity.[7,8] Sister chromatid exchanges caused by UVB-induced pyrimidine dimers are quite frequent in telomere regions, indicating that long repeats of telomere sequences are targets for UVB.[8] Although the precise mechanism is not known, it has been reported that UV-damaged telomeric DNA is less well-repaired than transcriptionally active genes.[9] Unrepaired UVB lesions cause daughter-strand gaps during DNA replication. DNA replication across a gap is likely to produce a double-strand break (DSB) in one of the sister chromatids,[10] resulting in substantial loss of terminal telomere repeats or telomere shortening. In addition, UVA can indirectly cause oxidative stress via reactive oxygen species generated after the absorption of light energy by cellular chromophores.[11-13] Oxidative stress can lead to telomere shortening.[14] The skin cells of mice over-expressing TRF2 are hypersensitive to UV and have marked telomere shortening, loss of the telomeric G-strand overhang, and increased risk of skin cancer. Telomere loss is mediated by the XPF gene, a key factor in the nucleotide excision repair pathway,[15] which is responsible for repairing UV-induced DNA photoproducts. In skin tissue, telomere disruption, whether due to acute DNA damage or progressive telomere shortening, triggers multiple DNA damage responses, including tanning (enhanced melanogenesis in pigment cells), activation of p53, cell-cycle arrest, and apoptosis.[16]

Friedrich et al.[17] measured telomere length in peripheral blood lymphocytes (PBLs) and that in skin tissue of nine elderly patients. Although the mean telomere length was shorter in the PBLs than in skin, lengths were significantly correlated among PBLs and skin (R^2=0.71, p=0.018). Even though overall telomere lengths were not directly measured in melanocytes and keratinocytes, PBLs represent a good proxy for telomere length in skin tissues of the same individual. In addition, the correlation between the PBL telomere length and mole counts observed in our study[18] as well as in one previous study[19] further suggests the biological relevance of the PBL telomere length in the tissue of skin.

The Role of Telomere Shortening in the Etiology of Different Types of Skin Cancer

Association between telomere length and skin cancer risk

We preliminarily examined the association between pre-diagnostic overall telomere length in PBL and the risk of three different types of skin cancer simultaneously in the Nurses' Health Study.[18] The blood samples were collected in 1989-1990. All the cases were diagnosed of skin cancer anytime after the blood collection up to 2000. Controls were matched on age and free of skin cancer up to 2000. The fourth quartile (the longest telomere length) serves as the reference (Figure 1). Women in the second and first quartiles (those with the shortest telomere length) had ORs for melanoma of 0.54 (95% CI, 0.29-1.01) and 0.59 (95% CI, 0.31-1.13), respectively, compared with those in the fourth quartile (P, trend = 0.09). There was no clear trend between telomere length and SCC risk. In contrast, we found that shorter telomere length was associated with an increased risk of BCC. Compared with those in the fourth quartile, women in the first quartile had an OR of 1.85 (95%CI, 0.94-3.62) (P, trend =0.09). We plan to replicate these intriguing findings in a much larger study.

Association between telomere-related genetic variants and skin cancer risk

Most recently, through a GWAS on BCC risk, Rafnar et al. identified a locus (rs401681[C]) harboring the TERT gene with an increased risk of BCC along with other cancer sites [20]. The OR for BCC is 1.25 ($P = 3.7x10^{-12}$) among 2,565 cases and 29,405 controls. However, this SNP was associated with a decreased risk of melanoma (OR, 0.88, $P= 8.0x10^{-4}$) among 2,381 cases and 30,839 controls.

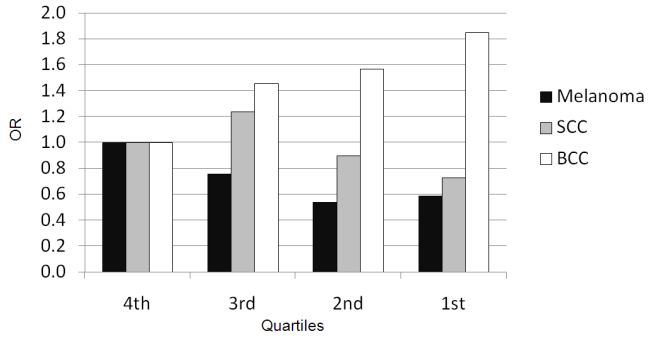

Figure 1. Prospective study of overall telomere length and the risk of skin cancer.

Discussion

The opposing associations observed between overall telomere length and the various skin cancers may stem from the proliferative characteristics of the corresponding cell types from which the cancers arise and how they deal with telomere shortening.

Melanocytes: Presumably cutaneous melanocytes are evolutionarily preserved because they produce melanin, which is responsible for constitutional skin pigmentation and protective tanning response to UV. They are characterized by low levels of proliferation and a limited capacity to undergo apoptosis, perhaps due to a high content of anti-apoptotic proteins, such as BCL2 and Slug.[21] Frequently, activating mutations of the BRAF oncogene occur in melanoctyes, resulting in a transient increase in proliferation and the formation of melanocytic nevi.[22] Rather than undergo

apoptosis, these melanocytes are more likely to senesce in response to oncogenic stress, which allows them to remain functional while preventing the propagation of the oncogenic mutation.[21] Replicative senescence may act as a defense in melanocytes. Cells with short telomeres will reach critical length earlier, causing them to undergo replicative senescence. It has been hypothesized that mutated cells with longer telomere lengths experience a delay in senescence as a result of their greater replication potential. Longer telomeres in melanocytes, which already have two oncogenic mutations (activating BRAF and silenced/deleted p16), may result in delayed senescence, providing these cells with a greater opportunity to acquire additional mutations and increasing the probability of malignant transformation. Prolonged senescence leads to the increased formation of nevi, which are strongly associated with an increased risk of melanoma.[23] The positive association we identified between overall telomere length and both nevus count and melanoma risk would be consistent with such a mechanism.

Recent advances have convincingly demonstrated that senescence represents a true barrier to the progression of many types of cancer, including melanoma. Thus, understanding the mechanism(s) by which melanoma evades senescence has become a priority in the research community. It is important to emphasize that senescence appears to be regulated in melanocytes in a manner that is, at least partially, distinct from other studied cell types.[24]

Squamous keratinocytes: In contrast to melanocytes, squamous keratinocytes are well-differentiated cells that form the uppermost layer of skin. These cells have a lower apoptotic threshold, making the apoptotic pathway the predominant protective mechanism, especially when cells are challenged by toxic stress such as UV-induced DNA damage. Sunburn cells are squamous keratinocytes undergoing apoptosis. Programmed cell death is also part of the normal terminal differentiation process that squamous keratinocytes undergo to form the water-resistant, outermost protective layer of the epidermis [25]. This process is presumably independent of telomere length. We did not find an association between overall telomere length and SCC risk.

Basal keratinocytes: Basal cells are less susceptible to apoptosis than squamous keratinocytes [1] and have a lower tendency to senescence than melanocytes. With much less protection from either senescence or apoptosis, proliferative basal cells coupled with UV-induced damage of telomeric DNA may increase the likelihood of unstable telomeres and trigger chromosomal rearrangements. Under these circumstances, cells with comparatively shorter telomere lengths may reach genomic instability within a smaller number of cell divisions and therefore be at greater risk for malignant transformation. Such a mechanism may explain the association we found between shorter overall telomere lengths and an increased risk of BCC.

In summary, telomere length may play opposing roles in tumorigenesis dictated by the characteristics of the particular cell type and the differences in the biological consequences of telomere shortening. We hypothesize that shorter telomere length protects against the malignant transformation of cells within melanocytic nevi, which already harbor oncogenic mutations, by limiting proliferative capacity. The apoptosis of squamous keratinocytes is protective against malignant transformation, which may be independent from telomere shortening. Shorter telomere length in basal keratinocytes may trigger chromosomal aberrations that could then lead to the development of BCC.

Telomere length in PBLs has emerged as a potential biomarker of aging and risk of age-related diseases such as cancers. However, telomere shortening is implicated in several aspects of tumorigenesis, including senescence, apoptosis, and genomic instability. Because of the distinct proliferative features of different cells, telomere length may play roles in both suppressing and facilitating carcinogenesis.[26] It has recently become well-recognized that cancer cells are substantially heterogeneous in tumorigenesis.[27] Understanding this heterogeneity is key for the development of targeted cancer-preventative and -therapeutic interventions. Current models explaining inter- and intratumoral diversity include the cancer stem cell and the clonal evolution hypotheses.[27] The genetics of early-stage cancers determines the future of clinical behavior. Distinct genetic constitutions among different types of cells and tissues evoke different DNA damage responses against telomere shortening and malignant transformation.

References

1. Gilchrest BA, Eller MS, Geller AC, Yaar M. The pathogenesis of melanoma induced by ultraviolet radiation. N Engl J Med. 1999;340(17):1341-8.
2. Society AC. Cancer Facts and Figures; 2008.
3. Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. Eur J Cancer. 2005;41(14):2040-2059.
4. Goldstein AM, Tucker MA. Genetic epidemiology of cutaneous melanoma: a global perspective. Arch Dermatol. 2001;137(11):1493-6.
5. Elwood JM, Jopson J. Melanoma and sun exposure: an overview of published studies. Int J Cancer. 1997;73(2):198-203.
6. Rigel DS. Cutaneous ultraviolet exposure and its relationship to the development of skin cancer. J Am Acad Dermatol. 2008;58(5 Suppl 2):S129-S132.
7. Miracco C, Margherita De Santi M, Schurfeld K, et al. Quantitative in situ evaluation of telomeres in fluorescence in situ hybridization-processed sections of cutaneous melanocytic lesions and correlation with telomerase activity. Br J Dermatol. 2002;146(3):399-408.
8. Jin G, Ikushima T. Frequent occurrence of UVB-induced sister chromatid exchanges in telomere regions and its implication to telomere maintenance. Cytogenet Genome Res. 2004;104(1-4):310-314.
9. Kruk PA, Rampino NJ, Bohr VA. DNA damage and repair in telomeres: relation to aging. Proc Natl Acad Sci U S A. 1995;92(1):258-262.
10. Wang TC, Smith KC. Postreplication repair in ultraviolet-irradiated human fibroblasts: formation and repair of DNA double-strand breaks. Carcinogenesis. 1986;7(3):389-392.
11. Brash DE. Sunlight and the onset of skin cancer. Trends Genet. 1997;13(10):410-414.
12. Hall M, Johnson RT. The role of DNA repair in the prevention of cancer. Mol Aspects Med. 1996;17(3):235-283.
13. Kielbassa C, Roza L, Epe B. Wavelength dependence of oxidative DNA damage induced by UV and visible light. Carcinogenesis. 1997;18(4):811-816.

14. Houben JM, Moonen HJ, van Schooten FJ, Hageman GJ. Telomere length assessment: biomarker of chronic oxidative stress? Free Radic Biol Med. 2008;44(3):235-246.
15. Munoz P, Blanco R, Flores JM, Blasco MA. XPF nuclease-dependent telomere loss and increased DNA damage in mice overexpressing TRF2 result in premature aging and cancer. Nat Genet. 2005;37(10):1063-1071.
16. Gilchrest BA, Eller MS. The tale of the telomere: implications for prevention and treatment of skin cancers. J Investig Dermatol Symp Proc. 2005;10(2):124-130.
17. Friedrich U, Griese E, Schwab M, Fritz P, Thon K, Klotz U. Telomere length in different tissues of elderly patients. Mech Ageing Dev. 2000;119(3):89-99.
18. Han J, Qureshi AA, Prescott J, et al. A prospective study of telomere length and the risk of skin cancer. J Invest Dermatol. 2009;129(2):415-421.
19. Bataille V, Kato BS, Falchi M, et al. Nevus size and number are associated with telomere length and represent potential markers of a decreased senescence in vivo. Cancer Epidemiol Biomarkers Prev. 2007;16(7):1499-1502.
20. Rafnar T, Sulem P, Stacey SN, et al. Sequence variants at the TERT-CLPTM1L locus associate with many cancer types. Nat Genet. 2009;41(2):221-227.
21. Mooi WJ, Peeper DS. Oncogene-induced cell senescence--halting on the road to cancer. N Engl J Med. 2006;355(10):1037-1046.
22. Gray-Schopfer VC, Cheong SC, Chong H, et al. Cellular senescence in naevi and immortalisation in melanoma: a role for p16? Br J Cancer. 2006;95(4):496-505.
23. Bastian BC. The longer your telomeres, the larger your nevus? Am J Dermatopathol. 2005;25(1):83-84.
24. Ha L, Merlino G, Sviderskaya EV. Melanomagenesis: overcoming the barrier of melanocyte senescence. Cell Cycle. 2008 Jul 1;7(13):1944-8.
25. Nemes Z, Steinert PM. Bricks and mortar of the epidermal barrier. Exp Mol Med. 1999;31(1):5-19.
26. Artandi SE, DePinho RA. A critical role for telomeres in suppressing and facilitating carcinogenesis. Curr Opin Genet Dev. 2000;10(1):39-46.
27. Polyak K. Breast cancer: origins and evolution. J Clin Invest. 2007;117(11):3155-3163.