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### Telomeres, Aging, and Tumorigenesis

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## Telomeres, Aging, and Tumorigenesis

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Telomeres are the repetitive DNA sequences at the end of all linear chromosomes. In humans, there are 46 chromosomes and thus 92 telomere ends that consist of thousands of repeats of the six nucleotide sequence, TTAGGG. The telomere-telomerase hypothesis of aging and cancer is based on findings that most human tumors have telomerase activity while normal human somatic cells do not. Telomere length is maintained by a balance between processes that lengthen telomeres (telomerase) and processes that shorten telomeres (the end-replication problem). Telomerase (TEE-LOM-ER-ACE) is a ribonucleoprotein enzyme complex (a cellular reverse transcriptase) that has been referred to as a cellular immortalizing enzyme, which stabilizes telomere length by adding hexameric (TTAGGG) repeats onto the telomeric ends of the chromosomes, thus compensating for continued erosion of telomeres that occurs in its absence. The enzyme is expressed in adult reproductive cells, but is undetectable in normal somatic cells except for proliferative cells of renewal tissues (e.g., bone marrow cells, basal cells of the epidermis, proliferative endometrium, and intestinal crypt cells). In all dividing telomerase silent somatic cells and in nearly all dividing telomerase competent stem cells, progressive telomere shortening is observed, eventually leading to greatly shortened telomeres and to a limited ability to continue to divide. It has been proposed that telomere shortening may be a molecular clock mechanism that counts the number of times a cell has divided and when telomeres are short, cellular senescence (growth arrest) occurs. It is believed that shortened telomeres in mitotic (dividing) cells may be responsible for some of the changes we associate with normal aging.

Cellular senescence may have evolved in part to protect long-lived organisms, such as humans against early development of cancer. Thus, it has been proposed that upregulation or reexpression of telomerase may be a critical event responsible for continuous tumor cell growth. In contrast to normal cells, tumor cells show no net loss of average telomere length with cell division, suggesting that telomere stability may be required for cells to escape from replicative senescence and proliferate indefinitely. Most, but not necessarily all, malignant tumors may need telo-

merase to sustain their growth. Immortalization may occur through a mutation of a gene in the telomerase repression pathway. Thus, upregulation or reactivation of telomerase activity may be a rate-limiting step required for the continuing proliferation of advanced cancers. There is now much experimental evidence that telomerase activity is present in nearly all human tumors but not in tissues adjacent to tumors. Thus, clinical telomerase research is currently focused on the development of methods for accurate diagnosis of cancer and on novel anti-telomerase cancer therapeutics.

The expression of telomerase in nearly all malignancies suggests that overcoming the proliferative limits imposed by telomere shortening represents a key step in oncogenesis. Expression of the catalytic subunit of human telomerase (hTERT) reconstitutes telomerase activity and circumvents induction of senescence. Interestingly, human fibroblasts and epithelial cells with introduced telomerase have continued to divide for over 500 generations past the time they normally would stop dividing and continue to divide. Importantly, the cells are growing and dividing in a normal manner, giving rise to normal cells with the normal number of chromosomes. Thus, telomerase expression and maintenance of telomere integrity does not bypass cell-cycle induced checkpoint controls and does not lead to genomic instability. While this may appear paradoxical, it is important to remember that cancer is a multi-step process that occurs over many years. Telomerase does not directly affect the molecular processes leading to uncontrolled cell cycles, invasion, or metastases. Thus, the main function for telomerase is to maintain telomeres and permit continued cell growth that is initially limited by shortened telomeres.

Because telomerase does not cause cancer directly, it may be possible to rejuvenate cells for tissue engineering purposes. We have used hTERT to telomerize a variety of human cell types including skin keratinocytes, dermal fibroblasts, muscle satellite (stem) cells, endothelial cells, retinal-pigmented epithelial cells, breast epithelial cells, and both corneal fibroblasts (keratocytes) and corneal epithelial cells. Corneal epithelial cells expressing introduced hTERT require growth on collagen IV, while skin keratinocytes require feeder layers to prevent premature

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growth arrest due to inadequate culture conditions. Human corneal and skin cells expressing hTERT can be used to form organotypic cultures. Such organotypic cultures express differentiation-specific proteins, suggesting that hTERT does not inhibit normal differentiation functions of cells. Using an excimer laser, we have induced specific lesions in organotypic cultures and have investigated repair processes. Production of hTERT-engineered tissues offers the possibility of producing cells and tissues to treat a variety of diseases and aged-related medical conditions due to telomere-based replicative senescence. While there are concerns about the long-term effects of using immortalized cells for tissue engineering, the present results suggest that immortalization or reversible immortalization of specific cell types that can be thoroughly characterized prior to transplantation may have manageable risks.

For additional information, see review issue of the journal *Oncogene* (Volume 21, Number 4, January 21, 2002) on "Telomeres and Telomerase"

## References

- Kim NW, Piatyszek MA, Prowse KR, Harley CB, West MD, Ho PLC, Coviello GM, Wright WE, Weinrich SL, Shay JW. Specific association of human telomerase activity with immortal cells and cancer. *Science*, 1994;266:2011-2015.
- Wright WE, Piatyszek MA, WE Rainey, W Byrd, Shay JW. Telomerase activity in human germline and embryonic tissues and cells. *Dev Genet* 1996;18:173-179.
- Shay JW, Bacchetti S. A survey of telomerase in human cancer. *Eur J Cancer* 1997;33:787-791.
- Bodnar AG, Ouellette M, Frolkis M, Holt SE, Chiu C-P, Morin GB, Harley CB, Shay J W, Lichtsteiner S, Wright WE. Extension of lifespan by introduction of telomerase in normal human cells. *Science* 1998;279:349-352 .
- Morales CP, Holt SE, Ouellette M, Kaur KJ, Ying Y, Wilson KS, White MA, Wright WE, Shay JW. Lack of cancer-associated changes in human fibroblasts after immortalization with telomerase. *Nature Gen* 1999;21:115-118.
- Shay JW, Wright WE. The use of "telomerized" cells for tissue engineering. *Nature Biotech* 2000;18:22-23.
- Shay JW, Wright WE. Hayflick, his limit and cellular ageing. *Nature Reviews: Molecular Cell Biol* 2000;1:72-76.
- Wright WE, Shay JW. Telomere dynamics in cancer progression and prevention: fundamental differences in human and mouse telomere biology, *Nature Medicine* 2000;6:849-85.
- Shay JW, Wright WE. When do telomeres matter? *Science*, 2001;291:839-840.
- White L., Wright WE, Shay JW. Telomerase inhibitors, *Trends in Biotechnology*, 2001;19:114-120.
- Herbert BS, Wright WE, Shay JW. Telomerase and breast cancer, *Breast Cancer Research* 2001;3: 146-149.
- Wright W E, Shay JW. Cellular senescence as a tumor-protection mechanism: the essential role of counting. *Cur Opin Gen Dev* 2001;11:98-103.
- Komata T, Kondo Y, Hirohata S, Koga S, Srinivasa M, Barna BP, Takakura M, Inoure M, Alnemri ES, Kyo S, Shay JW, Kondo S. Treatment of malignant glioma cells with the transfer of constitutively active caspase-6 using the human telomerase catalytic subunit (hTERT) gene promoter. *Cancer Res* 2001;61:5796-5802.
- Shay JW, Zou Y, Hiyama E, Wright WE. Telomerase and cancer. *Human Mol Genetics* 2001;10:677-685 .
- Gryaznov S, Pongracz K, Matray T, Schultz R, Pruzan R, Aimi J, Chin A, Harley CB, Shea-Herbert, Shay JW, Oshima Y, Asai A, Yamashita Y. Telomerase inhibitors – oligonucleotide phosphoramidates as potential therapeutic agents. *Nucleosides, Nucleotides, and Nucleic Acids*, 2001;20:401-410 .
- Baur JA, Shay JW, Wright WE. Telomere position effect in human cells. *Science* 2001;292:2075-2077.
- Aisner DL, Wright WE, Shay JW. Telomerase regulation: Not just flipping the switch. *Cur Opin Gen Dev* 2002;12:80-85.

## References related to telomeres, telomerase, and hematologic issues

- Hiyama K, Hirai Y, Kyoizumi S, Akiyama M, Hiyama E, Piatyszek MA, Shay JW. Activation of telomerase in human lymphocytes and hematopoietic progenitor cells. *J Immunol* 1995;155:3711-3715.
- Ohyashiki K, Ohyashiki JH, Iwama H, Hayashi S, Shay JW, Toyama K. Telomerase reactivation in leukemia cells. *Int J Oncol* 1996;8:417-421.
- Zhang W, Piatyszek MA, Estey E, Kobayashi T, Andreff M, Deisseroth AB, Wright WE, Shay JW. Telomerase activity in acute myelogenous leukemia: Inhibition of telomerase activity by differentiation-inducing agent. *Clin Cancer Res* 1996;2:799-803.
- Shay JW, Werbin H, Wright WE. Telomeres and telomerase in human leukemias. *Leukemia* 1996;10:1255-1261 .
- Ohyashiki K, Ohyashiki JH, Iwama H, Hayashi S, Shay JW, Toyama K. Telomerase activity and cytogenetic changes in chronic myeloid leukemia with disease progression. *Leukemia* 1997;11:190-19 .
- Ohyashiki JH, Ohyashiki K, Iwama H, Hayashi S, Toyama K, Shay JW. Clinical implications of telomerase activity levels in acute leukemia. *Clin Cancer Res* 1997;3:619-625.
- Yamanishi Y, Hiyama K, Maeda H, Ishioka S, Murakami T, Hiyama E, Kurose Y, Shay JW, Yamakido M. Telomerase activity in rheumatoid synovium correlates with the mononuclear cell infiltration level and disease aggressiveness of rheumatoid arthritis. *J Rheumatol* 1998;25:214-220.
- Iwama H, Ohyashiki K, Ohyashik J, Hayashi S, Yahata N, Ando K, Toyama K, Hoshika A, Takasaki M, Shay JW. Telomere length and telomerase activity vary with age in peripheral blood cells obtained from normal individuals. *Human Gen* 1998;102:397-402.
- Shay JW. Accelerated telomere shortening in recipients of bone marrow transplant. *The Lancet (commentary)*, 1998; 351:153-154.
- Ohyashiki JH, Iwama H, Yahata N, Hayashi S, Shay JW, Ohyashiki K. Telomere stability is frequently impaired in high risk groups of patients with myelodysplastic syndromes. *Clin Can Res* 1999;5:1155-1160,.