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Review Article

# The role of telomeres in the ageing of human skin

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**Abstract:** Skin is a self-renewing tissue that is required to go through extensive proliferation throughout the lifespan of an organism. Telomere shortening acts as a mitotic clock that prevents aberrant proliferation such as cancer. A consequence of this protection is cellular senescence and ageing. The telomerase enzyme complex maintains telomere length in germline cells and in cancer cells. Telomerase is also active in certain somatic cells such as those in the epidermis but is almost undetectable in the dermis. Increasing evidence indicates that telomerase plays a significant role in maintenance of skin function and proliferation. Mutations in telomerase component genes in the disease dyskeratosis congenita result in numerous epidermal abnormalities. Studies also indicate that telomerase activity in epidermal stem cells might have roles that go beyond telomere elongation. Telomeres in skin cells may be particularly susceptible to accelerated shortening because of both proliferation and DNA-damaging agents such as reactive oxygen species. Skin might present an accessible tissue for manipulation of telomerase activity and telomere length with the potential of ameliorating skin diseases associated with ageing.

**Key words:** ageing – keratinocytes – reactive oxygen species – senescence – skin – telomerase – telomeres

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## Telomeres and telomerase

Telomeres are critical structures at the end of eukaryotic chromosomes made up of numerous copies of G-rich repeats. In mammals, the telomere repeat is TTAGGG reiterated thousands of times (1). Telomeres protect the ends of chromosomes from degradation and from being recognized as double-stranded breaks. Without telomeres, chromosomes will fuse and genetic instability will occur (2). The telomere repeats bind a large number of proteins called the shelterin complex that stabilizes the telomere to fold back onto itself into what has been referred to as a T loop (Fig. 1) (3). Telomere shortening, telomere damage or expression of mutant telomere-binding proteins can disrupt the shelterin complex and lead to activation of a DNA damage response and cellular senescence (4). Telomere shortening occurs during normal DNA replication because of what has been called the end replication problem, which simply means that DNA polymerase cannot completely replicate the 5′ ends of newly synthesized DNA strands (5). It has been proposed that telomere shortening acts as a mitotic clock to prevent unregulated cell proliferation such as occurs in cancer (6). This mechanism of cancer prevention, however, is believed to come at a cost. Accumulating evidence indicates that telomere-mediated replicative senescence can lead to ageing (7).

Telomeres can be maintained by the enzyme complex telomerase (8). Telomerase was originally discovered in the unicellular eukaryote, Tetrahymena, by Elizabeth Blackburn and Carol Greider (9). For their work on telomerase and telomeres, Blackburn, Greider and Jack Szostek recently shared the 2009 Nobel Prize in Medicine. Telomerase consists of a reverse transcriptase component called TERT and an RNA component called TERC (also referred to as TR or TER) that is utilized by TERT to add telomere repeats to the chromosome end (Fig. 2) (10). Other proteins are also involved in the telomerase complex including dyskerin (DKC), which stabilizes small nucleolar RNAs (snoRNAs) such as TERC (8).

Expression of telomerase components is tightly regulated in human cells (11). Telomerase is active in germline cells but most differentiated somatic cells do not exhibit much if any telomerase activity (12). However, detectable levels are observed in certain stem cell components, in various hematopoietic lineages, and in cells of the basal epidermis (13–15). Telomerase is highly active in over 90% of all cancers (16). This rate approaches 100% in squamous cell carcinomas and, in fact, the small numbers of cancers that do not have active telomerase are usually not of epithelial origin and maintain telomeres through a modified form of mitotic recombination called alternative lengthening of telomeres (ALT) (17). For example, the ALT mechanism of telomere elongation is more frequent in liposarcomas, fibrosarcomas and sarcomas (18). TERT has been generally viewed as the rate-limiting component of telomerase activity, and much work has been performed to understand how it is regulated during development and carcinogenesis [for reviews see (11,19–22)]. TERT levels can be upregulated in cancer by a variety of mechanisms, including transcriptional upregulation, protein stabilization and gene amplification (23). Low levels of TERT expression are detectable in human epithelial cells, which goes along with the observation that these cells have some telomerase activity (15,24,25). Fibroblasts, on the other hand, have little to no TERT and, concomitantly, have barely detectable telomerase activity (26). The RNA component TERC is expressed at readily detectable levels in most cell types, including skin fibroblasts and epidermal cells (27). Evidence is now accumulating, however, that in addition to upregulation of TERT, upregulation of TERC levels can also increase the amount of telomerase activity in stem cells and other cells, and there have been several reports that many cancers exhibit amplification of the TERC gene and high TERC expression (23,28,29). In normal cells, it would appear that both TERT and TERC levels are fine-tuned to carefully regulate telomerase activity but that this regulation becomes dysfunctional in cancer cells.



 