

TELOMERES, TELOMERASES AND CELLULAR SENESENCE. 2009 NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE

Summary

The 2009 Nobel Prize in Physiology or Medicine was awarded to Elizabeth H BLACKBURN, Jack W SZOSTAK and Carol W GREIDER for their discovery of how chromosomes are protected by telomeres and the enzyme telomerase. They solved a fundamental problem in biology, namely how can the ends of chromosomes (telomeres) avoid erosion during cellular divisions. First, working on unicellular organisms, such as yeast and ciliate, they demonstrated that chromosomal ends have an evolutionary conserved structure and function. Then, in a series of meticulous biochemical studies, they revealed the existence of a previously predicted enzyme, named telomerase, responsible for the synthesis of telomeres. Telomerase appeared to be a nucleoprotein, reverse transcriptase with an intrinsic RNA template. The active telomerase was shown by others in cancer but not in normal somatic cells and telomere erosion was immediately considered as a “replicometer” or mitotic clock” counting divisions of somatic normal cells and inducing permanent cell growth arrest (replicative senescence). The discovery of te-

lomerase has deeply influenced biomedical research and paved the way for the development of cancer therapies based on telomerase inhibition. However, subsequently it appeared that cellular senescence is beneficial because it protects the division of cells with short labile chromosomes being potentially prone to cancer transformation. Recently, it has been shown that senescence is a cell stress response to telomeric and nontelomeric DNA damage induced by oncogenic viruses, oxygen or genotoxic stress and critically short or nonfunctional telomeres, respectively. This reinforced the idea of cellular senescence as a cancer barrier but raised doubts in “replicometer” as a main cause of cellular senescence. However the story seems to be even more complicated and double-dealing as senescent cells secrete a myriad of factors, including pro-inflammatory cytokines, creating a microenvironment supporting organismal ageing and the development of age-related diseases, including cancer. Altogether, it seems, that the hopes put in telomerase as a key to eternal youth turned out to be vain.