Aging and cancer: telomeres, telomerase and radiation. Shay J. https://three.jsc.nasa.gov/articles/AgingCancerSummary.pdf.
Posted date: 04-13-2009.

Aging and Cancer:
Telomeres, Telomerase and Radiation

Jerry W. Shay
UT Southwestern Medical Center
Department of Cell Biology
5323 Harry Hines Blvd
Dallas, TX 75309

Email: Jerry.Shay@UTSouthwestern.edu
Phone: 214-648-3282

Presented at the NASA Space Radiation Summer School, June 12, 2008

J. Shay Presented June 12, 2008

The increased average age of astronauts (~45 years) suggests that diseases associated with increased age may be exacerbated by the space radiation environment. Aging can be defined as the gradual decline in performance and reserve capacity of organ systems leading to impaired responses to stress and increased risk of disease. Major diseases associated with aging include: Alzheimer's disease, arthritis, cancer, diabetes, heart disease, osteoporosis and stroke. In addition, normal changes associated with aging include shortsightedness and deterioration of color vision, hearing, taste and smell loses, loss of skin elasticity, graying and loss of hair, musculoskeletal changes, loss of cartilage, decreased heart, lung, kidney and pancreas function, decreased immune function, and loss of neural cells. A central question that needs to be addressed is how does the space environment impact on these normal and disease associated aging processes?

Over the last decade significant amounts of information about changes in astronaut health have been accumulating. For example, there are decreases in bone mineralization, decreases in muscle mass including cardiovascular changes, decreases in immune function which may correlate with increased risk for cancer, early appearance of cataracts, changes in thyroid function, and loss of neural cells. It is now important to discover the underlying causes of these changes to determine if we can slow down or reverse these changes. The major theories of aging include protein cross linking, DNA damage, free radical damage, mitochondrial DNA damage and cellular senescence. The presentation of slides accompanying this introduction covers many of the proposed causes of aging with a special focus on the telomere theory of aging.

Telomeres (the ends of linear chromosomes) progressively shorten in most human tissues with each division and may become limiting in chronic diseases. Replicative senescence is a general stress-response program that restrains cellular proliferation. Under optimal growth conditions, the onset of senescence depends on telomere status, even though there are other factors that can induce a stress or senescence-like state when telomeres are not critically short. However, when telomeres are sufficiently short (or uncapped), a DNA damage response-induced growth arrest occurs. The senescence pathway involves the formation of telomere dysfunction induced foci that contain DNA damage response factors. Importantly, the DNA-damage response observed in

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senescent cells is not a transient phenomenon, but consists of a permanent activation of the DNA damage checkpoint machinery. The long-term growth arrest at senescence may be thought of as an initial anti-tumor protection mechanism in organisms that live a long time. In situations where normal cell cycle checkpoints are altered, cells can bypass the normal senescence signaling pathway and continue to grow until they reach a second growth arrest state known as crisis. In crisis, telomeres are terminally short resulting in telomeric fusions and breakage-fusion-bridge cycles. In rare cells, up-regulation or reactivation of telomerase occurs. Telomerase is the cellular enzyme complex that is able to add telomeric repeats to the ends of chromosomes and thus prevent their shortening. In pre-neoplastic cells, telomeres are exceptionally short and generally telomerase is silent. Human malignant tumors express high levels of telomerase to maintain these short telomeres. This activity is absent or at lower levels in normal tissues, making the inhibition of telomerase an attractive target for cancer therapeutics. There is mounting evidence that radiation, similar to what is present in space, may result in preferential telomere damage and this may in turn be important in some of the age-associated changes that we are observing in astronauts.

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J. Shay presented June 12, 2008