

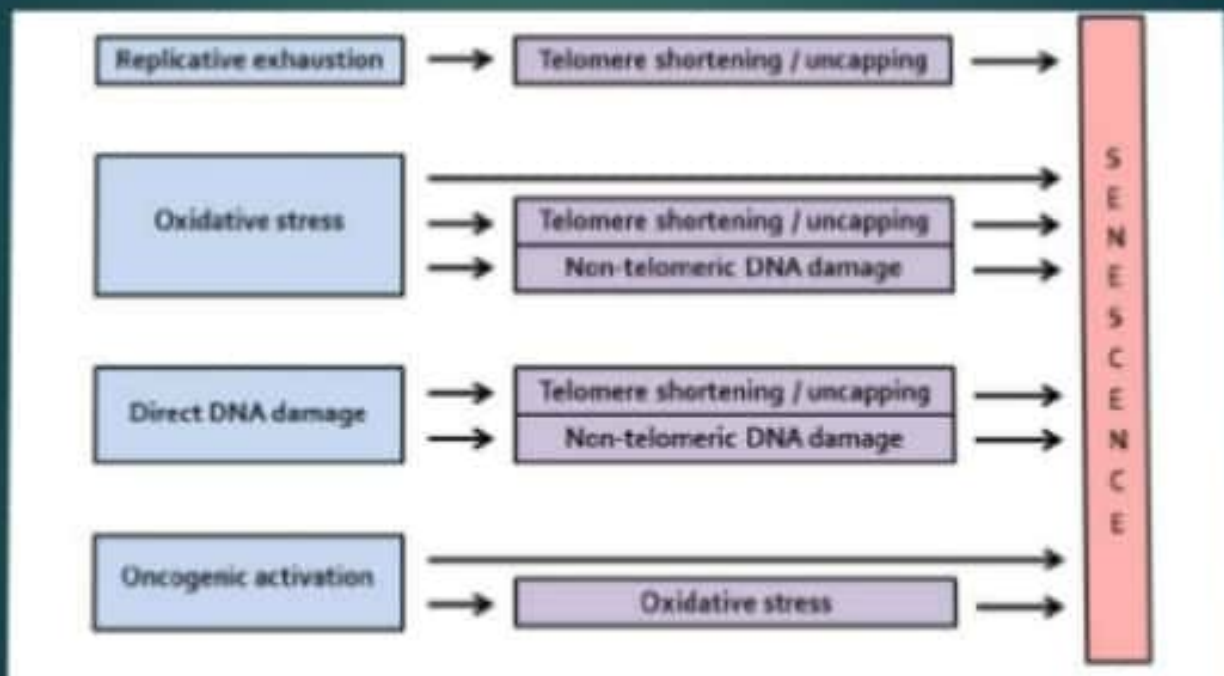


Senescence

WHAT IS SENESENCE ?

- ▶ The process by which a cell loses its ability to divide, grow, and function. This loss of function ultimately ends in death.
- ▶ In terms of cancer, it is the response of normal cells to potentially cancer-causing events.
- ▶ It is a strictly degenerative process and has no positive features.
- ▶ It is characterized by the declining ability to respond to stress, increasing homeostatic imbalance and increased risk of aging-associated diseases.
- ▶ Senescent cells secrete many inflammatory cytokines (e.g., IL6, IL8), growth factors (e.g., PDGF), proteases (e.g., MMPs)

Factors responsible for senescence



Senescent cells: Many characteristics change

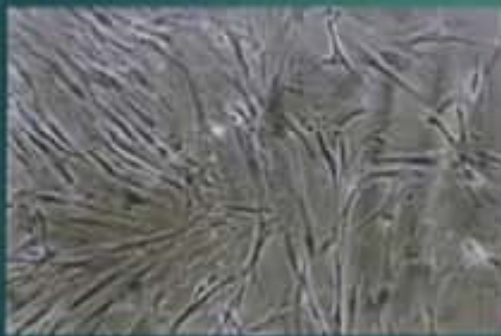


Genes Responsible for Senescence

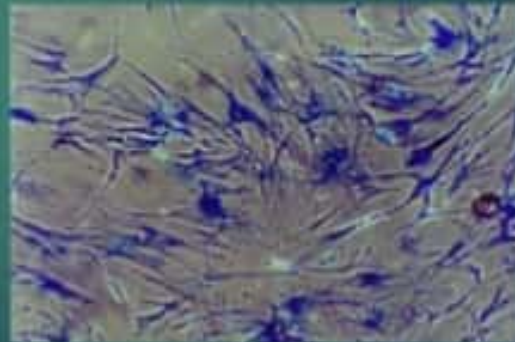
- ▶ *Klotho* gene : responsible for down regulation of insulin signaling and causes progeria.
- ▶ *p53* : important regulator of cell division, stops cell cycle causing cell senescence, provides protection against cancer, "guardian of the genome".
- ▶ *sirtuin* gene : encode histone deacetylation enzymes and blocks chromosomal rearrangement, sirtuin proteins prevent aging.

Senescence morphology

- Senescent cells become flattened, enlarged and have increased β -galactosidase activity
- Increased size of nucleus and nucleoli
- Increased number of multinucleated cells
- Increased number of lysosomes, Golgi and cytoplasmic microfilaments



'Young'
Pre-senescent

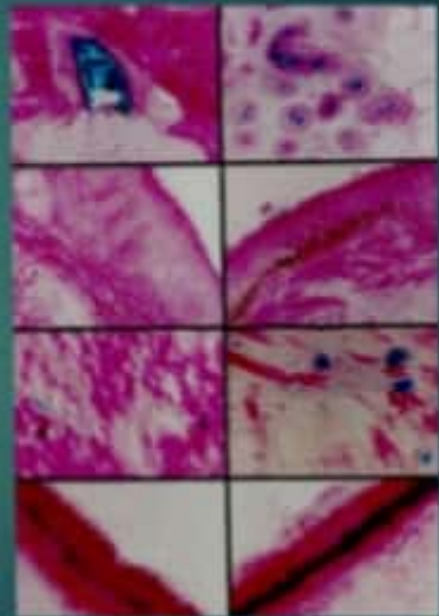


'Aged'
Senescent

Markers of a senescent cell

- ▶ *p16* expression
- ▶ Heterochromatic foci damage
- ▶ Telomeric-DNA damage
- ▶ DNA damage foci

*Human skin,
stained for SA- β gal*

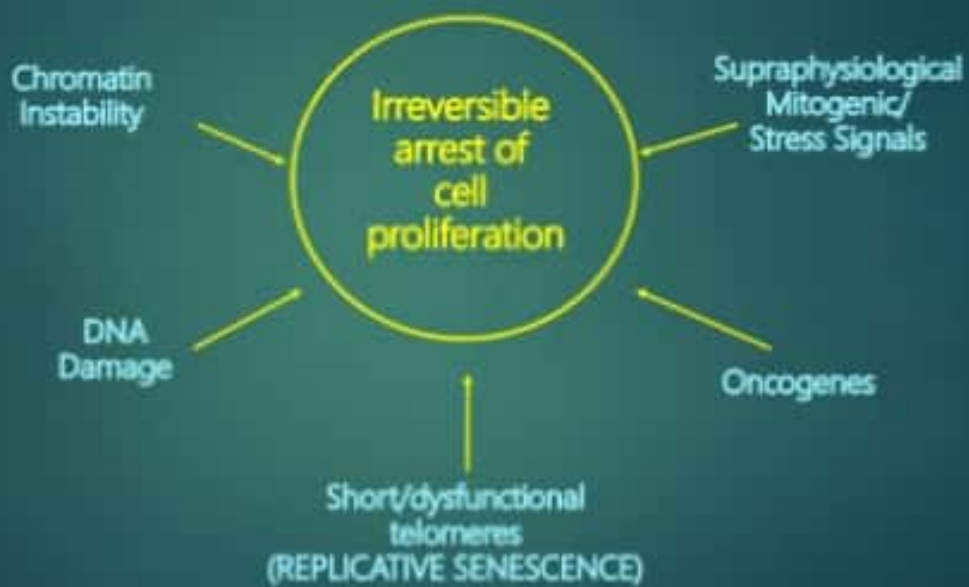


Dimri et al., Proc Natl Acad Sci USA, 1995

Cell senescence and cancer

- ▶ Cellular senescence is an important tumour suppressor mechanism.
- ▶ The senescence response may be an example of evolutionary antagonistic pleiotropy.
- ▶ The rationale for antagonistic pleiotropy rests on the fact that most organisms evolve in environments that are replete with fatal extrinsic hazards.
- ▶ The age-related increase in senescent cells occurs in mitotically competent tissues, which, of course, are those that give rise to cancer

Cellular Senescence Induced by Many (Cancer-Causing) Stimuli



Progeria

- ▶ Progeria is a premature aging syndrome in humans that appears to be caused by mutations in DNA repair enzyme
- ▶ In humans, Hutchinson-Gilford progeria is a rapid-aging syndrome;
- ▶ children born with this condition age rapidly, dying (usually of heart failure) as early as 12 years of age.
- ▶ Hutchinson-Gilford progeria is the result of a dominant mutation in the gene that encodes lamin A, a nuclear membrane protein, and these same mutations can be seen in age-related senescence
- ▶ *p53* can be activated by the absence of lamin A, thereby suggesting a mechanism for Hutchinson-Gilford progeria

Symptoms

All symptoms are the characteristics of the human senescent phenotype.

- ▶ skin with age spots,
- ▶ resorbed bone mass,
- ▶ hair loss, and
- ▶ arteriosclerosis

