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Short Communication

Cellular Senescence: Its Role in Aging and Disease Process

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DESCRIPTION

Aging is a complex biological process characterized by a gradual decline in physiological function and an increased susceptibility to diseases. One of the critical mechanisms underlying aging is cellular senescence, a state of irreversible cell cycle arrest that contributes to tissue dysfunction and organismal aging. Understanding cellular senescence is important for developing strategies to promote healthy aging and combat age-related diseases.

Cellular senescence

Cellular senescence is a state in which cells lose the ability to divide and proliferate. This process is triggered by various stressors, including DNA damage, oxidative stress, telomere shortening, and oncogenic signals [1]. Senescent cells undergo distinct morphological and functional changes, such as enlarged cell size, altered gene expression, and secretion of pro-inflammatory cytokines, growth factors, and proteases collectively known as the Senescence-Associated Secretory Phenotype (SASP).

Mechanisms of cellular senescence

Several molecular pathways regulate the onset and maintenance of cellular senescence. The primary pathways include the p53, p21CDKN1A, and p16INK4A tumor suppressor pathways.

p53/p21 pathway: DNA damage activates the p53 protein, which in turn induces the expression of p21, a cyclin-dependent kinase inhibitor. p21 inhibits the activity of cyclin-dependent kinases (CDKs), leading to cell cycle arrest. This pathway is important for the initial response to DNA damage and the induction of senescence.

p16INK4A pathway: The p16INK4A protein inhibits CDK4 and CDK6, preventing the phosphorylation of the retinoblastoma (Rb) protein. Hypophosphorylated Rb binds to E2F transcription factors, blocking their ability to promote cell cycle progression [2,3]. This pathway plays a critical role in the maintenance of the senescent state.

Telomere shortening

Telomeres are repetitive DNA sequences at the ends of chromosomes that protect them from degradation and end-to-end fusion. With each cell division, telomeres shorten due to the end-replication problem. When telomeres become critically short, they trigger a DNA damage response that leads to cellular senescence [4,5]. This process acts as a tumor suppressive mechanism by preventing cells with unstable genomes from proliferating. However, it also contributes to aging by depleting the pool of proliferative cells.

Senescence-Associated Secretory Phenotype (SASP)

Senescent cells secrete a variety of bioactive molecules collectively known as the SASP. The SASP includes pro-inflammatory cytokines (e.g., IL-6, IL-1β), chemokines, growth factors, and proteases. While the SASP can reinforce the senescent state and mediate immune surveillance by attracting immune cells to clear senescent cells, it also has detrimental effects [6,7]. Chronic SASP secretion leads to tissue inflammation, remodeling, and disruption of normal tissue function, contributing to age-related pathologies such as cancer, fibrosis, and degenerative diseases.

Cellular senescence and aging

The accumulation of senescent cells in tissues is an attribute of aging. Senescent cells are found in various tissues of aged organisms, including the skin, liver, lungs, and kidneys. These cells impair tissue repair and regeneration by secreting SASP factors that create a pro-inflammatory and pro-fibrotic environment [8,9]. The chronic presence of senescent cells contributes to the decline in tissue function and the onset of age-related diseases.

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Therapeutic approaches targeting cellular senescence

Given the role of cellular senescence in aging and age-related diseases, targeting senescent cells has emerged as a potential therapeutic strategy. Two primary approaches are being explored: senolytics and senomorphics.

Senolytics: These are agents that selectively induce apoptosis in senescent cells, effectively clearing them from tissues. Senolytic drugs, such as dasatinib and quercetin, have shown potential in preclinical studies by reducing the burden of senescent cells, improving tissue function, and extending healthspan.

Senomorphics: These agents modulate the SASP without necessarily killing senescent cells. By inhibiting the detrimental effects of the SASP, senomorphics aim to alleviate inflammation and tissue dysfunction associated with senescence [10]. Examples include inhibitors of the JAK/STAT pathway and NF-κB signaling, which are involved in SASP regulation.

CONCLUSION

The cellular senescence is a fundamental process contributing to aging and age-related diseases. By resolving the molecular mechanisms of senescence and developing targeted therapies, we can prepare for interventions that promote healthy aging and extend the human health span.

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