Cellular senescence and metabolic shifts: Biomarkers and intervention points.

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Introduction

Cellular senescence is a complex and dynamic biological process whereby cells irreversibly cease to divide in response to various forms of stress, including DNA damage, oxidative stress, oncogene activation, telomere attrition, and mitochondrial dysfunction. While senescence serves important physiological roles, such as tumor suppression, wound healing, and embryonic development, the accumulation of senescent cells over time contributes significantly to aging and age-related diseases [1]. A hallmark of senescent cells is their ability to remain metabolically active despite their growth arrest, often acquiring a pro-inflammatory secretory phenotype known as the senescence-associated secretory phenotype (SASP). The metabolic rewiring that accompanies cellular senescence plays a crucial role in maintaining the viability of senescent cells, driving their secretory behavior, and modulating their interaction with the tissue microenvironment. Understanding these metabolic shifts offers insights into reliable biomarkers of senescence and provides promising intervention points for therapeutic strategies aimed at extending healthspan and combating degenerative diseases [2].

Senescent cells exhibit a unique metabolic profile that differs markedly from that of proliferating or quiescent cells. One of the most consistent metabolic alterations observed in senescence is an increase in glycolysis. Despite the availability of oxygen, senescent cells often favor aerobic glycolysis—similar to the Warburg effect seen in cancer cells—leading to increased glucose uptake and lactate production. This shift supports the biosynthetic and energy demands of maintaining SASP, including the production and secretion of cytokines, chemokines, proteases, and growth factors. Key glycolytic enzymes such as hexokinase 2 (HK2) and pyruvate kinase M2 (PKM2) are often upregulated in senescent cells, and glucose transporters such as GLUT1 are overexpressed, highlighting the glycolytic dependency of the senescent phenotype [3].

Mitochondrial metabolism is also profoundly altered in senescent cells. While some forms of senescence show a decline in mitochondrial function and biogenesis, leading to reduced oxidative phosphorylation (OXPHOS) and increased production of reactive oxygen species (ROS), other contexts exhibit enhanced mitochondrial mass and activity. This paradoxical increase in mitochondrial respiration is often dysfunctional, characterized by inefficient electron transport and heightened oxidative stress. Mitochondrial dysfunction-associated senescence (MiDAS) has been described as a subtype of senescence specifically driven by mitochondrial impairment. The resulting ROS not only reinforces the senescent growth arrest via DNA damage and activation of the p53 and p16^INK4a^ pathways but also amplifies SASP expression through NF-κB and other redox-sensitive transcription factors [5].

Another key metabolic pathway implicated in senescence is the tricarboxylic acid (TCA) cycle and its associated anaplerotic inputs. Metabolomic studies have revealed alterations in TCA intermediates such as citrate, succinate, and fumarate in senescent cells. These changes can modulate epigenetic regulation, as certain TCA metabolites serve as cofactors or inhibitors of chromatin-modifying enzymes. For example, α-ketoglutarate (α-KG) acts as a cofactor for dioxygenases that regulate DNA and histone demethylation, and a shift in the α-KG/succinate ratio can influence gene expression programs associated with senescence. Additionally, alterations in NAD^+/NADH and FAD/FADH2 redox states in the mitochondria can influence both energy metabolism and signaling pathways involved in cell fate decisions [6].

Lipid metabolism is another area of significant alteration in senescent cells. Senescence is associated with increased lipid synthesis, accumulation of lipid droplets, and altered fatty acid oxidation. These changes contribute to the maintenance of the senescent phenotype and may play a role in immune evasion and SASP modulation. Senescent cells often upregulate enzymes involved in the synthesis of prostaglandins and leukotrienes, which are inflammatory lipid mediators contributing to tissue dysfunction and chronic inflammation. Cholesterol metabolism also changes in senescent cells, with some studies reporting increased expression of sterol regulatory element-binding proteins (SREBPs), leading to enhanced cholesterol biosynthesis and uptake [7].

Autophagy, a process of cellular self-digestion that recycles damaged organelles and proteins, is intricately linked to cellular senescence and metabolism. While autophagy can suppress senescence by mitigating cellular stress and preserving mitochondrial function, senescent cells may exhibit either enhanced or impaired autophagic flux depending on context. Selective autophagy, such as mitophagy, is often defective in senescence, contributing to the persistence of dysfunctional mitochondria and exacerbating metabolic imbalance. Conversely, increased general autophagy has

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been implicated in supporting the bioenergetic and anabolic demands of SASP production. Thus, autophagy represents both a modulator and a consequence of metabolic changes in senescence, with potential as a therapeutic target [8].

The identification of reliable biomarkers of cellular senescence is critical for detecting senescent cells in vivo, assessing the efficacy of anti-senescence therapies, and understanding their role in disease. Biomarkers that reflect metabolic alterations provide a dynamic and functional readout of senescence. Increased glycolytic activity, measurable by glucose uptake tracers like FDG in positron emission tomography (PET), has been used as a proxy for senescent cell burden in tissues. Elevated levels of lactate, both intracellular and secreted, can serve as indicators of enhanced glycolysis. Changes in mitochondrial membrane potential, ROS production, and oxygen consumption rates are measurable using fluorescent probes and respirometry, offering insights into mitochondrial health in senescent populations [9].

At the molecular level, senescent cells often express specific markers such as senescence-associated beta-galactosidase (SA-β-gal), cell cycle inhibitors p16^INK4a^ and p21^CIP1^, DNA damage markers like γ-H2AX, and components of the SASP. However, these markers lack universal specificity and are not always expressed across all types of senescence. Metabolomic profiling and lipidomic analyses are emerging as complementary tools that can provide distinct metabolic signatures of senescence, which may improve biomarker specificity and sensitivity. Additionally, circulating metabolites and exosomes containing senescence-related metabolites or enzymes have the potential to serve as non-invasive biomarkers [10].

Conclusion

In summary, cellular senescence is a metabolically active state characterized by profound alterations in glycolysis, mitochondrial function, lipid metabolism, and redox balance. These metabolic shifts are not only integral to the maintenance of the senescent phenotype but also provide valuable biomarkers and intervention targets. Advances in metabolomics, imaging, and drug development are bringing us closer to clinical applications that can detect, monitor, and manipulate senescent cells in vivo. By targeting the metabolic vulnerabilities of senescent cells, we can potentially delay aging, prevent disease progression, and promote tissue regeneration, paving the way toward a healthier and more resilient lifespan.

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