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POTENTIAL OF SGLT2 INHIBITORS TO INFLUENCE CELL AGING PATHWAYS

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Introduction. Cellular senescence is a fundamental biological process characterized by irreversible cell-cycle arrest, altered chromatin structure, mitochondrial dysfunction, metabolic reprogramming, and secretion of pro-inflammatory mediators collectively known as the senescence-associated secretory phenotype (SASP). Although senescence serves protective functions in tumor suppression and tissue repair, the chronic accumulation of senescent cells contributes to aging and the development of chronic diseases such as cardiovascular disease, chronic kidney disease, metabolic syndrome, and frailty.SGLT2 inhibitors—empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin—were originally approved for glycemic control by promoting renal glucose excretion. However, large clinical trials have shown their ability to reduce cardiovascular events, improve heart failure outcomes, and slow chronic kidney disease progression in both diabetic and non-diabetic individuals. These wide-ranging benefits have accelerated interest in understanding whether SGLT2 inhibitors influence aging pathways, including cellular senescence.Emerging evidence indicates that SGLT2 inhibitors may act as senomorphics (agents that suppress SASP and senescent cell activity) or even senolytics (agents that facilitate senescent cell clearance)[2]. Their effects on oxidative stress, inflammation, mitochondrial integrity, and autophagy intersect with central mechanisms of cellular aging, suggesting an important therapeutic potential beyond diabetes management.

Key words: SGLT2 inhibitors, cellular senescence, senolytics, aging, chronic diseases, type 2 diabetes mellitus, cardiovascular protection, renal protection.

Senescent endothelial cells lead to endothelial dysfunction, impair vascular function and predispose to cardiovascular diseases. Senescence is also considered a trigger for endothelial dysfunction observed in diabetes. Indeed,endothelialcell senescencedevelopsinthediabeticrataorta66 andan increase in the expression of senescence-associated β-galactosidase (SA β-gal) and p16Ink4a has been reported in endothelial cells exposed to high concentrations of glucose. It has been reported that high glucose promotes endothelial cell senescence through ROS mediated by superoxide dismutase (SOD) and SIRT as well as increased pro-inflammatory cytokines3,69. Increased proinflammatory cytokines like IL-1β, IL-6and tumour necrosis factor-α (TNF- α), observed in plasma samples from COVID-19 patients, led to an upregulation of SGLT2 expression in endo thelial cells, resulting in endothelial dysfunction and senescence[1]. Fur thermore, the same authors have recently demonstrated that SGLT2 expressionisassociated withlevelsoflow-gradeinflammationandoxidative stress in the internal thoracic artery and left ventricle of patients undergoing bypass and aortic valve surgery, respectively. In addition, increased pro inflammatory cytokines have been observed to increase SGLT2 expression in porcine coronary endothelial cells, thereby promoting endothelial dys function and potentially leading to senescence. Of note, it is important to emphasise that the baseline expression of SGLT2 in endothelial cells remains relatively low compared to renal proximal tubules, and the phy siological and pathological role of SGLT2 expression in endothelial cells is not yet fully understood. Endothelial senescence is associated with reduced endothelial nitric oxide synthase (eNOS)-mediated nitric oxide (NO) production and oxi dative stress. SGLT2 inhibitors have been reported to increase endothelium-derived NO bioavailability and improve vasodilatation in db/db mice.Althoughitisconceivablethatthiseffectmaybeassociated withtheir glucose-lowering activity, the acute effect of dapagliflozin was also investigated in aortic rings of C57BL/6J mice

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and vasodilation was observed. Inaddition,dapagliflozin treatment was found to reverse the decrease in NO levels in oxidative stress induced HUVECs.Besides,two different SGLT2 inhibitors (dapagliflozin and empagliflozin) were reported to restore NO bioavailability in TNF-α induced inflammation model of human coronary arterial endothelial cells. SGLT2 inhibitors also have regulatory effects on endothelial cell proliferation, migration and differentiation. In addition, they have been shown to ameliorate endothelial cell senescence through their anti inflammatory effects and suppression of ROS, and these protective effects have been associated with the activation of AMPK and SIRT1 signalling[4]. It is well established that AMPK and SIRT1 play a crucial role in the vasculature by reducing inflammation and oxidative stress[5], and SGLT2 inhibitors could modulate these pathways in vascular aging. A recent study indicated that dapagliflozin reduced apoptosis, ROS and inflammation in high glucose-induced endothelial dysfunction by regulat ing the AMPK/SIRT1 pathway[3].Thereductionofinflammatory cytokine and chemokine secretion with another SGLT2 inhibitor, canagliflozin, in vascular endothelial cells was also mediated through an AMPK-dependent mechanism[2]. Moreover, it was reported that dapagliflozin treatment increased cell viability, suppressed elevated inflammatory factors (IL-1β,IL 6andTNF-α), and induced autophagy by inhibiting the protein kinase B (AKT)/mTOR signalling pathway in HUVECs exposed to high glucose[3].

Under healthy conditions, the immune system actively surveils and removes senescent cells, thereby limiting their harmful effects. Yet, as individuals age or experience chronic metabolic dysfunction, this immune surveillance weakens, resulting in increased senescent cell burden and sustained inflammation. In response, researchers have turned to senolytics, compounds that selectively clear senescent cells, to restore immune function, mitigate inflammation, and potentially slow or even reverse aspects of aging. Among recent breakthroughs, a surprising class of candidate senolytics has emerged: SGLT2 (sodium–glucose cotransporter 2) inhibitors, drugs already widely prescribed to manage type 2 diabetes. Originally developed to control blood glucose levels by increasing urinary glucose excretion, these drugs have unexpectedly demonstrated profound benefits beyond their intended metabolic effects—including protection against cardiovascular and kidney diseases and extended lifespan in animal models. Now, according to a landmark study recently published in Nature Aging, SGLT2 inhibitors appear capable of actively enhancing the immune system's clearance of senescent cells, suggesting that their benefits extend far beyond metabolic regulation alone. These findings are particularly significant as they illuminate a novel, indirect mechanism of senescence clearance and position SGLT2 inhibitors as a potentially transformative therapy to address multiple dimensions of aging. The potential influence of SGLT2 inhibitors on cellular senescence opens new prospects for developing therapeutic strategies targeting multi-morbidity associated with chronic diseases. By modulating pathways linked to cellular aging, SGLT2 inhibitors may not only optimize glycemic control but also help prevent age-related disorders, support tissue regeneration, and improve overall clinical outcomes.

Cardiovascular Disease:

As cellular senescence contributes to the development and progression of cardiovascular conditions, the senolytic-like effects of SGLT2 inhibitors may enhance cardioprotective outcomes in patients with type 2 diabetes and related comorbidities.

Kidney Protection:

The renoprotective actions of SGLT2 inhibitors may also stem from their capacity to reduce senescent cell accumulation in renal tissues, thereby slowing the advancement of chronic kidney disease.

Aging and Frailty:

By influencing biological aging through the regulation of cellular senescence, SGLT2 inhibitors may help reshape clinical strategies for managing frailty and other age-associated syndromes[6].

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Conclusion. In this review, we will critically analyze the recent Nature Aging study, dissect the underlying mechanisms by which SGLT2 inhibitors enhance senescent cell clearance, and discuss their broader implications for optimizing tissue function, mitigating age-related pathologies, and ultimately extending both longevity and healthspan The impact of SGLT2 inhibitors on cellular senescence represents a promising direction for future research, potentially expanding their therapeutic value beyond glucose lowering. Through their anti-senescent effects and their ability to modulate fundamental mechanisms underlying aging and chronic illnesses, SGLT2 inhibitors may offer a broader spectrum of clinical benefits and contribute to innovative approaches in the treatment of age-related and multi-system diseases.

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