Short review

On the wake of metformin: Do anti-diabetic SGLT2 inhibitors exert anti-aging effects?

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ABSTRACT

Here we propose that SGLT2 inhibitors (SGLT2i), a class of drugs primarily used to treat type 2 diabetes, could also be repositioned as anti-aging senomorphic drugs (agents that prevent the extrinsic harmful effects of senescent cells). As observed for metformin, another anti-diabetic drug with established anti-aging potential, increasing evidence suggests that SGLT2i can modulate some relevant pathways associated with the aging process, such as free radical production, cellular energy regulation through AMP-activated protein kinase (AMPK), autophagy, and the activation of nuclear factor (NF)-kB/inflammasome. Some interesting pro-healthy effects were also observed on human microbiota. All these mechanisms converge on fueling a systemic proinflammatory condition called inflammaging, now recognized as the main risk factor for accelerated aging and increased risk of age-related disease development and progression. Inflammaging can be worsened by cellular senescence and immunosenescence, which contributes to the increased burden of senescent cells during aging, perpetuating the proinflammatory condition. Interestingly, increasing evidence suggested the direct effects of SGLT-2i against senescent cells, chronic activation of immune cells, and metabolic alterations induced by overnutrition (meta-inflammation). In this framework, we analyzed and discussed the multifaceted impact of SGLT2i, compared with metformin effects, as a potential anti-aging drug beyond diabetes management. Despite promising results in experimental studies, rigorous investigations with well-designed cellular and clinical investigations will need to validate SGLT2 inhibitors' anti-aging effects.

1. Introduction

Sodium-glucose co-transporter-2 (SGLT2) inhibitors (SGLT2i) (empagliflozin, dapagliflozin and canagliflozin) have emerged in type 2 diabetes (T2D) therapy because they inhibit glucose reabsorption at the tubular level, thus promoting better metabolic control (Shaffner et al., 2021).

Their anti-inflammatory role seems quite evident (D'Onofrio et al., 2021; Sciscola et al., 2022), whereas potential anti-aging roles of SGLT2i are currently under investigation, and preliminary results focused on a series of cellular and molecular mechanisms strongly associated with aging process and age-related diseases development, such as inflammaging and cellular senescence. The influence of senescent cells in aging and age-related diseases is becoming more evident. Inflammaging is a systemic, chronic, and subclinical proinflammatory condition that increases during aging (Franceschi et al., 2000). Cellular senescence, the steady growth and proliferation arrest state, despite mitogenic stimuli and optimal growth conditions, contributes to fuel inflammaging, since senescent cells acquire a proinflammatory secretory phenotype, Senescence-Associated Secretory Phenotype (SASP) (Di Micco et al., 2021; Franceschi et al., 2018).

Various factors inducing cellular senescence have been described (Huang et al., 2022), including a) nuclear DNA damage , which activates a cascade of signals known as the DNA Damage Response (DDR), which in turn causes cell cycle arrest, and eventually triggers cellular senescence (Kumari and Jat, 2021); b) Telomere shortening, which contributes to persistent DDR mainly via oxidative stressors. When telomeres become too short to protect DNA, cells cease to divide, leading to replicative senescence (Rossiello et al., 2022); c) Oncogenic activation. Indeed, an initial hyperproliferative phase is intrinsically associated with replication-induced DNA damage, partly by producing reactive oxygen species (ROS) (Di Micco et al., 2021). Eventually, cells acquire a proinflammatory secretory phenotype, the SASP, which contributes to the spread of inflammation at systemic level (inflammaging) (Franceschi et al., 2018).

2. The emerging scenario of anti-aging drugs

Several experiments on animal models demonstrated that genetic ablation of senescent cells in tissues lengthened health span and reduced the risk of age-related pathologies (Baker et al., 2011). Therefore, innovative strategies to target senescent cells are an emerging field of research aimed at the extension of health span.

"Senotherapeutic" strategies are classified into two categories: pharmacological agents called "senolytics," which eliminate senescent cells, and "senomorphic" agents that prevent the extrinsic harmful effects of senescent cells, primarily inhibiting SASP (Chaib et al., 2022). Various senolysis strategies have been developed. Senescent cells have increased resistance to apoptosis due to up-regulation of cell survival pathways, such as the anti-apoptotic BCL-2 protein family (Yosef et al., 2016). Recently, the cardiac glycoside Ouabain has been discovered to possess senolytic activity, at least in part, by inducing a pro-apoptotic protein belonging to the BCL-2 family (Guerrero et al., 2019). Senomorphic drugs do not directly eliminate senescent cells but modify the secretory phenotype associated with senescence, thereby maintaining stable cell cycle arrest. Drugs in this category include commonly used clinical agents such as Rapamycin, which inhibits the Mammalian Target of Rapamycin (mTOR), Etanercept, which inhibits Tumor necrosis factor (TNF)-alpha, or Metformin which inhibits the Nuclear factor kappa B (NF-κB) (Moiseeva et al., 2013). All these drugs reduce pro-inflammatory conditions that can fuel inflammaging (Kulkarni et al., 2020).

3. Metformin: the interesting path from anti-diabetic to anti-aging drug

Metformin is an oral hypoglycemic drug that has been demonstrated to exert anti-aging effects. Although the molecular mechanisms by which metformin regulates aging-related pathways are not fully understood; however, different pathways have been suggested (Chen et al., 2022).

Metformin exerts anti-oxidative, anti-inflammatory, and metabolic effects at the cellular level. It acts extracellularly by reducing the activation of the insulin receptors, insulin-like growth factor (IGF)-1 growth factor receptor, and cytokine receptors. Entering into the cell by the cationic transporter I (OCTI), metformin inhibited the mitochondrial complex I, resulting in lower ROS production and an increased AMP/ATP ratio that directly activates AMP-activated protein kinase (AMPK), the cell's energy sensor (Tulipano, 2021). Moreover, metformin promotes AMPK activation by increasing the expression of PPAR-gamma-coactivator 1α (PCG-1α) (Suwa et al., 2006). AMPK activation reduces Advanced Glycation End (AGE) products that can ignite proinflammatory effects by linking with AGE receptors expressed on various cells, including immune cells (Zgutka et al., 2023). AMPK activation also reduces pro-apoptotic stimuli and promotes the inhibition of mTOR1 (Herzig and Shaw, 2018). mTOR1 is a serine-threonine kinase capable of regulating metabolism and cell growth, and it is implicated in the aging process. Its inhibition activates autophagy signals, preventing the accumulation of damaged proteins. The anti-inflammatory effects are independent of AMPK activation and are determined by the downregulation of pro-inflammatory NF-κB activity (Kulkarni et al., 2020; Osorio et al., 2012).

Interestingly, metformin enhanced anabolic signaling activating Sirtuin (SIRT) 1 (Cuyas et al., 2018). Several studies have evaluated the potential effect of metformin on aging. In *Caenorhabditis elegans*, metformin leads to a dose-dependent increase in average lifespan, ranging from 18 % to 36 %. Subsequent studies on animal models have shown that mice treated with metformin for 9 months exhibited an extension of lifespan by around 14 % (Wang et al., 2020).

3.1. Prospective trials investigating the potential anti-aging metformin effect

Based on the previous findings, several trials have been conducted to assess the anti-aging effect of metformin in humans (Glossmann and Lutz, 2019). The MILES study (Metformin in Longevity Study) is a crossover study conducted in a double-blind manner, involving 14 subjects over the age of 70 with impaired carbohydrate tolerance. This study evaluates the transcriptomic changes (in muscle and adipose tissue) induced by metformin for 6 weeks. Genomic analysis revealed that metformin exerts not only metabolic effects at the tissue level but also influences the expression of genes involved in DNA repair in muscle and mitochondrial genes in adipose tissue, impacting the aging process (Kulkarni et al., 2018; Triggle et al., 2022). Furthermore, inflammation mediators (NF-kB, TNF-α, and Interleukins (ILs)) act as standard upstream regulators of differentially expressed genes in the two tissues (Kulkarni et al., 2020). The effects of metformin on age-related diseases have also been evaluated through prospective trials such as GLINT and TAME. The GLINT study (Glucose Lowering In Non-diabetic Hyperglycemia Trial) is a randomized, multicenter, double-blind study that assessed the effects of extended-release metformin compared to a placebo in elderly obese patients with non-diabetic-hyperglycemia and high cardiovascular risk on a composite endpoint of myocardial infarction, stroke, and death from cardiovascular diseases over approximately five years of follow-up. Secondary endpoints aimed to evaluate the impact of metformin on the functional status of enrolled subjects, the incidence of diabetes, non-melanoma oncological pathologies, cancer-related deaths, all-cause mortality, and the cost-effectiveness of treatment. A total of 249 patients aged ≥40 years,

with HbA1c levels ≥36.6 mmol/mol but <47.5 mmol/mol (≥ 5.5 % but < 6.5 %) and estimated 10-year cardiovascular risk ≥20 by Framingham Risk Score or QRISK2 scores, were enrolled. Metformin was associated with slightly improved HbA1c values, glomerular filtration rate, and average low-density-lipoprotein (LDL) cholesterol levels. No statistically significant outcome was observed for the predefined endpoints (Griffin et al., 2018). However, a series of recommendations for future studies emerged: a) modifying inclusion criteria to enroll individuals with and without pre-existing cardiovascular diseases to increase the number of recruitable subjects and event rates; b) utilizing large databases to improve participant identification; c) conducting remote follow-up to reduce costs and enhance efficiency. Additionally, based on data from this study, a 2 % reduction in cardiovascular events can be achieved by enrolling at least 20,000 subjects (Griffin et al., 2018). Lastly, the Targeting Aging with Metformin (TAME) trial, a double-blinded placebo-controlled multi-center (14 centers involved) trial, has been designed to determine whether treatment with metformin (1500 mg/day) for 6 years will delay the onset of age-related diseases in 3000 ethnically diverse subjects (aged 65–80). The study focused on three major outcomes: i) clinical outcomes: new age-related chronic disease (myocardial infarction, stroke, hospitalized heart failure, cancer, dementia or mild cognitive impairment (MCI)) or death; (ii) functional outcomes: major age-related functional outcomes (major decline in mobility or cognitive function, or onset of severe activities of daily living limitation); (iii) biological outcomes: biomarkers of aging comprise an exploratory trial outcome intended to strengthen the biological underpinnings guiding the TAME trial (TAME BIO) (Barzilai et al., 2016). Unfortunately, TAME had several limitations. Actually, T2D, a disease object of accelerated aging, was removed from the primary clinical disease outcome even though metformin is an antidiabetic drug previously shown to reduce the risk of T2DM.

4. New potential therapeutical field for SGLT2 Inhibitors: do they have an anti-aging effect?

Sodium-glucose co-transporter-2 (SGLT2) inhibitors (SGLT2i) (empagliflozin, dapagliflozin, and canagliflozin) have emerged in T2D therapy because they inhibit glucose reabsorption at the tubular level, thus promoting better metabolic control (Scheithauer et al., 2020).

However, their anti-inflammatory role seems quite evident (D'Onofrio et al., 2021; Scisciola et al., 2022). So far, the potential anti-aging role of SGLT2i could be explained through a series of cellular and molecular mechanisms underpinning the aging process and the development of the most common age-related diseases (ARDs). It has been demonstrated that SGLT2is can: a) have an anti-low-grade tissue inflammation effect; b) reduce the production of free radicals; c) exhibit an inhibitory effect on NF-kB/inflammasomes activation; d) modulate AMPK production; e) regulate autophagy; f) modulate of nutrient-sensing pathways; g) modulate gut microbiome: h) suppress cell senescence and increase the lifespan in animal models.

4.1. Inhibitory effect on "low-grade tissue inflammation/inflammaging"

Chronic low-grade inflammation, or inflammaging, is a key feature associated with T2DM and its complications. SGLT2 inhibition plays anti-inflammatory actions, and the underlying mechanisms to explain anti-inflammatory effect are multiple which may involve weight loss, reduction in adipose tissue inflammation, slight increase in ketone bodies and diminution of uric acid levels or attenuation of oxidative stress (La Grotta et al., 2022a).

In overweight or obese patients, with or without T2DM, there is an excess of circulating free fatty acids (FFA) that bind to toll-like receptors (TLR) 2 and 4, especially in cells involved in metabolic processes such as skeletal muscle tissue, adipose tissue, and the liver. This leads to the activation of kinases, such as c-Jun N-terminal kinase (JNK), IκB kinase (IKK), and protein kinase R (PKR). These kinases are responsible for

phosphorylating insulin receptor substrate (IRS-1), which leads to increased insulin resistance (itself an additional pro-inflammatory factor activating NF-κB, activator protein 1 (AP-1), and interferon regulatory factor (IRF)) (Ahmed et al., 2021; Bendotti et al., 2023; Paolisso et al., 1986). In elderly patients, especially those with reduced mobility and T2DM, tissue hypoxia can occur due to adipose tissue expansion, even in the absence of changes in the vascular bed or with a vascular bed that can no longer vasodilate, as in young non-diabetic individuals. This hypoxia is associated with the infiltration of adipose tissue by macrophages, undergoing phenotypic conversion from M2 with predominantly anti-inflammatory phenotype to M1 with pro-inflammatory activities (Norouzirad et al., 2017). Empagliflozin has demonstrated its anti-inflammatory capabilities, reducing the production of IL-6, TNF-α, monocyte chemoattractant protein-1 (MCP-1), interferon-gamma (IFN-γ), P-selectin, and intracellular adhesion molecules (ICAM-1) in the hearts of diabetic Zucker rats (Elrakaybi et al., 2022; Lee et al., 2021). Human studies have highlighted that the use of canagliflozin is associated with a decline in IL-6 levels, while empagliflozin therapy has anti-inflammatory effects (reducing levels of high-sensitivity C-reactive protein [hs-CRP] and myeloperoxidase and increasing IL-10 levels) (Kounatidis et al., 2023; Liu et al., 2022; Paolisso et al., 2022). Moreover, multiple studies suggested that the treatment with gliflozins reduced the secretion of IL-1β through the inhibition of the nucleotide-binding oligomerization domain (NOD)-like receptor family pyrin domain containing 3 (NLPR3) inflammasome (Leng et al., 2016; Ye et al., 2017) (Table 1).

While not yet proven and thus tied to scientific speculation, it is likely to hypothesize that these anti-inflammatory effects of SGLT2i could be systemic, like what has been demonstrated for metformin, as their impact might be independent of the presence of the SGLT2 protein (Fig. 1A).

4.2. Reduced production of free radicals

Free radicals are essential in regulating immunity, cellular differentiation, and autophagy. Excessive free radicals, which occur when the cell's antioxidant capacity is insufficient to counteract their production, cause DNA damage and apoptosis, collectively called oxidative stress (Phaniendra et al., 2015). Free radicals promote the activation of NF-κB and of cytokines like endothelin-1, vascular cell adhesion molecule-1 (VCAM-1), and intracellular adhesion molecule-1 (ICAM-1), facilitating macrophage infiltration and vascular inflammation. Free radicals also increase inducible nitric oxide synthase (iNOS) production to compensate for reduced nitric oxide (NO) production. Still, excess NO can combine with superoxide (O_2) to form peroxynitrite, which is involved in lipid peroxidation. SGLT2i have been shown to indirectly reduce oxidative stress by inducing cellular metabolic changes that favor the activation of antioxidant enzymes (Nabrdalik-Lesniak et al., 2023; Scisciola et al., 2023). Additionally, dapagliflozin increases the levels of antioxidants, also known as Parkinson's disease protein 7 (PARK7), Protein deglycase 1 (DJ-1), and Nuclear factor erythroid 2-related factor 2 (Nrf2), which are elevated as compensatory mechanisms to neutralize excess lipid peroxides in rats with Parkinson's disease, another typical condition in the elderly (Unal et al., 2023). Similarly, the same model demonstrated reduced activation of NF-κB and its associated apoptosis (Arab et al., 2021). In rats with myocardial infarction, dapagliflozin has led to Signal transducer and activator of transcription (STAT) 3 activation, a critical factor in macrophage polarization, promoting the expression of anti-inflammatory M2 macrophages and the release of anti-inflammatory cytokines such as IL-10 (Tian et al., 2023) (Fig. 1B).

4.3. Modulation of AMP-activated protein kinase (AMPK)

AMPK is a cellular energy regulator that enhances ATP production and increases the ATP/ADP ratio during stress conditions. AMPK can also modulate key metabolic pathways essential for cellular function

Table 1
Anti-aging effect of SGLT2 inhibitors.

DRUGS	DAILY DOSAGE IN HUMANS	EXPERIMENTAL MODEL	MECHANISMS	REFERENCE
Antioxidant effects				
Dapagliflozin	5 – 10 mg	Zebrafish Parkinson's Disease Model, Rats with myocardial infarction	↑ DJ-1 and Nfr2, ↑STAT3 activation	Unal et al. (2023) Tian et al. (2023)
Anti- inflammatory action				
Empagliflozin	10–25 mg	Diabetic Zucker rats, human studies	↓ IL-6, TNF-α, MCP-1, IFN-γ, P-selectin, ICAM-1, hs-CRP, myeloperoxidase ↑ IL-10	Elrakaybi et al. (2022); Lee et al. (2021); Kounatidis et al. (2023); Liu et al. (2022); Paolisso et al. (2022)
Canagliflozin	100 – 300 mg	Human studies	↓ IL-6	Kounatidis et al. (2023); Liu et al. (2022); Paolisso et al. (2022)
Dapagliflozin	5 – 10 mg	Diabetic ApoE (-/-) Mice, Mice with Type 2 Diabetes	↓ NLPR3 activation, IL-1β	Leng et al. (2016); Ye et al. (2017)
Autophagy regulation				
Empagliflozin	10–25 mg	High Fat Diet Fed ApoE(-/-) Mice	↑AMPK, SIRT1 ↓ mTOR, HIF-1α	Nasiri-Ansari et al. (2021); Fukushima et al. (2021)
Modulation of nutrient-sensing pathways				
Empagliflozin	10–25 mg	Obese mice and diabetic mice	↑ FFA beta-oxidation and hepatic gluconeogenesis ↓ insulin levels	Fukushima et al. (2020); Lee et al. (2019)
Canagliflozin	100 – 300 mg	Obese mice	↑ FGF-21	Osataphan et al. (2019)
Gut microbiome modulation				
Empagliflozin	10–25 mg	Patients with type 2 diabetes	↑ Roseburg, Eubacterium, and Faecalibacterium ↓ Escherichia-Shigella, Bilophila, and Hungatella	Deng et al. (2022)
Cell senescence suppression				
Empagliflozin	10–25 mg	Endothelial cells, Zucker diabetic lean rats,	↓ ICAM-1, VCAM-1, senescence markers	Zhou et al. (2018); Park et al. (2020)

and is crucial in autophagy (Steinberg and Carling, 2019). Additionally, AMPK has a significant anti-inflammatory role as it inhibits the NLRP3 inflammasome and the release of IL-1β while promoting the polarization of macrophages toward an anti-inflammatory M2 phenotype. The inhibitory effect of AMPK on the inflammasome is even more pronounced under pro-inflammatory stress conditions, such as applying Lipopolysaccharide (LPS) to cell cultures. In such cases, AMPK negative modulation of inflammation becomes clear (Noor et al., 2020; Vinaik et al., 2020). The mechanism through which gliflozins drugs activate AMPK involves inhibiting complex I of the mitochondrial chain, leading to increased ADP and AMP levels. Finally, AMP binds to the γ subunit of AMPK, activating threonine phosphorylation at position 172 (Hawley et al., 2016). Notably, dapagliflozin can inhibit the progression of diabetic nephropathy by increasing AMPK activity and inhibiting NLRP3 (Birnbaum et al., 2018). Similarly, empagliflozin reduces the expression of IL-6, TNF, and MCP-1 in the hearts of diabetic rats, thereby reducing the likelihood of fibrotic processes, which contribute to premature cardiac aging and heart failure in elderly patients (Gotzmann et al., 2023) (Fig. 1**C**).

4.4. Autophagy regulation

Autophagy is a cellular process that lets cells rid themselves of misfolded proteins, damaged organelles, and pathogens by degrading them by lysosomes. As a result, autophagy indirectlysirtuins are alsoregulators regulates inflammation (Levine and Kroemer, 2019). This process is governed by the AMPK/(mTOR signaling pathway. Therefore, modulating this pathway restores autophagy and contributes to the anti-inflammatory effect (Ge et al., 2022; Yaribeygi et al., 2023).

Moreover, it was well demonstrated that also Sirtuins are key regulator of all steps of autophagy (Jing and Lin, 2015; Kim et al., 2022).

Regarding SGLT2i, previous studies demonstrate that empagliflozin enhances autophagy by stimulating AMPK and reducing mTOR in an experimental liver disease model with a further effect leading to autophagosome accumulation (Nasiri-Ansari et al., 2021). In addition, SGLT2i, acting on SIRT1 and mTOR, regulate autophagy suppressing Hypoxia-inducible factor (HIF-1α), a main regulator of mitochondrial autophagy (Fukushima et al., 2021) (Fig. 1**D**).

4.5. Modulation of nutrient-sensing pathways

The mechanisms of aging are intertwined with nutrient-sensing pathways regulating insulin/insulin-like growth factor-1 (IGF1) signaling (IIS), mTOR, AMPK, and SIRT1 signaling pathways (Hoong and Chua, 2021; Ong and Ramasamy, 2018).

Experimental evidence supported that SGLT2i, mimic the catabolic state by reducing insulin levels, increasing FFA beta-oxidation and hepatic gluconeogenesis (Fukushima et al., 2020; Lee et al., 2019). Furthermore, SGLT2i can inhibit mTOR activity via an indirect effect on AMPK, i.e. increasing fibroblast growth factor (FGF) 21, hormones responsible for downstream AMPK and SIRT1 signaling pathway activation (Osataphan et al., 2019)(Fig. 1 **E**).

4.6. Gut microbiome modulation

Increasing evidence suggests that oral glucose-lowering drugs might modify the gut microbiome and modulate gastrointestinal metabolites to improve host health (Wang et al., 2022).

Recently, some trials investigated SGLT2i effects on the human gut microbiota of T2DM patients; one study suggested no effects (van Bommel et al., 2020), whereas in another study empagliflozin treatment of T2DM patients with risk factors for cardiovascular disease (CVD) was associated with increased amount of short-chain fatty acids (SCFAs)-producing bacteria such as species from *Roseburia*, *Eubacterium*, and *Faecalibacterium*, and reduced amount of harmful bacteria including *Escherichia-Shigella, Bilophila*, and *Hungatella* (Deng et al., 2022). Notably, in the same study, it was demonstrated that empagliflozin improved CV risk factors and glucose control in correlation with an increase in SCFA-releasing bacteria when compared to metformin therapy. These differences between empagliflozin and metformin regarding the effects on microbiota occurred despite similar glucose control, suggesting that the established CV and renal protection exerted by empagliflozin may be partly due to its action on gut microbiota (Bica et al., 2023). A trial aimed to validate the effects of empagliflozin on gut
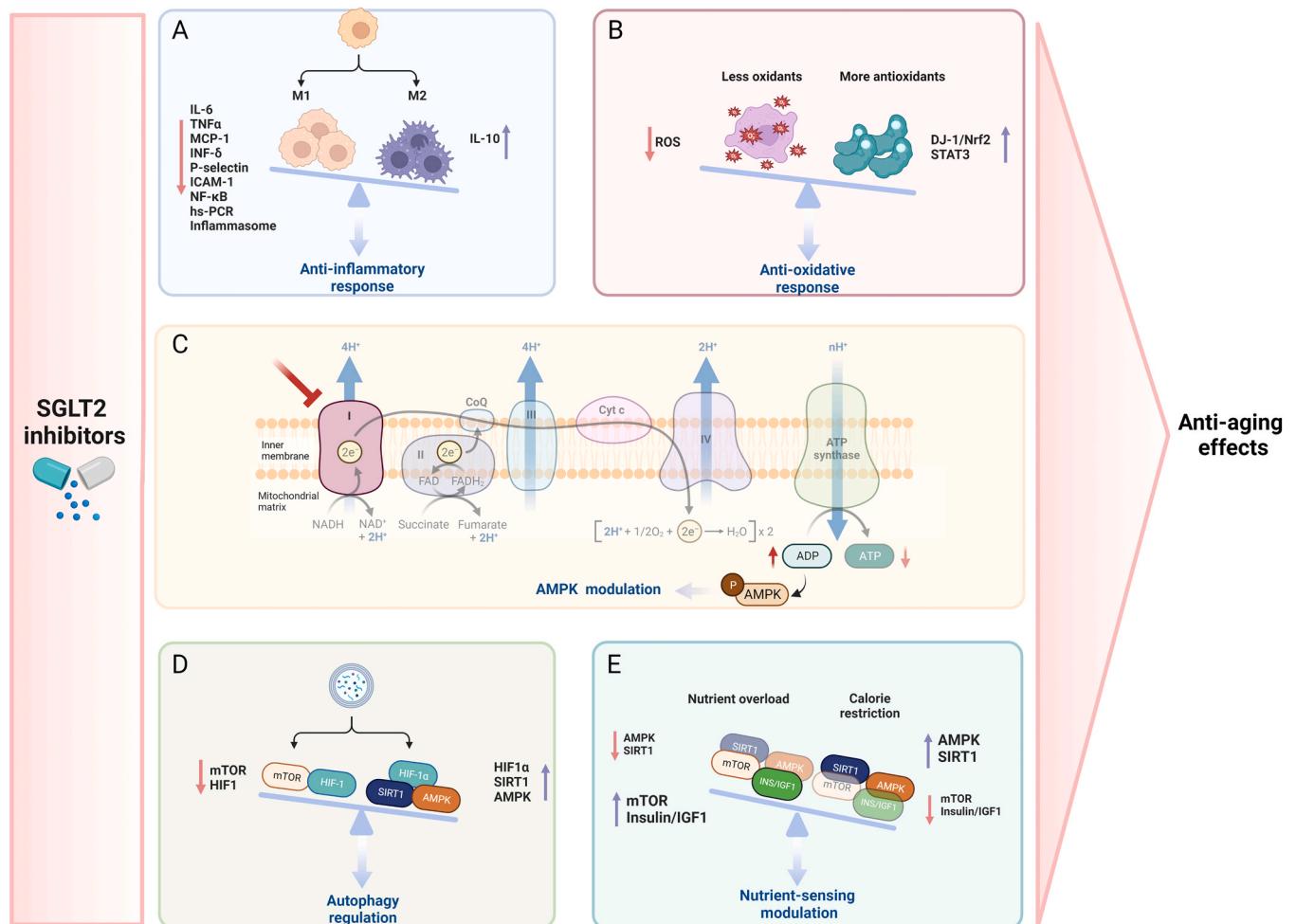
Fig. 1. **Anti-aging cellular effects of SGLT2 inhibitors. A)** SGLT2 inhibitors promote macrophage phenotypic conversion from M1 to M2, inducing reduced pro-inflammatory markers and an upregulation of IL-10. **B)** SGLT2 inhibitors upregulate the antioxidant enzymes, DJ-1/Nrf2/STAT3. **C)** SGLT2i inhibit complex I of the mitochondrial chain, leading to increased ADP and, consequently, the phosphorylation of AMPK. **D)** SGLT2i inhibitors regulate autophagy via mTOR and HIF-1 down-regulation and HIF-1α, SIRT1, and AMPK up-regulation. **E)** SGLT2 inhibitors modulate nutrient-sensing pathways. In caloric restriction conditions, gliflozins revert the nutrient overload phenotype, inducing an upregulation of AMPK and SIRT1 and a downregulation of mTOR/Insulin/IGF1. **SGLT2**: Sodium-glucose co-transporter-2; **SGLT2i**: SGLT2 inhibitors; **ILs**: interleukins; **DJ-1**: Protein deglycase-1; **Nrf2**: Nuclear factor erythroid 2-related factor 2; **STAT**: Signal transducer and activator of transcription; **AMPK**: AMP-activated protein kinase; **mTOR**: Mammalian Target of Rapamycin; **HIF-1α**: Hypoxia-inducible factor-1α; **SIRT-1**: Sirtuin-1; **IGF-1**: insulin-like growth factor-1.

microbiota in patients affected by heart failure with preserved ejection fraction (HFpEF) is currently ongoing (Guan et al., 2023).

4.7. Cell senescence suppression and increased lifespan in animal models

Empagliflozin can prevent the induction of senescence and the related-phenotypic changes in endothelial cells, and these effects are associated with an upregulation of SGLT2 receptors (Durante et al., 2021). Mechanistic studies revealed that empagliflozin inhibits endothelial cells senescence via an AMPK-mediated suppression of mitochondrial fission and a subsequent drop in mitochondrial ROS generation, in association with a suppression of ICAM-1 and VCAM-1 expression and restoration of eNOS activity (Zhou et al., 2018). Empagliflozin also represses the expression of senescence markers in athero-prone regions of the aorta in Zucker diabetic lean rats (Park et al., 2020).

Interestingly, it was demonstrated that SGLT2i Canagliflozin can extend the median lifespan of UM-HET3 male mice by 14 % but did not affect the female lifespan (Miller et al., 2020). However, both male and female mice treated with SGLT2i have lower body weight and fasting glucose and improved glucose tolerance, insulin sensitivity, locomotor activity and overall motion behavior, suggesting a significant reduction

in the age-associated proinflammatory response in both sexes (Jayarathne et al., 2022). Recently, this agent was found to diminish the incidence or severity of cardiomyopathy, glomerulonephropathy, arteriosclerosis, hepatic microvesicular cytoplasmic vacuolation (lipidosis), and adrenal cortical neoplasms, in male mice only, whereas protection against atrophy of the exocrine pancreas was seen in both males and females (Snyder et al., 2023). Thus, the extension of lifespan in Cana-treated male mice is accompanied by parallel retardation of lesions in multiple tissues.

Average and maximal lifespan can be increased in mice, in one or both sexes, by four drugs, such as rapamycin, acarbose, 17a-estradiol, and canagliflozin. Notably, these four drugs induce a common set of changes in fat, macrophages, muscle, and brain when evaluated in young adult mice (Li et al., 2023). Overall, Canagliflozin can be considered a drug that acts to slow the aging process in the animal models, supporting the hypothesis that SGLT2i should be evaluated for their potential anti-aging effects in humans.

5. Conclusions

Comparing SGLT2i and metformin highlights that drugs share

common activities in modulating cellular metabolic pathways that regulate aging through common anti-inflammatory properties (Hoong and Chua, 2021; La Grotta et al., 2022b). However, SGLT2i seem to play also pleyotropic effects superior to those observed for metformin, including additional cardiovascular benefits and renal protection, that could be partly due to its anti-inflammatory action. It is noteworthy that besidestheir anti-diabetic effects, SGLT2i could also be repositioned as senomorphic anti-aging drugs precisely for the capability to reduce the inflammatory phenotype. To analyze the anti-aging effect of SGLT2 inhibitors, the possible adverse effects of long-term SGLT2 inhibition in healthy subjects should be discussed. However, to our knowledge, studies on long-term SGLT2 inhibition effects on healthy subjects are missing. In some studies, healthy subjects were treated but only for some days(Packer et al., 2023). Studies on patients with type 2 diabetes mellitus treated in real-world clinical practice confirmed the long-term durability of glycemic control with SGLT2i, and compared to the conventional treatment groups, the frequencies of total and serious adverse events did not vary significantly (Katakami et al., 2023).

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Lucia Scisciola: Writing – original draft; **Fabiola Olivier:** Writing review & editing; **Concetta Ambrosino:** Writing review & editing; **Michelangela Barbieri:** Writing review & editing; **Maria Rosaria Rizzo:** Writing review & editing; **Giuseppe Paolisso:** Conceptualization, Supervision, Writing review & editing.

Declaration of Competing Interest

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