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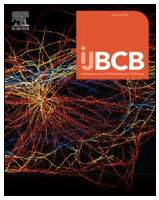

Immunosenescence and macrophages: From basics to therapeutics

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ABSTRACT

Ageing decreases the function of the immune system and increases susceptibility to some chronic, infectious, and autoimmune diseases. Senescence cells, which produce senescence-associated secretory phenotypes (SASPs), can activate the innate and adaptive immune responses. Macrophages are among the most abundant innate immune cell types in senescent microenvironments. Senescence-associated macrophages, recruited by SASPs, play a vital role in establishing the essential microenvironments for maintaining tissue homeostasis. However, it's important to note that these senescence-associated macrophages can also influence senescent processes, either by enhancing or impeding the functions of tissue-resident senescent cells. In this discussion, we describe the potential targets of immunosenescence and shed light on the probable mechanisms by which macrophages influence cellular senescence. Furthermore, we analyze their dual function in both clearing senescent cells and modulating age-related diseases. This multifaceted influence operates through processes including heightened inflammation, phagocytosis, efferocytosis, and autophagy. Given the potential off-target effects and immune evasion mechanisms associated with traditional anti-ageing strategies (senolytics and senomorphics), 'resetting' immune system tolerance or targeting senescence-related macrophage functions (i.e., phagocytotic capacity and immunosurveillance) will inform treatment of age-related diseases. Therefore, we review recent advances in the use of macrophage therapeutics to treat ageing and age-associated disorders, and outline the key gaps in this field.

1. Introduction

Ageing is a gradual process involving the decline of both physiological and psychological aspects in humans. This progression is influenced by several key factors, including cellular senescence, chronic inflammation, and altered intercellular communication, among others (Lopez-Otin et al., 2023). Cellular senescence, first described in 1961, is defined as a permanent state of cell cycle arrest, which is influenced by senescent cells and the microenvironment they reside in. In addition to senescent cells, the senescent microenvironment encompasses both cellular and acellular elements, comprising blood vessels, fibroblasts, immune cells, and the extracellular matrix. Immunosenescence, characterized by the deterioration in the structure and function of the body's immune system, manifests as an accumulation of memory and non-functional immune cells, compromised signaling due to a limited repertoire of receptors, an overall pro-inflammatory milieu, and complete dysregulation of the immune system. Infiltrating macrophages and tissue-resident macrophages are major constituents of the senescent microenvironment, indicating that macrophages are critical mediators of immunosenescence (Burton and Stolzing, 2018).

Macrophages (also called phagocytes), with a stellate morphology and high phagocytic activity, are key players in the regulation of innate and adaptive immunity. Initially, through the ingestion of particles and/or other cells, phagocytosis was heralded as a protective mechanism against pathogens (Metchnikoff, 1907). In most ageing-related disorders, macrophage dysfunctions have been associated with degenerative lesions in tissues or organs, limited therapeutic responses, and poor prognostic outcomes. Senescence-associated macrophages are not a homogeneous cell population but a highly dynamic, heterogeneous population that is regulated by specific local stimuli. Macrophages

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possess the capacity to perceive and react to the microenvironments within all organs, participating in a multitude of cellular processes (Guilliams et al., 2022; Qi et al., 2022). This establishes them as more than just innate immune cells (Mosser et al., 2021). The phenotypes of macrophages exhibit significant adaptability and are subject to influence from diverse factors, encompassing microenvironmental cues, immune conditions, tumor presence, and hypoxic conditions (Dong et al., 2021). Moreover, various endogenous and exogenous stresses, such as telomere dysfunctions, DNA damage, and oncogenesis activate cellular senescence, which is characterized by irreversible growth arrest and senescent phenotypes. The senescent cell motility and microenvironment sensing are reshaped by senescence-associated secretory phenotypes (SASPs), a new mechanism that links senescence to tissue malfunction (He and Sharpless, 2017; Malaquin et al., 2019). SASP, which is characterized by a substantial increase in pro-inflammatory factors, contributes to a progressive decline in the functional capacity of organ systems. Aberrant accumulation of SASP from senescent or damaged cells is associated with ageing and contributes to frailty as well as age-associated disorders, including cancer, autoimmunity, cardiovascular disease, and degenerative diseases (He and Sharpless, 2017; Lewis-McDougall et al., 2019).

During ageing, clearance of aged and senescent cells is vital for inhibiting their harmful effects (Ge et al., 2021). Macrophage recruitment and interactions with SASP senescent cells is crucial for the maintenance of tissue homeostasis (Huang et al., 2021). Removal of aged and senescent cells by macrophages (along with other immune cells) is a continuous process that recycles about 2 million red blood cells each second, and releases their iron into the systemic iron pool (Hampton-O'Neil et al., 2020; Korolnek and Hamza, 2015). Apart from phagocytosis, studies have revealed links between tissue homeostasis, and inflammasome activation (Camell et al., 2017), autophagy (Chen et al., 2022), as well as efferocytosis (Juhas et al., 2018), indicating that macrophages have efficacious regulatory mechanisms in response to senescence microenvironments. Thus, the ability of macrophages to sense and alter cell states in senescence microenvironments can be leveraged to develop strategies for improving the diagnosis, prognosis, and treatment of various diseases, including ageing and age-associated disorders.

The growing field of immune-targeted therapies has elucidated on how various novel treatments influence the host immune system. However, the high plasticity and heterogeneity of macrophages are practical obstacles in development of anti-ageing therapies (Blacher et al., 2022). Recently, macrophage immunotherapy, aimed at ablation or re-education of macrophages (Ramesh et al., 2021), has emerged as a powerful component of combination therapies designed to target senescent cells and reverse cognitive ageing (Minhas et al., 2021), and to inhibit cancer development (Li et al., 2019). Most of the published reviews on senescence-associated macrophages have focused on how they modulate microenvironment inflammation (Neves and Sousa-Victor, 2020), influence cell senescence (Campbell et al., 2021), or on how they interplay with senescent cells (Behmoaras and Gil, 2021). A limited number of reviews have discussed the application of macrophage-specific therapies in the treatment of cancer (Belgiovine et al., 2016), age-related liver diseases (Stahl et al., 2018), and metabolic diseases (Peterson et al., 2018). Furthermore, the exact importance of macrophages in anti-ageing strategies remains incompletely understood. We discuss several therapeutic mechanisms underlying the anti-ageing effects of macrophages, as well as the clinical strategies and future directions in the study of macrophages in senescence and associated disorders.

2. Roles of macrophages in senescence responses: the bright and dark sides

2.1. Polarization

High heterogeneity and plasticity are important macrophage characteristics, which may be much more complex than anticipated (Fig. 1). Immune cell populations may be heterogenous in older organisms (human ≥65 years old and mice ≥1.5 years old). Functional heterogeneity of macrophages can be grouped into two classes; M1/M2 (pro-inflammatory/immunosuppressive) macrophage polarization (Mau et al., 2020). In humans, macrophages temporally or spatially exhibit multiple phenotypes. Advances in multi-omics, single-cell RNA sequencing (scRNA-seq), high throughput biology and systems immunology have facilitated studies on cellular and functional heterogeneity, as well as on dynamic changes in the immune system (Mogilenko et al., 2021a; Wu et al., 2023) (Table 1). Compared to young individuals, the dominant phenotype of macrophages in elderly adipose and hepatic tissues primarily exhibit M1 phenotype (Jackaman et al., 2017). If the heightened SASP activation tends to subside and return to baseline levels, macrophages may adjust their responses to changes in the microenvironment. This could lead to their disengagement from damaged cells while under immunosurveillance (Sturmlechner et al., 2021). Given the intricate nature of in vivo macrophage polarization, recent single-cell RNA sequencing (scRNA-seq) discoveries have questioned the traditional M1/M2 categorization of macrophages. There is a possibility that senescent cells can induce differentiation of M2 macrophages into three subtypes (M2a, M2b, and M2c). However, additional research is needed to confirm this (Burton and Stolzing, 2018). Additional resident macrophage populations have recently been identified in various tissues, including lungs (Lyve1^{lo} MHCII^{hi} and Lyve1^{hi} MHCII^{lo} macrophages) (Chakarov et al., 2019) and mammary glands (M_a/M_b macrophages) (Li et al., 2020a). In addition to M1/M2 subtypes, SASP might mediate macrophage polarization into other subtypes.

Macrophages, found in various organ systems, can regulate cellular lifespans by eliminating senescent cells (Kay and Goodman, 2003). However, their effectiveness may diminish with age (Campbell et al., 2021). Within senescent microenvironments, tumor suppressors like p16, p21, pRB, and p53 halt the cell cycle irreversibly. Behmoaras et al. coined the term "senescent-like macrophages" to describe macrophages in a senescent state, marked by lipid accumulation, SASP, and a sustained DNA damage response (Behmoaras and Gil, 2021). An alternative term for these is senescent associated macrophages (SAMs) (Campbell et al., 2021). Nonetheless, some macrophages, exhibiting growth arrest or abnormal polarization, might contribute to the development of various age-associated diseases, including atherosclerosis, cancer, and macular degeneration (Jiang et al., 2023; Sene et al., 2013). Exosomes derived from tumors deliver miRNA cargo to macrophages, suppressing host innate immunity and facilitating metastasis (Bieniasz-Krzywiec et al., 2019; Gao et al., 2018). For instance, the aged murine macrophages display disrupted ceramide and phospholipid profiles compared to their younger counterparts. Modulating macrophage dysfunction for immune regulation through miRNA-based therapeutics shows promise in combating age-associated diseases (Lin et al., 2018). It's worth noting that once senescent cells are cleared, they cannot be replaced and play important structural and functional roles in the ageing organism (Grosse et al., 2020). Thus, different types of macrophages play different roles during various senescence stages. However, due to the complexity of macrophage polarization, the mechanisms through which macrophages affect senescence have yet to be conclusively determined. Elucidation of macrophage phenotypes at specific times may be key to preventing and treating senescence.

2.2. Phagocytosis

The health of elderly individuals is intricately tied to the

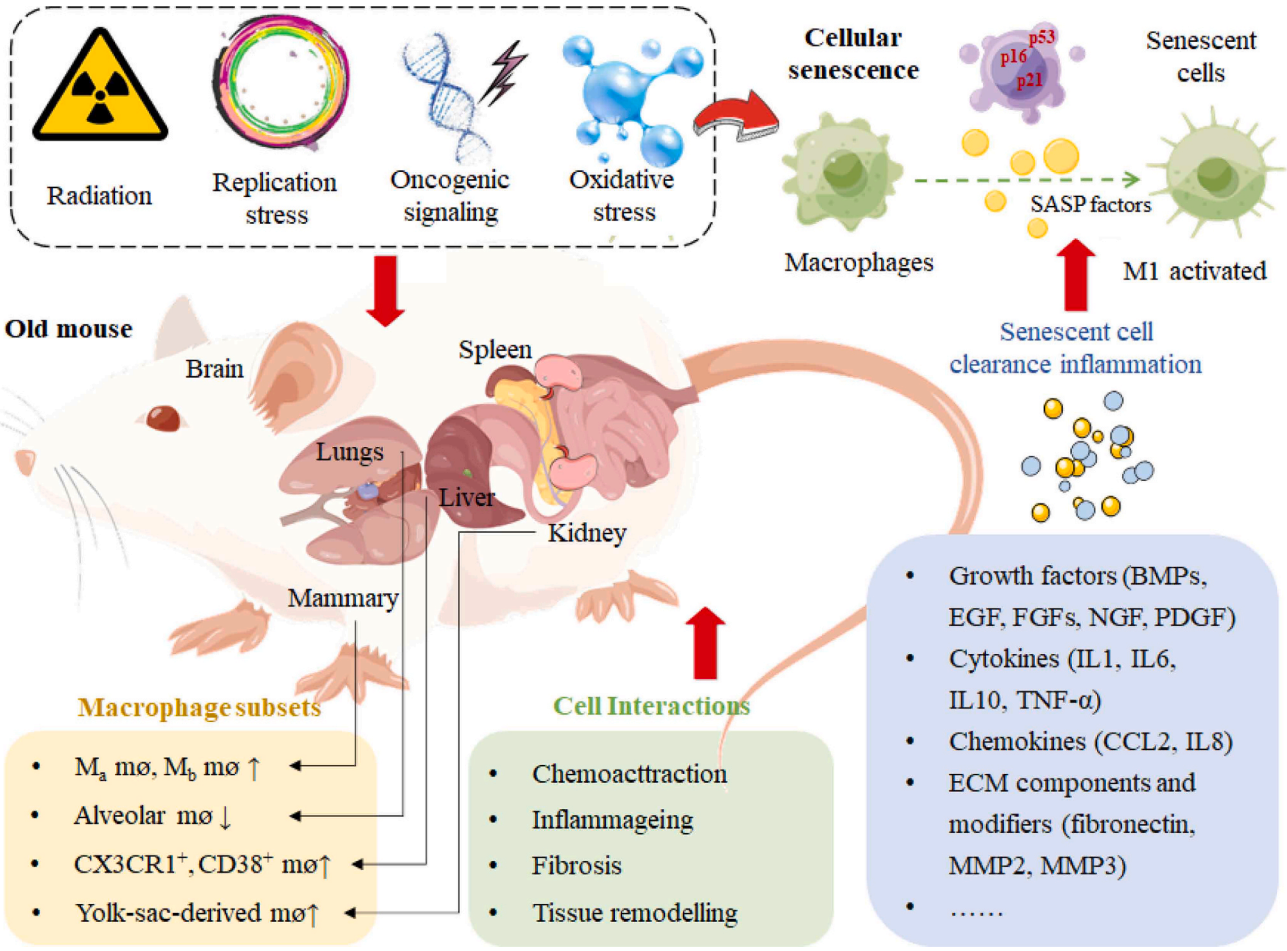

Fig. 1. Overview of senescence inducers, changes in macrophage physiology and activation of SASP factors. Senescence can be activated by various stress stimuli (shown in red), including ionizing radiation, replicative stress, oncogenic signaling, and oxidative stress. Senescent cells are shown in purple while macrophages (undergoing polarization) are shown in green. Macrophages, which are recruited by most senescent cells, respond to endogenous and exogenous regulators in senescent microenvironments. Single-cell techniques have revealed the expansion and reduction of macrophage populations with distinct phenotypes/subsets in various organs of old mice. The main SASP factors (depicted in blue) include growth factors (BMPs, EGF, FGFs, NGF, PDGF), cytokines (IL1, IL6, IL10, TNF-α), chemokines (CCL2, IL8), and metalloproteinases (fibronectin, MMP2, MMP3). Growth factors can enhance tissue fibrosis in ageing tissues, while chemokines and cytokines create proinflammatory environments. SASP chemokines attract immune cells that can recognize and interact with senescent cells and eliminate them. Secreted factors may signal in an autocrine fashion, reinforcing the senescence phenotype, or in a paracrine manner with multiple effects on neighboring cells and resident tissues, including chemoattraction, inflammageing, fibrosis, and tissue remodeling. **Abbreviations**: BMPs: bone morphogenetic proteins; CCL: CC-chemokine; EGF; epithelial growth factor; FGFs: fibroblast growth factors; IL: interleukin; MMP: matrix metallopeptidase; PDGF: platelet-derived growth factor; SASP: senescence-associated secretory phenotype; TNF: tumor necrosis tactor.

functionality of their immune system, which not only affects their ability to resist apoptosis but also stands as the initial defense against invading pathogens (Wong et al., 2017). Macrophage senescence, characterized by diminished phagocytic capacities, lies at the core of both cellular senescence and immunosenescence. However, SASP factors in senescent microenvironments trigger age-related defects in macrophage phagocytosis (Linehan et al., 2014). Ogata Y. et al. (Ogata et al., 2021) proposed that macrophages might first induce apoptosis in senescent cells before engulfing them. Phagocytic receptors are categorized into two; opsonin-dependent receptors (Fc receptors, complement receptors, and integrins) and opsonin-independent receptors (C-type lectins and scavenger receptors) (Linehan and Fitzgerald, 2015). The mechanisms involved in macrophage-mediated recognition and engulfment of senescent cells have yet to be fully established, however, the processes are probably not unique to senescent cells (Burton and Stolzing, 2018). Indeed, the mechanisms underlying macrophage recognition in other pathological contexts, such as during cancer senescence surveillance, may be involved in immunosurveillance and clearance of apoptotic cells (Jiang et al., 2023; Ye et al., 2017).

Senescent cells preferentially express specific cell surface antigens to be distinguishable from mature cells and to be recognized by naturally occurring antibodies (ie., IgMs), which enables macrophage phagocytosis and removal (Kay, 1981). In a previous study aimed at exploring antibodies that specifically target senescent cells, it was postulated that IgM clone 9H4, recognizing the oxidized membrane on the surface of senescent human fibroblasts, could serve as an "eat me" signal, prompting macrophage phagocytosis (Fig. 2) (Frescas et al., 2017). High expression of transmembrane proteins in senescent cells has demonstrated their potential as vaccine targets for lifespan extension (Suda et al., 2021). Apoptotic factors, including TNF-α and p53 can propagate the senescence phenotype and accelerate immune system ageing by inducing apoptosis (Hafner et al., 2019). Various receptors contribute to this effect, indicating that cluster of differentiation (CD) 36 (Puig et al., 2020), receptor of advanced glycation endproducts (RAGE) (Xu et al., 2016) and other class I/II scavenger receptors (Beguin et al., 2020) are also involved in this process. The release or display of sphingosine-1-phosphate (S1P) by apoptotic cells is known to trigger phagocytic uptake, functioning as a “find me” and “eat me” signal for macrophages (Kugelberg, 2016). Although this occurs during apoptosis, it may also enhance immune surveillance of senescent cells by

Table 1
Macrophages (MΦ) in senescent tissues.

Tissue	Abundance	Key markers of monocyte-derived origin
Aorta	M1/M2 ↑	IL1β, IL-6, IL-10 ↑ (Ciaglia et al., 2022)
Brain	M1/M2 ↑	PGE_2, EP2, GYS1, p16↑ (Minhas et al., 2021; Stojiljkovic et al., 2022)
Bone marrow	MΦ↑	p16, p21, Mcp1, TNF, IL6, IL1β ↑ (Yousefzadeh et al., 2021)
Kidney	Yolk-sac-derived MΦ↑	TNF-α, IFN-γ, IL-12 ↓ (Ide et al., 2020; Kim et al., 2019)
Lung	Alveolar MΦ↓	Pparg, IL10, CBFβ↓; IL6, IL1β, TNF, Ifng, Cebpb, Spp1, Gpnmb, Mfge8, H2-K1, H2-Q7, H2-D1, B2m, p16, p21↑(Angelidis et al., 2019; Mogilenko et al., 2021b; Prieto et al., 2023; Wu et al., 2023)
Liver	$CX3CR1^{+}$, $CD38^{+}$ MΦ↑	CCR2, CX3RC1 (Mogilenko et al., 2021b), CD38 ↑(Wu and Zhang, 2020)
Skeletal muscle	M1/M2 ↑	p21, Ccl2, Il-1α, IL-1β, TNF, Gdf15 ↑, Adamts1, Pdgfb ↓(Dungan et al., 2022)
Spleen	M1/M2 ↑	Lamin B1↓, p16, IL-1α, IL-6, MCP-1, VEGF ↑ (Palacio et al., 2019)
Skin	M1/M2 ↑	LPC, TNF-α↑ (Narzt et al., 2021; Ogata et al., 2021)

Abbreviations: Adamts1, A Disintegrin and Metalloproteinase with Thrombospondin 1; B2m, B2 Microglobulin; CBFβ, core binding factor β; Ccl2, Chemokine Ccl2; CCR2, Chemokine C-C-Motif Receptor 2; Cebpb, C/EBP Beta; CX3RC1, CX3C Chemokine Receptor1; EP2, Prostaglandin E Receptor 2; Gdf15, Growth/Differentiation Factor 15; Gpnmb, Glycoprotein Nmb; GYS1, Glycogen Synthase 1; H2-K1, Histocompatibility 2-K1 Region; Ifng, Interferon Gamma; IL, Interleukin; LPC, Lysophosphatidyl Choline; Mcp1, Monocyte Chemoattractant Protein 1; Mfge8, Milk Fat Globule EGF Factor; Pdgfb, Platelet Derived Growth Factor B; PGE2, Prostaglandin E2; Pparg, Peroxisome Proliferator-Activated Receptor Gamma; Spp1, Secreted Phosphoprotein 1; TNF, Tumor Necrosis Factor; VEGF, Vascular Endothelial Growth Factor.

macrophages. In physiology and disease, surface expressions of CD24 and CD47 often act as "don't eat me" signals (Bradley, 2019; Kelley and Ravichandran, 2021). Upon contact, inhibitory signals are sent through signal-regulatory protein alpha (SIRPα), a receptor on macrophage surfaces, ensuring that healthy cells avoid inappropriate phagocytosis. Therefore, CD47 downregulation is necessary for macrophages to target damaged "self" cells (Liu et al., 2017). CD47 downregulation of via c-MYC inactivation promotes tumor regression by inducing tumor cell senescence (Casey et al., 2016). Thrombospondin-1 (TSP1) from senescent cells prevents senescence escape, which can be explained by emergence of CD47-low cells (Guillon et al., 2019). However, it has not been established if CD47 downregulation in microenvironments specifically modulates c-MYC inactivation and senescence. Modified cell surface glycans, a class of potential senescence antigens, can also be recognized by members of C-type lectin receptor (CLR) family, such as macrophage galactose-type lectin (MGL), which are exclusively expressed by macrophages (Ward et al., 2018). N-glycan and O-glycan modification of cell surface proteins might regulate sialylation and galactose exposure during cell senescence (Itakura et al., 2016) and viral entry (Yang et al., 2020). Thus, studies should elucidate on the phagocytic functions of macrophages in removal of impaired or senescent "self" cells.

2.3. *Efferocytosis*

Billions of cells that are turned over every day are continually phagocytosed by macrophages, thereby protecting against ageing and promoting injury resolution by removing apoptotic and senescent cells. The ability of individual macrophages to efficiently internalize multiple senescent cells over consecutive rounds of engulfment, referred to as continual efferocytosis, may be particularly vital in alleviating ageing or regulating wound repair in damaged tissues, even though apoptotic cells often significantly outnumber macrophages (Puleston and Pearce, 2020). Additionally, since the human body contains 37 trillion cells, senescent cells in ageing organisms easily outnumber professional secretory cells (Lopes-Paciencia et al., 2019). Ageing is associated with impaired efferocytosis, but the mechanisms underlying this process have yet to be fully established. Efferocytosis-induced macrophage proliferation results in secretion of anti-inflammatory cytokines, including TGF-β and IL-10, expanding the pool of resolving macrophages via

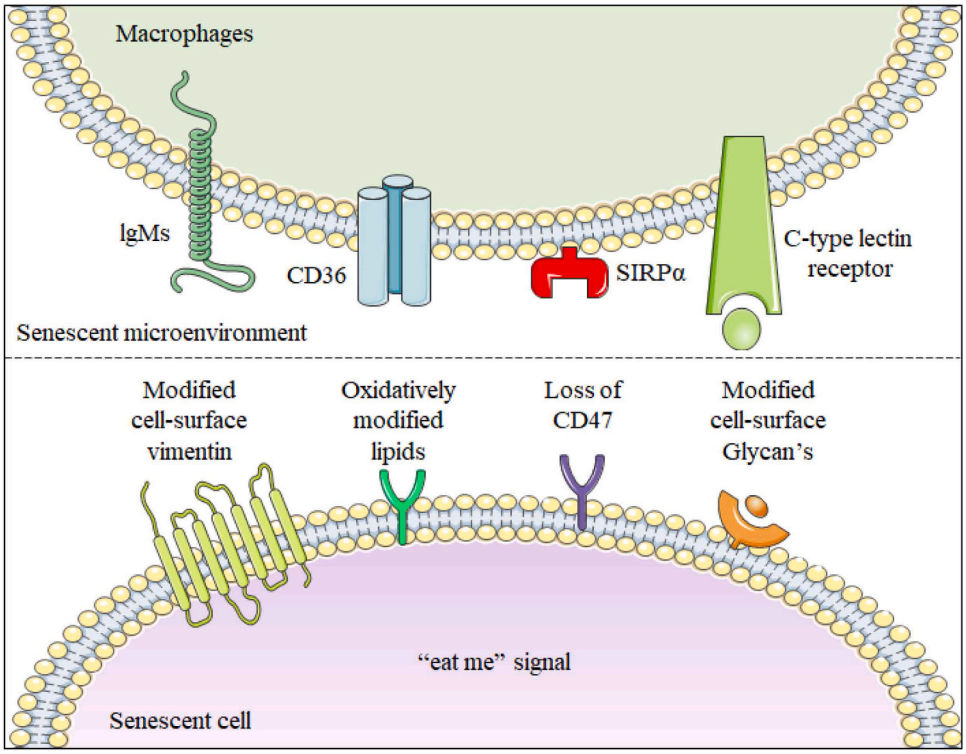

Fig. 2. Possible mechanisms involved in anti-ageing effects of macrophages in senescent microenvironments.

DNase2a (Gerlach et al., 2021). The M1 macrophages that are activated by senescent cells via SASP factors exhibit higher levels of glycolysis, while macrophages that exhibit pro-resolving properties acquire more energy (Covarrubias et al., 2020). Senescent cell efferocytosis induces the release of senescent cell-derived arginine into macrophage cytoplasm via PQ loop repeat-containing 2 (PQLC2), a lysosomal cationic amino acid transporter (Yurdagul et al., 2020; Zhu et al., 2021). During macrophage metabolism, arginine or ornithine are derived from engulfment of a first-encountered senescent cell, which is vital for subsequent rounds of efferocytosis (Fig. 3). Mechanistically, arginine serves as a precursor of polyamine synthesis by arginase 1 (Arg1), which converts arginine into ornithine. Ornithine, which is either synthesized from the senescent cell-derived arginine or taken up directly from senescent cells, enters macrophages for metabolism (McCubbrey et al., 2022; Yurdagul et al., 2020). Ornithine is metabolized into the first polyamine putrescine by ornithine decarboxylase (ODC), a rate-limiting enzyme in polyamine synthesis. Then, arginine is converted to putrescine via Arg1 and ODC as earlier described, thereby elevating the expressions of Rac1 GTPase's guanosine triphosphate (GTP)-exchange factor (GEF), which causes cell line derived transforming sequence (Mcf2) mRNA stabilization by the human antigen R protein (HuR) (Gupta et al., 2013). Rac1 kinase activation is enhanced by elevated Dbl levels, thereby promoting actin polymerization-mediated internalization of subsequent senescent cells (Fig. 3) (McCubbrey et al., 2022).

2.4. Autophagy

Phagocytosis and phagosome maturation are major physiological processes in multicellular organisms (Gray and Botelho, 2017). Senescent cells have an expanded lysosomal compartment that is associated with increased lysosomal numbers and monocyte–macrophage differentiation. Various stress conditions can trigger autophagy, a process by which cytoplasmic constituents are degraded by lysosomes (Azzman, 2019). Activities of senescence-associated-beta-galactosidase (SA-β-gal, encoded by the GLB1 gene) are widely accepted as senescence markers and are markedly elevated in senescent cells because of increased lysosomal levels (Martinez-Zamudio et al., 2021). However, as one of the limitations for β-galactosidase staining, senescent macrophages are well stained (Hedblom et al., 2019). In macrophages, endosomes and lysosomes (endolysosomes) are required for removal of senescent cells. Macrophages promote lysosomal fusion (via TFEB activation) and expanded endo-lysosomal volume (via mTORC1 dependent translation), thereby remodeling these organelles upon proinflammatory stimulation to maintain phagosome integrity (Hipolito et al., 2019) and sustain macrophage effector functions (Westman et al., 2020). Chromatin structure remodeling via the autophagy/lysosomal pathway is vital for recycling of cell constituents and cell remodeling, which are involved in cell senescence (Ivanov et al., 2013). Nevertheless, there is a lack of direct and strong evidence linking lysosomal expansion to SASP in senescent cells.

The lysosome, a fluid-filled organelle, serves as a crucial signaling platform at the intersection of cell metabolism and function, playing a vital role in the energy metabolism and nutritional status of macrophages. Activation of the highly conserved kinase, mechanistic target of rapamycin complex 1 (mTORC1), on the lysosomal surface triggers anabolic pathways while simultaneously suppressing the catabolic process of autophagy (Kim and Guan, 2019). Dysregulated autophagy is associated with lysosomal dysfunctions. In macrophages, autophagy decreases with ageing, aggravates inflammation (Chen et al., 2022) and restores autophagy, making it a promising strategy for slowing senescence (Tai et al., 2017). The mTOR activities and autophagy have been implicated in the generation of SASP during senescence (Narita et al., 2011), as well as in guiding the maturation of macrophages into various phenotypes (Hedblom et al., 2019). In the context of cellular senescence, the interplay with factors from mononuclear phagocytes may influence autophagy. For example, although autophagy can facilitate senescence, rapamycin-induced autophagy may also alleviate radiation-induced bystander effects (Huang et al., 2014). Moreover, due to its pivotal role in muscle repair, autophagy induced by macrophages presents itself as a promising therapeutic target in counteracting age-related declines

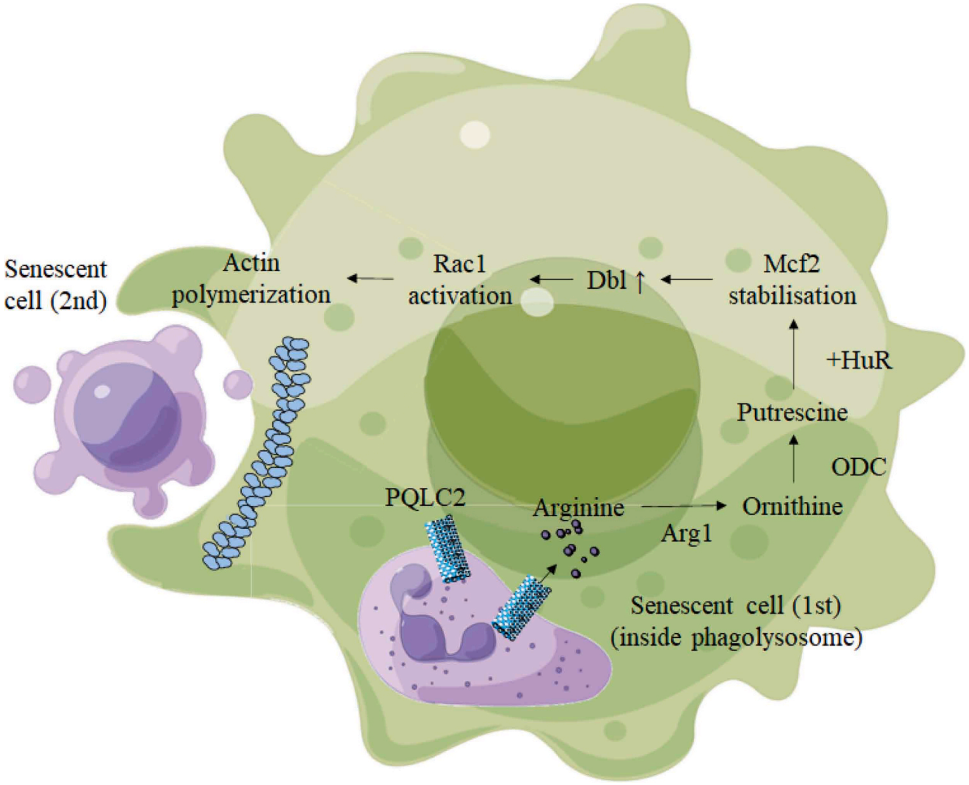

Fig. 3. Continuous efferocytosis of senescent cells by macrophages.

in skeletal muscle regenerative capacity (Lee et al., 2019). Studies have reported a link between mitochondrial homeostasis and lysosomes during monocyte–macrophage differentiation (Nicolas-Avila et al., 2020), and deterioration of mitochondria with age is attributed to impaired lysosome-like vacuoles (Hughes et al., 2020). Therefore, a causal relationship may link lysosomal remodeling to mitochondrial functions in macrophages and senescent cells. The study of mitochondrial dysfunction and metabolic dysregulation is of particular interest when examining the role of macrophages during senescence. (Ademowo et al., 2017). In senescent cells, defects in mitochondrial functions mediate the proliferation of proinflammatory M1-like macrophages and the decline in tissue NAD^+ levels (Covarrubias et al., 2020), leading to induction of macrophage-derived SASP factors via activation of cGAS-STING (cyclic GMP-AMP synthase–stimulator of interferon genes), a cytosolic DNA sensing pathway (Vizioli et al., 2020). It is likely that there exists a signaling axis between lysosomes and mitochondria, which is common to both senescent cells and macrophages. This is significant, given that SASP plays a crucial role in their maturation and activation (Behmoaras and Gil, 2021). Nonetheless, modulation of autophagy has shown significant promise in senescence and senescence-associated diseases because most of the autophagy induction strategies (including caloric restriction) that modulate autophagy maturation to regulate autophagy flux are currently in clinical trials (Fig. 4) (Azzman, 2019; Minhas et al., 2021; Pallauf and Rimbach, 2013).

3. Leveraging macrophage therapeutics against ageing and age-associated disorders

3.1. Beyond senolytics: Immunotherapeutic targeting of senescent cells

Senescent cells have been known to accumulate during the development of various age-associated diseases, thus, their elimination is therapeutically beneficial without long-term negative health consequences. Senotherapeutic strategies are classified into two;

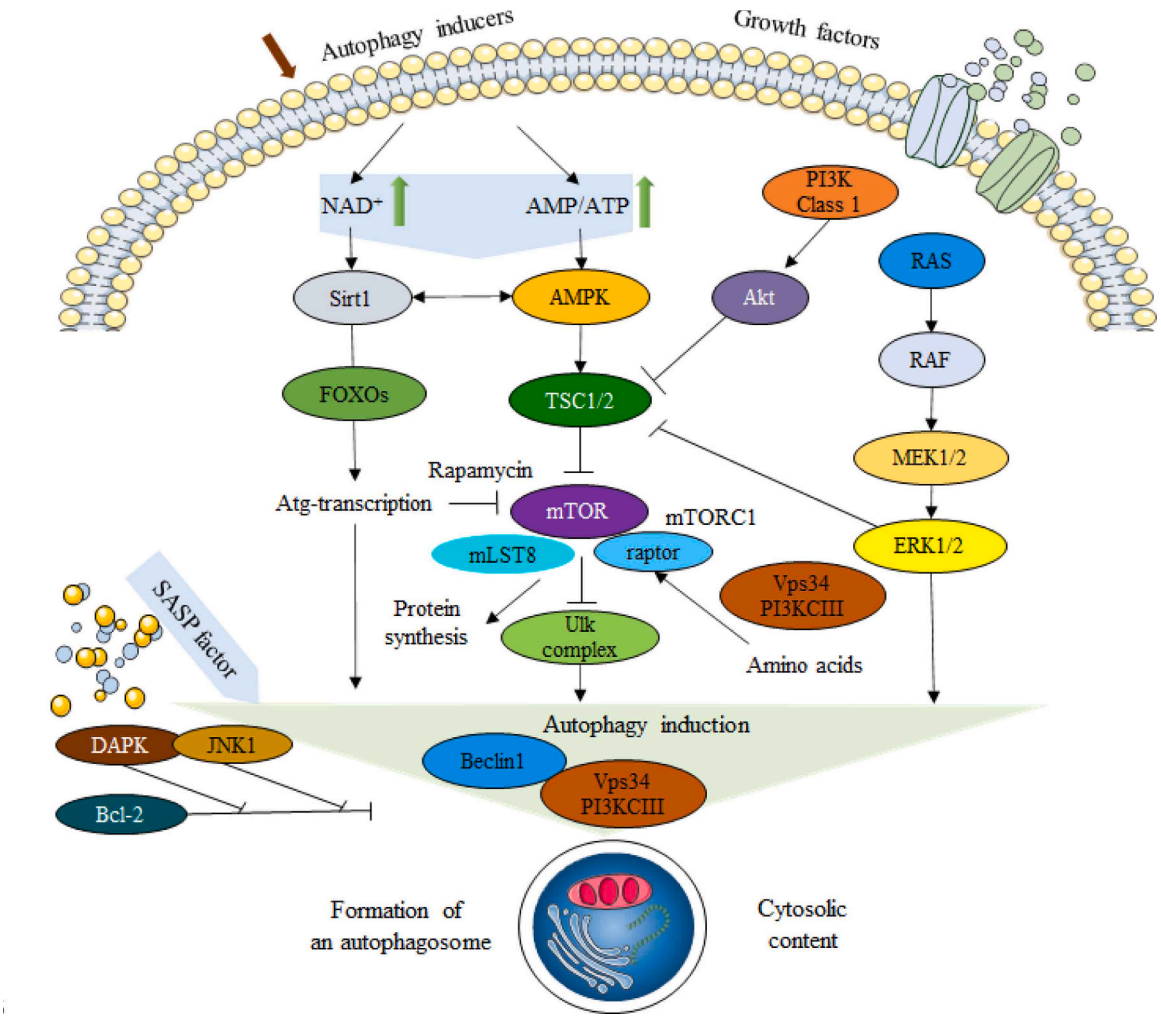

Fig. 4. Signaling pathways involved in macrophage autophagy. Autophagic flux is enhanced by autophagy inducers via deacetylase, sirtuin1 (Sirt1) and activation of Forkhead box O (FOXO) transcription factors. In senescent microenvironments, defects in mitochondrial functions induces the proliferation of proinflammatory M1-like macrophages and the decline in tissue levels of nicotinamide adenine dinucleotide (NAD)+ and adenosine triphosphate (ATP). Alternatively, adenosine monophosphate activated protein kinase (AMPK), a sensor for falling energy levels, is activated, leading to inhibition of the mechanistic target of rapamycin complex 1 (mTORC1) formed around mammalian target of rapamycin (mTOR), which acts as a key mediator of protein synthesis. Rapamycin, an inhibitor of mTORC1, induces autophagy via the Unc-51-like kinase 1 (Ulk1) complex. In contrast, mTORC1 activation and downstream targets like insulin and growth factor signaling, including PI3 kinase class I/Akt (protein kinase B, PKB) and rat sarcoma/mitogen-activated protein kinase /extracellular signal-regulated kinase (Ras/Mek/Erk) pathways inhibit autophagy. Erk1/2 induces autophagy upon amino acid depletion, which negatively regulates autophagy via phosphatidylinositol-3-kinase (PI3K) class III vacuolar protein sorting 34 (Vps34). Upon autophagy induction, a Vps34-Beclin1 complex is formed, resulting in autophagosome formation. Beclin1 is inhibited by B-cell lymphoma 2 (Bcl-2), which is in turn inhibited by death-associated protein kinase (DAPK) and Jun N-terminal protein kinase 1 (JNK1), thereby inducing macrophage autophagy.

pharmacological agents referred to as senolytics, which selectively kill senescent cells (Zhu et al., 2015), and senomorphics (including SASP inhibitors), which suppress the harmful effects of senescent cells (Di Micco et al., 2021). Senolytics, including dasatinib, quercetin, and fisetin, have been reported to delay or alleviate many age-related diseases in animal models. However, most senolytics target antiapoptotic proteins and the limitations of this strategy are emerging (Kim et al., 2023). Interest in immunotherapeutic targeting of senescent cells has been growing (Xu et al., 2022). Recently, immune-targeted therapies have provided insights into several novel strategies for eliminating senescence in the context of host immune system (Burton and Stolzing, 2018; Ramesh et al., 2021). Thus, among the elderly, immunotherapy may safely and effectively prevent, delay, or treat multifactorial, age-related diseases.

Since senescent cells can be recognized and eliminated by macrophages, transplanted macrophages can migrate to target sites, where they become tissue-resident macrophages with long-term self-renewal capacities (Hashimoto et al., 2013). Apart from various other types of immune cells, therapeutic macrophages also target age-associated diseases (Lee et al., 2016). Macrophages are mainly activated by regulating macrophage metabolism via the CD47 pathway (Liu et al., 2019). Activated macrophages draw upon glutamine and glucose as their primary energy sources, enabling them to effectively combat and engulf harmful cytopathic cells. In the realm of immunotherapy, innovative approaches have emerged, such as the transplantation of induced pluripotent stem cells or allogeneic macrophages sourced from youthful donors (Ackermann et al., 2017). Thus, macrophage therapeutics may be more effective at removing senescence, as metabolic rewiring of macrophages have at least a 4-fold higher phagocytic capacity treated by carnosine (Li et al., 2020b) or TLR agonists (CpG) (Ackermann et al., 2017) compared with the control group.

3.2. Senomorphics: Immune sensing and surveillance functions

In recent decades, the concept of immune surveillance has been extensively investigated in the field of anti-ageing research. Senescence-associated decline in immune system functions impairs the sensing and surveillance of senescent cells by macrophages, which are key in ageing (Yun et al., 2015). Inhibitors of SASP that target immune cells, including rapamycin, metformin, and ruxolitinib, have demonstrated the ability to enhance immune sensing and surveillance. Due to phenotypic plasticity of macrophages, some senescent cells have the cancer cell-like strategy of expressing “don’t eat me” signals to avoid elimination (Baker et al., 2011; Ide et al., 2020). Over time, through immune evasion, senescent cells accumulate in ageing tissues and induce age-associated diseases (Zhou et al., 2021b). Generally, senescent cells upregulate nuclear factor kappa B (NFκB)-dependent proinflammatory signaling, which engages SIRPα and activates transcriptional expressions of CD47, an inhibitory receptor of NFκB on macrophages, thereby facilitating their escape from immune surveillance (Lo et al., 2015).

Hall et al. (Hall et al., 2016) reported that when implanted into SCID mice, alginate beads containing senescent cells promoted macrophage recruitment, which were attracted by secretory factors. This was attributed to innate immune system activation, as evidenced by upregulated expressions of macrophage-specific transcripts, as well as NK cells and neutrophils. Treatment with the antioxidant, N-acetylcysteine (NAC), significantly alleviates oxidative stress and the senescent phenotype associated with knockout of the Hippo kinase, Mst1/2, in macrophages (Wang et al., 2019). Mst1/2 functions as an intracellular ROS sensor, drawing it towards regions of ROS release from organelles. Upon activation, Mst1/2 further activates and stabilizes the pivotal transcription factor, Nrf2, consequently bolstering antioxidant defenses. This equips macrophages to effectively combat pathogens while simultaneously fortifying their resistance against oxidative stress, thereby mitigating the effects of ageing. Macrophage-induced tumor cell senescence may have anticancer properties. Xue et al. (Xue et al., 2007) found that p53 reactivation promoted cellular senescence in p53-deficient tumors. Macrophages can be reprogramed to activate cytotoxic T cells via macrophage-secreted IL-12 and TNF-α, thereby modulating systemic anti-tumor immune responses (Sun et al., 2021). Some immunotherapies have been engineered to turn off the SIRPα co-receptor signal on macrophages to overcome immune evasion (Ray et al., 2018).

Additionally, microbiota-based interventions have also been evaluated as potential anti-ageing therapies (Bárcena et al., 2019). Regulation of the crosstalk between macrophages and microbiota may be exploited to protect epithelial barrier functions, microbiota balance, and to prevent chronic systemic inflammation as well as p16INK4a accumulation-associated senescence, thereby delaying age-related diseases (Zhou et al., 2021a). The potential commercial value of macrophage therapeutics has been widely recognized in the field of ageing and age-associated disorders (Peterson et al., 2018; Stahl et al., 2018). However, more studies should evaluate the long-term effects of therapeutic macrophages.

4. Challenges and future directions

4.1. Similarities and interplay between senescent cells and macrophages

The evolving demographics have increased the need for further research into ageing. Given the intricate nature of human ageing, the journey of scientific exploration is frequently hindered by conflicting evidence across multiple facets (Linehan and Fitzgerald, 2015). Recent years have witnessed the pivotal roles of senescent and immune cells in both the processes of ageing and the development of immunotherapies for a diverse array of age-related conditions. Investigations into the kinetics of senescence accumulation reveal a notable exponential rise in the production of senescent cells within ageing tissues (Katzir et al., 2021). This is corroborated by a pronounced escalation in the levels of specific senescence-associated markers (Table 1). Senescence accumulation is majorly ascribed to increased telomere dysfunction, DNA repair, and/or a decrease in their clearance by the immune system. While inflammatory macrophages can eliminate senescent cells, the senescent microenvironment can also reprogram macrophages into a senescence-like phenotype (SLP) by fine-tuning $p^{16INK4a}$ expression, and induce the formation of other resident cells in a paracrine manner (Mosser et al., 2021; Ogata et al., 2021; Yue et al., 2021). Therefore, strategies that specifically target senescent cells or macrophages represent a promising therapeutic paradigm.

Given the shared phenotypic characteristics between macrophages and senescent cells, including an increased number of lysosomes, heightened secretory activity, and the potential for inflammasome activation (Behmoaras and Gil, 2021), several questions remain unanswered: a) Could senolytic agents be applicable for eliminating specific sub-populations of macrophages, particularly in conditions like atherosclerosis (Childs et al., 2016; Suda et al., 2021) and virus-induced senescence (Lee et al., 2021)? b) Is it possible that senolytic drugs, originally designed to target and eliminate senescent cells, may also have an active or passive effect on macrophages? Tailoring these drugs to selectively target either senescent cells or macrophages will necessitate a comprehensive understanding of their cellular phenotypic similarities, interactions, as well as gene-phenotype and gene-gene relationships in both cell types.

4.2. Combinatorial immunotherapies targeting multiple pathways

Unlike macrophages, T cells are adaptive immune system components that respond to senescence signals (Minhas et al., 2021). The non-specific immune system, mediated by macrophages, mounts a mild response with low specificity. Adaptive immune checkpoint inhibitors, including anti-CTLA-4, anti-PD-1, and anti-PD-L1, which target T cells have shown good therapeutic efficacies in clinical trials (Ye et al., 2017). Macrophage-targeted drugs have been developed to treat various

conditions, including cognitive decline in ageing (Minhas et al., 2021). Studies on macrophage biology have resulted in the discovery of new targets for disease treatment. For instance, the colony-stimulating factor 1 receptor (CSF1R) is a macrophage target that promotes immunosuppression and tumor angiogenesis. The relationship between macrophages and ageing has been reported. This has opened a new window for development of antibody-based drugs that target this relationship. Several drugs targeting macrophages, such as Magrolimab, TTI-621/622, ALX148 targeting CD47, and OSE-172 targeting SIRP-α are undergoing clinical trials. The two CD47 inhibitors, TTI-621/622, are SIRPa-Fc fusion proteins, which produce Trillium. Although they are relatively similar, the Fc region is coupled to IgG1 in TTI-621, whereas it is coupled to IgG4 in TTI-622. IgG4 forms a slightly weaker binding to Fc receptors on immune cells, which enhances protection against CD47-expressing non-tumor cells. Recently, a new class of CSF-1R inhibitors, including pimicotinib (ABSK021), has entered clinical trials, representing a promising breakthrough (Falchook et al., 2023). Furthermore, the observed synergistic effects in combination therapies involving anti-GD2 or CD24 along with anti-CD47 (Theruvath et al., 2022) highlight their potential as potent immunotherapies for senescence. The advent of advanced technologies, particularly the development of single-cell sequencing techniques, has propelled research into the intricate biological functions of diverse macrophage subsets within various senescent microenvironments. Additionally, this technology has facilitated a comprehensive exploration of the interplay between macrophages and tumor immunotherapy. Hence, it is imperative to conduct thorough investigations into the biological characteristics of macrophages in senescent cells.

4.3. *Factors limiting clinical applications of bioactive materials*

To promote the engulfment or to induce macrophage-mediated autophagy of senescent cells, several therapeutic agents have been developed, including biomaterial-based or bioactive materials (Fig. 5). However, these agents have low specificity and are also associated with side effects that limit their clinical applications. However, compared to free drugs, nanomedicines and bioactive materials are efficient for targeting of macrophages and senescent cells, without causing toxic effects (Chen et al., 2022; Lee et al., 2016). Several biomaterial materials, including aptamer-drug conjugates have been developed for various clinical applications. Abraxane (albumin-bound paclitaxel nanoparticles) and Doxil (PEGylated liposome doxorubicin) have been approved by the FDA (Zhou et al., 2021b). The "biomimetic concept", which refers to biomimetic materials and devices, has been proposed to improve the clinical outcomes of various degenerative diseases in aged patients (Tampieri et al., 2021). Hence, nanomedicines and bioactive materials hold promise as effective anti-senescent therapeutic agents. Combination strategies appear to offer distinct advantages compared to monotherapy, enhancing local therapeutic efficacy through the use of bioactive materials. For example, a silk fibroin/gelatin (SG) patch

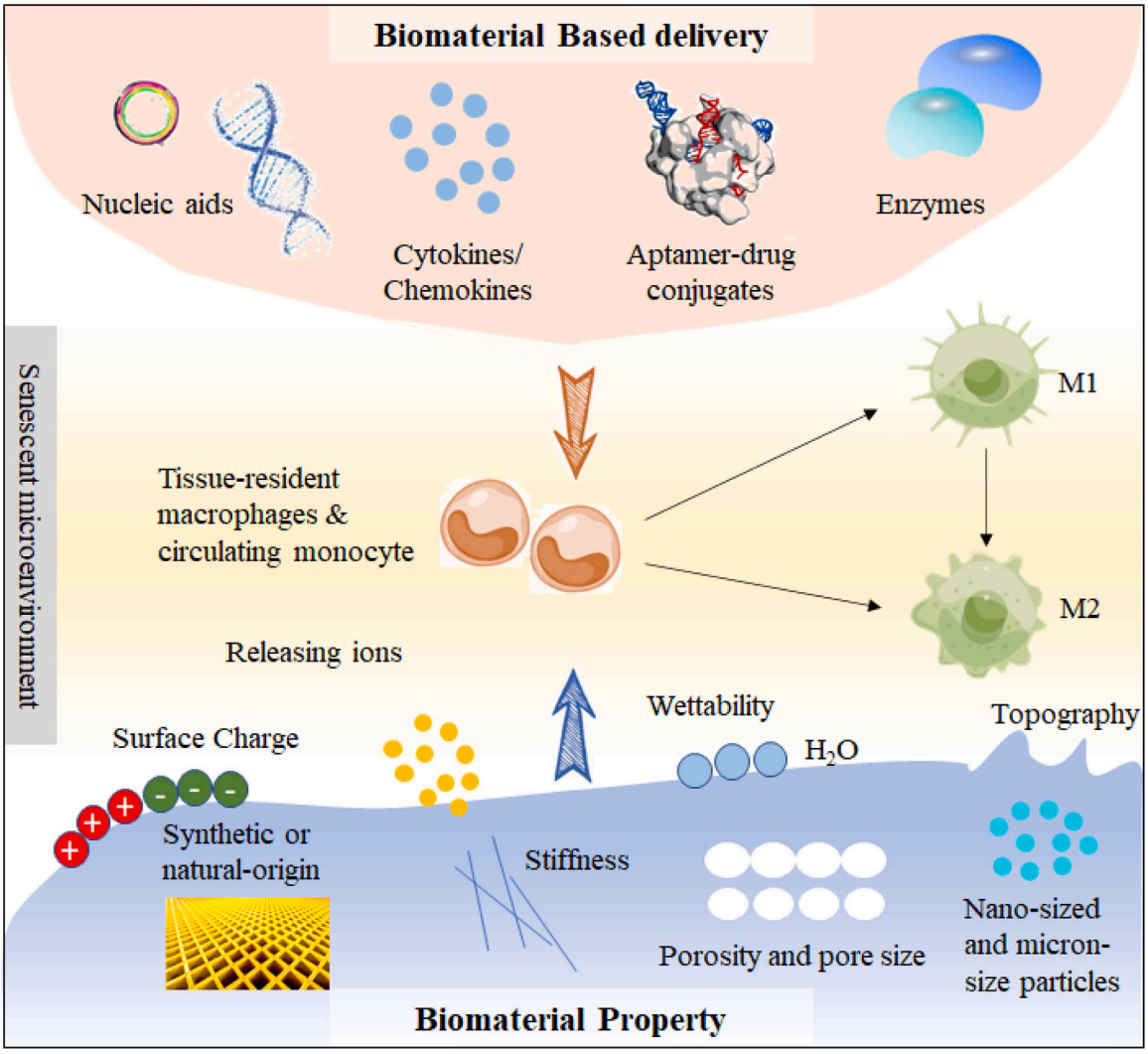

Fig. 5. Biomaterial based delivery of bioactive signals to regulate senescence-macrophage polarization in ageing.

incorporates a polydopamine-mediated ultralong silk microfiber (PDA-mSF) and metformin-loaded zeolitic imidazolate framework (ZIF), which helps regulate the immunomodulatory microenvironment for tissue regeneration by suppressing M1 macrophage polarization (Gong et al., 2023). These consistent findings have also been observed in both medical and cosmetic applications (de Souza Silva et al., 2023). However, several challenges should be addressed before nanoparticle-based therapies can be translated into clinically usable agents. Among such challenges include the lack of preclinical research models that can accurately mimic responses of the human ageing process to the therapies. In addition, some bioactive materials have poor targeting specificity on macrophages or senescent cells. The accumulation, biocompatibility, and bioactivity of nanoparticles are not sufficient for clinical use. Therefore, studies should investigate the cytotoxicity or systemic toxicity of nanoparticles and bioactive materials. Artificial intelligence technology should also be adopted to improve the implementation of precision medicine. For instance, exosomes carrying the macrophage migration inhibitory factor (MIF) have been used to mediate the cross talk between macrophages and senescent tissue cells (Zhuang et al., 2020). However, this technology is at its infant stage and requires optimization.

5. Conclusions

Macrophage metabolism is an important factor in senescence-associated multimorbidity. It is involved in regulation of low-grade inflammageing and drives systemic senescence, implying that they have crucial roles in age-associated diseases. Pro-inflammatory factors and SASP factors promote ageing events while macrophage re-education or transplantation are more likely to promote rejuvenation events. However, the roles of different macrophage subsets vary with the senescent context or type of tissue. The balance of activated macrophages (differentiation into various functional subsets) ultimately dictates the global outcome. Macrophages eliminate cell senescence and can act as modulators of age-related diseases by promoting inflammation, phagocytosis, efferocytosis, and autophagy. Targeting the phagocytic activity of macrophages in senescent cells is one of the strategies for achieving an efficient anti-ageing immunity. Nanomedicines and bioactive materials have shown the potential to be effective SASP inhibitors, which promote senescent cell accumulation, resulting in improved tissue and organ repair in ageing and age-associated disorders. Overall, impaired immune tolerance due to malfunctioning macrophages is prevalent in older people. Therefore, macrophage-based immunotherapies are promising strategies for controlling senescence.

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CRediT authorship contribution statement

Hongkang Zhu: Writing – original draft preparation. **Fanglin Shen:** Visualization, Data curation, Investigation. **Tingting Liao:** Software. **He Qian:** Validation. **Yu Liu:** Conceptualization. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Competing Interest

The authors declare no conflicts of interest related to this work.

Data Availability

Data will be made available on request.

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