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Role of hypoxia in cellular senescence

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ABSTRACT

Senescent cells persist and continuously secrete proinflammatory and tissue-remodeling molecules that poison surrounding cells, leading to various age-related diseases, including diabetes, atherosclerosis, and Alzheimer's disease. The underlying mechanism of cellular senescence has not yet been fully explored. Emerging evidence indicates that hypoxia is involved in the regulation of cellular senescence. Hypoxia-inducible factor (HIF)− 1α accumulates under hypoxic conditions and regulates cellular senescence by modulating the levels of the senescence markers p16, p53, lamin B1, and cyclin D1. Hypoxia is a critical condition for maintaining tumor immune evasion, which is promoted by driving the expression of genetic factors (such as p53 and CD47) while triggering immunosenescence. Under hypoxic conditions, autophagy is activated by targeting BCL-2/adenovirus E1B 19-kDa interacting protein 3, which subsequently induces $p21^{WAF1/CIP1}$ as well as $p16^{Ink4a}$ and increases β-galactosidase (β-gal) activity, thereby inducing cellular senescence. Deletion of the *p21* gene increases the activity of

Abbreviations: HIF, hypoxia-inducible factor; SA-β-gal, senescence-associated β-galactosidase; PARP-1, poly (ADP-ribose) polymerase-1; NHEJ, nonhomologous end joining.; ROS, reactive oxygen species.; miRNA, microRNA; lncRNA, long noncoding RNA; SASP, senescence-associated secretory phenotype; SMS, senescence messaging secretome; CXCR2, C-X-C chemokine receptor type 2; GROα, growth-related oncogene-α; OIS, oncogene-induced senescence; PAI-1, plasminogen activator inhibitor-1; C/EBPβ, CCAAT/enhancer-binding protein B; ROS, reactive oxygen species; H4K16ac, H4K16 acetylation; SESAME, serine-responsive SAM-containing metabolic enzyme; HAT, histone acetyltransferase; SAS, something about silencing; Rack1, receptor for activated C kinase 1; TGF, transforming growth factor; AMPK, AMP-activated protein kinase; PI3K, phosphatidylinositol 3-kinase; SIRT, sirtuin; mTOR, mammalian target of rapamycin; LTL, leukocyte telomere length; TERT, telomerase reverse transcriptase; MSC, multipotential stromal cell or mesenchymal stem cell; geroconversion, gerogenic conversion; PD-L1, programmed cell death-ligand 1; PD-1, programmed cell death-1; AREG, amphiregulin; SDGF, schwannoma-derived growth factor; Treg cell, regulatory T-cell; Teff cell, effector T-cell; CTLA-4, cytotoxic T lymphocyte antigen-4; KLRG1, killer cell lectin-like receptor subfamily G member 1; mtp53, mutant p53; NF-κB, nuclear factor-kappa B; STAT3, signal transducer and activator of transcription 3; LDH, lactate dehydrogenase; NK cell, natural killer cell; LT-Atg5i mice, Atg5i mice on long-term doxycycline; TAF, telomere-associated γ-H2AX foci; LC3, light chain 3; BNIP3, BCL-2/adenovirus E1B 19-kDa interacting protein 3; VPS34, vacuolar protein-sorting 34; PKC, protein kinase C; JNK, c-Jun-N-terminal kinase; FoxO3a, forkhead box class O 3a; GBM, glioblastoma; ATG9A, autophagy-related 9 homolog A; PHB2, prohibitin 2; MNGC, multinucleated giant cell; NHEJ, nonhomologous end joining; DSB, double-strand break; BRG1, brahma-related gene 1; DTX3 L, Deltex E3 ubiquitin ligase 3 L; ISG, interferon-stimulated genes; BM, bone marrow; SLE, systemic lupus erythematosus; IFN-I, ligand type I interferon; NEMO, NF-κB essential modifier; ATM, ataxia-telangiectasia mutated; DDR, DNA damage response; CCHD, cyanotic congenital heart disease; HCC, hepatocellular carcinoma; DCA, deoxycholic acid; HSC, hepatic stellate cell; CAT, catalase; IPA, indole propionic acid; TMAO, trimethylamine-N-oxide; proteostasis, protein homeostasis; SCFA, short-chain fatty acid; LPS, lipopolysaccharide; DPSC, dental pulp stem cell; TLR4, toll-like receptor 4; MyD88, myeloid differentiation factor 88; *E. coli*, *Escherichia coli*; EV, extracellular vesicle; VEGFR, vascular endothelial growth factor receptor; GC, granulosa cell; PCOS, polycystic ovary syndrome; CDCA4, cell division cycle-associated 4; PASMC, pulmonary artery smooth muscle cell; DC, dendritic cell; PgDCexo, exosomes from dendritic cells cocultured with *Porphyromonas gingivalis*; ceRNA, competing endogenous RNA; LincRNA, long intergenic noncoding RNA; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; ANRIL, antisense noncoding RNA in the INK4 locus; VSMC, vascular smooth muscle cell; TERRA, telomeric repeat-containing RNA; Exo1, exonuclease 1; BTG3, B-cell translocation gene 3; Sp1, specific protein 1.

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the hypoxia response regulator poly (ADP-ribose) polymerase-1 (PARP-1) and the level of nonhomologous end joining (NHEJ) proteins, repairs DNA double-strand breaks, and alleviates cellular senescence. Moreover, cellular senescence is associated with intestinal dysbiosis and an accumulation of D-galactose derived from the gut microbiota. Chronic hypoxia leads to a striking reduction in the amount of *Lactobacillus* and D-galactose-degrading enzymes in the gut, producing excess reactive oxygen species (ROS) and inducing senescence in bone marrow mesenchymal stem cells. Exosomal microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) play important roles in cellular senescence. miR-424–5p levels are decreased under hypoxia, whereas lncRNA-MALAT1 levels are increased, both of which induce cellular senescence. The present review focuses on recent advances in understanding the role of hypoxia in cellular senescence. The effects of HIFs, immune evasion, PARP-1, gut microbiota, and exosomal mRNA in hypoxia-mediated cell senescence are specifically discussed. This review increases our understanding of the mechanism of hypoxia-mediated cellular senescence and provides new clues for anti-aging processes and the treatment of aging-related diseases.

1. Introduction

Cellular senescence is a process in which the normal physiological function and proliferation ability of cells gradually decline with the passage of time or in the face of external stress, thus leading to irreversible or sustained cell cycle arrest [1,2]. Organismal aging is a process of gradual degradation of functions at the organelle, cell, tissue, organ, and organism levels with the passage of time, resulting in multiple organ damage and failure, leading to the end of life [3,4]. Senescent cells secrete a cascade of factors known as the senescence-associated secretory phenotype (SASP) (interleukin [IL]−6 and IL-8 are key factors) or senescence messaging secretome (SMS) [5,6]. SASP-induced "paracrine senescence" is observed in both normal cells and *in vivo* human and mouse models of oncogene-induced senescence (OIS) [7]. Cellular senescence is associated with other aging-derived comorbidities, such as retinopathy [8], osteoporosis and osteoarthritis [9], type 2 diabetes mellitus [10], and neurodegenerative diseases [11]. In addition, senescent fibroblasts promote epithelial cell growth and tumorigenesis [12]. Thus, cellular senescence is considered a major cause of aging and age-related conditions [13]. Exploring the mechanism of cellular senescence is significant for the treatment of senescence-associated pathologies. In addition to previous studies, the occurrence of cellular senescence is mainly due to the depletion of telomerase during cell replication and external senescence-related stimuli, such as oncogene activation, the accumulation of reactive oxygen species (ROS), and DNA damage [14,15]. Importantly, recent studies have identified various novel mechanisms that regulate cellular senescence. For example, acetate specifically promotes the level of histone H4K16 acetylation (H4K16ac) in the vicinity of telomeres by enhancing the interaction between the serine-responsive SAM-containing metabolic enzyme (SESAME) complex and the histone acetyltransferase (HAT) something about silencing (SAS) protein complex, disrupting telomere heterochromatin structure and accelerating cellular senescence [16]. Furthermore, the receptor for activated C kinase 1 (Rack1) inhibits activation of the transforming growth factor (TGF)-β/Smad signaling pathway by interacting with Smad3, thereby inhibiting p21-dependent cell senescence [17].

Hypoxia-inducible factor (HIF)− 1α, a key transcription factor ubiquitously expressed in nucleated cells, is upregulated under hypoxic conditions and plays a critical role in regulating cellular senescence [18]. Hypoxia or the hypoxic microenvironment, one of the hallmarks of tumors, triggers the sustained activation of HIF-1α to maintain or enhance mitochondrial biogenesis, thereby impeding tumor cellular senescence [19]. Hence, reducing the activity of HIF-1α can effectively induce cellular senescence and can be used as a treatment for aging-derived comorbidities, such as cancer [20]. The regulation of miRNAs is a major epigenetic mechanism associated with cellular senescence [21]. Certain miRNAs, such as miR-20a, miR-34a-5p, and miR-125a-5p, are involved in cellular senescence by regulating senescence-related molecules [22,23]. The gut microbiota is dominated by anaerobic bacteria [24]. Profound hypoxia leads to a decrease in *Lactobacilli*, which subsequently facilitates the accumulation of D-galactose derived from dysbiosis of the gut microbiome, causing premature senescence of bone marrow-derived mesenchymal stem cells [25]. Poly (ADP-ribose) polymerases (PARPs) are a class of enzymes that repair cellular DNA and are associated with cellular senescence and death [26,27]. When DNA is damaged, the body will automatically activate the PARP pathway for DNA repair, consuming a large amount of oxidized nicotinamide adenine dinucleotide (NAD^+). Conversely, the reduction in NAD^+ indirectly inhibits the activity of SIRT1, which subsequently leads to a decrease in DNA repair capacity [28–30]. This series of chain reactions creates a vicious cycle. All of these studies may contribute to understanding the mechanism correlating hypoxia and various signaling pathways in the process of cellular senescence.

In this review, we provide a comprehensive outline of recent advances contributing to elucidating the molecular mechanisms underlying the role of hypoxia in cellular senescence. We especially focus on the underlying function of HIF, PARP-1, the gut microbiota, and exosomal mRNA in hypoxic cellular senescence. This review improves our understanding of the mechanism of hypoxia in cellular senescence and provides new ideas for the clinical treatment of aging-related diseases and the development of anti-aging drugs.

2. Hypoxia-inducible factors in the regulation of cellular senescence

HIF is involved in cellular senescence. Intermittent hypoxia, which is associated with oxidative stress and chronic inflammation, accelerates the progression of cellular senescence [31,32]. Under intermittent hypoxia, leukocyte telomere length (LTL) is mostly shortened, leading to cellular senescence [33,34]. Obstructive sleep apnea characterized by intermittent hypoxia has also recently been found to induce mitochondrial oxidative stress, which subsequently leads to DNA damage and increases the expression of senescence markers, such as p16, γH2AX, and senescence-associated β-galactosidase (SA-β-gal) [35]. HIF-1α overactivation results in overexpression of telomerase reverse transcriptase (TERT) to further maintain telomere stability [36,37]. In addition, HIF-1α is also involved in endothelial cell senescence mediated by p16, p53, lamin B1, and cyclin D1 [38,39] (Fig. 1). In contrast to the above studies, evidence also shows that HIF-1 regulates other pathophysiological cellular processes and may play an important role in delaying premature cellular senescence [40]. Hypoxia downregulates E2A-p21 through the expression of TWIST induced by HIF-1α, thus preventing the senescence of multipotent stromal cells (MSCs) [41]. Moreover, hypoxia inhibits cellular senescence caused by multiple stimuli, demonstrating the appearance of a reversible quiescent state [42]. The conflicting results of hypoxia and HIF in the regulation of cellular senescence are not completely understood, but we suspect that the conditions of hypoxia employed in these studies potentially explain these differences, as different authors have different definitions of hypoxia. Some define an oxygen concentration of 0.2% as hypoxia [43,44], whereas others consider 1% or 5% as hypoxia [45–48]. Different definitions of hypoxia may limit the generalizability of experimental results. In addition, it should be noted that most experiments are based

on a specific cell, and it remains to be seen whether different conclusions will be drawn if different cells or the same cells in a different cycle are used. HIF-1α is also a key transcription factor and is intertwined with aging-related pathology, especially in regulating cellular senescence related to vascular aging [49–51]. Gerogenic conversion (geroconversion) was first proposed in 2011 and indicates a progression from reversible cell cycle arrest to senescence [52]. Given that mTOR inhibitors restrain geroconversion and hypoxia inhibits mTOR [53], it can be hypothesized that hypoxia may suppress geroconversion. However, the inhibition of geroconversion is p53 and HIF-1 independent given that hypoxia also inhibits geroconversion in cells that lack functional p53 and HIF-1α [54].

HIF-2α (also known as EPAS1) has high structural similarity to HIF-1α but minimal similarity in terms of function [55]. The expression of HIF-2α and the senescence marker p21, but not p16, was increased in an *in vitro* model of doxorubicin-mediated senescence. However, HIF-2α knockdown did not affect p21 expression or the cellular senescence process, implying that the upregulation of HIF-2α expression in senescent osteoblasts may be the result of organismal aging rather than the cause of cellular senescence [56]. On the other hand, this study suggests that HIFs regulate aging via different pathways but not through cellular senescence in this context. Indeed, in addition to cellular senescence, other factors, including telomere attrition, mitochondrial dysfunction, and stem cell exhaustion, are also key factors involved in aging mechanisms [57]. Nevertheless, exploring the mechanism of HIF in cellular senescence is definitely beneficial for understanding the organismal aging process.

Therefore, HIF-1 not only plays a role in cell adaptation to hypoxia but also, unexpectedly, seems to be involved in normoxic environments by delaying the onset of cellular senescence. The inhibitory effect of SASP under hypoxia is independent of HIF-1α, whereas elimination of HIF-1α under normoxia inhibits SASP expression. In addition, although senescence is physiologically related, HIF-1α plays a key role in the formation of a senescent phenotype and the progression of atherosclerosis. However, the exact mechanism by which endothelial cells become senescent in the vascular wall is still not fully understood. Although important questions about miRNA/HIF-1α crosstalk remain to be answered, *HIF-1α* is a common target gene in some miRNAs. HIF-1α and miR-126 levels were eliminated or decreased in the microvesicles of senescent endothelial cells, respectively, indicating that they are positive regulators among cells [38]. MiR-125a-5p activates downstream NF-κB through the specific protein 1 (Sp1)/SIRT1/HIF-1α signaling pathway and promotes SASP secretion, thereby inducing lung epithelial cell senescence [21]. HIF-2α activity is more specific to different cell types, such as osteoblasts, osteoclasts, or endothelial cells, and is often the downstream effector of cellular senescence.

3. Hypoxia triggers cellular senescence by mediating immune evasion

The hypoxic microenvironment can shield tumors from the natural antitumor immune response by promoting immune evasion, thereby regulating cellular senescence [58,59]. Hypoxia stimulates mitochondrial ROS production and cytokine expression. Programmed cell death-ligand 1 (PD-L1) is upregulated by these cytokines. PD-L1 combines with programmed cell death-1 (PD-1) and enhances immune evasion [60]. Amphiregulin (AREG, schwannoma-derived growth factor (SDGF)), the expression of which is positively correlated with PD-L1 expression, is one of the SASP factors. Amphiregulin forms an immunosuppressive microenvironment and enable cells to escape immune surveillance [61,62]. Moreover, AREG expression is upregulated under hypoxic conditions [63–65]. However, in human diploid fibroblast and

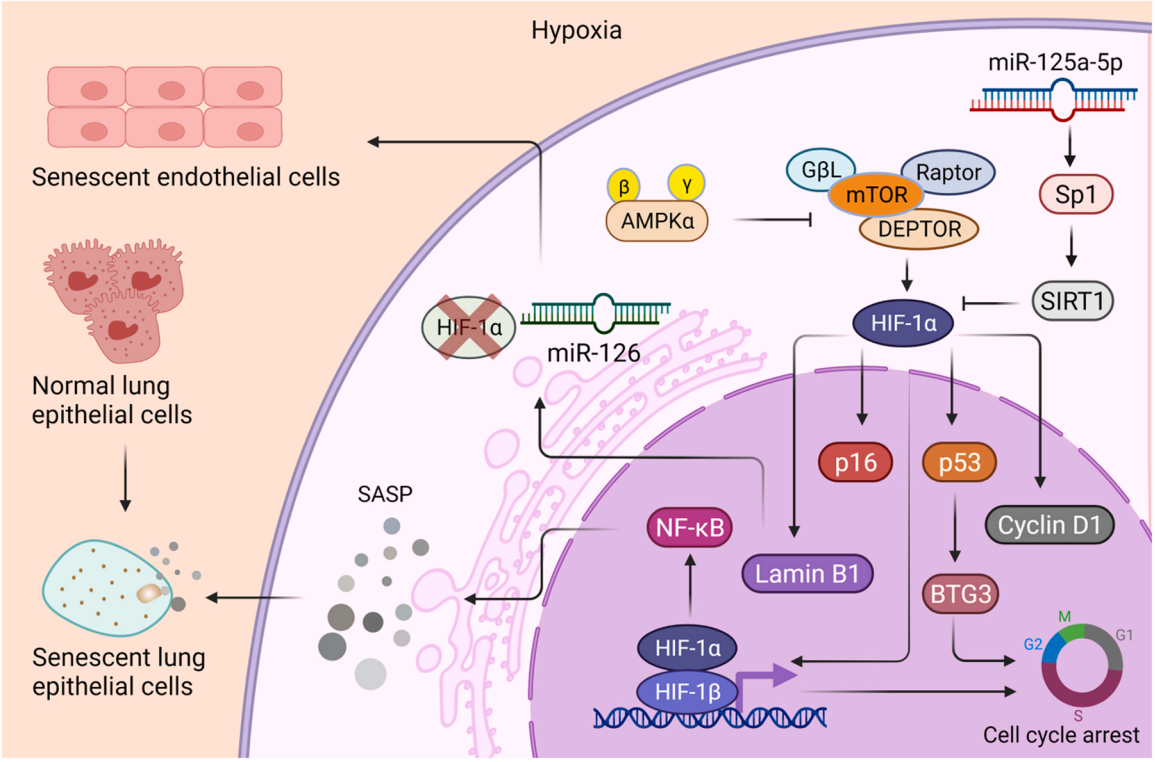

Fig. 1. The proposed function of hypoxia-inducible factor (HIF)− 1α signaling in the mechanisms of cellular senescence. Hypoxic environments upregulate the AMP: ATP ratio, leading to AMP-activated protein kinase (AMPK) activation and AMPK-mediated mTOR inhibition. HIF-1α is a downstream protein of mTOR that activates p16, p53, lamin B1, and cyclin D1, which are involved in endothelial cell senescence. Furthermore, the disappearance of HIF-1α and a reduction in miR-126 levels were also observed in microvesicles of senescent endothelial cells compared with normal endothelial cells. B-Cell translocation gene 3 (BTG3) is activated by p53 and causes cell growth arrest. Another microRNA (miRNA), miR-125a-5p, activates downstream NF-κB signaling through the specific protein 1 (Sp1)/sirtuin 1 (SIRT1)/HIF-1α signaling pathway and promotes the transcription of various proinflammatory factors of SASP, thereby inducing lung epithelial cell senescence.

mouse embryonic fibroblast lines, the effect of AREG on cellular senescence is limited, indicating that the overexpression of AREG itself is insufficient to induce cellular senescence or to lead to SASP development [61].

A hypoxic environment is the result of an imbalance in oxygen demand as well as supply, and intraluminal hypoxia is a key hallmark of cancer. Hypoxia increases the number of regulatory T (Treg) cells, thereby preventing the activation of effector T (Teff) cells through cytokine production and increased cytotoxic T lymphocyte antigen-4 (CTLA-4, or CD152) [66]. *In vivo*, $CD8^+$ T cells lacking CTLA-4 reduced the expression of the senescence marker killer cell lectin-like receptor subfamily G member 1 (KLRG1) during viral infection, thus suggesting that T-cell senescence may be inhibited [67]. CTLA-4 is an immune checkpoint molecule that plays an important role in restraining immune cells from attacking themselves and recalling the immune response [68,69].

Hypoxia can induce the expression of chemical factors, thus regulating immune evasion and cellular senescence. p53, a critical regulator of immune evasion and an important factor affecting hypoxic cell injury, is enriched in the nucleus under hypoxia and helps cells respond to hypoxia signals quickly to promote cellular senescence [70,71]. p53 also activates endogenous retroviruses and inhibits tumor immune evasion [72]. However, mutant p53 (mtp53) suppresses innate immune signal transduction, leading to immune evasion [73]. After PD-1, another immunosuppressive signaling molecule, CD47, has also been demonstrated to be related to immune evasion. In breast cancer, bladder cancer, and other tumor tissues under hypoxic conditions, HIF-1α upregulates CD47 expression through nuclear factor-kappa B (NF-κB), SMAD2, signal transducer and activator of transcription 3 (STAT3), and other transcription factors, resulting in immune evasion from tumor cells that are not recognized by macrophages. However, further research is required to completely understand the mechanisms [74]. Given that the expression of the cell cycle kinase inhibitors p16, p53, and p21 is reduced while CDK4, CDK6, and cyclin D1 expression is increased in CD47-deficient endothelial cells, we suggest that CD47 may promote cellular senescence by regulating cell cycle kinase and its inhibitors [75].

The survival and metastasis of tumors in organisms are inseparable from the special immune evasion characteristic of immune surveillance [76]. Lactate dehydrogenase (LDH) mediates tumor immune evasion by inhibiting the immune killing effect and promoting immunosuppression [77]. Lactic acid can even directly induce apoptosis in T-cells and natural killer (NK) cells, which are the cellular components of the nonspecific tumor immune response, participate in immune surveillance, and prevent tumor occurrence and development [77–79]. In addition, LDH overexpression prevents cell necrosis in hypoxic conditions to favor tumor growth [77,80]. Therefore, the main mechanism by which LDH suppresses immunity involves increasing the secretion of

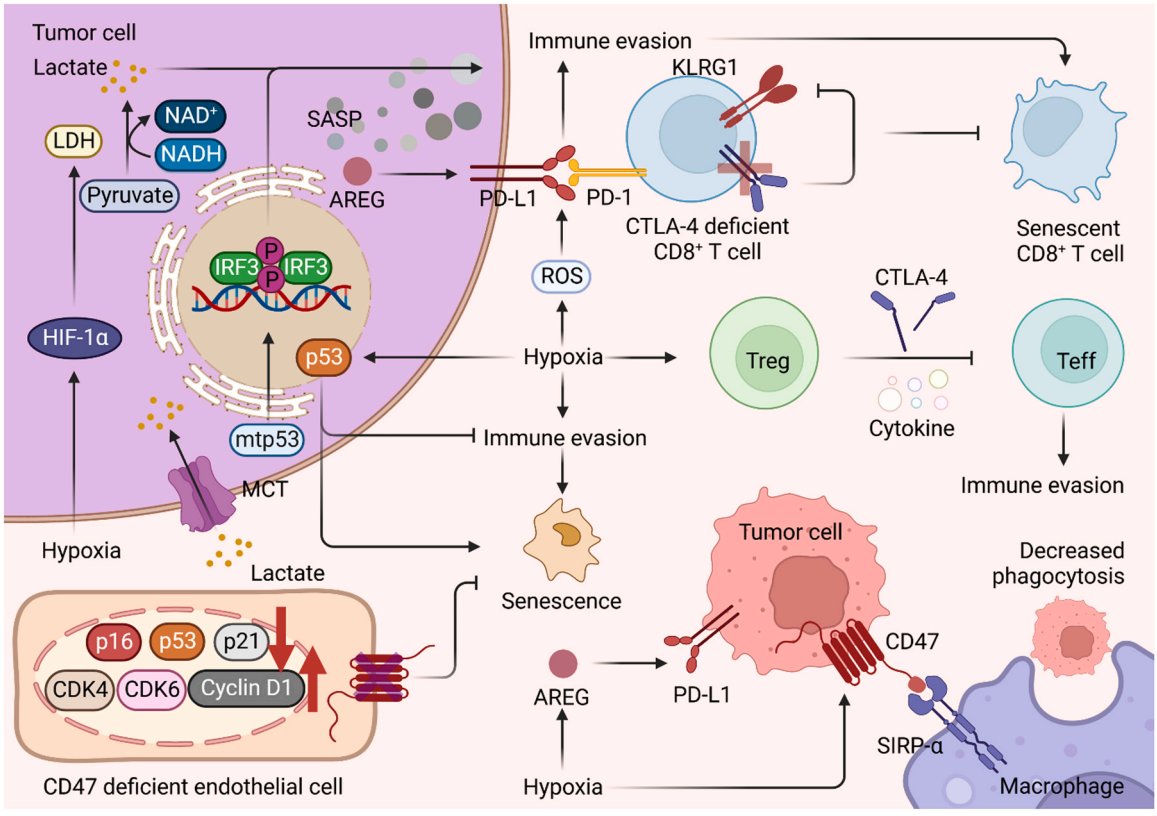

Fig. 2. The regulatory mechanism of immune evasion mediating cellular senescence in hypoxic microenvironments. Hypoxia upregulates the levels of amphiregulin (AREG), a factor that allows tumor cells to escape immune surveillance by increasing the levels of programmed cell death-ligand 1 (PD-L1). PD-L1 subsequently binds to programmed cell death-1 (PD-1), and this binding is increased by high levels of ROS and cytokines, thus enhancing immune evasion. The increased number of regulatory T (Treg) cells under hypoxic conditions, with the participation of CTLA-4 and cytokines, results in immunosuppression by hindering the activation of effector T (Teff) cells. Killer cell lectin-like receptor subfamily G member 1 (KLRG1), a T-cell senescence marker, is decreased in the absence of cytotoxic T lymphocyte antigen-4 (CTLA-4), thereby impeding senescence. The immunosuppressive signaling molecule CD47 is upregulated under hypoxic conditions, resulting in the diminished ability of macrophages to phagocytose tumor cells. However, the expression of the cell cycle kinase inhibitors p16, p53, and p21 was decreased in CD47-deficient endothelial cells, whereas CDK4, CDK6, and cyclin D1 expression was increased, thereby restraining cellular senescence. In hypoxic microenvironments, p53 is enriched in the nucleus, contributing to the cellular response to hypoxic signals and promoting cellular senescence. Mutant p53 (mtp53) suppresses innate immune signaling and promotes immune evasion. The main mechanism by which lactate dehydrogenase (LDH) suppresses immunity involves the conversion of pyruvate into lactate and increased secretion of lactate. NADH is converted to NAD^+ in this process, which disrupts the function of immune factors.

lactic acid and destroying the function of immune factors. LDH inhibition also affects the heat shock response and induce senescence in liver cancer cells [81], but whether this process is intertwined with hypoxia remains to be verified.

Above all, cellular senescence is considered a key barrier to tumor suppression due to the permanent state of cell cycle arrest. However, some senescent cells can evade clearance and disrupt the immune system by secreting proinflammatory factors, leading to immune evasion and the promotion of tumor growth (Fig. 2). Senescent human-derived stromal cells develop the classic SASP and release AREG, which is upregulated under hypoxic conditions. This factor induces cancer cells to upregulate PD-L1 expression and creates an immunosuppressive environment that allows cancer cells to evade immune surveillance. CTLA-4, an immune checkpoint molecule associated with increased Treg cells under hypoxic conditions, is associated with KLRG1, a T-cell senescence marker. Upregulation of the immunosuppressive signaling molecule CD47 under hypoxic conditions leads to immune evasion, and its deletion leads to a reduction in cell cycle enzyme inhibitors (such as p53) and an increase in cell cycle enzymes to regulate cellular senescence. Senescent cells can be recognized and cleared by the immune system. However, as the immune system ages, senescent cells undergo immune evasion [58,59,82]. Therefore, replenishing the immune system or immune cells may represent a method to delay cellular senescence.

4. The trio of hypoxia, autophagy, and cellular senescence

In addition to immune evasion, autophagy is highly involved in the process of cellular senescence. Autophagy is a significant mechanism for maintaining the stability of the intracellular environment, which is intertwined with cellular senescence caused by hypoxia [83,84]. Autophagy is also a mechanism involved in the senescent effect [85]. In the tissue of ATG5i mice on long-term doxycycline (LT-ATG5i), the expression of senescence markers was upregulated, SA-β-gal staining was positive, and the abundance and frequency of telomere-associated γ-H2AX foci (TAF) was increased. These results indicate that the loss of basal autophagy promotes cellular senescence [86]. Conversely, basal autophagy maintains homeostasis via cellular senescence inhibition and stem cell maintenance [87–90]. Light chain 3 (LC3)-II is upregulated in senescent cells induced by oncogenes but not in quiescent cells, indicating that the accumulation of autophagosomes was implicated in cellular senescence rather than cell cycle arrest [85]. In addition, senescent cells can further activate autophagy by triggering negative feedback regulation in the PI3K-mTOR pathway and fostering the production of SASP to facilitate senescence in an autocrine or paracrine fashion [91].

Hypoxia is a stimulus that induces autophagy [92,93]. The signaling pathway of autophagy induced by hypoxia is complex. Hypoxia promotes HIF-1 activation to induce downstream BCL-2/adenovirus E1B 19-kDa interacting protein 3 (BNIP3). BNIP3 destroys the Bcl-2-Beclin1 complex, thereby releasing free Beclin1 to form the vacuolar protein-sorting 34 (VPS34)-Beclin1 complex and activating autophagy [94,95]. In addition, BNIP3 fibroblasts showed an induction of $p21^{WAF1/CIP1}$ and $p16^{Ink4a}$ expression, significant cell hypertrophy, and increased β-galactosidase activity, indicating that BNIP3 induces not only autophagy but also cellular senescence under hypoxia [42]. Protein kinase C (PKC) is a serine/threonine protein kinase family member [96]. In the hypoxia response stage, hypoxic stress-activated PKC activates the downstream c-Jun-N-terminal kinase 1 (JNK1) and destroys the Bcl-2-Beclin1 complex, thereby promoting autophagy [97]. Downregulation of PKC induces cellular senescence in HCT116 and HEK293 cells via the AKT-forkhead box class O 3a (FoxO3a)-ROS-p53-$p21^{Cip1/WAF1}$ pathway [98].

Hypoxia strongly induces the autophagy pathway in glioblastoma (GBM) [99]. After autophagy-related 9 homolog A (ATG9A) depletion, GBM cells are unable to activate autophagy under hypoxia, suggesting that the lack of autophagy activation under hypoxia may be due to the inhibition of *de novo* autophagosome synthesis [100]. Furthermore, the expression of *ATG9A*, a gene that initiates autophagosome assembly, is upregulated in senescent cells [101], and whether this upregulation subsequently triggers cellular senescence remains to be explored. Autophagy is involved in renal aging [102]. ATG5 is also associated with cellular senescence, and downregulated expression of senescence markers $p19^{ARF}$, $p16^{INK4a}$ and SA-β-gal is observed in $ATG5^{\Delta flox/\Delta flox}$ tubular epithelial cells [103–105]. The LC3-I:LC3-II ratio is commonly used to assess the induction of autophagy [106]. High levels of the LC3-II isoform were detected in all GBM cells treated with chloroquine under hypoxic conditions. Similarly, decreased p62 levels and an increased number of autophagosomes further confirmed that hypoxia induces autophagy [107]. Taken together, these data suggest that GBM cells induce autophagy under severe hypoxia. However, LC3 is not necessary to initiate autophagy. Transcriptional induction of *LC3* may be required for the replenishment of LC3, which is degraded during hypoxia-induced autophagy [108,109]. Moreover, Prx1 silencing induces cellular senescence by mediating the p53/p21 pathway, and mitophagy is dependent on its binding to prohibitin 2 (PHB2)/LC3B, suggesting that LC3 may also be involved in the process of cellular senescence [110].

Therefore, it is clear that autophagy and cellular senescence are interconnected and can be regarded as a continuum or two related stages of the same overall biological process, and both are closely associated with hypoxia (Fig. 3). Hypoxia disrupts the Bcl-2-Beclin1 complex, releasing free Beclin1 to induce autophagy, whereas fibroblasts expressing BNIP3 typically exhibit an increase in cellular senescence markers. Notably, although it has been widely recognized that hypoxia induces autophagy, HIF-1α levels remain stable regardless of whether cells are cultured at high cell densities in normoxia or at low cell densities under hypoxic conditions [111]. These conditions result in the induction of autophagy under “hypoxic” conditions, although it is normoxic in theory. BNIP3 and BNIP3L are also induced [112]. Similarly, PKC can also destroy the Bcl-2-Beclin1 complex or activate the JNK1 pathway, thereby promoting autophagy. Furthermore, hypoxia also activates autophagy by inhibiting mTOR, which normally induces cellular senescence. Similarities are noted between the BNIP3 and BNIP3L promoters and that of ATG9A. ATG9A contains a HIF1 response element that is transcriptionally activated to initiate autophagy in hypoxic GBM cells. However, whether this process is involved in cellular senescence remains unclear. LC3 is a cryptic marker of autophagy but is not required to initiate autophagy. Under hypoxic conditions, autophagy is often involved in cellular senescence along with other signaling pathways, such as Nrf2 signaling [113]. Interestingly, the levels of most autophagy activities are decreased, whereas senescent cells accumulate gradually with age [114–116]. In addition, recent studies on mesenchymal stem cells have demonstrated that autophagy either facilitates or restrains cellular senescence, which depends on the context, time of action, and type of autophagy [117–119]. However, the extent to which cell-specific features may contribute to the final effect is worthy of further investigation.

5. Effects of PARP-1 signaling on cellular senescence under hypoxia

In addition to autophagy, emerging evidence further demonstrates that PARP-1 is involved in cellular senescence. NAD^+ is a major cofactor for PARP and SIRTs, which play a critical role in the regulation of cell cycle arrest and SASP during senescence [120,121]. Metabolic drivers of senescence, for example, changes in cellular redox states and loss of PARP or sirtuin activities, lead to the loss of NAD^+, thus triggering cell senescence [122]. In the cytoplasm of senescent cells, pyruvate is converted to lactate by LDH to maintain the NAD^+/reduced nicotinamide adenine dinucleotide (NADH) ratio [123]. Furthermore, hypoxia also maintains the NAD^+/NADH ratio by stably activating glycolysis [124]. P53 promotes p21 activation but inhibits SASP [122]. NAD^+ not only

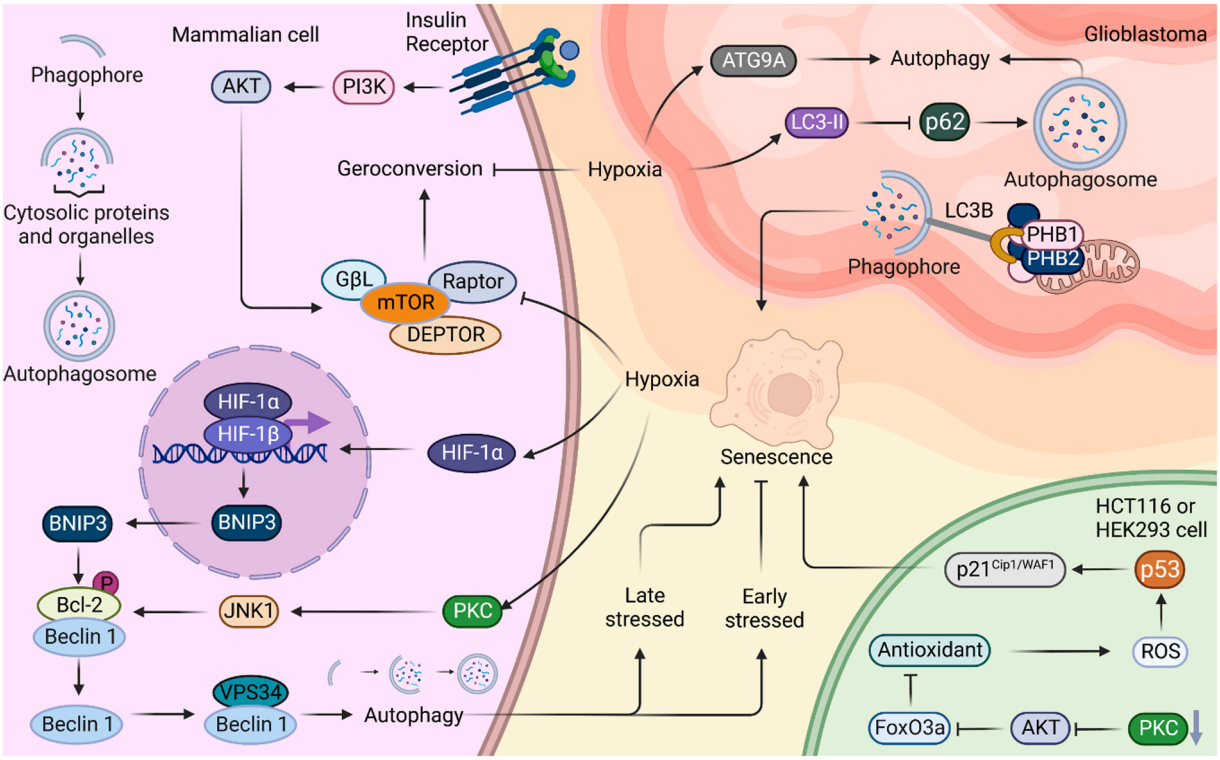

Fig. 3. Hypoxia regulates cellular senescence through autophagy. HIF-1α activation is regulated by hypoxia, which triggers autophagy through the stimulation of the downstream target BCL-2/adenovirus E1B 19-kDa interacting protein 3 (BNIP3). Hypoxia activates downstream c-Jun-N-terminal kinase 1 (JNK1) through protein kinase C (PKC), disrupting the Bcl-2-Beclin1 complex. Dissociated Beclin1 interacts with vacuolar protein-sorting 34 (VPS34) to induce autophagy. PKC downregulation leads to AKT activation, thereby increasing intracellular reactive oxygen species (ROS) levels through forkhead box class O 3a (FoxO3a) downregulation mediated by AKT phosphorylation and inducing cellular senescence. Hypoxia delays the activation of mammalian target of rapamycin (mTOR) to induce autophagy. However, mTOR normally induces cellular senescence, whereas hypoxia restrains gerogenic conversion (geroconversion). In glioblastoma (GBM) cells treated with chloroquine under hypoxic conditions, high levels of LC3 (light chain 3)-II, decreased p62 and an increased number of autophagosomes were observed. Similarly, autophagy-related 9 homolog A (ATG9A) initiates autophagy in hypoxic GBM. Prohibitin 2 (PHB2) externalizes to the outer mitochondrial membrane and interacts with LC3B to trigger senescence through mitophagy. However, in the framework of mesenchymal stem cells, general autophagy exerts early action in stressed cells or under normal conditions, mainly inhibiting cell senescence. However, in late stressed and long-term cultured cells, autophagy plays a role in promoting senescence.

prevents p53 activation through PARP and SIRTs but also inhibits the expression of AMPK, which is an upstream protein of p53 [125]. Furthermore, treatment with the PARP-1 inhibitor olaparib in combination with ionizing radiation increases multinucleated giant cell (MNGC) SA-β-gal activity and the levels of macroH2A1, thus promoting MNGC formation and senescence [126].

Sustained DNA damage leads to cellular senescence, and both PARP-1 and $p21^{CDKN1A}$ are involved in DNA damage repair [127–129]. Deletion of the senescence marker $p21^{CDKN1A}$ leads to the increased activity of PARP-1 and enhanced levels of nonhomologous end joining (NHEJ) proteins that repair double-strand breaks (DSBs) in DNA [130]. Thus, DNA damage-triggered cellular senescence is attenuated by $p21^{CDKN1A}$ deficiency. Additionally, PARP-1 recruits SIRT1 and brahma-related gene 1 (BRG1) by producing poly (ADP-ribose) (PAR) molecules. The former deacetylates BRG1 of residues K1029 and K1033, stimulating BRG1 to remove nucleosomes and promote the repair of DNA DSBs [131].

PARP-1 regulates the hypoxia response [132–135]. Under the regulation of ROS, PARP-1 is activated and interacts with HIF-1α at its C-terminal domain. HIF-1α is stabilized and accumulated by PARylation and binds to the HRE. This progression enhances the expression of hypoxia genes, allowing cells to adapt to hypoxia [136]. Moreover, HIF-1α expression is downregulated upon suppression or knockdown of PARP-1 under hypoxic conditions [132,133,137]. As previously mentioned, HIF is intertwined with cellular senescence; therefore, PARP-1 may also regulate cellular senescence via HIF.

PARP9 interacts with the E3 ubiquitin ligase Deltex E3 ubiquitin ligase 3 L (DTX3L) to form a complex that promotes STAT1 activation, migration from the cytoplasm to the nucleus and the transcriptional regulation of interferon (IFN)-stimulated genes (ISGs) [138]. The senescence of bone marrow (BM)-MSCs in patients with systemic lupus erythematosus (SLE), an autoimmune disease known to produce excess ligand type I interferon (IFN-I), is associated with the upregulation of certain IFN-I ISGs [139]. In addition, receptors on the plasma membrane that are responsive to hypoxic conditions, such as IL-6R, upregulate HIF-1α levels through the Janus kinase (JAK)- signal transducer and activator of transcription (STAT) signaling pathway, promoting the expression of hypoxia-related genes [140–142]. The NF-κB signaling pathway is also closely associated with cellular senescence. H2AX is one of the markers of senescence [143]. H2AX is phosphorylated to γH2AX after DSBs and promotes the phosphorylation of NF-κB essential modifier (NEMO) [144,145]. Autophosphorylated ataxia-telangiectasia mutated (ATM) kinase binds to it and subsequently promotes canonical NF-κB signaling. The levels of some SASP factors are increased, and the binding of these factors with corresponding receptors triggers the activation of the NF-κB signaling pathway, thus mediating cellular senescence [146]. In addition, PARP-1, as an upstream regulator of NF-κB, also promotes its expression when the DNA damage response (DDR) is activated and may be involved in the above process [147]. Under hypoxic conditions, the activity of hydroxylase is inhibited, whereas HIF is activated and works together with p50 and p65 released by the canonical NF-κB signaling pathway in the nucleus to send out signals, such as those related to cellular senescence [147–149].

Cellular senescence is the consequence of the accumulation of

changes in cell structure and function to a certain extent. The PARP-1 signaling pathway regulates senescence through crosstalk with other signaling pathways, including the p53/p21, AMPK, JAK-STAT, and NF-κB signaling pathways. Most crosstalk regulates cellular senescence through the secretion of senescence markers, DNA damage and repair, and cell cycle arrest (Fig. 4). Signaling pathways can also drive senescence via apoptosis resistance [150], metabolism [151], and endoplasmic reticulum stress [152]. In addition, hypoxia is closely implicated in these signaling pathways and is often involved in this process. HIF acts up- or downstream of the key elements of these signaling pathways and binds to pathway components to participate in the regulation of cellular senescence. However, the relationships among these signaling pathways are intricate, and the opposite outcomes may occur in different cells. Most of the links among hypoxia and these signaling pathways remain at the level of the links with HIFs. Few studies have shown whether hypoxia modulates other factors involved in signaling to trigger cellular senescence. Therefore, more in-depth research is needed to fully elucidate the mechanism.

6. Regulation of cellular senescence by the gut microbiota under hypoxic conditions

Many diseases are characterized by systemic chronic hypoxia. The gut microbiota is also associated with many disorders, and structurally dysregulated microbiota may represent an important factor in the induction of cellular senescence [153]. Premature senescence of bone marrow mesenchymal stem cells (BMSCs) was observed in cyanotic congenital heart disease (CCHD) patients with chronic hypoxia, which is associated with the accumulation of gut microbiota-derived D-galactose and gut dysbiosis [25]. Chronic profound hypoxia leads to altered gut microbial community diversity and a significant reduction in *Lactobacillus*, resulting in a reduction in lactase and the accumulation of D-galactose. D-galactose is converted into galactitol, which accumulates in cells and then generates excess ROS, thereby resulting in oxidative stress. D-galactose also destroys antioxidant enzymes, leading to chronic oxidative stress [154–156]. The accumulation of ROS is considered to be a key mediator of distinct aspects of cellular senescence, as ROS both prompt telomere attrition and disrupt cellular oxidative as well as inflammatory homeostasis [157–159]. Moreover, oxidative stress is directly correlated with the gut microbiota, and the accumulation of D-galactose, or oxidative stress, can subsequently affect the gut

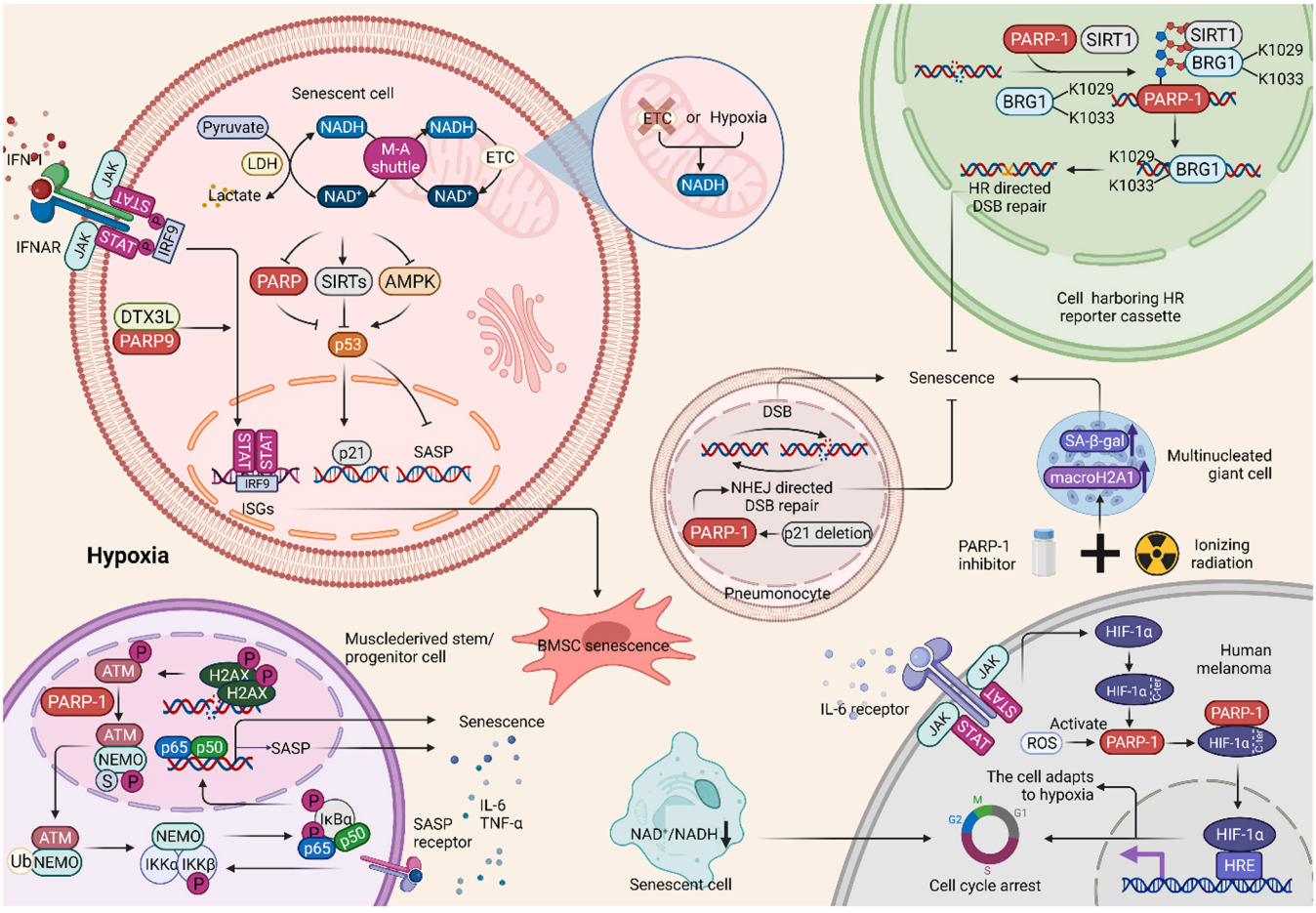

Fig. 4. Schematic diagram of poly (ADP-ribose) polymerase (PARP) activating various signaling pathways to drive cellular senescence and the senescence-associated secretory phenotype (SASP) under hypoxic conditions. PARPs regulate cellular senescence not only through the JAK/STAT signaling pathway but also by participating in NF-κB signaling. In addition, PARP-1 also inhibits senescence by promoting the repair of DNA double-strand breaks (DSBs). Mitochondrial dysfunction-associated senescence is principally induced by the accumulation of NADH in the cytoplasm, and a reduction in the NAD^+/NADH ratio ultimately leads to cell cycle arrest. Either electron transport chain (ETC) dysfunction or hypoxia leads to NADH accumulation. In senescent cells, the NAD^+/NADH ratio is maintained either by the conversion of pyruvate to lactate in the cytosolic solution or by the malate-aspartate (M-A) shuttle or ETC in the mitochondria. Afterward, NAD^+ regulates the transcription of downstream senescence-related genes in the nucleus through signals, such as PARP, SIRTs, and AMP-activated protein kinase (AMPK). The PARP-1 inhibitor olaparib combined with ionizing radiation treatment increases senescence-associated β-galactosidase (SA-β-gal) activity and macroH2A1 levels in multinucleated giant cells (MNGCs), which subsequently promotes cellular senescence.

microbiota [160]. For example, D-galactose-induced oxidative stress downregulates the relative abundance of *Tenericutes* [161]. A link between microbial dysbiosis with a senescence response and SASP has been established. Specifically, in the study by Yoshimoto et al. [153], SASP was found to play an important role in promoting obesity-associated hepatocellular carcinoma (HCC). Obesity induces alteration of gut microbiota and increases deoxycholic acid (DCA) levels, which induces the SASP phenotype in hepatic stellate cells (HSCs), further secreting inflammatory factors in the liver and facilitating HSC senescence and HCC development. Therefore, a gut microbiota and cellular senescence axis, in this study, namely, the "DCA-SASP axis", exists in HSCs in the development of HCC. In addition, most gut microbes exist in hypoxic conditions, and some of them can also produce antioxidants, which reduce oxidative stress and thus delay cellular senescence. For instance, *Bifidobacterium adolescentis* significantly increases catalase (CAT) enzyme levels and activity, thereby reducing the oxidation reaction of free radicals and inhibiting cellular senescence [162]. Indole propionic acid (IPA) is an antioxidant with free radical scavenging activity that reduces oxidative stress [163,164]. Most of the strains belonging to the order *Clostridiales* produce IPA [165]. Whether IPA is involved in oxidative stress-induced senescence should be explored [165]. In contrast, other gut microbiota metabolites, such as trimethylamine-N-oxide (TMAO), promote endothelial cell senescence via oxidative stress and activation of the p53/p21/Rb pathway [166]. This type of gut microbiome metabolite is mostly converted from a high-fat diet and carnitine found in red meat [167,168], providing information for people to prevent senescence and aging based on their diet. In addition, studies have shown that protein homeostasis (proteostasis) failure and cellular senescence have overlapping molecular mechanisms [169]. A large amount of TMAO accumulated in Greenland sharks can be used as a chemical chaperone to induce normal protein folding, thus maintaining proteostasis [170–173]. This finding seems to contradict what we discussed earlier, namely that TMAO induces cellular senescence. We suspect that Greenland sharks (*Somniosus microcephalus*) possess survival skills to cope with the harsh environment of the polar deep sea, but the living environment of *Homo sapiens* is not in the deep sea. Therefore, we cannot simply apply the experimental conclusions to humans. However, this method of intervening with cellular senescence through proteostasis may provide a direction for future research on cellular senescence.

Given that the gut microbiota is highly influenced by diet, it is likely that caloric restriction modulates the gut microbiota and thus affects cellular senescence, such as increasing Bacteroidetes and decreasing Proteobacteriacea. This alteration may induce a shift toward naive T- and B-cell compartments, thus delaying immunosenescence [174]. In addition, tryptophan plays an important role in exploring the effects of nutrient restriction on immunosenescence and maintaining the homeostasis of gut microbiota [175–177]. The genotoxin colibactin produced by resident bacteria in the gut microbiota causes DNA DSBs in eukaryotic cells and generates DNA interstrand crosslinks, which induce cellular senescence in the host [178–180]. Furthermore, as a metabolically active organ, the gut microbiota degrades substrates into short-chain fatty acids (SCFAs) and polyamines [181,182]. Moreover, telomere length is associated with cellular senescence [183,184], but the gut microbiota but not fecal SCFA concentrations is strikingly correlated with telomere length in the pediatric population [185]. Butyrate, one of the main components of SCFAs, exhibits anti-inflammatory effects and protects epithelial cells from lipopolysaccharide (LPS)-induced damage under hypoxic conditions [182,186]. In dental pulp stem cells (DPSCs) repeatedly stimulated by LPS, the activity of SA-β-gal was increased, and the protein and mRNA expression levels of toll-like receptor 4 (TLR4) and myeloid differentiation factor 88 (MyD88) were enhanced, resulting in NF-κB signaling activation. In addition, the expression of p53 and p21, downstream proteins of NF-κB signaling, was increased, leading to senescence in DPSCs [187]. Therefore, in view of the powerful functions of SCFAs *in vivo*, it is reasonable to hypothesize that the more abundant the SCFA-producing microbiota, especially the butyrate-producing microbiota, the greater the effect on delaying cellular senescence.

The gut microbiota predominantly exists in the colon [182,188]; thus, most studies on gut microbes and cellular senescence are based on hypoxic conditions by default. In addition, the gut microbiota, as a dynamic organ, also participates in various functions of the human body [189,190], which provides a theoretical basis to hypothesize that the gut microbiota may regulate cellular senescence in hypoxic conditions (Fig. 5). Chronic profound hypoxia results in a significant decrease in the number of *Lactobacillus*, which leads to oxidative stress triggering cellular senescence. Calorie restriction is closely implicated in immunosenescence, but the exact mechanism has not been investigated in depth. The SCFAs and polyamines produced by gut microbiota delay senescence through anti-inflammatory and antioxidant effects [191–194] and are related to the AMPK signaling pathway [195–197]. However, whether these SCFAs and polyamines regulate cellular senescence via this signaling pathway remains unknown. However, despite most gut microbiota being anaerobic, aerobes or facultative anaerobic bacteria, such as *Escherichia coli* (*E. coli*) and *Streptococcus*, are present. Whether these gut microbes regulate cellular senescence under hypoxic conditions remains elusive.

7. The role of exosomal microribonucleic acid in hypoxic cellular senescence

Exosomes are extracellular vesicles (EVs) that are extensively secreted under hypoxic stimulation [198,199] and contain a variety of nucleic acids, including miRNAs, mRNAs, and lncRNAs [94,200,201]. Exosomal miRNAs have emerged as new biomarkers of senescence [202]. Senescent osteoblasts regulate the function of endothelial cells through the exosomal pathway and promote cellular senescence. MiR-139–5p is upregulated in the exosomes of senescent osteoblasts and promotes the senescence of vascular endothelial cells [203]. Furthermore, increased levels of miR-139–5p and decreased levels of vascular endothelial growth factor receptor-1 (VEGFR-1) were found in hypoxia-treated human umbilical vein endothelial cells [204]. These results indicate that miR-139–5p may inhibit endothelial cell viability by inhibiting VEGFR-1 under hypoxic conditions, thereby promoting cellular senescence. Exosome-enriched miR-424–5p inhibits primary granulosa cell (GC) proliferation and induces senescence in polycystic ovary syndrome (PCOS) cells by blocking cell division cycle-associated 4 (CDCA4) gene-mediated Rb/E2F1 signaling [205]. Interestingly, the endogenous expression level of miR-424–5p was saliently reduced in hypoxia-treated pulmonary artery smooth muscle cells (PASMCs) [206]. Exosomes from dendritic cells (DCs) cocultured with *Porphyromonas gingivalis* (PgDCexos) promote the immunosenescence of recipient young DCs when taken up by recipient DCs derived from the BM of young mice [202]. Furthermore, miRNAs are particularly active in the post-transcriptional regulation of genes involved in cellular senescence [207–210]. MiR-24–3p is frequently found in PgDCexos, and studies have found that there is a positive correlation between hsa-miR-24–3p and breast cancer [202,211]; exposure to hypoxia increases miR-24–3p in endothelial cells, and ciPVT1 (circBaseID: hsa_circ_0008849) may act as a competing endogenous RNA (ceRNA) to regulate CDK4 and its downstream genes by sponging miR-24–3p, thereby delaying endothelial cell senescence [212,213].

LncRNAs regulate miRNAs [214,215]. Recently, a plethora of lncRNAs have been found to be associated with the regulation of cellular senescence and its related signaling pathways, affecting critical cell cycle processes [216–218]. For example, DDR induces long intergenic noncoding RNA-p21 (LincRNA-p21) by activating p53 to regulate senescence by targeting p21 [219–221]. However, lncRNAs are either up- or downregulated under hypoxic conditions [222], and their relationship with cellular senescence under hypoxic conditions remains to be elucidated. Hypoxia may induce cellular senescence by inducing lncRNA-metastasis-associated lung adenocarcinoma transcript 1

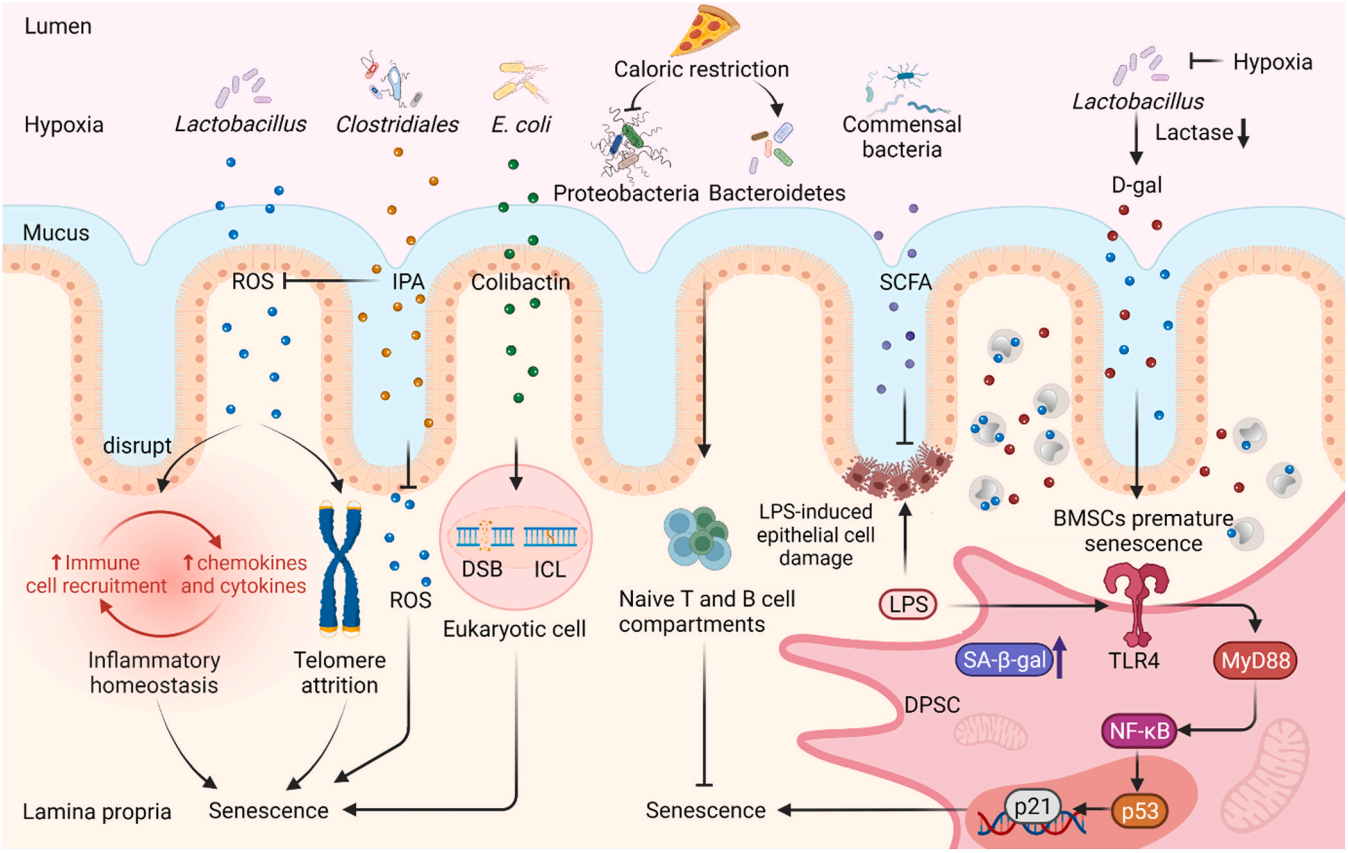

Fig. 5. Interaction between the gut microbiota and cellular senescence in hypoxic states. Chronic profound hypoxia significantly reduces the number of *Lactobacillus*, resulting in a reduction in lactase secretion that degrades D-galactose. D-galactose that has accumulated in blood and bone marrow produces excess reactive oxygen species (ROS), which disrupt cellular oxidation and inflammatory homeostasis and accelerate telomere attrition, thereby promoting premature senescence of bone marrow mesenchymal stem cells (BMSCs). Most strains belonging to the order *Clostridiales* produce indole propionic acid (IPA), an antioxidant that reduces oxidative stress and delays cellular senescence by scavenging free radicals. In addition, cellular senescence is also related to the state of DNA. Colibactin, a genotoxin produced by *Escherichia coli* (*E. coli*), induces DNA double-strand breaks (DSBs) and DNA interstrand crosslinks (ICLs) in eukaryotic cells and triggers cellular senescence in the host. Lipopolysaccharide (LPS) not only induces senescence through repeated stimulation of dental pulp stem cells (DPSCs) but also drives epithelial cell damage. Short-chain fatty acids (SCFAs) produced by colonic microbial fermentation of monosaccharides and oligosaccharides protect epithelial cells from this damage under hypoxic conditions. Caloric restriction reduces the concentration of bacteria belonging to the Proteobacteria family while increasing the abundance of taxa in the phylum Bacteroidetes. These alterations induce a shift toward naive T- and B-cell compartments, thus delaying senescence.

(MALAT1), which subsequently inhibits miR-92a-3p [223,224]. Antisense noncoding RNA in the INK4 locus (ANRIL) is a type of lncRNA that plays a significant role in cellular senescence. ANRIL may promote cell viability and restrain the senescence of vascular smooth muscle cells (VSMCs) by regulating miR-181a/Sirt1 [225]. Furthermore, ANRIL expression is significantly enhanced in hypoxia-injured H9c2 cells and plays a protective role in hypoxia-induced H9c2 cell injury by regulating the miR-7–5p/SIRT1 axis [214]. Replicative cell senescence is associated with progressive shortening of telomere length [226]. Telomeres have recently been shown to also include a lncRNA known as telomeric repeat-containing RNA (TERRA) [227]. TERRA has the unique function of inducing premature senescence and telomere recombination [228–230]. Previous studies have shown that in THO complex mutants, transcribed TERRA can invade duplex DNA to form DNA—RNA hybrids and inhibit chromosome end cap formation and protection from telomere exonuclease 1 (Exo1), thereby ultimately inducing telomere shortening [231]. Recent studies have found that TERRA also increases telomere length, thus delaying cellular senescence [229,232]. For example, in the absence of telomerase and THO complex mutants, telomeric R-loops promote telomere reorganization, which may delay cellular senescence [230]. Hypoxia is associated with the regulation of telomere length [47,233]. Therefore, we wondered whether hypoxia can also regulate TERRA to induce telomere recombination and drive cellular senescence.

Furthermore, HIF-1α is associated with exosomal cargo, such as microRNAs (miRNAs) [234]. An emerging number of studies employ miR-126 and HIF-1α as new markers for endothelial senescence progression [38,235]. However, the complete functions of this HIF-dependent molecular effector remain unclear. B-Cell translocation gene 3 (BTG3) is a downstream target of p53 [236]. Senescence caused by BTG3 deletion is accompanied by secretory groups rich in cytokines and growth factors. The level of miR-125a-5p is positively correlated with cellular senescence [237]. Knockdown of miR-125a-5p reduces the senescence of lung epithelial cells. In contrast, high miR-125a-5p is involved in the senescence of lung epithelial cells through Sp1/SIRT1/HIF-1α [21].

Above all, we summarized the mechanism by which some exosomal nucleic acids regulate cellular senescence and proposed their relationships with senescent cells under hypoxic conditions (Fig. 6). For example, miR-24–3p and lncRNA-ANRIL delay cellular senescence; the level of miR-424–5p is decreased under hypoxia; and lncRNA-TERRA can either induce or delay cellular senescence depending on the subject of the study. Exosomes may exhibit new molecular mechanisms in the senescent process, and miRNAs and lncRNAs may be involved in the regulation of cellular senescence. However, different regulatory factors may have distinct regulatory mechanisms for diverse cells and distinguished responses to hypoxia. Therefore, it is currently difficult to consistently determine how hypoxia regulates exosomes and how

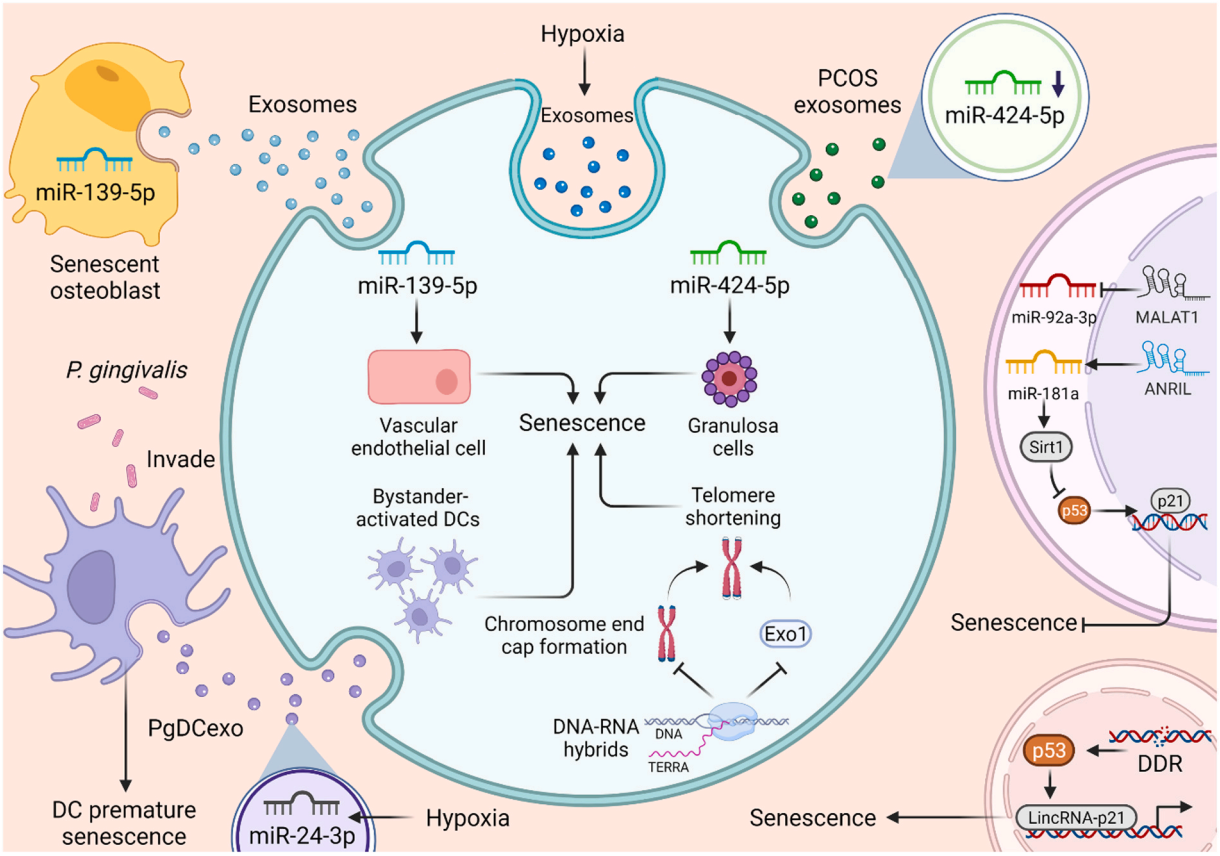

Fig. 6. Exosomal microribonucleic acids in the regulation of hypoxic cellular senescence. MiR-139–5p is upregulated in senescent osteoblasts and facilitates the senescence of vascular endothelial cells via the exosomal pathway. *Porphyromonas gingivalis* (*P. gingivalis*) induces dendritic cell (DC) premature senescence through direct cell invasion and amplifies the senescence of bystander DCs in a paracrine manner through the release of exosomes from DCs that are cocultured with *P. gingivalis* (PgDCexos). MiR-24–3p, a common miRNA in PgDCexos, is positively correlated with hypoxia and facilitates the senescence of endothelial cells by targeting CDK4. Exosome-enriched miR-424–5p promotes granulosa cell senescence, although its expression is reduced in polycystic ovary syndrome (PCOS) exosomes. The expression of lncRNA MALAT1 is increased under hypoxic conditions and causes cellular senescence by inhibiting miR-92a-3p. ANRIL reduces vascular smooth muscle cell (VSMC) senescence through the miR-181a/Sirt1 pathway and alleviates cell cycle arrest by inhibiting the p53/p21 pathway. However, the DNA damage response activates p53 to induce increased expression of lincRNA-p21, thereby modulating senescence by targeting p21. LncRNA-TERRA forms DNA—RNA hybrids with double-stranded DNA, interferes with the formation of chromosomal end caps and protects against the telomere end-trimming enzyme exonuclease 1 (Exo1), which eventually induces telomere shortening and leads to cellular senescence.

exosomes regulate cellular senescence. The role of hypoxia in the regulation of cellular senescence and the underlying mechanisms are summarized in Table 1.

8. Concluding remarks and prospects

We describe the pathways of hypoxia-mediated cellular senescence from multiple perspectives (Fig. 7). First, HIF-1α, the accumulation of which is promoted by hypoxia, modulates cellular senescence by (*a*) regulating quintessential senescence markers (e.g., p53, p16); (*b*) combining with the components of exosomes, such as miR-126; (*c*) participating in signaling pathway crosstalk, for example, in the JAK-STAT signaling pathway under hypoxia; and (*d*) cooperating with other antiphagocytic molecules, such as CD47. Second, we found that the gut microbiota and its metabolites also promote cellular senescence mainly through sustained DNA damage and oxidative stress. Chronic profound hypoxia leads to a reduction in *Lactobacillus* in the gut, which produces a myriad of ROS and thus induces cellular senescence. Gut microbiota metabolites, such as butyrate, protect cells from LPS-induced damage under hypoxic conditions, thus delaying senescence. In addition, caloric restriction also alters the gut microbiota and delays immune cell senescence. Third, each anti-senescence pathway is interconnected and participates in the regulation of cellular senescence. For example, HIF-1α integrates with HRE to promote the expression of LDH and participate in immune evasion. However, in senescent cells, LDH promotes the conversion of pyruvate into lactate to maintain the NAD^+/NADH ratio, thereby inducing the PARP/p53 signaling pathway and promoting cellular senescence.

Therefore, cellular senescence can be regulated in hypoxia through the above-discussed mechanisms. However, it is unclear whether hypoxia inhibits cellular senescence and promote tumorigenesis, thereby establishing an immune evasion mechanism, or leads to the evasion of clearance and destruction by the immune system through secreting proinflammatory cytokines, resulting in immune evasion and promoting tumor growth. As we mentioned before, autophagy is affected by cellular and environmental stimuli. When cells are stimulated by hypoxia, intracellular-related signaling pathways can drive autophagy. ROS are important inducers of autophagy, which may provide a potential strategy for explaining oxidative stress-induced cell senescence. However, the specific mechanisms remain controversial. Furthermore, given that cellular senescence is a dynamic rather than static process, senescent cells are heterogeneous [239,240]. A single cellular senescence marker cannot prove whether the cell is senescent, and most of the typical senescence markers are not unique to senescent cells. For example, the expression of $p16^{INK4a}$ and SA-β-gal increases during macrophage activation [241]. More intriguingly, markers of senescence are often present in postmitotic terminally differentiated cells, such as osteoblasts and osteoclasts [242], which seems to contradict the

Table 1
The role of hypoxia in the regulation of cellular senescence.

Target	Model	Regulatory mechanisms	Reference
HIF-1α	Endothelial cells	The accumulation of HIF-1α is regulated by reduced oxygen availability (defined as hypoxia), and HIF-1α regulates cellular senescence by mediating p16, p53, lamin B1, and cyclin D1 expression in endothelial cells.	[38,238]
	Mesenchymal stem cells and endothelial cells	HIF-1α binds to components in exosomes, such as miR-126, to regulate cellular senescence, which plays a protective role in the hypoxia/reoxygenation of endothelial cells mediated by the PI3K/Akt/endothelial nitric oxide synthase (eNOS) signaling pathway.	[18]
AREG	Human diploid fibroblast and mouse embryonic fibroblast lines	AREG is one of the SASP factors; its expression is upregulated under hypoxic conditions, allowing cells to escape immune surveillance.	[61,64]
CTLA-4	T-cells	Hypoxia leads to an increase in the amount of Treg cells, which prevents the activation of Teff cells via cytokine production and increased CTLA-4. $CD8^+$ T cells lacking CTLA-4 exhibit reduced expression of the senescence marker KLRG1 during viral infection and inhibit T-cell senescence.	[66,67]
BNIP3	Fibroblasts	Hypoxia triggers BNIP3 and disrupts the Bcl-2-Beclin1 complex, thereby releasing free Beclin1 to form the VPS34-Beclin1 complex to activate autophagy. In addition, $p21^{WAF1/CIP1}$ and $p16^{Ink4a}$ are activated, significantly increasing the cell size as well as the β-galactosidase activity.	[42,95]
LC3	Glioblastoma cells	Increased levels of LC3-II isoforms are detected in all GBM cells treated with chloroquine under hypoxia, and Prx1 silencing induces cellular senescence by mediating the p53/p21 pathway and mitophagy dependent on its binding to PHB2/LC3B.	[107, 110]
PARP-1	Epithelial cells	Hypoxia can maintain the NAD^+/NADH ratio by stably activating glycolysis, and the loss of PARP activities lead to the loss of NAD^+, thus triggering cell senescence.	[122, 124]
	Tumor cells	PARP-1 is a regulator of the hypoxia response, and knockdown or inhibition of PARP-1 in hypoxia downregulates the expression of HIF-1α and the accumulation of HIF-2α, which may regulate cellular senescence.	[133]
	Neutrophils	PARP-1 acts as an upstream regulator of NF-κB. Under hypoxia, hydroxylase activity is inhibited and HIF is activated. HIF cooperates with p50 and p65 released by canonical NF-κB signaling in the nucleus to promote cellular senescence.	[147, 148]
Lactobacillus	Bone marrow mesenchymal stem cells	Chronic profound hypoxia drives a salient decrease in the number of *Lactobacillus* in the gut, which reduces the enzymes that degrade D-galactose. D-galactose accumulates, thereby inducing premature cell senescence.	[25]
Butyrate	Epithelial cells and dental pulp stem cells	Butyrate protects epithelial cells from LPS-induced damage under hypoxia, thereby preventing the enhancement of SA-β-gal activity and the expression of p53 and p21. These effects lead to the postponement of dental pulp stem cell senescence.	[182, 187]
miR-139–5p	Human umbilical vein endothelial cells	MiR-139–5p inhibits endothelial cell viability and promotes cellular senescence by inhibiting VEGFR-1 under hypoxia.	[204]
miR-424–5p	Pulmonary artery smooth muscle cells	Exposure to hypoxia increases miR-24–3p in endothelial cells, and ciPVT1 may act as a ceRNA to regulate CDK4 and its downstream genes by sponging miR-24–3p, thereby delaying endothelial cell senescence.	[212, 213]
lncRNA-MALAT1	Human-induced pluripotent stem cell-derived cardiomyocytes and human adipose-derived mesenchymal stem cells	Hypoxia induces cell cycle regulation by inducing lncRNA-MALAT1, which subsequently inhibits miR-92a-3p, thereby causing cellular senescence.	[223, 224]

definition of senescence as permanent cell cycle arrest.

Currently, anti-senescence drugs on the market are roughly divided into senolytics (such as dasatinib plus quercetin) targeting the elimination of senescent cells [243–246] and senomorphic/senostics (such as rapamycin) disturbing SASP [247]. Taken together, all the mechanisms by which hypoxia induces cellular senescence may provide insights for

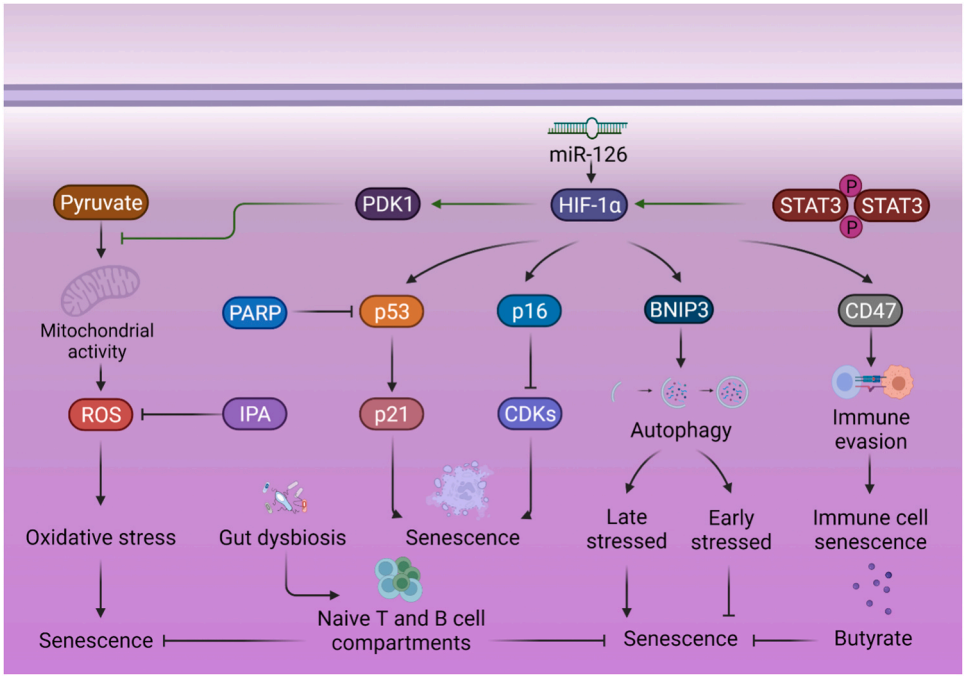

Fig. 7. The hypoxia-mediated mechanism involved in cellular senescence.

the future manufacture of anti-senescence drugs. Probiotics and their secreted metabolites (such as urolithins) have recently been found to have potential senolytic, anti-senescence, and anti-SASP properties, and these products can also be mixed with plant polyphenols (such as curcumin and catechins) to yield a second generation of synbiotics that jointly regulate cellular senescence [181,248]. However, due to the limited understanding of the mechanism between the microbiome and cellular senescence, further exploration of the downstream mechanism of the microbiome should be the focus of relevant research in the future.

Ethics approval and consent to participate

Not applicable.

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CRediT authorship contribution statement

Haoyu Gao: Conceptualization, Methodology, Writing - original draft. **Eugenie Nepovimova:** Methodology, Writing – original draft. **Zbynek Heger:** Methodology, Writing – review & editing. **Marian Valko:** Methodology, Writing – review & editing, Funding acquisition. **Qinghua Wu:** Conceptualization, Writing – review & editing, Visualization, Supervision, Funding acquisition. **Kamil Kuca:** Conceptualization, Writing - review & editing, Supervision, Funding acquisition. **Vojtech Adam:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Not applicable.

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Consent for publication

Not applicable.

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