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The role of oxygen tension in cell fate and regenerative medicine: implications of hypoxia/hyperoxia and free radicals

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Abstract Oxygen pressure plays an integral role in regulating various aspects of cellular biology. Cell metabolism, proliferation, morphology, senescence, metastasis, and angiogenesis are some instances that are affected by different tensions of oxygen. Hyperoxia or high oxygen concentration, enforces the production of reactive oxygen species (ROS) that disturbs physiological homeostasis, and consequently, in the absence of antioxidants, cells and tissues are directed to an undesired fate. On the other side, hypoxia or low oxygen concentration, impacts cell metabolism and fate strongly through inducing changes in the expression level of specific genes. Thus, understanding the precise mechanism and the extent of the implication of oxygen tension and ROS in biological events is crucial to maintaining the desired cell and tissue function for application in regenerative medicine strategies. Herein, a comprehensive literature review has been performed to find out the impacts of oxygen tensions on the various behaviors of cells or tissues.

Keywords Oxygen · ROS · Cell morphology · Cell proliferation · Cancer · Senescence · Angiogenesis

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Introduction

Oxygen homeostasis is a pivotal factor in preserving the physiological survival of vertebrate species (Semenza 2009a, b). The atmospheric oxygen is estimated about 21.1% (160 mmHg), which is decreased to about 19% (150 mmHg) in the upper airways. However, it has been demonstrated that the oxygen levels could vary between 0 and 19% in non-pathological tissues in a normal state (Carreau et al. 2011). Hyperoxia leads to the production of reactive oxygen species (ROS), including superoxides, hydroxyl radicals, and hydrogen peroxide groups. These chemical groups can cause cellular damage

through lipid peroxidation, enzyme destruction and protein/nucleic acid oxidation, leading to apoptosis or necrosis (Jamieson et al. 1986). ROS production causes higher levels of injury in unhealthy cell types; however, ROS toxic effects are needed to suppress the proliferation of cancer cells in tumor tissues (Fang et al. 2009). The mechanism by which ROS enforces cell abnormalities and even death is not clear. Normal cells can neutralize the destructive impacts of ROS by cellular anti-oxidative reactions. For instance, heme-oxygenase-1 (HO-1) catalyzes the breakdown reaction of heme to bilirubin and superoxide dismutase (SOD) converts superoxide ion to hydrogen peroxide. However, anti-cancer drugs target tumor ablation through ROS synthesis. In a study, the effect of ROS production and accumulation was examined in a lung cancer cell line. The results confirmed that the high levels of developed H_2O_2 cause DNA damage, ATP deficiency, and acute cytotoxicity. In contrast, the low levels of exogenously produced H_2O_2 resulted in a moderate level of ATP concentration, late toxicity, G2/M cell cycle arrest and cell senescence. The H_2O_2 produced by mitochondria causes a decline in ATP production, although this reduction is reversible without any negative impact on cell growth except cell senescence due to the cell cycle arrest in G1/S phase. Simultaneously, the glycolysis pathway was inhibited in cells, and subsequently, ATP restoration was inhibited (Panieri et al. 2013). On the other hand, hypoxia has been defined as a state without sufficient oxygen for cellular metabolic reactions. However, oxygen levels are determined in accordance with the metabolic requirements of the cell (Semenza 2000). Chronic wounds remain a global health challenge and hypoxia is one of main causes of delayed wound closure in diabetic wounds. To this end, a variety of oxygen therapeutics, including hyperbaric oxygen therapy, topical pressurized oxygen therapy, topical continuous oxygen therapy, and/or oxygen diffusion enhancer, have been successfully developed over the last decade in order to alleviate the hypoxia for an improved wound healing. In a recent study, a hybrid hydrogen that supply oxygen and provide anti-bacterial activity through promoting cell proliferation improved healing in diabetic wounds (Lin et al. 2022; Rasouli et al. 2023a, b, c). Hypoxia causes cellular stress through epigenetic-related mechanisms that are regulated by hypoxia induced factors (HIFs). HIFs mainly control oxygen homeostasis in cells by regulating the genes involved in oxygen metabolism, erythrocyte production, angiogenesis, and mito-chondrial metabolism (Choudhry and Harris 2018; Al Tameemi et al. 2019). As a whole, oxygen levels could alter different aspects of cell biology through specific mechanisms. Accordingly, achieving an in-depth understanding in this regard will pave the way toward improving tissue regeneration and promoting tissue engineering strategies (Rasouli et al. 2021). In this review, we will concisely discuss the effect of oxygen tension on cell fate and tissue function/regeneration in terms of cell proliferation, angiogenesis, cellular senescence, and cell death.

Oxygen tension and cellular growth and morphology

In general, molecular oxygen is a metabolic and signaling compound for cells, both in vitro and in vivo. One of the most important effects of oxygen tension on cell biology is related to cell proliferation. In normal cell populations, following hypoxia, cell proliferation is weakened since the higher cell population is accompanied by more O_2 demand. However, specific cell types sustain their growth in hypoxic conditions. Cancerous cells adapt to hypoxic stress and continue cell growth by decreasing their O_2 consumption. However, another important issue is the high levels of non-physiological oxygen that lower cell viability. Therefore, excess oxygen can be toxic to cells because of the increasing influence of ROS (Cipolleschi et al. 1993). Hypoxia induces stem cell proliferation and inhibits their differentiation via stimulation of the Notch signaling pathway (Hubbi and Semenza 2015). For instance, in a study, human embryonic stem cells (hESC) were cultured in both physiological (2–6.5%) and atmospheric (21%) oxygen conditions to evaluate the potential variations in the impacts of different oxygen concentrations on colony formation and genetic stability. It turned out that physiological oxygen conditions better supported clone recovery than atmospheric oxygen conditions, in which the mean increase was six fold. Furthermore, karyotype abnormalities declined in the cultured hESCs under physiological oxygen conditions compared to the cultured hESCs under atmospheric oxygen conditions, which suggests the likelihood of genomic stability during the prolonged in vitro hESCs expansion

in physiological oxygen culture conditions (Forsyth et al. 2006).

In certain types of adult stem cells, low oxygen concentrations in vitro cause the multiplication and maintenance of a multi-potency state (Csete 2005; Grayson et al. 2007; Samal et al. 2021). Some researchers believe that hypoxia is a strong stimulus for the differentiation of specific cell lines. For example, hypoxia is a strong stimulus for chondrogenesis by stem cells (Rehman et al. 2004; Sadat et al. 2007; Thangarajah et al. 2009). In most tissue cultures, the oxygen level is approximately 20% in vitro, where cells have much lower oxygen levels. The mean arterial blood oxygen concentration is approximately 12% and about 3% in tissues (Csete 2005). Therefore, optimizing and understanding stem cell growth and function has an important relationship with their condition in the microenvironment of in vivo. Embryonic stem cells live in a low oxygen environment at the time of implantation in the uterus due to the lack of access to maternal circulation. Uterine oxygen levels are 2% in early pregnancy, which increases to only 8% after fetal-maternal blood contact. This relative hypoxia is the natural physiological environment of embryonic stem cells (Genbacev et al. 1997; Cowden Dahl et al. 2005). Similarly, adult stem cells live in conditions of oxygen poverty in the body, such as the environment in which bone marrow-mesenchymal stem cells (BM-MSC) reside (Ma et al. 2009). It was shown, some cells are persistently in hypoxic states between 1 and 2% (Kofoed et al. 1985; Harrison et al. 2002). MSCs are one of the most common candidate cells in clinical trials due to their therapeutic capabilities and ability to be transplanted allogeneically (Rasouli et al. 2022; Shirbaghaee et al. 2023).

Hypoxia can alter the properties of cytoskeleton proteins, resulting in morphological changes in targeted cells (Glass et al. 2015). For example, the phenotype of differentiated chondrocytes could be restored after applying oxygen tension, as shown in vivo. When the encapsulated chondrocytes in alginate were exposed to 20% oxygen, the morphology changed to fibroblastic form, and the expression of specific genes related to human articular chondrocytes like collagen II, aggrecan and sox9 genes were lost in contrast to the cells cultured in 5% oxygen tension. Also, the expression of matrix glycosaminoglycan (GAG) was enhanced statistically significant in physiological oxygen level (5%) compared to the

culture condition of 20% oxygen tension (Murphy and Polak 2004).

It seems cell behavior changes in accordance with the with the cell type employed. Regarding this, the adipose-derived MSCs lost their differentiation potential both into chondrocytes and osteocytes after culturing in condition with a lower oxygen level of 2% compared to higher levels of 21% (Malladi et al. 2006). The stem cells derived from rat CNS (Studer et al. 2000), rat neural crest (Chen et al. 2017), murine skeletal muscle (Sharkey 2020), rat bone marrow (Kim et al. 2016), human CD34+bone marrow (Guitart et al. 2011) and human cord blood (Peng et al. 2016) showed higher proliferation rate when cultured at lower oxygen pressure (2% vs 20%). The addition of antioxidants enhances the self-renewal of hematopoietic cells via the activation of the ataxia telangiectasia mutated (ATM) gene. On the contrary, in the presence of ROS, the self-renewal of hematopoietic progenitor cells was reduced (Ghaffari 2008). The effect of oxygen tension on cell fate is much more complicated. It seems any oxygen response mechanism in case of inducing the differentiation into a lineage suppresses differentiation into other lineages. The oxygen pressure lower than below 20% stimulates myogenesis more than adipogenesis in skeletal muscle stem cells and MSC lines. In the high-oxygen condition the peroxisome proliferator-activated receptor (PPAR)-gamma, a main regulator of adipogenesis, is upregulated, thereby suppressing the activation of the MyoD promoter (Villarroya et al. 2007). In contrast, in the hypoxic condition, the satellite cells undergo an increase in the expression level of multiple myogenic basic-loop-helix genes (Wang et al. 2015). In addition, HIF-1α, an activated factor following diminished oxygenation, inhibits adipogenesis via DEC1/Stra13-mediated repression of PPAR-gamma under hypoxic conditions (Yun et al. 2002). In a study, an innovative channeled scaffold and culture medium containing perfluorocarbon (PFC) were employed to mimic the oxygen carrier function of hemoglobin and capillary network architecture, respectively. Scaffolds are 3D structures that support cell adhesion and proliferation and are commonly used for tissue regeneration purposes (Fattahi et al. 2023; Rasouli et al. 2023a, b, c). Compared to the control group, the oxygen pressure was better maintained, whereas the decline in the control group was twofold. Accordingly, the DNA content, cardiac markers (troponin I, connexin-43)

and contractile properties were improved in comparison to the control group. Eventually, the biomimetic approach served as an important strategy to replenish oxygen and increase cardiac differentiation (Radisic et al. 2006). Tissue/organ damage leads to changes in the local microenvironment, including reduced oxygen concentration and degradation of the extracellular matrix (ECM) (Rasouli et al. 2021). The response of surrounding stem cells to these changes is of particular importance. Culture under low-oxygen conditions increased cell proliferation and migration by activating the ERK signaling pathway and related integrins. ECM degradation materials increase ROS levels in cells through mitogenic and chemotactic responses. Under low oxygen conditions, high cell growth rates in progenitor cells were observed without any changes in morphology, differentiation, DNA synthesis process or metabolic activity (Tottey et al. 2011). There is a report that approving the optimum physiological oxygen (5%) inhibits karyotypic abnormalities in cardiac and embryonic stem cells. Aneuploidy occurs following the addition of high doses of antioxidants. Antioxidants also reduce the cellular amount of DNA repair enzymes by removing all intracellular ROS. Therefore, ROS has a physiological value that activates DNA repair pathways and maintains the stem cell genome's stability (Li and Marbán 2010). Since MSCs following implantation are sensitive to microenvironmental stresses such as low oxygen and limited nutrition, In a study, hypoxia preconditioning and/or transforming growth factor-β3 (TGF-β3) were investigated to enhance performance upon their in vivo implantation for cartilage and disc regeneration. Increased MSC survival and extracellular matrix production were observed in a low-oxygen and nutrient-limited environment. The results showed that hypoxic preconditioning led to the upregulation of genes related to growth, cell signaling, metabolism, and cellular stress response pathways and significantly increased the survival of MSCs. These results strongly support the use of hypoxic preconditioning to improve MSC survival after implantation in avascular tissues such as cartilage (Peck et al. 2021). The hypoxia-cultured human MSCs either young and old ones perform better than cultured cells under normoxia. Hypoxia improves MSC's capacity for self-renewal and multipotent differentiation. The underlying mechanisms are Inhibition of miR-627, miR-193a, miR-196a, miR-148b expression and up-regulation of mir-7977 and mir-195 expression (Mohd Ali et al. 2016; Rasouli et al. 2023a, b, c).

Reactive oxygen species (ROS) act to regulate various signaling pathways in cell physiology. Previous studies have shown that hydrogen peroxide (H_2O_2), a non-radical ROS, is required for cytokines, growth factors, insulin, AP-1 and NF-KB signaling (Finkel 1998). H_2O_2 can also inactivate phosphatase by oxidizing cysteine, which confirms that ROS can interfere with the signaling pathway (Rhee et al. 2000). The physiological flux of H_2O_2 results in reversible oxidation to a sustained state of specific protein targets. As a result, protein activity changes localization and interactions. On the other hand, it helps coordinate processes such as cell reproduction, differentiation, migration and angiogenesis (Jones and Sies 2015; Siegrist and Sies 2017). The low-level H_2O_2 maintenance status and the associated physiological redesign signals are called "oxidative stress" (Sies 2017). The total cellular concentration of radical anions is much lower than that of H_2O_2. Molecular redox initiation in signaling is one of the physiological targets of oxidants that respond to external stress by regulating cells at different levels. In addition to physiological H_2O_2 levels, which are important for signal transmission, high physiological H_2O_2 concentrations (approximately over 100 nM) also lead to nonspecific protein oxidation, altered reaction patterns, and reversible and irreversible damage to protein biomolecules. Finally, cell death is accompanied by pathological complications (oxidative distress) (Sies and Jones 2020). Most superoxide is generated by the partial reduction of oxygen in the electron transfer chain. In addition, they are formed at different rates in a cell, and their activity is different. In terms of activity, the hydroxyl radical is the most reactive species known and is mainly responsible for the cytotoxic effects of ROS (Bolisetty and Jaimes 2013). Most of the superoxide produced is found either in the matrix or in the inner membrane of the mitochondria facing the matrix. Although hydrogen peroxide is more stable than superoxide, it can be released from the mitochondria into the cytosol through voltage-gated anion channels, thereby reducing the deleterious effects of these reactive species on the mitochondria (MacMillan-Crow et al. 1998; Lacza et al. 2003). Besides mitochondrial metabolism, ROS also produce cellular enzymes known as nicotinamide adenine dinucleotide phosphate oxidases (NADPH) (Lassègue et al. 2012).

Other cellular sources of ROS include neutrophils, monocytes, cardiomyocytes, endothelial cells, xanthine oxidases, cytochrome P450, lipoxygenases, and nitric oxide synthase (Izyumov et al. 2010; Cubero and Nieto 2012). Another physiological factor of ROS is aging caused by ROS toxicity through a destructive cycle. Damage from mitochondrial ROS is greater. It was also shown that mitochondrial ROS production is higher in mitochondria isolated from older animals (Sohal and Sohal 1991; Balaban et al. 2005). On the other hand, protein, lipid, and DNA levels in oxidative diseases are strongly associated with aging (Bardaweel et al. 2018). Therefore, a negative relationship between mitochondrial ROS production and longevity can be understood in different organisms (Lambert et al. 2007). In the chronic inflammatory state (Dröge 2002), excess ROS inhibits mitophagy and activates a specific type of autophagy used to eliminate dysfunctional mitochondria (Salminen et al. 2012). Thus, increased levels of ROS are produced, which activate more inflammation (Zhou et al. 2011). However, high concentrations of generated ROS are involved in other biological processes.

It is obvious that the low tension of oxygen forms ROS and finally causes chromosomal instabilities, and the physiological signals try to eliminate the harm. In this manner, VEGF and erythropoietin are increased after hypoxic conditions over injuries and lead to the migration of bone marrow stem cells into the blood circulation and their mobilization into the site (Greenwald et al. 2019). Furthermore, these two factors play a role in the tumor core following hypoxia, where they promote cancer stem cell survival and radiation resistance (Lugano et al. 2020). Moreover, in the ischemic tissues, the stromal cell-derived factor (SDF-1) is expressed, and thereby this factor stimulates the migration of stem cells into the injury sites (Miller et al. 2005). Although, the corresponding factor acts as a metastatic agent, such as other oxygen-regulated factors, matrix metalloproteases and hepatocyte growth factor (Bragg et al. 2019).

When the hypoxic condition is applied to MSCs in an in vivo model, the apoptosis happens through the down-regulation of pro-survival genes like Akt, which causes cell death. In contrast, in in vitro studies, the proliferation rate of the corresponding cells is enhanced and their differentiation into various lineages is started. The lower oxygen tension induces the paracrine activity of MSCs and increases the expression of angiogenic factors such as VEGF and interleukin-6 (IL-6). Also, hypoxia causes the migration and homing of MSCs via the stimulating expression of stromal cell–derived factor-1 (SDF-1) and its receptor, CXCR4 (Das et al. 2010).

The effects of hypoxia on cell morphology lead to different results that could be beneficial or harmful to cell functionality. Yuan et al. illustrated that after culturing the human HCC cell line HepG2 in 1% O_2 for 72 h, the cells morphology changed to a spindle shape and their cellular junctions were destroyed (Yuan et al. 2012). Also, neuronal IMR-32 cells rounding and detachment from the growth surface were observed by Huang et al. under hypoxia (Huang et al. 2013). The same result was achieved by Song et al. In this evaluation, three breast cell lines (MDA-MB-231, MCF-7 and MCF-10A) were stored in a hypoxic state for 72 h and their morphology was compared with that of control cells in a normal condition. The cell–cell junctions, form, and shape of cells under normoxia (21% oxygen) were normal, but the cells were flattened and lost their tight cell–cell junctions and looked like fibroblasts. Indeed, the cell phenotype had changed under hypoxia stress (Song et al. 2018). Furuta et al. incubated Lewis lung carcinoma (LLC) cells in hypoxia. They observed that the cell morphology was altered to a spindle-shape under hypoxia (Furuta et al. 2015). However, a reverse report was published by Ahmed et al. Their findings revealed that the dental pulp stem cells (DPSCs) cultured under normoxia condition had a larger and more flattened morphology than under hypoxia. Also, the cells exhibited larger nuclei and were hardly detached from surface culture by trypsinization under hypoxia than the cells cultured under normoxia condition (Ahmed et al. 2016). Peixoto et al. showed that under hypoxia, bladder cancer cell lines (T24) had a morphology with a more elongated semblance and larger intercellular spaces (Peixoto et al. 2016). Moreover, Lim et al. cultured human embryonic stem cells under hypoxia and examined the effects of O_2 tension on embryoid body (EB) formation and their morphology. Significant cell death was observed, and also, the smaller EBs were formed under hypoxia than those grown under normoxia (300 ± 50 μm vs. 500 ± 100 μm, respectively) (Lim et al. 2011). On the other hand, the content of

extracellular vesicles (EV) obtained from MSCs can be adjusted under different culture conditions. These cells respond to exposure to hypoxia by activating hypoxia-inducible factor (HIF) at low O_2 concentrations. HIF has direct and indirect pleiotropic effects and modulates the expression of hundreds of genes involved in processes such as inflammation, migration, proliferation, differentiation, angiogenesis, metabolism, and cell apoptosis. Several studies have shown that MSC-derived EVs subjected to hypoxia have a greater regenerative capacity than those obtained under normoxia (Pulido-Escribano et al. 2022). Morphological studies of 3 cell types have been presented in Fig. 1. Since hypoxia increases the proliferation of BM-MSCs, in a study,

the proliferation of BM-MSCs along with zinc was investigated. All tissues, fluids, and organs of the human body contain zinc. Zinc is essential for cell proliferation and differentiation, especially for the regulation of DNA synthesis and mitosis. It significantly increases the proliferation of BM-MSC and reduces the doubling time of the cell population in hypoxic and normoxic environments compared to control cells. MSC migration to the injury site was increased, and HIF1-α expression significantly decreased in hypoxic conditions compared to untreated and control hypoxic cells. Zn-preconditioned mesenchymal cells maintained their spindle-shaped and fibroblast-like morphology at high passage (Rizvi et al. 2022).

Fig. 1 Morphological differences of cell cultured under normoxia and hypoxia by light microscopy. **A** H9C2 cells under hypoxia condition; **B** H9C2 cells under normoxia condition (Fan et al. 2018); **C** OCUM-2MD3 (Gastric cells) under normoxia condition; **D** OCUM-2MD3 (Gastric cells) under hypoxia condition (Matsuoka et al. 2013); **E** Renal Carcinoma Cell Lines in normoxia condition; **F** Renal Carcinoma Cell Lines in hypoxia condition (Zhang et al. 2017)
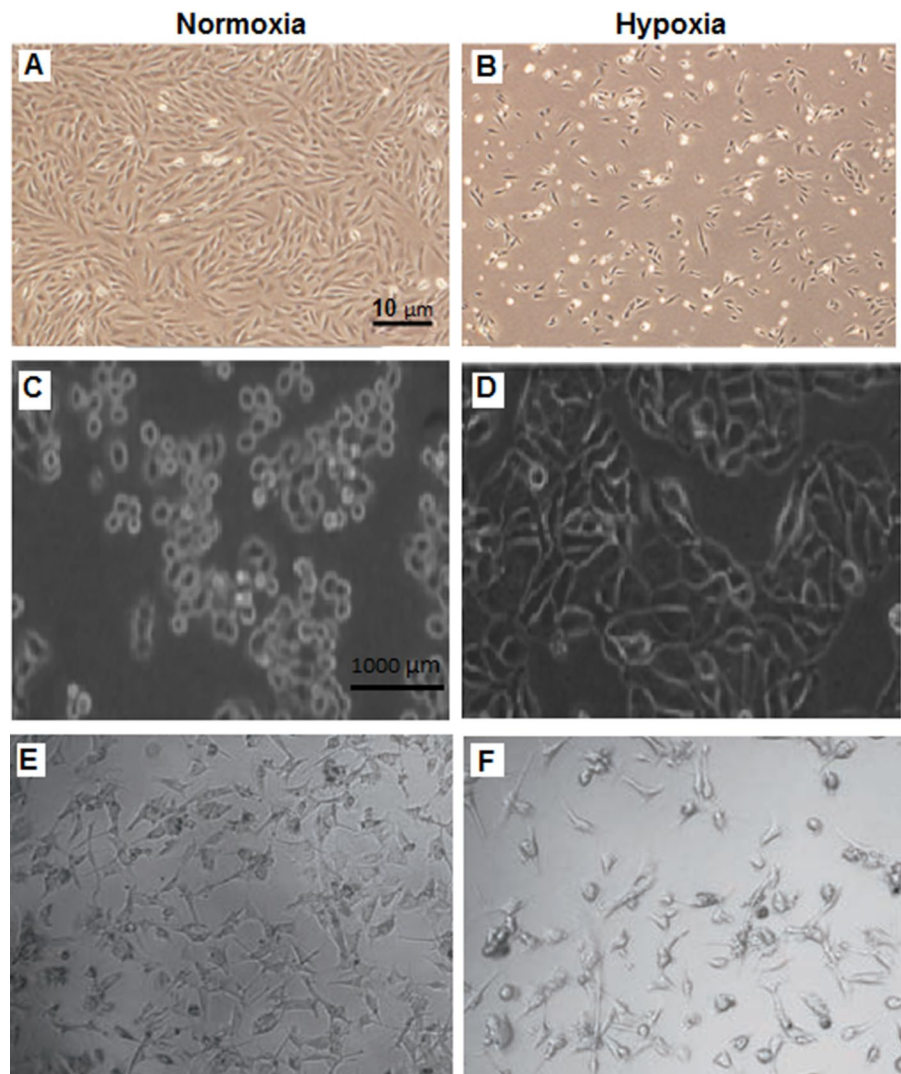
Oxygen and inflammatory pathways

Inflammatory mechanisms are complex biological processes by which tissues respond to combat injurious stimuli and defend the host. This event can be associated with tissue remodeling and metabolic changes, in order to maintain cell homeostasis (Medzhitov 2008). The inflammatory reactions involve multiple specific cell activities that could cause different processes, such as the activation of immune cells (leukocytes, granulocytes, monocytes, lymphocytes, and dendritic cells) and the stimulation of the different bioactive mediators' production (such as cytokines, chemokines, or prostanoids). Also, this complex biological process leads to epigenetic regulation of the important related genes expression, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB/AP1) activity or IL-6 expression (Martínez et al. 2012; Nayadu et al. 2012). The NF-κB family contains members of transcription factors that regulate inflammation, coordinate immune responses and tissue homeostasis (Vallabhapurapu and Karin 2009). The hypoxia of intestinal ischemia reperfusion causes the activation of NF-κB in intestinal epithelial cells, which in turn leads to the higher production of tumor necrosis factor α (TNF-α); a pro-inflammatory cytokine, but simultaneously reduces intestinal epithelial apoptosis (Chen et al. 2003). Accordingly, the increased TNF-α production strongly inhibits skeletal (Chen et al. 2008) and cardiac (Suematsu et al. 2003) muscle differentiation by decreasing myocyte enhancer factor 2C (MEF2C) (Csete 2005). Another point worth noting is that hypoxia enhances the NF-κB pathway through the increased expression and signaling of Toll-like receptors (TLRs) (Kuhlicke et al. 2007). The TLRs family, as a class of pathogen-recognition receptors, provides antimicrobial factors and stimulates phagocytosis in the first line of defense against pulmonary infection. The function is carried out via the recognition of unique microbial structures and the initiation of inflammatory and adaptive immune responses (Bals and Hiemstra 2004). Macrophages are homed to inflammation site after the activation step by damaged tissue, and they increase the levels of cytokines, chemokines, and other molecules in the blood circulation. These macrophages are called polarized type, having M1 or M2 phenotype. The M1 macrophage after inhibition of arginine metabolism, and the M2 macrophage, under inhibitory induction of cytokines, produce ROS and inflammatory cytokines (Brown et al. 2012).

The HIFs are another important factors in hypoxic situations. HIFs are a family of transcription factors whose role is response regulation to hypoxic stimuli. Over 100 target genes whose expression are involved in a broad range of physiological functions, including metabolism, autophagy, and other physiological responses to hypoxia, can be regulated by the HIF signaling pathway (Semenza 2009a, b). Members of this κB (NF-κB) family interact with the members of PHD–HIF pathway associated with inflammation (Taylor 2008). The HIF gene expression in hypoxia and NF-κB in inflammation conditions have been shown to have several common target genes, common regulators, and specifically, common stimuli (Bandarra and Rocha 2013; Nath et al. 2022; Dvornikova et al. 2023). NF-κB activation has been shown to stabilize HIF-1α activation in hypoxia and HIF-1β expression in inflammation (Van Uden et al. 2008). On the other hand, HIF-1α factor has been shown to inhibit NF-κB expression in vivo and in vitro under inflammatory conditions (Bandarra et al. 2015, Dvornikova et al. 2023). Cellular adaptation to hypoxia is based on the transcription factor HIF-1α, which is inactive under normoxic conditions. In mammals, HIF-1α plays an important role in the cellular response to systemic oxygen levels by influencing metabolic and inflammatory pathways (Di Girolamo et al. 2022). It has been confirmed that the concentration of environmental oxygen levels and inflammation as a physiological process are closely related. Inflammation is often accompanied by hypoxia and on the other hand, hypoxia itself can cause inflammation (Corcoran and O'Neill 2016). In spite of the important role of ROS in pathogen killing, it could increase vascular permeability through endothelial cell damage (Tiidus 1998). In one investigation, the adhesion of eosinophils to nerve cells and the release of their products were investigated due to the plausible contribution of eosinophil products in developing some inflammatory diseases. Eosinophils caused neurite contraction in IMR32 neuroblastoma cells, which resulted in tyrosine phosphorylation of some neuronal cell proteins, activation of p38 MAP kinase, and ROS production. If eosinophil adhesion is suppressed, the reaction will stop. However, attenuation of p38 MAP kinase could not stop ROS

production despite inhibition of neurite contraction. Thus, there may be two distinct pathways that work separately: by producing tyrosine kinase-dependent MAP kinase and by p38 MAP kinase. Therefore, the results show that the consequences of eosinophil adhesion and degranulation of neurons, change the morphology of neurons with the release of a number of proteins (Kingham et al. 2003). ROSs are produced by cells engaging in host-defense responses. These cells, called polymorphonuclear neutrophils (PMNs), promote endothelial dysfunction by oxidizing crucial cellular signaling proteins. ROS acts as a signaling molecule and also as an inflammation mediator. Thus, the production of ROS is a central occurrence in the progression of many inflammatory diseases (Salvemini et al. 2003). Moreover, recent studies indicated that TLRs expression participates in the response to

oxidant stress and that ROS is correlated with the inflammatory signaling pathway of TLR4 in neutrophils (Jiang et al. 2005) (Fig. 2).

In some patients, it had been shown that their inflamed tissues had a lower oxygen value than normal. There are several diseases that result from the de-regulation of hypoxia and inflammation pathways such as rheumatoid arthritis (RA), inflammatory bowel disease, and colorectal cancer (CRC) (Taylor 2008; Näthke and Rocha 2011). Recently, a few scientific studies have been focused on attempting to better understand how these pathways are regulated and respond to in diseases. In the gastrointestinal (GI) tract, the mice with the experimental models associated with inflammatory bowel disease (IBD) confirmed that more inflammation was accompanied by lower oxygen levels in their
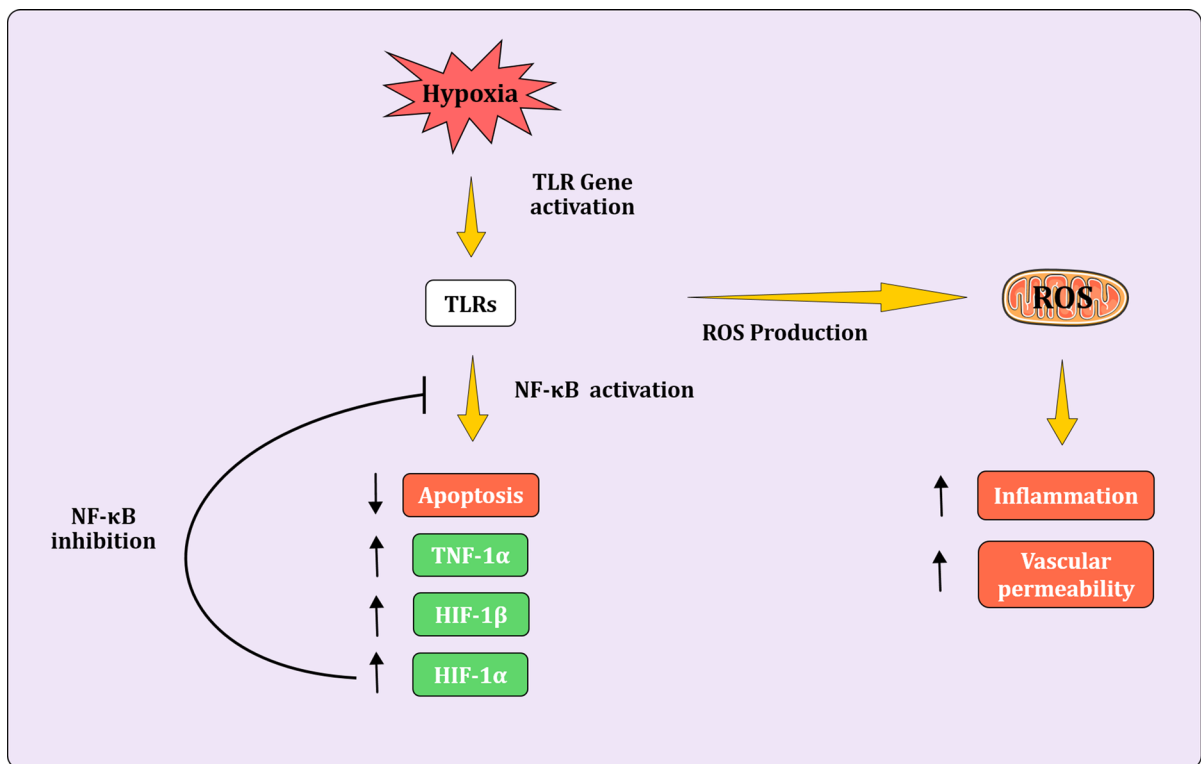

Fig. 2 Oxygen and inflammation pathways. Hypoxic conditions lead to increased expression and signaling of Toll-like receptors (TLRs), and thereby NF-κB pathway activation. An increased NF-κB signaling pathway is associated with higher levels inflammatory cytokines, including TNF-α, and simultaneously decreased cell apoptosis. Furthermore, expression and activation of both HIF-1α HIF-1β increased as a result of

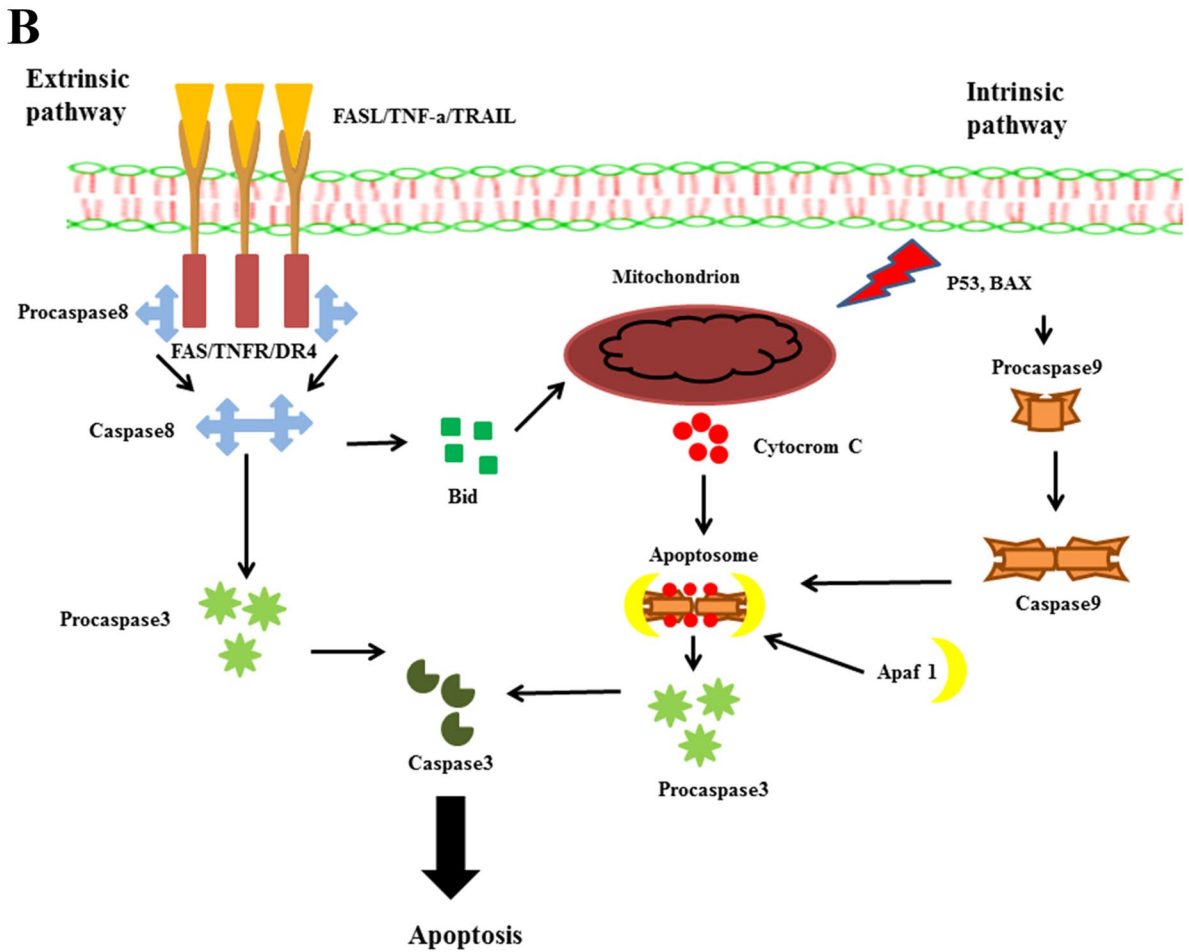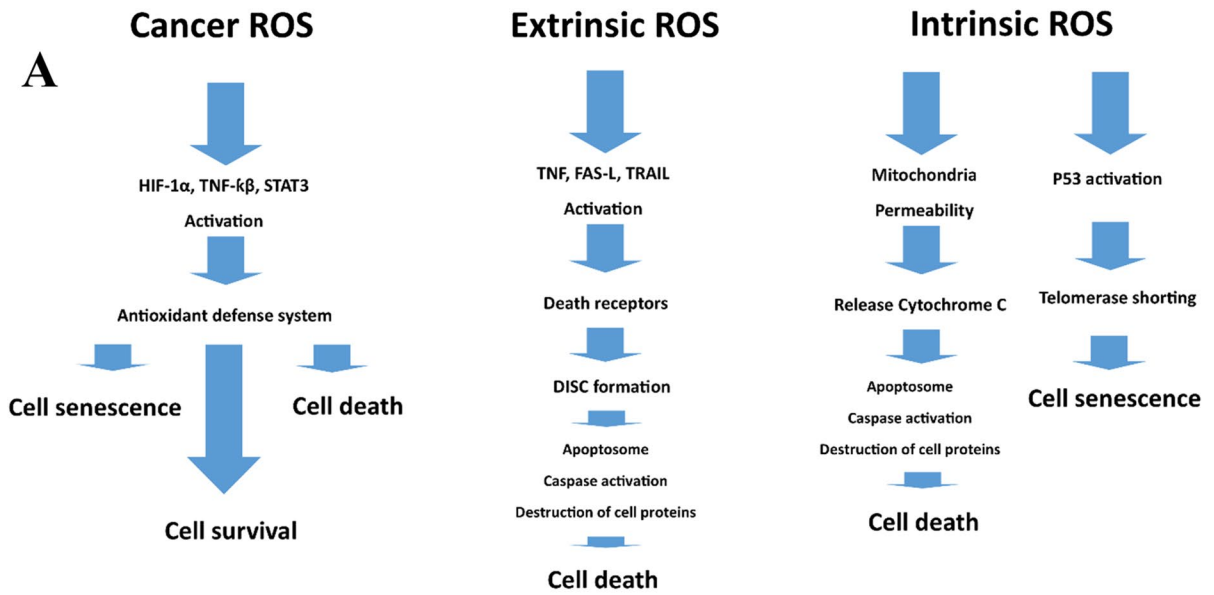NF-κB activation. However, following HIF-1α activation the NF-κB pathway is suppressed. It is worth noting, TLRs not only activate NF-κB, but also drive ROS production. Subsequently, generated ROS plays a role in promoting inflammation and rising vascular permeability through endothelial cell damage

colonic tissues (Karhausen 2004). The result correlates with the pathology that was investigated in IBD patients (Taylor and Colgan 2007). Inspecting the role of hypoxia in epithelial cells and immune cell responses could open a new field for the development of new therapeutics for treating IBD (Lewis et al. 1999). The fact that hypoxia can induce inflammation has attained general acceptance from studies related to hypoxia signaling pathways. In people with mountain sickness, for example, the levels of circulating pro-inflammatory cytokines would be increased subsequently (Grocott et al. 2009). By the examination of all inflammation markers, it was shown that the serum levels of interleukin-6, the interleukin-6 receptor, and C-reactive were increased in healthy volunteers who spent three nights at elevations higher than 3400 m (Hartmann et al. 2000). Furthermore, the increase of inflammatory cells in multiple organs and greater serum levels of cytokines were approved in mice after short-term exposure to low oxygen concentrations (Rosenberger et al. 2009). In various studies, it has been reported that higher oxygen concentrations can regulate the mRNA expression of several genes related to protein secretion. For example, after 5 h of HBOT (90 min at 97.5% O_2 at 2.4 ATA), 19 genes involved in adhesion, angiogenesis, inflammation, and oxidative stress were downregulated (Kendall et al. 2012). While, T cells showed different relationships with oxygen when they regulated their function in response to environmental oxygen levels (Ruigrok et al. 2019). In addition, Mitchel et al. showed that necrosis can lead to acute inflammation, and among pro-inflammatory cytokines, the mRNA expression of IL-6 and TNF-α were elevated upon exposure to 80% O_2 in 48 h, although they decreased after 96 h (Ruigrok et al. 2019). In an In vivo study of Wang C. et al. the higher expression of IL-1β mRNA after 24 h confirmed by the examination of the blood samples from individuals under hypobaric hypoxia (Wang et al. 2018). At the end, the molecular mechanisms of the interactions between hypoxia and inflammation are intertwined at cellular and clinical levels. Therefore, oxygen-sensing mechanisms and hypoxia signaling pathways could be potential therapeutic targets for the treatment of inflammatory diseases. Moreover, this evaluation could be tested in patients with acute lung injury, myocardial ischemia, inflammatory bowel disease, or cancer. There are studies focused on the impact of oxygen levels on the expression of inflammatory genes, as summarized in Table 1.

Table 1 ROS impacts on inflammatory genes

Treatment condition	Model/tissue	Gens/proteins	References
Hypoxia	Serum	IL-6↑,CRP ↑	Hartmann et al. (2000)
Hypoxia	Blood sample	IL-1β ↑	Wang et al. (2018)
Hypoxia	Rat model	IL-6 ↑	Chaddha et al. (2020)
Hypoxia	blood sample	IL-1β ↑,IL-3 (n.s), IL-6↑, TNF-a (n.s), IL-10 ↑	Kammerer et al. (2020)
Hypoxia	HUVEC cells	IL -1a ↑, IL-6 ↑, IL-8 ↑	Ali et al. (1999)
Hypoxia	Human IVD Cells	IL-1β↑, IL-6↑, IL-8↑, and IL-20↑	Hsu et al. (2020)
Hyperoxia	Mice tissue	IL-6 and Tnf-α: (46 h ↑), (96 h ↓)	Ruigrok et al. (2019)
Hyperoxia	3T3-L1 adipocytes	Hif-1α ↑, Il-6 ↑, ROS↑	Quintero et al. (2012)
Hyperoxia	C56BL/6 J mice	Hif-1α ↑	Benderro et al. (2012)
Hyperoxia	Human alveolar macrophage	IL -lp↑, IL-6↑, IL-8↑ TNF-a↓	Desmarquest et al. (1998)
Hyperoxia	C57BL/6 female mice	TNF-a↓	Barazzone-Argiroffo et al. (2001)
Hyperoxia	A549 cells	IL-6↑, IL-8↑, ROS ↑	Huang et al. (2016)
Hyperoxia	Sprague–Dawley rat	ROS ↑	Kwak et al. (2006)
Hyperoxia	hematopoietic stem cells	ROS ↑	Cipolleschi et al. (1993)
Hyperoxia	lung capillary endothelial cells in rats	ROS ↑	Brueckl et al. (2006)
Hyperoxia	C57BL/6 J mice	ROS ↑	Zangl et al. (2014)

Oxygen and cancer/cell senescence

There are two types of cell death, necrosis and apoptosis, that are influenced by different factors. Oxygen depletion is one of the main factors involved in necrosis, but apoptosis is a form of programmed cell death (Elmore 2007). The cells that get necrotic, can be identified with these morphological features. The appearance of flocculent densities in mitochondria was detected with the progressive swelling and degeneration of cellular components. The Madin-Derby canine kidney (MDCK) cell line was cultured in hypoxia and normoxia conditions by Allen et al. (Allen et al. 1992). They showed that the cell death pathway could change from apoptosis to necrosis by adding hypoxia stress to renal tubule structures. Although, this phenomenon has already been proven by Sheridan et al. for human melanoma cells in semi-solid agar medium (Sheridan et al. 1984). It was recently shown that hypoxia can modulate the anti-proliferative response in tumor cells (oncogene-induced senescence). Intracellular levels of ROS increases following hypoxia. ROS acts as a double-edged sword in cancer cells by altering two signaling pathways, such as ras-raf-mek1/2-ERK1/2 and the P38 mitogen-activated protein kinases (MAPK) pathways, that have opposing roles in tumorogenesis. It was concluded that ROS may not be an absolute tumor suppressor or activator factor (Eren 2023).

Risk factors such as cancer, stress, tobacco, environmental pollutants, radiation, viral infection, diet, and bacterial infection produce ROS molecules after their interactions with cells (Zhang et al. 2016). ROS molecules act as a double-edged sword in cancer cells (Schumacker 2006) depending on ROS dosage and type. The site of ROS production can either lead to apoptosis or increase tumorigenesis (Raza et al. 2017; Kumari et al. 2018). The destruction of cancer cells

occurs at a high ROS level (Nishikawa 2008), while at a modest level of ROS, cancer cells can survive (Kong et al. 2000). ROS-dependent apoptosis in cancer cells, both in vitro and in vivo, has been shown in many studies in the past years (Trachootham et al. 2006). Both extrinsic and intrinsic pathways of apoptosis are activated through ROS (Ozben 2007). In the intrinsic pathway, apoptosis occurs through the opening of mitochondrial permeability transfer pores and the release of cytochrome C into the cytosol. These events cause the formation of an apoptosome, caspase activation, and the decomposition of intracellular proteins, and finally, cell death occurs (Martindale and Holbrook 2002; Redza-Dutordoir and Averill-Bates 2016). Extrinsic pathways are composed of external stimuli, ligand molecules, and death receptors. In this pathway, extracellular ligands such as Fas-L, TNF, and TNF-related apoptosis-inducing ligand (TRAIL) are attached to death receptors, and a death-inducing signaling complex (DISC) is developed. Then, apoptotic signaling happens and facilitates cell death (Uchikura et al. 2004; Jin et al. 2005). On the other hand, for the role of ROS tumorigenesis, ROS can target transcription factors, and among the various transcription factors that are activated by ROS, HIF-1 α, NF-κB and STAT3 could be introduced. Transcription factors activated by ROS are capable of enhancing the activation of the antioxidant defense system and promoting the expression of cell survival proteins and the genes involved in inflammation, cell transformation, tumor cell death or survival, proliferation, invasion, angiogenesis, and tumor migration (Dewhirst et al. 2008; Gupta et al. 2012). It was shown that the antioxidant compatibility of tumor cells is very limited. Increased activity of antioxidants such as SOD2/MnSOD or inactivation of inhibitory enzymes, including PRX1, are both seen in the development and progression of cancer (Janssen et al. 1999). The summarized pathways of ROS impacts are indicated in Fig. 3.

Singlet oxygen is one of the most famous non-radical factors, but ROS compounds are active, and their levels decrease after the addition of antioxidants. A balance between the levels of antioxidants and ROS is required to suppress cell damage ranging from signal transduction and gene expression to cell transformation and necrosis/death. Thus, a lower or higher amount of oxygen could, respectively, lead to hypoxia or oxidative stress (Matés and Sánchez-Jiménez

2000). Tumor cells adapt to hypoxia through glucose metabolism, which contributes to an invasive phenotype. Glycolysis plays a role in redox homeostasis in cancer through the production of reducing agents such as NADPH and glutathione (GSH). Also, studies have shown that tumor cells adapt by increasing glycolysis to prevent H_2O_2-induced cell death (Harris 2002). On the other hand, depending on the type and concentration of ROS they impose complex effects on cells. A slight increase in reactive species causes different cell signaling cascades that enable cell growth and survival (Bäumer et al. 2008). If ROS levels are decreased using antioxidants in tumor tissue, it would induce senescence, although cancer stem cells still remain. The incidence of antioxidant defense signaling in the following could occur and reactivate cancer cells (Achuthan et al. 2011). Moreover, ROS could not only be a reason for cell death but also activate a signaling pathway for cell survival. Hypoxia or oxidative stress induces ROS generation, and autophagy in cancer may lead to a healthy state (Azad et al. 2009). However, it is worth mentioning that hypoxia can participate in tumor progression through alternations in the gene and protein expression of the ECM, and these proteins play a main role in angiogenesis. Hielscher et al. showed that the fibrous structure of ECM in the co-cultures of neonatal fibroblasts (NuFF) with MDAMB-231 breast cancer cells after incubation in hypoxia, converted to more compact and aligned fibers with a larger diameter compared to the fibers formed in the atmospheric oxygen condition. This architecture regulated the expression of angiogenic factors and matrix metalloproteinases (Hielscher et al. 2013).

Singlet oxygen is a toxic molecule and can be implicated in many human diseases. It is derived directly from oxygen gas and relates extremely well to the oxygen level of *an* in vitro or in vivo environment. Also, when antioxidants such as NAC are used to inhibit HIV-virus replication, oxidative stress starts and disrupts the balance of cellular protein kinase/phosphatase (Waris and Ahsan 2006). Intracellular ROS is produced after higher expression of p53 and induces senescence or apoptosis in normal and cancer cells. While, exogenous ROS in combination with p53's physiological level could change senescence into apoptosis (Macip et al. 2003). There are differences between the reactions of human and mouse cells to oxygen pressures. Human cells showed a

senescence-associated secretory phenotype (SASP) for the secretion of cytokines. Both senescent mouse and human fibroblasts were cultured in physiological (3%) and normal cell culture conditions (20%) of oxygen tension. Mouse cells did not expose SASP like human cells. When the mouse cells were incubated in 3% oxygen pressure and induced by radiation, SASP appeared and the synthesis of metalloproteinases started. Furthermore, the cell proliferation of mouse cells was inhibited, although with SA-bGal activity, DNA synthesis, and serum-inducible c-Fos expression (Coppé et al. 2010). In a study, human umbilical vein endothelial cells (HUVECs) were treated with indoxyl sulfate (IS) that had a concentration similar to the serum level in hemodialysis patients. IS caused ROS synthesis and cell senescence through p53 activation (Adelibieke et al. 2012). A group studied the effect of physiological oxygen pressure (3%) vs. high oxygen tension (20%) in an in vitro analysis of mouse embryonic fibroblasts (MEFs) derived from *lacZ* mice. Senescence and immortalization with a three-fold increase in mutations occurred when the cells were cultured in a 20% oxygen condition, contrary to the cells in a 3% oxygen condition. The results clearly exposed the critical role of oxidative conditions on genomic integrity (Busuttil et al. 2003). It has recently been claimed that physiological levels of O_2 should be maintained in cell culture to better mimic the in vivo redox reactions associated with specific cell types (Sies et al. 2022). Aging is a stochastic process that happens as a result of genetic and epigenetic changes such as oxidants (Colavitti and Finkel 2005). ROS induces telomerase shortening and premature senescence increases ROS levels as a positive feedback system (Passos and Von Zglinicki 2006). Also, it was reported that the activation of the checkpoint gene CDKN1A (p21) for a long time caused mitochondrial dysfunction and finally ROS synthesis, which is a major proof of DNA damage and then senescence (Passos et al. 2010). The senescence of endothelial cells accelerates in diabetes. The antidiabetic hormone glucagon-like peptide 1 (GLP-1) was studied by a group to reduce the aging rate of these cells which were under oxidative stress. The peptide decreased intracellular H_2O_2 and activated the transcription factor of cAMP response element-binding (CREB) levels through the cAMP/protein kinase A (PKA) pathway. In addition, the oxidative defense genes *HO-1* and *NQO1* were activated after applying

GLP-1 (Oeseburg et al. 2010). Exogenous hydrogen peroxide at ≥ 1 mM, induced cell death, 100–500 µM caused senescence, and lower values did not lead to cell proliferation. This non-specific behavior of ROS has been related to the random injury of cell components and some activation of specific cell pathways (Lu and Finkel 2008).

Oxygen and angiogenesis

Hypoxia or ischemia conditions could activate the expression of VEGF and angiopoietin-1 genes, triggering the activation of NADPH oxidase. This enzyme produces ROS compounds such as superoxide and the resultant H_2O_2 leads to the auto-phosphorylation of VEGFR2 and finally angiogenesis. This ROS dependent angiogenesis happens via endogenous antioxidant enzymes such as SOD and thioredoxin. Hence, NADPH oxidase has been introduced as a main producer of ROS. The deep insight into oxygen's role in cell fate may provide a better understanding of stem cell requirements for desirable proliferation, migration, homing, commitment, or differentiation (Ushio-Fukai and Nakamura 2008). The related mechanism is summarized in Fig. 4.

The singlet oxygen, as a chemical formula of O_2 is classified as the non-radical form of ROS that could lack unpaired electrons but is chemically reactive and can be changed to radical ROS through mitochondria, peroxisomes, endoplasmic reticulum, and the NADPH oxidase (NOX) complex in cell membranes (Luis et al. 1992; Inoue et al. 2003). There is a major relationship between tissue oxygenation status and active angiogenesis, in which the accumulation of genes as hypoxia-inducible factor (HIF)-α subunits, plays a major role in the activation of angiogenic transcription factors. HIF-α is regulated by a subset of dioxygenases called prolyl hydroxylase (PHD), which use oxygen as a substrate. Therefore, in the absence of oxygen, HIF-α subunits are gathered due to lower hydroxylation function. After their formation of heterodimers with HIF-1ß, the expression of angiogenic factors is activated and thus, cells could adapt to hypoxia. The regulation of angiogenesis involves two different mechanisms. The mechanism of paracrine (non-endothelial expression of angiogenesis factors) induced by VEGF-A, in which the factor interacts with surface receptors on endothelial cells to
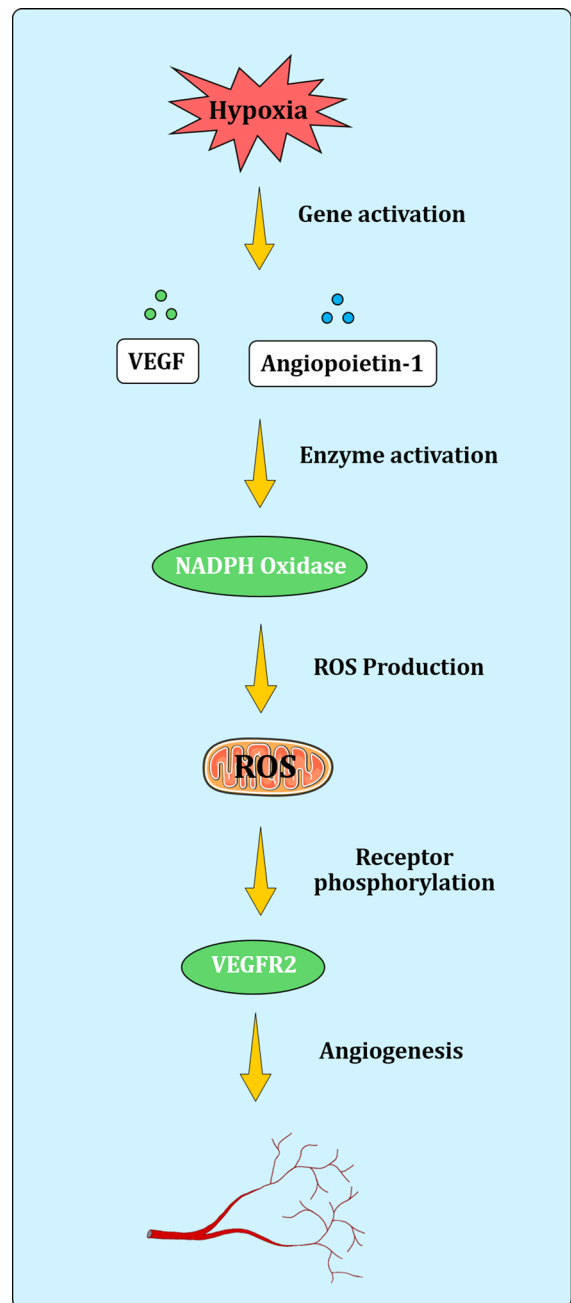

Fig. 4 ROS impacts on angiogenesis. In hypoxic conditions, the expression of VEGF and angiopoietin-1 genes is activated, which contributes to the activation of NADPH oxidase. Subsequently, the activated enzyme generates ROS compounds. Thereby, ROS molecules induce the auto-phosphorylation of VEGFR2 and eventually angiogenesis

initiate angiogenic activity. The autocrine mechanism induces endothelial cells to express VEGF-A, which supports angiogenesis and protects vascular integrity. These two mechanisms interact with each other (Fong 2009). The therapeutic use of MSC transplantation has proposed a new strategy for hypoxic preconditioning through angiogenesis. For example, in ischemic heart disease, a major problem with using this treatment is the low survival of transplanted cells around the infarct, which leads to cell death due to endogenous and environmental factors such as the inflammatory response. Therefore, improving the survival of transplanted cells is crucial to increasing the efficiency and effectiveness of stem cell therapy. Angiogenesis is one of the effective mechanisms for improving the function of stem cells after transplantation. Transplanted MSCs stimulate angiogenesis after myocardial infarction (MI) by secreting multiple angiogenic cytokines and undergoing differentiation into endothelial cells. Hypoxia preconditioning (HP) stimulates endogenous mechanisms to express multiple proteins to protect against hypoxia. This condition can reduce neuronal apoptosis by inducing HIF-1α and protecting myocytes from oxygen-induced damage and reperfusion. As a result, studies show that HP-treated MSCs have better therapeutic effects in ischemic heart cases. The functional advantages of HP-MSC transplantations are as follows: (1) With HP, autocrine and paracrine signaling of MSCs is increased, and it reduces the apoptosis of transplanted cells and endogenous cardiomyocytes; (2) the higher survival of HP-MSCs provides better and longer support in a compensation process; and (3) the higher survival of the transplanted cells increases angiogenesis. These factors generally repair tissue and provide a simple but effective strategy for treating clinical MSC transplantations. The important point in this regard is to study its effect on mortality for long time (Hu et al. 2008). In addition, mechanical stress has been shown in in vivo studies to lead to angiogenesis and vascular regeneration. In this regard, related evidence has shown that blood vessels contain stem/progenitor cells that are activated by physiological and pathophysiological biomechanical pressures and released into the bloodstream (Sharifpanah et al. 2016). Also, hypoxia stimulates the angiogenic effects of fat-derived older MSCs. Since the exact concentration of oxygen in adipose tissue is unknown, hypothetical oxygen levels were used for bone marrow. Hypoxic

ventilation has shown beneficial effects on bone marrow-derived MSCs by enhancing their angiogenic properties. Activation of HIF-1 leads to the expression of more genes for angiogenic stimuli such as VEGF, angiopoietin, platelet-derived growth factor B subunit (PDGFB), beta-1 growth factor conversion (TGFb1), and SDF-1. Thus, hypoxic ventilation of human fat-derived MSCs can increase angiogenesis through secretory factors (Efimenko et al. 2011).

Because oxygen is an important signaling molecule in stem cells, hypoxia can increase the expression of specific genes, including glycolysis, erythropoiesis, and angiogenesis (Glut-1, Epo, and VEGF, respectively) (Cameron et al. 2008). Satellite cells are muscle progenitor cells that are normally inactive and activated by muscle damage and have a number of growth factors, including hepatocyte growth factor (HGF), fibroblast growth factor (FGF) and VEGF. Their strong VEGF gene expression happens during muscle fiber regeneration. In ischemic muscle, HIF transcribes 100 genes involved in metabolism, erythropoiesis (Rhoads et al. 2009). Exogenous oxygen supply could increase nerve regeneration through Schwan cell survival and angiogenesis. Schwan cells were protected from hypoxia and angiogenesis was improved in vitro by perfluorotributylamine (PFTBA)-VEGF core–shell system. Furthermore, In vivo investigations shown that the VEGF could induce neovascularization, and the emerging blood vessels served as consecutive oxygen supplies for SCs during nerve regeneration when the oxygen transported by PFTBA was depleted (Ma et al. 2022). The physiological niches of MSCs have much less oxygen stress. Therefore, the stimulus of oxygen stress plays an important role in the balance between cell proliferation and commitment to differentiation. The presence of blood vessels and HIF-1α in fetus is not known. HIF-1α shows anomalous evidence about its role in NSCs fate via glycolytic metabolism. In drosophila neuroblasts, during the development of anaerobic metabolism, it is converted to oxidative phosphorylation, and the induction of oxidative phosphorylation is required for cell cycle exit and neuroblast differentiation. Similarly, in adult mammals, the oxygen consumption of NSCs, increases with their differentiation in vitro and accordingly, the inhibition of electron transfer chain enhances the proliferation of these cells (Lange et al. 2016). In a study, the adhesive proteins secreted from oysters (MAPs) were

found to be biocompatible natural adhesives due to their attractive physicochemical properties such as non-accumulation in water, low surface tension and strong adhesion underwater. In addition, it enhances angiogenesis(Park et al. 2019). Studies have shown that HP can alter MSC function, aging, and epigenetic patterns by modulating chromatin-modifying enzyme gene expression levels (Isik et al. 2021). Another example is about cancer-like stem cell (CSC) interactions that occur between microvascular endothelial cells and endothelial progenitor cells in hypoxia within tumor niches. These interactions could induce an angiogenic response by the evaluation of micro-RNA expression in spheroid cells (Klimkiewicz et al. 2017).

Conclusion

Taking everything into account, ROS concentration, as a dependent factor of oxygen tension, plays a pivotal role in the regulation of cell fate and tissue function/regeneration. However, the underlying mechanism varies to some extent depending on the type of cell/tissue. Obviously higher concentrations of ROS alter cell growth, typical cell morphology, tissue angiogenesis, and cancer/senescence pathways. Anyway, these molecules must be neutralized by antioxidants, especially at higher concentrations. Moreover, it seems that the production site of this factor is important to determining the cell's fate. In the case of TNF activation by extrinsic ROS, cells are strictly doomed to die. In contrast, cell's death is not the only fate and their survival/senescence may occur in the case of originating ROS from tumor tissue.

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