



# Therapeutics effect of mesenchymal stromal cells in reactive oxygen species-induced damages

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## Abstract

Reactive Oxygen Species are chemically unstable molecules generated during aerobic respiration, especially in the electron transport chain. ROS are involved in various biological functions; any imbalance in their standard level results in severe damage, for instance, oxidative damage, inflammation in a cellular system, and cancer. Oxidative damage activates signaling pathways, which result in cell proliferation, oncogenesis, and metastasis. Since the last few decades, mesenchymal stromal cells have been explored as therapeutic agents against various pathologies, such as cardiovascular diseases, acute and chronic kidney disease, neurodegenerative diseases, macular degeneration, and biliary diseases. Recently, the research community has begun developing several anti-tumor drugs, but these therapeutic drugs are ineffective. In this present review, we would like to emphasize MSCs-based targeted therapy against pathologies induced by ROS as cells possess regenerative potential, immunomodulation, and migratory capacity. We have also focused on how MSCs can be used as next-generation drugs with no side effects.

**Keywords** Reactive oxygen species · Electron transport chain · Oxidative stress · Cancer · Metastasis · Mesenchymal stromal cells

## Abbreviations

ROS	Reactive oxygen species
MSCs	Mesenchymal stromal cells
EMT	Epithelial–Mesenchymal transition
ATM	Ataxia–telangiectasia mutated
JNK	C-Jun N-terminal kinases
HGF	Hepatocyte growth factor
ERK	Extracellular regulated kinases
MD	Mascular degeneration
NDs	Neurodegenerative diseases
CKD	Chronic kidney disease
ETC	Electron transport chain
FoxO	Forkhead box protein O
SOD3	Superoxide dismutase 3
PGE2	Prostaglandin E Synthase 2
SOD1	Superoxide dismutase 1
TGF-β	Transforming Growth Factor Beta 1

MAPKs	Mitogen-activated protein kinase
CNS	Central nervous system
hUMSCs	Human umbilical cord mesenchymal stromal cells
HSV-TK	Herpes simplex virus-thymidine kinase
CCL5	C–C motif chemokine Ligand-5
SLE	Systemic lupus erythematosus
GVHD	Graft versus host disease
IL1RN	Interleukin-1 receptor antagonist
TNF-γ	Tumor necrosis factor-γ

## Introduction

Various cells and organelles, for instance, mitochondria peroxisomes, phagocytic cells, and endoplasmic reticulum produce reactive oxygen species (ROS) during their biological functioning [1–3]. Phagocytic cells, peroxisome, and endoplasmic reticulum contribute less towards ROS production as compared to mitochondria (80% of free radicals are generated in mitochondria) [4]. ROS are generated as a combination of free electrons with a by-product of oxygen molecules [5]. The intracellular presence of two free electrons in the outer orbital of oxygen molecule

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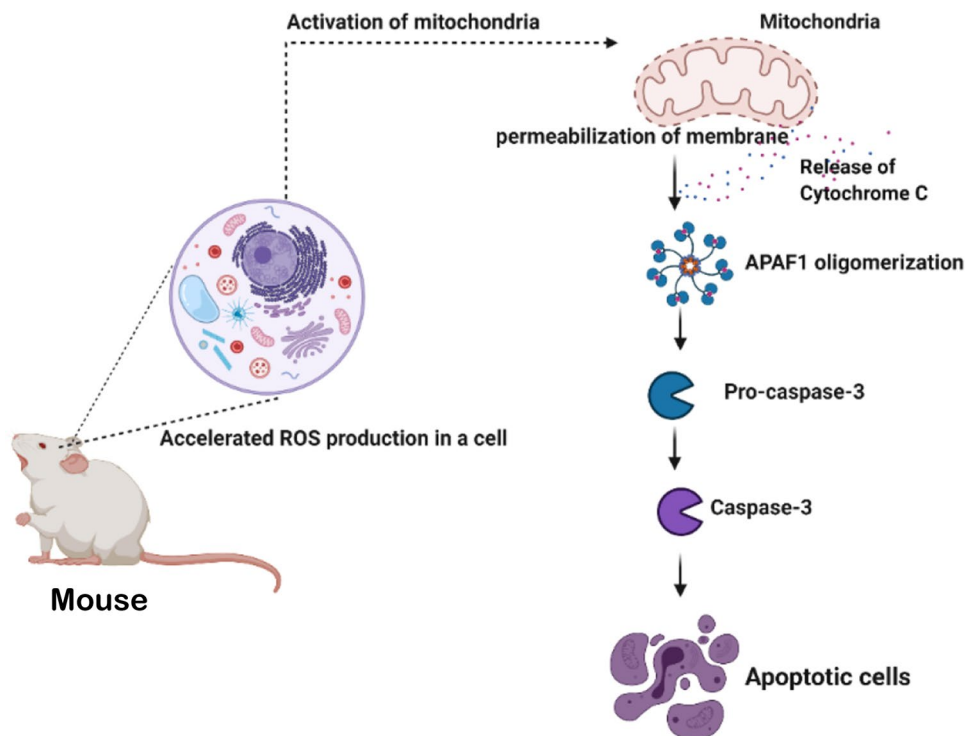
makes cells more susceptible to form free radicals [6]. The addition of free electrons to these oxygen molecules leads to the formation of several other ROS species, such as superoxide, hydrogen peroxide, hydroxyl radical, hydroxyl ion, and nitric oxide [7–10]. These free reactive species influence various functions, such as gene expression, cell cycle activation, proliferation, angiogenesis, and apoptosis [11–13]. Furthermore, ROS are known to play a role in intra- and inter-cellular signaling for a variety of cellular processes [14]. Oxidative balance is one of the critical factors responsible for normal cellular growth and maintenance [15]. In the past few decades, disruption of redox balance has been illustrated as an important reason underlying cancer progression, angiogenesis, and metastasis in human cells [16–18]. ROS are also responsible for acute and chronic kidney disease (CKD), neurodegenerative diseases (NDs), macular degeneration (MD), and biliary diseases [19–22]. The disproportionality in redox homeostasis is associated with increased free radicals, predominantly ROS [23]. The ROS and highly active radicals act intrinsically and extrinsically in the cell microenvironment and cause severe consequences; cancer is one among them [24]. Because of mesenchymal stromal cells (MSCs) therapeutic and regenerative potential, as well as the recent development of MSCs as targeted-based therapeutics, scientists are increasingly turning to MSCs as a better alternative to cure ROS-induced damage. Among all the stem cells, MSCs have very high disease-based targeted potential due to their multilineage differentiation potential,

migratory capacity to injured sites, and response to environmental signals through paracrine mediators [24, 25]. Nevertheless, several new emerging data support the beneficial effects of MSCs for oncological pathogenesis [26].

### ROS-induced inflammation

Inflammation is a natural defence mechanism against pathogens [27], but ROS-induced inflammation is associated with chronic diseases, such as kidney failure, neurodegeneration, and many types of cancer [28, 29]. Generally, cells contain a limited amount of ROS in their microenvironment as it is necessary for their cellular function, but if there is an imbalance in their concentration, it leads to perturbations [30]. ROS exerts a negative effect on nucleic acid (DNA/RNA), protein, and fatty acids [31, 32]. ROS causes unfavorable changes in these molecules, resulting in the release of inflammatory signaling molecules and the progression of cancers and chronic diseases [33]. These inflammatory molecules disrupt normal cellular functions by activating signaling pathways mediated by NF- $\kappa$ B, JAK-STAT3, MAPK, PI3K/Akt/mTOR, Wnt/ $\beta$ -catenin, and TGF- $\beta$ /Smad [34–37]. There are few ROS, like superoxide, which combine with NO to form another highly unstable peroxynitrite molecule [38] and have pro-inflammatory effects [39]. Some ROS directly influence cell death by activating apoptotic signaling (Fig. 1), implying a role in cell aging.

**Fig. 1** Mitochondrial-induced inflammation and apoptosis



## Mechanism of inflammation

### Uncoupled NOS-derived ROS in inflammation

Nitric oxide synthase (NOS) mediates synthesis of nitric oxide (NO) from L-arginine. NOS belongs to the large family of enzymes known as nitric oxide synthases (NOSs) [40]. In a cell, there are three isoforms of NOS, namely, neuronal (nNO), inducible (iNO), and endothelial (eNO), having significant functions [41]. Among these, eNOS is a predominant source of NO in the vascular endothelial cells [42]. It is a dimer protein with a reductase domain at its N-terminal, responsible for binding three cofactors, namely NADPH, FMN, and FAD. Its oxygenase domain binds to prosthetic heme group, cofactor tetrahydrobiopterin (BH<sub>4</sub>), and molecular oxygen. During synthesis of NO, free electrons are generated, which are transferred from tightly bound NADPH (reductase domain) to the heme prosthetic group of oxygenase domain [43]. The synthesis of NO by eNOS is a controlled process. eNO tightly regulates electron transfer, however, any change may result in the production of superoxide radicals, which have been linked to a variety of inflammatory diseases, including acute lung injury, diabetes mellitus, and others [44].

### Mitochondrial role in inflammation

As discussed earlier, 80% of ROS are generated in mitochondria, known as mtROS. These ROS are prominently involved in inflammation [45]. An increased level of mtROS has been reported in patients' blood samples (having monocytes and neutrophils) compared to the normal healthy individual. A low level of ROS activates mitochondrial-targeted ubiquitin (MitoQ), suppresses p38MAPK activation, and leads to production of pro-inflammatory cytokines, such as IL-6 and TNF- $\alpha$  [46, 47]. Some new studies suggest that tumour necrosis factor receptor 1 (TNFR1) associated mutation elevates mROS level, although the mechanism is not very clear [48]. However, one of the possible mechanisms may be retention of the mutated protein in endoplasmic reticulum (ER), which releases calcium and further alters the ETC of mitochondria. Any discrepancy in ROS level and rate of ROS synthesis is sensed by two complex proteins viz. Trx and thioredoxin interacting protein (TXNIP). When these proteins dissociate, TXNIP binds to NLRP3 for its activation, which enables recruitment of apoptosis-associated speck-like protein (Asc) and Pro-caspase1/2protein (precursor of NLRP3 inflammasome formation). The active form of NLRP3 inflammasome changes pro-IL-1 $\beta$  and pro-IL-18 into an active form by cleaving nascent peptide that is subsequently secreted by the inflammatory cells. These nascent peptides subsequently promote angiogenesis, tumour cell migration, and tissue invasion [49, 50].

## ROS-induced pathologies

The ROS as inflammatory mediators trigger various health complications, as they influence many signaling cascades which hamper the function of nucleic acids, proteins, and fatty acids. This results in the onset of various abnormalities, as discussed further.

### Neurodegeneration

Neurons play a pivotal role in regulating sensory organ functions. Any defect in neurons' function and associated signaling causes neurological disorders (Alzheimer's, dementia, Parkinson's, etc.) [39]. These cells are more sensitive to oxidative damage due to the unavailability of antioxidant molecules [30]. As a result, any mitochondrial dysfunction elevates ROS levels, which subsequently activates c-Jun N-terminal kinase (JNK), and sterol regulatory element-binding proteins (SREBP), causing accumulation of lipid droplets and consequent neurodegeneration [10].

### Cardiac diseases

An imbalance of ROS level in cardiac cells stimulates TNF- $\alpha$ , Angiotensin II, and norepinephrine. ROS are considered prime molecules responsible for cardiac diseases, such as myocardial infarction and heart failure [51]. Myocardial ischemia (heart muscles with insufficient blood supply) is the most prominent cause of heart attack. A high level of ROS is associated with ischemia–reperfusion injury, resulting in the apoptosis of cardiomyocytes [52]. During ischemia, the heart suffers from a lack of ATP supply, which causes calcium accumulation and, as a result, an increase in ROS levels destabilizes the integrity of the plasma membrane and ultimately leads to cell death [39].

### Inflammatory diseases and infection

Under standard conditions, ROS regulate immune response and bring about oxidative damage [53]. They stimulate Nod-like receptor (NLR) family and pyrin domain-containing 3 (NLRP3) caspase 1, IL-1 $\beta$ , and IL-18 [54]. The sensitivity of T-cells for ROS affects their development and function. For instance, TH17 cells participate in several inflammatory and autoimmunity diseases such as Encephalomyelitis (EAE) [55]. Controlled regulation of ROS level aborts EAE development. Any imbalance in ROS level engenders cytotoxicity and damage to DNA, protein, and lipids. These damages further trigger

apoptosis, inflammatory bowel disease, and autophagy [56].

### Organ failure

Prolonged oxidative stress can severely affect the functioning of organs and, in extreme conditions, kindle organ failure. ROS activate signaling through tumor necrosis factor (TNF- $\alpha$ ), responsible for liver failure. The activation of TNF- $\alpha$  downstream molecules, JNK, and cytochrome-c results in necrotic cell death. In parallel, Ferritin heavy chain (FHC) induces downstream NF- $\kappa$ b. This subsequently suppresses accumulation of ROS by iron sequestration, thereby inhibiting JNK signaling [57].

### Cancer development

In the development of cancer, ROS has a detrimental role. Oxidative stress, caused by an imbalance between ROS production and antioxidative defense mechanisms, promotes mutation in DNA, RNA, protein, and cell signaling activation. Moreover, an elevated level of ROS has been observed in most cancers as they manipulate the cancer microenvironment, upregulate metabolic activity, cell cycle progression (accelerate proliferation), interrupt cell cycle regulation, apoptosis, and angiogenesis [58]. An oxidizing agent and disinfectant, hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), causes hydroxylation of DNA via the Fenton reaction (in this reaction, metals like Fe, Cu use H<sub>2</sub>O<sub>2</sub> as a catalyst for accepting or donating electrons). The hydroxyl radicals thus produced damage DNA by generating lesions, single- and double-stranded breaks, and suppressing DNA repair machinery.

As a consequence, these changes provoke mutation and cancerous growth. ROS also affect the protein functioning through oxidative modification, thus resulting in altering amino acids' sequence and elevating the chances of protein carbonylation, nitration of tyrosine and phenylalanine residues, and protein degradation. The oxidation of amino acids and enzymes can influence the function of proteins; for instance, the enzymatic activity of DNA repair enzyme, the fidelity of DNA polymerase, replication/transcription activity induce the onset of cancer. Besides DNA, ROS also affects lipids as they beget peroxidation when interacting with poly-saturated and poly-unsaturated fatty acids. Some studies suggest that lipid peroxidation is also responsible for tumorigenesis. For instance, presence of thiobarbituric acid in the serum of colorectal cancer patients indicates a high level of lipid peroxidation.

### Cancer progression

Several types of cancer are triggered by ROS, such as hydrogen peroxide, superoxide, etc., which enhance cell proliferation. Manganese Superoxide Dismutase (MnSOD) enzyme acts as mitochondrial ROS switch and regulates cell proliferation and quiescence. The decreased level of MnSOD stimulates cell proliferation, while on the other hand, its elevated level promotes quiescence [59]. In case of breast cancer, translocation of estrogen to the mitochondria has been reported to induce oxidative stress affecting Erk1/2 MAP signalling and activation of cyclic AMP response element-binding protein (CREB). This results in excessive cell proliferation. Some studies have suggested a pivotal role of ROS in tumor cell-cycle regulation, as ROS control the expression of cyclins, such as cyclin B2, D3, E1, and E2. In addition, ROS upregulates the mRNA level of these cyclins during G1- to S-phase transition. Some carcinogenic substances, such as sodium arsenite and benzopyrene quinines, stimulate ROS synthesis and adversely affect growth factor signaling to induce cell proliferation. Ataxia-telangiectasia mutated (ATM) protein, involved in cell cycle regulation, is also influenced by ROS. The absence of ATM heralds cancer proliferation.

### Cancer metastasis and angiogenesis

After tumor establishment, cells start migration from the primary site and invade distant secondary organs through metastasis [60, 61]. It is a multistep, complex process involving many transcription factors, such as NF- $\kappa$ B, ETS proto-oncogene 1 transcription factor (ETS-1), AP-1, Twist, zinc finger E-box-binding homeobox (Zeb); metalloproteins, such as MMP-2, MMP-9; and chemokines such as TGF- $\beta$ . The leading cause of metastasis is the epithelial-mesenchymal transition (EMT), where epithelial cells lose contact inhibition and acquire mobility and penetrance. Several studies have suggested that ROS play a role in EMT [62]. Activation of cell migration and invasion is regulated by the Urokinase-type plasminogen activator and MMP-9, which are activated by TGF-1 and NADPH oxidase 4 (NOX-4) [63]. All these factors are shown to be triggered by ROS. Mitochondrial Ca<sup>2+</sup> also plays a pivotal role in the onset of metastasis; the expression of mitochondrial calcium uniporter regulator 1 (MCUR1) is increased during hepatocellular carcinoma, resulting in EMT of tumour cells by ROS/Notch/Nrf 2 signalling pathway. Due to critical involvement of MCUR1 in hepatocellular carcinoma, it is a prime target during treatment of such cancer. According to Aydin and his colleagues, NOX-2 influences ROS-mediated metastasis by downregulating NK cells, and NOX-2 inhibition can restore IFN dependent clearance of myeloma cells by NK cells. Vimentin is a type III intermediate filament protein

that is expressed in mesenchymal cells [64]. Oxidative stress caused by HIF-1 regulates unnecessary gene transcription during cancer cell progression, EMT, and metastasis. Inhibition of vimentin by RNAi is used in the treatment of various cancers.

Angiogenesis is a process of establishment of new blood vessels. These new blood vessels accelerate the progression and spread of cancer as they supply oxygen and cellular nutrients required by cancerous cells [65]. Vascular epithelial growth factor (VEGF) and hypoxia elevate intracellular ROS in the cellular niche, resulting in new blood vessels development. HIF-1 initiates VEGF expression during hypoxia, but suppressing endogenous ROS levels reduces HIF-1 and VEGF expression (Hypoxia-Induced Angiogenesis). ROS stimulates MMP1 secretion from tumor cells, which promotes blood vessel spread in the tumor cell's center. Moreover, transitions of MMP-1, MMP-2, and MMP-9 are associated with elevation of the endogenous level of ROS, which promotes capillaries formation, vasodilation, and increased blood supply through activation of heme oxygenase-1 (induces nitric oxide synthesis) in tumour cells [66].

## Anti-ROS therapeutics

Various ROS inhibitors, such as ascorbic acid,  $\alpha$ -tocopherol, and  $\beta$ -carotene, have been studied for their beneficial effects in mitigating ROS-induced damage. The mechanisms of ROS suppression are different from each other; for example, vitamin C aids in reversing endothelial dysfunction in patients with coronary artery disease [67]. While

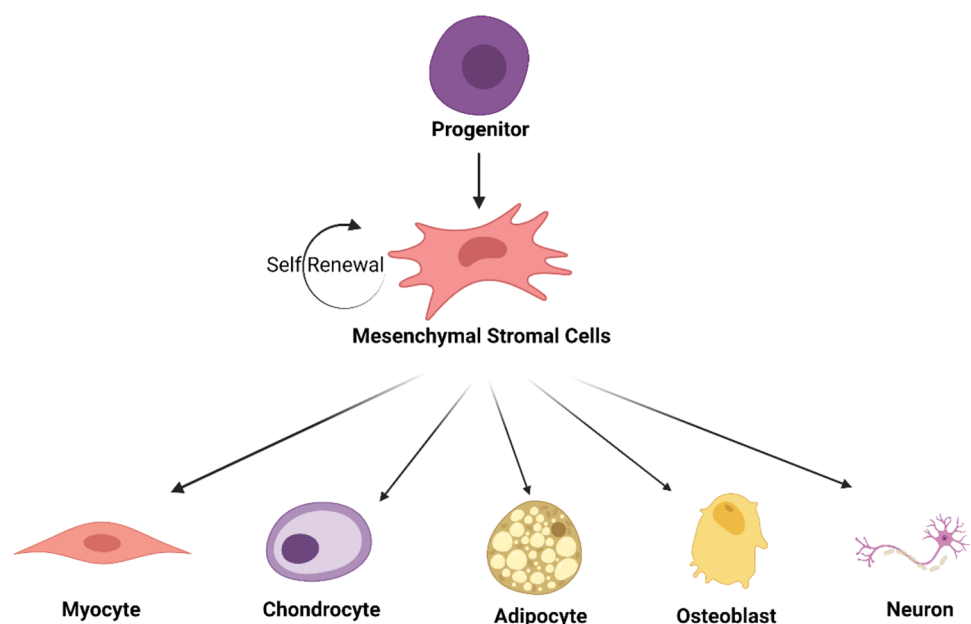
$\alpha$ -tocopherol positively reacts with lipid radicals to protect the cell membrane, whereas  $\beta$ -carotene prevents oxidative cellular damage by converting itself into bioactive retinol form.

## Mesenchymal stromal cells (MSCs)

MSCs are non-hematopoietic, multipotent and a heterogeneous group of stromal stem cells isolated from various sources, including bone marrow, adipose tissue, umbilical cord matrix, tendon, lung, and periosteum [68, 69]. These cells can potentially differentiate into mesodermal lineages, such as adipocytes, chondrocytes, osteocytes, ectodermal and endodermal lineages [70].

There are three golden standards for MSCs characterization as defined by the International Society of cellular therapy [71]. First, MSCs are adherent cells having a plastic-adherent nature. These cells attach to a culture plate in standard culture conditions. Second, a flow cytometry study revealed that more than 95% MSCs population express CD105, CD73, and CD90 cell surface antigens, and they were originally recognized by the mAb SH2, mAb SH3, and SH4 and Thy-1, respectively. Furthermore, MSCs lack the expression of CD45 (leukocyte marker), CD34 (hematopoietic progenitors and endothelial cells), CD14 (monocytes marker), or CD11b (macrophages marker), CD79a or CD19 (B cells antigen), and HLA class II antigen. Third and last criteria, one special property that is uniquely present in MSCs, the ability to differentiate into osteoblasts (Fig. 2) (identified using Alizarin Red or von Kossa staining), adipocytes (identified using Oil Red O), and chondroblasts

**Fig. 2** Differentiation of MSCs into lineages, such as myocyte, chondrocyte, adipocyte, osteoblast, and neurons





(identified using staining with Alcian blue) under the standard condition *in vitro*.

The differentiation of progenitor MSCs into a specific lineage is mediated by both intrinsic and extrinsic factors present in their niche. These factors also control molecular and cellular patterns of MSCs-derived lineages. MSCs readily interact with the immune system (both innate and adaptive immune systems) and mediate the functioning of immune response; for instance, NK cell cytotoxicity, antigen presentation by dendritic cells (DCs), and activation of neutrophils are regulated by MSCs. These cells also promote peripheral tolerance by migration to an inflammatory site and release pro-inflammatory cytokines, resulting in enhanced survival of damaged cells [72].

### Multipotentiality of MSCs

#### (a) Differentiation and regenerative potential

MSCs possess self-renewal and differentiation capabilities [73]. Some studies have suggested that MSCs can also differentiate into ectodermal and endodermal lineages, including hepatocytes and neurons. This is beyond their conventional mesodermal speciation due to limited power of differentiation. There is little information available on MSCs differentiation *in vivo* owing to lack of specific MSCs markers. MSCs engraftment and trans-differentiation *in vivo* into bone, cartilage, myocardium, neuron, and hepatic tissues cannot be identified, this requires a better understanding of MSCs markers [73, 74].

#### (b) Immune modulation

MSCs are known to display potent immunosuppressive and anti-inflammatory effects when they interact with lymphocytes. These cells negatively regulate T cell, B cell, NK cell proliferation, cytokines production, and maturation of dendritic cells [75]. Importantly, MSCs can overcome all the complications associated with allogeneic rejection in human and animal models due to hypo-immunogenic properties as they do not express major histocompatibility complex type II (MHC-II) and other costimulatory molecules [76–78].

#### (c) Migratory capacity

The migratory potential of MSCs plays a significant role in reducing the ROS-induced inflammation as these cells migrate to the inflammatory site with the help of chemokines and cell surface receptors {stromal cell-derived factor 1 (SDF-1), C–X–C chemokine receptor type 4 (CXCR4), stem cell factor, hepatocyte growth factors (HGF), vascular endothelial growth factor (VEGF)/VEGF receptor,

platelet-derived growth factor (PDGF), monocyte chemoattractant protein-1 (MCP-1), and C–C chemokine receptor type 2} [79].

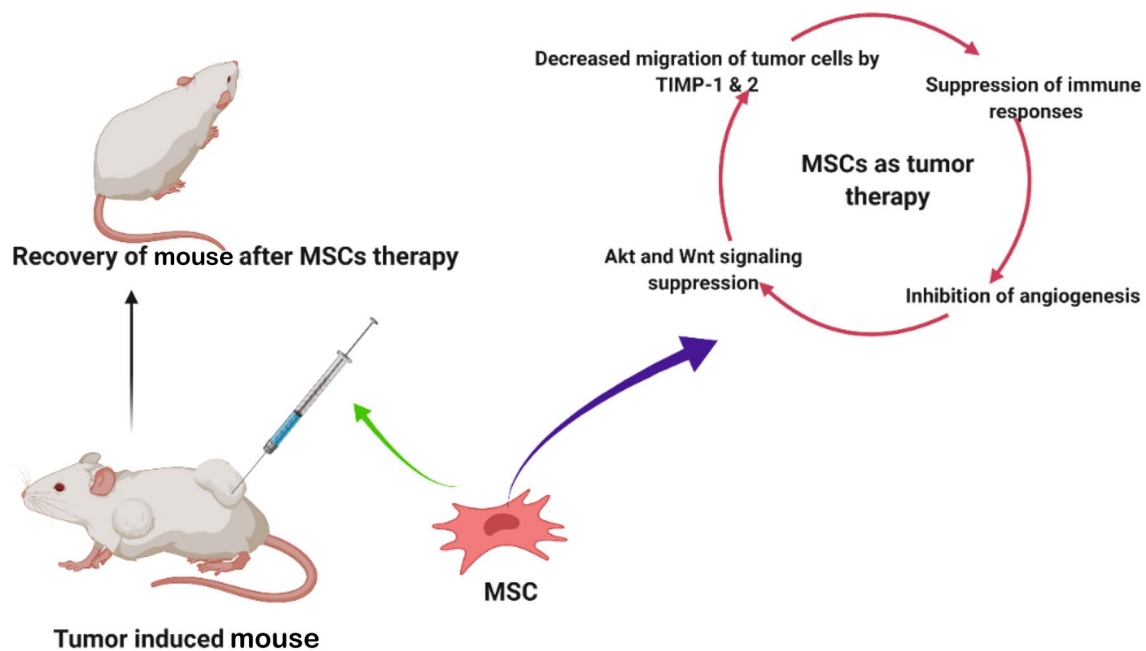
The tumor microenvironment constantly produces many cytokines, chemokines, and other adhesion molecules as inflammatory mediators, which serve as chemoattractants for MSCs at the site of inflammation [80]. For example, the chemokine receptor pair, SDF-1, and CXCR4 act as an important mediator of stem cell recruitment, especially MSCs at the tumor sites [81]. The tumor microenvironment arouses hypoxic conditions and upregulates hypoxia-induced transcription factor, HIF-1 $\alpha$ . This protein activates proangiogenic molecules, such as vascular endothelial growth factors (VEGF), fibroblast growth factors (FGF-2), macrophage migratory inhibitor factors, tumour necrosis factors, and numerous proinflammatory cytokines. Simultaneously inducing MCP-1 chemokine, involved in migration of MSCs toward tumor [25].

In the tumor niche, MSCs interact directly or indirectly with tumor cells and affect tumor development. In indirect mode, MSCs secrete various inhibitory growth factors and cytokines as paracrine factors, which act on inflammatory cells (cancer) and disrupt cellular proliferation, cell survival, angiogenesis, etc. In direct mode, MSCs interact with tumor cells and exert their therapeutic effects through inhibiting proliferation-related signaling pathways, such as PI3K/AKT, cell cycle, etc. [82, 83] (Fig. 3).

### Thepaetics mechanism of MSCs and HSCs

Most stem cells prefer anaerobic glycolysis over oxidative phosphorylation to maintain a low ROS level in the cell [84]. During oxidative phosphorylation, the rate of ROS generation is increased due to continuous electron transport through various metabolic cycles. MSCs are ideal contender for cell-based therapy for tissue injury [85]. They regulate various kinases, such as mitogen-activated protein kinases (MAPKs), c-Jun N-terminal kinases (JNKs), p38, and extracellular signal-regulated kinases (ERKs), that positively accelerate ROS synthesis. In the elevated ROS environment, MSCs differentiate themselves into three lineages, namely adipocyte, osteocyte, and chondrocyte. Under pathological conditions, production of ROS is increased [39]. The regulatory mechanism of ROS in stem cells is governed by ATM (the gene responsible for ataxia-telangiectasia). After serial transplantation, an increased level of ROS in ATM mutation was observed due to deregulation of major antioxidative systems and activation of p38 MAPK, resulting in depletion of normal HSCs.

Furthermore, this decreased reconstitution capacity was normalized by treatment with an antioxidant. These studies suggest ROS's role in the impaired function of ATM-deficient HSCs. Some evidence has also suggested the



**Fig. 3** Anti-tumorogenic effect of MSCs

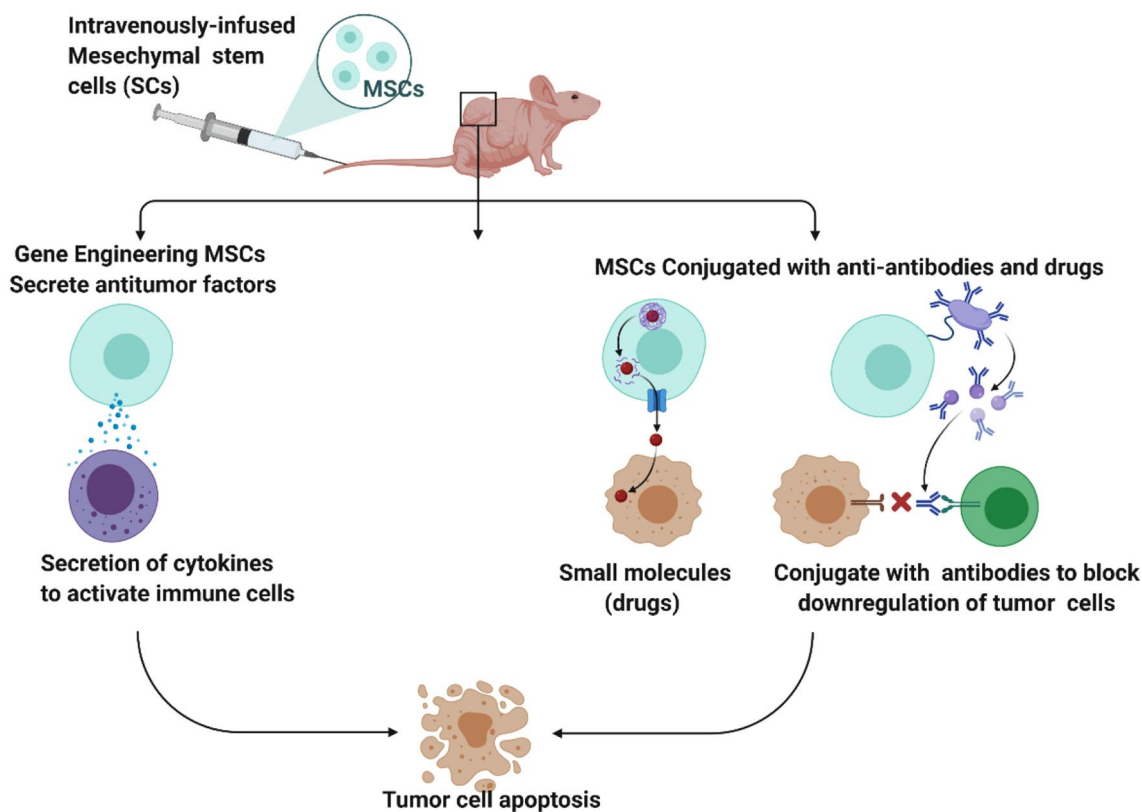
involvement of ROS in the regulation of forkhead homeobox type O (FoxO) transcription factors, promotion of glycolysis, and autophagy [86]. These molecules serve as key regulators of tumour suppression through cell-cycle arrest and metabolism regulation of tumour cells. Currently, available therapeutics applications of MSCs in several diseases are listed in (Table 1).

### Role of MSCs-derived secretome

ROS stimulate a cascade of processes, including inflammation, angiogenesis, programmed cell death (Fig. 4), autophagy, and crosstalk of activated signal transduction pathways [87]. These processes participate in generating proinflammatory cytokines, such as interleukin-1 $\alpha$  (IL-1 $\alpha$ ), IL-1 $\beta$ , IL-6, and profibrogenic cytokines, such

**Table 1** Application of MSCs in various complications

S. no.	Diseases	Role of MSCs therapy
1	Bone and cartilage diseases	Osteogenesis imperfections and other bone disorders have reported a positive effect of MSCs-based therapy [94]
2	BMT and GVHD	Graft versus host disease (GVHD) treatment have yielded promising result, but the therapeutic efficacy of MSCs is less clear [94]
3	Cardiovascular diseases	MSCs-based therapy has shown a positive role in improving cardiac repair [95]
4	Autoimmune diseases	The systemic lupus erythematosus (SLE) is an autoimmune inflammatory disease where the positive role of MSCs therapy has been reported. SLE involves multiorgans, such as kidney, brain, lung, and hematopoietic systems [96]
5	Liver diseases	The immunomodulatory properties of MSCs have been used in the treatment of liver diseases In a phase I trial, four patients suffering from end-stage liver cirrhosis were treated with autologous MSCs resulted in the improvement of liver function I to II clinical trial in eight patients with last-stage liver diseases received autologous MSCs. It improved liver functions [97]
6	Cancer	MSCs inhibit tumor growth and angiogenesis as they may contain regulatory mechanism responsible for growth and angiogenesis of tumour cells Various preclinical gene-modified MSCs have been used to treat cancer [98, 99]
7	COVID19	MSCs can increase the lymphocyte count and regulatory DCs to raise their antiviral characteristic, resulting in the decreased level of C-reactive protein and pro-inflammatory cytokines (IL-6, TNF $\alpha$ , IL-8, and so on), which are the main markers of inflammation [100]



**Fig. 4** Anti-viral therapy of mesenchymal stromal cells (MSCs)

as transforming growth factor  $\beta 1$  (TGF- $\beta 1$ ), etc. [88, 89]. MSCs secrete paracrine cytokines, superoxide dismutases, or soluble inflammatory cytokine receptors, which activate anti-inflammatory and anti-fibrotic signalling or neutralizing proinflammatory and profibrotic cytokines [90]. All these activities may assist in reducing ROS-induced damage. The sT $\beta$ R protein down-regulates expression of TNF- $\alpha$ , IFN- $\gamma$ , IL-6, and TGF- $\beta$  (Fig. 5). While the MSCs-derived HGF inhibits TNF- $\alpha$ , IFN- $\gamma$ , IL-6, TGF- $\beta$ , and myofibroblasts in ROS-damaged cells [91]. Another factor, PGE2, increases anti-inflammatory IL-10. Whereas SOD helps in scavenging ROS and subsequently decreases the amount of ROS-induced damage [92]. A family member of SOD family, SOD3, also reduces inflammatory cell infiltration and oxidative stress in cells. IL1RN, like others, also suppresses the inflammation by inhibiting the IL-1 $\alpha$ , IL-1 $\beta$ , and TNF- $\alpha$  and thus prevents cellular damage (Fig. 5) [93].

### Clinical trials of MSCs for therapeutics

A large number of clinical trials were performed emphasizing the therapeutic role of MSCs in various pathologies, for example, heart disease, liver failure, neurodegeneration, and cancers [79, 101–103]. Many MSCs-based clinical trials are also registered to find their role in the treatment of solid

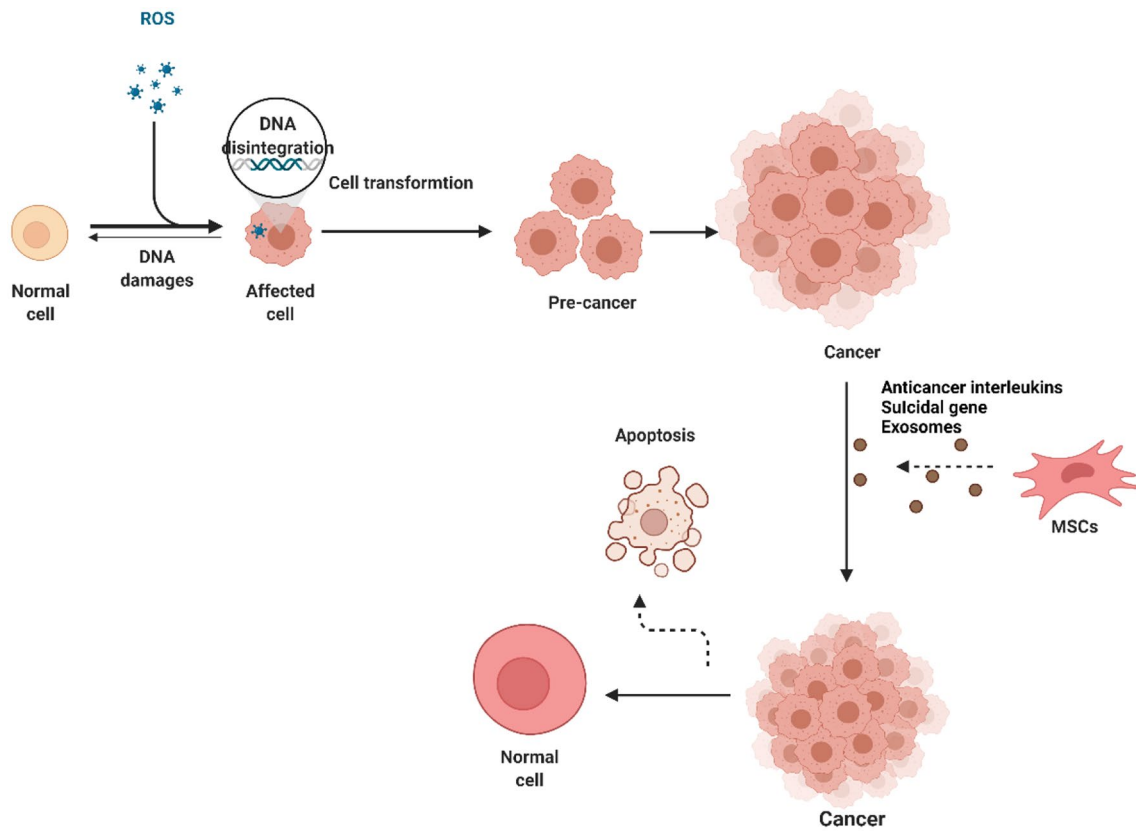
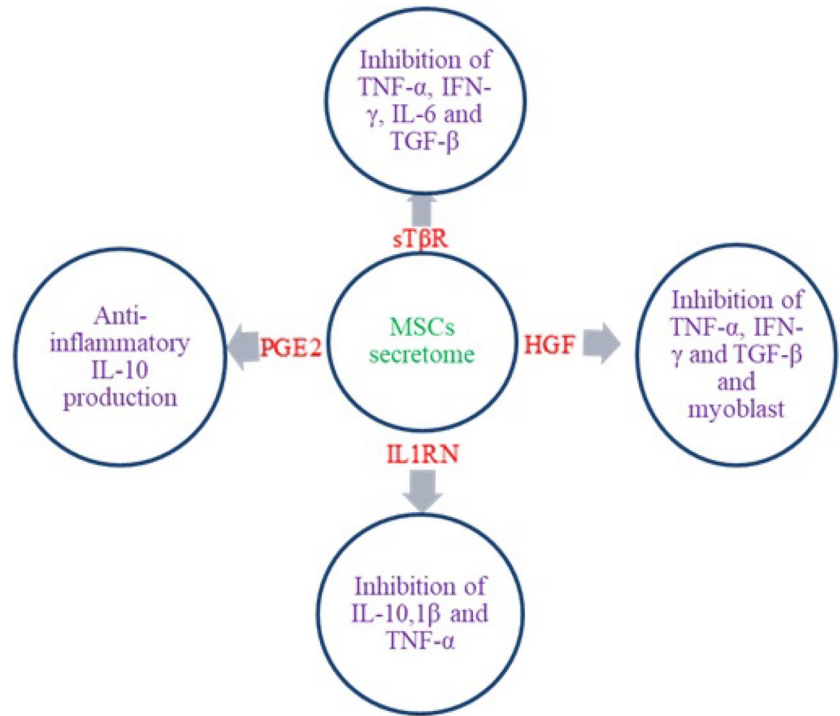
tumors. For the first time, engineered MSCs-based treatment was performed against gastrointestinal tumors. In this study (phase I/II stage), researchers used MSCs for the delivery of herpes simplex virus-thymidine kinase (HSV-TK) under the control of the C–C motif chemokine Ligand-5 (CCL5) promoter. Recently, a clinical trial was registered to evaluate the safety and highest tolerable dose of human MSCs expressing interferon- $\beta$  that can be administered to patients undergoing treatment for the last stage of ovarian cancer. Like MSCs, secreted exosomes derived from MSCs also have a potent therapeutic potential against targeted tumour therapy (Fig. 6) [104, 105]. Meanwhile, to accelerate and transform preclinical research to clinical application, the research fraternity needs to emphasize the efficacy and safety of these therapeutic approaches provided by preclinical studies [74, 106]. The current clinical trials of MSCs are listed in Table 2.

### MSCs as a novel cell-based drug

The application of medication can have adverse effects, whether a prescription drug or an alternative that includes herbals or vitamin supplementation provided through external sources. The novel idea is that the application of cell-based therapy against diseases like cancer, Alzheimer's,



**Fig. 5** Role of MSCs-derived secretome in ROS-induced damages



**Fig. 6** Clinical application of genetically modified MSCs as anti-tumorigenic

**Table 2** List of clinical trials on stem cells/MSCs in various pathologies caused by ROS [107]

Clinical trial number	Title	Study phase	Status	Responsible party	Country
NCT03106662	MSCs infusion in a haploidentical patient with haematological malignancies	Phase 3	Completed	OnderArslan, Ankara University	Turkey
NCT02530047	MSCs for ovarian cancer	Phase 1	Completed	University of Texas, MD Anderson Cancer Center	Texas, United States
NCT03096782	Umbilical cord blood transplant with added sugar and chemotherapy and radiation therapy in treating patients with leukaemia or lymphoma	Phase 2	Recruiting	M.D. Anderson Cancer Center	Texas, United States
NCT04074408	Intracavitary injection of hUMSCs in acute basal ganglia hematoma after stereotactic aspiration	Phase 2	Recruiting	Second affiliated hospital, School of Medicine	Zhejiang, China
NCT02068794	MV-NIS infected MSCs in treating patients with recurrent ovarian cancer	Phase 1/ Phase 2	Recruiting	Mayo Clinic	Rochester, Minnesota, United States
NCT02804945	MSCs for treatment of acute respiratory distress syndrome (ARD) in patients with malignancies	Phase 1	Completed	M.D. Anderson Cancer Center	Texas, United States
NCT02181478	Intra-osseous co-transplant of Cord Blood and MSCs	Early Phase 1	Active, not recruiting	Marcos de Lima, Case Comprehensive Cancer Center	Ohio, United States
NCT00790413	Haploidentical stem cell transplantation in neuroblastoma	Early Phase 1	Active, not recruiting	JacekToporski, Lund University Hospital	Lund, Sweden

and aging could be a next-generation therapy in the field of drug development. Thus far, MSCs-based therapy has been reported in the diseases mentioned above. Conventional cancer treatment involves the use of chemotherapeutic drugs, which are designed to suppress rapidly growing cancerous cells; however, long-term use of chemotherapy drugs has resulted in resistance to the therapy for which they were used. Chemotherapy is also known to cause damage to healthy cells, specifically the dividing cells in the bone marrow and the gut. Several adverse effects have been observed depending on the nature of the drug. For instance, alkylating agents are known to damage DNA to prevent cancerous cells from dividing directly but at the same time are capable of inducing long term damage to the bone marrow and eventually resulting in leukaemia [108]. MSCs may serve as a potential cell-based therapy for diseases like cancer in a personalized manner and can be effectively used as delivery vehicles to carry therapeutic factors. Furthermore, finding a cure for neurodegenerative disease such as Alzheimer's has been a real challenge because they are not only difficult to diagnose, but drug delivery to the brain is also an intricate process. MSCs-based therapy can reinforce nerve growth

by reconstructing the neural microenvironment and reducing the factors involved in damaging the nerve structure, thereby providing a treatment [109]. Another application of MSCs-based therapy has been observed for frailty, although it is known that certain diets can improve the symptoms of frailty. There is currently no treatment available to prevent the frailty syndrome. MSCs can be drawn to the injury site and reduce inflammation while promoting cellular repair to improve frailty conditions. [110].

### Complications and controversies on MSCs therapies

MSCs have tremendous potential for targeted cellular therapy against several chronic inflammatory diseases [101]. The ongoing application of MSCs in clinical trials suggests that these cells can target therapy in several types of cancers. However, recent research on anti-tumour properties of MSCs still revolves around several controversies. Researchers have differing perspectives on MSCs-targeted cell therapy. Some studies have demonstrated proliferative effects of MSCs, while others have demonstrated an inhibitory role in tumour progression. For example, MSCs

have a direct tumoricidal impact on lung and liver cancer cells, while proliferation and metastasis affects breast and colon cancer [111]. Because most MSCs-based clinical trials are still in their infancy, the efficacy and efficiency of these therapies may improve further with refinement of the route of delivery, dosage, and a better understanding of the biological action [112]. Initial successful results of MSCs-based therapy in animal models may create complications in a patient due to various factors that are not accounted for in animal models. It has been observed that relatively small lesions generated in CNS of mice are easy to repair by MSCs in comparison to large lesions in humans. It was also revealed that immune cells respond differently to MSCs-derived signals in human and animal models [113]. The safety and potential side-effects of MSCs infusion in humans need a better understanding before starting with MSCs therapy as the risk of infection needs to be assessed in case of MSCs treatment due to its suppressing immunosuppressive properties that increase the likelihood of tumor formation. Still, several ongoing clinical trials of MSCs have revealed minimal potential complications. However, treatment of chronic conditions requires multiple infusions of MSCs over a protracted period. In that case, the risk of adverse events may increase [102, 114].

## Conclusion

There are cases in which the appropriate increase in ROS level is associated with various diseases, such as cancer, neurodegeneration, kidney failure, etc. Stem cells, especially MSCs, have evolved various redox systems that protect them against ROS-induced oxidative stress. The fine-tuning between the cell cycle and redox status is an important mechanism that stem cells adopt during oxidative stress. FoxO is a transcription factor that controls the intrinsic ROS level. Like MSCs, some other stem cells, like HSCs also regulate ROS stress through ATM gene expression. The potential of cellular metabolism regulation by MSCs helps control ROS production, which decreases oxidative stress. The anti-tumor properties and anti-inflammatory potential of MSCs help regulate oxidative stress through the secretion of various soluble factors, such as sTβR, HGF, PGE2, SOD1, IL1RN, and SOD3. These soluble factors control the inflammatory reaction and help in the regulation of oxidative damages induced by ROS present in the cells. MSCs can also regulate MAPKs, JNKs, p38, and ERKs activated downstream of ROS in the cell. These properties may increase the likelihood of using MSCs as an alternative therapy to reduce oxidative stress.

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## Declarations

**Conflict of interest** We have no conflict of interest.

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