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Review

Targeting p53-p21 signaling to enhance mesenchymal stem cell regenerative potential

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ABSTRACT

Mesenchymal stem cells (MSCs) are properties of self-renewal and differentiation potentials and thus are very appealing to regenerative medicine. Nevertheless, their therapeutic potential is frequently constrained by senescence, limited proliferation, and stress-induced apoptosis. The key role of the p53−p21 biology in MSC biology resides in safeguarding genomic stability while promoting senescence and limiting regenerative capacity upon over-activation demonstrated. This pathway is a key point for improving MSC function and exploiting the inherent limitations. Recent advances indicate that senescence can be delayed by targeting the p53-p21 signaling and improved MSC proliferation and differentiation capacity. PFT-α pharmacological agents transiently inhibit p53 from increasing proliferation and lineage-specific differentiation, while antioxidants such as hydrogen-rich saline and epigallocatechin 3 gallate (EGCG) suppress oxidative stress and attenuate p53 p21 signaling. Genetic tools like CRISPR-Cas9 and RNA interference also precisely modulate TP53 and CDKN1A expression to optimize MSC functionality. The interplay of p53-p21 with pathways like Wnt/β-catenin and MAPK further highlights opportunities for combinatorial therapies to enhance MSC resilience and regenerative outcomes. This review aims to offer a holistic view of how p53−p21 targeting can further the regenerative potential of MSCs, resolving senescence, proliferation, and stress resilience towards advanced therapeutics built on MSCs.

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1. Introduction

Among other commonly used cells, MSCs are multipotent stromal cells capable of differentiating into different cell types, including osteoblasts, adipocytes, and chondrocytes, and it is imperative in regenerative medicine [1]. Due to their unique properties (self-renewal, immunomodulation, tissue repair), MSCs have been identified as promising candidates for treating degenerative diseases, injuries, and immunomodulation-related disorders [2]. Nevertheless, their enormous potential therapeutic effect is hampered by several critical challenges associated with the senescent, limited proliferative potential, and environmental stress sensitivity of these cells [3]. The senescence that limits MSC-based therapy typically occurs during in vitro expansion and is characterized by reduced proliferation, poorly differentiated cells, and upregulation of senescence markers such as p53, p21, and β galactosidase [4]. The presence of senescent MSCs reduces their regenerative capacity and secretes proinflammatory cytokines, which aggravate tissue damage [5]. Functional impairment of MSCs occurs through oxidative stress-induced senescence by pathways including the SIRT1/p53/p21 axis and can be reversed by antioxidants [6]. In addition, the culture of MSC for a long duration leads to a reduction in MSC proliferative capacity, which is undesirable in large-scale expansion needed for clinical applications [7]. MSC dysfunction is exacerbated by environmental stressors, which induce cell cycle arrest, apoptosis, and senescence through the activation of pathways that pertain to these responses [8]. It can also prevent acetyl-p53 and p21 expression, preserve MSC viability, and enhance therapeutic capabilities by reducing oxidative stress [9]. As inflammatory stress adds insult to injury, MSC function is further disrupted through activation of pathways like TLR4/NF-κB that drive senescence through p53 p21 dependent pathways [10]. These challenges suggest that immunosuppression-linked senescence and stress pathways have greater potential for rather than hinder the therapeutic potential of MSCs [11].

MSC biology depends on the p53-p21 signaling pathway functioning as both a protector and a barrier [12]. p53 is known as the guardian of the genome, and p21 as its downstream effector, both mediate cell cycle arrest in response to stress, DNA damage, and oncogenic signals to prevent the propagation of damaged cells [13]. This pathway helps maintain genomic stability and attenuate the risk of tumorigenesis, but activation of this pathway leads to senescence, apoptosis, and decreased repair capacity [14]. Transient inhibition of p53 can improve MSC proliferation and enhance their differentiation to specific lineages, providing a novel means of improving therapeutic outcomes [15]. On the other hand, the therapeutic value of activating p53-p21 signaling is presented in some cancers, such as apoptosis and cell cycle arrest, to control tumor progression [16]. This dual role highlights the importance of pathway precision modulation for clinical applications [17]. New avenues for modulating p53-p21 signalling through genetic and pharmacological tools have been opened by advances in genetic and pharmacological tools [18]. CRISPR Cas9-based gene editing technologies now permit finely tuned modulation of TP53 and CDKN1A expression, allowing researchers to tailor the response of MSCs [19]. RNA interference (RNAi) and antisense oligonucleotides (ASOs) have also been used to modulate p53 and p21 expression, reduce stress responses, and improve MSC viability [20]. RNAi targeting ribosomal stress regulators stabilize p53 and induce senescence, highlighting the interconnected nature of p53 regulation and cellular homeostasis [21]. These approaches offer precise methods to address senescence and stress induced apoptosis in MSCs [22].

The efficacy of some pharmacological agents targeting p53−p21 signaling has been shown in MSC rejuvenation and cancer treatment [23]. Small molecule suppression of p53 delays senescence and increases MSC proliferation [24]. Oxidative stress, which decreases antioxidant levels and increases p53-p21 signalling, impairs MSC functionality and is corrected by downregulating p53-p21 signalling through antioxidants [25]. The versatility of pharmacological interventions is illustrated by the compounds, such as cholesterol, that reduce senescence by modulating autophagy and the ROS/p53/p21 axis [26]. Agents that downregulate p53-p21 or SASP factors diminish tumour-promoting behaviours and limit senescence associated with cancer progression in cancer therapy [27].

This review presents mechanisms of regulation of p53-p21 signaling and its implication in MSC biology. This review focuses on how targeted strategies, including genetic, pharmacological, and combinatorial approaches, highlight how the precise modulation of p53-p21 can overcome senescence, impaired proliferation, and stress-induced apoptosis.

2. Overview of p53-p21 signaling pathway

The p53-p21 signaling pathway is a central regulator of cell response to DNA and oxidative stress, essential for maintaining genomic stability and cellular fate [28]. The molecular safeguard

responds to DNA damage, oncogenic stress, and other cellular insults to eventually control cell cycle arrest, senescence, or apoptosis of damaged cells to stop the propagation of such cells [29]. This pathway is an essential area for further exploration of its MSC biology, and the potential regenerative implications and knowledge of molecular mechanisms and biological interactions of this pathway are required. The p53 tumor suppressor protein, a transcription factor activated by diverse stress signals, including DNA damage, oxidative stress, and oncogenic signals, acts at the heart of the p53-p21 pathway [30]. Although the molecular pathway leading to p53 activation following IR was elusive, upon its activation, p53 translocates to the nucleus, binds to the promoter regions of target genes, including CDKN1A that encodes the p21 protein, a key effector of p53 mediated responses [31]. p21 inhibits cyclin-CDK complexes, preventing cell cycle progression from the G1/S and G2/M checkpoints to allow time for DNA repair or, if DNA is irreparably damaged, senescence occurs [32]. The pathway also contains feedback mechanisms. For instance, p53 has a negative feedback loop through MDM2, a p53 target gene that promotes p53 degradation by ubiquitin-mediated degradation, constituting a tightly controlled regulatory loop [33]. It maintains that balance so cells can undergo the appropriate activity of p53, modulating the cell cycle arrest and apoptosis in physiological conditions [34].

DNA damage, repair, apoptosis, and senescence are associated intricately with the p53-p21 pathway [35]. Normally, p53 is p21 positive and is activated by sensors such as ATM and ATR on DNA damage, stopping the cell's cycle with p21 through a cascade [36]. If repair mechanisms fail, p53 shifts from stimulating cell cycle arrest to activating pro-apoptotic genes BAX and PUMA, thereby promoting programmed cell death [37]. p53 has dual functionality to safeguard cellular integrity, highlighting the p53 [38]. Persistently activated p53 and p21 promote senescence in which p53 and p21 expression leads to irreversible cell cycle arrest and increased expression of the β galactosidase marker of senescence-associated β gal and secretion of inflammatory cytokines [39]. Senescence functions as an antiapoptotic tumor suppressor, yet senescence accumulation in MSCs during in vitro expansion reduces their regenerative function [40]. Consequently, the balance between cell survival, repair, and elimination is important to maintain cellular homeostasis [41].

The p53-p21 pathway is double-edged in MSC. On one hand, it shields MSCs from genomic instability and potential transformation by not allowing stalled DNA polymerases or other damaged cells to multiply [42]. However, over-activation of this pathway, especially in oxidative stress or prolonged culture, induces senescence and regenerative capacity decline [43]. Senescent MSCs have elevated p53 and p21, leading to reduced proliferation, impaired differentiation, and increased secretion of inflammatory factors [44]. The pathway also plays a role in the survival of MSC under stress [45]. p53 and p21 are inappropriately activated in many oxidative and/or inflammatory environments that can subsequently lead to the apoptotic death of transplanted MSCs [46]. This highlights the need for strategies to modulate the p53-p21 pathway to improve MSC resistance and functionality.

3. p53-p21 signaling and MSC function

3.1. Senescence and aging in MSCs

Due to MSC's self-renewing and differentiation capacities, these cells are invaluable for regenerative medicine [47]. However, senescence, an irreversible cell cycle arrest often caused by long culture or environmental stress, dramatically limits their therapeutic potential [48]. The process is reduced proliferation, impaired differentiation, and increased p53, p21, and β galactosidase [49]. Numerous interconnected drivers of senescence include oxidative stress, DNA damage, and chronic inflammation, which can activate the pathways of p53-p21 and p16-pRB, among others [50]. Moreover, these mechanisms impede MSC function and restrict the scalability and efficacy of MSCs in clinical applications [51]. To advance MSC-based therapies, it is necessary to understand and target these drivers [52]. Induction of DNA damage and activation of p53-p21 signalling are other major ways of MSC senescence being driven by oxidative stress [53]. In both a protecting and a barrier capacity, this pathway protects genomic stability and a barrier, invoking senescence in response to persistent stress [54]. Xiang et al. further illustrated this duality by showing that TRLs aggravate the senescence of MSCs through the SIRT1/p53/p21 axis. Here, we found that a combined increase in p53 and p21 from abnormal ROS accumulation and reduced SIRT1 expression impeded MSC proliferation as shown in Fig. 1. [55]. Similarly, Zhang et al. demonstrated that hydrogen-rich saline mitigates oxidative damage by reducing ROS and downregulating p53 and p21, thereby enhancing MSC proliferation and differentiation. This study underscores the potential of antioxidants to counteract stress-induced senescence and suggests that interventions targeting oxidative stress could provide a conceptual framework for delaying MSC ageing [56]. While oxidative stress is a key driver, chronic inflammation compounds MSC ageing through sustained activation of inflammatory signalling pathways, including TLR4/MyD88-NF-κB and p53-p21 [57]. Feng et al. demonstrated that repeated exposure of dental pulp stem cells (DPSCs) to lipopolysaccharide (LPS) triggered senescence by activating TLR4-mediated NF-κB and p53/p21 pathways. This inflammatory environment increased senescence markers and disrupted cellular morphology and differentiation potential [58].

MSC senescence also plays a pivotal role in the progression of autoimmune and haematological disorders, where senescence impairs immunomodulatory functions [59]. Gu et al. observed that bone marrow MSCs (BM-MSCs) from systemic lupus erythematosus (SLE) patients exhibited elevated p53 and p21 levels, leading to reduced proliferation and increased senescence [60]. Similarly, Fei et al. showed that p53/p21-induced senescence in BM-MSCs from myelodysplastic syndrome (MDS) patients impaired hematopoietic support, suggesting that targeting this pathway could improve MSC-based interventions for haematological disorders [61].

The complexity of MSC aging is further underscored by interactions between p53/p21 and other signalling pathways [62]. Zhang et al. revealed that hyperactivation of Wnt/β-catenin signalling exacerbates senescence in lupus-associated BM-MSCs, while β-catenin inhibitors reversed these effects and restored MSC proliferation [63]. Additionally, Deryabin et al. highlighted the crosstalk between the p53/p21 and MAPK pathways under oxidative stress. Their study showed that MAPK inhibition elevated p53/p21 levels, leading to senescence, whereas p53 inhibition enhanced MAPK activity [64]. Senescence within the tumor microenvironment (TME) further exemplifies the intricate role of MSCs in pathological contexts [65]. MSCs in the TME adopt a senescence-associated secretory phenotype (SASP), which promotes tumor progression, metastasis, and immune evasion [66]. Li et al. demonstrated that colorectal cancer-derived MSCs suppressed p53 expression in tumor cells via conditioned media, enhancing tumor cell proliferation and survival [67].

Emerging molecular regulators, such as miR-29c-3p and p300, provide additional avenues for therapeutic intervention [68]. Shang et al. showed that miR-29c-3p overexpression activated p53/p21 and p16 pathways, driving MSC senescence, while knockdown reversed these effects and enhanced proliferation [69]. Similarly, Li et al. identified p300 as a critical regulator of MSC ageing, with its reduced expression accelerating p53/p21 activation and

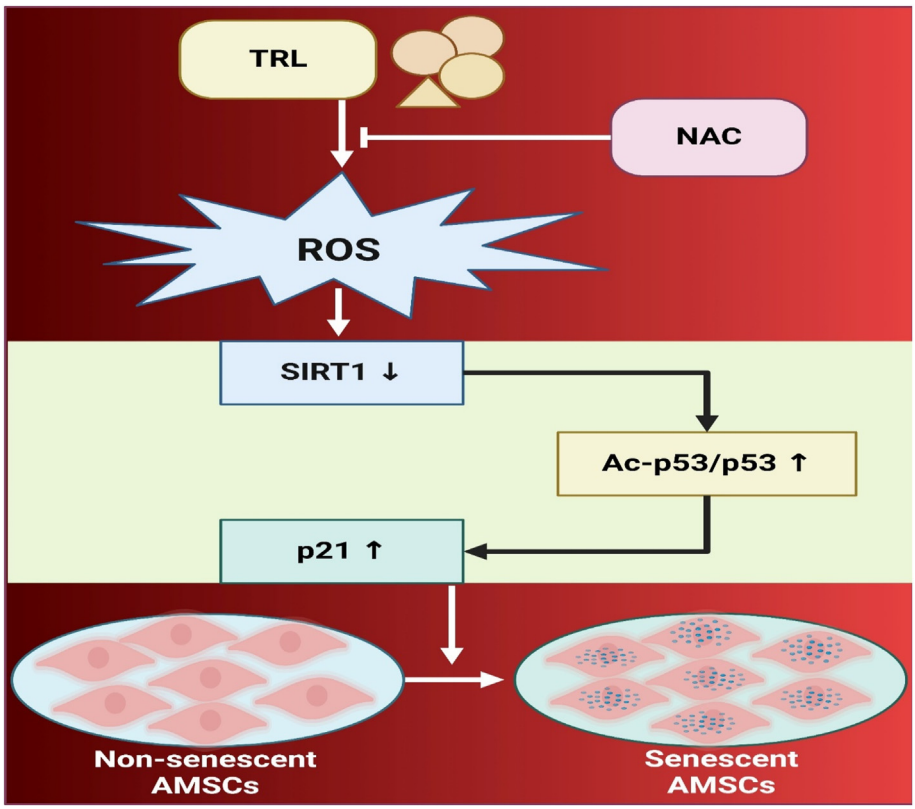

Fig. 1. Oxidative Stress-Induced Senescence: Role of ROS, SIRT1, and p53-p21 Pathway. This diagram illustrates the relationship between oxidative stress, cellular senescence, and the role of key molecular regulators. The central element, reactive oxygen species (ROS), is elevated due to triggers such as TRL (a stressor). Antioxidants like NAC (N-acetylcysteine) can inhibit ROS accumulation, mitigating its downstream effects. Elevated ROS levels lead to a decrease in SIRT1 activity, a critical regulator of cellular stress resistance. This reduction enhances the levels of Ac-p53/p53 (acetylated p53) and p21, two markers that promote cellular senescence.

senescence. These studies emphasize further exploring epigenetic and molecular regulators to develop precise therapeutic strategies for delaying MSC aging [70]. MSC senescence is propelled by the complex interplay between oxidative stress, chronic inflammation, and signalling with other pathways, representing major challenges for MSC therapeutic application. This is supported by expert analysis of the need for a multimodal approach to balance p53/p21 signaling through the modulation of antioxidants, anti-inflammatory strategies, and molecular regulators, improving MSC functionality and scalability. These insights further provide a conceptual framework for moving the field of MSC therapy forward in advancing underserved and underutilized patient populations and overcoming age-related barriers in clinical settings (Fig. 1).

3.2. Regulation of MSC proliferation and differentiation

MSCs are ideal for tissue repair, regeneration, and immune modulation because they can self-renew and differentiate into osteoblasts, chondrocytes, and adipocytes [71]. These processes are orchestrated by an intricate balance between genetic, molecular, and environmental factors with key pathways [72]. Transcription factors, as well as non-coding RNAs, regulate MSC behaviour. Still, external stimuli like mechanical stress, oxygen levels, and biochemical cues influence their plasticity, proliferation, and differentiation potential [73]. Impaired regenerative capacity, pathological conditions including fibrosis and cancer, and dysregulation of these processes can result from this dysregulation [74]. However, the mechanisms underlying MSC proliferation and their differentiation must be understood before optimizing their therapeutic applications [75]. The p53-p21 signaling pathway mediates the modulation of MSC proliferation and differentiation [76]. However, too much activation is detrimental to MSC function, while its activation is critical to maintaining genomic stability and blocking oncogenic MSC transformation [77].

Additionally, Yan et al. showed that p53 signalling inhibition promotes the differentiation of bone marrow mesenchymal stem cells (BM-MSCs) into cardiomyocyte-like cells. Their study demonstrated that p53 inhibition suppressed apoptosis, increased proliferation, and increased expression of both cardiomyocyte-specific markers, cTnI and CX-43. These findings provide implications for targeting the p53p21 pathway in cardiovascular regenerative medicine, where promoting lineage-specific differentiation is critical [78,79]. Similarly, Zhang et al. discovered that p53/p21 regulates Bmi-1 in the vasculogenic differentiation of DPSCs. The authors determined that p53 and p21 suppress endothelial differentiation by restricting the expression of endothelial markers and by preventing capillary formation, while Bmi-1 promotes self-renewal. A reciprocal interaction between p53/p21 and Bmi-1 was observed to underscore the complex tuning required to maximize MSC functionality for vascular regeneration [80,81].

MSC proliferation is vital for maintaining their regenerative potential and scalability in therapeutic applications [82,83]. However, environmental stressors and senescence can impair this process by disrupting key signaling pathways [84,85]. Lin et al. investigated the impact of palmitic acid methyl ester (PAME) on human bone marrow MSCs (hBM-MSCs), finding that PAME induced G2/M phase arrest via stabilization of p53, increased p21 expression, and reduced cyclin B1 and Cdk1 levels. Although

apoptosis and ROS levels remained unaffected, as shown in Fig. 2, the inhibition of MSC proliferation highlights the potential role of fatty acid metabolites in modulating MSC behaviour [86,87]. The p53-p21 pathway is also implicated in the anti-cancer effects of MSCs [88,89]. Byun et al. found that adipose tissue-derived MSCs (ASCs) inhibit HCC cell proliferation by activating the JAK/STAT1 pathway and increasing p53/p21 expression, with IFN-β as a key mediator. This suggests ASCs could be therapeutic agents in cancer treatment by exploiting the p53-p21 pathway's tumour-suppressive properties. However, the study highlights the minimal role of TRAIL in MSCs' anti-cancer activity, necessitating further investigation [90,91].

Beyond their roles in proliferation and differentiation, the p53-p21 axis also regulates cellular reprogramming [92]. Brosh et al. explored the role of p53 in mesenchymal-to-epithelial transition (MET) during somatic cell reprogramming, demonstrating that p53 restricts MET by inhibiting Klf4-mediated epithelial gene activation. The study identified p21-mediated suppression of *E*-cadherin and other epithelial markers as key mechanisms [93]. The control of MSC proliferation and differentiation is exercised through a tight control that requires both genomic stability and enhancement of therapeutic functionality. While the p53-p21 pathway is indispensable in surveillance against oncogenic transformation, its overactivation is a major obstacle to MSC plasticity. This pathway is effectively modulated through specific combinations of compounds. It offers a way to target it simultaneously with knowledge of how it interacts with other critical regulators, such as Bmi-1 and the JAK/STAT1 pathway, to advance MSC-based therapies (Fig. 2).

3.3. Stress response and apoptosis

Stress response and apoptosis are closely related cellular processes critical to maintaining homeostasis under adverse conditions to the cell, relieving the burden of damage and preserving cell viability [94,95]. Pathways like p53, the MAPK, and the unfolded protein response (UPR) are part of the stress response that helps counteract oxidative stress, DNA damage, and metabolic imbalances [96,97]. Through apoptosis, unsustainable stress induces the death of irreparably damaged cells to prevent ensuing harmful outcomes, such as inflammation or tumorigenesis [98]. Regulators, such as proapoptotic proteins (e.g., Bax and Bak) and antiapoptotic proteins (e.g., Bcl-2 and Bcl-xL), mediate the delicate equilibrium between cell survival and apoptosis [99,100]. By dysregulating such processes, these processes become critically dysregulated and compromise MSC's viability and therapeutic potential [101,102]. This molecular switch mediates the coordination of MSC stress responses. The p53 p21 pathway operates as a p53 p21 pathway to execute cell cycle arrest or apoptosis [103]. Under oxidative stress, p53 and MAPK signaling pathways regulate senescence and apoptosis in interplay [104,105]. Deryabin et al. demonstrated that MAPK suppression in human endometrium-derived MSCs (hMESCs) increased p53 phosphorylation, p21 expression, and Rb hypophosphorylation, promoting senescence. Conversely, p53 inhibition activated ERK1/2 signaling, highlighting a reciprocal regulatory relationship, as shown in Fig. 3 [64,106]. The impact of chemotherapeutic agents on MSC apoptosis further highlights the vulnerability of MSCs under stress [107,108]. Yang et al. investigated the effects of doxorubicin, a DNA-damaging agent, on bone marrow-derived MSCs (BMSCs). Doxorubicin increased ROS levels, depolarized mitochondrial membranes, and triggered apoptosis via activation of p38, JNK, and p53 pathways. Notably, inhibitors of p38 and JNK, but not ERK, mitigated apoptosis, suggesting specific therapeutic targets to preserve MSC viability during chemotherapeutic stress. Furthermore, doxorubicin reduced VEGF and IGF-1 secretion, impairing the regenerative potential of BMSCs [109,110].

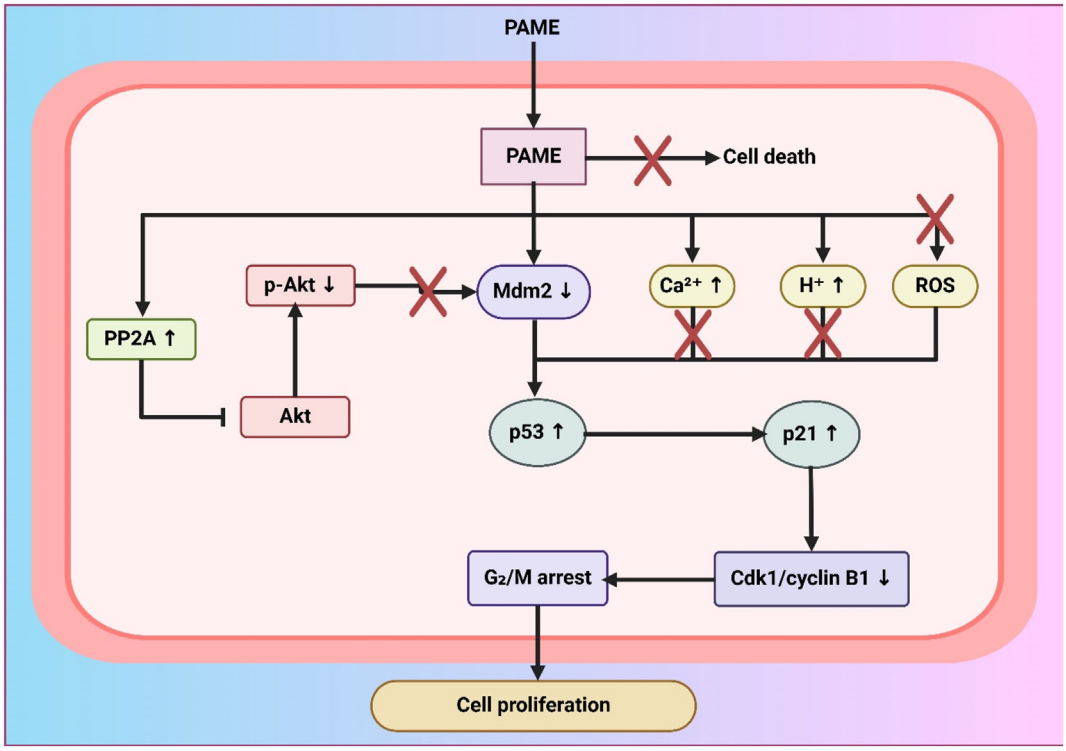

Fig. 2. PAME-Mediated p53 Activation and Cell Cycle Arrest in MSCs. This diagram illustrates the signalling pathways influenced by PAME and its effects on cell proliferation and survival. PAME activates PP2A, leading to a reduction in *p*-Akt levels, which inhibits Akt signalling. This suppression disrupts Mdm2 function, resulting in the stabilization and activation of p53. Elevated p53 levels increase p21 expression, leading to G2/M cell cycle arrest and downregulation of Cdk1/cyclin B1, thereby inhibiting cell proliferation. Additionally, PAME disrupts calcium (Ca^{2+}), hydrogen ion (H^{+}), and ROS homeostasis, further contributing to stress responses and cellular dysfunction.

The role of inflammation in MSC apoptosis and dysfunction has also been extensively studied [111,112]. Gu et al. examined bone marrow MSCs from non-obese diabetic (NOD) mice and found that elevated p21 and NF-κB-p65 levels were associated with reduced proliferation and increased apoptosis. Knockdown of p21 or inhibition of NF-κB-p65 improved MSC functionality, suggesting that the NF-κB-p53/p21 axis is a critical mediator of MSC dysfunction in inflammatory conditions such as type 1 diabetes mellitus [113,114]. The role of metabolic stress in MSC apoptosis further highlights the multifaceted regulation of stress responses [115]. Lin et al. investigated the effects of PAME on hBM-MSCs, finding that PAME stabilized p53 and increased p21 expression, leading to G2/M cell cycle arrest without inducing apoptosis. This study reveals the nuanced role of metabolic factors in modulating MSC proliferation and highlights the p53-p21 pathway as a key mediator of cellular responses to metabolic stress [86,116]. Stress response and apoptosis are critical to keeping MSC functionality, but dysregulated stress response and apoptosis can be detrimental. p53 p21 pathway emerges as the key regulator balancing cell cycle arrest, senescence, and apoptosis. Strategies that transiently modulate this pathway under oxidative, inflammatory, or metabolic stress promise enhancing MSC survival and functionality. Understanding the combined stress response and downstream mechanisms will be crucial to implementing these MSC-based therapies to optimize regenerative medicine (Fig. 3; Table 1).

4. Strategies to modulate p53-p21 signaling in MSCs

4.1. Gene editing technologies (CRISPR-Cas9) to regulate p53 or p21 expression

CRISPR-Cas9 and other gene editing technologies have now greatly advanced the capacity to precisely control the expression of fundamental regulatory genes, including TP53, encoding p53, and CDKN1A, coding for p21 [117,118]. Consequently, these genes are pivotal targets of therapeutic intervention in controlling cell cycle arrest, apoptosis, and senescence [119]. In MSCs, suppressing p53 or p21 expression using CRISPR-Cas9 delays senescence, enhances proliferation and improves regenerative potential [120]. On the other hand, this gene overexpression has therapeutic importance in suppressing tumours [121,122]. Reversible regulation that does not require permanent genetic alteration is made possible by advanced iterations of CRISPR, such as CRISPR activation (CRISPRa) and interference (CRISPRi) [123,124]. However, CRISPR technologies involve carefully considering off-target effects, genomic stability, and cellular stress responses to avoid off-target effects and promote the safety and efficacy of the applications [125,126]. One of the challenges in applying CRISPR-Cas9 is the potential activation of the p53-mediated DNA damage response [127]. Haapaniemi et al. observed that CRISPR-Cas9 genome editing induces a p53-dependent cell cycle arrest in human retinal pigment epithelial cells. This response decreases editing efficiency in cells with functional p53 pathways but can be mitigated by inhibiting p53, thereby enhancing homologous recombination [127,128]. Sun et al. developed a dynamic p21-mNeonGreen reporter system to evaluate TP53-p21 pathway activation during CRISPR-Cas9 editing. Their findings revealed that specific delivery methods, such as double-stranded oligodeoxynucleotides and adeno-associated viral vectors, induced higher p21 activation than single-stranded counterparts. Lentiviral vectors demonstrated lower activation, making them more suitable for editing sensitive cells like hematopoietic stem cells [129,130]. The potential for CRISPR-Cas9 to cause off-target effects and genomic instability is especially pronounced in stem cells [131]. Ihry et al. reported that Cas9-induced double-strand breaks (DSBs) triggered a p53-dependent toxic response in human pluripotent stem cells (hPSCs), leading to cell death and significantly reducing editing efficiency in wild-type p53 cells [132,133].

Large-scale analyses have further elucidated the role of p53 in CRISPR-Cas9-mediated gene editing [134]. McKinley et al. performed a comprehensive study of CRISPR/Cas9 knockout cell lines targeting cell-cycle genes, uncovering diverse phenotypes associated with p53-dependent responses to cell-cycle defects. Their findings demonstrated that p53 modulates cell cycle progression through distinct mechanisms depending on the specific defect, reinforcing its critical role in maintaining cellular integrity [135,136]. The expression of Cas9 itself can also impact p53 signalling, as highlighted by Enache et al. in human cancer cell lines. They demonstrated that Cas9 activity induced p53 pathway activation in TP53 wild-type cells at both mRNA and protein levels while increasing DNA repair activity. Cas9 expression favoured the selection of p53-inactivating mutations, which could reduce editing efficiency in wild-type cells [137,138]. Although CRISPR-Cas9 offers unprecedented precision in gene editing, its application for regulating p53 and p21 expression must dance between therapeutic objectives and safety concerns. Modulating the p53p21 pathway with CRISPR may delay senescence and improve regenerative capacity for MSC-based therapies. Still, this full potential must be carefully evaluated for the effects on off-target effects, cell toxicity and long-term genomic stability. Refining CRISPR delivery methods, including advanced tools such as CRISPRa and CRISPRi, along with context-specific approaches to minimize their risks and maximize the therapeutic potential of MSCs, need to be researched in the future.

4.2. RNA interference (RNAi) or antisense oligonucleotides

RNA interference (RNAi) and antisense oligonucleotides (ASOs) offer the ability to alter precisely p53 or p21 expression, which allows for determining the potential to regulate cellular functions, including proliferation, apoptosis, and senescence, as therapeutic tools [139]. RNAi is a method of reducing the synthesis of a target protein by using small interfering RNAs (siRNAs) or short hairpin RNAs (shRNAs) to degrade the corresponding target mRNA [140]. We used this strategy to inhibit the overactivation of p53 or p21, delaying senescence and rejuvenating MSC regenerative capacity [141,142]. However, unlike 'organic', ASOs are synthetic single-stranded nucleic acids that bind complementary mRNA sequences, either blocking translation or RNA degradation [143]. They are based on these mechanisms, and thus, ASOs can effectively suppress p53 or p21 expression, opening up therapeutic avenues for degenerative diseases and cancer [144,145]. However, delivery efficiency, off-target effects, and cellular stress responses have significant barriers yet to the first safe and effective clinical applications of delivery [146]. Recent demonstrations of the potential of RNAi-mediated regulation in p53 and p21 in cancer and senescence therapeutics [147]. RNAi targeting the HPV16 E7 oncogene in cervical cancer cells was investigated by Sima et al. They found that siRNA silencing of HPV16-E7 induced p53 and p21 levels and hypophosphorylation of Rb and resulted in apoptotic HPV-positive cells without affecting cells lacking HPV [148,149].

Beyond cancer, RNAi has been used to elucidate regulators of p53 in cellular homeostasis. Moudry et al. conducted a genome-wide RNAi screen to identify p53 regulators, revealing that WDR75 is critical in ribosome biogenesis. Depletion of WDR75 activated the RPL5/RPL11-dependent p53 stabilization pathway, resulting in p53 accumulation, impaired proliferation, and cellular senescence [150]. ASOs targeting p53 or p21 also provide compelling strategies for therapeutic intervention [151,152]. Wang et al. evaluated an antisense anti-MDM2 oligonucleotide in colon cancer

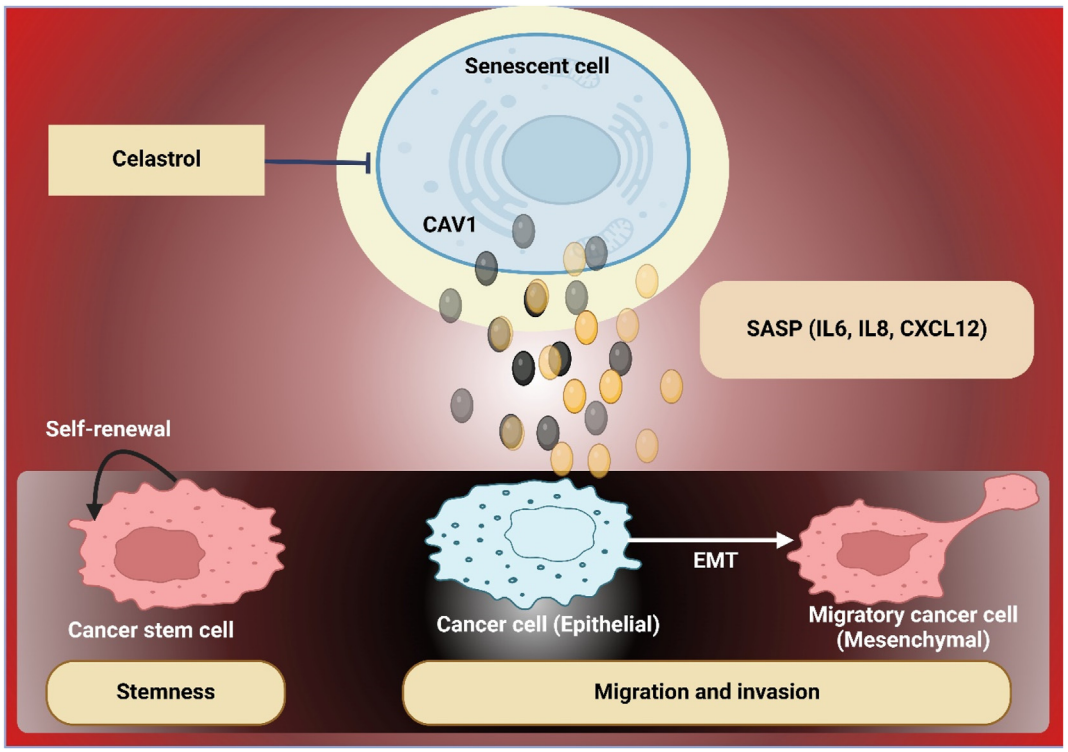

Fig. 3. Senescence-Associated Secretory Phenotype (SASP) in Cancer and the Inhibitory Role of Celastrol. This diagram illustrates the role of senescent cells and their secretory phenotype (SASP) in cancer progression, alongside the inhibitory effects of Celastrol. Senescent cells release SASP factors such as IL-6, IL-8, and CXCL12, which promote cancer stem cell (CSC) self-renewal and enhance stemness. SASP factors also drive epithelial-to-mesenchymal transition (EMT), converting epithelial cancer cells into migratory mesenchymal cells, thereby facilitating invasion and metastasis. Caveolin-1 (CAV1) is depicted as a key regulator within senescent cells, modulating SASP release. Celastrol inhibits CAV1, reducing SASP secretion and potentially mitigating CSC proliferation and EMT-driven migration and invasion.

models, demonstrating reduced tumour growth in both wild-type and mutant p53 cell lines. MDM2 inhibition synergized with chemotherapy agents like 5-fluorouracil, enhancing antitumor effects [153]. Further expanding the potential of ASOs, Zhang et al. investigated mixed-backbone oligonucleotides (MBOs) targeting MDM2. MBOs inhibited MDM2 expression dose-dependently, effectively reducing tumor growth in vitro and in vivo.

Additionally, MBOs enhanced the efficacy of chemotherapy and radiation therapy via both p53-dependent and p53-independent mechanisms. These findings underscore the utility of ASOs not only as direct therapeutic agents but also as chemosensitizers and radiosensitizers, broadening their scope of application in cancer treatment [154]. The versatility of ASOs extends beyond cancer, as demonstrated by Swiatkowska et al., who investigated the role of structural elements in the 5′-terminal region of p53 mRNA in regulating translation under stress. Using antisense oligomers, they identified critical hairpin motifs involved in internal ribosome entry site (IRES)-mediated translation of p53 and Δ40p53 isoforms, particularly under stress conditions. Their study highlights the potential of ASOs to modulate stress-induced translation of p53, providing insights into RNA-based regulation in cellular stress responses [155]. RNAi and ASOs are effective gene silencing tools for manipulating p53 and p21 but face delivery efficiency and stability challenges. Future technologies, like lipid nanoparticles and cell-specific targeting systems, may overcome these limitations and advance their use in regenerative medicine and cancer therapy. p53 and p21 are attractive therapeutic targets in cancer, degenerative diseases, and ageing-related conditions, which can be modifiable through RNAi and ASOs. Addressing delivery and specificity challenges could enable the advancement of MSC-based therapies and other targeted treatments despite the challenges in delivery and specificity.

4.3. Pharmacological modulation

The p53 and p21 expression can be pharmacologically modulated to optimize MSC functionality and therapeutic potential [156]. The p53–p21 axis has been modulated with small molecule inhibitors, antioxidants, and novel compounds to delay senescence and enhance stress resistance [157]. Transient suppression of p53 with compounds such as PFT-α promotes MSC proliferation and survival, while p53 activation by Nutlin-3 induces cell cycle arrest and apoptosis in cancer cells to show therapeutic benefits [158]. In addition, resveratrol and epigallocatechin-3-gallate (EGCG) help imbue indirect modulation by lowering levels of oxidative stress and priming the cell for resilience. These approaches show the potential of pharmacological intervention. Still, with precise dosage, timing, and context-dependent application, one must be aware of them to avoid cancers or loss of stemness [159]. As a case of pharmacological modulation, for instance, cholesterol is utilized to reduce MSC senescence [160]. Zhang et al. showed that cholesterol attenuated senescence-associated β galactosidase activity and p53 and p21 expression by affecting autophagy and ROS p53-p21 pathway. Oxidative stress was also alleviated, cell proliferation was improved, and G1 cell cycle arrest was reduced in MSC through cholesterol treatment, improving MSC functionality [161]. Another promising compound is Celastrol, which has shown anti-senescence and anti-cancer properties [162]. Zhang et al. reported that Celastrol reduced p53, p21, and SASP factors in renal cancer cells, alleviating cellular senescence and suppressing tumour-promoting behaviours. By downregulating CAV1, a key senescence mediator, Celastrol inhibited invasion and stemness in cancer cells [163].

The role of antioxidants in pharmacological modulation is exemplified by epigallocatechin-3-gallate (EGCG), a compound

Table 1
p53-p21 signalling's impact on MSC biology and therapy.

Key Factors	Pathways	Mechanisms	Therapeutic Potential	Intervention	References
Oxidative stress, DNA damage, chronic inflammation	Activation of p53-p21 and p16-pRB pathways	DNA damage and ROS accumulation	Delaying MSC senescence	Antioxidant interventions	[55]
Oxidative stress, DNA damage, chronic inflammation	Activation of p53-p21 and p16-pRB pathways	Reduction of ROS levels	Enhancing MSC proliferation and differentiation	Hydrogen-rich saline	[56]
Chronic inflammation	TLR4/MyD88-NF-κB-p53/p21 pathway	Activation of inflammatory signalling	Reducing inflammation-driven senescence	LPS exposure in DPSCs	[58]
Autoimmune and haematological disorders	p53/p21 activation	Increased expression of senescence markers	Improving MSC proliferation and hematopoietic support	BM-MSC dysfunction	[60]
Autoimmune and haematological disorders	p53/p21 activation	Activation of senescence pathways	Targeting haematological disorders	MDS affects	[61]
Hyperactivation of Wnt/β-catenin, MAPK-p53/p21 crosstalk	Wnt/β-catenin and MAPK pathways	Dysregulation of β-catenin and MAPK signaling	Restoring MSC functionality	Wnt/β-catenin inhibitors	[63]
Hyperactivation of Wnt/β-catenin, MAPK-p53/p21 crosstalk	Wnt/β-catenin and MAPK pathways	Reciprocal regulation with p53/p21 signaling	Mitigating MSC senescence	MAPK suppression studies	[64]
Fatty acid metabolites	p53 stabilization and p21 upregulation	Stabilization of p53, increased p21 levels	Preventing MSC proliferation arrest	Role of PAME	[86]
Anti-cancer effects	JAK/STAT1-p53/p21 pathway	Upregulation of tumor-suppressive signals	Inducing tumour apoptosis	Therapeutic role in HCC	[90]
Oxidative stress	p53, MAPK signaling pathways	ROS-mediated activation of senescence	Preventing stress-induced MSC dysfunction	MAPK-related stress response	[64]
Chemotherapeutic agents	p38, JNK, and p53 pathways	Activation of apoptotic pathways	Protecting MSCs from chemotherapy-induced damage	Doxorubicin impact	[109]
Inflammation	NF-κB-p53/p21 axis	Upregulation of NF-κB and p53/p21 signalling	Reducing apoptosis and inflammation	NOD MSC dysfunction	[113]
Metabolic stress	p53 stabilization and p21 upregulation	Dysregulated cell cycle arrest at the G2/M phase	Maintaining MSC functionality	PAME-induced stress	[86]
Senescence in the tumor microenvironment	p53-p21 signaling suppression	MSCs adopt SASP phenotype	Reducing tumor progression, metastasis	Tumor-supporting MSCs	[67]
Epigenetic regulation	miR-29c-3p and p300	Upregulation of p53/p21 pathways	Reversing MSC senescence	miR-29c-3p modulation	[69]
Epigenetic regulation	p300 downregulation	Reduced MSC proliferation and differentiation	Enhancing genomic stability	p300 as a therapeutic target	[70]
Cardiomyogenic differentiation	p53/p21 suppression	Enhanced differentiation into cardiomyocytes	Cardiovascular regenerative medicine	BM-MSC differentiation	[78]
Vascular regeneration	p53/p21 and Bmi-1	Suppression of endothelial markers	Improving vasculogenic differentiation	DPSCs in vascular regeneration	[80]
Cellular reprogramming	p53-p21 regulation during MET	Suppression of epithelial gene activation	Enhancing cellular plasticity	Reprogramming efficiency	[92]

derived from green tea [164]. Shin et al. demonstrated that EGCG protects hMSCs from oxidative stress-induced senescence by activating the antioxidant regulator Nrf2. EGCG treatment reduced ROS levels and mitigated acetyl-p53 and p21 expression in hydrogen peroxide-exposed cells. However, in Nrf2-knockdown cells, EGCG failed to exert its protective effects, indicating that its senescence-preventing properties are mediated by Nrf2 activation [165]. In contrast, histone deacetylase inhibitors (HDACi) like Suberoyl anilide hydroxamic acid (SAHA) and MS-275 have been shown to impair MSC stemness [166]. Di Bernardo et al. found that SAHA preferentially activated apoptotic pathways, while MS-275 promoted senescence, disrupting MSC functionality by downregulating stem cell-regulatory genes. Interestingly, these effects were not mediated by the p53-p21 pathway but instead involved cyclin kinase inhibitors [167]. Pharmacological modulation of the p53-p21 pathway offers promising strategies to counteract apoptosis and enhance MSC proliferation [168]. Yan et al. demonstrated that PFT-α, a p53 inhibitor, effectively reduced p53 and p21 expression in 5-azacytidine (5-AZA)-treated BMSCs, promoting proliferation and reducing apoptosis. These findings suggest that transient inhibition of the p53-p21 pathway could protect MSCs from stress-induced damage while maintaining their regenerative potential [78]. Combinatorial therapies, which integrate pathways like Wnt/β-catenin, can enhance regenerative outcomes by manipulating the p53-p21 pathway. Combining antioxidants with p53/p21 targeting agents can enhance MSC stress resistance, mitigating genomic instability risk. However, careful dosing and timing are needed to minimize tumorigenesis effects or loss of differentiation capacity. Pharmacological intervention of the p53 p21 pathway offers versatile strategies for increasing MSC regenerative capacity and treating pathological conditions like cancer and senescence. Future research should optimize these compounds for clinical applications and explore advanced delivery systems and context-specific combinations to maximize efficacy with minimal risk.

5. Challenges and risks in modulating p53-p21 signaling

There is great potential for therapeutic modulation of the p53-p21 signaling pathway, but this modulating approach has inherent challenges and risks [169]. Another great concern is genomic instability and tumorigenesis [170]. However, studying how this pathway usually works could inadvertently promote unchecked cell proliferation. If mediated by p53, it might be tumour-suppressive or eliminate tumour growth, potentially increasing the probability of malignant transformation, particularly in genetically predisposed or high-risk patients [171]. The other challenge is balancing the safety of approaches with their therapeutic benefits [172]. Pathway modulation may be used to modulate regenerative capacity or to attenuate senescence, but inappropriate or excessive inhibition may disrupt normal cell cycle regulation and thus result in adverse effects [173]. Control of pathway activity is necessary to avoid unintended consequences [174]. Regulatory and ethical considerations are also critical in clinical translation [175]. Once these therapies receive rigorous preclinical and clinical evaluation, targeting p53-p21 therapies must be effective and safe [176]. These underscore the need for careful and well-designed approaches to exploit this pathway for therapeutic use.

6. Conclusion and future perspectives

The p53-p21 Signaling pathway is reviewed concerning its major roles in regulating MSC biology, including the issues of senescence, limited proliferation, and stress-induced apoptosis. The seemingly opposite roles of this pathway as a guardian of genomic stability and barrier to regenerative potential reinforce the necessity of fine-tuning its function to exploit MSC functionality fully. Recent progress in small molecule inhibitors such as PFTα enhances MSC proliferation and delay senescence, and antioxidants, including hydrogen-rich saline and ECGG, mitigate the effects of oxidative stress to maintain the viability of MSC. TP53 and CDKN1A expression can be precisely modulated by genetic tools such as CRISPR-Cas9 and RNA interference, and synergistic improvements in MSC resilience and regenerative outcome can be achieved by combining these with complementary pathways such as Wnt/β-catenin and MAPKs.

Importantly, these strategies show great promise, but challenges remain. Current studies tend to ameliorate senescence and enhance proliferation at the expense of less attention to the intricate interplay of pathways controlling MSC function in physiologic or pathological circumstances. One example is that pharmacological agents that target p53-p21 appear efficacious, but off-target effects, genomic stability, and long-term safety remain a concern. In addition, the MSC entry to variability across donor sources, culture conditions, and therapeutic applications complicates the development of standardized protocols. Future research will concentrate on targeted delivery systems to avoid off-target effects and enhance the specificity of p53-p21 modulation. Further therapeutic outcomes could be refined by combining genetic tools with targeted therapeutic agents, remaining safe and efficacious. In addition, understanding p53-p21 interactions with other signalling networks will be critical to creating multi-targeted approaches to solve complex problems in MSC-based therapies. However, as the field advances, it should be possible to harness these insights into translational applications through which the true therapeutic potential of MSCs in regenerative medicine, cancer, and age-related disorders can be realized.

Author contributions

AG, MA, NHK, KG: Conceptualization, Methodology, Software. SKS, GG and BKK: Writing – Original Draft Preparation. HA and MR: Data curation, Writing – Review & Editing. LSW: Data Curation and Methodology. VK: Methodology, Software. VS: Conceptualization, Methodology, Software.

Data availability

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Declaration of competing interest

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

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