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Review

The role of GATA4 in mesenchymal stem cell senescence: A new frontier in regenerative medicine

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ABSTRACT

The Mesenchymal Stem Cell (MSC) is a multipotent progenitor cell with known differentiation potential towards various cell lineage, making it an appealing candidate for regenerative medicine. One major contributing factor to age-related MSC dysfunction is cellular senescence, which is the hallmark of relatively irreversible growth arrest and changes in functional properties. GATA4, a zinc-finger transcription factor, emerges as a critical regulator in MSC biology. Originally identified as a key regulator of heart development and specification, GATA4 has since been connected to several aspects of cellular processes, including stem cell proliferation and differentiation. Accumulating evidence suggests that the involvement of GATA4-nuclear signalizing in the process of MSC senescence-related traits may contribute to age-induced alterations in MSC behavior. GATA4 emerged as the central player in MSC senescence, interacting with several signaling pathways. Studies have shown that GATA4 expression is reduced with age in MSCs, which is associated with increased expression levels of senescence markers and impaired regenerative potential. At the mechanistic level, GATA4 regulates the expression of genes involved in cell cycle regulation, DNA repair, and oxidative stress response, thereby influencing the senescence phenotype in MSCs. The findings underscore the critical function of GATA4 in MSC homeostasis and suggest a promising new target to restore stem cell function during aging and disease. A better understanding of the molecular mechanisms that underlie GATA4 mediated modulation of MSC senescence would provide an opportunity to develop new therapies to revitalize old MSCs to increase their regenerative function for therapeutic purposes in regenerative medicine.

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Contents

1. Introduction

MSCs are a very heterogeneous population of multipotent cells, and they differ with respect to the type and amounts of growth factors produced and their ability to differentiate toward distinct cell lineages [1]. Although they were originally found in the bone marrow, MSCs have been discovered in many tissues, such as adipose tissue, umbilical cord blood, and dental pulp [2]. These cells show some fundamental properties, such as plastic adherence, expression of different surface molecules like CD73, CD90 and CD105, and multipotential capabilities such as osteogenic, adipogenic, and chondrogenic differentiation under specific stimuli [3]. As the key leading cells involved in tissue regeneration and repair, MSCs are widely known for their multilineage differentiation capacity and secretion of trophic factors, which are involved in the tissue healing process [4].

MSC migrate to the injured tissue and help in wound healing through various cascades [5]. First, stem cells migrate to the site of injury, then they migrate through the blood vessels, including the capillaries [6]. MSCs differentiate into various cells in the healing wound, where these cells may form osteoblasts where tissue is injured, such as in bone fracture reattachment [7–9]. The cells then secrete a range of bioactive factors, including proangiogenic growth hormones, cytokines with their heling effect, and specific extracellular vesicles [10]. These effects improve the condition of tissues and minimize wound inflammation [11]. In addition, the MSC have immunosuppressive function where they regulate the natural functions of both innate and adaptive immune systems [12]. In MSCs, such as other cells, there is constant synthesis and degradation of extracellular matrix, whereby when the equilibrium to synthesize matrix in excess of degradation is hindered, the conditions for healing are not conducive [13].

1.1. Biological significance

Understanding the mechanisms of MSC aging and senescence is of vital importance in regenerative medicine and stem cell-based therapy [14]. MSCs are undoubtedly one of the most useful and viable solutions for regenerative therapy, but cells slowly lose their functionality and become less effective with their aging [15]. Certain mechanisms of aging enable ways to rejuvenate aging cells and eliminate their abnormalities [16–18]. The key components of MSC aging are reduced proliferative kinetics and impaired differentiation potential of MSCs [19]. The aging of MSCs also encompasses the production that alters the neurotrophic and immunosuppressive secretome of the cells, while the effects of aging are also observed on the molecular level [20]. Furthermore, the mechanisms of aging include the very process of telomere shortening, which contributes to gene instability and, ultimately, cell death [21]. In addition, the dysfunction of mitochondria and, in turn, the oxidative stress of the cell are further signs of MSC aging [22]. Finally, the epigenetic mechanisms are also involved in MSC aging as they adjust the changes in the course of aging [23]. Meanwhile, the process of senescence requires particular attention in that context as it comprises the production of a senescent-associated secretory phenotype, which makes the altered MSCs actively produce pro-inflammatory cytokines or factors and further impairs the cell's inhibitory function on T-cell proliferation, recruitment, and activation [24]. When senescent MSCs are transplanted into the patients' tissue that requires repair, the adverse effect takes place where the transplanted cells cause the local inflammatory responses of the patient, disrupting the tissue regeneration [25].

1.2. GATA4 transcription factor and its functions

One of the most pivotal transcription factors from the GATA family, GATA4, is involved in some biological processes starting from embryonic development, tissue homeostasis, and ending in disease development [26–28]. A diverse range of gene activities is due to the presence of a conserved zinc finger DNA-binding domain, which permits the factor to interact with a special GATA motif located on DNA [29]. The identified factor is well-known as

one of the activators necessary for cardiac development, and its defects are traced [30]. At the same time, by selecting sample tissues and exploring them independently, it is possible to conclude that GATA4 is not only activated between the second and the eighth weeks of gestation, making the heart begin pumping, but also during the whole developmental cycle [31]. Regulating the expression of thousands of cardiac-specific genes, GATA4 enhances cardiomyocyte proliferation differentiation and maturation [32]. However, even tissues demonstrate that GATA4's presence is noticed not only in the developing heart or adult heart but also in the liver and stomach, as well as its important for differentiation of gastrointestinal epithelium and useful in producing mucins and regulating the gastric intestinal barrier [33]. Similarly, the presence of GATA4 in endodermal derivatives such as the liver, pancreas, and lung shows that this transcription factor expresses every gene that needs to be regulated for differentiation from an endodermal cell into a specific tissue [34].

In addition to its vital role in the regulation of developmental events, GATA4 also plays a critical role in a number of pathological processes, such as the progress of cancer and subsequent fibrosis [35]. Synergistic associations that have been suggested to regulate GATA4 expression and function have been explored in a number of studies and have been shown to be disturbed in some cancers. In contrast, in some others, GATA4 may act as a tumor suppressor [36]. GATA4 has also been found to be one of the key molecules involved in the molecular cascades that regulate the activity of stem cells and which ultimately determine the feasibility of these cells to differentiate [37]. Another phenomenon that has been linked with the activity of GATA4 is cellular senescence; this process, which is related to aging, is defined as reversible growth arrest and somatic cell dysfunction [38].

2. Role of GATA4 in mesenchymal stem cells aging and senescence

2.1. Expression patterns of GATA4 in mesenchymal stem cells

GATA4 expression patterns in mesenchymal stem cells during aging and senescence highlight the complex underlying regulatory mechanisms that define MSC function and therapeutic potential [39–41]. Characterized by their high regenerative efficacy, the MSCs undergo significant changes in gene expression and cellular behavior with their age, lose their regenerative power, and become less effective in tissue repair [42]. GATA4, as the key transcriptional factor inherent to MSC biology, exhibits highly variable expression patterns highly convenient with the aging and senescence of entire MSC populations [43]. However, in early passages, and therefore, young ages, the MSCs generally demonstrate consistently high expression rates of GATA4 that ensure their maintenance of the multipotent differentiation capacity and proliferative potential [44]. In terms of their biological effects, the target genes of GATA4 encode the essential regulators of MSC self-renewal, as well as their proliferation and differentiation, leading to tissue regeneration and repair [45]. By contrast, as MSCs undergo replicative senescence with age and accumulate damage that can no longer be repaired, the expression of GATA4 might fall away from coordination, further contributing to reduced functional capacity and the development of SASP [46].

It has been reported that the expression of the GATA4 gene gradually diminishes in senescent MSCs established from different tissue layers and donors [47]. Changes in the levels of GATA4 gene expression are detected concurrently with modifications in the expression of genes related to cell cycle progression, DNA repair, and response to oxidative stress [48]. Thus, the decrease in GATA4 expression is thought to be significantly associated with aspects of the senescent phenotype observed in aged human MSC populations [49]. In addition, in the presence of cellular stress, loss of GATA4 function in MSCs may potentially inhibit the activation of important signaling molecules required for tissue repair and regeneration [50]. Moreover, the changes in the role and interaction of GATA4 with transcription regulatory partners largely depend on the tissue source of MSCs as well as donor age [51]. Therefore, the aging of MSCs is controlled by the concert effect of a number of intrinsic and extrinsic signals [52].

Additionally, GATA4 does not act independently in senescent MSCs [53]. Changes in the redox status or inflammatory factors can also contribute to one's specific aging process mitigated by GATA4 [54]. Thus, research to dissect the molecular mechanisms of GATA4 malfunction securing senescence initiation and progression is badly needed as this will shed light on age-related disease pathophysiology and on ways to rejuvenate aged MSCs for future use in cell therapies [55].

2.2. Molecular mechanisms regulating MSC aging and senescence by GATA4

2.2.1. Regulation of cell cycle progression

GATA4 is involved in the regulation of the cell cycle in mesenchymal stem cells. It controls the expression of cyclins and CDKs [56]. In particular, it was shown that GATA4 inhibited the transcription of cyclin D1, which is a key regulator of the G1/S transition [57]. This implies stopping the cycle and the induction of the senescence of mesenchymal stem cells [58]. It was also determined that GATA4 interacted with other factors and pathways of control [59]. Thus, it can be a low-proliferative potential and limited lifespan marker for these cells during aging [60]. GATA4 is also a part of the DNA damage response in MSCs [61]. It can influence the expression of several repair genes like RAD52 and LIG4 are involved in NHEJ, and SFR4 is linked to HR [62]. When genes were upregulated, this resulted in a stop of the cycle with the further induction of senescence [63]. In case of a downregulation, the response was suppressed, leading to genomic stability [64]. Wei et al. studied cellular senescence, in which normal cell division stopped as it was triggered by such factors as oncogenic genes, the high level of oxidative stress, and DNA damage. However, it contributed significantly to aging and such diseases as non-alcoholic fatty liver disease, obesity, diabetes, and pulmonary hypertension, as well as cancer. The key pathways are p53, NF-κB, mTOR, and TGF-β, whereas the accumulated cells caused chronic inflammation. Currently, special strategies are being created in order to control it [65].

GATA4 was associated with age-related cataracts, which is a common type of lens-impairing condition [66]. The obtained data showed that GATA4 with lens epithelial cells was expressionally dysregulated in the lenses with cataracts [67–69]. This resulted in the deregulated expression of critical lens transparency and homeostasis genes; the identified changes caused oxidative damage and protein aggregation which are the hallmarks of cataract formation [70]. A study by Xie et al. was a successful attempt to discover how GATA4 is involved in the pathogenesis and development of age-related cataracts. They showed that the expression of GATA4 was increased under the impact of senescence and different types of apoptosis-inducing treatment. The same was true for ARC lenses. Mitotic inactivation, apoptosis acceleration, and cell-viability decline are hallmarks of GATA4's overexpression, and when they occur in HLECs, they contribute to the dysfunctionality of these cells, leading to ARC formation [71].

The closely related transcription factor of GATA4, GATA6, also plays a role in the modulation of stem cell aging and senescence [72]. As with GATA4, GATA6 targets DNA damage response, the cell cycle, and the induction of the senescence-associated secretory

phenotype in various stem cell populations [73]. The regulation also affects mesenchymal stem cells and acts differently from but in synergy with the factors in modulating cell senescence and aging [74]. However, it is unknown whether the regulations act through the same mechanism and have the same target genes [75]. Iwata et al. investigated the regulatory mechanisms affecting bone marrow mesenchymal stem cell aging during cell passages. GATA6 and SOX11 were identified as key cell senescence regulators working through the Wnt and BMP pathways. Repetitive cell passage led to increased hMSC senescence and decreased proliferation and regulatory networks. The concentration of GATA6 went up while that of SOX11 lowered, meaning that these proteins affect some of the same genes, and further studies into the subject are needed. Silencing these factors affected the concentration of known cell senescence-associated genes and signalling pathways [76]. GATA4 takes part in the induction of cell cycle arrest in mesenchymal stem cells during aging and senescence [77]. It regulates the expression of essential cell cycle inhibitors including, but not limited to, p16INK4a or p21 [78]. In addition, it represses the transcription of cyclins and cyclin-dependent kinases which may help it block progression through the cell cycle at numerous checkpoints, particularly the G1/S transition [79]. GATA4-mediated cell cycle arrest is essential in terms of the establishment of the senescent phenotype in aged mesenchymal stem cells [80]. Markopoulos et al. studied the role of senescence-associated microRNAs, which target the cell cycle in the expression of normal human lung fibroblasts. They compared the expression of miRNAs in young and senescent human fibroblasts. They found that the expression of 15 miRNAs was significantly elevated in senescent cells. The agents targeted the cell cycle progression and the maintenance of telomers as their expression was either unaffected or reduced: E2F1, CcnE, Cdc6, CcnB1, or Cdc25C. MiR-221/222 overexpression led to G1/S phase arrest thus contributing to the development of the senescent phenotype [81].

FOXP1 is a transcription factor acting in combination with GATA4 to regulate mesenchymal stem cells aging and senescence [82–84]. FOXP1-GATA4 complex initiates control of key cell cycle inhibitors, including p16 INK4a and p21, to contribute to cell cycle arrest and senescence initiation [85]. In its turn, the complex also provides regulation of senescence-associated secretory phenotype genes to worsen the cellular microenvironment with aging [86]. In a study by Li et al., FOXP1 role in MSC commitment and senescence in the course of skeletal aging is discussed. It is stated that expression of FOXp1 decreases with aging, and its level is inversely correlated with that of senescence marker p16INK4A. The activity of the factor repressed pro-senescence gene marker expression and, thus, stimulated developmental potential reserve. Conditional deletion of the gene in MSC decreed in early aging effects with dec for the lineage to adipocytes and inclination for senescing with the loss of self-renewal and reduced bone mass. The target of the factor was a sequence in the promoter of p16INK4A to encode its binding sire. Finally, overexpression of the FOXp1 effectuating vector was capable of immortalizing mesenchymal stem cells [87]. Aging and senescence in mesenchymal stem cells comprise a complex of multifactorial processes involving a wide range of intracellular and extracellular signaling proteins and transcription factors [88]. Several interaction pathways between GATA4 transcription factor and insulin-like growth factors responsive binding proteins 4 and 7 have been examined [89]. These proteins are essential for the bioavailability and activity of insulin-like growth factors significant for the IGF axis, which plays a crucial role in stem cell maintenance and self-renewal [90]. According to Severino et al., IGFBP-4 and IGFBP-7 activated by GATA 4 led to the suppression of IGF function, eventually resulting in replicative potential decay and accelerative senescence in aged MSCs. The downstream inhibition was mediated through the suppression of GATA4 and the ERK signaling cascade. Moreover, several factors, such as IGFBP4 and IGFBP7, which stimulate inactivation and deficiencies in senescent cells, can be explored as potential cancer targets and in the development of novel regenerative medicine treatment options [91] (Fig. 1).

2.2.2. Influence on senescence-associated secretory phenotype (SASP)

GATA4 appears to be a critical regulator of various extracellular modulators during aged and senescent mesenchymal stem cell activity [92]. These modulators include cytokines, chemokines, proteases and growth factors that affect the extracellular milieu and, thereby, influence its impact on tissue homeostasis and regenerative response [93–95]. In this way, the identified mediator regulates certain age-related aspects, particularly inflammatory processes, tissue repair and stem cell activity [96]. Han et al. synthesize the information about potential regulators of the SASP during senescence and aging. The researchers state that during senescence, cells express and secrete cytokines, chemokines, proteases, growth factors and proteases and enzymes related to extracellular matrix production and remodeling. This set constitutes a phenomenon known as SASP, the senescence-associated secretory phenotype. The processes of SASP formation and regulation involve a complex range of activities at the chromatin, transcription, mRNA translation, intracellular trafficking and secretion levels [97]. In some types of cancer, GATA4 may act as a tumor suppressor through the induction of cell cycle arrest and senescence. In other types of cancer, this factor can contribute to cell growth and metastasis by regulating specific gene expression for cell proliferation, cell invasion and angiogenesis. Therefore, it is extremely important to understand the dual effects of GATA4 in the context of tumors for developing the most appropriate and successful therapeutic strategies for patient care. Omer et al. investigated the role of the rasGAP SH3-domain-binding protein 1 in the activation of the SASP, which can promote either tumor suppression or tumor development, depending on the tumor context. The findings suggested that G3BP1 can be a relevant factor for mediating cancer growth and progression through the activation of SASP [98] (Fig. 2).

2.2.3. Modulation of oxidative stress response

GATA4 is critical in modulating DNA damage response in MSCs during aging and senescence [99]. It regulates the expression of various genes in pathways of DNA repair, including NHEJ and HR [100]. Furthermore, the upregulation of GATA4 after DNA damage may inhibit cell cycle progression and promote senescence [101]. Conversely, the downregulation of GATA4 may impair DDR completion and exacerbate MSC genomic instability associated with accelerated aging [102]. Xiong et al. investigated the contribution of DNA damage response and GATA4 signalling to cellular senescence and aging-related pathologies. The study established the involvement of DDR in activating the kinases ATM and ATR. The activated kinases further phosphorylate p53 and its downstream target, p21.

Consequently, p53 and p21 induce cell cycle arrest and senescence. GATA4 is a transcription factor that is critical for the development of organs and is involved in DDR. GATA4 is also associated with aging and aging-related diseases such as atherosclerosis and heart failure. This highlight shows the link between GATA4 and DDR/cellular senescence. Aging of cells also contributes to the acceleration of some aging-related diseases [38] (Fig. 3).

One of the interacting proteins of the transcription factor GATA4 is Sirtuin 1 (SIRT1) [103]. The latter is an NAD-dependent protein deacetylase that is crucial for the regulation of cellular senescence and aging [104–106]. SIRT1 targets many transcription factors to

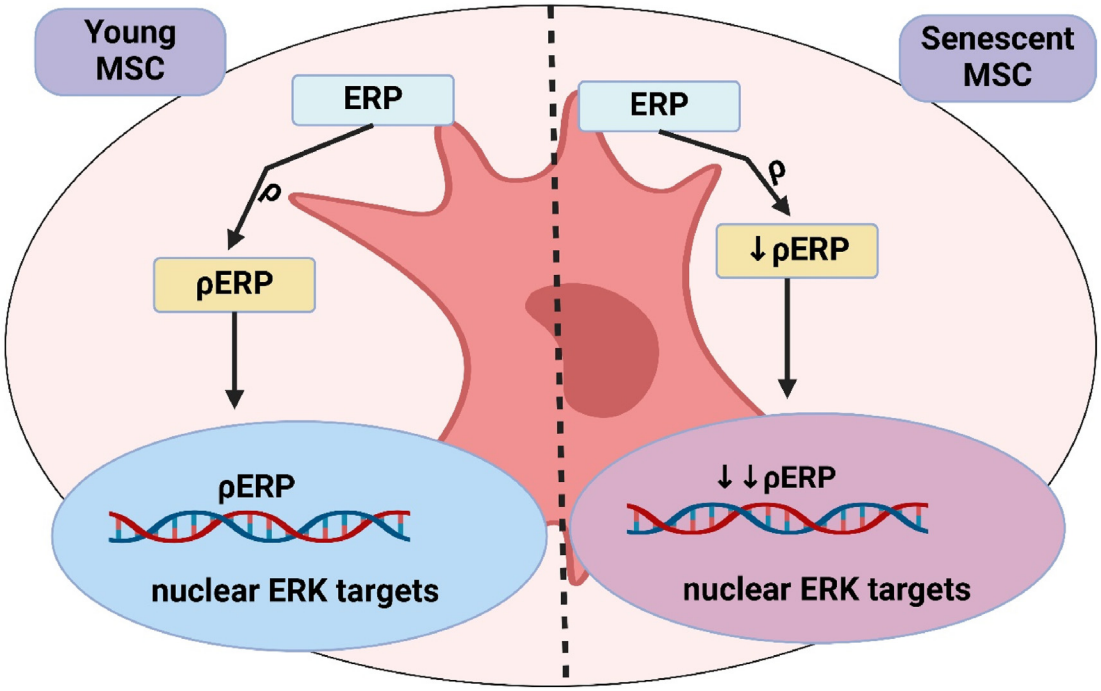

Fig. 1. The figure illustrates the differences in ERK pathway signaling between young and senescent mesenchymal stem cells (MSCs). In young MSCs, the ERK pathway is active, leading to phosphorylation (pERK) and activation of nuclear ERK targets. In senescent MSCs, there is a decrease in pERK, resulting in reduced activation of nuclear ERK targets.

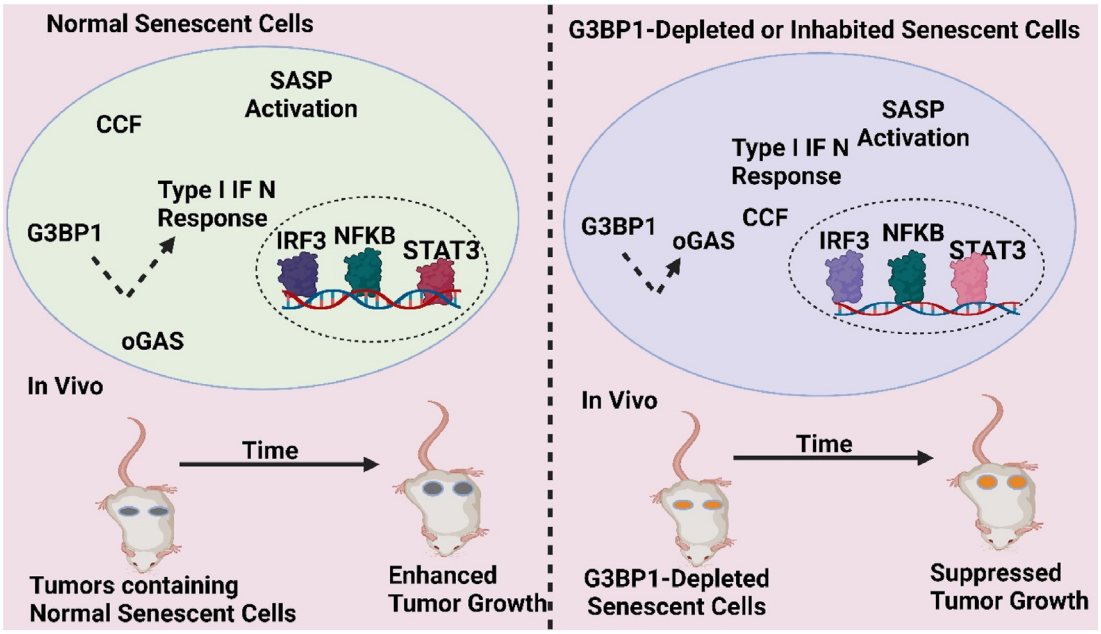

Fig. 2. The figure compares normal and G3BP1-depleted or inhibited senescent cells. Normal senescent cells activate SASP and Type I IFN response, enhancing tumor growth over time. In G3BP1-depleted senescent cells, reduced SASP and Type I IFN response led to suppressed tumor growth. Key pathways include CCF, oGAS, IRF3, NFKB, and STAT3.

modulate their activity, GATA4 among them [107]. The interplay between the transcription factor and SIRT1 is responsible for the expression of a considerable number of genes implicated in the control of the cell cycle, oxidative stress response, and the generation of the senescence-associated secretory phenotype [108]. Thus, the interaction could be considered as a potential target to modulate stem cell aging and senescence via the means that regulate the activity of GATA4 [109]. Another study explores the consequences of aging on the oxidative stress response of human endothelial cells [110]. Conti et al. discovered that human EA. hy926 endothelial cells at the older passage displayed a decreased expression or Sirt1 and Foxo3a as well as persistent high levels of TBARS and ineffective catalase activity under conditions of oxidative stress. The incidence of cellular senescence was much higher in older cells than in young ones. Thus, older endothelial cells are characterized by an inadequate response to oxidative stress, with

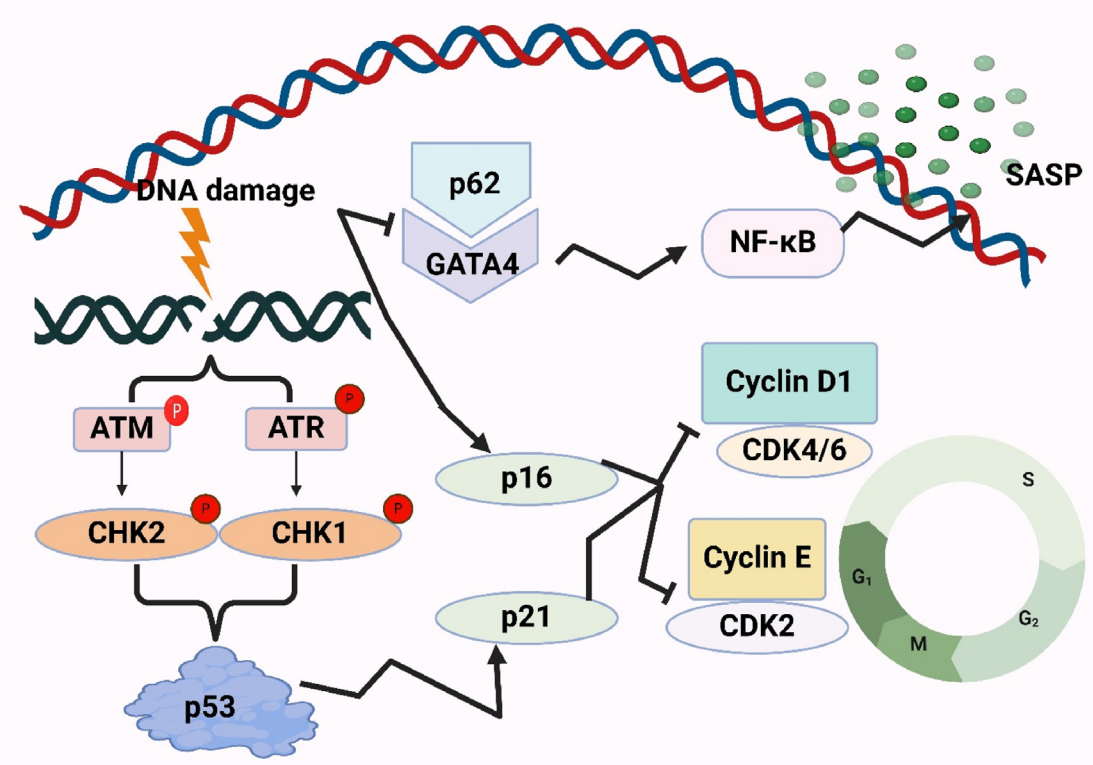

Fig. 3. The figure illustrates the DNA damage response pathway leading to cellular senescence. DNA damage activates ATM/ATR, which phosphorylates CHK1/CHK2, stabilizing p53 and upregulating p16 and p21. These inhibit CDK4/6 and CDK2, blocking cell cycle progression. GATA4, stabilized by p62, activates NF-κB, promoting the senescence-associated secretory phenotype (SASP). The pathway highlights the molecular interactions driving senescence.

the Sirt1 pathway being dysfunctional and instrumental in the maintenance of endothelial homeostasis and susceptibility to aging-related diseases [111].

GATA4 has the effect of regulating the inflammatory process of aging mesenchymal stem cells into fibrinous stem cells [112]. In the case of MSC aging and fibrinogenesis GATA4, it is possible to see cheats, which in turn include cells, chemists and inhibitors of SASP-dependent alcoholism, rapeseed and stem cell chronic diseases [113]. The death of such levels can take place as death [114]. Whirl GATA4 may help to identify and eliminate such age-related inflammatory diseases [115]. Quo et al. suggest that GATA4 plays a major role in regulating aging inflammation and its contribution to NFκB DNA response therapy. It has been shown that GATA4 inhibits the senescence-supported alcohol-producing inflammatory response NF-κB system. It has been found to undergo such growth in the degradation of GATA4 and fibrin acceptance. However, this was not the case at SMP, suggesting that extensive autophagy and fibrin-laden selia are not needed for breasts. It is recommended that autophagy also regulates the prayer state of GATA4. It is believed that increased GATA4 intake is unmanageable. Consideration of cancer and other age-related diseases [116].

2.2.4. Interaction with other signaling pathways (e.g., p53, mTOR, Wnt)

In MSC, GATA4 interacts with a critical PI3K/AKT/mTOR signalling pathway, which is a significant regulator of cell growth, proliferation, and survival [117–119]. It affects the pathway's activity, leading to differentially expressed downstream targets that are crucial for the cell cycle, cellular senescence, and stemness, changing the cell's phenotype [120]. The molecular connections between GATA4 and the PI3K/AKT/mTOR signalling pathway are of interest to investigate cell molecular mechanisms affecting cell aging and senescence to develop new treatment methods and provide insight into stem cell aging remission [121]. Glaviano et al. addressed the importance of the PI3K/AKT/mTOR PAM pathway in cancer, which regulates cell survival, growth, and cycle progression. Some of the dysregulations in the path include the hyperactivity of PI3K, loss of function of PTEN, and gain-of-function mutations of AKT responsible for cancer development and resistance to therapies. According to the authors, the review presents a discussion of the most significant dysregulations in the PAM pathway and the efficiency of the use of PI3K, AKT, and mTOR inhibitors on a monotherapy basis and in various combinations with other anticancer drugs. It also highlighted resistance mechanisms to targeted PAM therapies and focused on the application of the PAM pathway in immunology and immunotherapies [122].

GATA4 is the central regulator of the p53-p21 cellular senescence axis, indicating that it plays a central role in cellular aging [123]. Typically, the p53-p21 axis is involved in the process of cellular arrest, and it ensures that cells do not divide uncontrollably [124]. First, GATA4 can enhance the levels of p21, a potent enzyme that inhibits the functioning of cyclin-dependent kinases [125]. The action of GATA4 is facilitated by interaction with p53, which also regulates the expression of other genes used in the p53 pathway [126]. In this case, the GATA4-p53-p21 aging pathway is used to lower the functional proliferation ability in MSC age-related defects, therefore restricting cellular life [127]. Al-Azab et al. analyzed the mechanisms of aging, markers, and ways to alleviate human mesenchymal stem cell senescence. Accordingly, experiments indicated that the MSC also plays a role in human aging, aging-related diseases, and cellular treatments. The results showed that the development of adult stem cells contributes to reduced regeneration in humans. Both intrinsic and extrinsic pathways bring out this control [127] (Table 1).

3. Implications for tissue regeneration and therapeutic applications

3.1. Impact of GATA4 on MSC function and therapeutic potential

GATA4 initiates the sequence of events that leads to the differentiation of mesenchymal stem cells into the cardiac subtype [128]. This substance is a master regulator that provokes the expression of genes that are characteristic of the heart [129–131]. These genes fall into several categories: contraction, structural, and muscle function processes that are taking place within cardiomyocytes [132]. When used to stimulate MSCs to turn into cardia cells purposefully, GATA4 boosts the effectiveness of various approaches applied to regenerative medicine [133]. The study conducted by Välimäki et al. explored the potential of GATA-targeted compounds to support and modulate the differentiation of cells targeted at the cardiac subtype. The researchers experimented with a dual-reporter stem cell line. They found that some previously identified GATA4-targeted compounds used to promote differentiation during heart muscle injury could adjust the expression of atrial and ventricular genes by carriers of MSCs interested in cardiac disposition. Also, the authors established that 3i-1000 and 3i-1103 are crucial modulators. As part of the analysis of the compounds, the specialists realized that there are interactions between GATA4 and the family of BET proteins, such as Bromodomain-containing protein 4. It is supposed that epigenetic modulators are also influencing GATA-dependent transcription [134].

3.2. Potential strategies to modulate GATA4 expression or activity for rejuvenating aged mesenchymal stem cells

Mesenchymal stem cells are extremely critical when it comes to tissue regeneration and repair [135]. However, due to cellular senescence, their functionality reduces with age [136]. Also, due to low proliferation and reduced regenerative capability, MSCs lose their functional capacity [137]. GATA4 is a major transcriptional factor in the growth of organs [138]. It is a prominent player in the progression of senescence [139]. Various options in the genetic pathway can be employed to modulate GATA4 expression [36]. The clustered regularly interspaced short palindromic repeats [140]. It can be used to facilitate upregulation or downregulation of GATA4 and specifically target the gene to enhance its expression in CDCP [141]. It can also work against secession pathways that were not previously known. RNAi can also be employed to stimulate the activity or overexpression of GATA4 [142]. Short hairpin RNAs and short interfering RNAs that can target genes against GATA4 are stimulated, in turn stimulating the hormone [143]. Also, overexpression of gene techniques utilizing viral sine uses the GATA4 gene [144]. In the present work, the ability of the gene to age CDCPs is currently being evaluated [145].

Small molecules can also influence the activity of GATA4 [146]. Activators can be discovered and synthesized by high-throughput screening of chemical libraries [147]. Those include compounds that improve the binding affinity of GATA4 to its target DNA sites or increase the stability and activity of the TF [148]. Similarly, inhibitors could be utilized to transiently block GATA4 activity for controlled manipulation of the rejuvenation of MSCs [149]. Epigenetic modifications regulate mRNA expression [150]. The use of such modifications around the GATA4 gene is imperative to switch on or off [151]. Using histone modification, GATA4 can be modulated by histone deacetylase inhibitors, such as HDAC inhibitors or histone acetyltransferase inhibitors, affecting the acetylation status of the histones around the GATA4 gene [152]. Increased acetylation favors the expression of genes decrease – their suppression [153]. Agents, such as 5-azacytidine that demethylate DNA can remove a methyl group from the promoter of the GATA4 gene, hopefully enhancing its expression in aged MSCs [154].

GATA4 produces its effect by interacting with other proteins [155]. The enhancement of its activity by small molecules or peptides could be achieved by preventing an interaction between GATA4 and other proteins, particularly its co-repressor of other inhibitory ones [156]. Also, intracellular signaling pathways,

Table 1
This table summarizes the roles of GATA4 and related factors in MSC aging and senescence, highlighting key pathways and regulatory effects.

Notch Pathway Involvement	GATA4 Involvement	Disease Focus	Key Findings Summary	Regulation	Reference
DNA damage response (DDR)	GATA4 signalling	Cellular senescence	GATA4 upregulation leads to cell cycle arrest and senescence induction	↑ GATA4 ↑ senescence	[65]
DNA damage response (DDR)	GATA4 in lens epithelial cells	Age-related cataract (ARC)	GATA4 expression increases, causing cell viability reduction and apoptosis	↑ GATA4 ↑ apoptosis	[71]
Wnt and BMP signalling pathways	GATA6 and SOX11	MSC senescence	GATA6 upregulation and SOX11 downregulation affect cell senescence	↑ GATA6 ↓ SOX11	[76]
Cell cycle arrest (G1/S transition)	GATA4 and miRNAs	Cellular senescence	miRNAs upregulate and induce G1/S phase arrest, contributing to senescence	↑ miR-221/222 ↓ cell cycle	[81]
p16INK4A regulation	FOXP1-GATA4 complex	MSC aging	FOXP1-GATA4 complex modulates p16INK4A, contributing to cell cycle arrest and senescence	↓ FOXP1 ↑ p16INK4A	[87]
IGFBP-4 and IGFBP-7 modulation	GATA4	MSC aging and senescence	GATA4 upregulation leads to decreased IGF signaling and increased senescence	↑ IGFBP-4/7 ↓ IGF	[91]
SASP regulation	GATA4	Age-related inflammatory processes	GATA4 regulates SASP components, influencing tissue homeostasis and regeneration	↑ SASP	[97]
Senescence-associated secretory phenotype (SASP)	GATA4	Tumor progression	GATA4 involvement in SASP activation influences cancer growth and progression	↑ SASP	[98]
DNA damage response (DDR)	GATA4 signalling	Aging-related pathology	GATA4 activation in DDR leads to cellular senescence and genomic instability	↑ DDR ↑ GATA4	[38]
SIRT1 pathway	GATA4 interaction	Oxidative stress response	GATA4-SIRT1 interaction affects oxidative stress response in aging endothelial cells	↓ SIRT1 ↑ oxidative stress	[111]
NFκB activation	GATA4 in senescence and inflammation	Age-related diseases	GATA4 activates NFκB, inducing SASP and inflammation in senescent cells	↑ NFκB ↑ SASP	[116]
PI3K/AKT/mTOR signalling	GATA4 interaction	MSC aging and senescence	GATA4 modulates PI3K/AKT/mTOR pathway, influencing cell cycle and senescence	↑ PI3K/AKT/mTOR	[122]
p53-p21 axis	GATA4 and p53 interaction	MSC aging and senescence	GATA4 induces p21 expression, interacting with p53 to mediate cell cycle arrest	↑ p53 ↑ p21	[127]

leading to the stabilization of the interaction between GATA4 and its co-activators or facilitating the nuclear localization of the TF, can be used for that purpose [157].

Mechanical stimuli, in combination with gene expression manipulation, can be a novel method to rejuvenate aged MSCs [158]. MicroRNAs are small, non-coding RNAs that can post-transcriptionally regulate gene expression [159–161]. Therefore, inhibiting those miRNAs that regulate GATA4 may increase its level in MSCs [162]. Thus, miRNA mimics that inhibit miRNA targeting GATA4 can be used to improve the expression and activity of this gene [163]. Moreover, miRNA antagonists, or antagomirs, can also be employed to repress the action of miRNAs that target GATA4, thus elevating its yeast expression and activity [164]. There is evidence that some mechanical stimuli can affect MSC behavior and gene expression [165]. For instance, biomechanical stimulation, including cyclic strain or compression, may increase GATA4 expression [166]. This method of gene expression alteration seems promising as being affected by mechanical stimuli, the cells themselves regulate their actions [167]. Low frequencies of electromagnetic fields reportedly affect gene expression in stem cells [168]. Thus, a proper set of parameters of the given fields may enhance the activity of GATA4 in aged MSCs [51]. Therefore, the alteration of gene expression or activity mapped onto the regulation of mechanical stimuli seems to be a complex means leading to the rejuvenation of aged MSC [165]. There is no doubt that multiple approaches to enhance the regenerative potential of MSCs, including genetic, chemical, epigenetic, and physical ones [169]. By combining these approaches, it is possible to rejuvenate aged MSCs to make them more effectively treat age-related diseases and regenerate tissues [170].

3.3. Challenges and limitations in targeting GATA4 for therapeutic applications

Therapeutic applications for targeting GATA4 have to overcome several obstacles and bottlenecks [171]. A key limitation pertains to the pleiotropic nature of GATA4, which controls many genes and pathways other than the senescence and rejuvenation pathways studied in this work [172]. Manipulating GATA4 expression and activity under these conditions may cause unwanted side effects or off-target effects [173]. Yet another challenge is the nuances of the GATA4 regulatory networks [174]. This property may present extensive challenges in trying to selectively target GATA4 over the multitude of transcription factors, co-regulators, and signaling pathways with which GATA4 interacts without do damage into other biological processes that are necessary for normal cellular physiology [175].

Furthermore, additional tissue-specific approaches may be necessary for therapeutic targeting due to variations in the contribution of GATA4 across different tissues and cell types [176]. Delivery of GATA4 to specific cells *in vivo* also has been problematic [177]. However, selective delivery of drugs that target GATA4 to MSCs or restricted tissue distribution is still a challenging issue [178]. In addition, it is important to determine how to provide stable and maintainable therapeutic effects of GATA4 modulation *in vivo* for effective clinical translation [179].

The additional barrier would be the acquired resistance from the GATA4-directed therapeutics [180]. Like all targeted approaches, the effectiveness of GATA4 modulation will be limited by the eventual emergence of resistance mechanisms [181]. It will be critical for the efficacy of GATA4-targeted therapies that these resistance mechanisms are identified and abolished [182]. In addition, the safety and regulatory aspects relating to GATA4-directed treatment must be evaluated rigorously [183]. Avoiding undesired outcomes or severe side effects due to GATA4 modulation is a prerequisite for clinical applications [156]. Ethical standards and regulatory oversight regarding the use of GATA4-targeted interventions will be imperative for their productive and safe deployment [184] (Table 2).

4. Future perspectives

4.1. Areas for further research

More studies are warranted to elucidate molecular regulatory mechanisms of GATA4 expression and activity in MSCs [185]. Identification of the upstream regulators or downstream target genes downstream of GATA4 might provide evidence and clues for further exploration of GATA4 function on MSC senescence and rejuvenation [55]. This information might eventually be useful in devising targeted tactics to manipulate GATA4 expression or function and thus rejuvenate senescent MSCs [186]. Tissue-specific roles of GATA4 in MSCs represent an important additional focus of further research [187]. Research of how GATA4 works in MSCs that have been derived from different tissues and various microenvironments may uncover the roles of GATA4 in cellular senescence and rejuvenation in a tissue-specific manner [188]. This would provide clues for the rational design of MSC-based therapies for targeted tissue repair and regeneration [189]. That research, too, might be explored as a follow-up to discern the prolonged impacts of GATA4 modulation in MSCs [190]. As a consequence of the rejuvenation of aged MSCs, transient modulation of GATA4 in the short-term period appears to be a new approach that could lead to novel directions for the modulation of aging-related genes for clinical application but its nature of safety and stabilities of GATA4-modulated MSCs should be explored deeply over the long-term phase [191].

The effect in the long term is important, for the clinical translation of such GATA4 modulation approaches [192]. More importantly, the cross-talk between GATA and other signaling pathways in MSCs should be further investigated [193]. There are numerous signaling pathways that GATA4 can cooperate with to regulate MSC aging and rejuvenation together [194]. By routing these reactions, we could discover potential combinational treatments that could synergize with GATA4 changes to augment the recovering impacts of this course of recovery of GATA4 sign, growing brand new prospective regenerative approaches [195]. Animal models of aging and age-related disease are needed for translational and clinical studies to determine if GATA4-modulated MSCs are a feasible therapeutic approach [196]. Identifying robust delivery modalities that can be made scalable for practical clinical use is a crucial first step towards GATA4 modulation strategies becoming therapeutically relevant [197].

4.2. Potential applications of GATA4 modulation in other age-related disorders

In addition to rejuvenating aged MSCs, the ability to modulate GATA4 expression or activity may have wider applicability as well [198]. GATA4 has also been shown to have a function in other stem cell populations (another area of interest regarding the role of GATA4 in the regulation of cellular function) [199]. For instance, the manipulation of GATA4 in hematopoietic stem cells (HSCs) might increase their regenerative capacity and improve outcomes in diseases such as bone marrow failure or hematologic malignancies [200]. Moreover, GATA4 regulation might not be the only approach to modulate age-specific gene expression (and proposable rejuvenate the stem cell population), as it could also have therapeutic applications on age-related diseases other than those directly implicated in stem cell ageing [134]. These indications include the

Table 2
This table summarizes the modulation of GATA4 for therapeutic applications, detailing techniques, disease focus, key findings, and regulatory impacts. It covers genetic, chemical, epigenetic, and physical strategies, along with challenges, resistance, and safety considerations for clinical use.

GATA4 Role/Modulation	Technique/Involvement	Disease Focus	Key Findings Summary	Regulation
GATA4 for cardiac differentiation	GATA4-targeted compounds	Cardiovascular diseases	Compounds 3i-1000 and 3i-1103 modulate cardiac gene expression	↑ GATA4
Modulating GATA4 for rejuvenation	CRISPR/Cas9, RNAi, gene overexpression	MSC aging	Genetic approaches to upregulate or downregulate GATA4 expression	↑/↓ GATA4
Small molecules to modulate GATA4	Activators, inhibitors	MSC rejuvenation	Activators and inhibitors modulate GATA4 activity for MSC rejuvenation	↑/↓ GATA4
Epigenetic modifications for GATA4	HDACis, HATis, DNA demethylating agents	MSC aging	Histone modifications and DNA demethylation enhance GATA4 expression	↑ GATA4
Protein interactions affecting GATA4	Small molecules, peptides	MSC rejuvenation	Disrupting interactions with co-repressors or enhancing interactions with co-activators	↑ GATA4
miRNAs targeting GATA4	miRNA mimics, antagomirs	MSC rejuvenation	miRNA mimics inhibit, antagomirs block miRNAs targeting GATA4	↑ GATA4
Biomechanical stimulation	Cyclic stretching, compression	MSC behavior	Mechanical stimuli enhance GATA4 expression and activity	↑ GATA4
Electromagnetic fields	Low-frequency electromagnetic fields	Stem cell gene expression	Electromagnetic fields influence GATA4 activity in aged MSCs	↑ GATA4
Challenges in targeting GATA4	Pleiotropic effects, delivery methods	Therapeutic applications	Pleiotropic effects and complex regulatory networks pose challenges	Variable
Resistance to GATA4-targeted therapies	Resistance mechanisms	Long-term efficacy	Potential for cells to develop resistance to GATA4-targeted therapies	Variable
Safety and regulatory considerations	Ethical guidelines, regulatory frameworks	Clinical applications	Ensuring safety, avoiding adverse effects, and establishing guidelines	Variable

important role that GATA4 plays in cardiac development and function, in particular in cardiovascular diseases [146]. Targeting GATA4 for therapy through the selective modulation of its expression or activity, therefore, may represent an attractive approach to enhance cardiac regenerative response in pathological settings like myocardial infarction or cardiac failure [201].

In addition, other reports showed that GATA4 is also responsible for controlling inflammatory responses and immune cell function [202]. The modulation of GATA4 in immune cells would open new perspectives for the therapy of inflammatory disorders or modulation of immune response in autoimmune diseases [203]. Regarding neurodegenerative diseases, modulation of GATA4 could work by increasing the regenerative potential of neural stem cells, which would be accompanied by promoting neuronal repair in disorders such as Alzheimer's or Parkinson's disease [204].

5. Conclusion

GATA4 is a critical transcription factor controlling numerous mesenchymal stem cell (MSC) processes, including proliferation, differentiation, and senescence. Previous studies have suggested that the expression of GATA4 in MSCs decreases with aging, which results in elevated senescence markers and impaired regeneration capacity. It impairs the cell cycle, DNA repair and the stress response system to oxidative stress, with consequences in the senescent phenotype of aged MSC. Besides, several studies have shown that GATA4 regulates important pathways in MSC aging like the cell cycle, DNA damage response and senescence-associated secretory phenotype (SASP). As such, it interacts with important cell cycle inhibitors such as p16INK4a and p21 and changes their expression with the resultant increase in cell cycle arrest and senescence as well. GATA4 is also known to be involved in inflammatory and antioxidant pathways, to modulate the microenvironment of the stem cells, thus affecting both the tissue dysfunction observed with age. The interactions of GATA4 with other pathways, such as the PI3K/AKT/mTOR and p53-p21 axis, illustrate the complex nature of GATA4 in regulating MSC aging. Interventions aimed at restoring normal levels and activities of GATA4 may be beneficial for rejuvenating aged MSCs, and enhancing the regenerative potential of aged MSCs, which could carry important implications for regenerative medicine and age-related regenerative therapies.

Author contributions

MAB, RJS, IK and SK: Conceptualization, Methodology, Software. NS, MRK and PR: Writing – Original Draft Preparation. HA and GK: Data curation, Writing – Review & Editing. VS: Data Curation and Methodology. LSW: Methodology, Software. VK: Conceptualization, Methodology, Software.

Data availability

No datasets were generated or analyzed during the current study.

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Declaration of competing interest

The authors declare that there are no competing interests.

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