Chapter

Adipose-Derived Stem Cells (ADSCs) and Growth Differentiation Factor 11 (GDF11): Regenerative and Antiaging Capacity for the Skin

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Abstract

Adipose-derived stem cells (ADSCs) have proven their efficiency in wound healing and skin regeneration *in vitro* and *in vivo*. They were reported to differentiate into skin cell types and migrate to wounded sites to restore cell deficiencies and functions. Secretome of ADSCs is involved in the migration and proliferation of dermal fibroblasts (DFs) and keratinocytes where growth differentiation factor 11 (GDF11) and transforming growth factor-β (TGF-β) are expected to play the principal role. Both factors are implicated in immune responses, skin cell differentiation, proliferation and pigmentation, migration and secretion of the extracellular matrix proteins. Increasing evidence has pointed the fact that ADSCs are expected to cross-react with GDF11 to ensure DF and keratinocytes proliferation to reverse the aging process. Moreover, these factors share similar intracellular mechanisms pathways that are SMAD-dependent, and target different cellular mechanisms related to regeneration or rejuvenation. This intriguing balance between GDF11-dependent aging and TGF-β-dependent regeneration still remains unclear and might be regulated in a spatio-temporal manner. Considering the clinical relevance of the mechanisms slowing or delaying the onset of age, we aimed to clarify the involvement of cell signaling pathways related to GDF11 and TGF-β in balancing cell rejuvenation and cell regeneration. Increasing the organ lifespan and functionality might be challenging issues.

Keywords: adipose-derived stem cells, skin, aging, regeneration, rejuvenation, wound healing, GDF11, TGF-β, SMAD pathways

1. Introduction

Skin covers the human body and acts as a protective barrier against external aggressions; it consists of three component layers: epidermis, dermis, and hypodermis. Skin also has a pivotal role in thermoregulation, water retention, and cell regeneration. However, the skin remains the first exhibition of time passing characterized externally by skin winkles' manifestations, loss of integrity elasticity and functionality. These processes vary between individuals but altogether reflect

cellular and molecular changes leading to progressive reduction in cell proliferation and regeneration as a result of increasing cell senescence and apoptosis [1].

A recent work has testified that adult multipotent stem cells are present in the dermal sheets and in the interfollicular dermis; they can also be derived from the pericytes [2]. They are expected to play a crucial role in regulating skin function and turnover. Furthermore, these cells were considered as mesenchymal stem cell (MSC)-like expressing the specific mesenchymal markers and differentiating into adipocyte, chondrocyte, osteoblast and myocyte [3]. These cells are identified within the subcutaneous adipose tissue as adipose-derived stem cells (ADSCs) and have been reported to differentiate into skin cells, thus ensuring skin regeneration and maintaining homeostasis [4–6]. Several studies have shown the ability of ADSCs to act through cell-cell contact, but mostly by secreting a panel of cytokines and chemokines, being involved in different biological pathways including cell proliferation, differentiation, homing and migration, senescence, and apoptosis [7–11]. These mechanisms are implicated in the whole process of skin regeneration during wound healing.

ADSC-based therapy is very promising in treating damaged tissues and in completing full-thickness skin replacement. Some clinical applications benefit from its simple and abundant collection from adipose tissue. The capacity of these cells to proliferate and self-renew *in vitro* as well as *in vitro* added to their innate differentiation has targeted more scientific advancements in the field of regenerative medicine. Their immunomodulatory effects also make them more suitable for use compared to their counterpart from bone marrow and umbilical cord blood [12]. These cells have been used for many investigations and are largely used for graft improvement in cosmetic remodeling to prevent fat necrosis [13–15]. ADSCs have presented a great ability to migrate and were recruited rapidly into wounded sites where the process of cell differentiation toward various skin cell components occurred. ADSCs have helped in cicatrization and regulating inflammation and the phases of wound healing [6]. These cells secrete growth factors in their extracellular vesicles [16–18] and produce different amounts of the extracellular matrix (ECM) proteins, thus promoting and accelerating skin regeneration in 3D raft cultures from adult expanded human skin [19, 20]. This suggested that these cells represent a rich source of factors necessary for accelerating wound healing and tissue regeneration.

Among the secreted growth factors, transforming growth factor-β (TGF-β) and growth differentiation factor 11 (GDF11) are highlighted and both are involved in biology of skin and different organs [5, 21, 22]. Both factors belong to the same superfamily of TGF-β and target similar skin cells including dermal fibroblast (DF), keratinocytes, melanocytes, and dermal microvascular endothelial cells [23–25]. Moreover, these factors activate the intracellular SMAD signaling pathways, thus targeting skin cell properties to repair wounded tissues. Consequently, TGF-β reduces wrinkles and photoaging signs [24, 26, 27]. On the other hand, GDF11 has received more attention with its ability to produce age-reversing effects [25, 28] and increase skin cell proliferation and functionality [23–25].

In the current research, many questions have been raised about the involvement of GDF11 in the inflammatory, proliferative, and remodeling phases of wound healing. Adding to the fact that TGF-β was secreted by utmost epithelial cells and participated extensively in this cascade, an interaction between GDF11 and TGF-β for sustainable skin biology and function has been suggested. Additionally, they share similar intracellular mechanisms involved in healing and aging. Cross-talking with the surrounding cells, mainly resident ADSCs, keratinocytes, DF, melanocytes, and macrophages, these factors might be activated, autoactivated, and/or mediate other cytokines and chemokines to attain and orchestrate even similar

mechanism pathways but taking advantage for skin repair and cell regeneration or cell rejuvenation through resident's stem cell proliferation and differentiation.

When secreting TGF-β and GDF11, ADSCs underwent autoinduction by binding these factors to their transmembrane specific receptors ActIIBR and TGF-βR respectively and initiating the intracellular signal transduction cascade. However, circulating GDF11 has been reported to decrease with age [21, 29] and, in the same way, younger ADSCs and MSCs were found to be more proliferative, secrete more ECM proteins, and be more rejuvenating as compared to the aged ones [18]. On the other hand, positive effects on skin vasculature, skin integrity, density and strength, and wrinkles reduction have been reported when using recombinant GDF11 (rGDF11) [24] likely by cross-talk between DF, keratinocytes, ADSCs, and endothelial cells. Its beneficial involvement in skin microvasculature impaired during aging is highly expected through proliferation and differentiation of progenitor endothelial cells [30]. Other reports suggested that TGF-β was more involved in skin repair and cell regeneration during normal biological process or after injury and is considered as a key tool in the regulation of wound healing by promoting angiogenesis, cell proliferation, and migration [31]. Through its immunoregulating capacity, TFG-β and GDF11 were also specifically implicated in skin inflammatory process during wound healing and skin aging or inflamm-aging by downregulating proinflammatory cytokine genes expression [32, 33].

However, the relationships between TGF-β and GDF11 are not fully understood. With regard to their secretion levels and the skin regeneration and youth during aging, an expected ratio of TFG-β/GDF11 might be considered and regulated in a spatio-temporal manner and balance the whole cellular and molecular mechanisms associated to regeneration or rejuvenation. These regulating aspects must draw more attention as an important potential target attaining antiaging processes during wound healing.

2. Skin: anatomy and physiology

Skin thickness varies between people and with age and ranges on average from 0.05 to 2 mm. Skin is comprised of three layers: non-vascularized and stratified epidermis, underlying the dermis composed of a connective tissue and the subcutaneous adipose tissue forming the hypodermis including the adnexal structure [34]. The epidermis is preceded by an organized structure the *stratum corneum* formed by as interdigitated dead cells called corneocytes disposed as bricks between multiple lipid bilayers holding the structure defined as "brick and mortar" [35] and represent the first barrier to external factor penetration. The viable layers of the epidermis are *stratum lucidum*, *stratum granulosum, stratum spinosum,* and *stratum germinativum*. Keratinocytes composing these layers undergo progressive differentiation from the basal *stratum germinativum* to the outermost layer. These self-renewal and differentiation processes are important for epidermal regeneration and lead to generation of solid lipid-rich cornified layers [36]. Melanocytes are other cells present in the epidermis; they synthetize the melanin pigment being transferred to mature keratinocytes, providing principal skin protection against UV damages. Merkel cells, dendritic cells, adipocytes, and Langerhans cells are also present within the epidermis.

Fibroblasts are the principal cells constituting the dermis; they are mesenchymal and represent skin scaffolds where they support other epithelial cells and the epidermis through their elongation and shaped form, but especially through secretion of fibrous and elastic components constituting the ECM responsible for cutaneous strength and elasticity [34]. ECM is composed of fibrous proteins and a ground

substance. Both these components are rearranged to provide a three-dimensional microenvironment where epithelial cells, stem cells, and the vascular network are closely related to collagen, elastin, and fibronectin fibers [37]. In human skin, collagen fibers, mostly type I, III, and V, are the dominant components in the ECM accounting for 75% of the dry skin weight and confer elasticity and strength. Type I collagen represents 80–90% of the total collagen and type III up to 8–12% while type V collagen represents the remaining minor proportion [38]. ECM not only provides a structural support for skin cells but also plays very critical role in regulating cell behavior in normal conditions and wound healing [39]. This regulation occurs through molecular signaling mediated by integrin cell surface, which orients cells toward proliferation, differentiation, migration, or apoptosis [40].

Additional skin components residing in the dermis and sometimes in the hypodermis are immune cells represented by lymphocytes, macrophages, mast and dendritic cells. Adnexal structures are located in the dermis and hypodermis and include hair follicles, blood vessels, nerves, eccrine glands, sebaceous glands, and apocrine gland.

The hypodermis layer or subcutaneous layer is composed mostly by adipose tissue containing adipocytes, stem cells (ADSCs), and blood and lymph vessels. This adipose tissue is the main actor in regulating skin homeostasis, thermoregulation, metabolism, immune responses, and immunomodulation through a wide range of cytokines and chemokines secreted. This secretory panel conditions the microenvironment of the surrounding ADSCs and consequently their secretome to modulate skin cell proliferation, differentiation, migration, melanin production, and to induce skin rejuvenation [41–43].

3. Skin aging

3.1 Mechanisms of skin aging

Skin aging dependent on age or photoaging represents actually a real challenge of the new ADSCs advancements. The apparent skin physiology and morphology represent the first signal of cell aging. Skin aging is represented by epidermal atrophy, wrinkles appearance, reduction of dermal thickness, and ECM degradation; adnexal structures also decrease in their number and function. Decrease in the number of epithelial cells including DF, melanocytes, and Langerhans cells was reported as well. Their replicative ability decreases with age, leading to senescent and non-dividing cells.

The thickness of subcutaneous adipose tissue is also reduced, showing a decrease in mitotic activity and self-renewal of ADSCs and increase in senescence of the surrounding cells. ADSCs might behave differently according to the context of stimulation, but the mainly important factors that are relayed to cell proliferation, proinflammation, and angiogenesis altogether are involved in cell regeneration.

3.2 Physiological markers of skin aging

We believe now that aging is associated to many intrinsic signaling pathway related to epigenetic factors, some genetic predispositions, and extrinsic factors such as ultraviolet radiations, air and water pollution, resulting in the impairment of skin integrity and youth. One could consider that UV/infrared (IR) irradiations might lead to more cell damage than intrinsic factors. Indeed, following IR irradiation, skin cells present different DNA damages. Also, wrinkles, elasticity loss, pigmentation dysfunction, or hyperkeratosis are the most common symptoms reflecting the visual extent of aging as a result of the progressive atrophy of the

dermis. These manifestations rely on the impairment of cell senescence, a multifactorial event leading to skin integrity loss. Collagen production decreases and its degradation increases, leading to a quantitative and structural change in collagen fibers, which impact the dermis structure [44–46].

In humans, GDF11 is connected to age-related diseases and its serum level is associated with the physiology of aging [47, 48]. Its circulating level has been associated with aging in many human organs [23, 49, 50]. This factor was found to be able to antagonize aging specifically [29] and its remarkable action against myocardial hypertrophy and inflammation has been largely reported [28, 51, 52].

During skin aging, keratinocytes, DF and although endothelial cells secrete ubiquitous endopeptidases able to degrade the ECM proteins and called matrix metalloproteinase (MMP). Degradation of collagen fibers occurs with the major protease present in human skin MMP-1 that degrades type I and III collagen, followed by MMP-3 and MMP-9 [53]. The specific tissue inhibitors of metalloproteinases (TIMPs) regulate MMP processes where their increase in levels during aging was not concomitant with that of TIMPs leading to intrinsic collagen deficiency and accelerated skin aging. Moreover, Patel et al. have suggested that the ratio of MMP/TIMPs could be considered as a biomarker of wound healing and aging [54]. In photoaging, elastic fiber disorganization and degradation were observed, mainly due to activation of MMP-2, MMP-3, MMP-9, MMP-12, and MMP-13 [45, 55, 56]. UVA-treated fibroblasts presented a typical senescence phenotype including upregulation of α-SMA, MMP-1, and MMP-2 expression [25].

Behind the increase in MMP levels, another component generated in skin cells is represented by reactive oxygen species (ROS). When activating the mitogen-activated protein kinase (MAPK) family, transcriptional factors such as activator protein 1 (AP-1) and nuclear factor-kB (NF-kB) induce upregulation of MMP in DF and keratinocytes [57–60]. In addition, when cells aged, dysfunctions of mitochondrial electron transport chains and a decrease in mitochondrial activity were reported leading to higher production of ROS [61, 62]. Accumulation of ROS induced oxidative damages of structural proteins and lipoproteins, thus favoring cell senescence. On the other hand, this senescence might also be induced by the decline in replicative capacity due to DNA damage, including DNA methylation, histone deacetylation, or to chromatine architecture change and to gene expression which compromise the intended cellular function. The increase in mitochondrial ROS generation was also correlated to the decrease in DF size and spreading observed during progressive ECM degradation and impaired DF attachment due probably to the involvement of MMP production [57, 63, 64].

ROS also regulated different biological mechanisms including generation of inflammatory responses. Indeed, aging is associated to an increased secretion of proinflammatory proteins such as interleukin-6 (IL-6) and matrix metalloproteinase (MMP)-9, leading to immune changes. Prolonged release of ROS in skin might amplify the inflammatory injury and promote chronic inflammation [65].

Some transcription factors such as P63 (P53 related protein) and $P16^{INK4a}$ are reported as indicators of keratinocytes senescence. Indeed, expression of $P16^{INK4a}$ positive cells increased with chronological aging in human dermis and epidermis while P63 expression was reduced [66, 67].

4. Role of ADSCs in skin regeneration

During normal development, skin regeneration is performed by the resident ADSCs providing for cellular turnover during skin homeostasis and repair after injury [41]. The basal layer is the skin location where these active multipotent stem

cells are responsible for recruiting and sending mature differentiated cells (keratinocytes) to the outer layer of epidermis. Through a hierarchic gradient, these stem cells induced the regeneration of epidermis layer by ensuring self-renewal and a continuous production of transient amplifying cells [68]. Epidermal cells including ADSCs and DF closely interact to maintain local microenvironment propitious for cell turnover, leading to skin regeneration. Adding to their tendency to differentiate into keratinocytes, DF, and probably melanocytes, cross-talk of ADSCs and these cells is a part of normal skin function where ECM secretion leads to a physical environment critical for the maintenance of the stem cell niche [69].

Another proof of the interactions between fibroblasts and ADSCs has been provided by Hu et al. where skin fibroblasts cell line HS27 was found to activate ADSCs to differentiate into fibroblast-like cells highly expressing vimentin, HSP47, and desmin mRNA level [70]. The interactions of microvascular endothelial cells and ADSCs are also of great interest in skin cell regeneration and proliferation by providing IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1) and VEGF, leading to inflammation and angiogenesis regulation [71, 72]. In normal conditions, ADSCs are continuously activated by human serum and platelets to induce their proliferation and differentiation. While in wounded tissues, platelets induced stem cells to initiate the inflammatory phase by secreting platelet-derived growth factor (PDGF), IL-6 and IL-8, which lead to migration of macrophages and neutrophils to the wounded site [73], and TGF-β inducing induction of monocytes to macrophages (**Figure 1**).

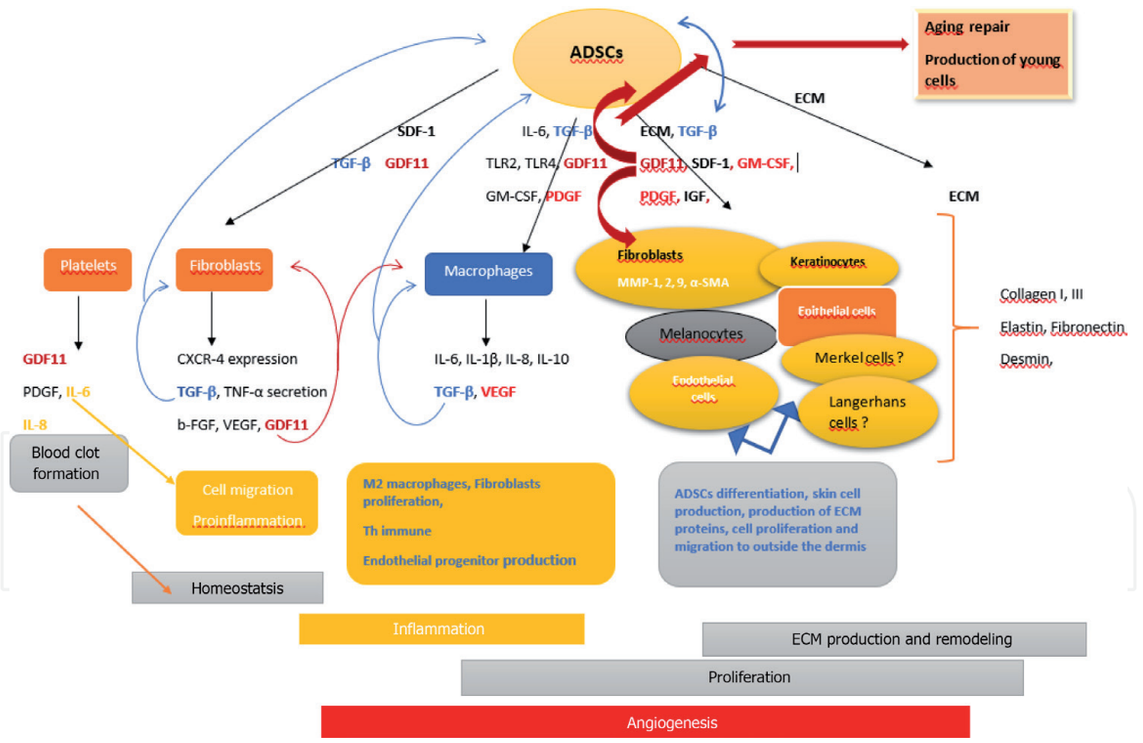

Figure 1.
Implication of adipose-derived stem cells in the different phases associated to wound healing and in the rejuvenation process. ADSCs act on fibroblasts, macrophages, and skin cells through their secreted growth factors. GDF11 and TGF-β are present in all the phases, amplify fibroblast, macrophage, and ADSC secretion, leading to immune response, cell proliferation, and angiogenesis. However, their interactions are more relevant during proliferation phases where GDF11 might induce TFG-β induction in a spatio-temporal manner in addition to boosting fibroblast proliferation, resulting in the production of skin cell presenting young profile. GDF11: growth differentiation factor, TGF-β: transforming growth factor, ECM: extracellular matrix, PDGF: platelets-derived growth factor, Il-1,6,8,10: interleukin-1, TNF-α: tumor necrosis factor-α, b-FGF: basic-fibroblast growth factor, VEGF: vascular endothelial growth factor, CXCR-4: C motif chemokine receptor 4, SDF-1: stromal derived factor-1, TLR2, 4: toll-like receptor2,4, GM-CSF: granulocyte monocyte-colony stimulating factor, IGF: insulin growth factor, MMP-1,-2, -9: matrix metalloproteinase-1, -2, -9, α-SMA: α-smooth muscle actin.

Similar to platelets, ADSCs additionally secrete prostaglandin E2 (PGE2), TNF-α, and GDF11, thus potentiating proinflammatory responses and later anti-inflammatory cytokine secretion by polarizing macrophages from M1 to M2.

In addition to TGF-β and GDF11, ADSCs secrete other growth factors such as basic-fibroblast Growth Factor (b-FGF), stromal-derived factor-1 (SDF-1), insulin-like growth factor (IGF), hepatocyte growth factor (HGF), and wingless 10b (Wnt10b), which are involved in the mechanisms regulating skin cell regeneration and repair [10, 23, 74]. The factors VEGF, PDGF, TGF-β, b-FGF, and HGF induce the formation of new blood vessels during the proliferative phase, probably through their differentiation into endothelial progenitor cells [10, 75]. The secreted GM-CSF can take part in this activation by inducing differentiation into committed monocytes potentially activated to macrophages and endothelial cells. In chronic radiation wounds, the use of ADSCs promoted new blood vessels damaged by the irradiation and increased the capillary density. These cells were found to act through stimulation of fibroblast proliferation and increase in VEGF secretion level [76].

However, endothelial cells and macrophages migration have been possible once after macrophages leaded to secretion of the ECM proteins especially collagen I and III, elastin and fibronectin and to activation of DF to proliferate and migrate. DF also secretes VEGF, TGF-β, and b-FGF, leading to angiogenesis [75, 77]. ADSCs are expected to participate actively in ECM production, whereby its abundant accumulation would facilitate cell migration and angiogenesis by autoinduction and amplification of the growth factor secretion implied. When miming injured conditions *in vitro*, ADSCs were indeed demonstrated to accelerate neovascularization through the expression of hypoxia-inducible factor-1α [78] by regulating VEGF gene expression in endothelial cells [79]. These observations were confirmed *in vitro* in addition to an activation of stem cell proliferation and to keratinocytes chemoattraction and migration [80] likely facilitated by MMPs [81].

Migration of ADSCs to the injured site is of pivotal interest; their immune profile and their potential shift toward a more anti-inflammatory phenotype is required for the proliferation and remodeling phases of healing [82–84]. The cytokine profile of T, B, and dendritic cells was influenced by ADSCs, which lead to the interruption of the inflammatory phase and starting the proliferation and remodeling phases in chronic wounds [6, 85, 86]. The potential involvement of GDF11 in disrupting the proinflammatory status toward the anti-inflammatory one is likely due to its highly stimulation of DF and ADSCs and also by amplifying the action of TGF-β on ADSCs proliferation and secretome. This epigenetic modification and regulation of ADSCs' microenvironment might be crucial in restoring cellular age defects and/or increasing cells' ability to differentiate and migrate. The impact of changing microenvironment on induction of cell proliferation, differentiation, and migration has already been reported [41–43].

The collagen production amplified by cross-talk between ADSCs, DF, and TGF-β would facilitate the remodeling phase through inhibiting ECM degradation by increasing TIMPs' secretion and their binding to MMPs [87]. Xiao et al. have reported that adipose tissue secretome increased N-cadherin and CD44 adhesion molecules involved in fibroblasts' motility during wound healing and stimulation of fibronectin expression during ECM remodeling [88]. Combination of activin B and ADSCs led to rapid wound closure and to accelerated epithelialization through promoting keratinocytes and fibroblasts proliferation [5]. The integrin αβ6 exclusively expressed by epithelial cells was associated to the regeneration of basement membrane zone during wound repair [89].

Figure 1 summarizes ADSCs' mechanisms involved in tissue repair.

5. ADSCs' interactions with TFG-β and GDF11 for skin regeneration

Increasing evidence has implicated ADSCs in maintaining skin homeostasis at a cellular level through cell differentiation and at the paracrine level. The exosomes they secrete respond to the hemostasis of skin microenvironment by releasing the growth factors promoting neo-angiogenesis, cell differentiation, cell proliferation, and migration [11, 16, 90–92].

5.1 Proliferation and differentiation of ADSCs into skin cells

Through their secreting growth factors, ADSCs impacted cell proliferation, migration, and senescence, which are the physiological parameters associated with wound injury and aging. During wound healing, ADSCs and DF have been reported to optimize and address their local environment, the secreted ECM proteins have been reported to modulate the activity of keratinocytes and DF through mediating secretion of growth factors such as TGF-β to activate the healing process [41–43, 69]. TGF-β plays a critical role in ECM protein production and especially collagen synthesis and degradation via the SMAD pathway [44]. Sasaki et al. were the first to identify the implication of MSCs in skin regeneration by their ability to differentiate and to repopulate damaged tissues [93]. Also, green fluorescent protein (GFP)-positive bone marrow MSCs were able to differentiate into keratinocytes, endothelial cells, and pericytes presenting altogether specific cell line markers [42].

Nevertheless, other factors are secreted by ADSCs or other epithelial cells that were recently identified to pave the way to the ones reported above or even have a place of honor in favoring skin regeneration or rejuvenation. In regard to this fact, the first on the list might be the GDF11, another member of the TGF-β family recently involved in the structural and functional amelioration of skin cell and supporting skin stem cell proliferation and differentiation [23, 24].

GDF11, also known as bone morphogenetic protein-11 (BMP-11), is a disulfide-linked dimer existing in a proactive form maturing after cleavage by furin-like proteases with 407 amino acids. This factor is expressed in embryonic tissues while mRNA and protein levels were differently appreciated with higher protein levels in soft tissue, cerebral cortex, adrenal gland, testis, and hippocampus [5]. Many physiological and pathophysiological functions are attributed to this factor, including cell embryonic development, erythropoiesis, proliferation and differentiation, cardiovascular diseases, diabetes mellitus, and age-related diseases [5, 94].

However, the mostly important fact reported is that secreting GDF11 by ADSC originates the mechanisms related to cell differentiation and proliferation and cell migration even by upregulating genes involved in skin barrier function, in cellular proliferation, to epidermal turnover and differentiation and via modulating the TGF-β/SMAD pathway. Genes related to ECM production were also found upregulated after Smad2 and Smad3 activation, in parallel to decrease in IL-1β proinflammatory cytokine-related gene [24]. Indeed, DF produced TGF-β and GDF11 [95, 96] in addition to laminin, collagen, elastin, and fibronectin to ensure mechanical stability of the dermis and participated to epidermis cell functions including those of keratinocytes and melanocytes. ADSCs were also reported to secrete ECM proteins participating in this activation loop.

Additionally, ADSCs might be automodulated by the secreted GDF11. On the other hand, GDF11 increased MMP-9 gene expression, which is known to interact with TGF-β to help wound closure and facilitate wound healing. However, high production of this protein is expected to improve matrix remodeling after injury rather than its degradation [97].

5.2 Skin cell migration

Subcutaneous MSCs mainly identified as ADSCs were considered as the principal actor in the process of skin cell migration [93] but their presence within skin layers has not been established yet. Additionally, adipose tissue extract containing evidently ADSC's secretome was able to significantly stimulate DF migration [25].

By expressing the chemokine receptor CCR7, which is the specific receptor of SLC/CCL21 involved in cell migration, MSCs accelerated their recruitment and migrated to the injured site, thus stimulating wound repair by giving rise to differentiated skin cells *in vivo*.

TGF-β is secreted by DF, macrophages, and ADSCs and consequently amplifies angiogenesis and migration of ADSCs, keratinocytes, and DF by stimulating the SMAD2/3 pathway and increasing the expression of CXCR-4 receptor of SDF-1. This migration has been confirmed *in vitro* while ADSCs were recruited into damaged sites by SDF-1 [98], using the SDF-1/CXCR-4 axis and the intracellular Jak/AKt regulation pathway [99]. GDF11 also stimulated DF and keratinocytes to migrate into wounded sites [23]. By activating the same SMAD2/3/pathway, GDF11 and TGF-β stimulate skin endothelial cells to migrate, thus improving angiogenesis. This suggested that GDF11 activates the identical pathway in other skin cells such as DF and keratinocytes to improve cell migration and wound repair [24].

Other mechanisms leading to ADSC migration were reported after their activation by activin B, JRK, and ERK signaling appeared to be responsible for actin stress fiber formation involved in cell migration [5]. Interestingly, activin B was found to promote ADSC migration by enhancing α-SMA expression and stress fiber formation.

5.3 Melanocytes regulation

ADSCs also interplay with the activation loop of melanocytes by modulating enzyme-producing melanin activity. ADSCs by increasing their TGF-β secretion induced melanocytes to downregulate the expression of melanogenic enzymes and prevent site-specific pigmentation in reconstructed skin grafts. These interactions might be of interest in clinical applications by modulating melanin synthesis and impacting whitening of the skin through TGF-β [100]. DF increased TGF-β secretion, thus maintaining melanocytes in an immature state, and acted on melanocytes to modulate melanin-producing enzymes and thus skin pigmentation [101], suggesting that dermal composition in cells might determine the production of mature melanocytes and hence melanin transfer to keratinocytes. However, a recent study has shown that rGDF11 significantly reduced melanin production in melanocytes and 3D skin equivalents [24]. On the other hand, during aging, ROS accumulation by cell proliferation was reported as the initiator of the occurrence of vitiligo and its progression [102].

These reports might increase our thought on a potential ratio of GDF11 and TGF-β in different skin type and color. This ratio could result on a balance between skin pigmentation and skin yought and lead to a sustainable skin biology and function through regulation of the mechanisms related to skin cell proliferation and rejuvenation. If this is the case, one should conclude that white skins should present higher amounts of GDF11 and youthful aspects and present less symptoms of cell apoptosis and senescence during cell life. These observations must draw more attention in the future to better understand the paradigms triggering the mechanisms related to skin aging and pigmentation.

6. TGF-β and GDF11 impacts on immunoregulatory effects of ADSC in skin

Evidence of involvement of ADSCs in immunomodulation of tissues and their presence within the epidermal layer have suggested that these cells might play a crucial role in skin immunological functions in physiologic and injured skin. Accumulation of senescent cells is related to the production of proinflammatory factors such as IL-6, IL-8, and TNF-α; we can postulate that the associated chronic inflammation is a promoting age-associated disease due to tissue aging. This skin inflamm-aging was also supported by highly secreted proinflammatory cytokine IL-1 β [32, 33]. Microvascular endothelial cells also interact with ADSCs to increase secretion of IL-6, IL-8, and MCP-1 to modulate skin inflammation [72].

TFG-β, secreted by ADSCs and other epithelial cells, is involved in the inflammatory, proliferative, and remodeling phases of wound healing. This factor activates M2 macrophages and secretion of ECM proteins involved in skin structure repair, in angiogenesis, in DF proliferation and cell migration, and re-epithelialization.

The integrin αβ6 secreted by epithelial cells was reported to activate TGF-β modulation and thus the innate immune surveillance in skin [89]. Recently, the collagen triple helix repeat containing one protein was reported to contribute to healing process via increasing M2 macrophages recruitment and TGF-β expression level [103].

In the same way, IL-6, the major proinflammatory component of ADSC's secretome, was reported to initiate the inflammatory phase in injured tissues. Autoactivated ADSCs amplify their secretion and stimulate the secretion of TNF-α, TLR2, TLR4, IL-10, b-FGF, VEGF, TGF-β, and GDF11. These secretions would take place to short and shift the ADSCs profile to an anti-inflammatory profile and enhance angiogenesis, cell migration, and proliferation (**Figure 2**). Like TGF-β,

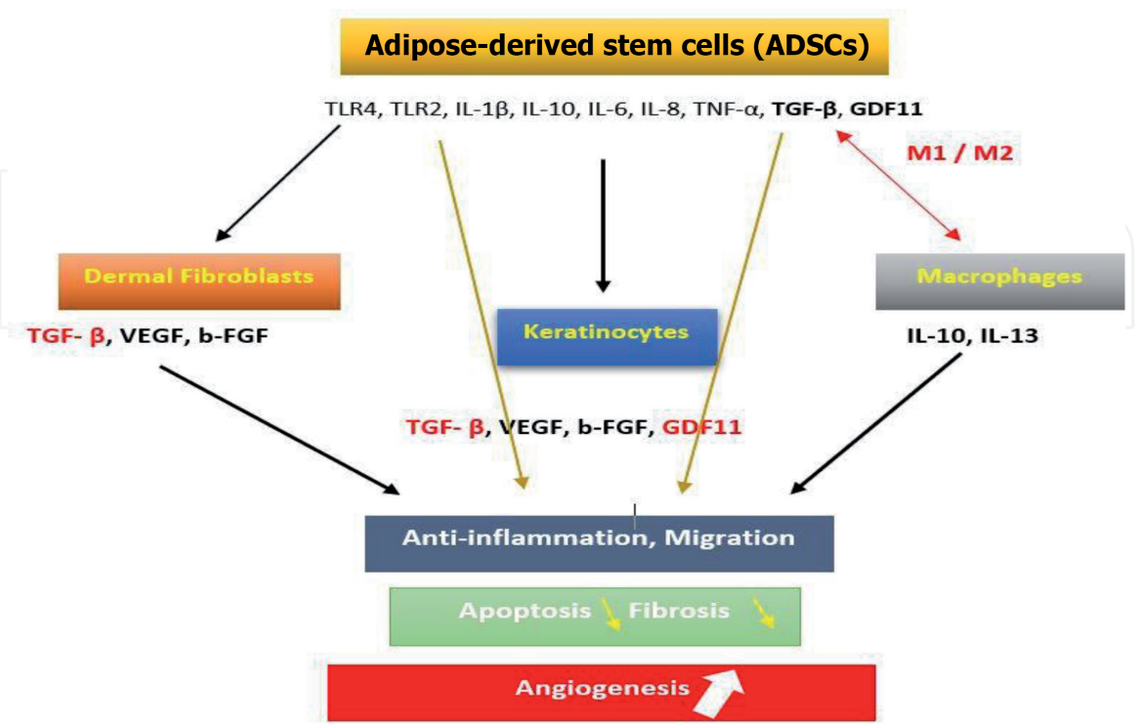

Figure 2.
Immunomodulatory effects of ADSCs. Through their secretome, these cells change the macrophages' polarization and acquire an anti-inflammatory profile to enhance skin cell proliferation and migration and accelerate angiogenesis.

GDF11 was found to be associated to the skin inflammatory status in both physiological process and injury and participate in the regulation of the immune response.

To determine the effect of GDF11 on skin inflammation, a recent work of Wang et al. has shown that skin treatment with rGDF11 decreased the secretion of inflammatory cytokines by immune cells *in vitro* and *in vivo* in mice models of psoriasis-associated inflammation, an extended infiltration of immune cells sustaining skin inflammation. Suppression of the severity of this inflammation by GDF11 was achieved by reducing macrophages infiltration to the skin and inhibiting the NF-kB signaling pathway [51]. Moreover, macrophages activation has been reported in skin autoimmune inflammatory diseases [104]. Other evidences argued on the protective effect of GDF11 from inflammatory reaction by inhibiting inflammatory responses in RAW264.7 macrophages [105], probably by inhibiting TNF-α release [106]. Additionally, TNF-α was activated by NF-kB signaling pathway during inflammation reaction, being suppressed by GDF11 in atherosclerosis. By reducing the NF-kB pathway, GDF11 also protected against apoptosis [105]. This suggested that the anti-inflammatory effect of GDF11 could open the way to potential new strategies for treating skin inflammations.

7. Antiaging mechanisms of ADSC within TFG-β and GDF11

7.1 Cellular implication

The mechanisms inducing tissue degeneration and cell aging remain multifactorial and still unclear. Senescent ADSCs were likely found to be impacted in their ability to sustain tissue hemostasis and hence resulted in loss of tissue and organ integrity. Even these cells display a rich secretory profile; their ability to secrete ECM proteins, cytokines, and chemokines was largely impaired *in vitro* during culture expansion [107].

A recent clinical study has demonstrated that secretome of adipose tissue lipoaspirate extracellular fraction stimulates epidermal and dermal cell proliferation in a dose-dependent manner. This secretome has also the ability to delay apoptosis, enhance fibroblasts proliferation and migration, and reverse specifically the aging process and the associated skin symptoms [25, 28]. Exposure of fibroblasts to UVA was followed by preventing the upregulation of MMP1, MMP2, and α-SMA expression as well as lower elastin and collagen production associated to the senescence-like phenotype [25]. Indeed, ADSCs have proven their superiority in improving and increasing dermal thickness and reducing wrinkles more likely by inducing paracrine DF and angiogenesis [17, 18, 108]. Administrated intradermally to an aged skin, skin texture and wrinkles as well as dermal thickness were found improved 8 weeks after treatment [74]. The extracellular vesicles released in ADSCs' secretome or conditioned media enable the targeted cells to increase the production and deposition of ECM proteins including collagen and elastin [11, 16, 90, 109, 110]. Among these autocrine/paracrine factors, TGF-β and GDF11 appeared to be strongly associated (**Figure 1**).

Indeed, ADSCs-conditioned media *in vitro* and *in vivo* have proven their efficiency in stimulating rejuvenation of human skin by improving skin elasticity and reducing wrinkles in a GDF11-dependent manner [111–113]. Their extract acted in a similar manner by activating DF and keratinocytes to proliferate and migrate into damaged sites [114]. An anti-wrinkle effect and dermal density increase were shown after *in vivo* treatment [23]. Moreover, the young cells secreting more GDF11 supported higher proliferation rate of keratinocyte stem cells than those from aged

donors [115]. In the same manner, using platelets-rich plasma (PRP) for anti-wrinkle and anti-aging skin aspects appeared legitime related to its higher quantities of GDF11 [116]. Interestingly, GDF11 expression and activity were reduced in adult DF compared to the neonatal ones [95].

Fibroblasts were also recognized to play a crucial role in skin regeneration through GDF11 secretion in both neonatal and adult cells [95]. MSCs derived from placenta and umbilical cord blood promote fibroblasts plasticity [117] probably through GDF11 release, thus stimulating the rejuvenation of human skin [118]. These authors have effectively demonstrated that GDF11 activated fibroblasts to increase ECM proteins' production and especially collagen I and III and fibronectin [23]. Also, MSCs have proven their proliferative superiority in young donors rather than the elderly [18].

In an animal model, transplanted autologous ADSCs improved skin-graft survival through secreting factors presenting anti-apoptotic activity [119]. In addition to ADSC, DF also appeared attractive in terms of protein secretion [109]. ADSC-conditioned media were anti-apoptotic and ensured skin tissue regeneration [119]; their protective and antiaging properties have been demonstrated on DF by preventing their oxidative stress and increasing their superoxide dismutase and glutathione peroxidase activities [120]. These cells act through their different and directed secretome to improve and induce tissue repair, consolidating their place as better candidate for regenerative medicine and opening recently the way for a new cell-free therapy [109, 121].

Moreover, by increasing collagenase matrix metalloproteinase-9 (MMP-9) secretion, rGDF11 participated in matrix remodeling maybe through interaction of MMP-9 with TGF-β1 to facilitate skin wound closure [97, 122]. These cell interactions reveal the role of the TFG-β and GDF11 mechanisms used by ADSCs to interfere with the aging process [24, 95, 101].

7.2 Intracellular mechanisms pathway balancing between TGF-β and GDF11 in skin aging

Aging of ADSCs and DF was associated to upregulation of apoptotic genes and, consequently, the number of senescent cells increased [123]. However, recent studies have demonstrated that this senescence can be induced by TGF-β/SMAD as a normal developmental process [124]. Also, in aged skin, accumulation of senescent cells and ROS likely impaired TGF-B pathway at least in DF. The mechanisms' pathways SMAD and Sirtuins are the mostly reported pathways whereby TGF-β and GDF11 acted.

The sirtuins are a family engaged in metabolism regulation and in aging-associated diseases, in addition to the mechanistic target of rapamycin (mTOR) signaling [16, 62, 125]. SIRT1 upregulation was reported to delay fibroblast's senescence and its expression is significantly reduced in aged skin [126]. Additionally, SIRT1, SIRT3, SIRT5, SIRT2, SIRT6, and SIRT7 are involved in the regulation of oxidative stress and ROS production [127, 128]. Moreover, SIRT6 is implicated in the relation of DNA repair proteins to chromatin [129].

In wound healing, phosphorylation of TGF-β/Smad2/3 intracellular pathways was increased and resulted in protein transfer to skin cell [16, 130, 131], in DF proliferation and ADSCs differentiation into fibroblasts [70], and in improvement of angiogenesis [24]. Interestingly, aging and cell differentiation have been reversed by inhibiting this pathway [132]. Indeed, activation of SMAD2/3-dependent-TGF-β signaling inhibits adipogenic and osteogenic MSCs' differentiation *in vitro* and *in vivo* [133, 134].

ADSCs self-renew is regulated by AKT signaling through targeting PDGFA and activating the PI3K/AKT2 axis is required for ADSCs proliferation and maintenance in the dermis [135]. Hypoxic conditions might play a pivotal role in wound repair, and the same pathway has been found leading to the activation of PI3K/AKt signaling [130]. In response to wound, ERK, AKt, and STAT-3 mechanisms pathways were activated and associated to stem cell proliferation and keratinocyte migration [80]. Interestingly, wound healing was specifically associated to microRNA and protein transfer to skin cells through the TGF-β/SMAD2 pathway, TGF-β being identified as a "mediator" [16, 132, 136].

TGF-β signaling pathway was recently reported as the main regulator of pluripotency [137]. Although epigenetically lacking myostatin is a highly homologous factor of GDF11, muscle multipotent stem cells can be reprogrammed to became pluripotent cells as embryonic cell-like. MicroRNA participates in this regulation probably by inhibiting TGF-β/Smad2 [132]. Epithelial differentiation was achieved by ADSCs through secreting Wnt10b and Wnt3a, a modulator of the Wnt/β-catenin implicated in replicative senescence regulation, suggesting that the regenerating and rejuvenating effect of GDF11 might also act via Wnt/β-catenin activation [138]. However, further investigations should be conducted to increase the knowledge on the intracellular mechanism used by the Wnt/β-catenin to delay the senescence of ADSCs and other targeted cells.

GDF11 is likely expected to act on other epidermal cells including DF, keratinocytes, and melanocytes by regulating the genetic expressions of the different proteins involved in the antiaging process. Recombinant GDF11 was likely reported to reinforce human skin by highly increasing ECM genes expression related to ECM production such as COL1A1, COL6A6, CL14A1, ELN, TGFBR3, and HAS1. Skin barrier function was likely improved by enhancing expression of ALOX12, ALOX12B, ALOXE3, DSG1, and DSP genes. Genes related to epidermal cell proliferation and differentiation were also upregulated in human skin through the Smad2/3mechanisms pathways [24].

Recently, fibroblast growth factors (FGFs) have been proposed as a therapeutic option to avoid skin aging aspects and to counter the cellular responses related to aging [139, 140]. Binding to tyrosine kinase receptors, they activate the autophosphorylation of Raf-1 belonging to the family of mitogen-activated protein kinase, kinase, kinase (MAPKKK), followed by that of MAPKK, which phosphorylates ERK (belonging to MAPK). Phosphorylation of these cyclin-dependent kinases in cell nucleus is involved in controlling cell division.

These FGFs are derived from fibroblasts and are decreased during their proliferative and metabolic activities, thus reducing ECM proteins' production. The decrease in FGF production also converge on the reduced amounts of collagen, decrease of dermal and epidermal integrity and elasticity and strength as signs of aging [141]. In addition to FGF secretion, fibroblasts are also targeted by TFG-β and GDF11 to activate the SMAD pathway leading them to have a pivotal role in skin regeneration. This suggests that FGF was expected to act independently but simultaneously to TGF-β and GDF11 to improve skin structure and aging aspects. Having a high mitogenic activity and high stability, rFGF-1 has been reported to strongly activate fibroblasts and keratinocytes proliferation with a potential use in angiogenesis, wound healing, and skin antiaging [142, 143]. In the same way, FGF-2 or b-FGF and keratinocyte growth factor (KGF) reduced wrinkles and increased proliferation of fibroblasts and keratinocytes modulating normal process of angiogenesis, tissue repair, and wound healing as well as significantly improving the antiaging process [27, 144, 145].

8. The spatio-temporal role of the TFG-β pathway in relationship with GDF11 in skin aging

When stimulating ADSCs through binding to their specific receptor membrane, activin type IIB (ActIIBR), GDF11 activates the SMAD2/3 pathways. Similar mechanism might be achieved on ADSCs by TGF-β, suggesting that interference with TGF-β and GDF11 mechanisms might be the key regulator of healing and aging. The same activated SMAD mechanisms pathway did not achieve similar biological activity and targeted probably different intracellular and intranuclear effectors. These considerations might suggest that even different specific receptors are involved in the extracellular interactions of these factors, a competitive attractivity might be observed between their intracellular effectors, which are the SMAD 2/3 proteins. When the factors compete for these proteins, one can speculate that the favored pathway would be associated either to the amount of the activated receptor (TGF-β or GDF11) or to the sensibility of these receptors to their respective ligands.

Another point of view that could be important to mention is the variation in secretion level of these factors during aging. At this fact, serum level of GDF11 has been reported to decrease during age while TGF-β variation was not really investigated. The antiaging pathway GDF11-dependent could be replaced progressively during aging by the TGF-β regenerating one. This might favor tissue regeneration and repair rather than rejuvenation, leading to the appearance of the symptoms of age.

Thus complicating the dilemma between rejuvenation and regeneration. Secretome composition of ADSCs might be impacted by the aging process or the different epigenetic factors.

9. Conclusion

In wound defects, ADSCs presented a great ability in migration and were recruited rapidly into wounded sites where the process of cell differentiation toward various skin cell components occurred. However, ADSCs participate more likely in all the phases of wound healing through autocrine and paracrine pathways [6]. Otherwise, during aging, senescent cells increase and the paracrine senescent secretome of ADSCs can trigger and reinforce senescence within their microenvironment [124]. This paracrine effect can be transmitted by ligands of TGF-β by mediating changes in the transcriptional program through SMAD family members [146].

Another surprising capacity of these cells is that secretome derived from younger cells is more suitable to increase proliferation than that derived from older cell [18], suggesting that younger cells have the potential to secrete a youth growth factor identified as GDF11, able to quantitatively increase cell proliferation at the younger stage. Targeted cells are the other crucial parameters leading to this increase; younger cells presented less senescence characteristics including DNA damage and ROS accumulation, thus, inducing cell rejuvenation. This process might be used to directly induce secretome of these cells toward tissue regeneration or rejuvenation.

We cannot exclude that MSCs and ADSCs secreted other cytokines than GDF11 and TGF-β, such as PDGF, IL-1, bone morphogenic protein (BMP)6, BMP9, and exerted autocrine and paracrine effects on DF and keratinocytes, promoting cell differentiation, proliferation, and migration. Nevertheless, the antiaging paracrine effect seemed to be induced, perhaps not exclusively but at least to

a significant degree, by a combinatorial effect of both GDF11 and TGF-β. It is probable that both signals vary with age and that the strength of each of them is reciprocal to the sites of secreted signals and to the length of the exposure to the signal. Based on these considerations, further investigations on TGF-β and GDF11 molecular mechanisms' implication on skin rejuvenation are needed to increase our knowledge and draw conclusions on the regulation of aging process. Exciting therapeutic approaches might arise from the implication of GDF11 as an antiaging mechanism to increase the lifespan and the long-lasting functionality of different organs.

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Conflict of interest

The authors declare no conflict of interest.

List of abbreviations

ADSCs	adipose-derived stem cells
GDF11	growth differentiation factor
TGF-β	transforming growth factor
ECM	extracellular matrix
DF	dermal fibroblasts
ROS	reactive oxygen species
MSCs	mesenchymal stem cells
MMP1, 2, 9	matrix metalloproteinase1, 2, 9
IL-1, −6, −8, −10	interleukin-1, −6, −8, −10
TNF-α	tumor necrosis factor-α
VEGF	vascular endothelial growth factor
PDGF	platelets derived growth factor
α-SMA	α-smooth muscle actin
MCP-1	monocyte chemoattractant protein-1

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