MEDWIN PUBLISHERS
Committed to create value for Researchers

Journal of Embryology & Stem Cell Research
ISSN: 2640-2637

Growth Differentiation Factor 11 (GDF11)/Transforming Growth Factor-β (TGF- β)/Mesenchymal Stem Cells (MSCs) Balance: A Complicated Partnership in Skin Rejuvenation

Mazini L[1]*, Rochette L[2] and Malka G[1]

[1]Laboratory of stem cells and Tissue Engineering, Mohammed VI Polytechnic University, Ben Guerir, Morocco

[2]Department of Cerebro-Cardiovascular Physiopathology and Epidemiology, University of Franche-Comte, France

Review Article

Volume 3 Issue 2

Received Date: July 29, 2019

Published Date: August 19, 2019

DOI: 10.23880/jes-16000122

***Corresponding author:** Loubna Mazini, Laboratoire Stem Cells and Tissue Engineering, Medical Applications Interface Center, Mohammed VI Polytechnic University, 43 150 Ben-Guérir, Morocco, Tel: +212 666 39 28 99; Email: loubna.mazini@um6p.ma

Abstract

Different theories on how cells aged and many strategies to overcome this have been thought and retained much more attention in designing research in tissue regeneration and skin anti-aging. Mesenchymal stem cells (MSCs) have showed great interest since identified as residual stem cells in almost adult organs. These cells presented great ability in migration and were recruited rapidly into wounded sites where process of cell differentiation towards various skin cell components occurred. MSCs senescence may be involved in the loss of tissue homeostasis, which could lead to organs failure and development of age-related diseases. Several studies have demonstrated that intravenously injected MSCs can migrate specifically to the sites of tissue damage, such as those caused by ischemic conditions or inflammation. A continuous state of inflammation in the wound creates a cascade that perpetuates a nonhealing state. During the inflammatory phase, MSCs coordinate the effects of inflammatory cells and inhibit the deleterious effects of inflammatory cytokines. Different proteins are secreted by these cells such as vascular endothelial growth factor (VEGF), Transforming Growth Factor-β (TGF-β), and Growth Differentiation Factor 11 (GDF11) are the key tools for ensuring tissue regeneration. The mechanisms inducing tissue degeneration and cell aging remained multifactorial and still unclear. The skin undergoes constant changes, with a high capacity of repair and renovation. In wound healing, evidence established the involvement of MSCs and dermal fibroblasts (DF) through sirtuins and SMAD pathways. Moreover, the mainly and recently studied secretome of MSCs is the extracellular vesicles involved in migration and proliferation of DF and keratinocytes where GDF11 and TGF-β were expected to play the principal role. Theoretically identical MSCs populations from individuals may display different secretome properties, depending on factors including age and health status. Another source of adult stem cells, called adipose-derived stem cells (ADSCs), is relatively newer and less invasive with a

similar cell differentiation potential. Further in-depth studies are needed to clarify the relationships between these factors in promoting wound healing and antiaging process. These new approaches might be adapted for various cell types and the specific secretome promising for application in regenerative medicine.

Keywords: Skin; Mesenchymal Stem Cells; Dermal Fibroblasts; Wound Healing; Aging; TGF-β; GDF11

Abbreviations: MSCs: Mesenchymal stem cells; TGF-β: Transforming Growth Factor-β; GDF11: Growth Differentiation Factor-11; ADSCs: Adipose Derived Stem Cells; DF: Dermal fibroblasts; ECM: Extracellular matrix.

Introduction

Rejuvenation is the undeniably the major concern of all peoples through time. Based on alchemy and mysticism, the attained unique objective was to identify the youth elixir. Nobody expected that this elixir really exists within our own cells.

Different theories on how cells aged and many strategies to overcome this have been thought and retained much more attention in designing research in tissue regeneration and skin anti-aging. Even age-dependent aging or photo-aging, these intrinsic and extrinsic factors were associated with wrinkles, elasticity loss, discoloration, irregular and dysfunction of pigmentation, hyperkeratosis and many other symptoms [1,2]. These manifestations rely on the impairment of a biological mechanism known as cell senescence, a multifactorial event leading to skin integrity loss.

To promote skin regeneration and ensure rejuvenation, most of strategies were based on the promising ability of multipotent stem cells to enhance cell proliferation, extracellular matrix (ECM) production and growth factors secretion. In this case, mesenchymal stem cells (MSCs) have showed great interest since identified as residual stem cells in almost adult organs. MSCs remain a promising tool for regenerative medicine as the efficacy of MSC-based cell therapy has been demonstrated for a broad spectrum of indications. Resident MSCs in skin are indeed playing an important role in wound healing and rejuvenation processes [3]. These cells have been demonstrated to differentiate into fibroblasts inducing thus ECM production [4]. They are located at the base of the hair follicle (dermal papilla cells), in the dermal sheets (dermal sheet cells), in interfollicular dermis and could derived likely from the perivascular pericytes [5,6]. MSCs secrete a variety of autocrine/paracrine factors, called secretome, that support regenerative processes in the damaged tissue. MSCs display a rich secretory profile and express a variety of chemokines and cytokines that aid in repair of degraded tissue, restoration of normal tissue metabolism and counteracting inflammation. Recently, the secretome of MSCs have drew more attention as a mechanism governing skin repair and regeneration through stimulatory factors secretion [7,8]. Within this secretome, proteins such as Vascular Endothelial Growth Factor (VEGF), Transforming growth Factor-β (TGF-β), Growth Differentiation Factor 11 (GDF11), Stromal Derived Factor-1 (SDF-1) and basic-Fibroblast Growth Factor (b-FGF) have come to the light as key tools ensuring tissue regeneration and rejuvenation [6,9].

In wound healing, the mainly and recently studied secretome is the extracellular vesicles involved in migration and proliferation of dermal fibroblasts (DF) and keratinocytes including collagen and elastin deposition [10-15]. At the same way, authors reported similar positive effects of MSCs-conditioned media on skin aging manifestations [9,16-19]. All these secreted growth factors are able to act directly on skin cell properties and specifically on DF inducing thus angiogenesis and enhancing ECM production, thus allowing structural support and accelerating cell growth whereby antiaging process is attained. This interplay between MSCs secretion and the other epidermal progenitors seems to orchestrate the hierarchical process of regeneration and repair by an important MSCs-resident cells crosstalk in aging or after injury. 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” [14,20-22].

This SMAD pathway is also strongly involved in the aging process through the GDF-11 highlighted during cell rejuvenation and aging damage [9,23]. GDF11 is a member of the TGF-β superfamily playing a pivotal role in cell development and aging. Circulating GDF-11 level has been associated with aging in many human organs [9,24-

28] as well as in animal models [29-31]. 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 [32,33]. MSCs derived from umbilical cord blood secreted significantly higher amounts of GDF11 compared to those from bone marrow and adipose tissue [9] and appeared highly concentrated in platelets [34]. In current research, this factor has raised many questions about its involvement 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 to this cascade, the suggestion of an interaction of GDF11 and TGF-β for a sustainable skin biology and function have become more appropriate. In this review, we will try to reveal the potential of GDF11/TGF-β mechanisms in normal and wounded skin and to understand the paradigms which trigger during cell life a potential balance between cell regeneration and aging-associated mechanisms.

GDF11/TGF- β Interferences in Skin Biology

Aging is undeniably associated to a decline in most of organ's functionality. The severity of this decline remained mainly dependent of health history, quality of life and genetic factors [35] (Rochette L et Mazini M 2019 submitted). The mechanisms inducing tissue degeneration and cell aging remained multifactorial and still unclear. Impaired skin regeneration failed to ensure maintenance of the barrier and prevent its protection from pathological conditions. During normal development, skin regenerative capability is performed by the resident MSCs providing for cellular turn over during skin homeostasis and repair after injury [36]. 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 of epidermis. Through a hierarchic gradient, these stem cells induced epidermis layer regeneration by ensuring self-renewal and a continuously production of transient amplifying cells [37]. Fibroblasts were also recognized to play a crucial role in skin regeneration through GDF11 secretion in both neonatal and adult cells [38]. Kim Y, et al. have demonstrated that GDF11 activated fibroblasts to increase ECM proteins production and especially collagen 1 and 3 and fibronectin [9].

Wound Healing

MSCs presented great ability in migration and were recruited rapidly into wounded sites where process of cell differentiation towards various skin cell components occurred [39]. ADSC identified within the basal layer might influence the physiological characteristics of the injured skin. During the proliferation phase, cytokines and chemokines secreted by these cells were involved in several fibroblasts' characteristics such as cell proliferation, migration and specifically collagen synthesis and other ECM proteins connected with tissue repair and regeneration [40-42]. Indeed, conditioned media from ADSCs, umbilical cord- and amniotic fluid-MSCs significantly enhanced proliferation of DF [43]. Involvement of MSCs and DF are essential for the cascade of the factors related to skin regeneration and reflected the importance of endogenous compounds such as sirtuins and SMAD pathways [44,45]. The sirtuins are a family of proteins that comprise class III of the histone deacetylases. These NAD+-dependent proteins have been found to be intricately involved in a variety of important and skin-relevant cellular functions and processes, including aging, UV damage response, and wound repair. Various endogenous factors have proven evidence of their crucial role in angiogenesis especially the VEGF. These ADSCs were reported to secrete ECM supporting thus the skin structure under normal and healing conditions [46,47]. The proteins of this ECM were reported to modulate the activity of keratinocytes and DF through mediating growth factors secretion such as TGF-β to activate healing process [48,49]. Recently, the collagen triple helix repeat containing 1 protein contributed to healing process via increasing M2 macrophages recruitment and TGF-β expression level [50]. On behalf the secreted proteins involved in this wound healing, the TGF-β/SMAD 2 pathways were increased and DF induced. TGF-β receptor has been identified in MSCs [40] and its activation resulted in enhancing MSCs homing ability CXC chemokine receptor 4 (CXCR4) dependent. CXCR4 regulates the retention of stem/progenitor cells in the bone marrow and other tissues [51,52].

At the other side, GDF11 has been recently associated to skin aging. However, there are discrepancies between its serum levels reported and first studies did not relate on the decrease of its circulating level during aging [24]. Improving GDF11-antigen specificity versus myostatin, the other TGF-β family sharing with it more than 90% of its amino acid sequences, has demonstrated this decrease in animal models [53] and in human [26,54].

Many reports have demonstrated that GDF11 levels were related to disturbance in sustainable biological process in many organs as in cardiovascular diseases [28,55], in skin wounds [56] and in neurologic deficits

[57]. Nevertheless, when activation of SMAD2/3 pathways through GDF11 and its specific receptor membrane Activin type IIB (ActIIBR) occurred on MSCs, similar mechanism might be achieved by TGF-β, suggesting that interference with TGF-β and GDF11 mechanisms might be the key regulator of healing and aging. If there is a relationship between both factors acting on the same cell, one might be able to speculate that healing process could be modulated by balancing the TGF-β pathway.

Skin Pigmentation

During a single day in the sun, each exposed keratinocyte receives up to 105 ultraviolet (UV) photoproducts in its DNA. Therefore, an elaborate system is needed to repair UV-induced damage. Skin pigmentation can be altered owing to the direct and indirect effects of solar radiation on melanocytes. Indeed, solar radiation directly affects melanocyte homeostasis through the induction of well- defined structural alterations in DNA. Skin pigmentation can also be activated as a photo protective and adaptive mechanism against the effects of UV radiation on skin. In this context, the crosstalk between keratinocytes, fibroblasts, immune cells, and melanocytes is mediated by paracrine signaling cascade. Among the endogenous protective factors, the central process is the endogenous MSCs which coordinate the repair response by recruiting other host cells and secreting growth factors and matrix proteins.

Evidences of implications of MSCs in dermal and epidermal proliferation have suggested that these cells might impact melanocyte functions in physiologic and wounded tissues. Derived from human adipose, MSCs increased their TGF-β secretion inducing melanocytes to down-regulate the expression of melanogenic enzymes and prevent site-specific pigmentation in reconstructs skin grafting. These interactions might be of interest in clinical application by modulating melanin synthesis [58]. These cells increased TGF-β secretion maintaining thus melanocytes in an immature state. Dermal fibroblasts also acted on melanocytes by secreting cytokines and growth factors as TGB-β modulating melanin-producing enzymes and thus skin pigmentation [59], suggesting that dermal composition in cells might determine the production of mature melanocytes and hence melanin transfer to keratinocytes. Klar et al have demonstrated the crucial role of TGF-β in the whitening of skin [58]. However, a recent study has shown that recombinant GDF11 (rGDF11) significantly reduced melanin production in melanocytes and 3D skin equivalents [60]. 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 [61,62].

Skin Aging

Skin aging is an apparent process associating morphologic disgraces and structural deficits. ECM mainly secreted by DF are composed of glycosaminoglycans, collagen type I and III and elastin and is continuously modified by physiological and extrinsic factors. UV-induced oxidative stress and energy metabolism alterations could also be a possible skin aging process and are responsible for the degradation of this ECM leading to an increase in enzymatic activity associated with collagen degeneration and loss of mechanical functions such as elasticity [63].

Other intrinsic factors are actually known to impair physiological functions of the skin and associated to cell senescence including DNA damage [64,65], telomeres shortening [66] and reactive oxygen species (ROS) production [67]. All these processes show major roles in inducing tissue-aging and carcinogenesis [68,69]. However, recent studies have demonstrated that this senescence can be induced by TGF-β /SMAD as a normal developmental process. Otherwise, an interesting concept of paracrine senescent cells have been proposed by Lunyak, et al. [70] where resident senescent MSCs can trigger and reinforce senescence within their microenvironment. This paracrine effect can be transmitted by ligands of TGF-β by mediating changes in the transcriptional program through SMAD family members [71].

Nevertheless, ADSC and DF appeared more attractive in term of protein secretion [72]. ADSC-conditioned media were anti-apoptotic and ensure skin tissue regeneration [19,73,74] and protected DF by increasing their superoxide dismutase and glutathione peroxidase activities [63]. This MSCs-conditioned medium has been reported to stimulate and enhance DF proliferation and ECM production. An anti-wrinkle effect and dermal density increase were shown after in vivo treatment [9]. Moreover, the young cells supported higher proliferation rate of keratinocyte stem cells than those from aged donors [75]. Interestingly, GDF11 expression and activity were reduced in adult DF compared to the neonatal ones [38] as its expected for MSCs [76].

ADSC were present within hypodermis cellular components suggesting their benefit in preventing skin aging induced by ROS production. In addition, these cells have been largely reported to induce re-epithelialization of injured skin and are used as promising therapy for remodeling and cosmetic surgery [16,77]. Indeed, ADSC have proven their superiority in improving and increasing dermal thickness and reducing wrinkles more likely by inducing paracrine dermal fibroblasts and angiogenesis [77-79]. Administrated intradermally to an aged skin, skin texture and wrinkles as well as dermal thickness were found improved 8 weeks after treatment [80].

Discussion

Finally, MSCs senescence may be involved in the loss of tissue homeostasis, which could lead to organs failure and development of age-related diseases. Several studies have demonstrated that intravenously injected MSCs can migrate specifically to the sites of tissue damage, such as those caused by ischemic conditions or inflammation. In this context, MSCs display a rich secretory profile and express a variety of chemokines and cytokines that aid in repair of degraded tissue, restoration of normal tissue metabolism. MSCs are considered as the best candidate in tissue repair and regenerative medicine. They seemed likely to act through a secretome release pathway rather than cell replacement [32,81]. Another surprising capacity of these cells is that MSCs from a young donor are more proliferative than cells of an elderly individual [77]; this process is a new way of cell therapy without cells [72,82], via the potential directed secretome of these cells towards a tissue regeneration or rejuvenation. GDF11 and TGF-β present within this secretome are involved in many biological mechanisms including cell proliferation, tissue repair and rejuvenation. These both signaling have been reported to promote cancer metastasis [83,84]. In skin biology, GDF11 significantly increased genes expression related to ECM production, to maintenance of skin barrier function, to skin cell proliferation and to epidermal turnover and differentiation [60] by triggering SMAD signaling in a TGF-β like fashion, suggesting that intracellular messengers related to TFG-β regulated the changes in GDF11 secretion and impact on skin architecture and function.

We cannot exclude that MSCs secreted other cytokines than GDF11 and TGF-β, such as Platelets Derived Growth Factor, Interleukin-1, Bone Morphogenic Protein (BMP)6, BMP9, might exert an 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's probably 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 the knowledge and draw conclusions on the regulation of aging process.

Conclusion

Due to complex composition of MSCs secretomes and its relationships between the other skin cell components, it was necessary to focus on the specific promising growth factors that would reflect the regenerative potency in the process of skin aging. These new approaches might be adapted for various cell types and their specific secretomes promising for application in regenerative medicine. The ability of MSCs to promote the transition from the inflammatory to the proliferative phase is particularly critical for treating chronic wounds. Many efforts are under way to develop novel bioengineered wound-healing products and considering the role of MSCs in the wound-healing process.

Authors Contributions

All authors participated in the research and writing of this manuscript

Funding

This work was supported by the University Mohammed VI polytechnic, Ben Guérir, Morocco

Conflicts of Interest

The authors declare no conflict of interest

References

1. Fisher GJ, Kang S, Varani J, Bata Csorgo Z, Wan Y, et al. (2002) Mechanisms of photo aging and chronological skin aging. Arch Dermatol 138(11): 1462-1470.

2. Warren R, Chestnut MH, Wong TK, Otte TE, Lammers KM, et al. (1991) An improved method for the isolation and cultivation of human scalp dermal

papilla cells: maintenance of extracellular matrix. Ann N Y Acad Sci 642: 436-438.

3. Balaji S, Keswani SG, Crombleholme TM (2012) The Role of Mesenchymal Stem Cells in the Regenerative Wound Healing Phenotype. Adv Wound Care (New Rochelle) 1(4): 159-165.

4. Marfia G, Navone SE, Di Vito C, Ughi N, Tabano S, et al. (2015) Mesenchymal stem cells: potential for therapy and treatment of chronic non-healing skin wounds. Organogenesis 11(4): 183-206.

5. Hu MS, Borrelli MR, Lorenz HP, Longaker MT, Wan DC (2018) Mesenchymal Stromal Cells and Cutaneous Wound Healing: A Comprehensive Review of the Background, Role, and Therapeutic Potential. Stem Cells Int 2018: 6901983.

6. Kilroy GE, Foster SJ, Wu X, Ruiz J, Sherwood S, et al. (2007) Cytokine profile of human adipose-derived stem cells: expression of angiogenic, hematopoietic, and pro-inflammatory factors. J Cell Physiol 212(3): 702-709.

7. Ozpur MA, Guneren E, Canter HI, Karaaltin MV, Ovali E, et al. (2016) Generation of Skin Tissue Using Adipose Tissue-Derived Stem Cells. Plast Reconstr Surg 137(1): 134-143.

8. Cappuzzello C, Doni A, Dander E, Pasqualini F, Nebuloni M, et al. (2016) Mesenchymal Stromal Cell-Derived PTX3 Promotes Wound Healing via Fibrin Remodeling. J Invest Dermatol 136(1): 293-300.

9. Kim YJ, Seo DH, Lee SH, Lee SH, An GH, et al. (2018) Conditioned media from human umbilical cord blood-derived mesenchymal stem cells stimulate rejuvenation function in human skin. Biochem Biophys Rep 16: 96-102.

10. Tooi M, Komaki M, Morioka C, Honda I, Iwasaki K, et al. (2016) Placenta Mesenchymal Stem Cell Derived Exosomes Confer Plasticity on Fibroblasts. J Cell Biochem 117(7): 1658-1670.

11. Choi EW, Seo MK, Woo EY, Kim SH, Park EJ, et al. (2018) Exosomes from human adipose-derived stem cells promote proliferation and migration of skin fibroblasts. Exp Dermatol 27(10): 1170-1172.

12. Komaki M, Numata Y, Morioka C, Honda I, Tooi M, et al. (2017) Exosomes of human placenta-derived mesenchymal stem cells stimulate angiogenesis. Stem Cell Res Ther 8(1): 219.

13. Ferreira FA, Cunha P, Carregal VM, Cássia P, Miranda MC, et al. (2017) Extracellular Vesicles from Adipose-Derived Mesenchymal Stem/Stromal Cells Accelerate Migration and Activate AKT Pathway in Human Keratinocytes and Fibroblasts Independently of miR-205 Activity. Stem Cells Int 2017: 9841035.

14. Ferreira A, Gomes DA (2018) Stem Cell Extracellular Vesicles in Skin Repair. Bioengineering (Basel) 6(1).

15. Kim YJ, Yoo SM, Park HH, Lim HJ, Kim YL, et al. (2017) Exosomes derived from human umbilical cord blood mesenchymal stem cells stimulates rejuvenation of human skin. Biochem Biophys Res Commun 493(2): 1102-1108.

16. Gaur M, Dobke M, Lunyak VV (2017) Mesenchymal Stem Cells from Adipose Tissue in Clinical Applications for Dermatological Indications and Skin Aging. Int J Mol Sci 18(1).

17. Son WC, Yun JW, Kim BH (2015) Adipose-derived mesenchymal stem cells reduce MMP-1 expression in UV-irradiated human dermal fibroblasts: therapeutic potential in skin wrinkling. Biosci Biotechnol Biochem 79(6): 919-925.

18. Wang T, Guo S, Liu X, Xv N, Zhang S (2015) Protective effects of adipose-derived stem cells secretome on human dermal fibroblasts from ageing damages. Int J Clin Exp Pathol 8(12): 15739-15748.

19. Zografou A, Tsigris C, Papadopoulos O, Kavantzas N, Patsouris E, et al. (2011) Improvement of skin-graft survival after autologous transplantation of adipose-derived stem cells in rats. J Plast Reconstr Aesthet Surg 64(12): 1647-1656.

20. Walter MNM, Wright KT, Fuller HR, MacNeil S, Johnson WEB (2010) Mesenchymal stem cell-conditioned medium accelerates skin wound healing: an in vitro study of fibroblast and keratinocyte scratch assays. Exp Cell Res 316(7): 1271-1281.

21. Fang S, Xu C, Zhang Y, Xue C, Yang C, et al. (2016) Umbilical Cord-Derived Mesenchymal Stem Cell-Derived Exosomal MicroRNAs Suppress Myofibroblast Differentiation by Inhibiting the Transforming Growth Factor-β/SMAD2 Pathway

During Wound Healing. Stem Cells Transl Med 5(10): 1425-1439.

22. Jun EK, Zhang Q, Yoon BS, Moon JH, Lee G, et al. (2014) Hypoxic conditioned medium from human amniotic fluid-derived mesenchymal stem cells accelerates skin wound healing through TGF-β/SMAD2 and PI3K/Akt pathways. Int J Mol Sci 15(1): 605-628.

23. Sinha M, Jang YC, Oh J, Khong D, Wu EY, et al. (2014) Restoring systemic GDF11 levels reverses age-related dysfunction in mouse skeletal muscle. Science 344(6184): 649-652.

24. Egerman MA, Cadena SM, Gilbert JA, Meyer A, Nelson HN, et al. (2015) GDF11 Increases with Age and Inhibits Skeletal Muscle Regeneration. Cell Metab 22(1): 164-174.

25. Jones JE, Cadena SM, Gong C, Wang X, Chen Z, et al. (2018) Supraphysiologic Administration of GDF11 Induces Cachexia in Part by Upregulating GDF15. Cell Rep 22(6): 1522-1530.

26. Schafer MJ, Atkinson EJ, Vanderboom PM, Kotajarvi B, White TA, et al. (2016) Quantification of GDF11 and Myostatin in Human Aging and Cardiovascular Disease. Cell Metab 23(6): 1207-1215.

27. Zhou Y, Jiang Z, Harris EC, Reeves J, Chen X, et al. (2016) Circulating Concentrations of Growth Differentiation Factor 11 Are Heritable and Correlate With Life Span. J Gerontol A Biol Sci Med Sci 71(12): 1560-1563.

28. Rochette L, Zeller M, Cottin Y, Vergely C (2015) Growth and differentiation factor 11 (GDF11): Functions in the regulation of erythropoiesis and cardiac regeneration. Pharmacol Ther 156: 26-33.

29. Duran J, Troncoso MF, Lagos D, Ramos S, Marin G, et al. (2018) GDF11 Modulates Ca2+-Dependent Smad2/3 Signaling to Prevent Cardiomyocyte Hypertrophy. Int J Mol Sci 19(5).

30. Zimmers TA, Jiang Y, Wang M, Liang TW, Rupert JE, et al. (2017) Exogenous GDF11 induces cardiac and skeletal muscle dysfunction and wasting. Basic Res. Cardiol 112: 48.

31. Du GQ, Shao ZB, Wu J, Yin WJ, Li SH, et al. (2017) Targeted myocardial delivery of GDF11 gene rejuvenates the aged mouse heart and enhances myocardial regeneration after ischemia-reperfusion injury. Basic Res Cardiol 112(1): 7.

32. Zhang Y, Wei Y, Liu D, Liu F, Li X, et al. (2017) Role of growth differentiation factor 11 in development, physiology and disease. Oncotarget 8: 81604-81616.

33. McPherron AC (2010) Metabolic Functions Of Myostatin And Gdf11. Immunol Endocr Metab Agents Med Chem 10(4): 217-231.

34. Bueno JL, Ynigo M, de Miguel C, Gonzalo Daganzo RM, Richart A, et al. (2016) Growth differentiation factor 11 (GDF11) - a promising anti-ageing factor - is highly concentrated in platelets. Vox Sang 111(4): 434-436.

35. Wang L, Lu M (2014) Regulation and direction of umbilical cord blood mesenchymal stem cells to adopt neuronal fate. Int J Neurosci 124(3): 149-159.

36. Blanpain C, Fuchs E (2009) Epidermal homeostasis: a balancing act of stem cells in the skin. Nat Rev Mol Cell Biol 10(3): 207-217.

37. Nurkovic J, Dolicanin Z, Mustafic F, Mujanovic R, Memic M, et al. (2016) Mesenchymal stem cells in regenerative rehabilitation. J Phys Ther Sci 28: 1943-1948.

38. Tito A, Barbulova A, Zappelli C, Leone M, Ruvo M, et al. (2019) The Growth Differentiation Factor 11 is Involved in Skin Fibroblast Ageing and is Induced by a Preparation of Peptides and Sugars Derived from Plant Cell Cultures. Mol Biotechnol 61: 209-220.

39. Sasaki M, Abe R, Fujita Y, Ando S, Inokuma D, et al. (2008) Mesenchymal stem cells are recruited into wounded skin and contribute to wound repair by transdifferentiation into multiple skin cell type. J Immunol 180: 2581-2587.

40. Zhen G, Wen C, Jia X, Li Y, Crane JL, et al. (2013) Inhibition of TGF-β signaling in mesenchymal stem cells of subchondral bone attenuates osteoarthritis. Nat Med 19: 704-712.

41. Na YK, Ban JJ, Lee M, Im W, Kim M (2017) Wound healing potential of adipose tissue stem cell extract. Biochem Biophys Res Commun 485(1): 30-34.

42. Hu L, Wang J, Zhou X, Xiong Z, Zhao J, et al. (2016) Exosomes derived from human adipose

mensenchymal stem cells accelerates cutaneous wound healing via optimizing the characteristics of fibroblasts. Sci Rep 6: 32993.

43. Yoon BS, Moon JH, Jun EK, Kim J, Maeng I, et al. (2010) Secretory profiles and wound healing effects of human amniotic fluid-derived mesenchymal stem cells. Stem Cells Dev 19(6): 887-902.

44. Khorraminejad Shirazi M, Farahmandnia M, Kardeh B, Estedlal A, Kardeh S, et al. (2018) Aging and stem cell therapy: AMPK as an applicable pharmacological target for rejuvenation of aged stem cells and achieving higher efficacy in stem cell therapy. Hematol Oncol Stem Cell Ther 11(4): 189-194.

45. Pillai VB, Sundaresan NR, Gupta MP (2014) Regulation of Akt signaling by sirtuins: its implication in cardiac hypertrophy and aging. Circ Res 114: 368-378.

46. Hodde JP, Johnson CE (2007) Extracellular matrix as a strategy for treating chronic wounds. Am J Clin Dermatol 8: 61-66.

47. Eckes B, Nischt R, Krieg T (2010) Cell-matrix interactions in dermal repair and scarring. Fibrogenesis Tissue Repair 3: 4.

48. Barrientos S, Stojadinovic O, Golinko MS, Brem H, Tomic Canic M (2008) Growth factors and cytokines in wound healing. Wound Repair Regen 16(5): 585-601.

49. Lynch SE, Nixon JC, Colvin RB, Antoniades HN (1987) Role of platelet-derived growth factor in wound healing: synergistic effects with other growth factors. Proc Natl Acad Sci USA 84(21): 7696-7700.

50. Qin S, Zheng JH, Xia ZH, Qian J, Deng CL, et al. (2019) CTHRC1 promotes wound repair by increasing M2 macrophages via regulating the TGF-β and notch pathways. Biomed Pharmacother 113: 108594.

51. Aspera Werz RH, Chen T, Ehnert S, Zhu S, Fröhlich T, et al. (2019) Cigarette Smoke Induces the Risk of Metabolic Bone Diseases: Transforming Growth Factor Beta Signaling Impairment via Dysfunctional Primary Cilia Affects Migration, Proliferation, and Differentiation of Human Mesenchymal Stem Cells. Int J Mol Sci 20(12).

52. Li M, Zeng L, Liu S, Dangelmajer S, Kahlert UD, et al. (2019) Transforming Growth Factor-β Promotes Homing and Therapeutic Efficacy of Human Mesenchymal Stem Cells to Glioblastoma. J Neuropathol Exp Neurol 78(4): 315-325.

53. Poggioli T, Vujic A, Yang P, Macias Trevino C, Uygur A, et al. (2016)Circulating Growth Differentiation Factor 11/8 Levels Decline With Age. Circ Res 118(1): 29-37.

54. Olson KA, Beatty AL, Heidecker B, Regan MC, Brody EN, et al. (2015) Association of growth differentiation factor 11/8, putative anti-ageing factor, with cardiovascular outcomes and overall mortality in humans: analysis of the Heart and Soul and HUNT3 cohorts. Eur Heart J 36(48): 3426-3434.

55. Rochette L, Meloux A, Rigal E, Zeller M, Cottin Y, et al. (2018) Regenerative Capacity of Endogenous Factor: Growth Differentiation Factor 11; a New Approach of the Management of Age-Related Cardiovascular Events. Int J Mol Sci 19(12).

56. Wang W, Qu R, Wang X, Zhang M, Zhang Y, et al. (2019) GDF11 Antagonizes Psoriasis-like Skin Inflammation via Suppression of NF-κB Signaling Pathway. Inflammation 42(1): 319330.

57. Anqi X, Ruiqi C, Yanming R, Chao Y (2019) Neuroprotective potential of GDF11 in experimental intracerebral hemorrhage in elderly rats. J Clin Neurosci 63: 182-188.

58. Klar AS, Zimoch J, Biedermann T (2017) Skin Tissue Engineering: Application of Adipose-Derived Stem Cells. Biomed Res Int 2017: 9747010.

59. Wang Y, Viennet C, Robin S, Berthon JY, He L, et al. (2017) Precise role of dermal fibroblasts on melanocyte pigmentation. J Dermatol Sci 88(2): 159-166.

60. Idkowiak Baldys J, Santhanam U, Buchanan SM, Pfaff KL, Rubin LL, et al. (2019) Growth differentiation factor 11 (GDF11) has pronounced effects on skin biology. PLoS ONE 14(6): e0218035.

61. Mohan R, Chintala SK, Jung JC, Villar WVL, McCabe F, et al. (2002) Matrix metalloproteinase gelatinase B (MMP-9) coordinates and effects epithelial regeneration. J Biol Chem 277(3): 2065-2072.

62. Kobayashi T, Kim H, Liu X, Sugiura H, Kohyama T, et al. (2014) Matrix metalloproteinase-9 activates TGF-β and stimulates fibroblast contraction of collagen gels. Am J Physiol Lung Cell Mol Physiol 306(11): L1006-1015.

63. Maity N, Nema NK, Abedy MK, Sarkar BK, Mukherjee PK (2011) Exploring Tagetes erecta Linn flower for the elastase, hyaluronidase and MMP-1 inhibitory activity. J Ethnopharmacol 137(3): 1300-1305.

64. Shibata KR, Aoyama T, Shima Y, Fukiage K, Otsuka S, et al. (2007) Expression of the p16INK4A gene is associated closely with senescence of human mesenchymal stem cells and is potentially silenced by DNA methylation during in vitro expansion. Stem Cells 25: 2371-2382.

65. Bell JT, Spector TD (2012) DNA methylation studies using twins: what are they telling us? Genome Biol 13(10): 172.

66. Ludke A, Li RK, Weisel RD (2014) The rejuvenation of aged stem cells for cardiac repair. Can J Cardiol 30: 1299-1306.

67. Alves H, Munoz Najar U, De Wit J, Renard AJS, Hoeijmakers JHJ, et al. (2010) A link between the accumulation of DNA damage and loss of multi-potency of human mesenchymal stromal cells. J Cell Mol Med 14(12): 2729-2738.

68. Ou HL, Schumacher B (2018) DNA damage responses and p53 in the aging process. Blood 131(5): 488-495.

69. Sperka T, Wang J, Rudolph KL (2012) DNA damage checkpoints in stem cells, ageing and cancer. Nat Rev Mol Cell Biol 13(9): 579-590.

70. Lunyak VV, Amaro Ortiz A, Gaur M (2017) Mesenchymal Stem Cells Secretory Responses: Senescence Messaging Secretome and Immunomodulation Perspective. Front Genet 8: 220.

71. Acosta JC, Banito A, Wuestefeld T, Georgilis A, Janich P, et al. (2013) A complex secretory program orchestrated by the inflammasome controls paracrine senescence. Nat Cell Biol 15(8): 978-990.

72. Niada S, Giannasi C, Gualerzi A, Banfi G, Brini AT (2018) Differential Proteomic Analysis Predicts Appropriate Applications for the Secretome of Adipose-Derived Mesenchymal Stem/Stromal Cells and Dermal Fibroblasts. Stem Cells Int 7309031: 11.

73. Wen L, Labopin M, Badoglio M, Wang D, Sun L, et al. (2019) Prognostic Factors for Clinical Response in Systemic Lupus Erythematosus Patients Treated by Allogeneic Mesenchymal Stem Cells. Stem Cells Int 2019: 7061408.

74. Kim WS, Park BS, Kim HK, Park JS, Kim KJ, et al. (2008) Evidence supporting antioxidant action of adipose-derived stem cells: protection of human dermal fibroblasts from oxidative stress. J Dermatol Sci 49(2): 133-142.

75. Ma N, Qiao C, Zhang W, Luo H, Zhang X, et al. (2017) Original Research: Adipose-derived stem cells from younger donors, but not aging donors, inspire the host self-healing capability through its secreta. Exp Biol Med 242(1): 68-79.

76. Fan M, Chen W, Liu W, Du GQ, Jiang SL, et al. (2010) The effect of age on the efficacy of human mesenchymal stem cell transplantation after a myocardial infarction. Rejuvenation Res 13(4): 429-438.

77. Zarei F, Abbaszadeh A (2018) Stem cell and skin rejuvenation. Journal of Cosmetic and Laser Therapy 20(3): 193-197.

78. Kim JH, Jung M, Kim HS, Kim YM, Choi EH (2011) Adipose-derived stem cells as a new therapeutic modality for ageing skin. Exp Dermatol 20(5): 383-387.

79. Kim WS, Park BS, Sung JH (2009) Protective role of adipose-derived stem cells and their soluble factors in photoaging. Arch Dermatol Res 301: 329-336.

80. Park BS, Jang KA, Sung JH, Park JS, Kwon YH, et al. (2008) Adipose-derived stem cells and their secretory factors as a promising therapy for skin aging. Dermatol Surg 34(10): 1323-1326.

81. Khan M, Kishore R (2017) Stem Cell Exosomes: Cell-FreeTherapy for Organ Repair. Methods Mol Biol 1553: 315-321.

82. Phelps J, Sanati Nezhad A, Ungrin M, Duncan NA, Sen A (2018) Bioprocessing of Mesenchymal Stem Cells and Their Derivatives: Toward Cell-Free Therapeutics. Stem Cells Int 2018: 23.

83. Yokoe T, Ohmachi T, Inoue H, Mimori K, Tanaka F, et al. (2007) Clinical significance of growth differentiation factor 11 in colorectal cancer. Int J Oncol 31: 1097-1101.

84. Lebrun JJ, Neel JC, Humbert L (2012) The Dual Role of TGFβ in Human Cancer: From Tumor Suppression to Cancer Metastasis. ISRN Mol Biol 2012: 28.