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The relation between adipose-derived stem cells and wound healing process - the review

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Abstract
Introduction and purpose: Wound healing is a process including complex overlapping stages requiring many components. Adipose tissue is an organ that is responsible for maintaining homeostasis through inflammatory responses, signal transmission, energy expenditure connected with different organs. Fat tissue is a rich and readily available source of multipotent stem cells. Adipose-derived stem cells (ADSCs) have the potential in tissue regeneration because of their self-renewal and ability to differentiate in various types of cells. This review discusses ADSCs in terms of basic knowledge, methods of acquisition, prospects for use in healthcare, focusing mainly on the potential application in the wound healing process.
Brief description of the state of knowledge: The article contains current knowledge about biology, specific properties of adipose-derived stem cells and also shows the relationship to the wound healing process. The review presents research that points to the possibility of using ADSCs in future medicine.
Conclusions: Adipose-derived stem cells may constitute a prominent role in tissue regeneration owing to the secretion of various cytokines, the ability to differentiate into multiple lineages, their immunomodulatory effects, and the ease of cell obtaining. Further

studies are required to explore the accurate mechanism of ADSCs action and their long-term safety in clinical application. Stem cell therapy brings new hope for the repair of chronic and refractory wounds and skin defects.

Key words: adipose tissue; stem cells; regeneration; wound healing

1. Introduction

Wound healing is a complicated, complex, and dynamic process that engages the coordination of various cell types, cellular processes, and maintain the integrity of the skin after injury, whether by accident or by purposeful action. This important physiological process has phases including hemostasis/inflammation, proliferation, and remodeling [1][2][3]. These stages demand cytokines, nutrients, inflammatory cells, chemokines, and many other molecules to the injury place where metabolism is greatly increased. Physiologic wound healing requires proper blood and oxygen supply, adequate protein and vitamins intake. It also depends on the extent, type, size, location, and depth of the damage [4].

Adipose tissue is an organ that is responsible for maintaining homeostasis, storage, expenditure, and generating energy. It has also endocrine functions associated with many cellular processes including inflammatory responses, signal transmission, energy expenditure connected with different organs [5]. There are two main classes of adipose tissue: brown and white. White adipose tissue may be distinguished into two types - subcutaneous adipose tissue, and visceral adipose tissue. The most important function of white adipose tissue is an energy source and thermal insulator. Brown adipose tissue mostly take part in heat generation and lipid oxidation. During aging, brown adipose tissue is converted into white adipose tissue [6]. The subcutaneous adipose tissue is one type of fat tissue whose main function is energy storage, thermoregulation control, and wound protection [5]. Adipose tissue is a rich and readily available source of multipotent stem cells [7].

Stem cells are specific kinds of cells with features that allowed them to differentiate into any cell of an organism and have the self-renewal capacity. Cell specialization requires several stages. Each step of cell developmental capability is reduced. It means that after every stage of development, the cell is not able to differentiate into as many types of cells as before [8]. Every stem cell can be grouped into totipotent, pluripotent, multipotent, oligopotent, and unipotent, according to their differentiation potential [9]. Totipotent stem cells can differentiate into every kind of cell of the organism, pluripotent stem cells from cells of all germ layers without extraembryonic structures. Multipotent stem cells can specialize in discrete cells of specific cell lineages. Oligopotent stem cells are characterized by the capability for differentiating into more than a few cell types. Unipotent stem cells have the narrowest differentiation capabilities and they can divide repeatedly [8]. Another classification categorized stem cells based on their origin into embryonic stem cells, fetal stem cells, adult stem cells, and induced pluripotent stem cells [9].

Adipose-derived stem cells (ADSCs) are one of the mesenchymal stem cells (MSCs) which have potential in tissue regeneration because of their self-renewal and ability to differentiate in diverse specific types of cells, among others in adipocytes [10]. This review discusses ADSCs in terms of basic knowledge, methods of acquisition, prospects for use in healthcare focusing mainly on the potential application in the wound care process.

2. State of knowledge

2.1 Biology of adipose-derived stem cells

Adipose-derived stem cells were first isolated from adipose tissue in 1964 by Rodbell and Jones [11]. After the first isolation of ASCs, interest in these cells grew which led to attempts to develop efficient procedures for isolation methods. In the 2000s, ASCs were isolated from adipose tissue after liposuction by applying existing enzymatic strategies [12].
Adipose-derived stem cells are identified by specific markers and the ability to change into cells from different lineages such as meso-, ecto-, and endodermal. Expression of antigens among others: CD24, CD29, CD44, CD73, CD90, CD105, Decorin, gp 38, NG2, PDGFRα, PDGFRβ, Sca1, VCAM1 and lack of presence CD14, CD34, CD45 or CD19, CD79α or CD11b, and HLA-DR recognized by antibodies can characterized ASCs [13][14][15]. ADSCs are capable to differentiate into lineages such as myogenic, cardiogenic, angiogenic, periodontogenic, tenogenic, chondrogenic, osteogenic, and adipogenic because of their mesodermal origin [16]. ADSCs have been shown to have a longer culture period and higher proliferative capacity than bone marrow mesenchymal stem cells. Due to these properties, adipose tissue represents a more favorable source of MSCs [17].
ADSCs as a subset of mesenchymal stem cells isolated from the stromal vascular fraction within adipose tissue by enzymatic digestion are particularly valuable because they can be easily obtained and are characterized by abundant and convenient separation [18].
The regulation and control of proliferation, differentiation, and distribution of adipose tissue-derived stem cells depend on receptors, cell kinases, and growth factors. In addition, these processes consist of complex interactions involving stem cell transcription factors that are cell-specific. The processes of cell lineage-specific differentiation by specific transcription factors are well understood, in contrast to mesenchymal stem cells, whose process is poorly understood. Adipogenic differentiation is mainly promoted by a peroxisome proliferator-activated receptor-gamma (PPARγ) [19]. This receptor is the main regulator of progenitor differentiation into adipocytes in all sources of adipose tissue. It has two isoforms: PPARγ1 and PPARγ2. PPARγ seems to be required for the maintenance of terminally differentiated adipocytes [15].
The ability to isolate ADSCs has led to an increase in the number of publications that describe the behavior of ADSCs and their regenerative effects on important processes: angiogenesis and fibroblast migration which are key processes in dermal wound healing [20].

2.2 Clinical applications of ASCs

ASCs have been studied as a potential solution to problems such as reducing neovascularization and reducing the number of cytokines released by local inflammatory cells, which are major pathways in the healing process. By providing components necessary for wound regeneration, these cells have been shown to effectively promote wound healing by modulating the immune response, secreting paracrine factors, and promoting therapeutic angiogenesis [21]. ADSCs affect inflammation during wound healing through immune action. They help initiate tissue reconstruction. ADSCs secrete TGF-β, which along with IL-1β and IL-6 increases macrophage influx and polarization. This is followed by a phase of anti-inflammatory cytokine secretion.
In vitro studies have shown that under controlled conditions ADSCs stimulate macrophages and increase the secretion of anti-inflammatory cytokines TNF and IL-10, which stimulate wound healing [22]. ASCs have been proven to have antioxidant activity [23].
Many evidence demonstrates that ADSCs can migrate into damaged skin or upper epidermis to regenerate aging cells and repopulate the skin. Furthermore, SDF-1 (stromal cell-derived factor 1) has been demonstrated to be an important protein involved in human skin cell

migration in normal and damaged tissues [24][25]. Adipose-derived stem cells in the situation of skin injury have been shown to overexpress SDF-1 to recruit to the injured site, and in return, this factor stimulates their migratory, proliferative, and paracrine abilities [26][27].
ADSCs can recruit and stimulate endogenous stem cells to participate in the wound healing process. This action results from the secretion of cytokines such as TGF-β, VEGF, GM-CSF, HGF [28].
Exosomes are structures capable of optimizing fibroblast properties: migration promoting, proliferation, collagen synthesis necessary for the wound healing process [31]. According to studies exosomes secreted by human adipose stem cells (ASCs-Exos) can be used in research and further clinical treatment because of the ease of acquisition and potential in the wound healing process. ASCs-Exoscan reduces the healing time and scar formation after skin incision in mice [29] [30].
ADSCs taken from the same individual do not elicit a reaction against the foreign body. Furthermore, they are found to have the highest concentration in the body of all mesenchymal stem cells, which is a very desirable feature [32].
The application of ADSCs in cell therapy in process of wound healing has only achieved the status of clinical experimental treatment. Currently, there are no prospective randomized clinical trials that would confirm postulated effects of adipose-derived stem cells in wound treatment [20]. It should be added that there are still concerns about the risk of carcinogenesis by transplanted ASCs. This is due to the potential biological effects of these cells, which may stimulate the proliferation of other cells, induce neoangiogenesis and create local immunosuppression. However, to date, there is no evidence that therapy with ASCs carries a risk of tumorigenesis or other severe adverse effects. Certainly, long-term, accurate clinical observations are needed to confirm the safety and therapeutic efficacy of ASCs and to clarify the mechanism of action of these cells [33].

3. Conclusions

Adipose-derived stem cells may constitute a prominent role in tissue regeneration owing to secreting various cytokines, the ability to differentiate into multiple lineages, their immunomodulatory effects, and the ease of cell obtaining. Many studies have been performed to determine the biology of ADSCs. Also, there are preclinical studies that try to help better understand the potential use of ADSCs in wound care. Further studies are required to explore the accurate mechanism of ADSCs action and their long-term safety in clinical application. Wounds that are hard to heal are a very important problem of modern healthcare. The increasing prevalence of civilization diseases and the steadily growing number of elderly people are the cause of the rising number of patients with diagnosed chronic and difficult to heal wounds. Despite the continuous progress in the treatment of serious injuries, through the use of various types of dressings or skin substitutes, the effectiveness of the methods used seems to be insufficient. One promising solution for severe cases of chronic wounds and difficulty to heal appears to be the use of adipose-derived stem cells. They can be obtained in larger numbers, unlike human bone marrow stem cells. In addition, their ability to differentiate into other cells allows their use in the regeneration of tissues and organs. The secretory abilities of these cells are also of great importance, which makes the culture filtrate of ADSCs a source of numerous growth factors that support the healing process. Safety, quality of cells as well as restrictive regulations seems to be the biggest challenge today before the wide use of ADSCs appears in routine therapy. However, ADSCs cells have great clinical potential to become the basis of modern tissue engineering and regenerative medicine. Further research is needed to advance the use of adipose-derived stem cells in clinical practice.

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