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Research Article

The Complexity of Burn Healing and the Possibility of Stem Cell Therapy Derive from Adipose Tissue: Review

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Abstract

Introduction: Burns are cutaneous lesions caused by the thermal energy of heat transfer, which can determine cell protein denaturation and damage to the skin with consequent biochemical imbalances delay and disrupt the healing process and may cause functional and aesthetic sequelae. Extensive burns lead to intense inflammation, immune compromise, shock from plasma leakage, and the sepsis is the leading cause of mortality.

Objective: This review aims to verify the distinctions of the burn process in burns and to identify how stem cells derived from adipose tissue may become allied in their healing.

Methods: A review of the literature was conducted, which included the Virtual Health Library, Google Scholar, PubMed, Scientific Electronic Library Online (SciELO) and Mendeley's catalog of academic literature articles and specialized literature. Different key areas amenable to stem cell therapy in burns are addressed in the literature review; these include on healing, burns, stem cells derived from adipose tissue published between 2012 and 2016.

Results: Burns differ from other lesions by the intensity of systemic inflammation and the overlapping of cicatricial phases. Adipose tissue-derived stem cells (ADSC) are found in the vascular stroma of adipose tissue and are obtained by liposuction. These cells can interfere distinctly in each cicatricial phase secreting immunomodulating substances, anti-inflammatory and growth cytokines.

Conclusion: Burns generate an isolated and severe thermal insult, which impairs the healing cascade with the generation of immunological defects and intense inflammation. ADSC can be allied in tissue repair in burns due to their regulatory effects on inflammation and supporting the healing process.

Keywords: *Healing; Burns; Stem Cells Derived from Adipose Tissue*

Introduction

The skin constantly protects the body from aggression by external agents. These hostilities may be able to cause skin injuries and break this protective barrier, when this occurs, a sequence of molecular events by biochemical mediations begins immediately, which aims

to restore them so that tissue homeostasis and consequent survival are preserved [1]. Advances in medicine in recovering critically ill patients have brought the benefit of increasing the number of survivors affected by severe burns, but with this, the psychosocial problems resulting from aesthetic and functional disfigurements have become frequent. Tissue engineering, which aims to optimize the aesthetic and functional reconfiguration of the skin, can use mesenchymal stem cells (MSC) [2].

The estimate that each year, eleven million people worldwide suffer burns, establishes the relevance of studies aiming at improvements in the treatment of recovery from these injuries, both in their initial phase and in the management of their chronic complications. Burns cause damage to the skin and underlying tissues, which as a result of biochemical maladjustments delay and disorganize the healing process and cause functional and aesthetic sequelae. The main form of treatment of burns that affect the total thickness of the skin are surgical grafts, which have the function of protecting and improving the appearance, however they are not exempt from complications such as infections and deformities, in addition, in extensive burns, may not there is sufficient donor skin area [3].

Among traumatic injuries, burns are the fourth most frequent cause and their injuries cause devastating damage. To make matters worse, 90% of burns occur in poor countries with poor infrastructure to reverse this situation, as well as implement preventive measures, with an incidence of burns of 1.3 per 100,000 inhabitants in low-income countries, while in high-income countries the incidence drops to 0.14 per 100,000 inhabitants. Victims of burns of up to 70% of the body surface, the stay in the hospital has a ratio of 1 day for each percent compromised by the burns [4]. Hardly, during life, a person will not be the victim of a burn. Certainly, the unpleasant sensation of this moment and its consequences, will never be forgotten. Lancinating, immediate pain signals the triggering of exacerbated processes, which undermine the biochemical logic of tissue repair. The skin faints, the body ignites, and if too much of it burns, it afflicts life with its specific lethal mechanisms. How is the complex healing process different from burns and how can stem cells derived from adipose tissue become allies in this healing process?

Method

The present work is a review of the literature, of a narrative and descriptive character, which sought to demonstrate how the healing process in burns is differentiated and to understand the capacity of interference in this process with the use of stem cells derived from adipose tissue. The literature survey was carried out by searching for articles that portrayed mechanisms of the healing process, burns and the use of adult stem cells. Works published in the period from 2012 to 2016 were included, both international and national articles. Queries were made at the Virtual Health Library, Google Scholar, PubMed and Scientific Electronic Library Online (SciELO) and Mendeley. The keywords used were: healing, burns, derived stem cells adipose tissue. The collection of information occurred between February 2016 and February 2017. 88 articles were found, of which 20 were selected for the composition of the present work.

Results and Discussion

Burns and healing

The external agent responsible for the traumatic skin rape, defines the presence of a lesion with its own characteristics. It is recommended to cover the burned areas and manage them with topical and systemic therapies, which is different from any other traumatic injury. In addition to this therapeutic difference, in extensive burns there is a loss of large amounts of plasma that lead to shock, unlike other injuries in which the shock results from blood loss. Another characteristic of burns is the impairment of the immune system, which although at the beginning the lesions are mostly not contaminated, the main cause of death is related to sepsis due to infection of the lesions [5].

Among the many challenges of repairing burns, the delay and disorganization of cell proliferation and revascularization, as well as the selectivity of apoptosis, are relevant. In all stages of healing, early activation of distant phagocytic cells, local endothelial cells and stimulating factors are required, which prepare the environment for neovascularization, phagocytosis of damaged tissues, mitotic stimulation and collagen filling. The structural damage and the exacerbated inflammatory response that occurs in burns, generate a disturbance in the formation of capillaries and an impediment to the arrival of the cells necessary for recovery [3].

Burns are skin lesions caused by the thermal energy of heat transfer, which cause the protein denaturation of cells as a consequence. These burns can be accompanied by systemic inflammation, changes in vascular permeability, shock, anemia, infections, malnutrition and severe pain. In these cases, treatment is done with balneotherapy, covering the lesions with dressings, debridement, grafts and multiple anesthesias. The severity of the burns can be estimated by the depth, which is the portion of the tissue involvement between the epidermis to the bones, and by the extent, which is usually measured by the rule of nine, in each region of the body it receives a multiple percentage graduation of nine [6].

Burns are different from other injuries due to the intensity of systemic inflammation, while healing is done by the three phases overlapping with the help of the cells of the immune system, endothelial and stroma. At first there is no bleeding, it seems that the inflammatory phase begins with fluid leakage, vasodilation and the arrival of neutrophils and monocytes, which by means of chemokines support the recruitment of macrophages. The proliferative phase begins by overlapping the inflammatory with cytokines and growth factors, stimulating the activation of fibroblasts and keratinocytes, which migrate over the burn, helping the closure and vascular recovery. The remodeling phase also begins by overlapping the proliferative with deposition and continuous reformulation of collagen and elastin [7].

Burns are often classified by the tissue depth affected from the first to the fourth degree. Superficial burns when only the epidermis is injured, dry and red and white when pressed, painful and heals in three to six days; the superficial partial thickness burn is characterized by blisters, erythema, humidity, pales under pressure, painful on exposure to air and temperature and heals in seven to twenty-one days; the deep partial thickness burn is characterized by blisters that may be broken, moist or serous, coloration between white and red, does not pale under pressure, perceptible to pressure with curing in more than twenty-one days, with the usual need for intervention surgical; the full-thickness burn of the skin is characterized by a waxy to black color, dry, inelastic, without pressure bleaching, sensitivity only with deep pressure and the healing process is rare without surgical intervention; the fourth degree burn extends to the muscular fascia, bone and joints, sensitivity to deep pressure and never heals if you do not receive surgical treatment [8].

A coagulation zone is formed in the central region, which undergoes necrosis due to the lack of oxygenation, which prevents the speed of the healing process, and which must be removed. Around this coagulation zone is located a tissue area with decreased perfusion, called the stasis zone, in which there is an increase in capillary permeability and an exacerbated inflammatory reaction, which also distinguishes burns from other injuries due to the persistence and progression of vasodilation and edema, in addition to the possibility that they may evolve as extended areas of necrosis with an increase in the size of the initial lesion. The hyperemia zone surrounds the stasis zone, characterized by vasodilation, inflammation and tissue viability, exactly where the healing process begins [9].

The recovery of comprehensive health as a result of burns, depends on the complete healing of the affected areas. Despite the advances, the results remain unsatisfactory and determining the correct time for the use of adjuvant therapies remains without a consistent elucidation. The knowledge acquired points to the qualities of stem cells, as the main expectation of changes in this undesirable level of cure. Exogenous stem cells improve the healing process, either by their tissue-rebuilding action or by the secretion of substances, which depend on the source of cells and their administration [10].

Burns and stem cells derived from adipose tissue

The goal of applying stem cells to burns is to improve the quality of healing with early closure of the lesion by accelerating the healing process and preventing contractures and scarring, preferably with skin regeneration with its appendages, in addition to attenuating the response systemic inflammation in extensive burns can help reduce infections. Some challenges remain to be defined as: the best donor tissue source, method of processing, mode of clinical application and its functionality [11].

Stem cells are undifferentiated and can divide without limits, and in these divisions they can remain undifferentiated, or give rise to one of the approximately two hundred specialization cell modalities. Adult stem cells are multipotent, like hematopoietic, mesenchymal

and neural stem cells, these can differ only in the tissues of their origin with the function of homeostasis, regeneration and replacement [12].

The need for a safe biomaterial, which can be differentiated into multiple adult cell lines and capable of producing cytokines of growth factors, point to the adipose tissue that is the source of ADSC, as excellent participants in regenerative medicine with cell therapy. Its main advantages are the abundance, control of differentiation, ease of obtaining, possibility of allogeneic or autologous transplantation with safety for the host and the production protocol [13].

The ADSC obtained by liposuction of the adipose tissue, belong to the fraction of the vascular stroma (SVF), which unlike the adipocytes sediment in aqueous medium. It is not possible to identify only with a marker antigen, but it was found that ADSC express CD29, CD49, CD73, CD90, CD105, but they must be negative for the endothelial marker CD31 and for the hematopoietic marker CD45, however CD34 can be negative in some subpopulations or may even lose protein expression when grown in plastic. After cultivation, ADSCs can be used in both autologous and allogeneic transplants, because it has been found that these cells do not stimulate mixed lymphocyte reaction, in addition to suppressing the response of cytotoxic T lymphocytes [14].

ADSC demonstrate relevance in tissue engineering and in conditions that require immune mediation. ADSC can be found in the microvascular network and in the capillary walls of adipose tissue and have the ability to differentiate into adipose tissue, muscle, cartilage and endothelial cells. The immunomodulatory capacity of ADSC was verified for not expressing the immune recognition protein HLA-DR (Human D-related leukocyte antigen) which is an MHC II (Main histocompatibility complex) of the cell surface receptor encoded by the human leukocyte antigen complex in the chromosome 6, that is, these cells may not be recognized as antigens by this immune system [15].

ADSC are capable of immunomodulation, because they measure the secretion of IL-10 by the cells of the immunity, although they do not produce it and it is one of the main molecules produced in the activity of Tregs. Although there was no evidence of an increase in this cytokine with the use of Tregs in the experiment, this may be due to the signaling of autocrine IL-10 in Tregs. ADSC in conjunction with Tregs inhibited alloreactivity, which may indicate that ADSC increases the production of IL-10 from Tregs. Only ADSC, but not Tregs, decrease the proinflammatory cytokine TNF-α and both decrease IFN- γ, however it increases IL-6, which demonstrates its duality in immunomodulation. However, IL-6 induces Tregs, which indirectly also produces an immunosuppressive effect [16].

ADSC contribute to healing by differentiating cells involved in the healing process and by secreting growth factors such as VEGF, FGF-β, keratinocyte growth factor, platelet growth factor, insulin-like growth factor 1. In local transplantation, even without going through the bloodstream, ADSC are incorporated into the capillary walls, express endothelial phenotype, improve the vascular network and recruit endothelial cells, as well as increase the granulation tissue and acquire the fibroblast phenotype. ADSC can moderate the healing of burns due to anti-inflammatory and immunosuppressive properties, as well as they can reduce the size, improve the scar's color and malleability [17].

After extensive burns, cells with a phenotype similar to that of bone marrow mesenchymal cells were found in the bloodstream, an increase in angiogenic cytokines and bone marrow-derived endothelial progenitor cells were determined in direct relation to the extension of the affected surface, the which led to the conclusion that stem cells interfere with the burn healing process. It was subsequently found that the use of adult mesenchymal cells applied to the edges of burns optimizes healing and reduces the inflammatory process by reducing interleukins 1 and 6, increasing levels of interleukin 10 and VEGF. In the transfected stem cells, the antibacterial capacity with B2-defencin and the improvement of re-epithelialization with hepatocyte growth factor were demonstrated. The transplantation of stem cells derived from adipose tissue, in thermal lesions, can lead to improvements in healing, decreased necrosis and pain intensity [18].

ADSC show the ability to integrate and adapt to the damaged tissue, but in addition to this local activity, it can also have therapeutic efficacy in distant organs. Naturally, the MCS in the bone marrow migrates and goes through the circulation to the microcirculation of the injured tissues guided by chemotactic signals, a mechanism called homing, and similarly this phenomenon also occurs with the MSCs administered by the intravenous route [19].

The contribution of stem cells in the inflammatory phase results from the decrease in inflammation and microbial activity by the secretion of interleukin-10 (IL-10), which is an anti-inflammatory cytokine of T cells and macrophages, due to the decrease in the tumor necrosis factor -alpha (TFN-alpha) and interferon gamma (INF-γ) which are pro-inflammatory agents and by the increase in the antimicrobial peptide LL-37; In the proliferative phase, neovascularization and cell recruitment of keratinocytes, endothelial cells 11 and fibroblasts develop, determined by the secretion of VEGF, by differentiation into endothelial cells and by the production of PDGF, FGF-β, EGF and KGF; In the remodeling phase, the regulation of collagen deposits and attenuation of scar formation, by the production of HGF, by the modulation of TGF-β reducing cell proliferation and by the co-secretion of HGF and VEGF promoting the balance between TGF-β1 and the TGF-β3 involved in the control of proliferation, differentiation and movement of dermal and epidermal cells in healing [10].

Future Perspectives

It has been shown that ADSC can improve common healing processes and although there is a recognition of its effectiveness, its use in the recovery of burns is restricted. The literature, in experimental studies, points out advantages, such as pain relief, reduction of inflammation, minor scars with smooth texture and adequate color, exuberant angiogenesis and early functional return. ADSC can improve results by promoting evolutionary changes in the remodeling phase, by decreasing apoptosis and increasing fibroplasia [20].

The complex processes involved in the healing of burns are reasons for study to obtain improvements in relation to the time and quality of the scar. Stem cell therapy is the gold of science to be unveiled and research shows promise in relation to scarring, and especially in burns it can promote benefits of quality, time and decrease in the intensity of inflammation [18]. At this point, the relevance of experimental and clinical research in seeking quality and safety in the predictability of transplantation and in the control of cell reproducibility is inserted, so that it can be established, if there will be healthy donors in the future, who will undergo the liposuction procedure, such as it is done nowadays to obtain blood derivatives [13].

Conclusion

Burns generate an isolated and severe thermal insult, which impairs the healing cascade with the generation of immunological defects and intense inflammation. ADSC can be allied in tissue repair in burns due to their regulatory effects on inflammation and supporting the healing process.

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