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The use of stem cells in burns treatment

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Abstract

Introduction and purpose: Burns are a real problem that can result in long hospitalization and scarring. Stem cells (SCs) have been shown to have a number of actions that accelerate and improve the healing process. The aim of this review is to explore the stem cell mechanisms that can be used to improve burn healing

Materials and methods: A comprehensive analysis of articles available on PubMed and Google Scholar was undertaken by entering keywords in appropriate configuration: Stem cells/ burn wound/ wound healing/ mesenchymal stem cells.

Description of the state of knowledge: In the physiological process of wound healing, migration and proliferation of stem cells initiate epithelialization. The therapeutic use of stem cells has many beneficial effects. Their regenerative potential is superior to conventional treatments. Stem cells due to their ability to differentiate, autocrine and paracrine activity and immunomodulatory activity - accelerate the wound healing process, promote cell proliferation, collagen production, regulate inflammation, prevent hypertrophic scarring, stimulate re-epithelialization, angiogenesis and granulation.

Conclusion: The mechanisms of action of stem cells appears to be promising in the context of treating burn wounds, but in order for them to fully replace current treatments, a deeper understanding of the complex biological mechanisms and further studies are needed to evaluate the efficacy and safety of different types of stem cells and to identify the most suitable ones.

Keywords
Stem cells; burn wound; wound healing; mesenchymal stem cells

Introduction

Burn injuries are a common problem, associated with high morbidity and mortality. They can affect any of us. Millions of people are affected annually and many require hospitalization.[1] They are associated with pain, but also with a final cosmetic defect, often unwanted by the patient, after completing traditional burn wound treatment. Stem cells are primitive, unspecialized cells with the ability to self-replicate and differentiate into specialized tissue cells, allowing them to be used to treat dysfunctional and damaged cells.[2]
Stem cells exhibit a number of properties, such as regenerative potential, ability to differentiate, autocrine and paracrine activity, immunomodulatory activity and suppression of inflammatory response. They secrete growth factors, anti-inflammatory cytokines, and promote protein secretion, which appears to be promising in the context of burn treatment, including the

prevention of hypertrophic scars.[3] The aim of this review is to explore the stem cells mechanisms that can be used to improve burn healing.

Materials and methods

A comprehensive analysis of articles available on PubMed and Google Scholar was undertaken by entering keywords in appropriate configuration: Stem cells/ burn wound/ wound healing/ mesenchymal stem cells.

Burn injury

Most burns are caused by hot liquids, solids or fire, but they can also be caused by radiation, chemicals and electrical substances, friction or cold. In all burn injuries, the surrounding tissues are destroyed by energy transfer, but depending on the cause, different pathophysiological reactions may occur.[4]
Burns can be complicated by shock, infection, electrolyte imbalance or respiratory failure, depending on the site of injury and depth.[5]

First-degree burns, include superficial burns, affecting the outermost layer of the skin, the epidermis. They are manifested by redness and transient pain.
Second-degree burns are distinguished by superficial partial-thickness burns and deep partial-thickness burns. The former manifest as soreness, blisters, swelling, but usually do not require surgery. The latter are drier, extend below the papillary layer of the dermis, the pain is dull, they usually leave behind scars and surgical treatment is required.
Third-degree, or full-thickness burns, which already involve the entire dermis, are characterized by less pain due to damage to nerve endings, and require surgery.
Fourth-degree burns lead to damage to muscles, joints and bones, and charring may be visible.[4,6]

Minor burns - involving less than 10% of TBSA (total body surface area), usually heal without major problems, while more extensive burns involving >20% of TBSA have a higher risk of complications.[1] They are a life-threatening condition associated with fluid loss due to external barrier dysfunction, metabolic disorders and infections.[7,8]

A burn consists of mechanical damage to the skin, as well as biological damage, leading to prolonged inflammation and impaired tissue blood supply.[9]
Inflammation response is desirable in the wound healing process, but in severe burns, this inflammatory response can become uncontrollable, resulting in prolonged healing time and hypertrophic scar formation.[10] It is estimated that severe scarring affects up to 70% of patients with severe burns.[11]
Traditional treatments include many steps such as debridement, advanced medical dressings, negative pressure therapy, hyperbaric oxygen, and finally skin grafting, but the end result may often not be satisfactory to the patient, which regenerative medicine and stem cell therapy can help with.[12.13]

Process of wound healing

The process of burn wound healing consists of various growth factors, receptors and cytokines. They are associated with homing, differentiation and proliferation of stem cells.[14]
First, an inflammatory reaction is initiated, in which the wound is sealed by fibrin, into which immune cells enter to deal with the removal of dead tissue. This is followed by cell proliferation. Fibroblasts are recruited and through the secretion of collagen, granulation tissue is formed, where angiogenesis occurs. Stem cell migration and proliferation initiates epithelialization. Finally, during the remodeling phase, restructuring of the extracellular matrix occurs, which can result in scar formation.[15]
Stem cells, through integration into the wound environment, exert a positive effect on healing by secreting signaling molecules and differentiating into desired cells, which also promotes differentiation in neighboring cells.[16]
In the fetus, wounds heal without leaving a scar, which is possible due to the reduced ability to produce pro-inflammatory mediators. Regulation of inflammation through the use of stem cells may be beneficial in the context of burn wound treatment.[17]

Stem cells

Stem cells are primitive, unspecialized cells with the ability to self-replicate and differentiate into specialized tissue cells, allowing them to be used to treat dysfunctional and damaged cells.[2]

Stem cells division

Totipotent cells are capable of differentiation into cells of a fully functional living organism, including germline and extra-embryonic tissues. Pluripotent cells can initiate the development of all cells of the body, including germ cells. Multipotent cells have the ability to differentiate into specific cell types. Unipotent cells can give rise to only one cell type.[18]

They are characterized by low turnover in vivo, but are valuable in tissue reconstruction and healing due to their ability to replicate rapidly.[19]

We can find stem cells in embryonic, adult and fetal tissues, for example in the umbilical cord - umbilical cord stem cells UCSCs, in amniotic fluid - amniotic fluid stem cells AFSCs, in blood - hematopoietic stem cells HSCs, in bone marrow - bone marrow stem cells BMSCs, in fat - adipose tissue-derived stem cells ADSCs, in dental pulp - dental pulp stem cells DPSCs.[20]

Adult/tissue (somatic) cells are multipotent, repairing the tissue in which they are found.[21]

What is important in tissue reconstruction is that stem cells have anti-inflammatory effects, promote proliferation, and reduce scar formation. The cells, along with their exosomes, are also involved in the regeneration of bone tissue and the nervous system.[22]

Embryonic stem cells (ECSs)

Embryonic stem cells can be found in the blastocyst of an embryo. They can be obtained from the inner cell mass of the early preimplantation blastocyst. ESCs can form all three germ layers, but due to ethical issues, their use is limited because obtaining them requires removing the embryo.[23]

Mesenchymal stem cells (MSCs)

Mesenchymal stem cells were first classified as fibroblast precursors, isolated from the bone marrow. After this discovery, MSCs were localized in a variety of organs including adipose, cartilage and muscle tissue, but in fact adult stem cells are found in almost all adult tissues.[8]

The most commonly used sources of mesenchymal stem cells are adipose tissue and bone marrow.

MSCs are multipotent and can differentiate into cells of mesodermal origin. Their ability to regenerate, as well as their autocrine and paracrine activities and immunomodulatory effects are promising in the context of burn treatment.[3]

Uncontrolled inflammatory reactions can lead to the postpone skin healing and to formation of hypertrophic scars. MCSs can suppress inflammatory response due to promote polarization of

macrophages to an M2-like phenotype, which interact with natural killer (NK) cells and inhibit the expression of NK activation-related proteins such as NKp44, CD25, CD69, and interferon-gamma (IFN-γ).[24]

Mesenchymal stem cells inhibit the inflammatory response, promote cell proliferation and stimulate angiogenesis and collagen production, gradually leading to wound closure.

MSCs inhibit T-cell proliferation and regulate the immune response through transforming growth factor-β (TGF-β) and hepatocyte growth factor (HGF). They have a polarizing effect on inducing macrophages towards the anti-inflammatory M2 phenotype. They activate multiple signaling cascades, which is also responsible for anti-inflammatory effects.[6]

Overexpression of caveolin-1(the main component of the caveolae plasma membranes) can enhance the function of MSCs in burns. It facilitates the expression of growth factors and immunoregulatory cytokines.[25] Overexpression of caveolin-1 promotes re-epithelialization of wounds, and increases vascularization. [26]

Adipose derived stem cells

Adipose derived stem cells are isolated from the stromal vascular fraction (SVF), extracted by enzymatic digestion from adipose tissue.[16]

ADSCs are characterized by easy and reproducible isolation and at the same time minimally invasive techniques. The high availability of stem cells in adipose tissue, makes them one of the most desirable stem cells for burn treatment. They are defined as plastic-adherent cells that exhibit a CD34+, CD31-, CD45- markers profile and have the ability to differentiate into mature bone, cartilage and fat.

In the context of wound healing - they have been shown to promote healing by enhance the angiogenesis and lymphogenesis, anti-inflammatory and antioxidant effects.[27]

ADSCs are immediately recruited to the wound area and then differentiate into dermal fibroblasts, keratinocytes and endothelial cells. Their secretomes cause a change in the inflammatory phenotype of macrophages, the formation of granulation tissue and skin cells, as well as an increase in endothelial cell differentiation and cell migration, resulting in enhanced angiogenesis.[28]

Adipose derived stem cells secrete prostaglandin E2, which contributes to suppression of the inflammatory process.[16]

The use of ADSCs leads to an increase in the secretion of growth factors such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF) and hypoxia-inducible factor (HIF-1α).
VEGF stimulates endothelial cells to differentiate and increases their migratory potential and proliferation. HGF can produce VEGF and act synergistically with it. HIF-1α leads to vascular growth and remodeling by stimulating VEGF, angiopoietin 2 and stromal cell factor 1.[10]
Adipose stem cells improve the healing process, but culturing these stem cells on scaffolds or combining them with hydrogels can further improve the process, as they help to extend the lifespan of these cells and promote the rate of healing to a greater extent.[29]

Bone Marrow stem cells

Bone Marrow stem cells, also known as non-hematopoietic stem cells, have the ability to migrate into injured tissue and differentiate into fibroblasts.
In an already healed wound, up to 20% of fibroblasts can be derived from BMSCs.[30]
In wound healing, BMSCs provide accelerated re-epithelialization. they improve regeneration through transdifferentiate and interaction with the epithelial cells.[31]

The characteristics of these cells depend on the age and pathological conditions of the possible donor. The older the donor, the lower the number of BMSCs and their ability to differentiate, due to DNA modifications.[32]
BMSCs are obtained by bone marrow aspiration. This is a safe and easy procedure, but can be painful and may be associated with complications such as infection or hemorrhage.[33]
In addition to multidirectional differentiation, they exhibit paracrine actions that accelerate fibroblast migration and proliferation. They promote endothelial cell migration, muscle reorganization, improved limb function and neovascularization.[22]

Subcutaneous injection of BMSC to treat burns leads to epidermal growth and granulation tissue formation. It inhibits the inflammatory response by reducing the levels of pro-inflammatory cytokines, transforming growth factor β (TGF-β), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), matrix metalloproteinase-9 (MMP-9) and microRNA21, while increasing the secretion of chemokine ligand 2 (CXCL2), granulocyte-macrophage colony-

stimulating factor (GM-CSF), L-selectin, intracellular adhesion molecule (ICAM)-1, tissue inhibitor of metalloproteinase (TIMP)-1 and interleukin-4 (IL-4).[7].

Fetal stem cells

Fetal stem cells are multipotent cells with minimal ethical restrictions and minimal oncogenic risk. They are more primitive cells and are found at a higher frequency possessing greater colony-forming capacity in comparison to adult mesenchymal stem cells.[34]
We can obtain these stem cells from perinatal tissues - placenta, amniotic fluid, Wharton's jelly, umbilical cord blood, decidua basalis and decidua parietalis, as well as from fetal tissues, namely blood and bone marrow.[18]

Human amniotic mesenchymal stem cells inhibit heat stress-induced cell apoptosis through activation of PI3K/AKT signaling and have cell proliferation-promoting effects through activation of GSK3β/β-catenin signaling. They accelerate re-epithelialization with increased expression of CK19 and PCNA in vivo. These actions of hAMSCs are also promising for the treatment of skin burns.[35]

Umbilical cord stem cells dominate over bone marrow stem cells due to much easier and simpler collection and processing. Collecting is quick and easy and the processing takes days to weeks, while collection and processing of bone marrow stem cells can takes from weeks to months.[2]
Cord blood can be collected from the umbilical vein before the placenta is born or after the placenta is born. Both methods are performed, but collection before the placenta is born is more popular in most public cord blood banks due to ability to be performed in the delivery room by birth unit staff.[36]

We can achieve better migration potential of human umbilical cord MSCs by preconditioning hU-MSCs with isorhamnetin. It is a methylated quercetin derivative with anti-inflammatory and antimicrobial activities. It improves the survival and migration potential of MSCs, reduces inflammation and enhances wound healing.[37]

The use of amniotic stem cells in a patient with severe burns, reduced the pain perception and also shortened the length of hospitalization almost twice, compared to the control group. The patient was discharged from the hospital with a completely healed wound after 12 days.[38]

In addition, IGF-1 transducted into placenta-derived mesenchymal stem cells (PMSCs) significantly improves the wound healing effects of PMSCs. This leads to inhibition of inflammation by reducing the levels of pro-inflammatory cytokines, including tumor necrosis factor α, interleukin 1β and interleukin 6. IGF-1 increases keratinocyte proliferation, migration, collagen synthesis and wound epithelialization in vitro. In contrast, a lack of IGF-1 impairs the rate of wound healing.[39]

Hair follicle stem cells.

Hair follicle stem cells (HFSCs), found in the hair follicle bulge, undergo dynamic molecular changes needed for hair growth and wound healing. HFSCs are regulated by transcription factors and signaling pathways such as BMPs, FOXC1, NFATC1, Shh and Wnt pathways.[40]

Hair follicle stem cells also have potential in the treatment of burn wounds. They are readily available and do not raise ethical concerns. They respond quickly to the resulting wound and produce short-lived Transit-Amplifying cells, which are responsible for acute wound healing. They stimulate neovascularization and increase the expression of proangiogenic CD31 on endothelial cells. In a rat experiment, HFSCs helped improve healing of partial-thickness burns and improved tensile strength. [41]

Induced pluripotent stem cells

Induced pluripotent stem cells are produced from adult cells through overexpression of embryonic genes or transcription factors.
At the cellular level, they are very similar to embryonic stem cells, but the fact that they are derived from adult cells allows for the elimination of ethical constraints, which expands the horizons of regenerative medicine.[18]

Human-induced pluripotent stem cells, derived from reprogrammed human skin fibroblasts, express CD200, integrin α-6 (ITGA6), integrin β-1 (ITGB1), transcription factor P63, keratin 15 (KRT15), and keratin 19 (KRT19)-like keratinocyte progenitor cells which can improve wound healing.[7]

Exosomes of stem cells

Exosomes are classified as members of small extracellular vesicles (EVs) secreted by MSCs. They have immunomodulatory potential to promote regeneration of injured tissues.
The main markers of exosomes are proteins associated with endocytosis and endosomal transport, such as caveolins, clathrin, transferrin receptors, tetraspanins (CD81, CD63, CD9), ALG-2-interacting protein X (Alix), also known as AIP1 and Tumor susceptibility gene 101, also known as TSG101.[42]
Exosomes carry a multitude of signaling moieties, including proteins, lipids, cell surface receptors, enzymes, cytokines, transcription factors, and nucleic acids, so they can support intercellular communication, cell differentiation and proliferation, angiogenesis, and immune signaling.[43]

Stem cell exosomes, e.g. BMSCs, ADSCs, human amniotic epithelial cells, and induced pluripotent stem cells facilitate paracrine signaling, have anti-inflammatory and anti-fibrotic effects, inhibit oxidative stress and enhance angiogenesis. They can facilitate a substantial fraction of the paracrine signaling.[44]
Bone marrow mesenchymal stem cells exosomes are related to activation of the PTEN/AKT signaling pathway which leads to inhibiting proinflammatory phenotype M1-type polarization and promoting macrophage anti-inflammatory phenotype M2-type polarization. Human umbilical cord MSC-derived exosomes by inhibition of TLR4 signaling pathway, increase the expression level of anti-inflammatory factors. Adipose-derived stem cells exosomes have ability to activate PI3K/AKT signaling pathway and Wnt/β-catenin pathway which affects matrix metalloproteinase-2 (MMP-2) and tissue inhibitor of metalloproteinase (TIMP)-1 expression and mediates h2o2-induced wound healing.[22]

Exosomes derived from induced pluripotent mesenchymal stem cells (iMSCs-exo) have a greater ability to enhance human keratinocytes and fibroblast proliferation in the treatment of burn wound, compared to exosomes derived from mesenchymal stem cells (MSCs-exo).[45]

Conclusion

The use of stem cells is crucial in the healthcare system. Stem cells have been shown to improve skin health via a complex series of pathways by enhancing antioxidant activity, promoting angiogenesis, collagen deposition, promoting cell proliferation, granulation tissue formation, having immunomodulatory effects and improving overall skin morphology.

Stem cells, their enrichment, or the use of paracrine factors from exosomes seems to be promising and may be the future of burn wound treatment.

A deeper understanding of complex biological processes is essential.

Stem cells of various origins, with their ability to penetrate the wound area, regulate inflammation and stimulate re-epithelialization, have undoubted potential in improving wound healing. Despite all the advantages and benefits more research is needed to analyze the efficacy and safety of using different types of stem cells, to explore the possibility of stem cells affecting other different cell types during all phases of wound healing and to identify the most suitable in terms of availability, ethical considerations, factors affecting differentiation potential, painless and least invasive collection technique and application method, and the impact of combining stem cells with scaffold-based cell sheet technology.

Author's Contribution Statement

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