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How to speed up the repair of skin wounds? Evidence with stem cells and amniotic membrane

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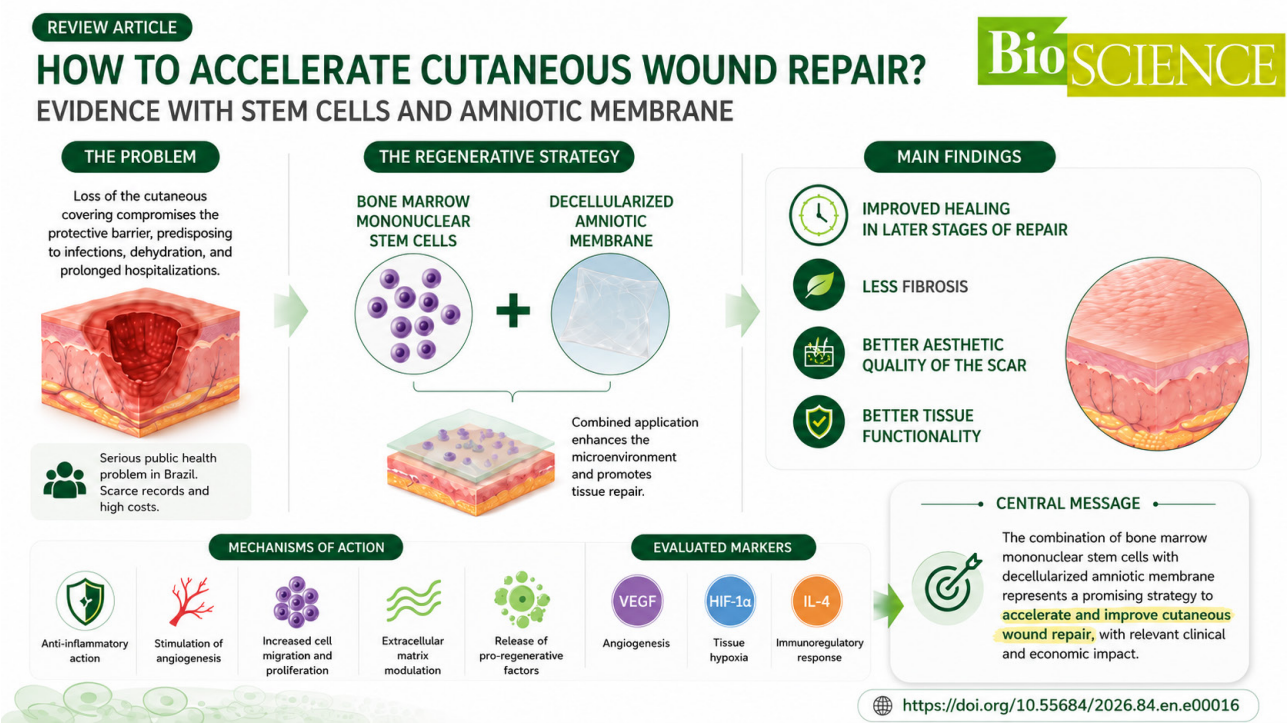

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Central Message
The skin plays a fundamental role as a biological barrier, acting to protect the body against physical, chemical and microbiological agents from the external environment. In this context, approaches based on tissue engineering have been widely investigated, especially those that combine the use of stem cells and biomaterials, such as the amniotic membrane

Perspective
Future research should focus on the detailed characterization of the underlying molecular and cellular mechanisms, as well as on the evaluation of the sustained effectiveness and safety of this approach in experimental models of greater complexity, especially in the presence of comorbidities that interfere with the dynamics of tissue repair.

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ABSTRACT

Introduction: The skin plays a fundamental role as a biological barrier, acting in the protection of the body against physical, chemical and microbiological agents of the external environment. In this context, approaches based on tissue engineering have been widely investigated, especially those that combine the use of stem cells and biomaterials, such as the amniotic membrane.

Objective: This review aimed to critically analyze the evidence available in the literature on the effects of the application of bone marrow-derived mononuclear stem cells, alone or in association with the decellularized amniotic membrane.

Method: Integrative review conducted with methodological rigor, gathering evidence for clinical practice. It was performed in the PubMed and Medline databases, using the Boolean operator "AND" to associate relevant descriptors.

Results: 97 articles were included that were related to the descriptors mentioned.

Conclusion: The findings demonstrate that mononuclear stem cells associated with the amniotic membrane improve healing in later stages of repair, and may generate less fibrosis, better aesthetic and functional quality of the scar.

KEYWORDS: Wound healing. Mononuclear stem cells. Amniotic membrane. Regenerative medicine.

INTRODUCTION

The skin is a complex organ that performs multiple functions, such as protection, temperature regulation, sensory perception, excretion and synthesis of vitamin D and melanin.[1] Several clinical situations, including burns, trauma, infections, autoimmune diseases, result in the loss of the skin lining, predispose to infections, increase insensible water losses and hypothermia, generating prolonged hospitalizations with high cost and even death.[2] In Brazil, wounds are a serious public health problem, due to the large number of patients with alterations in the integrity of the skin, although there are few records of these treatments.[3]

Skin healing is a dynamic process that involves a series of coordinated events with multiple levels of complexity and aims to restore local tissue integrity, resulting in scarring as the final product.[4] Several studies have been developed seeking new therapeutic strategies for extensive skin lesions,[5,6] with the objective of improving the quality of healing and reducing treatment time, factors that interfere not only in the quality of life of patients, but also in costs.

Studies with stem cells (SC) in acute or chronic wounds demonstrate acceleration in the healing process, due to the beneficial impact they bring to all phases of healing (inflammatory, proliferative, and remodeling).[7] An increase in epithelial migration, angiogenesis, and healing rate is observed, in addition to less evident scar formation.[8,9] The therapeutic possibilities offered by SC isolation and expansion techniques with the potential to regenerate and restore the function of injured organs and tissues represent an important step for the health area.[4]

The amniotic membrane (AM) is a biocompatible tissue and its mechanical properties such as stability, flexibility and permeability, make it a potential scaffold, which improves cell growth, adhesion and migration.[10] It acts to promote re-epithelialization, with anti-inflammatory, antifibrotic, and antiangiogenic actions. Its physical properties, particularly its thin thickness, smoothness and transparency also favor its use.[11]

Thus, recent studies in tissue engineering have been seeking the association of different cell types with biomaterials, accelerating the repair process by reducing the time required for cells to occupy the implanted matrix.[12,13] In this context, it has been demonstrated that the use of AM associated with SC can accelerate and improve the quality of tissue regeneration.[14,15]

Thus, the objective of this review was to update what the literature has been researching regarding the effect of mononuclear SC therapy associated or not with decellularized MA on the healing process of cutaneous wounds regarding immunohistochemical responses on the 28th postoperative day of the following markers: Vascular Endothelial Growth Factor (VEGF), Hypoxia-Induced Factor (HIF-1α) and Interleukin 4 (IL-4)

METHOD

Integrative review made by collecting information for reading and analysis from online research on virtual platforms. Initially, a search was carried out for DECs descriptors related to the theme, using the following terms: "Wound healing, mononuclear stem cells, amniotic membrane, regenerative medicine" with AND or OR search, considering the title and/or abstract. The material for reading and analysis was selected from the SciELO, Google Scholar, Pubmed and Scopus platforms, considering only those that were more related to the theme. The full texts were read, including 97 articles in this review.

DISCUSSION

Healing

When the skin is injured, the healing process initiates a series of dynamic events that trigger the coordinated interaction of blood cells, proteins, proteases, growth factors, and extracellular matrix components.[16] The objectives of this repair involve adequate and rapid wound closure, immediate improvement of pain, and the development of an aesthetically acceptable scar.[17] Some internal or external factors such as type 2 diabetes mellitus, radiotherapy and infections can cause delayed or impaired healing.[18]

The healing process is a complex multicellular process[19] that can be divided into three overlapping phases: inflammatory, proliferative, and remodeling.[16]

Inflammatory phase

Soon after the injury occurs, coagulation and hemostasis begin, which reduce blood loss. This protects the vascular system and maintains the function of vital organs despite injury. There is rapid vasoconstriction through the contraction of smooth muscle cells in the circular muscle layer of the injured vessels. This constriction is strong enough to stop bleeding in arteriole 0.5 cm in diameter. Associated with hemostasis, the coagulation cascade is activated by intrinsic and extrinsic pathways, promoting platelet aggregation and clot formation.[20]

Once blood loss is reduced, the priority is the removal of dead tissue and the prevention of infections. In the first five days, neutrophils reach a fibrin-rich region and perform phagocytosis and protease secretion. In course of this process, neutrophils destroy local bacteria and degrade devitalized tissues. On the third day of injury, macrophages penetrate the injury area and assist in pathogen phagocytosis and tissue debridement. In addition, macrophages also secrete large amounts of growth factors, chemokines, and cytokines, which are important molecules in the next stage of healing.[21] Tumor necrosis factor-α (TNF-α) promotes fibroblasts and angiogenesis; transforming β growth factor (TGF-β) stimulates keratinocytes, and vascular endothelial growth factor (VEGF), which is also produced by macrophages, initiates the production of granulation tissue in the transition to the next phase of healing.[16] Mast cells are also active and release granules with active enzymes, histamines, and other amines. These mediators are important for triggering the characteristic signs of inflammation at the wound site: flushing, warmth, pain, and edema.[22]

Lymphocytes produce lymphokines such as migration inhibition factor (MIF), interleukin-2 (IL-2), macrophage-activating factor (MAF), and chemotactic factors. They amplify the initial stage of healing through the stimulation of macrophages, endothelial cells, and fibroblasts.[23]

Phase proliferated

The proliferative phase is marked by epithelialization, angiogenesis, granulation tissue formation, and collagen deposition.[16]

In epithelialization, the keratinocytes of the wound edges and appendages of the dermis form a barrier that prevents bacterial invasion and continuous loss of fluids. Epithelialization is mediated by epidermal growth factors, fibroblast growth factors, and transforming growth factor beta.[24] Epithelialization occurs within hours of injury.[16] Epithelial cells migrate upward following standard epithelialization and the epidermis is restored in two to three days if the basement membrane remains intact. If this membrane is damaged, then the epithelial cells at the edges of the skin begin to proliferate and send projections to reestablish the protective barrier.[25]

Neovascularization is critical to provide nutrients and to maintain granulation tissue. Molecules responsible for angiogenesis include fibroblast growth factor, vascular endothelial growth factor, transforming growth factor beta, angiogenin, angiotropin, angiopoietin-1, tumor necrosis factor-alpha (TNFα-), and thrombospondin.[16] TNF-α promotes angiogenesis and is characterized by endothelial cell migration and capillary formation.[26]

Angiogenesis is a complex process that involves the migration and proliferation of endothelial cells, capillary creation, and neovascular remodeling.[27]

Several other growth factors have also been proven to stimulate angiogenesis, including fibroblast growth factor (FGF), transforming growth factor alpha (TGF-α), and vascular endothelial growth factor (VEGF).[27] VEGF also acts on lymphogenesis during tissue healing. The lymphatic vessels drain the lymph from the interstitial space, allowing the arrival of immune response cells. The reduction in lymphatic development can promote the perpetuation of edema and delay in the removal of debris and inflammatory cells.[28]

The final stage of proliferation is the elaboration of extracellular matrix (ECM) granulation tissue and collagen deposit. Fibroblasts from neighboring tissues migrate to the wound site, become active, and initiate collagen synthesis. Platelet-derived growth factors (PDGF) and epidermal growth factor (EGF) are the main signals for fibroblasts and are sourced from platelets and macrophages. Contraction of the wound occurs through the transformation of fibroblasts into myofibroblasts. Provisional matrix composed of type III collagen, glycosaminoglycans, and fibronectin is synthesized by fibroblasts in response to PDGF.[25]

Refurbishment phase

The last phase of healing is characterized by the transition of granulation tissue to scar tissue formation.[16] This stage can last 1-2 years or more.[22] Initially, the collagen produced is thinner than that of uninjured skin and is deposited parallel to it. Over time, this initial collagen is reabsorbed, and denser and more organized fibers are deposited in the skin's tension lines. However, even after a year of maturation, the collagen in the scar will never reorganize itself as in unharmed skin. The tensile strength of the wound will also not fully return, reaching 30% in the first three weeks and at three months (or more) approximately 80% of the strength of healthy skin.[25]

Collagen deposition is initially done in a highly disordered way, but over time the new collagen matrix becomes more organized. The underlying connective tissue contracts and brings the wound margins closer together. Several factors, mainly PDGF, TGF-β and FGFs promote this process. Finally, there is a decrease in the density of fibroblasts and macrophages by apoptosis. The rate of capillary growth and blood flow to the area is reduced, as is metabolic activity, resulting in a healed wound.[22]

Immunohistochemical markers

Vascular endothelial growth factor (VEGF)

VEGF is one of the most important growth signaling factors in vasculogenesis and angiogenesis.[29] It binds

to Flt-1 (VEGFR-1) and KDR (VEGFR-2) receptors that are located on the endothelial surface of developing and mature blood vessels.[31]

Three to five days after tissue injury, new capillaries become visible in the wound bed as granulation tissue, which acts as a matrix for blood vessel proliferation, fibroblast migration, and new collagen.[30] Subsequently, the formation of the capillary tube occurs, followed by the anastomosis of the capillary buds and finally, the formation of a new basement membrane.[31]

Progression to the remodeling phase results in a significant decrease in the metabolic needs of the new tissue. In this phase, there is a decrease in angiogenic molecules and an increase in angiostatic molecules, promoting vascular regression. The exact mechanism for vessel regression is not well understood, but it may be associated with upregulation of CXCL10 (IP-10) and secretion of CXCL11 (IP-9, ITAC). The neovasculature regresses to vascular density, similar to that of pre-wounding.[32]

Recent studies have indicated extra-angiogenic effects related to VEGF on tissue repair, contributing to the production of scar tissue. Johnson et al 33 showed that VEGF levels correlate with the amount of scar tissue produced in murine models of fetal and adult wound healing. The researchers also reported that VEGF can directly affect a variety of non-endothelial cells known to play an important role in the wound healing response, including keratinocytes and macrophages. Mogili et al 34 found increases in serum VEGF levels as well as increases in VEGF mRNA and protein in keloid vs. normal tissue. WILGUS et al 35 reported in a study that the mechanisms for VEGF-induced scarring in fetal wounds include an increase in the number of fibroblasts or an increased presence of myofibroblasts, a type of cell known to correlate with scars in fetal wounds. The study also demonstrated that injections with anti-VEGF antibodies resulted in a reduction of almost 75% in scar width compared to control.

Hypoxia-induced factor (HIF)

Relative hypoxia is essential in wound healing, as it plays a key role in regulating all critical processes involved in tissue repair. Hypoxia-induced factor (HIF) is a critical transcription agent that regulates adaptive responses to hypoxia.[36]

At the molecular level, HIF-1 transcriptional target products have been shown to regulate the process of survival, migration, and proliferation of endothelial cells (VEGF, ANGPT-1, ANGPT-2, ANGPT-4, FGF-2, PIGF, PDGF-B, RGC-32), vascular smooth muscle cell migration and proliferation (FGF-2, EGF, PDGF, thrombospondin), and mobilization of circulating angiogenic cells to the periphery (SFD-1/CXCR4).[37]

The regulation of angiogenesis by HIF-1 is critical for reintegrating oxygen and nutrient delivery to the healing site and improving cell survival. Without HIF-1 activation, continuous vascular disruption can lead to cessation of blood flow, ischemia, hypoxia, and tissue necrosis. In addition, HIF-1 also transcriptionally regulates the expression of many wound repair genes such as metabolic proteins, adhesion proteins, soluble growth factors, and MEC components (type 1 collagen and fibronectin). For these reasons, HIF-1α is generally seen as a positive regulator of wound healing and a potential regulator of tissue fibrosis.[38]

Interleukin 4 (IL-4)

Excessive inflammation is synonymous with tissue repair failure and its control is one of the first essential steps to move from initial containment to the construction of the provisional matrix. IL-4 has traditionally been associated with its anti-inflammatory properties and also for being one of the most important means by which type 2 immunity contributes to tissue repair.[39] IL-4 is mainly produced by T-Helper 2 (Th2) and other immune cells. It activates endogenous lymphocytes and promotes the polarization of M2 macrophages, both of which are crucial for tissue repair, playing a critical role in the regulation of immune responses. Recent research has revealed an important connection between immune function and tissue regeneration.[40]

According to Kucukcelebi et al 41, IL-4 has been shown to have several effects in vitro e in vivo which may be useful in the wound repair process, including monocyte stimulation to produce granulocyte and macrophage stimulating factors; neutrophil activation, improved fibroblast proliferation, and increased synthesis and secretion of ECM proteins by fibroblasts. Nguyen et al 42 showed that IL-4 is an essential profibrotic agent with an important role in mediating ECM synthesis to maintain tissue integrity. While IL-4 promotes collagen production to maintain normal physiological processes, its dysregulation can result in abnormal wound healing and fibrotic disease.

Tissue engineering

Tissue engineering comprises therapeutic strategies with materials that stimulate cell and tissue adhesion and proliferation. It also acts on cell-associated products and bioactive molecules or biophysical processes that promote cell proliferation and differentiation in the material.[43]

Regenerative medicine uses tissue engineering to develop biological substitutes to treat patients with changes in skin integrity. Through use of the body's own stem cells and growth factors, a therapeutic alternative capable of repairing these damaged tissues emerges.[44]

The combination of different cell types with biomaterials can help the repair process by reducing the time required for the patient's cells to occupy the implanted matrix.[12,13] Some studies have shown that the use of matrices, such as the amniotic membrane, associated with CT accelerates and improves the quality of tissue regeneration.[14,15]

Stem cells

Stem cell therapy (CT) has It has been shown to be an important artifice in tissue regeneration due to its capacity for differentiation and self-renewal. The CTs they can originate multiple cell lines and have low immunogenicity, a characteristic that favors

them for autografting; In addition, they exert an immunoregulatory effect, which brings new hope for the treatment of various diseases.[45]

Classification

The CTs can be classified according to their cellular plasticity, and can be totipotent, pluripotent and multipotent.[46] Totipotent cells can originate any cell type in the body, including the entire central and peripheral nervous system.[47] They correspond to the cells of the newly formed embryo and have the potential to originate even the cells of the extra-embryonic leaflet that will form the placenta.[48] Multipotent cells are a little more differentiated, present in the adult individual, with the ability to originate only a limited number of tissue types.[46] Pluripotent cells, on the other hand, can differentiate into all tissues and cells of the three germinal leaflets (endoderm, mesoderm and ectoderm), without gametes and embryonic appendages, these being the CTs embryonic arteries.[49,50]

As for the place of origin, CTs are divided into two large groups: embryonic cells, which come from the inner cell mass of the embryonic blastocyst; and adults, mainly from umbilical cord blood, bone marrow and peripheral blood. Research indicates that there are also resident CTs, which are for specific tissues or organs throughout the adult organism.[51,52] and that contribute to tissue homeostasis.

Studies have suggested that adult CTs or somatic cells would not be restricted to the production of tissue-specific cells from which they originate, and would be able to exhibit a wider spectrum of differentiation, characterizing the plasticity of CTs somatic.[53] These adult cells develop from ectoderm (epidermal cells, neurons, pigment cells), mesoderm (cardiac muscle, striated muscle, smooth muscle, kidney tubular, blood, adipose tissue), endoderm (pancreatic, thyroid, and lung cells), and germ cells.[54]

Bone marrow CTs are pluripotent and can undergo two differentiation processes: mononuclear cells, which are undifferentiated, and multinuclear cells. From the mononuclear cells, the hematopoietic lineage will originate blood cells (lymphocytes, eosinophils, basophils, neutrophils, red cells and platelets) and mesenchymal, which may originate muscle cells, hepatocytes, osteocytes, adipose tissue, chondrocytes and stroma.[55]

Studies have indicated that adult CTs present in the tissues themselves are reservoirs of reparative cells, being mobilized and differentiated in response to signs of wounds or diseases, thus contributing to the regeneration process of various tissues, such as the skin.[56,57]

Thus, it is possible to find adult CTs both in the skin and in other various organs. According to Rehen et al.[58,] they are present in the deepest layer of the skin, the hypodermis, where it matures with subsequent migration to the other layers, giving rise to the cells of the epidermis and cutaneous attachments. Alonso et al.[59] mention that the location of the CTs in the skin is in the basal layer of the epidermis, a membrane rich in extracellular matrix and growth factors. Alonso et al.[59] reported that, generally, the proliferation and differentiation of adult epidermal CTs can repair minor skin injuries; however, the low number of these cells does not allow the repair of larger lesions, which can lead to the formation of scars.

Biological properties

Regarding the functionality of CTs, the maintenance of skin integrity occurs through epidermals, which are faster, but less potent. Small repairs can be performed by the CT bulbs, which can be differentiated into different types of tissue. In the case of extensive lesions, adults present in the bone marrow could be recruited; However, it takes longer for them to be able to move from the site of origin to the wound, through circulation. This time can be reduced with the use of cell therapy, through the isolation of large number of cells from donor sites, which can be cultured if necessary and then returned to the patient.[57]

The main sources of CTs extraction are bone marrow and adipose tissue. Other sources of collection have been studied, such as hair follicles as a promising alternative for obtaining CT.[60]

Bone marrow is one of the most studied sources of adult CT, providing hematopoietic and mesenchymal sources (MSC). Among the mesenchymal cells, those of medullary origin are among the best described in the literature and originate from the marrow support stroma. These cells have already been differentiated into adipocytes in vitro, hepatocytes, osteoblasts, endothelial cells, chondrocytes, cardiac myocytes, neural cells, skeletal myocytes, myofibroblasts and renal tubular cells.[61]

Studies show that there are at least two pathways through which CTs aid healing: by paracrine signaling and by differentiation. The first shows that they have the property of secreting various growth factors and cytokines that are important for tissue repair or regeneration. When they migrate to the wound, they are activated when they come into contact with the environment of pro-inflammatory substances. The activation of CTs could potentiate the action as small "bioreactors" in the wound microenvironment and secrete growth factors and cytokines. Mesenchymal CTs also facilitate revascularization by paracrine action by secreting FGF and VEGF-A, which promote the proliferation, migration, and differentiation of endothelial cells from the vessels. In addition, the MSCs facilitate revascularization through differentiation into pericytes (vascular endothelial cells).[22]

The second pathway of action of CTs is related to the plasticity and the ability of these cells to differentiate into various cell types and to integrate into tissues. Thus, they would help the healing of lesions by differentiating into multiple cells that reside in the skin (keratinocytes, pericytes and endothelial cells).[9,62,63] However, the contribution of each of these mechanisms of action of CTs is not yet fully known, and is still an element of studies.[64]

The use of CT in acute or chronic wounds results

in acceleration in the healing process, due to the beneficial impact they bring to all phases of healing (inflammatory, proliferative and remodeling).[7]

In the inflammatory phase, CTs coordinate the effects of inflammatory cells and reduce the deleterious effects of inflammatory cytokines, such as TNF and IFN-γ.[22] Thus, the inflammatory process of the wound activates the CTs to initiate their immunomodulatory functions, including increased activation of cyclooxygenase-2 (COX-2) and activation of prostaglandin E2 (PGE2) expression, which have multiple fibroregulatory effects on the lesion.[8] In addition, CTs aid in the elimination of infections through the direct secretion of antimicrobial factors and stimulate phagocytosis by immune cells.[22]

The ability of CTs to promote the transition from the inflammatory to the proliferative phase is of utmost importance for the treatment of chronic wounds where high levels of inflammation prevent healing.[22]

Finally, they regulate the remodeling of the healed wound, promoting the organized deposition of the extracellular matrix (ECM). Several mechanisms are involved in TC-mediated wound healing, including anti-inflammatory and antimicrobial, immunomodulatory, and tissue repair activities.[22]

The usual routes of application of mesenchymal CTs (MSCs) in wound healing, they are intravenous and local, the latter being the most indicated.[62,63,65] Phalanga et al.[66] report that it is essential that the CTs remain in contact with the wound bed and remain viable in the environment for them to be effective. Methods of local application of cells include: injection around the wound, topical fibrin spray, and incorporation into a scaffold,[67,68] that is, matrices that are structures that keep cells adhered to the target site.[69] When CTs are applied directly to the lesion or its periphery, they adhere and differentiate into various types of skin cells (keratinocytes, endothelial cells, and pericytes), enhancing the healing process.[64]

Studies suggest that CTs injected alone with the defect do not respond satisfactorily. One strategy would be to combine cells with some components, known as a matrix or scaffold.[70] Thus, the development of strategies in tissue engineering, associating CTs with matrices, such as the amniotic membrane, becomes promising to achieve better results.

Amniotic membrane

The amniotic membrane (AM) has a range of specific and important properties for tissue engineering, such as reduced inflammation and scarring, cell proliferation and differentiation capacity, and the presence of growth factors, collagen, fibronectin, laminin, and proteoglycans in its extracellular matrix.[71]

Structure

MA is smooth, resistant, translucent, flexible and slender structure with a thickness of 0.02 to 0.05 mm.[72] It consists of three microscopically distinct layers: the epithelial, the basal and the mesenchymal layer.[73]

The epithelial layer, adjacent to the amniotic fluid and the amniotic cavity, is made up of a monolayer of cuboid epithelial cells, rich in immunomodulatory cytokines and epithelial growth factors. It joins through interdigitations to the second layer - basement membrane - which is thin and resistant, basically formed by reticular fibers, collagen and laminin.[74]

The basement membrane is responsible for the tension and elastic resistance that allows MA distend during the gestational period and resist the intense movements of the embryo/fetus.[75]

The outer layer of the amniotic membrane, known as the mesenchymal or stromal, can be subdivided into three avascular leaflets: compact, fibroblastic, and spongy. Compact leaflet forms the main fibrous skeleton of AM, while fibroblast is rich in fetal hyaluronic tissue, which suppresses cell proliferation by altering the regulation of TGF-β and decreases fibrosis by inhibiting the proliferation and differentiation of myofibroblasts.[76,77] The spongy leaflet, rich in mucin, is the most external from MA and the closest to the chorion. It has a high abundance of proteoglycans, glycoproteins and collagen, particularly type 3.[75,78]

Biological properties

The amniotic membrane assists in the epithelialization process by facilitating the adhesion and migration of basal epithelial cells, in addition to preventing apoptosis and restoring the epithelial phenotype. It reduces inflammatory, angiogenic and scarring processes and has antimicrobial action.[76,79-81]

Due to the structural integrity, transparency, and elasticity of the basement membrane, MA renders as ideal product for the growth of stem cells, as it increases cell life and prevents apoptosis of epithelial cells, facilitating re-epithelialization.[77,82]

MA presents several growth factors, which makes its use as a biological dressing, especially due to KGF, FGF, PDGF, EGF and VEGF. Of these, FGF stimulates the synthesis and deposition of ECM proteins. It also has some components also present in ECM, such as collagen types 1-7, elastin, laminin and fibronectin. Growth factors and ECM components give AM characteristics of re-epithelialization, reduction of fibrosis, inhibition of pain, infection and inflammation.[83]

A unique characteristic of AM is that it does not induce immune rejection, as it does not express histocompatibility antigens HLA-A, B or DR 5. Its use has covered several areas of medicine, such as the treatment of burns, prevention of tissue adhesion in surgical procedures of the head, vagina, abdomen, among others.[84]

MA It has metabolic functions such as the transport of water and soluble materials, production of bioactive factors such as vasoactive peptides, growth factors and cytokines.[75,85] It has a fundamental structural property in clinical application, as a support as a substrate for epithelial cell organization, acting as a biological support.[86] In addition, it reduces the contraction of the scar in its maturation phase and leaves the final area with macroscopic characteristics more similar to that of the local skin.[87]

The anti-inflammatory property of MA is related

to the high amounts of hyaluronic acid present in the basement membrane, which bind to the trypsin alpha inhibitor, forming an active complex.[88] Antiangiogenic activities, on the other hand, may be associated with large amounts of extracellular proteins such as type 4 and 7 collagen, laminins 1 and 5, fibronectin, angiostatin, and endostatin[82], which are involved in the neovascularization process.

MA adheres to the surface of wounds and burns and prevents the formation of space that allows serous secretion to accumulate, reducing bacterial infiltration. This natural barrier function of it, and also its ability to express numerous molecules - such as cystatin - provides antimicrobial and antiviral actions to this tissue.[81,89,90]

The patient's pain during wound care is an important factor and the use of MA It reduces this symptom by adhering to the wound surface, covering nerve endings, reducing bacterial contamination, and decreasing local inflammation.[80,91] Its antifibrotic effect may be associated with the inhibitory action of this tissue on TGF-β, responsible for activating the fibroblasts that participate in the healing process.[92]

Decellularization of the amniotic membrane

An important part of the use of MA is its preparation, which is done through decellularization; There is no change in the strength and elasticity of the fabric, nor in the barrier properties such as antimicrobial and antiviral action. During this process, the basement membrane remains intact due to the presence of collagen, fibronectin, and laminin. Decellularized MA promotes better cell proliferation and differentiation, adequate structural integrity, and also, a more uniform pattern of cell growth when compared to non-decellularized MA.[93] Wilshaw et al 94, compared the use of acellular human MA with the use of in natura. The study demonstrated that the decellularized amniotic membrane was able to support adhesion, viability, and proliferation of fibroblasts and keratinocytes, concluding that the acellular membrane has the potential to treat several conditions, such as diabetic foot ulcers, corneal defects, and severe burns.[95]

Due to its characteristics, it is possible that MA can be used as a bio-scaffold macromolecular, and can replace common dressings.[96] It acts by reducing healing time and/or complications of extensive wounds, acting in a way that allows more physiological wound repair, with better aesthetic and functional results in the final appearance of the scar. In addition, its low cost, as it is a disposal material, makes it advantageous due to the availability and ease of acceptance of donation by pregnant women.[97]

CONCLUSION

Among the therapeutic strategies investigated, the use of mononuclear CTs in association with MA has shown a more evident impact on the advanced stages of tissue repair, with signs of more organized remodeling, less fibrotic deposition, and superior scarring results from an aesthetic and functional point of view. However, it is still essential to deepen the understanding of the biological processes involved in this cellular and matrix interaction throughout all phases of skin healing. Future research should focus on the detailed characterization of the underlying molecular and cellular mechanisms, as well as on the evaluation of the sustained effectiveness and safety of this approach in experimental models of greater complexity, especially in the presence of comorbidities that interfere with the dynamics of tissue repair.

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