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Tissue Augmentation in Wound Healing: the Role of Endothelial and Epithelial Cells

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ABSTRACT

Introduction: Wounds and their complications present a frequent cause of morbidity and mortality in everyday clinical practice. In order to reduce the wound burden, much effort has been directed into the physiology of healing and new therapeutic approaches. **Aim:** This paper provides an overview from the literature about the role of endothelial and epithelial cells in tissue filler employment for wound healing. **Material and Methods:** The scientific literature was reviewed through PubMed, Medline and Science Direct. The articles were chosen in correlation with the study objective and their scientific relevance. **Results:** Successful wound healing depends on many diverse processes, cell types and molecular mediators. The definitive aim of wound healing is a properly healed wound. Tissue fillers are becoming an important alternative in wound management, although augmentation of soft tissue can present a demanding problem due to the difficulties in tissue survival. In order to prevent its failure, an optimal vascular network needs to form from wound edges into the filler. **Conclusions:** Because of the importance of chemotaxis and angiogenesis in various physiological and pathological processes, both events present an extensive area of intense research. Additionally, epithelial cells are needed to cover the wound defect and sealing the wound environment from outer world.

Keywords: wound, wound healing, angiogenesis, epithelialization, tissue filler.

1. INTRODUCTION

In everyday clinical practice, wounds occupy a significant place. As a result, a correct and efficient wound management is essential (1, 2). Much effort has been directed into understanding the physiology of healing and wound care with emphasis on new therapeutic approaches for both acute and chronic wound treatment (3, 4).

Wounds can be classified according to various criteria. According to the timeliness of healing, they are clinically categorized into acute and chronic wounds (5-7). Other criteria for wound classification include aetiology, morphological characteristics, degree of contamination and possible communication with hollow or solid organs (5, 7, 8). Wound healing begins at the moment of injury. It is a complex process and as such involves cell populations, extracellular matrix and the action of soluble mediators. Although the course of healing is continuous, it may be arbitrary classified into the four time-limited phases: I) coagulation and haemostasis, beginning immediately after injury; II) inflammation, which begins shortly thereafter; III) proliferation, starting within days after injury and encompassing major healing processes; and IV) wound remodelling as the last phase, in which scar tissue formation takes place and may last up to a year or even longer (9-11).

A correct approach to the wound treatment may effectively influence the clinical outcome. In clinical practice, various techniques have been implemented to promote and speed up the wound healing process. One novel technique for wound healing, still partly in the experimental phases, is a technique of tissue augmentation, which may be used for various reluctantly healing tissue defects, especially for bone, skin and subcutaneous tissue defects. As successful angiogenesis forms the basis of a tissue filler survival in the wound bed, this will in turn determine the outcome of the healing process. Because of the importance of chemotaxis and angiogenesis in various physiological and pathological processes, both events present an extensive area of intense research (12, 13). Additionally, epithelial cells are almost equally important, covering the wound and protecting it from infection and exterior noxious factors.

2. AIM

This paper provides an overview from the literature about the role of endothelial and epithelial cells in the technique of tissue augmentation, which is conducted with tissue filler employment and used for wound healing purposes.

3. MATERIAL AND METHODS

Literature search was conducted for this review. The data about wound healing, tissue augmentation and the importance of endothelial and epithelial cells was collected from various sources. These included electronic databases PubMed, Medline and Science Direct. The search was performed using a combination of the following terms: wound and wound healing, tissue augmentation, tissue filler, angiogenesis and epithelialization. The articles were selected in correlation with the study objective and their scientific relevance.

4. RESULTS

4.1. TISSUE DEFECTS AND THEIR AUGMENTATION WITH TISSUE FILLERS

The regeneration of damaged tissues is one of the major scopes in modern medicine. How the wound will heal, is determined by the size of the defect that the granulation tissue must fill (14, 15). A complex wound with wide tissue defects, wounds located in functionally active regions or fractures with bone shortage and large areas of exposed functional structures will heal very reluctantly or not at all (16). Such wounds may be successfully treated with a novel technique of tissue augmentation (17-19). The augmentation of bone tissue has already been implemented in clinical practice. The approach depends on the amount of the bone defect and the reconstruction procedure. Bone fillers must be optimally fitted to the recipient place in order to facilitate the revascularization (17). Widely used in maxillofacial surgery, facial defects and deformities, bone augmentation has also been successfully employed in the treatment of osteomyelitis and trauma caused bone defects (20-22). Soft tissue augmentation, on the other hand, may pose a demanding problem due to the difficulties connected to the survival of the tissue filler after the reconstruction, as enough nutrients and oxygen are needed by the cells in the filler. These could be provided only by a sufficient capillary network, in turn dependent on the endothelial cell action (23). For example, the irradiation and infection aligned complications may destroy the vascular network, thus preventing the use of tissue fillers by any means. Such wounds present a demanding problem for successful treatment (24-26).

4.2. THE IMPORTANCE OF ENDOTHELIAL CELLS

Wound healing is a complex event, where a variety of cell types interact with various functions (8, 27). Immediately after injury, coagulation and haemostasis are triggered in the wound (28-30]. The main aim is the prevention of exsanguination and the formation of supportive matrix for invading cells, needed later during the wound healing. A dynamic balance between endothelial cells, thrombocytes, coagulation and fibrinolysis regulates the haemostasis (30, 31). Humoral and cellular inflammatory phases follow with the formation of an immune barrier against invading microorganisms. The wound healing mechanisms in the acute wound are shifted toward tissue repair (32-34). Among the diverse processes in the proliferative phase, the angiogenesis and epithelialization are of particular importance. The endothelial cells have a special role. They make the growth and survival of newly formed tissue possible, as all tissues depend on a blood supply and this in turn depends on endothelial cells (36-38).

4.3. ANGIOGENESIS IN THE WOUND BED

The final aim of wound healing is a properly healed wound. Therefore, an optimal vascular network must form by extension from the wound edges into the provisional matrix or into the filler that may be placed into the wound defect. Angiogenesis, which takes place in tissue regeneration during wound healing, is initiated by a large number of biological effectors in the form of diverse growth factors (39). The variety of different biochemical stimuli evokes alterations in the vascular wall, influencing proliferation, survival, differentiation and migration of various cell types, including the endothelial cells (13, 40, 41).

New vessels start off as micro capillaries. Endothelial cells are quiescent in the beginning and must be activated at first. Resident endothelial cells are responsive to a number of angiogenic factors, including fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), angiogenin (ANG) and transforming growth factors alpha and beta (TGF-alpha, TGF-beta). The fine balance is kept by the action of inhibitory agents such as angiostatin and steroids (42-44). Stimulatory and inhibitory agents can act in concert on endothelial cells directly, activating and assisting in mitosis and promoting locomotion, or indirectly, by turning on the host cells to release endothelial growth factors. What is more, the growth of endothelial cells is stimulated by molecules secreted from tissue during the hypoxia conditions (45, 46). In response, endothelial cells undergo a complex set of four-step events: I) production of proteases for degradation of the basal lamina of the parent vessel in order to crawl through the extracellular matrix; II) chemotaxis; III) proliferation; and IV) remodelling and differentiation. FGF and VEGF play a vital regulatory role in all of the processes (45-49). New vessels are formed as capillary sprouts from already existing small vessels in the process of angiogenesis. Endothelial cells that form a new capillary proliferate and migrate into the surrounding tissue. Finally, cells differentiate and form a continuous lumen. After a capillary sprout has hollowed out into a tube, it connects to another capillary or the neighboring sprout, allowing blood to flow (42, 45). There is no vascular supply in the wound center initially and viable tissue is limited to the wound margins only. They are perfused by uninjured blood vessels and by diffusion through uninjured interstitium (5, 27, 51). As a result, when placing tissue filler into a wound, the cells there may survive only within the distance covered by diffusion, which covers one or two

centimeters from the wound margins. For cells at more distant locations, survival depends only on capillary formation. For this reason, neovascularization is a prerequisite for successful wound healing (50).

4.4. ENDOTHELIAL CELLS CHANGE IN MORPHOLOGY DURING THE ANGIOGENESIS

The endothelial cells are not static. During the growth of capillaries, they undergo a series of morphological alterations that are under biochemical control. Chemotactic agents direct the cell movement throughout the process. They act on cell surface receptors to guide migration, an important property in angiogenesis during the wound healing (12, 52). Factors that contribute to motility and act as mediators for vessel wall repair and neovascularization at the site of injury include endothelial cell growth factor (ECGF), VEGF, TGF-alpha, fibrin, angiopoietin 1, heparin and lipid growth factors. They are also important modulators of cell growth and differentiation (40).

By definition, the chemotaxis is the ability of cells to move along a chemical gradient (53, 54). This biochemical mechanism enables the cells to reply properly to the environmental stimuli determining the proliferation, differentiation and migration. Migration, the consequence of chemotactic activity, plays an important role in vascular remodelling and it is a necessary condition for angiogenesis. As a complex process that involves coordinated changes in cytoskeletal organization, signal transduction and cell adhesion, it is dependent on the actin rich network beneath the plasma membrane and regulated by physical and chemical factors in the vascular system. The regulation is achieved by three types of mechanisms: chemotaxis (migration towards the concentration gradient of the chemo attractive substance), haptotaxis (migration in response to a gradient of immobilized ligands) and mechanotaxis (migration induced by mechanical forces) (13, 55). The cellular motility requires three distinct actions: I) protrusion at the cell front; II) adhesion, to attach the actin cytoskeleton to the substratum; and finally III) traction, propelling the trailing cytoplasm forward (56-58).

Protrusion

The cell cytoskeleton is attached at cell-cell junctions and cell-extracellular matrix adhesions, providing mechanical support for the cell (55). The actin network acts as a mechano effector, being important in coordinating the cell migration. Multiple signalling pathways and regulatory proteins control actin dynamics and changes of cell morphology (55, 57, 59). During the first step of locomotion, the actin polymerization takes place at the leading edge of the cell, determined by the highest concentration of chemo attractive substance, pushing the plasma membrane outward. A protruding structure forms, in the case of endothelial cell known as filopodia, which is filled with filamentous actin. The unidirectional movement of the cell is maintained through the action of a cyclic assembly and disassembly of actin filaments in front of and behind the leading edge, respectively (58, 60, 61).

Adhesion

Adhesion to a solid substratum is particularly important step in cell migration (31, 61, 62). It is mediated by integrins, which act as primary receptors for extracellular matrix proteins. Endothelial cells can adjust the adhesion intensity, weakly adhesive cells moving faster than highly adhesive ones. After attachment to the extracellular matrix, the cell changes its morphology from an oval or spindle-shape to irregular flattened one. These alterations in shape are governed by integrin signalling and depend on integrin contacts with the extracellular matrix in focal complexes, forming initially at the ends of filopodia (56, 62). Not only important in cell motility, the integrins are also involved in signal transduction, regulating and stimulating migration. Endothelial cells migrate fastest immediately after injury. Then, they enter a slower migration rate, maintained during the healing process (59, 63).

Traction

The direction of migration requires initial polarization of the cell and both physical and chemical stimuli influence it, as has been discussed above (24, 25, 42, 50, 64-66). The contractile forces, transmitted through the integrin-cytoskeletal connections, allow the cell to pull its cytoplasm forward by generating the traction to the substratum. The force for movement is provided by myosin motor proteins, linked to contractile actin bundles along the cell. Interactions between myosin and actin fibres pull the cell body forwards. At the same time, the extracellular matrix-binding proteins on the trailing edge of the moving cell must release these connections (55, 62, 67). The degree of the strength of integrin coupling to the cytoskeleton is influenced by the rigidity of the substratum. With stronger couplings to a firm surface, the force can be transmitted through the migrating cell more efficiently (56). During the locomotion, traction forces generated at the sites of contact can be high enough to deform the extracellular matrix and to rearrange it significantly (54, 68).

5. DISCUSSION

5.1. THE ENDOTHELIUM AND EPITHELIUM ACTING IN CONCERT

As already discussed above, numerous cell mediators, such as cytokines, hormones and growth factors, are important in guiding the wound healing process. Angiogenesis is therefore not an exception. New blood vessel formation is critical in wound healing and takes place at the same time during all the stages of reparation (69, 70). In addition to attracting other cell types, the neutrophils and macrophages, platelet derived growth factor (PDGF) and transforming growth factor 1 (TGF-1) that are secreted during the hemostatic phase, promote angiogenesis. By cell migration, endothelial cells are capable of remodelling and extending the network of blood vessels in almost every tissue in the body. In addition, macrophages release a number of angiogenic substances, magnifying the endothelial cell proliferation (5, 28, 48). Capillary sprouts from the surrounding wound edges invade the blood clot in the wound gap and within a few days, a microvascular network is formed, composed of copious new capillaries. Proliferating fibroblasts, macrophages

and vascularized stroma, in concert with collagen, fibrinogen, fibronectin and hyaluronic acid, constitute acute granulation tissue that replaces the fibrin based provisional matrix, which was formed in the initial stages of wound healing. With collagen accumulation, density of blood vessels diminishes and granulation tissue gradually matures to produce a scar (48, 60, 71). The final stage of wound healing is the remodelling phase. New epithelium develops and final scar tissue formation takes place. With time, the growth of capillaries stops, blood flow to the area diminishes and the metabolic activity of the scar drops. The final result is a fully matured scar with a decreased number of cells, blood vessels and with a high tensile strength (72, 73).

Equally important to endothelium are the epithelial cells. Their migration starts from the wound edges within a few hours of wounding. A single layer of cells initially forms over the defect, accompanied by a marked increase in epithelial cell mitotic activity around the wound edges. Cells migrating across them attach to the provisional matrix in the wound bed. After 12 to 24 hours, when the advancing epithelial cells meet, migration is stopped and basement membrane starts to form. The wound is covered with epithelium and isolated from the outer world (27, 37, 74).

6. CONCLUSIONS

Successful wound healing depends on many biochemical processes, molecular mediators, cell types and structural elements. New blood vessel formation through the process of angiogenesis is critical in wound healing (75, 76). It can be affected by numerous pathophysiological and metabolic factors resulting in poor outcome. However, the angiogenesis is not important only during wound healing, but also in several pathological conditions. Progress in this area brings new opportunities for developing therapies that enhance or inhibit vascular formation, such as inhibitors of aberrant vessel formation and stimulators of angiogenesis in ischemic conditions (27, 77, 78).

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