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Extracellular matrix and wound healing

Matrice extracellulaire et cicatrisation

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ABSTRACT

Extracellular matrix has been known for a long time as an architectural support for the tissues. Many recent data, however, have shown that extracellular matrix macromolecules (collagens, elastin, glycosaminoglycans, proteoglycans and connective tissue glycoproteins) are able to regulate many important cell functions, such as proliferation, migration, protein synthesis or degradation, apoptosis, etc., making them able to play an important role in the wound repair process. Not only the intact macromolecules but some of their specific domains, that we called "Matrikines", are also able to regulate many cell activities. In this article, we will summarize main findings showing the effects of extracellular matrix macromolecules and matrikines on connective tissue and epithelial cells, particularly in skin, and their potential implication in the wound healing process. These examples show that extracellular matrix macromolecules or some of their specific domains may play a major role in wound healing. Better knowledge of these interactions may suggest new therapeutic targets in wound healing defects.

RÉSUMÉ

La matrice extracellulaire est connue de longue date comme support architectural pour les tissus. De nombreux résultats récents indiquent, cependant, que les macromolécules matricielles (collagène, élastine, glycosaminoglycannes, protéoglycannes et glycoprotéines du tissu conjonctif) sont capables de réguler de nombreuses fonctions cellulaires telles que la prolifération, la migration, la synthèse ou la dégradation des protéines, l'apoptose, etc., les rendant capables de jouer un rôle important dans le processus de cicatrisation. Non seulement les molécules intactes, mais aussi certains de leurs domaines spécifiques, que nous avons appelés « Matrikines », sont capables de réguler de nombreuses activités cellulaires. Dans cet article, nous résumerons les principales découvertes montrant les effets des macromolécules matricielles et des matrikines sur les cellules des tissus conjonctifs et les cellules épithéliales, en particulier dans la peau, et leur implication potentielle dans le processus de cicatrisation. Ces exemples montrent que les macromolécules de la matrice extracellulaire ou certains de leurs domaines spécifiques peuvent jouer un rôle majeur dans la cicatrisation. Une meilleure connaissance de ces interactions peut suggérer de nouvelles cibles thérapeutiques dans les déficits de cicatrisation.

1. Introduction

Wound healing is a very complex process, associating cellular, molecular, biochemical and physiological events, which permit living organisms to repair accidental lesions. It necessitates the coordinated intervention of many partners, among which blood cells, epithelial and connective tissue cells, inflammatory cells and many soluble factors, mainly coagulation factors, growth factors and cytokines. It is a dynamic and strongly regulated process implicating molecular, cellular and humoral components, which starts immediately after the initial lesion and will last until complete closure of the wound and restitution of a tissue as functional as possible. In the case of fetal wound, complete

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regeneration of the initial tissue may occur whereas in adults, the wound healing process conducts in most case to the formation of a collagenic scar [1].

Among the factors implicated in the control of the wound healing process, an important partner is the extracellular matrix. It is now well admitted that extracellular matrix is not only an architectural support for the tissues but also plays a major role in cell regulation. Presently, many data show that nearly all the extracellular matrix components are able to regulate cell behaviour. It is clear that the important extracellular matrix alterations that occur during wound healing make it a very important player in this process.

This review will summarize main findings showing the effects of extracellular matrix macromolecules on the cells implicated in the wound healing process. A better understanding of the mechanisms involved in these cell-extracellular matrix interactions may suggest new targets for therapeutic strategies in the management of the wound healing defects.

2. The fibrin clot: a provisional matrix

As pointed out by Richard Clark many years ago, the fibrin clot by itself constitutes a provisional extracellular matrix, composed of 95% fibrin and many other components, mainly fibronectin, SPARC/osteonectin, thrombospondin and vitronectin. These components may support cell migration necessary for wound healing, but also trigger the inflammation process. For instance, fibrin itself induces the secretion of IL-8 by endothelial cells and of TNFα, IL-1ß, IL-6, MIP-1, MIP-2 and MCP-1 by mononuclear cells [2].

Fibrin is rapidly degraded by plasmin and neutrophil elastase. This degradation may induce the release of plasma growth factors trapped in the fibrin lattice, which might play an important role in the early events of wound healing. Fibrin also releases fibrin degradation products, most of which may stimulate the healing process. Fibrin degradation products can induce or amplify the inflammatory process. For instance, fibrinopeptides A and B are chemo-attractant for neutrophils, monocytes and macrophages; D-dimers induce secretion of IL-1ß and IL-6 by mononuclear cells; fragment E induces secretion of IL-1ß and IL-6 by mononuclear cells; fragment ß15-42 is chemo-attractant for neutrophils and fibroblasts (for review, see ref [3]). Fibrin degradation products were also shown to stimulate extracellular matrix deposition [4], fibroblast proliferation [5] and angiogenesis [6].

3. Extracellular matrix macromolecules as modulators of cell functions in wound healing

Extracellular matrix (ECM) is made of collagen and elastic fibers dispersed in a ground substance made of glycosaminoglycans, proteoglycans and connective tissue glycoproteins. Many data have shown that ECM is able to modulate wound repair, either directly by modulating important aspects of cell behaviour such as adhesion, migration, proliferation or survival, or indirectly by modulating extracellular protease secretion, activation and activity, or modulating growth factor activity or bioavailability. Actually, sequestration/release of growth factors by the ECM may prolongate growth factor action or modulate their activity on the cells implicated in the wound healing process.

3.1. Glycosaminoglycans

Glycosaminoglycan chains are very important players in wound healing. The most important is hyaluronic acid, a non-sulfated glycosaminoglycan, very abundant in skin [7] where it forms long filaments (500 nm–10 μm) and provides to the tissue its viscoelasticity and hydrophilicity. Hyaluronic acid, also called hyaluronan, interacts with cell surface receptors, mainly CD-44 and RHAMM (Receptor for HyaluronAn Mediated Mobility), but also Toll-like Receptors TLR-4 and TLR-2, and Inter Cellular Adhesion Molecule-1 (ICAM-1). The interaction of hyaluronan with its receptor induces very important events in the wound repair process: modulation of inflammation, chemotaxis, cell migration, collagen secretion and angiogenesis [8–10]. The abundance of hyaluronan in fetal skin is likely one of the factors which permits to the early gestation fetal skin wound to heal without scar formation [11]. Similarly, the over-expression of hyaluronan synthase-1 is able to induce regenerative wound repair in C57Bl/6 mice [12].

Many data demonstrated that the biological effects of hyaluronan are dependent of its molecular size. For instance, recent data from Ghazi et al. [13] showed that hyaluronan with a molecular weight comprised between 100–300 kDa was able to strongly stimulate keratinocyte migration whereas high molecular weight (1000–1400 kDa) and low molecular weight (5–20 kDa) hyaluronan fragments had no effect. Earlier, David Raoudi et al. [14] demonstrated that native hyaluronan of high molecular weight (1.7 MDa) stimulated type III collagen production whereas low molecular weight hyaluronan fragments (12 disaccharide units) stimulated type I collagen production by human dermal fibroblasts. Low molecular weight fragments of hyaluronan (10 saccharide units) were also shown to stimulate angiogenesis in rat experimental wounds [15].

Sulfated glycosaminoglycans (chondroitin-sulfate, dermatan-sulfate, keratan-sulfate and heparan-sulfate) are linked to core proteins to form proteoglycans in normal tissues, especially in skin. Proteoglycan degradation by proteases in the wounds may, however, lead to the release of free glycosaminoglycan chains, which may modulate the wound healing process [16]. For instance, chondroitin-sulfate and dermatan-sulfate regulate growth factor activity and may stimulate nitric oxide production which, in turn, can modulate angiogenesis. Heparan-sulfate stimulates the release of IL-1, IL-6, PGE2 and TGF-ß, inhibits elastase and cathepsin-G activity, complexes chemokines, cytokines and growth factors. It is also well known to stabilize tetrameric complexes between FGF2 or other heparin-binding growth factors and their receptors, improving signal transduction [17]. Heparan sulfate chains may also bind VEGF and contribute to the modulation of its pro-angiogenic effects in the tissues [18].

3.2. Proteoglycans

Many proteoglycans are involved in the wound healing process. Main skin proteoglycans are small leucine-rich proteoglycans (SLRPs) family and versican, essentially present in the dermis, perlecan in the basement membrane, syndecans and glypicans on the cell surface. Decorin, the first known member of the SLRP family, was shown many years ago to negatively regulate TGF-ß [19]. Delayed wound healing was observed in perlecan-deficient mice, due to an impaired angiogenesis [20]. The V3 isoform of versican was shown to stimulate elastin production [21], to promote angiogenesis [22], and to induce transition of normal dermal fibroblasts to myofibroblasts [23]. Syndecans 1 and 4 are strongly expressed in wounds [24]. Their increased expression stimulate keratinocyte and endothelial cell migration whereas invalidation of the syndecan-4 chain delays wound closure and angiogenesis in mice [25,26]. Three-dimensional migration of fibroblasts into fibrin is also decreased when syndecan-4 core protein synthesis is suppressed by anti-sense oligodeoxynucleotides [27].

3.3. Connective tissue glycoproteins

Connective tissue glycoproteins are a group of extracellular matrix macromolecules strongly involved in cell regulation and