Wound Healing

Subjects: Cell Biology

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Wound healing is a multistage dynamic process including haemostasis, inflammation, cell proliferation and tissue remodelling.

Keywords: wound healing ; fibroblasts ; epithelial mesenchymal transition ; tissue regeneration ; fibrosis ; inflammation

1. Introduction

The haemostasis phase occurs immediately after injury and results in the formation of a provisional wound matrix [1]. To prevent exsanguination, vasoconstriction occurs and platelets undergo activation, adhesion and aggregation at the site of injury. The key glycoproteins released from the platelet alpha granules include fibrinogen, fibronectin, thrombospondin and von Willebrand factor [2]. As platelet aggregation proceeds, clotting factors are released, resulting in the deposition of a fibrin clot at the site of injury. Near to the damaged area, platelet alpha granules release pro-inflammatory cytokines such as Transforming Growth Factor-α (TGF-α), TGF-β, Epidermal Growth Factor (EGF), Fibroblast Growth Factor (FGF), Platelet-derived Growth Factor (PDGF) and Vascular Endothelial Growth Factor (VEGF) [3]. PDGF is a chemotactic factor which promotes neutrophils migration to the wound site for eliminating contaminating bacteria. With the help of TGF-β, monocytes are transformed to macrophages, which play a key role in increasing the inflammatory response and tissue debridement. Macrophages start the formation of granulation tissue and secretion of various proinflammatory cytokines as IL-1 and IL-6 and growth factors as FGF, EGF, TGF-β and PDGF. Due to the release of VEGF and FGF by platelets, endothelial cells proliferate, resulting in angiogenesis initiation. This event is of vital importance for the synthesis, deposition and organization of a novel ECM. FGF, TGF-β and PDGF then allow fibroblast infiltration. Moreover, TGF-β and PDGF begin phenotypic modifications, transforming fibroblasts into myofibroblasts [4]. Neutrophils, monocytes and macrophages are the fundamental cells of the inflammatory phase [5].

Neutrophils are crucial for eliminating the microbes and cellular debris in the wound site; they release inflammatory factors such as IL-1, IL-6 and TNF-α, and also produce molecules such as proteases and Reactive Oxygen Species (ROS), which may contribute to tissue damage [6].

Macrophages are responsible for the clearance of apoptotic cells, including the removal of dying neutrophils, which terminates the inflammatory response. As inflammation occurs, macrophages undergo a phenotypic transition to a reparative state that activates keratinocytes, fibroblasts and endothelial cells to induce angiogenesis that restores tissue integrity [7]. Angiogenesis, growth of new blood vessels, supply essential nutrients and oxygen to the damaged tissues and play a crucial part in wound healing [8][9]. Macrophages positively regulate the transition to the proliferation phase of healing [10][11].

The third event in wound healing is the proliferation phase. The proliferation stage is characterized by epithelial proliferation and migration over the provisional matrix within the wound, which is referred to as re-epithelialization [12]. The main events during this phase are the substitution of the provisional fibrin matrix with a novel matrix of collagen fibres, proteoglycans and fibronectin to renew the structure of the tissue and help regain its function [13][14].

Once the wound is closed, the immature scar can proceed to the final remodelling phase. The remodelling phase can last up to a year, depending on the severity of the wound [15]. The wound also undergoes physical contraction through the complete wound healing event, which is considered to be orchestrated by contractile fibroblasts (myofibroblasts) that emerge in the wound [16][17].

In pathological wound healing, however, myofibroblasts activity persists and drives tissue alterations, which is particularly evident in hypertrophic scars developing after burn injury and in the fibrotic phase of scleroderma [18]. Myofibroblasts-generated contractions are also typical for fibrosis, affecting vital organs such as the liver [19], heart [20], lung [21][22] and kidney [23].

2. Modulation of EMT by Biomaterials

Biomaterials present the capability to promote or prevent EMT in a highly regulated manner, permitting the modulation of EMT event. Biomaterials' features, such as form, surface topography, wettability and crosslinking capacity, influence their functions [24]. In particular the biochemical and biophysical characteristics can regulate the local tissue microenvironment by modulating the immune system from scarring to total regeneration [25]. Potential approaches require the design of materials with controlled moduli, gradients of ECM proteins and/or soluble factors, multifactiorial strategies utilizing different mechanics, ECM components and soluble factors [7]. All these aspects represent a starting point to take into consideration for the design of novel materials implicated in the modulation of EMT in regenerative medicine and tissue engineering [26]. For example, polyacrylamide (PA) hydrogels, which are synthetic hydrogel matrices with an adjusted stiffness, represent a valuable platform to modulate the EMT event and for evaluating the molecular mechanisms controlling EMT.

It is well known that a rise in the thickness of collagen fibers can be correlated with some diseases, such as fibrosis. Anitha Ravikrishnan et al., in 2016, reported that micro/nano fibrous scaffold to reproduce a proper environment for evaluating the key events leading EMT, demonstrating that the nanofibrous scaffolds represent a valuable tool for investigating EMT during pathology advance [27]. Based on the literature, graphene derivatives are capable to promote lung fibrosis in vivo. In a study reported by Lia et al., in 2018, it was reported that reduced graphene oxide induced EMT activation in A549 cells via a mechanism that involves epithelial markers downregulation and mesenchymal markers upregulation, raising cell migration and invasion capacities [28].

Furthermore, in a work published by Christine-Maria Horejs et al., in 2017, a biomaterial-based approach to target tissue fibrosis in vitro was described: they interface epithelial cells with a cryptic fragment of the laminin b1-chain displayed by the action of MMP2 to trigger a inhibition of MMP2 activity, the gene and protein expression of EMT-related molecules and the morphological alterations linked with fibrosis [29]. Even if the comprehension of molecular events represents a crucial part for the modulation of EMT, the features of the materials are essential factors to take into consideration to regulate EMT process. Thus, in the tissue engineering field are necessary emerging strategies and solutions to prevent or decrease the undesirable side effects of biomaterials.

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