Biomedicine & Pharmacotherapy 84 (2016) 42–50

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Review

Growth factor pathways in hypertrophic scars: Molecular pathogenesis and therapeutic implications

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ARTICLE INFO

Article history:
Received 9 July 2016
Received in revised form 26 August 2016
Accepted 5 September 2016

Keywords:
Hypertrophic scars
Wound healing
Growth factor
Signaling pathway
Therapeutic implication

ABSTRACT

Hypertrophic scars represent the most common complication of skin injury and are caused by excessive cutaneous wound healing characterized by hypervascularity and pathological deposition of extracellular matrix (ECM) components. To date, the optimal and specific treatment methods for hypertrophic scars have not been available in the clinic. Current paradigm has established fibroblasts and myofibroblasts as pivotal effector cells in the pathophysiology of wound healing. Their biological properties including origin, proliferation, migration, contraction and ECM regulation have profound impacts on the progression and regression of hypertrophic scars. These complex processes are executed and modulated by a signaling network involving a number of growth factors and cytokines. Of particular importance is transforming growth factor-β, platelet-derived growth factor, connective tissue growth factor, epidermal growth factor, and vascular endothelial growth factor. This review article briefly describes the biological functions of fibroblasts and myofibroblasts during hypertrophic scars, and thereafter examines the up-to-date molecular knowledge on the roles of key growth factor pathways in the pathophysiology of hypertrophic scars. Importantly, the therapeutic implications and future challenges of these molecular discoveries are critically discussed in the hope of advancing therapeutic approaches to limit pathological scar formation.

Contents

1. Introduction

Hypertrophic scars represent abnormal healing responses secondary to burn injuries, traumatic injuries and surgical procedures [1]. Hypertrophic scars are also associated with contractures and hypervascularity that may lead to considerably reduced functional performance and erythematous appearances in

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http://dx.doi.org/10.1016/j.biopha.2016.09.010
0753-3322/

patients [2]. Consequently, hypertrophic scars cause significant abnormality in aesthetic and functional symptoms. The formation of hypertrophic scars involves a constitutively active proliferative phase of wound healing, during which proliferation of the dermal tissue and excessive deposition of fibroblast-derived extracellular matrix (ECM) proteins result in persistent inflammation and fibrosis [3]. The net result is that the original skin defect is replaced by a nonfunctional mass of tissue. Substantial advances in understanding the pathogenesis of hypertrophic scars have established growth factors as key players in the pathophysiology. This article summarized the up-to-date molecular discoveries of important growth factor pathways involved in hypertrophic scars and critically discussed their therapeutic implications in the hope of providing novel therapeutic approaches for hypertrophic scars.

2. Cellular basis of hypertrophic scars

Fibroblasts and myofibroblasts are pivotal effector cells in hypertrophic scars. Fibroblasts are spindle-shaped cells, and initially appear at the location of injury at the end of the inflammatory phase and beginning of the proliferative phase of healing wound [4]. Commonly, fibroblasts are activated and differentiate into myofibroblasts, which are a phenotypically intermediate cell type between fibroblasts and smooth muscle cells. Persistence of myofibroblasts in granulation tissues may result in the formation of hypertrophic scars. It is known that myofibroblasts in hypertrophic scars are primarily originated from local dermis and subcutaneous tissues around the wound site [5]. Other origins include pericytes and vascular smooth muscle cells [6], bone marrow-derived peripheral blood fibrocytes [7], tubular epithelial cells through epithelial-mesenchymal transition (EMT) [8], and tissue specific stem cells [9] (Fig. 1). Whether these myofibroblasts exhibit different characteristics or play distinct roles in the pathogenesis of hypertrophic scars remains unknown.

No matter where myofibroblasts originate from, they must migrate to the wound bed and into the fibrin clot. Fibroblasts travel along the fibronectin rather than collagen fibers in the wound area [10]. Fibroblast migration can be motivated by chemoattractants or

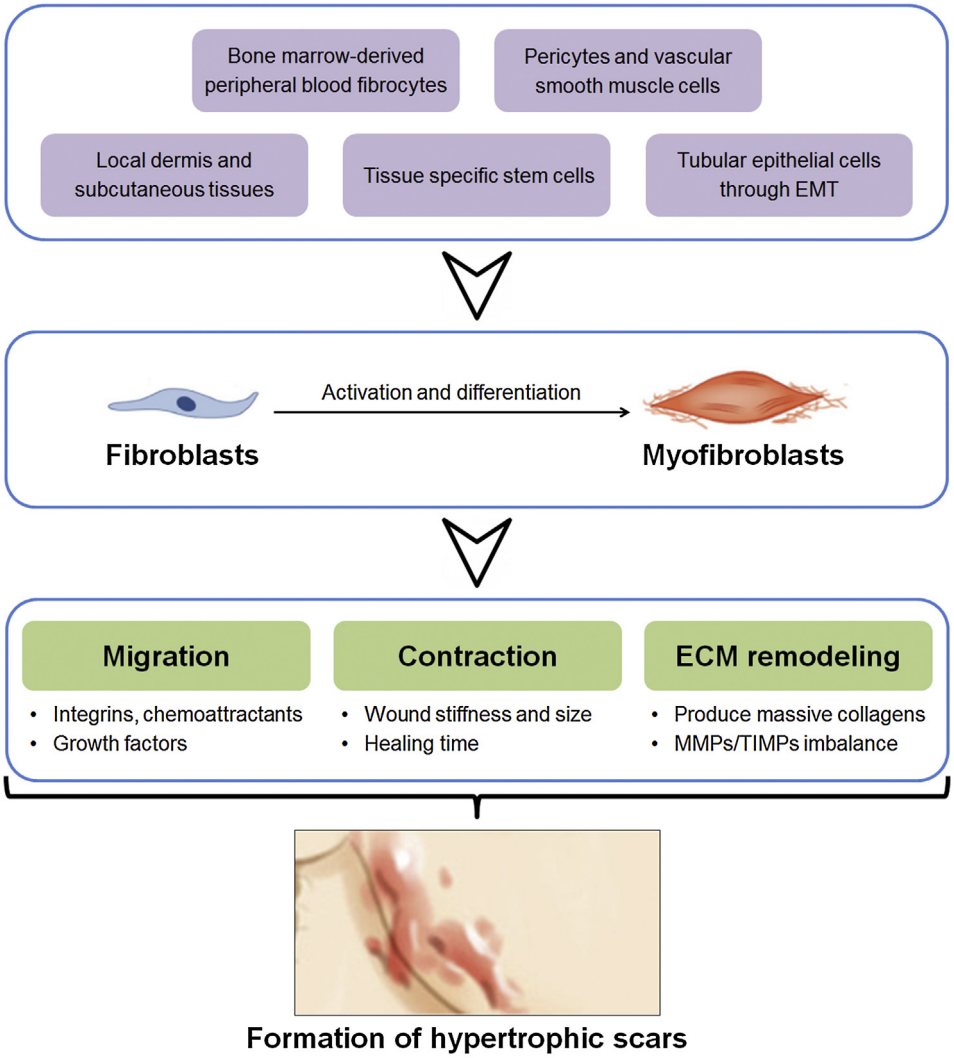

Fig. 1. Overview of the cellular mechanisms of hypertrophic scars. Activation of fibroblasts and differentiation into myofibroblasts are the central processes in the pathophysiology of hypertrophic scars. To date, many origins of fibroblasts or myofibroblasts have been characterized, including local dermis and subcutaneous tissues around the wound site, pericytes and vascular smooth muscle cells, tubular epithelial cells through epithelial-mesenchymal transition (EMT), tissue specific stem cells, and bone marrow-derived peripheral blood fibrocytes. Although little is known about whether these fibroblasts or myofibroblasts of different origins exhibit different characteristics or play distinct roles in the pathogenesis of hypertrophic scars, they have several common biological properties including migration, contraction, and regulation of ECM remolding, which critically affect different facets of hypertrophic scars. Many growth factors may modulate these biological properties as discussed in the later section of this review in detail.