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Review

New molecular medicine-based scar management strategies

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ABSTRACT

Keloids and hypertrophic scars are prevalent disabling conditions with still suboptimal treatments. Basic science and molecular-based medicine research have contributed to unravel new bench-to-bedside scar therapies and to dissect the complex signalling pathways involved. Peptides such as the transforming growth factor beta (TGF-β) superfamily, with Smads, Ski, SnoN, Fussels, endoglin, DS-Sily, Cav-1p, AZX100, thymosin-β4 and other related molecules may emerge as targets to prevent and treat keloids and hypertrophic scars. The aim of this review is to describe the basic complexity of these new molecular scar management strategies and point out new fibrosis research lines.

Contents

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1. Introduction

Cutaneous scar management has relied heavily on the experience of practitioners rather than on the results of large-scale randomised, controlled trials and evidence-based techniques [1]. Massage therapy, adhesive tape support, silicone gel sheeting, pressure therapy, intralesional corticoids, laser, radio- and immunotherapies, antimetabolites and botulinum toxin A represent the most popular strategies for keloids and hypertrophic scar management [1,2]. Being severe and mild forms of excessive scarring, respectively, keloids particularly extend beyond the original wound margins, in contrast to hypertrophic scars. However, both abnormal wound healing processes still remain unresolved problems, potentially causing a severe impairment of quality of life in affected patients [3]. New developments in molecular and regenerative medicine emerge as key tools to design new excessive-scar preventive and therapeutic options. These include the superfamily of transforming growth factor-beta (TGF-β) [4], with its complex signalling crosstalks with other cytokines and pathways. Hence, this complexity is even enlarged by cell context characteristics, multiple on/off regulatory switches and, especially, sequential timing and age differences during the *per se* complex wound healing cascade [4,5]. Indeed, it is noteworthy to consider that these subtle properties warrant that pre-clinical research with TGF-β should be carefully conducted and analysed and, even so, it may have unexpected or non-reproducible consequences *in vivo*. The aim of this review is to describe current research targets on keloid and hypertrophic scars and to shed new light on the complex TGF-β derivatives and their basic characteristics (first part of molecular introduction), with a special focus on its clinical translation (second part of the article).

2. Human recombinant TGF-β3 and TGF-β superfamily-related products

The scarless healing of cutaneous wounds (regeneration instead of reparation) in early gestational foetuses has been suggested to occur due to the predominance of the antifibrotic TGF-β3 isoform over the profibrotic TGF-β1 and 2, as well as an immaturation of the cellular immune response [4,6]. TGF-β1 has been reported to decrease collagen III expression in foetal murine skin fibroblasts [7]. Hence, in contrast to adult cells, early gestational foetuses show predominance of type III collagen over type I: from the normal 20%, type III collagen increases to 50%; this increase causes decreased fibril diameter [8]. Early gestational foetuses also display significant expression of hyaluronan [9] and fibromodulin [10], which are known to suppress TGF-β activity [10]. It has been reported that the described scarless phenomenon in early gestational phases is independent of the intrauterine environment, but dependent on the particular foetal fibroblast [4]. Development of hypertrophic scars and other fibrotic diseases is linked to overexpression of TGF-β1 and its downstream mediators connective tissue growth factor (CTGF) and plasminogen activator inhibitor-1 (PAI-1), among others [11].

2.1. *Description of the TGF-β superfamily*

The TGF-β superfamily of growth factors includes not only TGF-β but also other peptides (Fig. 1). The TGF-β growth factors are homodimers consisting of two identical subunits of ~12 kDa each. In the animal kingdom, there are currently five distinct isoforms or ligands of TGF-β with 64–82% identity, with only the TGF-β1, -β2 and -β3 forms expressed in mammalian tissues. TGF-β1 was the first discovered member of the family, and it was first characterised in human placenta in 1983. In humans, the three isoforms are located on three different chromosomes, 19q13, 1q41 and 14q24. Each isoform has specific functions but structural and signalling pathways similarity [12].

TGF-β family members are widely expressed in all cells. They control cellular behaviour in embryonic and adult tissues, including cell proliferation, differentiation, apoptosis, migration, epithelial-to-mesenchymal transition (EMT), extracellular matrix (ECM) remodelling, immune functions and tumour invasion/metastasis [13–17]. Therefore, they play crucial roles in embryonic development, adult tissue homeostasis and the pathogenesis of a large group of high prevalent diseases, including fibrosis, cancer (where they can be oncogenic or antitumour agents), autoimmune and cardiovascular illnesses, among others [14,18–20] (Fig. 2).

Regarding wound healing, TGF-β plays a major role and it is produced by all cells participating in the wound healing