New developments on skin fibrosis - Essential signals emanating from the extracellular matrix for the control of myofibroblasts

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https://doi.org/10.1016/j.matbio.2018.01.025

Abstract

Many different diseases are associated with fibrosis of the skin. The clinical symptoms can vary considerably with a broad range from isolated small areas to the involvement of the entire integument. Fibrosis is triggered by a multitude of different stimuli leading to activation of the immune and vascular system that then initiate fibroblast activation and formation of matrix depositing and remodeling myofibroblasts. Ultimately, myofibroblasts deposit excessive amounts of extracellular matrix with a pathological architecture and alterations in growth factor binding and biomechanical properties, which culminates in skin hardening and loss of mobility. Treatment depends certainly on the specific type and cause of the disease, for the autoimmune driven localized and systemic scleroderma therapeutic options are still limited, but recent research has pointed out diverse molecular targets and mechanisms that can be exploited for the development of novel antifibrotic therapy.

Introduction

The skin is our largest organ that forms a barrier towards the outside world and protects from dehydration, entry of pathogens, UV irradiation and thermal or mechanical injury. The skin is composed of an epidermal (outer) and dermal (inner) compartment, which are connected by a specialized ECM network, the basement membrane. The dermis rests on the innermost subcutaneous adipose layer that connects the skin to the underlying muscle and fascia and acts as thermoinsulator. Embedded in the skin are epidermal appendages such as hair follicles, sweat and sebaceous glands. Their formation as well as overall skin development and homeostasis rely on extensive crosstalk between the epidermal and dermal compartments [1].

General aspects of skin structure

The epidermis is a keratinized stratified squamous epithelium containing keratinocytes as the predominant cell type. Its essential function is to provide a barrier towards the outside world and protecting against dehydration, pathogen entry, UV irradiation and other insults [1–3]. The epidermis rests on a specialized dermo-epidermal junctional zone, the basement membrane that contains as key components laminins, collagen IV, proteoglycans and nidogens arranged in a tightly interconnected network with a major function in connecting as well as separating the epidermis and dermis (recently reviewed by [4]).

In contrast to the cell-rich epidermis, the dermis is rich in ECM, into which the cellular components of this layer are embedded, e.g. fibroblasts, some immune

Please cite this article as: J.-N. Schulz, et al., New developments on skin fibrosis - Essential signals emanating from the extracellular matrix for the control of myofibroblasts, Matrix Biol (2017), https://doi.org/10.1016/j.matbio.2018.01.025

cells and a variety of vascular and nerve structures. The dermal ECM is composed of diverse collagenous structures including the fibrils built of collagens I, III and V with FACIT collagens XII and XIV decorating the fibril surface, collagen VI in microfilaments, collagen VII in anchoring fibrils. There are also many different glycoproteins including fibronectin, fibrillin in microfibers, elastin, tenascins, and various proteoglycans, which constitute the dermal matrisome [5–8]. Embedded into this environment are fibroblasts, some interspersed immune cells, the vasculature, nerves and the major parts of hair follicles and sebaceous as well as eccrine glands. The dermal ECM is a highly interconnected network that provides to cells a scaffold, positional and mechanical information through ECM receptors expressed at the surface of dermal cells. These include the large family of integrins sharing the β1 subunit but also syndecans, receptor tyrosine kinases such as discoidin domain receptors (DDR) and others [9–11]. A major function of the ECM includes the local storage of growth factors whereby the activity and availability of these mediators is regulated. Well characterized examples are the binding of FGF-2 to heparan sulphate proteoglycan, of BMPs to fibrillin and binding of TGFβ1 to decorin or fibrillin microfibrils that results in TGFβ1 inactivation or to thrombospondin-1 that leads to activation (reviewed in [12–14]).

Characteristics of fibrotic skin

Fibrosis of the skin as in all other fibrotically altered organs is characterized by activation of fibroblasts to deposit excessive amounts of a collagen-rich ECM with an abnormal type of crosslinks, leading to stiffening and impaired tissue function. Fibroblast activation as such also occurs as a physiological response following injury in order to ensure tissue restoration [15,16]. The problem in fibrosis is its persistence driven by ECM stiffening promoting fibroblast proliferation and production of ECM and TGFβ1, which together result in persistent fibroblast activation, driving a vicious circle. This is best investigated in systemic sclerosis, a general autoimmune disease, in which skin fibrosis is a hallmark. Systemic sclerosis is thought to represent a model disease for most of the other fibrotic processes [17–21].

Activated fibroblasts, termed myofibroblasts, can derive from a number of sources including tissue resident quiescent fibroblasts, circulating precursors or from other cell types through epithelial-mesenchymal or endothelial-mesenchymal transition, from pericytes or adipocyte precursors [22–24]. Since long, myofibroblasts have been recognized as the key effector cells in fibrosis that deposit the characteristic ECM; they are mainly identified by their production of α-smooth muscle actin (αSMA) and its incorporation into prominent stress fibers [25], although this characteristic is not reliable and sufficient to identify the activated fibroblasts that drive fibrosis, and markers may differ in different organs [26]. Fibroblast activation has recently been associated with the innate immune system [15,27,28], but activation is always induced by 2 major triggers: the transduction of mechanical tension across the fibroblast surface and TGFβ1 in the vicinity [29]. Force transduction is dependent on properly assembled matrix adhesion structures, which connect the outside ECM to the actin cytoskeleton. These are the sites where the cell surface is in direct physical contact with the surrounding ECM. Such structures are dynamic, complex associations of clustered ECM receptors (integrins), adaptor proteins (integrin-linked kinase (ILK), kindlins, talins, vinculin) and kinases (focal adhesion kinase), among many others [30,31]. Quantitative analysis of the 'adhesome' revealed that more than 200 different proteins are assembled in these structures in a dynamic and likely cell type-specific manner [32–37].

TGFβ1, the second major prerequisite for myofibroblast formation, is released by inflammatory cells as well as fibroblasts, and is stored in the ECM bound to fibronectin and fibrillin microfibrils in a latent form that is not accessible to its receptors [38–41]. Activation of latent TGFβ1 can be achieved by MMP- or plasmin-mediated proteolysis of the LTBP component [42–45], by ECM proteins such as thrombospondin-1 [14] and by integrin-dependent forces acting on the latent TGFβ1 complex such that free growth factor is released [46–48]. The pivotal pro-fibrotic role especially of the TGFβ1 isoform has been highlighted by many reviews [17,18,38,49–51].

This review concentrates on myofibroblasts as the key effector cells in skin fibrosis. To describe their diverse origins and triggering mechanisms by dysfunction of the immune and vascular system are not within the scope of this review and the reader is referred to chapter xx in this issue by Pakshir and Hinz [52] and excellent recent reports [23,26,53–58]. Here, we will highlight the importance of 3 mechanisms that have emerged as novel regulators controlling the formation and function of myofibroblasts in the skin and thereby the development of fibrosis: (i) integrin α11β1 is a critical collagen receptor on myofibroblasts mediating pro-fibrotic signals from the collagenous environment; (ii) the ECM protein COMP has a non-structural role in collagen secretion; and (iii) ILK is a central player in the transmission of forces across matrix adhesions and transmits signals controlling TGFβ1 secretion.

Integrin α11β1 mediates pro-fibrotic signals in dermal fibroblasts

The fibrotic ECM deposited by myofibroblasts differs considerably from the ECM of healthy skin with respect to its composition and its supramolecular organization [7,17,59]. This was demonstrated already in the 1970's when Carwile LeRoy reported that fibroblasts in the skin of patients with systemic sclerosis produced much

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