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# Skin fibrosis: Models and mechanisms

N.N. Do, S.A. Eming *

*Department of Dermatology, University of Cologne, 50937 Cologne, Germany*

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ABSTRACT

Matrix synthesis, deposition and remodeling are complex biological processes that are critical in development, maintenance of tissue homeostasis and repair of injured tissues. Disturbances in the regulation of these processes can result in severe pathological conditions which are associated with tissue fibrosis as e.g. in Scleroderma, cutaneous Graft-versus-Host-Disease, excessive scarring after trauma or carcinogenesis. Therefore, finding efficient treatments to limit skin fibrosis is of major clinical importance. However the pathogenesis underlying the development of tissue fibrosis is still not entirely resolved. In recent years progress has been made unraveling the complex cellular and molecular mechanisms that determine fibrosis. Here we provide an overview of established and more recently developed mouse models that can be used to investigate the mechanisms of skin fibrosis and to test potential therapeutic approaches.



## 1. Introduction

Cutaneous fibrosis is the accumulation of extracellular matrix (ECM) components in the dermis, leading to compromised function and altered architecture of the dermis (Fig. 1). Development of fibrosis occurs naturally during scar formation in wound repair or is a pathological process in pro-fibrotic diseases [1]. During wound healing the clotting cascade is activated followed by an influx of immune cells that initiate the early inflammatory phase. The recruited immune cells not only act in host defense, but also induce tissue growth characterized by angiogenesis and fibroplasia. During fibroplasia fibroblasts are activated and transform into myofibroblasts that contribute to the formation of the provisional extracellular matrix that later transforms into a persistent scar and promote wound contraction [2,3].

Tissue fibrosis is determined by two major processes, the synthesis and the degradation of the ECM. During skin homeostasis both processes are in equilibrium and can be (transiently) shifted in specific conditions as for example toward ECM synthesis during wound healing. A tight regulation of ECM synthesis is necessary to avoid excessive scar formation in pathological conditions as e.g. in hypertrophic scarring or keloid formation, chronic cutaneous Graft-versus-Host-Disease (GvDH), nephrogenic fibrosing dermopathy or Scleroderma (Ssc) [4–6]. The exact mechanisms leading to fibrotic skin conditions are still unclear. Chronic inflammation often precedes or accompanies the development of skin fibrosis, and is considered a critical underlying cause. Macrophages are especially thought to play an important role in fibrosis, they are often found in close proximity to myofibroblasts and have been referred to as "master regulators of inflammation and fibrosis" [7–11].

In order to enable efficient clinical treatment of tissue fibrosis, it is essential to understand the complex underlying mechanisms. A variety of mouse models have been developed to investigate various pro-fibrotic mechanisms. Although none of the current models recapitulate a fibrotic condition in its entire proposed pathogenesis, each model has its advantages and limits. For example, some models focus on the vasculopathological aspects of specific diseases entities such as Scleroderma while other models emphasize inflammation as a common underlying cause for skin fibrosis.

## 2. Mechanisms and regulators

The structure and composition of the ECM is important for its various functions such as providing integrity, elasticity, water retention, morphological organization and physiological function by binding growth factors and enabling signal transduction via interaction with cell-surface receptors [12,13]. There are different ECM macromolecules including proteoglycans which mainly confer buffering, hydration and force-resistant properties and fibrous proteins that provide tensile strength, cell adhesion and migration [12,13]. Besides elastins, fibronectins and laminins, collagens are the most abundant matrix components within the

* Corresponding author at: Department of Dermatology, University of Cologne, Kerpenerstr. 62, 50937 Köln, Germany. Tel.: +49 221 4783196; fax: +49 221 4200988.
*E-mail address:* sabine.eming@uni-koeln.de (S.A. Eming).

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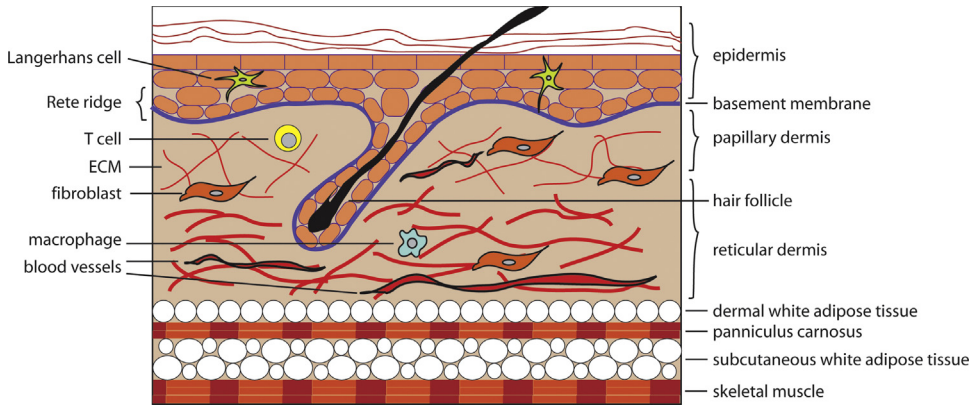


**Fig. 1.** Structure of murine skin.

fibrotic tissue. In principle these matrix components can be remodeled through synthesis, degradation and post-translational modifications including glycosylation or cross-linking. Induction of either of these processes can be mediated by growth factors, cytokines or in response to mechanical stress [14,15].

### 2.1. Growth factors and cytokines in ECM synthesis

ECM synthesis is primarily conducted by activated fibroblasts and myofibroblasts with transforming growth factor β (TGFβ) signaling being the major inducer of collagen synthesis [16] (Fig. 2). Other growth factors and cytokines, such as the connective tissue growth factor (CTGF, also known as CCN2) and the pro-inflammatory cytokine interleukin-6 (IL-6) [17–20], are also implicated to possess the ability to induce collagen synthesis in fibroblasts either directly or indirectly. IL-4 is also considered to be a pro-fibrotic mediator. It has been detected in various diseases with fibrotic symptoms or examined in fibrotic models [10,21]. Human fibroblasts stimulated with IL-4 showed increased induction of collagen expression, which was even more efficient at higher IL-4 concentration as compared to the respective TGFβ stimulation [22]. As IL-13 is usually thought to share functional activities with IL-4, its pro-fibrotic properties were tested in several fibrosis models. Various studies revealed that IL-13 could regulate fibrosis independently of IL-4Rα/Stat6 signaling. IL-13 can either directly affect fibroblasts and induce fibroproliferation or first induce the expression of the CC chemokine C10 which recruits mononuclear phagocytes affecting fibroblast activation [23]. Additionally, IL-13 induces expression of latent TGFβ in macrophages and activates TGFβ via augmentation of matrix metalloprotease 9 and urinary

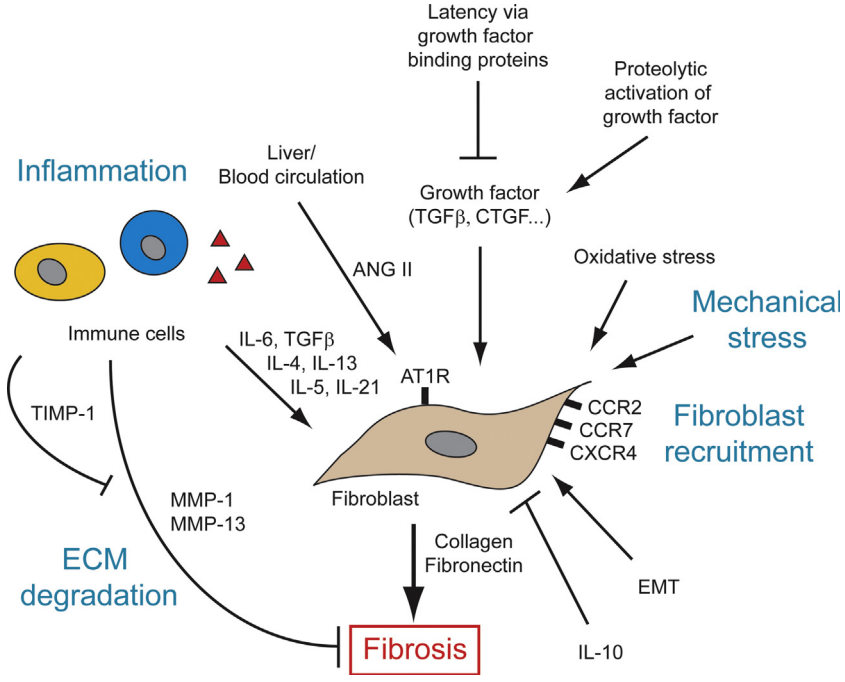


**Fig. 2.** Regulators of fibrosis. Multiple mediators play a role in the development of fibrosis, all of them converge onto fibroblasts representing the central effector cell in fibrosis. Fibroblasts can originate from resident mesenchymal cells, can be recruited via their chemokine receptors (CCR2, CCR7 or CXCR4) or transform from other cells, e.g. endothelial or epidermal cells, in a process called EMT. Oxidative stress, mechanical tension, pro-fibrotic and pro-inflammatory cytokines and growth factors can all induce ECM synthesis in fibroblasts. Immune cells are an important source of pro-fibrotic mediators. ECM deposition can be suppressed on several levels, e.g. by latency of growth factors, through the direct effect of the anti-fibrotic cytokine IL-10 or by MMP secretion. MMPs can be inhibited via TIMP. ANG II: angiotensin II, AT1R: angiotensin II type I receptor, CCR: CC chemokine receptor, CTGF: connective tissue growth factor, CXCR: CXC chemokine receptor, EMT: epithelial-to-mesenchymal transition, IL: interleukin, MMP: matrix metalloproteinase, TIMP: tissue inhibitor of metalloproteinases, TGFβ: transforming growth factor β.

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