Injury- and inflammation-driven skin fibrosis: The paradigm of epidermolysis bullosa

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Abstract

Genetic or acquired destabilization of the dermal extracellular matrix evokes injury- and inflammation-driven progressive soft tissue fibrosis. Dystrophic epidermolysis bullosa (DEB), a heritable human skin fragility disorder, is a paradigmatic disease to investigate these processes. Studies of DEB have generated abundant new information on cellular and molecular mechanisms at play in skin fibrosis which are not only limited to intractable diseases, but also applicable to some of the most common acquired conditions. Here, we discuss recent advances in understanding the biological and mechanical mechanisms driving the dermal fibrosis in DEB. Much of this progress is owed to the implementation of cell and tissue omics studies, which we pay special attention to. Based on the novel findings and increased understanding of the disease mechanisms in DEB, translational aspects and future therapeutic perspectives are emerging.

Introduction

One medically highly relevant form of fibrosis results from frequent cycles of injury, wound healing and tissue regeneration. Physiological wound healing runs in well-orchestrated stages [1], but repeated injury before completion of wound healing evokes excessive inflammation, derailing of the regenerative processes, abnormal architecture of the extracellular matrix (ECM), pathological scarring and fibrosis and, commonly, epithelial cancer as a late complication. Clinical examples of such situations encompass genetic skin fragility disorders, chronic skin or mucosal lesions after burns, destructive infections, or irradiation therapy, and chronic leg ulcers due to vascular insufficiency and stasis.

At molecular level, upregulation of matricellular and other ECM proteins upon damage and wound healing [2–6] can be viewed as an attempt to provisionally restore tissue integrity as a part of natural tissue regeneration [7]. However, the above conditions are associated with inability to properly restore the integrity of the ECM, and these changes become rather permanent. Furthermore, they can be aggravated into fibrosis-associated remodeling and perpetuated by repeated cycles of injury and inflammation. A paradigmatic disease to investigate these processes is dystrophic epidermolysis bullosa (DEB), a heritable human skin fragility disorder.

We have used DEB as a genetic model to delineate mechanisms of injury- and inflammation-driven progressive skin fibrosis. Investigation of human and transgenic murine models has delivered ample new information on cellular and molecular mechanisms of skin fibrosis, revealed novel targets for disease-modifying therapeutic approaches, and identified small molecule drugs that seem valuable for inhibiting tissue alterations and for alleviating symptoms.

DEB is a member of the epidermolysis bullosa family of mechanobullous disorders [8]. It manifests with life-long mechanically induced skin blistering, painful chronic wounds and healing with scarring, but is a clinically and genetically heterogeneous disease. In severe DEB, progressive soft tissue fibrosis leads to joint contractures, mucosal strictures and mutilating deformities of hands and feet early in life. Systemic multiorgan involvement and highly increased risk of aggressive cutaneous squamous cell carcinomas

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(cSCCs) at young age increase the disease burden tremendously [9].

The pathology of DEB is caused by mutations in the *COL7A1* gene that encodes collagen VII, the major component of the anchoring fibrils at the epidermal basement membrane (BM) zone. Correspondingly, the anchoring fibrils are morphologically and functionally deficient in DEB skin. More than 1000 distinct *COL7A1* mutations are known [10], but the genotype-phenotype correlations are only starting to emerge.

We have generated transgenic mouse models for DEB, a collagen VII hypomorphic mouse (referred to as the DEB mouse) [11] and inducible knockouts of collagen VII expression [12]. The DEB mouse has about 10% of physiological levels of collagen VII and recapitulates the phenotype of the human disorder. These mice not only represent ideal models to elucidate cellular and molecular mechanisms in DEB, but have also been valuable for determining the quantity of collagen VII required for skin integrity [13,14].

Dermal fibrosis in DEB

Multiple mechanisms contribute to dermal fibrosis in DEB

It is now apparent that dermal fibroblasts are not a homogenous population but are composed of multiple subpopulations with distinctly different capabilities in terms of functions during tissue homeostasis and regeneration [15]. Fibroblast subpopulations have not been characterized in DEB, but during physiological wound healing, fibroblasts from deeper reticular dermis first populate the wound, followed by fibroblasts from the superficial papillary dermis, once re-epithelialization is completed [16]. Based on mouse studies, it has been suggested that such fibroblast populations exhibit distinct expression profiles, with reticular fibroblasts being the main producers of fibrillar collagens [16], but this was not confirmed by transcriptomic studies on human skin [17]. In line with this, one study followed distinct lineages of dermal fibroblasts during development and regeneration of mouse skin and suggested that despite similar expression of fibrillar collagens and other genes linked to fibrosis, one lineage was significantly more fibrogenic [18]. The more fibrogenic lineage was characterized by high abundance of the serine exopeptidase DPP4, although collagen fibrils and the composition of the dermal ECM were not analyzed in detail [18]. A subpopulation DPP4 positive dermal fibroblasts, has also been identified in human skin and suggested to be involved in ECM deposition [19]. Taken together, these studies emphasize the importance of contributions from minor ECM components and cues from the microenvironment for ECM deposition and assembly [17,18].

Based on the distinct appearance of the ECM in the papillary and reticular dermis, it was proposed that fibroblasts of the reticular dermis would contribute to scarring and fibrosis [20]. More recent studies have identified different mesenchymal cell subpopulations or lineages with distinctly different abilities to support tissue regeneration, and their dysregulation could be one potential mechanism contributing to scarring and dermal fibrosis [15].

Interestingly, one of the most prominently upregulated ECM genes in papillary fibroblasts is *COL7A1* [17], which based on the above discussed articles [17] suggests an association between dermal collagen VII synthesis and maturation of the dermal ECM. In line with this, we showed that healing of acute wounds in collagen VII deficient mice is impaired and that the wounds display fibrosis-associated changes [12]. In DEB, frequent blistering at body sites exposed to mechanical and frictional challenges contributes to wound pathology and finally results in a chronically injured, inflamed skin that promotes fibrosis [21,22]. Multiple mechanisms contribute to this at the cellular and microenvironmental level (Fig. 1). Collagen VII deficient fibroblasts appear to be intrinsically profibrotic by increasing expression of transforming growth factor βs (TGFβs) and reducing expression of fibrosis-limiting growth factors, such as FGF2 [12,23,24]. The general destabilization of the BM zone and the papillary dermis conferred by loss of collagen VII, is an additional mechanism driving fibrosis. This may lead to release of growth factors, including TGFβs, sequestered by ECM structures such as fibrillin-rich dermal microfibrils, which are fundamentally linked to regulation of dermal TGFβ bioavailability [25,26].

Inflammation plays a vital role in regulation of fibrogenic processes in general [27,28]. Inflammatory cells produce growth factors and cytokines such as TGFβ, interleukin (IL)-4 and IL-13 that directly stimulate dermal fibroblast activation and ECM production [29]. Type 1 immunity defends against multiple pathogens, whereas type 2 immunity is restricted to response to parasites and helminthes [30,31]. Type 2 immunity involves a strong fibrogenic response to encapsulate the parasites [30]. Both types of immunity are also crucially linked to tissue repair, with type 1 immunity protecting against infection, clearing dead cells and kick-starting tissue repair by releasing soluble factors, and type 2 immunity promoting the proliferative phase of wound healing [32]. Inability to switch off or exaggerated type 2 immunity is frequently associated with fibrosis [31,32], and increased proteolytic activity in persistent inflammation releases growth factors and destabilizes the tissue architecture [27,28]. Both innate and adaptive immune cells are involved in the fibrogenic type 2 response, principal cells on both immune arms are Thelper 2 cells and IL-4 and -13 activated M2 macrophages [31]. In skin wound repair, IL-4 and IL-

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