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# PDGF in organ fibrosis

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ABSTRACT

Fibrosis is part of a tissue repair response to injury, defined as increased deposition of extracellular matrix. In some instances, fibrosis is beneficial; however, in the majority of diseases fibrosis is detrimental. Virtually all chronic progressive diseases are associated with fibrosis, representing a huge number of patients worldwide. Fibrosis occurs in all organs and tissues, becomes irreversible with time and further drives loss of tissue function. Various cells types initiate and perpetuate pathological fibrosis by paracrine activation of the principal cellular executors of fibrosis, i.e. stromal mesenchymal cells like fibroblasts, pericytes and myofibroblasts. Multiple pathways are involved in fibrosis, platelet-derived growth factor (PDGF)-signaling being one of the central mediators. Stromal mesenchymal cells express both PDGF receptors (PDGFR) α and β, activation of which drives proliferation, migration and production of extracellular matrix, i.e. the principal processes of fibrosis. Here, we review the role of PDGF signaling in organ fibrosis, with particular focus on the more recently described ligands PDGF-C and -D. We discuss the potential challenges, opportunities and open questions in using PDGF as a potential target for anti-fibrotic therapies.



## 1. Pathological importance of fibrosis

Fibrotic diseases represent an increasing cause of morbidity and mortality worldwide. Fibrotic diseases can potentially affect all organs and tissues and their consequences contribute to an estimated 45% of all-cause mortality in the United States (Thannickal et al., 2014). Currently, there are very few approved direct anti-fibrotic treatments, most of them for idiopathic pulmonary fibrosis. For the vast majority of diseases associated with fibrosis, there are currently no specific anti-fibrotic treatments available.

Fibrosis is an essential part of the wound healing process after injury, involving the interaction of a multitude of cells. In the vast majority of cases, fibrosis develops secondary to epithelial or endothelial injury and/or during inflammation by paracrine signaling, with PDGF being centrally involved (Fig. 1). Fibrosis is characterized by excessive formation and deposition of extracellular matrix (ECM) by activated and expanded tissue mesenchymal stromal cells, i.e. fibroblasts, pericytes and myofibroblasts (Fig. 1). The ECM is not simply a passive scaffold providing tissue stability, but actively contributes to controlled tissue homeostasis and wound healing e.g. by binding of a variety of cytokines and growth factors, including the PDGFs (Karsdal et al., 2017). For example, PDGF-A and −B can bind to ECM proteins, and this binding is reduced by cleavage of the COOH-terminal retention sequence.

Evolutionary, fibrosis evolved to provide fast wound closure, a tissue scaffold for regeneration, organ integrity and to encapsulate pathological processes not cleared by the immune system, particularly after localized tissue destruction due to trauma and infection. This results in rapid albeit incomplete regeneration, e.g. a scar of the skin is fully re-epithelialized, providing physiological barrier to infections, but it lacks skin appendages like hair follicles or glands, and is therefore not fully functional. Only during prenatal development a healing process can lead to full regeneration without involving fibrosis (Gurtner et al., 2008). Fibrosis is triggered in all tissues in response to virtually all types of insults, in particular if these are severe or repetitive. Fibrosis is tissue protective in instances of localized scar formation after tissue destruction, e.g. after myocardial infarction to protect from fatal cardiac rupture, to support organ integrity after destructive bacterial infection, e.g. in pyelonephritis, or to promote mucosal repair in early inflammatory bowel disease (Principi et al., 2013). However, even localized scar formation is not always beneficial. For example, in the central nervous system (CNS) the glial scar after trauma blocks

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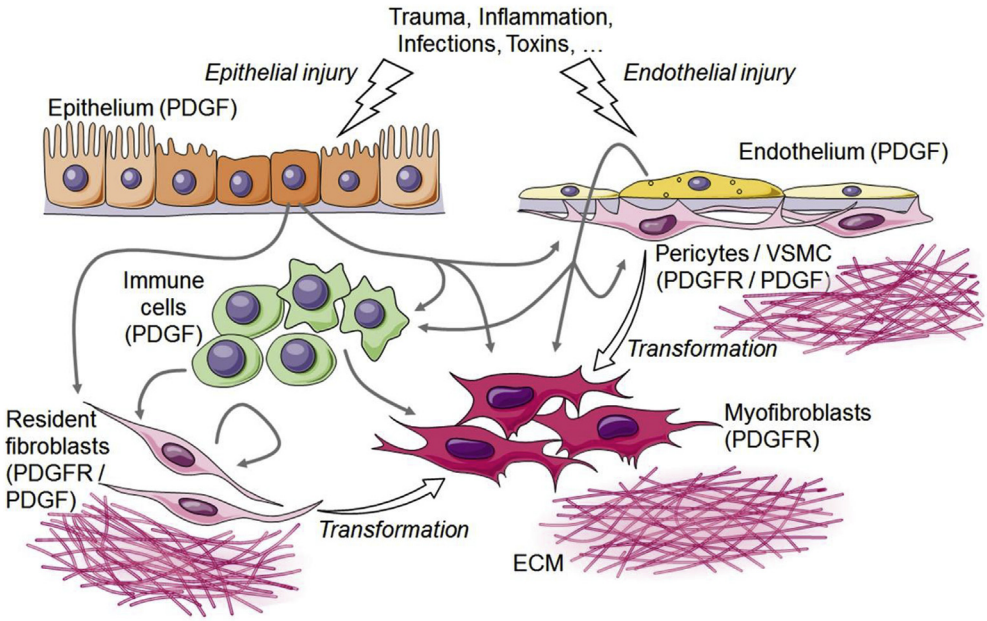


| | PDGFR bearing cells - fibrosis executors (also autocrine PDGF producers) | Local resident PDGF producers |
|---|---|---|
| Vessel | VSMC (media), Pericyte (capillary or adventitial) | Endothelium |
| Bone marrow | Mesenchymal stem cell, Fibroblast (reticular cells), Megakaryocyte, Endosteal cell, Pericyte | Macrophage |
| Kidney | Interstitial fibroblasts, Pericyte, Mesangium (glom.) | Tubular epithelium, Podocyte (glom.), Parietal epithelial cell (glom.), Dendritic cell |
| Liver | Portal fibroblast, Hepatic stellate cell, Pericyte | Hepatocyte, Kupffer cell |
| Intestine | SMC (muscularis mucosae), Intestinal (myo)fibroblast (mucosa), Interstitial cell of Cajal, Pericyte | Intestinal epithelium (mucosa), Intestinal dendritic cell, Intestinal macrophage |
| Heart | Cardiac fibroblast, Pericyte | Cardiomyocyte |
| Lung | Alveolar SMC, Alveolar fibroblast, Pericyte | Lung epithelium, Alveolar macrophage |
| Brain | Astrocyte, Oligodendrocyte precursor, Pericyte, Neuron | Microglia |
| Skin | Dermal fibroblast, Pericyte | Keratinocyte, Langerhans cell |

**Fig. 1. Schematic overview of major cell types involved in organ fibrosis.**
Various cell types are involved in fibrogenesis. Injured epithelial and/or endothelial cells as well as inflammatory cells produce PDGF and stimulate (grey arrows) PDGFR expressing mesenchymal cells, such as fibroblasts, pericytes or vascular smooth muscle cells (VSMC), which give rise to myofibroblasts (black arrows) and produce exaggerated amounts of extracellular matrix (ECM).
The table shows PDGF producing and PDGFR expressing cell types in the respective organs. For most PDGFR bearing cells also an autocrine PDGF production is described. We only listed cells which are reported to be involved in fibrosis.

regeneration of severed axons (Cregg et al., 2014) and exaggerated wound-healing of the skin results in pathological hypertrophic scars or even keloids, i.e. benign tumorous fibrotic tissue expansion. However, most of the clinically relevant diseases nowadays associated with fibrosis are due to insults, which are unlikely to have been relevant during evolution. These include long-standing chronic diseases such as hypertension or diabetes combined with and magnified by an ever more aging population. In these types of insults, there is no localized organ wound with primary tissue destruction as found after infection or trauma, but a diffuse organ involvement without prominent tissue loss. In these instances, cells nevertheless activate pro-fibrotic pathways albeit this is not required for tissue regeneration. This results in a morphologically distinct, pathological fibrosis, i.e. diffuse interstitial tissue fibrosis. This type of fibrosis contributes to disease progression by destroying the normal tissue architecture, which e.g. alters microvascular perfusion and function, innervation or epithelial functionality. The vast majority of experimental studies provided evidence that reduction of the extent of fibrosis results in improved organ functionality and reduced disease progression. Ongoing fibrosis becomes autonomously progressive by epigenetic mechanisms independent of whether the underlying insult persists or not (Bechtel et al., 2010). Taken together, in the majority of diseases, reduction of the extent of fibrosis is likely organ-protective.

## 2. The PDGF system and its role in fibrosis

The PDGF family comprises of five isoforms: PDGF-AA, -AB, -BB,

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