

Editorial

Mediators of Fibrosis

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Progressive, uncontrolled deposition of extracellular matrix proteins leading to scar tissue formation and organ failure represents a final common pathway of tissue response to chronic injury. The nature of the insult varies between organs and tissues and may include viral infections or toxic agents, but in most cases the specific trigger remains unknown. Extensive research on the mechanisms of fibrosis has greatly contributed to a better understanding of the pathological mechanisms involved in this process. While we are learning more about the pathways that contribute to fibrosis, it would be important to integrate this new information with the large body of existing knowledge on the profibrotic mediators, especially Transforming Growth factor β (TGF β). TGF β is one of the most potent inducers of extracellular matrix and has long been considered to be a principal mediator of fibrosis. In addition to activation of both Smad-dependent and Smad-independent signaling pathways, TGF β is involved in an extensive crosstalk with multiple other cellular pathways. Better understanding of the regulatory networks governing the fibrotic response at the cellular level will help to define the key regulatory molecules and advance the design of logical therapeutic targets. This series of articles will highlight some of the new developments in the field of fibrotic mediators.

There is a renewed interest in immune mediators and their influence on the process of fibrosis. In their article, Lafyatis and Farina provide an overview of the innate immune sensors and describe how they are linked to the inflammatory and profibrotic pathways. In a related article Artlett further explores the role of the NLRP3 inflammasome in inducing inflammatory and fibrotic responses.

Excessive production of Reactive Oxygen Species (ROS) leading to oxidative stress plays a major role in impairment of physiological processes. Oxidative stress has been associated with various diseases, including organ fibrosis, as well as aging. The article by Gabrielli provides an in depth discussion on the role of ROS in the pathogenesis of scleroderma. Recent studies using ROS-induced mouse models of scleroderma have revealed an important role of Notch-activation in the development of organ fibrosis. The Notch signaling pathway regulates the differentiation process

in many cell types and its dysregulation is associated with several diseases, including cancer. More recently activation of Notch signaling has been linked to fibrotic diseases. Kaviani and colleagues present new insights into the mechanisms of Notch signaling in fibrosis.

Peroxisome proliferator activated receptor γ (PPAR- γ) is a well-known regulator of lipid metabolism and glucose homeostasis. In their review article Wei and colleagues summarize a large body of evidence that links aberrant expression of PPAR- γ to the process of fibrosis. PPAR- γ agonists are currently used to treat type 2 diabetes and novel PPAR- γ based drugs are being actively developed; in the future these or similar compounds may also be helpful in treating scleroderma and other fibrotic conditions. Another attractive therapeutic target for scleroderma lung disease is caveolin-1. Caveolin-1 is a master regulator of several signaling cascades and its deficiency in pulmonary fibrosis affects multiple pathways in collagen producing cells. Tourkina and Hoffman discuss a novel strategy to restore caveolin-1 function that may be utilized to treat patients with pulmonary fibrosis. There are also accumulating data that bioactive sphingolipids play an important role in regulating inflammation and other aspects of the fibrotic process in numerous organ systems. Shea and Tager review the role of sphingolipids in organ fibrosis and discuss the prospect of targeting components of the sphingolipid signaling pathway for treatment of fibrotic diseases.

Although, only discovered in the past decade, microRNAs are now recognized as critical regulators of post-transcriptional gene expression across various biological processes. The human genome is now predicted to encode nearly 1,000 miRNAs that likely regulate at least one third of all human transcripts. In their article, Vettori and colleagues provide a comprehensive overview of those microRNAs that are involved in regulating profibrotic pathways. The authors also discuss the pros and cons of the microRNA-based therapies.

Another area of active research involves various extracellular signaling molecules that affect fibrosis through novel mechanisms. Two of the articles describe the properties of such profibrotic molecules: Veraldi and Feghali-Bostwick discuss the role of Insulin-like growth factor binding protein -3 and -5 (IGFBP-3 and -5), while Trombetta-eSilva and Bradshaw summarize the potential profibrotic function of Secreted protein acidic and rich in cysteine (SPARC).

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[§]Guest Editor

Although TGF β represents an attractive therapeutic target, its pleiotropic nature and complexity of signaling present significant challenges in considering anti-TGF β therapies. Nakerakanti and Trojanowska review the specific components of the TGF β signaling cascade that are altered in human fibrotic diseases. Targeting those dysregulated downstream signaling molecules may provide alternative strategies to ameliorate excessive TGF β signaling.

Activated fibroblasts or myofibroblasts are the final effector cells responsible for excessive matrix deposition. As pointed out in the review article by Leask, dysregulation of

multiple pathways contribute to this condition. It is clear that targeting a single pathway may not be effective therapeutically and that a combination therapy, as currently used to treat cancer or cardiovascular diseases, would be more beneficial. Although there is no shortage of potential therapeutic targets, currently there is no proven effective treatment for organ fibrosis. Since many pathological pathways relevant to the progression of fibrosis are also shared by other disorders, there is hope that effective treatments will be available in the near future.

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