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Review Article

Fibrogenesis: Mechanisms, Dynamics and Clinical Implications

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ABSTRACT

Fibrosis is the pathological condition resulting in the growth of excess fibrous connective tissue in an organ or body system as a reparative or reactive process. In the field of clinical pathology, clinicians and medical scientists are endeavoring to translate experimental knowledge into effective, innovative treatments for a range of fibrotic conditions. The amelioration of whole organ function is at the forefront of research involving new treatment modalities. The augmentation of cardiac function following myocardial infarction is one area of research currently undergoing rapid growth internationally, but pulmonary and hepatic functions are both affected by fibrosis in numerous disease states, and chronic allograft fibrosis is an increasingly recognized problem in organ transplantation; novel treatments are thus undergoing development with ever increasing urgency. An attempt will be made to explore the dynamics of fibrosis in a range of disease states not classically recognized as having a common etiology.

Keywords: **Fibrosis; Pathogenesis, Clinical Implications**

Introduction

Fibrosis is the pathological condition resulting in the accumulation of fibrous tissue and can be a reparative or reactive process. Increasingly, in the field of clinical pathology, clinicians are translating experimental knowledge into effective treatments for a range of fibrotic conditions, chiefly for musculoskeletal, cutaneous and cardiac conditions. The restoration of whole organ function is at the forefront of research involving new treatment modalities, with the end result being in the domain of tissue engineering and regenerative medicine. The augmentation of cardiac function following myocardial infarction is one area of research currently undergoing rapid growth internationally, but pulmonary and hepatic functions are both affected by fibrosis in myriad disease states, and chronic allograft fibrosis is an increasingly recognized problem in organ transplantation. Indeed, clinicians are called upon to utilize treatments that are undergoing development with ever increasing urgency, many of which do not have a sound evidence base. This review will attempt to ex-

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plore the dynamics of fibrosis in a range of disease states not classically recognized as having a common etiology.

Cardiac Fibrosis: Ischaemic Insults in the Absence of Atherosclerosis

The hypereosinophilic syndrome is a disease categorized by a persistently elevated eosinophil count ($\geq$ 1500 eosinophils/mm^3) for at least a six-month period in the absence of any precipitating or predisposing factor (1). The two forms of the hypereosinophilic syndrome are endomyocardial fibrosis (EMF) and Loeffler's endocarditis. EMF is most commonly found in South America and Africa; Loeffler's endocarditis does not have any known geographical or climatic predisposition. EMF and Loeffler's endocarditis are classified as restrictive cardiomyopathies; diseases of the myocardium that result in impaired ventricular diastole (2).

Both EMF and Loeffler's endocarditis lead to scarring of the endocardial surface of the heart, resulting in reduced compliance and impaired cardiac function (3). The hypereosinophilic syndrome principally involves the inflow tracts of the left and right ventricles, and usually affects the atrioventricular (AV) valves, leading to varying degrees of tricuspid and mitral regurgitation (3). The earliest, most discernable changes in the hypereosinophilic syndrome have not been adequately delineated, primarily because most patients do not present with symptoms until relatively late in the disease's course (1, 2). Nevertheless, the demarcation of both EMF and Loeffler's endocarditis into three basic stages greatly assists scientists and clinicians alike (3, 4).

The first stage of the hypereosinophilic syndrome is characterized by eosinophilic infiltration of the myocardium with concomitant necrosis of the subendocardium, usually associated with acute, worsening myocarditis (5). The second stage, typically observed after ten to twelve months, is associated with thrombogenesis over the initial lesion, with a reduction in local inflammatory activity. Eventually, after several years of untreated disease, the fibrotic stage is reached; dense collagenous networks replace the endocardium itself, an arrangement that is pernicious to overall cardiac function (3). Not only is systolic function impaired, but also diastolic filling is greatly compromised as the relatively inelastic ventricles fail to relax sufficiently.

The etiopathogenesis of the hypereosinophilic syndrome has not been clearly defined, however infectious, biochemical, inflammatory, and nutritional factors have been implicated as causative agents (1-3). Endomyocardial fibrosis is frequently associated with attendant parasitic infections; tropical and sub-tropical regions provide a suitable milieu for pathogens, including mosquitoes, thus giving EMF a geographic predisposition, unlike Loeffler's endocarditis. The eosinophil plays a vital role in the pathogenesis of the hypereosinophilic syndrome; however, the exact nature of eosinophil-induced tissue damage has not been comprehensively described in the literature (5). Two plausible hypotheses regarding eosinophil behavior are cell-induced myocardial necrosis and subsequent fibrosis or eosinophil attraction towards the endocardial surface as a result of the initial insult (2, 3).

Both EMF and Loeffler's endocarditis involve repeated attacks of angina due to endothelial coronary obstruction, each representing a micro-infarct and can occur in the absence of a significant atherosclerotic burden (3, 4). This disorder leads to heart failure because of insufficient blood pressure and impaired contractile force due to the fibrosis itself. Palliative treatments include nutrient supplementation, but effective treatments should be targeted at the causative agents, including effective cholesterol, diabetes and blood pressure management when atherosclerosis is present (4, 5). Chelation therapy can ameliorate the inflexible condition of the heart, but further clinical trials are needed to examine its efficaciousness in the patient population (2).

The Myriad Forms of Pulmonary Fibrosis and Their Impact on Quality of Life

Diffuse parenchymal lung disease (DPLD) refers to a group of lung diseases, including idiopathic pulmonary fibrosis and pneumoconiosis, both of which affect the alveolar epithelium, pulmonary capillary endothelium, and perivascular and perilymphatic vessels (6). As the name suggests, idiopathic pulmonary fibrosis has no known cause (6, 7). It is generally recognised that the condition leads to substantial illness and disability. However, pneumoconiosis is perhaps more significant because of its public health effects, and the fact that many of the disease's precipitating factors can be readily found in the industrial workplace (8).

Pneumoconiosis is an occupational lung disease characterized by the formation of fibrotic nodules in the lungs caused by chronic inhalation of silica and silicates in dusty workplaces, for example coalmines and factories. The condition is normally first identified as industrial bronchitis, a condition which subsides three to six months following the cessation of exposure (8). However, pathological changes in the lung parenchyma, including the formation of micronodules and macronodules, as well as inflammation-induced fibrosis, are inevitable and progressive in nature (9). Various substances can cause pneumoconiosis, including asbestos, coal dust, and a variety of metal compounds (9, 10). Inflammation-induced fibrosis is considered a precipitating factor for carcinogenesis, especially pneumoconiosis-related squamous cell carcinomas (SCCs) of the lung. Currently, pneumoconiosis is treated with prednisolone and an assortment of anti-inflammatories and anticoagulants (11). Patients with hypoxemia and respiratory distress may be given supplemental oxygen as palliative or definitive treatment (12).

Lung disease can also result from the restriction of airways due to the inflammatory response itself. Cystic fibrosis (CF) causes incessant coughing and copious mucous production; these and other symptoms are largely brought about by bacterial infection (12). In later stages of CF, however, changes in the histology of the lung exacerbate chronic respiratory problems. The pathophysiology of CF is complex. Most airway injury in CF is thought to be secondary to an accumulation of neutrophil products, namely proteases and free radicals (13). The role of the endothelium in contributing to this neutrophil infiltration has not been clearly defined, however an examination of heparin sulfate-containing proteoglycans (protein complexes) in control and CF-affected lungs revealed that interleukin 8 (IL-8), a key modulator in CF, has a protracted duration in CF endothelium, indicating that the maintenance of inflammation is central to this process (10-13).

Furthermore, the process of mucus plugging is a key pathophysiologic and clinical feature of CF; the mechanisms of which are not fully understood (12, 13). A study of the expression of Bcl-2, an apoptosis inhibitor *in vivo*, in goblet cells from human tissue, as well as in murine models, concluded that the expression of Bcl-2 is associated with increased goblet cell hyperplasia in CF, leading to increased mucous production which exacerbates mucus plugging (14,15). Although it is clear that epithelial injury is intimately involved in airway pathophysiology in CF, studies of epithelial injury and repair have been inconclusive and much work remains to be done to clarify the precise mechanisms involved.

Hepatic Fibrosis: When a Reparative Process Becomes Pathological

Cirrhosis of the liver is a consequence of chronic liver disease characterized by replacement of liver tissue by fibrotic scar tissue, as well as regenerative nodules, leading to progressive loss of liver function (16). The cirrhotic liver manifests anomalous hepatocyte growth and inadequate regenerative capacity (17, 18). Cirrhosis is most commonly caused by hepatitis C and alcohol abuse (19). Cirrhosis is generally irreversible once it occurs, and effective treatment focuses

on preventing its progression and complications, rather than reversing it and restoring the liver to its baseline level of function. In advanced stages of cirrhosis, the only effective treatment option is transplantation (17).

The cirrhotic liver may be initially macroscopically enlarged, but with progression of the disease, it usually becomes smaller and nodular in nature. The hepatic surface is irregular, yet the consistency is firm (20). On the basis of the size of the nodules present, there are three definable macroscopic sub-types; namely, micronodular, macronodular and mixed cirrhosis (18, 19). The micronodular regenerating nodules are less than 3 mm, whereas the macronodular (post-necrotic cirrhosis) nodules are larger than 3 mm. As the name suggests, the mixed cirrhosis condition consists of a variety of nodules of different sizes. In all of these cases, cirrhosis is characterized by the formation of fibrous septa throughout the regeneration nodules (18). Indeed, at the cellular level, regenerating hepatocytes are disorderly positioned, and are analogous to islands in a sea of fibrous connective tissue (21). Portal tracts, central lobular veins and the characteristic radial pattern seen in the healthy liver are absent. Fibrous septa may represent areas of increased inflammatory infiltration by lymphocytes and transient phagocytes, which potentiates the 'inflammatory soup', thus leading to the vicious cycle that is cirrhosis of the liver

As the disease progresses, liver biopsies may reveal ongoing hepatocyte necrosis, which is of an inherently variable, but progressive nature (20). Neutrophilic infiltration with vascular inflammation is readily observed at this stage. Primary cirrhotic hepatocytes resist TGFbeta-induced apoptosis and consequently lead to an increase in carcinogenesis (21). Therefore, pharmacological regulation of hepatocellular apoptosis may, in the future, lead to a reduction in the severity of this condition and the associated risk of malignancy, although much work remains to be done in this multidisciplinary area (21).

Idiopathic liver fibrosis, however, is the primary cause of organ failure in chronic liver diseases of any etiology (20). Fibrosis develops with characteristic spatial patterns and is a consequence of the different causes of parenchymal damage (19, 20). Fibrosis observed as a consequence of chronic viral infection is initially concentrated in the region of the portal tract, whereas fibrosis caused by toxic or metabolic damage is located chiefly in the centrolobular areas (18). Moreover, it is evident that different cell types play a role in the deposition of fibrillar extracellular matrix (ECM) during hepatic fibrogenesis. Hepatic stellate cells are mainly involved when hepatocellular damage is within the liver lobule substance (21). Portal myofibroblasts and fibroblasts play a key role when the damage is located proximal to the portal tracts, as in secondary insults (21). As the disease progresses towards septal fibrosis, it is likely that all ECM-producing cells contribute to fibrogenesis and the process becomes irreversible and increasingly resistant to treatment (21). A major advancement towards the understanding of the molecular mechanisms of fibrogenesis is derived from a number of in vitro experiments investigating the pathophysiological role of growth factors and cytokines, and these basic science investigations inform clinicians about the common pathways and fundamental mechanisms which underpin fibrosis in a host of disease states (16, 19).

Chronic Allograph Fibrosis: The Emerging Blight of Organ Transplantation

The benefits of organ transplantation on quality of life are enormous (22). The improvements in short-term graft survival and the attenuation of acute rejection rates have been greatly assisted by the latest research in immunotherapy and immune system modulation with anti-rejection agents. Late graft loss following organ transplantation, especially of the kidney, limits the success of this procedure and often necessitates a re-transplant operation, which is technically de-

manding for the surgeon and confers a mortality risk greater than the index procedure (23). In the kidney, graft loss is associated with the development of tubular atrophy and interstitial fibrosis within the kidney, in a condition called chronic allograft nephropathy (CAN) (22-24). At the present time, treatment strategies for this condition are largely ineffective, aside from steroids and the maintenance of a safe fluid balance, often with the use of dialysis; the focus is therefore on prevention. Nevertheless, the mechanisms of CAN have been largely delineated and it can now be appreciated to represent a condition where aberrant, uncontrolled fibrosis is the final common pathway (22).

Following graft injury, proliferative and infiltrative responses mediated by chemokines/cytokines and growth factors lead to graft fibrosis (22). Indeed, TGFbeta has been strongly implicated in the pathogenesis of chronic graft injury and epithelial-mesenchymal transformation (EMT) (16, 24). The combination of these processes result in ECM accumulation due to an increase in production of matrix; matrix degradation may also be impeded, so that its net accumulation is the end result (23). Recent investigations into the pathogenesis of tissue fibrosis have suggested a number of novel strategies to improve matrix synthesis (22). The majority of therapies have focused on TGFbeta, but alternative targets need to be identified and examined (16, 25).

Conclusion

Form and function are inextricably linked; indeed, disordered structure leads to impaired function. The management of organ fibrosis through a range of treatments is therefore essential for the preservation of normal health. Chronic allograft fibrosis is an increasingly recognized problem in organ transplantation; novel treatments are thus undergoing development with ever increasing urgency. The prevention of graft fibrosis should be pursued as vigorously as the elimination of acute and chronic organ rejection. The amelioration of whole organ function is at the forefront of research involving new treatment modalities. The augmentation of cardiac function following myocardial infarction is one area of research currently undergoing rapid growth internationally, but much work remains in finding permanent, effective solutions to the myriad conditions of the liver and lung characterized by fibrogenesis.

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