The Molecular and Cellular Landscape of Fibrosis: Translational Insights and Emerging Therapeutic Avenues.

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1 Abstract

This literature review explores the intricate mechanisms of fibrosis, underscoring its dual role in short-term tissue repair and long-term deleterious health implications. This essay states the pivotal role of inflammation in the fibrotic process and also discusses in detail the development of fibrosis spurred by chronic inflammation. It also enumerates the consequences of an uncontrolled fibrotic process. Furthermore, this essay focuses on the molecular and cellular factors influencing fibrotic and anti-fibrotic processes, and mainly discusses about one specialized type of cell: myofibroblasts, which is a key cellular component in fibrosis. The review suggests the necessity and importance of a balanced approach between the two general processes, the process of fibrosis and anti-fibrosis, emphasizing the potential of mathematical modeling in understanding these dynamics. It concludes by projecting future research directions, particularly the promising avenue of employing accurate experimental studies to simulate and potentially curb fibrosis, thereby alleviating its burden on affected individuals.

2 Understanding Fibrosis: An Introduction to Its Role in Tissue Repair and Potential Health Implications

Damage to tissues can result from various stimuli, including infections, autoimmune reactions,toxins, radiation and mechanical injury. When our bodies are seriously injured, many people choose to go to the hospital for treatment. However, in more not-so-bad situations, our bodies can actually repair themselves. The repair-process typically involves two steps: a regenerative phase, in which injured cells are replaced by cells of the same type,leaving no lasting evidence of damage; and another phase is known as fibrosis, in which connective tissues replaces normal parenchymal tissue [Wyn08]. In this aspect, fibrosis can be viewed as a self-preservation or self-repair response. To some degree, tissue fibrosis acts to mend the damage experienced. However, the 'self-repair' process is initially advantageous, if not properly regulated, it can turn detrimental, leading to significant accumulation of ECM components and the subsequent replacement of regular tissue with irreversible scar tissue [SRSH01]. Diseases caused by fibrosis can result in the demise of organs and even lead people to dead, such as idiopathic pulmonary fibrosis, liver cirrhosis, and cardiovascular fibrosis [BB$^+$05].

Generally speaking, fibrosis is a very important step for any individual to get a whole self-repairing process. While excessive fibrosis also can caused death in organs and individuals. Thus, it is very important and necessary to discuss whether fibrosis is manageable and controllable.

3 Elucidating the Mechanisms of Fibrosis: Pathogenesis, Reversibility, and the Multifactorial Role of Myofibroblasts

As it has been mentioned above, fibrosis can be seen as a self-repair process that occurs spontaneously in biological internal environment. The prevailing view now posits that fibrosis is commonly a consequence of chronic inflammation. It is a type of sustained immune response lasting several months [Wyn08]. However, fibrosis commonly discussed in medicine refers to fibrosis containing disease factors, which is mainly because fibrosis will always cause scars and other trauma to the human body when it can be observed. These scars and trauma also includes the fatal fibrosis disease we mentioned before. Therefore, it's imperative to incorporate mechanisms that halt or switch-off this process to protect the body from excessive self-repairing [CEH$^+$18], and it will be discussed below.

Compare to acute inflammation, fibrosis is typically a slow and long term process, which includes several processes that occur together. It includes the process that stop fibrosis that can be seen as another self-repair process [Wyn08]. This anti-fibrosis process can not only prevent the continued occurrence of fibrosis, but also can repair tissues or organs that have become fibrotic, which means reversing fibrosis. This has been proved by the experiment of eliminating of hepatitis B virus (HBV) and hepatitis C virus (HCV) in chronically infected individuals is associated with huge regression of disease, which provide evidence that human hepatic fibrosis is reversible [FKI06]. Actually, the cessation of fibrosis is influenced by the balance between antifibrotic and profibrotic inputs [CEH$^+$18], which can be seen as two general functions in one system. More exactly, there are many corresponding factors in these two functions. The cessation of fibrosis, which is called as anti-fibrosis is influenced by several factors: elimination of the causative pathogen, the inhibition of cytokines, chemokines, specific MMPs, and adhesion molecules [DFC$^+$05]. These factors can be seen as inner factors. As for external factors, the medicine is undoubtedly the most important factor. In fact, there was an experiment had already showed that treating schistosomiasis patients with praziquantel have a certain effect on liver fibrosis [VD04]. As for the process of fibrosis, although the factors that can cause fibrosis are various, most of them can be seen as inner factors (since fibrosis is always caused by long-term inflammation, which was mentioned above). Based on the classification of factors, the different functions might be constructed, the functions can be used to describe the influence of fibrosis or anti-fibrosis that caused by inner or external factors. Please notice that the classification of the factors is not specific or accurate enough but just providing a basic idea to study the influence and balance between process of fibrosis and anti-fibrosis mathematically. More exactly, the influence caused by the process relating to fibrosis can seen as a functional, which is a function of functions of two processes that based on different variables.

Focus on the molecular and cellular factors, the key cellular factor of fibrosis is the myofibroblast, which is a specialized cell type. It takes responsibility to product and deposit the ECM components which may cause fibrosis [Wyn08]. On the other hand, inhibiting the activation can effectly help slow the progression of fibrosis [PTR07][TTW$^+$04]. Thus, the activation of myofibroblast is important and the study of the activation is necessary. In fact, pathogenic organisms are not the reasons for all fibrotic disorders, there

are lots of other mechanisms that participate in the activation of myofibroblast [Wyn08]. For instance, the process involves contributions from signals emitted by lymphocytes and macrophages, autocrine factors released by myofibroblasts, and pathogen-associated molecular patterns (PAMPs) originating from infectious agents that engage with pattern recognition receptors [MH+07]. PAMPs, encompassing elements like lipoproteins, bacterial DNA, and double-stranded RNA, are byproducts of pathogenic activity. These molecular patterns are identified by pattern recognition receptors (PRRs) present on an array of cells, fibroblasts included [AT04]. Moreover, bacteria who lives in the gut can also activate the myofibroblasts [ORP03]. There are also many other factors that will effect on the activation of myofibroblast, which will not be listing here. In summary, myofibroblasts are activated by a variety of mechanisms, which is also can be considered as a complex function of process that based on different types of variables.

4 Future Perspectives and Concluding Remarks on Fibrosis Research

In conclusion, this review mainly introduces and discuss about the mechanisms of fibrosis. Fibrosis can be seen as a self-repair process in a short period but will harm or even cause death if the fibrotic process cannot be stopped, it is also a slow and long term process that mainly caused by inflammation. The review also mentions and discusses the anti-fibrosis process. This essay provided an idea of constructing a functional based on two functions: the functions of the profibrotice process and the antifibrotic process, these functions are mainly influenced by many different types of variables or factors. The molecular and cellular factors are the most considered part in above sections. By observing and measuring the influence of different factors, the balance between those two processes can be studied in one system. Researching the activation of myofibroblasts is very important, as it is a key cellular factor in fibrosis.

In future study, if the balance between anti-fibrosis and fibrosis can be studied and simulated by modelling, also the functional can be constructed correctly, numerous people will overcome the struggle with diseases caused by fibrosis. Undoubtedly, these studies will be based on lots of accurate related experiments.

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