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Review

Cytokine mediated tissue fibrosis ☆

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ABSTRACT

Acute inflammation is a recognised part of normal wound healing. However, when inflammation fails to resolve and a chronic inflammatory response is established this process can become dysregulated resulting in pathological wound repair, accumulation of permanent fibrotic scar tissue at the site of injury and the failure to return the tissue to normal function. Fibrosis can affect any organ including the lung, skin, heart, kidney and liver and it is estimated that 45% of deaths in the western world can now be attributed to diseases where fibrosis plays a major aetiological role. In this review we examine the evidence that cytokines play a vital role in the acute and chronic inflammatory responses that drive fibrosis in injured tissues. This article is part of a Special Issue entitled: Fibrosis: Translation of basic research to human disease.

1. Introduction

Physiological wound repair is a complex, highly orchestrated process that allows for the replacement of dead or damaged cells and is critically important in restoring homeostasis to a tissue after injury. Wound repair can be loosely defined by three overlapping stages; an initial response, a recovery of integrity, followed finally by resolution of the wound back to a functional epithelium. It requires a tightly regulated spatial and temporal response from key structural cells in the organ such as epithelial cells, endothelial cells and fibroblasts but also from immune and progenitor cells drawn from the circulatory system [1]. Acute inflammation is a recognised part of normal wound healing by serving as an innate immune response to the disrupted epithelial surface until it is reinstated. However, when inflammation fails to resolve and a chronic inflammatory response is established this process can become dysregulated resulting in pathological wound repair and the accumulation of permanent fibrotic scar tissue at the site of injury (Fig. 1). This fibrosis is characterised by the excessive accumulation of extra cellular matrix (ECM) components including collagens, fibronectin and hyaluronic acid at the site of tissue injury, leading to a decrease in organ function and, in some cases, organ failure and death [2]. It is estimated that 45% of deaths in the western world can now be attributed to diseases where fibrosis plays a major aetiological role [3]. Fibrosis can affect any organ including the lung, skin, heart, kidney and liver and may represent an aberrant response to a single major injury but more commonly is a response to a persistent or repetitive injury. In this review we examine the evidence for cytokines released as part of an acute or chronic inflammatory response in driving fibrosis in injured tissues.

2. Pathogen and damage associated molecular patterns in fibrosis

A functional epithelium provides an efficient barrier against microorganisms and other potentially harmful molecules *via* a wide range of mechanisms including mucociliary clearance, maintenance of epithelial adherence and tight junctions, homeostasis of ion and water transport and secretion of antibacterial, antimicrobial and antiprotease molecules [4]. However the epithelium is often located on vulnerable surfaces that receive significant challenges to their integrity such as the gut, skin and lungs. These tissues are routinely exposed to the external environment and a range of harmful molecules including bacteria and viruses, tobacco smoke, asbestos, silica and diesel exhaust that can lead to epithelial activation and, in cases of chronic exposure, epithelial damage, shedding and denudation.

Numerous fibrotic diseases are believed to have an infectious aetiology with bacteria (*Pseudomonas aeruginosa*, *Mycobacterium tuberculosis*), viruses (HCV, Respiratory syncytial virus), fungi (*Aspergillus fumigatus*, *Cryptococcus neoformans*) and multi-cellular parasites (*Schistosoma mansoni*, *Toxoplasma gondii*) driving wounding,

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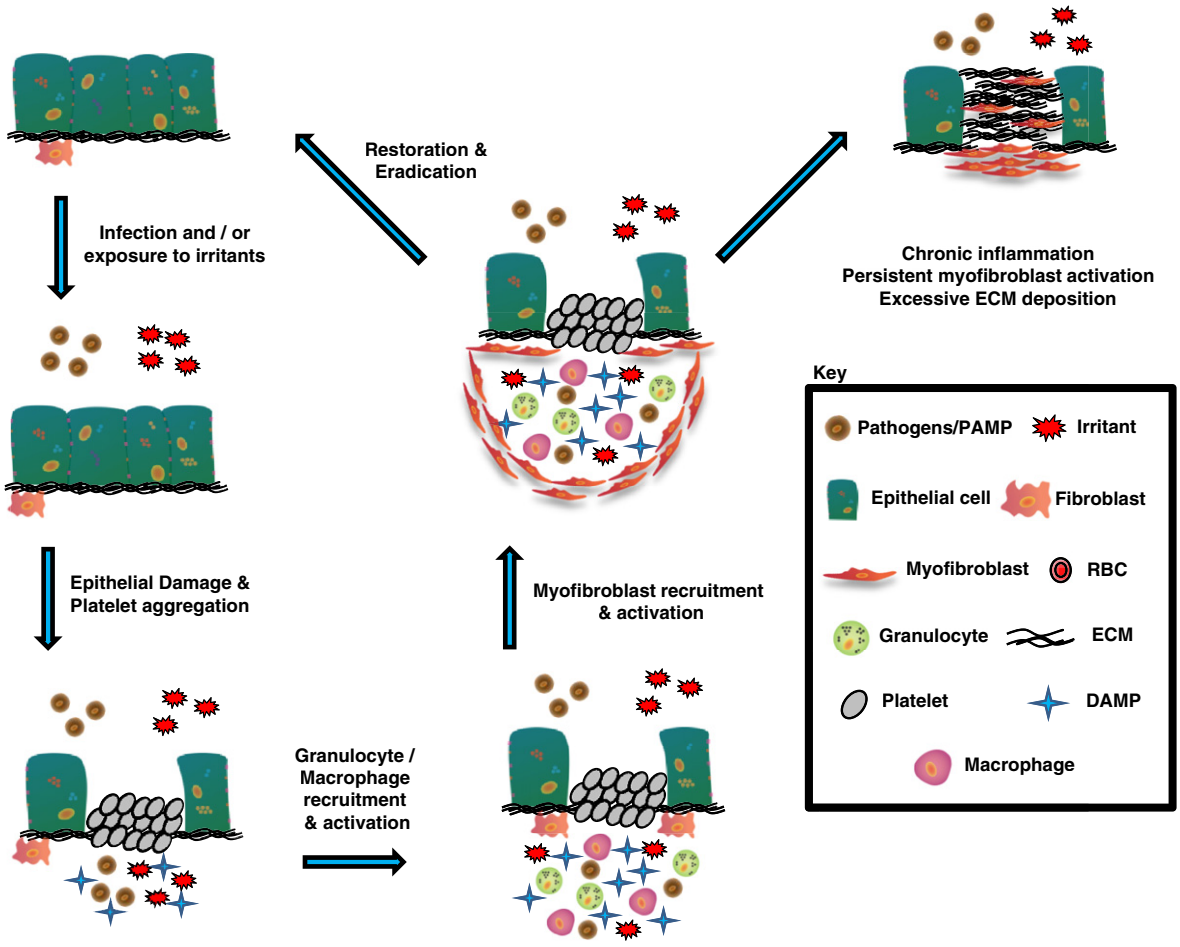

Fig. 1. Pathological vs. physiological wound healing. Infection or exposure to harmful molecules can lead to epithelial damage and loss of epithelial integrity. Following injury fibroblasts, endothelial cells, and neighbouring epithelial cells release a range of soluble factors that trigger clotting and initiate the development of a provisional ECM. The aggregation and subsequent degranulation of platelets triggers increased blood flow, vasculature dilation and vasculature permeability allowing the effective recruitment of inflammatory cells to the site of tissue injury. The first responders are the neutrophils, eosinophils and basophils that are responsible for neutralising any invading pathogens *via* an oxidative burst response and eliminating cell debris/dying cells by phagocytosis. The granulocyte number in the site of epithelial injury peaks rapidly, within minutes, but is followed by a rapid decline. Once in the wound micro-environment the recruited monocytes mature to increase the number of macrophages in the wound and perform similar functions to those described for granulocytes. In addition they produce cytokines and chemokines that amplify the wound response by promoting the formation and stabilisation of a provisional ECM and promoting angiogenesis. Myofibroblast numbers are increased at the wound site from several sources (see Fig. 2). Once recruited to the wound area the myofibroblasts become activated and traverse the provisional ECM until they reach the edge of the wound and initiate contraction of the wound. Finally epithelial cells at the edge of the wound loosen adherence junctions and migrate over the ECM to restore a continuous epithelium and tissue homeostasis. At this point the myofibroblasts in the wound area undergo apoptosis and the macrophage numbers are significantly reduced *via* egress into the lymphatic system. Fibrosis occurs when the initial wound is severe, the wound repair process becomes dysregulated or the source of epithelial damage persists resulting in repeated injury and chronic inflammation.

chronic inflammation and subsequent fibrosis in multiple organs [5–13]. Pathogen by-products including bacterial DNA and double stranded RNA, peptidoglycan, lipopolysaccharide and flagellin, collectively referred to as pathogen-associated molecular patterns (PAMPs), are recognised by pattern recognition receptors (PRR) on a wide range of cell types including immune cells (macrophages, neutrophils, T-cells, B-cells, dendritic cell, eosinophils) and structural cells (epithelial cells, fibroblasts, adipocytes) [14,15]. The interaction between PAMPs and PRR provides an evolutionarily conserved mechanism that provides the first line of defence against invading pathogens and activates numerous proinflammatory cytokine and chemokine pathways, leading to the eradication of the pathogen. The failure to clear the pathogen or its PAMPs provides a persistent source of tissue injury, chronic inflammation and creates an environment that might favour fibrosis. For example persistent colonisation of the allograft with *Pseudomonas aeruginosa* following lung transplantation is strongly associated with the subsequent development of bronchiolitis obliterans syndrome (BOS) [16] and prolonged infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) leads to loss of liver architecture and function and ultimately cirrhosis [17,18].

It is also increasingly apparent that PRRs provide mechanisms for mounting inflammatory and wound-healing responses to sterile tissue trauma [19]. When epithelial cells are damaged or dying their membranes lose integrity and intracellular proteins leak into the external environment. These damage associated molecular pattern molecules (DAMPs) or alarmins include high-mobility box group 1 (HMGB-1), heat-shock proteins (HSP60, HSP70), interleukin (IL)-33 and IL-1α among others [20]. DAMPs can trigger innate immune responses in a wide variety of cell types *via* engagement of PRR and provides an important homeostatic mechanism by which the immune system can sense and mount wound-repair responses in damaged tissues [21]. However, there is also evidence that DAMPs can contribute to the pathogenesis of many inflammatory and fibrotic diseases. For example IL-33 is strongly associated with fibrosis in chronic liver injury [22] and is increased in systemic sclerosis patients, correlating with the extent of skin sclerosis and the severity of pulmonary fibrosis [23]. In addition HMGB-1 levels are elevated in the bronchoalveolar lavage (BAL) of patients with idiopathic pulmonary fibrosis (IPF) and hypersensitivity pneumonitis [24].

Fibroblasts express a number of PRR including toll-like receptors (TLR) and IL-1R therefore PAMPs and DAMPs can directly activate

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