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Macrophages and fibroblasts during inflammation, tissue damage and organ injury

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1. ABSTRACT

Inflammation is a highly complex cellular surveillance system that is essential for anti-microbial defense and wound healing. The inflammatory process relies on multifaceted coordination among various body systems. Many host cells including leukocytes, fibroblasts, endothelial cells and epithelial cells are involved in the inflammatory process. Cellular receptors, such as Toll-Like-Receptors (TLRs), and cytokine receptors, are responsible for recognizing and processing diverse foreign and host challenges. In addition, they regulate the expression of secondary inflammatory mediators such as cytokines, chemokines, complement proteins, and co-stimulatory molecules. These mediators modulate cellular responses by the activation and recruitment of immune cells mediating host cellular and tissue remodeling. Although inflammation is beneficial for host wound healing and defense toward infection, excessive or altered inflammation often leads to a wide range of tissue injuries and human diseases including cardiovascular diseases, diabetes, and multi-organ failure. This review specifically addresses the contribution of macrophages and fibroblasts to inflammation and tissue injury.

2. INTRODUCTION

The term inflammation was first coined by a Roman scientific writer Aulus (Aurelius) Cornelius at the turn of the first century. The four cardinal features ascribed to inflammation include swelling, redness, heat, and pain. Triggers for inflammation range from microbial infection, physical shock, chemical and biological irritants, as well as abnormal metabolites. Various germ line-coded innate receptors such as cell surface Toll-Like-Receptors (TLR), NOD-Like-Receptors (NLR), cytokine receptors, scavenger receptors, and G-protein-coupled-receptors (GPCR) can specifically recognize diverse molecular patterns embedded within various danger signals (1-3). Subsequent activation of intracellular signaling pathways eventually leads to the activation of transcription factors, such as nuclear factor kappa B (NFkB), signal transducers and activators of transcription protein (STATs), Smad proteins, and nuclear factor of activated T-cells (NFATs), which are responsible for the expression of pro- or anti-inflammatory genes.

Among the various cells involved in mediating inflammation, macrophages and fibroblasts are two types of cells universally present in almost all tissues and organs.

The differential activation of macrophages and fibroblasts are involved in many facets of inflammation and tissue injury. Classically activated macrophages (M1 macrophages) express pro-inflammatory cytokines, interferon gamma (INF-gamma) and reactive oxygen/nitrogen species, which are involved in the phagocytosis and killing of microbes (4). During chronic inflammation, M1 macrophages lead to exacerbation of inflammation and tissue damage. Consequently, classically activated macrophages are associated with inflamed tissues during the course of diabetes, atherosclerosis, and multi-organ injury (5). On the other hand, alternatively activated macrophages (M2 macrophages) fail to express pro-inflammatory mediators, and may contribute to resolution of inflammation. Fibroblasts form the connective tissues of various organs and participate in the wound healing process. However, excessive proliferation of fibroblasts and production of extracellular matrix proteins during chronic inflammation can lead to pathological fibrosis.

T helper cells play critical roles in modulating the differential activation of macrophages as well as fibroblasts. Type 1 T-helper (Th1) cells produce pro-inflammatory cytokines, such as interferon-gamma (IFN gamma and tumor necrosis factor alpha (TNF alpha), which skew macrophages into the M1 phenotype (6). In contrast, type 2 T-helper (Th2) cells produce IL-4, IL-5, and IL-13 cytokines, which are responsible for inducing the alternatively activated macrophages (6). On the other hand, differentially activated macrophages can also change the cytokine environment and modulate the differentiation of T helper cells. The cross-talks among diverse immune cells as well as non-immune cells enable the host to elicit complex inflammatory responses involved in tissue repair or injury.

3. CONTRIBUTION OF MACROPHAGES AND FIBROBLASTS DURING TISSUE DAMAGE AND ORGAN INJURY

3.1. Macrophages in inflammation and tissue injury

Macrophages are key innate immune cells capable of diverse functions including the phagocytosis of foreign cells and particulates, the expression of reactive oxygen species, the production of proteins/enzymes involved in tissue remodeling, and the expression of chemokines and pro/anti- inflammatory cytokines. As a result, macrophages are involved in modulating the inflammatory process during the pathogenesis and resolution of tissue injury and inflammation. Despite the fact that macrophages exhibit significant plasticity and are capable of expressing mediators with distinct pro- or anti-inflammatory effects, local macrophages subjected to particular challenges often adopt unique phenotypes. The phenotypes are characterized by either preferentially secreting pro-inflammatory mediators such as tumor necrosis factor, IL-6, inducible nitric oxide synthase (iNOS), or anti-inflammatory mediators such as IL-10, arginase-1, which differentially modulate inflammation, and tissue injury and repair. Macrophages exposed to lipopolysaccharide (LPS) and IFN gamma are the classically activated macrophages (M1) which express pro-inflammatory cytokines that are involved in many inflammatory diseases, including diabetes and insulin resistance, atherosclerosis and stroke, shock, and ischemia/reperfusion injury (7-9). In contrast, macrophages exposed to IL-4 are the alternatively activated macrophages (M2), which preferentially express arginase-1 and other anti-inflammatory mediators that counteract the effect of pro-inflammatory mediators. M2 macrophages are critical for wound repair and resolution of inflammation (10, 11). Despite the fact that M2 macrophages exhibit anti-inflammatory effects, excessive differentiation and proliferation of M2 macrophages may be exploited by tumor cells and can contribute to tumor cell proliferation (12-14).

Intra-cellular molecular signaling pathways responsible for the differentiation of M1 or M2 macrophages are not clearly understood. Synergy among TLR signaling and IFN gamma mediated signaling may be required to induce the activation of NFkB and STAT1/3. Collectively, NFkB and STAT1/3 may lead to elevated expression of typical M1 genes such as TNF alpha, IL-6, and iNOS. Regarding M2 macrophages, IL-4 activates at least three downstream effector pathways, including PI3K, RAS-MAPK, and STAT6 (15). Thus far, STAT6 has been shown to be important for the expression of selected M2 marker genes, including arginase-1, YM1, and found in inflammatory zone (FIZZ1) (16-18). The contribution of the PI3K and RAS pathway has not been fully studied. Intriguingly, the differentiation of M1 and M2 macrophages seems to be mutually exclusive. We recently demonstrated that LPS/IFN gamma not only induces M1 differentiation, but also suppresses IL-4 mediated expression of arginase-1 1 (unpublished data). In contrast, IL-4 has been shown to suppress LPS-induced expression of iNOS and TNF alpha (19). Conceivably, yet-to-be-defined cross-talks and feedbacks exist among these pathways that contribute to the orderly macrophage differentiation.

The contribution of macrophages to the pathogenesis and resolution of many inflammatory diseases and tissue injuries has become increasingly evident. Several recent studies demonstrated that M1 macrophages are highly elevated in fat tissues from diabetic patients and animals (7, 20). Lumeng *et al* demonstrated that a novel F4/80+CD11c+ macrophage population exists in fat tissues harvested from obese and diabetic mice (7). In addition, these macrophages expressed elevated levels of TNF alpha and iNOS. A separate study by Kanda *et al* reported that the serum levels of chemokines (MCP-1) and cytokines (TNF, IL-6) are elevated in obese mice (21). Furthermore, elevated M1 macrophages were shown to exacerbate inflammation, and cause related complications including diabetic fibrosis, nephropathy, and retinopathy (22). In contrast, adipose tissue macrophages (ATM) found in lean and non-diabetic mice expressed genes characteristic of M2 macrophages including arginase-1 and Ym1. The Chawla group demonstrated that peroxisome proliferator-activated receptor delta (PPAR delta) is at least partially required for maturation of alternatively activated macrophages (10). IL-4 can activate PPAR delta and induce the expression of the

alternative phenotype in Kupffer cells and adipose tissue macrophages of lean mice. Consequently, interventions that skew macrophages into the M2 phenotype have been shown to be beneficial for the resolution of insulin resistance (10).

During the pathogenesis of atherosclerosis, activated macrophages not only exacerbate local injury by secreting pro-inflammatory cytokines and reactive oxygen species, but also by actively assimilating cholesterol and low density lipoproteins (LDL) leading to the formation of foam cells and plaques on vessel walls (23). In addition, M1 macrophages can also attract other immune cells to aggravate the pathogenesis of atherosclerosis (24). During the late phase of atherosclerosis, M1 macrophages may also contribute to the rupture of plaques by secreting proteases such as metalloproteases (MMPs) (25).

Inflammatory processes mediated by M1 macrophages not only contribute to chronic inflammatory damages and diseases, but also acute injuries. Studies demonstrated that macrophages play important roles in acute septic shock, ischemia and reperfusion injuries of multiple organs and tissues (26, 27). Elevated levels of inflammatory mediators during septic shock and ischemia injury are closely linked with the severe outcome of organ damage and mortality.

Conceivably, therapies aimed at reducing M1 macrophage populations during inflammatory responses may hold potential in treating various inflammatory diseases. Indeed, a recent study showed that the Sphingosine-1-phosphate agonist FTY720 can potentiate M2 differentiations and decrease M1 differentiation (5). FTY720 has shown promise in treating diabetes and related complications (28, 29). Several separate studies indicate that depletion of M1 macrophages attenuated ischemia/reperfusion mediated lung or kidney inflammation and damage (30, 31).

Despite recent progress, the complexity of macrophage differentiation and subsequent physiological/pathological implication are far from fully defined. A recent study suggests that intermediate macrophage phenotype may exist and correlate with the severity of diabetes and insulin resistance in humans (20). Macrophages collected from human adipose tissues express M2 genes (arginase-1 1 and TNF alpha. Mosser *et al* reported that LPS and IgG can induce a unique macrophage phenotype expressing TNF and IL-10 (32). However, the physiological implication for this phenotype is not yet defined. Future studies are clearly warranted to explore the combinatory effects of various agents on macrophage differentiation and function.

3.2. Fibroblasts in inflammation and tissue injury

Fibroblasts maintain the extracellular matrix by undergoing proliferation and secreting proteins involved in the generation and remodeling of extracellular matrix. Proper remodeling of the extracellular matrix is required for wound healing. On the other hand, excessive proliferation or secretion of extracellular matrix proteins often leads to pathologic progression of fibrosis and tissue injury.

Pathological signals that can trigger altered expression profile of extracellular matrix molecules include paracrine signals from activated immune cells such as lymphocytes and macrophages, autocrine factors secreted by fibroblasts, and pathogen-associated molecular patterns (PAMP) produced by pathogenic organisms that interact with Toll-Like-receptors on fibroblasts (33) (34). Cytokines (IL-13, IL-4, and TGF beta), chemokines, angiogenic factors (VEGF), growth factors (PDGF), and acute phase proteins (SAP) have also been identified as important inducing signals of fibrosis (35). Molecular pathways responsible for the fibroblast response to these signals include G-protein coupled pathway (in response to angiotensin), Smad pathway (in response to TGF beta), TLR pathway (in response to PAMP), and JAK-STAT pathway (in response to cytokines, leptin, and others) (1, 36-38). Molecular signaling processes regarding these pathways have been extensively reviewed elsewhere, and will not be further discussed here. However, it is worth note that less focus has been paid regarding the cross-talk and integration of these pathways, which likely play a critical role in the balancing act of injury and repair.

Recent evidence increasingly indicates that cross-talks are prevalent among pathways affecting tissue injury, repair, and fibrosis. Cross-talk between TGF beta and IFN gamma. signaling pathways has been shown to exist by Massague *et al* (39). In addition, TGF was shown to synergize with angiotensin to exacerbate fibrosis and tissue injury in the lung and heart (40, 41). In contrast, PPAR agonists can inhibit angiotensin-induced cardiac fibrosis (42). In addition, IL-4 can inhibit cytokine-induced expression of MMPs in fibroblasts, preventing remodeling and exacerbating fibrosis (43). The detailed molecular mechanisms responsible for the effects of cross-talks are not clearly understood. Several scenarios exist. For example, TGF beta has been shown to induce the expression of angiotensin receptor (40). Likewise, angiotensin can also induce the expression of TGF beta (44). Alternatively, the transcription factor Smad activated by TGF beta may synergize with NFkB, AP-1 or others activated by angiotensin to induce the transcription of genes involved in fibrosis (40). On the other hand, PPAR gamma has been shown to bind with Smad, STAT, and others to alleviate the expression of collagens involved in the pathogenesis of fibrosis (45, 46).

Since many of the above-mentioned fibrotic signals are also involved in regulating inflammatory and metabolic processes, it comes with no surprise that fibrotic tissue injury is associated with diverse inflammatory and metabolic diseases including diabetes and cardiovascular diseases. For instance, kidney fibrosis is one of the most common complications of late stage diabetes (47, 48).

Undoubtedly, the fine cross-talks among various inflammatory and metabolic signaling pathways dictate the fates of macrophages as well as fibroblasts, which consequently play crucial balancing acts modulating

homeostasis or tissue injury. Dissecting out these molecular cross-talks is essential for subsequent successful intervention of numerous inflammatory diseases and related tissue injuries.

4. SUMMARY AND PESPECTIVE

Over the past few decades, an enormous amount of information has been collected to reveal the significant roles that macrophages and fibroblasts play in the process of tissue injury and inflammation. A plethora of genes are expressed and tightly regulated in macrophages and fibroblasts depending on their environments and challenges, which are involved in either tissue repair or injury. Molecular and cellular networks responsible for the complex gene expression patterns are intertwined and exhibit feed-back as well as feed-forward cross-talks. Unless we have a clear picture of these complex cross-talks, it is a challenge to identify viable therapeutic targets to treat tissue injuries associated with various inflammatory diseases. A combination of experimental approaches with computational simulation is needed to dissect the complex signaling networks.

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Abbreviations: FIZZ: Found In Inflammatory Zone; IgG: Immunoglobin G; IL-4: Interleukin 4; IL-6: Interleukin 6; IL-10: Interleukin 10; iNOS: inducible nitricoxide synthase; JAK: Janus activated kinase; LPS: Lipopolysaccaride; MAPK: Mitogen-Activated Protein Kinase; MCP-1: Monocyte chemoattractant protein; NFAT: Nuclear Factor of Activated T-cells; NFkB: Nuclear Factor kappa B; PDGF: Platelet-derived growth factor; PI3K: Phosphoinositide 3 Kinase; SAP: Serum Amyloid P-component Precursor; STATs: Signal Transducer and Activators of Transcription; TNF: Tumor Necrosis Factor; VEGF: Vascular endothelial growth factor; PPAR delta: peroxisome proliferator-activated receptor delta.

Key Words: Inflammation, Signaling, Macrophage, Fibroblast, Tissue Repair, Injury, Shock, Innate Immunity, Review

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