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Review article

Interplay of extracellular matrix and leukocytes in lung inflammation

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ABSTRACT

During inflammation, leukocytes influx into lung compartments and interact with extracellular matrix (ECM). Two ECM components, versican and hyaluronan, increase in a range of lung diseases. The interaction of leukocytes with these ECM components controls leukocyte retention and accumulation, proliferation, migration, differentiation, and activation as part of the inflammatory phase of lung disease. In addition, bronchial epithelial cells from asthmatic children co-cultured with human lung fibroblasts generate an ECM that is adherent for monocytes/macrophages. Macrophages are present in both early and late lung inflammation. Matrix metalloproteinase 10 (MMP10) is induced in alveolar macrophages with injury and infection and modulates macrophage phenotype and their ability to degrade collagenous ECM components. Collectively, studies outlined in this review highlight the importance of specific ECM components in the regulation of inflammatory events in lung disease. The widespread involvement of these ECM components in the pathogenesis of lung inflammation make them attractive candidates for therapeutic intervention.

Contents

Abbreviations: ECM, extracellular matrix; GAG, glycosaminoglycan; MMP, matrix metalloproteinase; CS, chondroitin sulfate; ADAMTS, a disintegrin and metalloproteinase with a thrombospondin type-1 motif; PSGL-1, P-selectin glycoprotein-1; TLR, toll-like receptors; TNFα, tumor necrosis factor α; LMW-HA, low molecular weight hyaluronan; LPS, lipopolysaccharide; HAS1, hyaluronan synthase 1; CSPG, chondroitin sulfate proteoglycan; COPD, chronic obstructive pulmonary disease; HLF, human lung fibroblast; TGF-β, transforming growth factor-β; FMT, fibroblast-to-myofibroblast transition; α-SMA, alpha smooth muscle actin; BEC, bronchial epithelial cell; Hyal, hyaluronidase; BALF, bronchoalveolar lavage fluid; HMW-HA, high molecular weight hyaluronan; FEV_1, forced expiratory volume over one second; CRA, cockroach antigen; M1, classically activated macrophages; M2, alternatively activated macrophages; IPF, idiopathic pulmonary fibrosis.

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1. Introduction

The extracellular matrix (ECM) is a critical component of normal lung tissue that not only provides structural support for cells and tissue architecture of the airways and lung parenchyma, but also is a major effector of cell behavior and fate. Indeed, we now know that the ECM has considerable control over cellular function during lung development, homeostasis, normal repair, immunity, inflammation, and disease. The airways, blood vessels, interlobular septa, and visceral pleura are bordered and embedded in specialized ECM structures. As for all visceral organs, the lung ECM consists of two distinct compartments. One compartment is the basement membrane (basal lamina), which is a thin, organized layer of laminins, type IV collagen, nidogen/entactin, and perlecan, a heparan sulfate proteoglycan. Basement membrane is the substratum on which endothelial and epithelial cells reside and is well established as a key driver of differentiation and cell survival. The second compartment is the interstitium, which is mostly a loose connective tissue composed of an array of structural and nonstructural ECM components such as fibrillar collagens (e.g., types I and III), elastin, fibronectin, fibrillins, various proteoglycans, matricellular proteins (e.g., CCN proteins, SPARC, tenascins, thrombospondins) and polysaccharides, such as hyaluronan, an abundant and physiologically important glycosaminoglycan (GAG) [1,2]. Within the interstitium are blood and lymph vessels, airway smooth muscle bundles and cartilage, and a range of cells types, including fibroblasts, pericytes, and resident leukocytes. Furthermore, the ECM includes numerous related proteins, such as the enzymes that form fibers, proteinases that remodel ECM, cytokines and growth factors that are stored within the ECM, and more.

Recent studies have further indicated that specific individual components of the ECM can impact developmental and pathological events within the lung. For the purpose of this review, we will focus on versican and hyaluronan, two interstitial ECM components [3] that can serve as ligands for leukocytes and impact immune and inflammatory responses in lung disease [3–7]. In addition, we will discuss how specific leukocytes, such as the macrophage, interact with the ECM and the importance of a specific matrix metalloproteinase (MMP), MMP10, in controlling the state of macrophage activation in lung disease.

2. The ECM as a regulator of the innate immune response

Inflammatory responses as a result of tissue infection require the emigration of leukocytes from the vasculature to the infected area as part of the innate immune response. Upon extravasation into the subendothelial and/or subepithelial compartments, leukocytes encounter an ECM enriched in versican and hyaluronan that functions as a scaffold or "landing strip" for cell adhesion and subsequent retention and activation [8] (Fig. 1). These components are highly interactive and bind chemokines, growth factors, proteases, and receptors on the surface of the immune cells to provide intrinsic signals and influence immune cell phenotype [9–11]. We recently demonstrated that hyaluronan interacts with the surface of T-regulatory cells through CD44 and promotes their differentiation [12–14]. Furthermore, once bound, these leukocytes modify the ECM in such a way as to generate pro-inflammatory ECM fragments to further drive the inflammatory response [15,16]. Fragments of ECM affect multiple functional properties of inflammatory and immune cells [17]. Since different types of infection may demand extravasation of certain immune cell types, the ECM often undergoes compositional changes which regulate the appropriate cellular responses. Such compositional changes may enrich for specific ECM molecules that actively participate in the recruitment and activation of specific immune cell types to either promote or inhibit the inflammatory cascade [18]. Such findings suggest that the ECM may be a useful therapeutic target to control various aspects of the immune response associated with inflammation in a variety of diseases [19].

3. ECM components: interaction with leukocytes

A number of different ECM components interact with leukocytes and it has become clear that these interactions are a critical part of the inflammatory response [20]. It has also become clear that the ECM exhibits specificity for binding leukocytes and impacting their phenotype [6]. We have become interested in versican and hyaluronan, which increase during inflammation. Versican is a proteoglycan that exists in at least four different isoforms due to alternative splicing of the major exons that code for the attachment regions of the chondroitin sulfate (CS) GAGs attached to the core protein [21,22]. Versican interacts with a number of other molecules, many of which are involved in promoting tissue inflammation [6]. For example, versican interacts with hyaluronan [23,24], link protein, TSG-6, and CD44 through a common structural domain in each of the proteins called the link module [25,26]. These macromolecules form higher ordered macromolecular complexes that increase as part of the inflammatory response [27–31]. Known functions for versican include controlling tissue space due to its ability to entrap water such as observed in the lung [32,33], as well as influencing cell adhesion, proliferation, migration, and survival [21,34–36]. Versican is highly interactive due to the negatively charged CS side chains. For example, versican regulates the availability and activity of several inflammatory chemokines [37–41]. In addition, the CS chains of versican interact with MMPs [42], influencing their catalytic activity [43–45]. As versican accumulates in diseased tissues, it can be degraded by a number of proteases including five members of the a disintegrin and metalloproteinase with a thrombospondin type-1 motif (ADAMTS) family of proteases [46,47]. Cleavage of versican generates biologically active fragments that have been associated with inflammatory cytokine release and cell death through apoptosis [48,49]. In addition, the G3 domain of versican can interact with P-selectin glycoprotein-1 (PSGL-1) and cause macrophage aggregation [50]. Several studies indicate that versican is a danger-associated molecular pattern (DAMP) molecule that interacts with toll-like receptors (TLRs), such as TLR2 on alveolar macrophages to promote production of inflammatory cytokines such as tumor necrosis factor α (TNFα), IL-6, and other pro-inflammatory cytokines [51–57]. As such, versican has been implicated in regulating several key events in the inflammatory response [3,6,36,58,59].

Several studies have demonstrated that hyaluronan, a binding partner of versican, influences inflammatory responses [60–62].