EDITORIAL

Immune functions of constitutive pulmonary cells: the salt in the soup

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Inflammation may be defined as a local or general response of living tissue to injury or to the presence of injurious agents. Teleologically, inflammation is presumably designed as both a protective and reparative response, which aims at restoration of optimal organ function. Thus, inflammation may be viewed as an essentially self-curtailling process-loop, in which a complex series of interdigitating cytological, biochemical, and immunological components serve to return to a physiological baseline of optimal organ function.

Processes which constitute inflammation form an intricate functional network, in which almost every single constituent influences the activities of other constituents. This influence may have a triggering or promoting character, often with an amplifying result. In other instances, certain factors may have modifying or outright suppressing effects. Some of these activities are overlapping, and others may be capable of substituting for one. Others again may exert different biological effects in the context of additional soluble or tissue factors within the immediate local environment. The realization that inflammatory responses are highly complex may best be conceptualized as an inflammatory network, in which the nature and the duration of exposure to the offending agent determines the outcome of inflammation.

In this context, the infiltration of affected tissue by circulating immune cells represents a hallmark of inflammation. Infiltrating cells, such as lymphocytes, neutrophils, eosinophils and basophils, have traditionally been regarded as the propagating component of the pathophysiological processes in inflammation. These cells are believed to transiently or chronically inflict further injury to tissue-residing constitutive cells. This may be exemplified by the function of eosinophils in bronchial epithelial damage in asthma [1, 2], which is believed to play a crucial role in the development of bronchial hyper-reactivity [2], thus determining the chronic course of the disorder. Another example may be the exuberant inflammatory reaction underlying the adult respiratory distress syndrome, during which infiltrating neutrophils may contribute to severe lung injury, which ultimately affects host survival [3]. Recent advances in the physiological and pathophysiological role of these cells have been extensively portrayed in previous contributions of the

current Review Series on 'Pulmonary Immune Cells' in The Journal [4–11].

However, as has emerged throughout recent years, constitutive cells may not simply represent targets or be passive recipients of inflammatory injury caused by an inciting agent or infiltrating cells. On the contrary, modern advances in biological, immunological, and molecular techniques suggest that tissue residing cells may actively respond to injury and participate in inflammation, with both offensive injury promoting and defensive repair inducing properties. In order to pay tribute to these recent developments, we extended the current Review Series on respiratory immune cells to include constitutive cell types in the airways. Forthcoming papers will cover immunological functions of pulmonary epithelial cells, endothelial cells and fibroblasts.

The primary role of fibroblasts is presumably to restore the matrix necessary for the regeneration of normal lung structure and function during repair processes and remodelling of tissue matrix elements, by both degradation of damaged matrix and synthesis of new matrix structures. Matrix proteins have, in turn, been demonstrated to influence not only tissue structural cells but also haemopoietic cells. In addition, production of various growth factors, including platelet-derived growth factor (PDGF), transforming growth factor- β (TGF- β), and insulin-like growth factors (IGFs), suggests that fibroblasts are actively involved in regulating reparative responses following acute or chronic inflammatory injury. However, as will be reviewed by JORDANA *et al.* [12] in this issue of The Journal, fibroblasts may also play a significant role in the amplification of inflammatory processes *via* the secretion of certain cytokines, such as monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 α (MIP-1 α) and granulocyte/macrophage colony-stimulating factor (GM-CSF). On the other hand, fibroblasts have been shown to release significant amounts of prostaglandin E₂, a mediator which is intrinsically associated with inhibitory or modulatory effects. Thus, fibroblasts may also exert a regulatory function in inflammation.

Pulmonary epithelial cells have been considered to play a crucial role in maintaining normal lung function. As the cells are strategically located at the interface between air and tissue, they primarily provide a morphological and functional barrier to the environment. In addition, airway epithelial cells clear the lung from exogenous environmental noxae, whereas, alveolar epithelium serves

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the pulmonary gas exchange. However, recent data suggest that pulmonary epithelial cells may also modulate the inflammatory response to injurious agents. As will be outlined by THOMPSON *et al.* [13] in a forthcoming issue of The Journal, epithelial cells of the lung may, in addition, contribute to the inflammatory network, by means of regulating recruitment of circulating cells through adhesive and other immunological activities.

In contrast to epithelial cells, endothelial cells are strategically located between the vascular compartment and the interstitium of the lung, where mesenchymal cells such as fibroblasts are found. Thus, endothelial cells may first and foremost play a passive structural and barrier role in the course of physiological processes. However, as has become evident throughout the past decade or so, endothelial cells have the potential to participate in repair processes and even perpetuation of inflammation. As will be discussed in great detail in a forthcoming article of this series, endothelial cells may not only regulate tissue growth, such as angiogenesis by adjacent cells, *e.g.* macrophages/monocytes and mesenchymal cells, but may also produce growth factors themselves.

Historically, the lung has been perceived as an organ primarily involved in gas exchange. Its capacity to generate an inflammatory response in an effort to clear the organism from exogenous noxae has only recently been appreciated. The lung with its mucociliary clearance apparatus, the extensive capillary system, the large alveolar membrane containing both immune and non-immune cells, as well as the interstitium with its mesenchymal cells and intercellular matrix elements, functions as an important barrier against inhaled and haematogenous challenges. As has been emphasized in the introductory Editorial [14], the series on pulmonary immune cells intends to provide the reader with an update of recent advances in pulmonary immunology. In the forthcoming papers, special emphasis will be placed on the potential immunological role of resident pulmonary cells, which may turn out to be the salt in the soup of the interacting inflammatory network.

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