EDITORIAL

Pulmonary immune cells: villains and confederates

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Over the past ten years or so, we have been witnessing a slow but enduring change of mainstream research in respiratory medicine. From being widely dominated by studies of lung function and pulmonary physiology, research in respiratory medicine has begun to move into the complex field of cellular and molecular biology, in its effort to understand the basic mechanisms of disease. This progress has been due not only to advances in immunological and biological science but also to the introduction of the bronchoalveolar lavage (BAL) procedure which provides access to the various cell populations of the lower respiratory tract.

This issue of the Journal contains the first of a series of reviews planned to highlight the recent knowledge on pulmonary immune cells in health and disease [1]. Written by experts fully familiar with the modern laboratory techniques applied to the studies of immune cells, each of the articles will be devoted to a specific cell type, including dendritic cells, macrophages, lymphocytes, neutrophils, eosinophils, mast cells, and platelets. Their beneficial role in host defence against invading pathogens, but also their harmful effects in chronic lung injury, will be addressed. The series will describe the origin, maturation and differentiation of the cells, surface antigens and receptor repertoires, enzyme and mediator contents, as well as the mechanisms of cellular recruitment and activation. In addition to biological cell functions such as secretion of lipid mediators and cytokines, migration, adherence and interactions with other cells, the potentially deleterious role in the pathogenesis of human diseases, will be summarized with an emphasis on respiratory disorders. Lastly, the potential implications for therapeutic strategies based on this new approach to lung diseases will be assessed.

The article appearing in this issue deals with dendritic cells and Langerhans cells [1]. Langerhans cells are thought to be derived from dendritic cells. However, they differ from dendritic cells, since the latter are characterized by typical cytoplasmic organelles called Birbeck granules, visible only by electron microscopy. Both cells are potent accessory cells or antigen-presenting cells and stimulate lymphocyte proliferation, whereas alveolar macrophages function rather poorly in this respect [2]. An important lung disease, eosinophilic granuloma or histiocytosis X, has been renamed Langerhans cell granulomatosis, following the recognition that the offending cell is the Langerhans cell. Current concepts suggest that the disease results from an abnormal immune response in cigarette smokers, initiated and maintained by Langerhans cells [1].

The alveolar macrophage undoubtedly plays a central role in the orchestra of immune cells and serves as the first line of host defence against inhaled organisms and soluble and particulate molecules. Macrophage effector functions include phagocytic, microbicidal and tumouricidal activity, mediated by release of oxygen radicals, proteases and cytokines like tumour necrosis factor and others [3, 4]. These cells also produce a variety of pro- and anti-inflammatory agents including arachidonic acid metabolites of the cyclooxygenase and lipoxygenase pathways. Macrophages are involved in the induction phase of inflammation but they also participate in tissue reorganization and repair by secretion of proteolytic enzymes and fibroblast stimulating factors. In certain interstitial lung disorders like sarcoidosis and idiopathic pulmonary fibrosis, alveolar macrophages are likely to be involved in the pathogenetic process.

A forthcoming article of this series will review the current concepts of physiological activities of lymphocytes in response to immunological challenges [5]. Lymphocytes in the alveoli help protect the lung against microbes and probably against neoplasia. They produce antibodies, cytokines, and lytic factors, and participate in delayed type hypersensitivity and cytotoxic responses. They also regulate cellular functions and interactions of lymphocyte populations and other cells. The pathogenetic role of pulmonary T-lymphocytes in human disease is evident in patients with interstitial lung disease, in HIV-infected individuals, in patients with asthma, and in lung transplant recipients [5]. In certain instances, the phenotypical analysis of lymphocytes recovered by BAL may contribute to diagnosis in interstitial lung disease, by dissecting diseases presenting with lymphocytic alveolitis into three subgroups depending on whether the CD4/CD8 ratio is elevated, normal, or decreased [6].

The neutrophil is a rare cell within the extravascular alveolar structures of a healthy lung, as will be outlined in one of the future reviews [7]. In disease states, however, neutrophils are attracted from the pulmonary circulation in large numbers by chemotactic factors including interleukin-8, LTB4, platelet activating factor (PAF), and others. This rapid recruitment of neutrophils, associated with acute inflammatory processes, appears to be crucial for the effective host defence against bacterial and fungal infections. Following the killing of microorganisms by the release of toxic oxygen radicals, neutrophils contribute to tissue reorganization in inflammatory lesions by the secretion of proteolytic enzymes such as elastase, collagenase, cathepsin G and others. However, apart from their beneficial role in infectious disorders, neutrophils may also display harmful effects in the pathogenesis of several lung diseases, including chronic bronchitis and emphysema, cystic fibrosis, the adult respiratory distress syndrome, and

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idiopathic pulmonary fibrosis [4, 7–9]. The oxidative and proteolytic mediators which effectively kill the microorganisms are also able to injure lung parenchymal cells, to degrade extracellular matrix components, and to inactivate important defensive enzymes like alpha-1-proteinase-inhibitor, thereby causing irreversible structural changes in these acute and chronic progressive lung disorders.

Since their discovery by Paul Ehrlich more than 100 years ago, both mast cells and basophils have been put on centre stage in allergic disease [10]. They share several notable features in addition to the metachromatic staining properties of their cytoplasmic granules. Both cell types represent a major source of potent chemical mediators implicated in a wide spectrum of inflammatory and immunological processes. Mast cells and basophils express plasma membrane receptors that specifically bind the Fc portion of IgE antibody with high affinity. After active or passive sensitization with IgE, exposure to specific antigen triggers both cell types to undergo a series of biochemical and morphological alterations that eventually results in the release of preformed (granule associated) as well as newly generated inflammatory mediators. Despite these similarities, mammalian mast cells and basophils are clearly not identical. While mast cells are ordinarily distributed throughout normal connective tissue, basophils circulate in the bloodstream. Recent investigations suggest that basophils share a common precursor with other granulocytes and exhibit kinetics of production and tissue infiltration similar to that of eosinophils. While mast cells may dominate the process underlying early phase allergic reactions, basophils appear to be mainly associated with the late phase response. In addition, significantly increased numbers of mast cells have been demonstrated in interstitial lung disease, such as pulmonary fibrosis whereas evidence on the participation of basophils is, as yet, less compelling.

The eosinophil leucocyte, also discovered by Paul Ehrlich in 1879, has been associated with a number of human diseases such as parasitic infections, allergic diseases and certain pulmonary syndromes. Among these, asthma can be considered as the most thoroughly studied eosinophil-related disease because of its high prevalence worldwide. Although the role of the eosinophil in related diseases remains somewhat undefined, modern scientific technology has provided persuasive evidence which suggests that eosinophils may be the prime effector cell in maccroal damage in asthma through the synthesis and release of cationic proteins, enzymes, oxygen radicals and various lipid mediators [11]. In addition, various studies have established a close correlation between eosinophilic inflammation and the clinical severity and chronicity of asthma. Because of its detrimental effects inflicted on infiltrated tissue, further evidence suggests that eosinophils may also contribute to the pathogenesis of other diseases such as pulmonary fibrosis, eosinophilic pneumonia, or hypersensitivity pneumonitis. Platelets are known to play a pivotal role in haemostasis and thrombosis. However, recent evidence suggests that platelets may also function as accessory inflammatory cells in their own right [12]. Platelets may undergo chemotaxis and phagocytosis and represent a major source of lipid mediators such as PAF. In addition, platelets have been demonstrated to exert cytocidal properties against parasites mediated by the release of oxygen radicals. Moreover, evidence suggests that platelets participate in allergic disease such as atopic rhinitis or asthma. For instance, a low-affinity IgE receptor has been identified on platelets. In addition, levels of granular platelet products, such as platelet factor 4 (PF4) and B-thromboglobulin (B-TG), were found raised in asthmatics after antigen challenge. Furthermore, platelet depletion prevents smooth muscle contraction and bronchial hyperreactivity induced by platelet activating factor. Finally, evidence suggests that platelets may be involved in eosinophil recruitment. However, the mechanism as to how platelets become involved in pulmonary disease other than thromboembolic disorders remains unknown.

The series on pulmonary immune cells starting in the current issue of the European Respiratory Journal intends to provide the reader with an update of recent advances in pulmonary immunology. It will become apparent that pulmonary immune cells conduct themselves like confederates helping to defend integrity of the organism. However, they may turn out to behave like a villain causing severe and chronic pulmonary disease. Hence, a major challenge for future research will be to delineate the factors which switch the immune response from being beneficial to detrimental. The series also reflects the on-going move of respiratory medicine away from physiology to cellular and molecular biology. It intends to encourage researchers to submit their best work on respiratory immunology and molecular biology to the Journal.

References