Central inflammation is more important than peripheral inflammation

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Inflammation is present in the airways of asthma patients even during stable periods of the disease. In post-mortem samples of the proximal airways, inflammation can be visualised as T-cell infiltration of the bronchial wall. Lymphocyte accumulation is also evident around the small airways, indicating that inflammation is present in the peripheral regions of the lungs. However, the major inflammatory events associated with asthma appear to occur in the proximal airways.

Inflammatory Cell Accumulation

One indication of the distribution of inflammation in the airways is the relative accumulation of inflammatory cells in distal and proximal tissues. In asthma patients, T-cells accumulate in both these regions in numbers greatly in excess of those found in normal individuals, with the number of T-cells accumulating in the proximal area being higher than in the distal region. Differences in accumulation of other cell types between the two sites are also apparent, with CD68+ macrophages, eosinophils and activated eosinophils all accumulating significantly more in proximal tissues compared with distal areas (1).

Acquired Immunity in Different Regions of the Lung

Notable differences are evident between the acquired immunity processes occurring in proximal and distal areas of the lung. In the proximal region, the antibody response is predominantly secretory IgA, and T-cell responses are strictly down-regulated by suppressor macrophage activity (2). Both CD4+ and CD8+ cells may be involved in the immune response, and eosinophils and mast cells are readily recruited into peri-bronchial tissues, but the system appears designed to avoid inflammatory reactions which may damage the epithelium. Chronic inflammation in asthma may represent a fundamental problem with this regulatory control.

In the distal area, antibody responses are predominantly IgG (2). T-cells are rapidly recruited from the vascular bed. However, the alveolar blood supply is pulmonary in origin, as opposed to the systemic circulation which supplies proximal tissues, and these vessels may express different adhesins on the endothelium. Further differences in immune responses include the presence of activated, scavenging macrophages in distal airways, which are less evident in proximal airways, where ciliated epithelium is responsible for removing debris.

Studies of the ratios of subsets of T-cells indicate a dramatic difference between distal and proximal regions of the lung. In stable asthma patients, CD4+ cells dominate within the lamina propria of the bronchial wall, giving a median CD4+:CD8+ ratio of 4.5:1. In contrast, CD8+ dominance occurs in the distal region (1).

Traffic of macrophages and lymphocytes throughout the lung provide further evidence in support of asthma as a proximal airway disease. The balance between various types of macrophage (effector, inductive and suppressor cells) is noticeably different in the proximal and distal compartments of the lung and this leads to variations in functional capacity (3,4). In distal areas, effector phagocytes dominate, whereas in proximal areas more than 50%
of macrophages found in the tissues are suppressive. A loss of suppressive macrophages from this area may be a critical factor in T-cell stimulation in asthma, and could be a major therapeutic target (5).

Lymphocyte traffic in large and small airways also shows differences (6). More than 80% of T-cells in the lung are activated and express the marker CD45Ro. The majority of these cells are CD4+ with some interepithelial CD8+ cells in the bronchial wall. The balance between populations of CD4+ cells releasing interleukin 2 (IL-2) and interferon γ (IFNγ) (T_H1 cells) or IL-4, IL-5 and IL-10 (T_H2 cells) is thought to be significant in asthma. Studies using CD30 as a marker to identify the T_H2-cell population have identified increased numbers of these cells within proximal tissues, whereas a similar imbalance in the CD4+ population was not evident in distal tissues, where few CD30+ cells are located (7). Thus, if increased production or release of the cytokines IL-4, IL-5 and IL-10 is important in asthma, this is likely to be associated with the proximal areas. In support of the role of T_H2 cells in asthma, the level of expression of CD30 (found on T_H2 cells) has been found to correlate with the symptom score for asthma (8). This correlation occurs in both atopic and non-atopic patients, indicating that T_H2-cell activity is not solely related to atopy, and demonstrates that there is a close relationship between parameters of immunopathology and the proximal airways.

References