Asthma is an obstructive disease of the airways characterized by chronic inflammation in which mast cells, T lymphocytes and eosinophils are implicated [1]. Cytokines are almost certainly influential in the recruitment of these cell types to the lung: studies on bronchial biopsies and bronchoalveolar lavage (BAL) cells from patients with asthma have revealed increased mRNA expression for multiple cytokines including interleukin (IL)-4, IL-5, IL-6, IL-8, granulocyte-macrophage-colony-stimulating factor (GM-CSF) and tumour necrosis factor (TNF)-α [2-Λ↑]. However, the precise role of these and undiscovered cytokines is largely unresolved.

To understand fully the role of cytokines in inflammatory lung disease, the development of appropriate animal models is essential. One such potential model may be that of Sephadex-induced lung injury in the rat. Here, Sephadex particles become lodged in the capillaries of the lung and this leads to eosinophil recruitment and airway hyperresponsiveness [5, 6]. Although this pathology is typical of asthma, the molecular mechanisms underlying Sephadex-induced lung inflammation and the relevance of this model to the antigen-driven disease are poorly understood; in particular, it is not known whether cytokine genes are induced. To begin to address this question, we measured levels of IL-5, IL-6, TNF-α and macrophage inflammatory protein-2 (MIP-2) mRNA in bronchoalveolar lavage cells and studied histological changes in the lung during the progression of inflammation in this model.

Male Wistar rats (150-180 g) were administered Sephadex suspension (0.5 g in 1.0 ml) intravenously. Twenty four hours later, extensive lung alveolar granuloma formation was observed. Granulomas increased in size up to 72 h but declined considerably by 7 days. Granulomas comprised predominantly mononuclear cells but appreciable numbers of neutrophils and eosinophils were also observed.

Sephadex treatment of the rats produced a substantial increase (approximately 3-fold) in numbers of BAL mononuclear cells (from a baseline of approximately 6 million) which peaked at 72 h. Neutrophils and eosinophils were also recruited to the bronchoalveolar lumen, each reaching
approximately 2 million per rat after 48 and 72 h, respectively. Numbers of all BAL cell types declined to baseline by 7 days.

Messenger RNA encoding IL-5, IL-6 and MIP-2 was either undetectable or was detected very weakly by the reverse-transcription-polymerase chain reaction (RT-PCR) in BAL cells from saline-treated control rats, whereas mRNA encoding TNF-α was readily detectable. Following a single intravenous injection of Sephadex particles, BAL cell mRNA encoding each of the four cytokines was elevated markedly at various stages during the inflammatory response. Analysis of RT-PCR product band intensities by laser densitometry revealed that the Sephadex-induced increase in IL-5 mRNA was statistically significant after 48 and 72 h, with peak values at 72 h; IL-6 mRNA levels were significantly elevated only at 48 h; TNF-α mRNA levels were significantly elevated from 6 to 72 h.

In conclusion, this study has demonstrated that Sephadex-induced lung inflammation in the rat is associated with transient increases in lung mononuclear cells, neutrophils and eosinophils, and these changes occur alongside transient induced expression of genes encoding the cytokines IL-5, IL-6, TNF-α and MIP-2. At this stage, we are unable to say whether these changes in cytokine mRNA levels are a cause or a consequence of the recruitment of the various inflammatory cell types. Nevertheless, more so than previously suspected, the pathological processes and molecular events observed in this model resemble closely those seen in antigen-driven asthma [1,2] suggesting common patho-eti-ological mechanisms in asthma driven by either a physical or an immunological stimulus. These similarities suggest that the rat Sephadex lung model has potential for exploration of the relationships between cytokine induction, cell recruitment and progression of asthma-like disease.

References


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