

The Biology of T-Cells in Allergy and Asthma: Beyond the TH1/TH2 Concept

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Bronchial asthma is characterized by chronic airway inflammation, development of airway hyperreactivity and subsequently of airway remodelling. In allergic bronchial asthma, recurrent and reversible airway obstruction is induced by allergen inhalation¹. In the late 80s and early 90s, the concept has been developed that Th-2 T-cells orchestrate many aspects of pathologic immune responses including effector functions of the B-cells, mast cells and eosinophils. Th-2 cells produce an array of cytokines including interleukin-4, interleukin-5, interleukin-9, and interleukin-13. In B-cells, interleukin-4 and interleukin-13 are involved in isotype switching towards IgE (immunoglobulin E), while interleukin-5 processes pro-inflammatory properties including development, differentiation, recruitment and survival of eosinophils. The importance of T-cells and T-cell driven processes in these diseases is further underlined by the effectiveness of anti-inflammatory therapies including corticosteroids and others.²

Although the currently available anti-inflammatory drugs are effective in reducing symptoms and improving quality of life, they are not followed by complete disappearance of symptoms³. This observation suggests that, in addition to the immunological dysregulation in allergy and asthma, other aspects need to be considered in the pathology of this complex disease. In this regard, airway hyperreactivity, for example, represents an important hallmark in the pathogenesis of the disease. Non-specific bronchial hyperresponsiveness may be defined as an increase in the ease and degree of airway narrowing in response to a wide range of bronchoconstrictor stimuli⁴. The development of airway hyperresponsiveness is mediated by multiple independent and additive pathways working in concert. The airway changes leading to airway narrowing mainly include: (a) altered neuronal regulation of airway tone, (b) increases in muscle content or function.^{4,5}

Growing evidence indicates neuronal dysregulation on several levels in bronchial asthma⁶. Neurotrophins, initially characterized as growth and differentiation factors in the nervous system, are now recognized to exert similar biological effects also in other tissue compartments. Especially their effects as differentiation and survival factors for immune cells are becoming into the focus of immunological research. In airway inflammation result-

ing from allergic or viral genesis, e.g. bronchial asthma or RSV infection, a complex interaction between the nervous and immune system mainly contribute to the pathogenesis of the disease. This neurogenic inflammation is amplified by an enhanced neurotrophin signaling which results in changes in lung innervation (neuronal plasticity) as well as in the ongoing immune reaction (immunological plasticity). The immunotrophic properties of neurotrophins in addition to their "traditional" function as neurotrophic factors are now becoming more evident. Thus the widespread function of neurotrophins as modulators of cell survival and differentiation throughout the nervous system may needs a renaming of these factors in the future.

As has been discussed in this article different types of immune cells are able to produce and also to respond to neurotrophins within the inflamed lung. These findings raises the question: are leukocyte-derived neurotrophins always detrimental to the host by causing neuronal hyperreactivity or may they are also necessary to maintain integrity of nervous and immune systems in inflamed mucosal tissues?

Indeed the present data indicate that neurotrophins function as common survival factors promoting the differentiation and functional activity of various cell types in the body. Physiologically, the homeostasis of immune cells such as eosinophils or mast cells within the lung mucosa compartment is mediated by neurotrophins. On the other hand, enhanced neurotrophin expression during an inflammatory process also support an actual immune reaction irrespective of the mode of Th2-driven allergic or Th1-mediated viral response. Nevertheless, blocking this pathological overexpression of neurotrophins during lung inflammation may be a novel tool in the therapeutic intervention of chronic inflammatory lung diseases in the future.^{7,8,9,10,11,12,13}

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