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SCIENCE DIRECT
Pulmonary Pharmacology & Therapeutics 18 (2005) 217–228
PULMONARY PHARMACOLOGY & THERAPEUTICS
www.elsevier.com/locate/ypupt

Immune dysregulation in allergic respiratory disease: the role of T regulatory cells

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Received 1 November 2004; revised 13 December 2004; accepted 15 December 2004

Abstract

Although earlier research focused on the role of the polarity of T helper cell signalling as the defining factor in immune responses, it is now recognised that other cells with regulatory properties have a more key role. It has been recently proposed that allergic disease may result from an inappropriate balance between regulatory cells (including but not limited to CD4+ CD25+ T regulatory cells) and T helper type 2 (Th2) effector cells. In the airways, a number of other cells also have important regulatory effects on local immune responses, including epithelial cells and airway dendritic cells (DC). Allergic respiratory disease appears to be the culmination of both local epithelial dysfunction and generalised immune dysregulation resulting in Th2 propensity (atopic predisposition). Although these processes are related they also appear to occur independently. This review examines evolving models of allergy pathogenesis, including the newly recognised role of diverse groups of regulatory cells. Increasing rates of allergic disease (and other immune diseases) suggest that environmental changes may be having fundamental effects on common regulatory pathways. Understanding these influences and their mechanism of action could lead to strategies to prevent disease.

Keywords: Immune dysregulation; Atopy; Allergic disease; T regulatory cells; Th1/Th2 cytokines; IL-10, TGFβ

1. Allergic disease and the epidemic of immune dysregulation

Recently reaching epidemic proportions, allergic diseases are now among the most common chronic debilitating conditions affecting industrialised societies. These heterogeneous inflammatory conditions are associated with both a systemic propensity for allergic immune responses (atopy) and local manifestations of allergic inflammation, typically at cutaneous and mucosal surfaces in contact with the environment. Although these parallel processes are clearly linked, they appear to be controlled through independent mechanisms [1]. The local immune events which lead to disease associated inflammation, such as that seen in the respiratory mucosa in asthma and allergic rhinitis, are still poorly understood. As knowledge of underlying immunological processes has evolved, so have working models of pathogenesis and aetiology.

1.1. Humoral dysregulation:

Allergic disease was initially recognised as a disorder of humoral immune responses to environmental allergens. Inappropriate production of IgE antibodies (discovered in the 1960s [2,3]) was associated with the atopic state. In the following decade allergic disease was largely regarded as an 'excessive' inappropriate reactions to the environment, and the search for causal pathways focused largely on the role of allergen exposure. IgE antibodies are associated with many end-organ manifestations of disease and remain a principal diagnostic tool.

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doi:10.1016/j.pupt.2004.12.009

1.2. T cell dysregulation and the emergence of the "hygienehypothesis"

In the 1980s the role of T cell signalling in regulating antibody production was recognised with the discovery of dichotomous T helper (Th) cell subsets in rodents [4]. Although less distinct in humans [5], the increased propensity for Type 2 helper T cell (Th2) responses in allergic individuals is well established. There is also accumulating evidence that most Th2 cytokines ([interleukin] IL-4, IL-5, IL-9, IL-13) are implicated in the expression and development of airways inflammation and hyperactivity (AHR) [6–8]. Reciprocal inhibition between interferon γ(IFNγ) producing Th1 cells and IgE promoting 'pro-allergic' Th2 lead to the proposal that allergic responses were the result of a 'skewing' of T cell responses. Accordingly, efforts to identify environmental causes of the rise in allergic diseases focused on candidate factors with potential 'pro-Th2' or 'anti-Th1' properties.

During the following 10 years there was growing recognition that allergens may not cause allergy, and the "hygiene hypothesis" gathered momentum. While the original hypothesis was based on epidemiological associations [9], the well recognised 'pro-Th1' effects of bacteria provided a biological basis for the proposal that a reduction in 'microbial burden' may be implicated in the dramatic rise in allergic disease. It also became increasingly apparent that these effects were likely to be most relevant in early life when immune response are first initiated. Th1 responses normally mature gradually during the first years of life, not consolidating until after 18 months of age [10], so that responses during this early period are relatively skewed towards the Th2 pattern which normally characterised allergic disease [11,12]. However, despite this, the majority of infants do not go on to develop atopy. There has been longstanding speculation that delayed development of Th1 function in infancy is an important contributing factor in the development of Th2 immune disease [13]. Bacterial exposure during this period arguably provides the strongest signal for maturation of Th1 immune function (which is logically involved in defence against these same organisms). A reduction in the level and variety of early microbial burden is an obvious candidate in the search for culprits in the spiralling levels of allergic disease. Thus the 'hygiene hypothesis' could readily be explained within the Th1/Th2 paradigm, and there is still a body of evidence to support this (as recently reviewed by Romagnani [14]).

However, the advent of molecular technology failed to confirm a primary defect in either the IgE or T cell pathways in allergic or asthmatic individuals. Although numerous polymorphisms have been associated with these immune pathways, susceptibility appears to be determined by multiple genes, and different genes appear to feature in different populations. Of interest, however, is the recent association between serum IgE levels and polymorphisms in CD14 pathway, which is involved in the recognition of bacterial 'pathogen associated molecular patterns' (PAMPs) [15]. Although still speculative, it is possible that functional polymorphisms in these pathways confer altered susceptibility to Th2 allergy responses secondary to altered sensitivity to Th1-inducing bacterial products such as lipopolysaccharide (LPS) [16]. More recently, other genes involved in PAMP recognition (such as Toll like receptor [TLR]2 have also been associated with asthma [17] and TLR4 polymorphisms have been associated with endotoxin hyporesponsiveness [18].

Collectively, these observations provided powerful support for the 'hygiene hypothesis' and a highly plausible mechanism although there is still no definitive proof of this.

1.3. Antigen presenting cell (APC) dysregulation

As the key cells involved in programming T-cell responses, antigen presenting cells (APC) became of central interest in explaining the polarisation of T cell responses in allergic disease. As aptly coined by Solbach et al. in 1991, 'Lymphocytes play the music but the macrophage calls the tune' [19]. These and other APC dictate the pattern of T cell activation and Th1/Th2 polarisation. Mature APC provide pro-Th1 cytokine signalling in the form of IL-12 (and other cytokines IFNα, IL-18, IL-23) which influence the cytokine profile of a T cell once activated. The relative absence of IL-12 signalling, appears to favour the development of default Th2 cytokine profile. Because these cells are all strongly simulated by microbial products, notions that reduced bacterial exposure may delay maturation of the pro-Th1 APC functions integrated well into the 'hygiene hypothesis'. During early life when APC function is known to be less mature [20], less efficient pro-Th1 cytokine production and costimulation is likely to contribute to the observed increased susceptibility to both tolerance [21], and Th2 responses [22]. Although there is some preliminary evidence that atopic heredity, was associated with reduced numbers of IL-12 producing cells [23] and that APC IL-12 signalling in the neonatal period is inversely related to Th2 responses [24], it is still not clear how variations in APC function influence the development of atopy. The role of specific APC (particularly dendritic cells [DC]) in local airways inflammation is discussed further below.

1.4. The emerging role of regulatory pathways

Although the association between allergy and Th2 immune responses remain conclusive, other paradoxical observations challenge the concept that disease states arise from simple polarisation of responses (away from 'normal' Th1 responses). At a population level, there has been a parallel rise in both Th1-mediated autoimmune diseases (such as type 1 diabetes, inflammatory bowel disease, multiple sclerosis) and Th2-mediated allergic diseases [25],