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CD26$^+$ T cells in the pathogenesis of asthma

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Asthma is a chronic inflammatory disease of the small airways, being clinically characterized by reversible airway obstruction and bronchial hyperreactivity [1]. These clinical features result from a chronic inflammation of the airways, caused by a migration of leucocytes and an increase of inflammatory mediators in the bronchial wall [2]. This pathological reaction in asthma is thought to arise from a complex interaction between genes and the environment.

Although allergens and infection appear to be environmental modifiers of asthma [3,4], it is now estimated that at least a dozen polymorphic genes regulate asthma and control the chronic inflammatory response and production of immunoglobulin E (IgE), cytokines and chemokines. By genetic-linkage analysis on 460 pairs of siblings from asthmatic families in the USA and UK, Van Eerdewegh *et al.* [5] identified a locus on the short arm of chromosome 20 which was linked to asthma and bronchial hyperreactivity. They identified the *ADAM-33* gene as significantly associated with asthma. ADAMs are a subfamily of metalloproteinases expressed on the cell surface, and have proteolytic functions such as shedding tumour necrosis factor receptors, and other cell-surface cytokines, adhesion molecules, and growth factors and receptors that are involved in inflammation, cell proliferation, and cell death. *ADAM-33* is expressed by lung fibroblasts and bronchial smooth muscle cells, and is suspected to be associated with small-airway remodeling in patients with asthma.

Regarding immunological aspects of asthma genes, the human homologue of *Tim1* has been identified as an asthma susceptibility gene [6]. *Tim1* lies at chromosome 5q33.2, a region that has been repeatedly linked to asthma, and codes for the cellular receptor for hepatitis A virus [6]. The *Tim1* gene product is expressed on T cells and appears to regulate the production of interleukin-4 (IL-4) in T cells by affecting CD4+ T cell differentiation, the development of T_H2 cells and development of airway hyperreactivity. As observed in the *Tim1* hypothesis, the inappropriate T_H2 response causes pulmonary inflammation, airway eosinophilia, and airway hyperreactivity to a variety of specific and nonspecific stimuli that result in the clinical symptoms of asthma.

In the T_H1-T_H2 paradigm, T_H1 cell responses are thought to protect against asthma, by dampening the activity of T_H2 responses [7–9]. However, other investigators have shown that T_H1 cells may exacerbate asthma, as human asthma is associated with the production of IFN-γ which appears to contribute to pathogenesis of asthma [10,11]. Allergen-specific T_H1 cells, when adoptively transferred into naïve recipients, migrate to the lungs but fail to counterbalance T_H2 cell-induced airway hyperreactivity. Instead, allergen-specific T_H1 cells cause severe airway inflammation [12]. Moreover, Dahl *et al.* [13] showed virus-induced T_H1-dependent enhancement of allergic pulmonary inflammation via T_H1-polarized dendritic cells (DCs). Thus, although T_H2 cells play an important role in the pathogenesis of asthma, the binary T_H1-T_H2 paradigm cannot explain all the immunological processes that occur in asthma. These processes in asthma may be much more complex than is hypothesized by a T_H1-T_H2 paradigm. In this regard, Kruschinski *et al.* [14], in this issue of *Clinical and Experimental Immunology*, show a critical role for CD26$^+$ T cells, which are T_H1 cells, in asthma, by examining CD26-deficient and CD26-reduced rats in ovalubmin (OVA)-induced asthma models. They show in their article that the decrease in T cell recruitment to the airway observed in CD26^{low} and CD26-deficient rats is associated with significantly reduced OVA-specific IgE-titres. They suggest a role for CD26$^+$ T cells in the pathogenesis of asthma by means of T cell migration and T cell-dependent IgE production in the airway.

CD26/dipeptidyl peptidase IV (DPPIV) is a 110-kDa cell surface glycoprotein that belongs to the serine protease

family [15]. It is expressed on a variety of tissues including T lymphocytes, endothelial and epithelial cells. It is composed of a short cytoplasmic domain of 6 amino acids, a transmembrane region of 22 amino acids, and an extracellular domain of 738 amino acids, with DPPIV activity which selectively removes the N-terminal dipeptide from peptides with proline or alanine in the second position [16]. Possible substrates of DPPIV include several critical cytokines and chemokines. Activity of CCL5 (RANTES, regulated on activation, normal T cell expressed and secreted) is altered by the enzymatic cleavage of DPPIV, as CD26-processed CCL5(3–68) has a more than 10 times lower chemotactic potency for monocytes and eosinophils. CCL5(3–68) also has impaired binding and signalling properties through CCR1 and CCR3, but remains fully active on CCR5, leading to T_H1 polarization [17,18]. Other important chemokines that appear to be substrates of the enzymatic activity of DPPIV include CCL11 (eotaxin), CCL22 (macrophage-derived chemokine), CXCL10 and CXCL11 (interferon inducible chemokines), and other chemokines [19,20]. Besides its ability to regulate the effect of biological factors through its enzymatic activity, CD26/DPPIV has an essential role in human T cell physiology.

Originally characterized as a T-cell differentiation antigen, CD26 is preferentially expressed on a specific population of T lymphocytes, the subset of CD4+ memory T cells, and is up-regulated after T cell activation [21,22]. As well as its enhanced expression on activated T cells, various lines of evidence have converged to demonstrate that CD26 is functionally associated with T cell signal transduction processes, which are capable of transmitting signals relating to T cell activation [22,23]. In addition CD26 serves as a functional collagen receptor with a role in T cell activation, as well as having a potential role in thymic ontogeny [24]. The enzymatic activity of CD26 appears to be very important in enhancing cellular responses to external stimuli. For example, Jurkat cells transfected with wild type CD26 consistently demonstrated greater activation than parental CD26 nega-

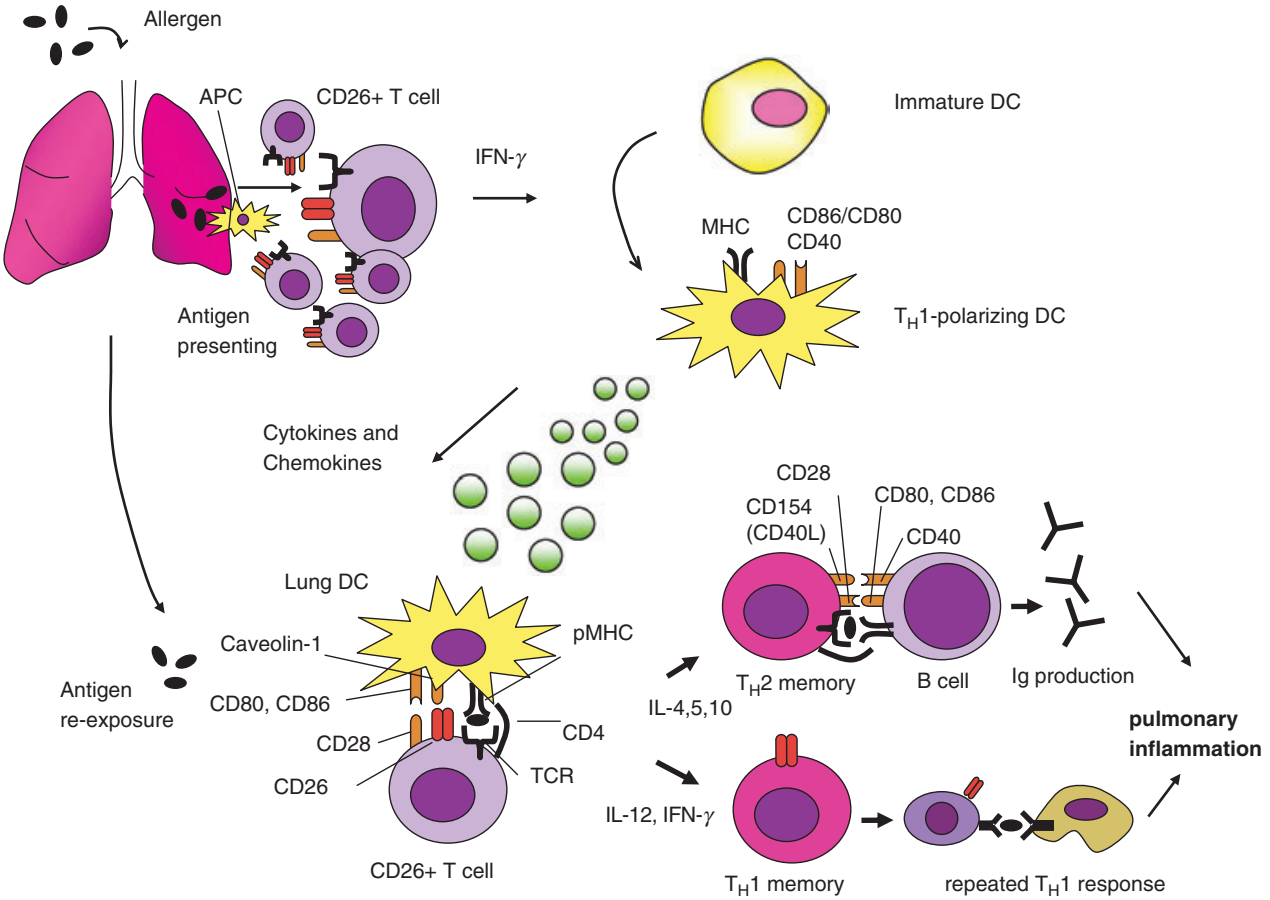

Fig. 1. T_H1-dependent enhancement of allergic pulmonary inflammation. Initially, antigens such as sensitizing-allergens stimulate $CD26^+$ T cells via antigen presenting cells (APC), and subsequently generate $CD26^+$ T_H1 response to produce IFN-γ and stable T_H1-polarizing DCs. Later, these DCs are capable of augmenting both T_H1 and T_H2 controlled immune responses in allergen-induced pulmonary inflammation, partly via interaction of CD26 on T cells and caveolin-1 on APC loaded with sensitized allergens. Ig, immunoglobulin; MHC, major histocompatibility complex; pMHC, peptide-loaded major histocompatibility complex.

tive Jurkat or cells transfected with CD26 mutated at the DPPIV enzymatic site [25].

CD26 expression is tightly regulated on human T lymphocytes, with its density being markedly elevated following T cell activation [21,26]. At the resting state in the peripheral blood, CD26 is preferentially expressed on the helper/memory T cell population [21]. High CD26 cell surface expression is correlated with the production of T_H1-like cytokines by T-cell clones, and CD26 expression is induced by stimuli that favour the development of the T_H 1 response [27,28]. CD26 is able to conduct IL-2-dependent comitogenic signals in conjunction with activation through the CD3/T cell receptor complex or the CD2 pathway of mature human T lymphocytes when crosslinked with solid-phase immobilized antibodies [22].

Meanwhile, recombinant soluble CD26/DPPIV molecule up-regulates expression of CD86 on antigen presenting cells (APC), leading to greater APC–T cell interaction and enhanced T cell proliferation, with important implications for immunoregulation [29]. More recently, T cell proliferation via CD26 driven by recall antigens such as tetanus toxoid is mediated by means of caveolin-1 on APC, leading to up-regulation of the costimulatory molecule CD86 [30]. Thus, $CD26^+$ T cells play a critical role in inflammation responding to recall antigen.

Of clinical relevance, patients with autoimmune diseases such as Graves' disease and rheumatoid arthritis have been found to increase numbers of $CD26^+$ T cells in inflamed tissues such as thyroid and synovial fluids [26,31]. In addition, enhancement of CD26 expression in these autoimmune diseases may correlate with disease severity [32,33]. Moreover, we have shown that T cells migrating through endothelial cell monolayers *in vitro* express high levels of CD26 [34], and the fact that chemokines play a key role in T cell migration supports the notion that CD26/DPPIV may interact with chemokines [18–20]. These findings imply that $CD26^+$ T cells play a role in the inflammation process and subsequent tissue damage not only in autoimmune diseases, but also in asthma.

In the context that $CD26^+$ T cells preferentially play an important role in allergic pulmonary inflammation, it is hypothesized that allergens such as OVA incite a robust T_H1-type cytokine response, such as IFN-γ, in the lung, promoting the development of durable T_H1-polarizing DCs, partly via a CD26–caveolin-1 interaction, subsequently leading to enhancement of CD28-CD86 costimulation (Fig. 1). These DCs support subsequent immunity in a T_H2-dependent process of allergen-induced pulmonary inflammation, and so enhance both T_H1 and T_H2 immune cytokines and IgE production.

Interestingly, a recent report on single-nucleotide polymorphism in asthmatic patients revealed that polymorphism of DPP-10, a CD26/DPPIV-like peptidase, was observed [35]. Further elucidation on DPPs and asthma will open an avenue for our understanding the pathophysiology of asthma.

Although the precise effects rely on the exact timing, intensity and dose of cytokines and antigens as well as how these interactions alter T helper regulatory cells and cytokines, $CD26^+$ T cells play an important role in asthma and targeting CD26/DPPIV may contribute to the elucidation of the pathophysiology and therapeutic means to treat asthma, and other inflammatory disorders.

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