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Strategies for targeting T-cells in allergic diseases and asthma

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Abstract

T helper (Th) 2 lymphocytes play a crucial role in the initiation, progression and persistence of allergic diseases, including asthma. Drugs that interfere with the activation of T-cells or more selectively Th2-specific signaling molecules and drugs that prevent the selective migration into lung tissue are promising novel strategies for the treatment of allergic asthma. Although the mainstay asthma therapy of inhaled glucocorticoids is rather effective, targeting Th2 cells may be an important alternative in childhood. Regulatory T-cells (Treg cells) have a physiological role in protection of unwanted immune responses to auto-antigens and allergens. Literature data indicate that an imbalance between Th2 and Treg cells may underlie development and disease expression of allergic asthma. Drugs or immunotherapies that stimulate these counter-Treg cells may limit aberrant Th2 responses leading to suppression of symptoms. Furthermore, these types of treatments may offer the perspective of disease modification and long-term relief of symptoms.

Keywords: Allergy; Asthma; T lymphocyte; Immunomodulation; Costimulation; Inflammation

Abbreviations: AHR, airway hyperreactivity; AP, activator protein; APC, antigen-presenting cell; BAL, bronchoalveolar lavage; cAMP, cyclic adenosine monophosphate; CBP, CREB-binding protein; CpG DNA, CpG-containing immunostimulatory deoxyribonucleic acid; CsA, cyclosporin A; CTLA4, cytotoxic T lymphocyte antigen 4; DC, dendritic cell; ERK, extracellular-regulated kinase; GR, glucocorticoid receptor; GRE, glucocorticoid response elements; ICAM, intercellular adhesion molecule; Ig, immunoglobulin; IL, interleukin; ITAM, immunoreceptor tyrosine-based activation motif; JNK, Jun N-terminal kinase; LFA, leukocyte function-associated antigen; MAPK, mitogen-activated kinase; NF-AT, nuclear factor for activated T-cells; PAMP, pathogen-associated molecular patterns; PBMC, peripheral blood mononuclear cells; PDE, phosphodiesterase; PGD2, prostaglandin D2; PI3-K, phosphoinositide-3 phosphate; SAPK, stress activated protein kinase; STAT, signal transducer and activator of transcription; TARC, thymus and activation-regulated chemokine; TCR, T-cell receptor; TGF-β, transforming growth factor β; Th, T helper; TLR, toll-like receptor; Treg cells, regulatory T-cell; VCAM, vascular cell adhesion molecule; VLA, very late antigen.

Contents

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1. Introduction

High serum levels of immunoglobulin E (IgE) antibodies to common environmental allergens like house-dust or pollen is a key determinant of allergic diseases like allergic asthma, allergic rhinitis and atopic dermatitis. IgE mediates the type-I immediate hypersensitivity reaction that is characterized by crosslinking of receptor-bound IgE on mast cells with allergen, inducing the release of preformed and newly generated mediators that elicit the symptoms of allergic disease. The prevalence of allergic diseases is very high and has shown a considerable increase during the last decades, especially in children, although this increase appears to level off (van Schayck & Smit, 2005). Allergic rhinitis alone affects more than 155 million people worldwide and over 80 million people in Europe have some form of allergic disease. Asthma is one of the most common chronic diseases with over 300 million people worldwide (GINA report 2004). While approximately 90% of children with asthma are allergic, only 50–60% of adult asthmatics display elevated serum levels of allergen-specific IgE. Asthma is further characterized by reversible airway obstruction, chronic eosinophilic airway inflammation, airway remodelling, mucus hypersecretion, and airway hyperresponsiveness (AHR) to bronchospasmogenic stimuli. T-helper (Th) 2 lymphocytes play a critical role in the initiation, progression and persistence of allergic diseases, asthma included. Initially, a disturbed balance between Th1- and Th2-mediated immune responses has been postulated to underlie aberrant Th2 reactions to harmless inhaled allergens. Indeed, allergen-specific T-cell clones isolated from the blood of allergic individuals express a typical Th2 cytokine profile secreting interleukin (IL)-4, IL-5 and minimal IFN-γ and IL-2, whereas those clones from non-atopic individuals displayed a Th1 profile (Kapsenberg et al., 1992). Furthermore, allergic asthma is associated with expression of IL-3, IL-4, IL-5 and GM-CSF in bronchoalveolar cells, strongly supporting Th2 activation (Robinson et al., 1992). Nowadays, Th2-type cytokines Il-4, IL-5, IL-13 are known to be critical for IgE production, airway eosinophilia, mucus hypersecretion and non-specific airway hyperreactivity (AHR). However, it appears that susceptibility to allergic diseases cannot solely be explained by an imbalance between Th1 and Th2 responses (Wills-Karp et al., 2001; Herrick & Bottomly, 2003). Recently, an important immunoregulatory role for regulatory T-cells (Treg cells) has been put forward, capable of suppressing both Th1- and Th2-mediated adaptive immune responses (van Oosterhout & Bloksma, 2005). Targeting these different T-cell subsets for the treatment of allergic asthma is an interesting strategy that has not yet been widely explored. Interestingly, some T-cell-directed therapies harbour the potential to induce long-lasting suppression or even complete remission of disease.

2. Modulation of T-cell receptor-induced signal transduction during T-cell activation

Activation of T-cells is initiated by processed antigen-derived peptides presented by antigen-presenting cells (APC) to the T-cell receptor (TCR)/CD3 complex. An accessory signal provided by co-stimulatory molecules on APC leads to full T-cell activation and this prevents the induction of T-cell tolerance (T-cell unresponsiveness, also called anergy), which normally occurs when T-cells are stimulated by antigen-derived peptide in absence of an appropriate accessory signal. The most potent accessory signal is provided by CD80/CD86, which interacts with CD28 on the T-cell. TCR/CD3 protein complex activation induces a cascade of phosphorylation reactions. First, non-receptor tyrosine kinases, for example, the Src family kinases Lck and Fyn, phosphorylate immunoreceptor tyrosine-based activation motifs (ITAM) located in the CD3 complex (Pitcher and van Oers, 2003), which serve as a docking site for downstream adaptor molecules containing SH2 and phosphotyrosine domains. This induces recruitment of Syk family tyrosine kinases and activation of adaptor molecules, leading to activation of more downstream signaling molecules, for example, phospholipase C and phosphoinositide-3 phosphate kinase (PI3-K) (Nel, 2002). These molecules can activate multiple signaling cascades, including the Ca^{2+} mobilization/calmodulin pathway, the mitogen-activated kinases (MAPK) extracellular-regulated kinase (ERK) pathway, Jun N-terminal kinase (JNK)/stress activated protein kinase (SAPK) pathway and the p38/Mpk2 MAPK pathway, finally resulting in activation of the transcription factors, nuclear factor for activated T-cells (NF-AT) and activator protein (AP)-1. NF-AT and AP-1 can bind to the promoter of many T-cell cytokine genes and enhance their transcription. Full activation of AP-1 and NF-AT requires co-stimulation of the TCR-induced signal by CD28. Similar to TCR/CD3 signaling, CD28 signaling is mediated by tyrosine kinases (e.g. Lck and Ltk) and subsequent