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Targeting T cells for asthma

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The type 2 T-helper (Th2) lymphocyte can be regarded as an important target cell for the treatment of allergic asthma as it plays a crucial role in the initiation, progression and persistence of disease. Several strategies to target Th2 cells can be envisioned. Drugs that prevent Th2-cells from migrating into the lung tissue, such as antibodies to the chemokine receptor CCR4 and inhibitors of the adhesion molecule VLA-4, are promising for the treatment of asthma. To inhibit Th2-cell activation, novel asthma drugs that act on Th2-selective transcription factors such as GATA3 are being developed. Although initial strategies aimed to block the action of Th2-derived cytokines, the generation of counter-regulatory Th1 lymphocytes and regulatory T cells is currently being explored.

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Introduction

Allergic asthma is a complex disease that is characterized by reversible airway obstruction, elevated serum levels of immunoglobulin E (IgE), chronic eosinophilic airway inflammation, airway remodelling, mucus hypersecretion and airway hyperresponsiveness (AHR) to bronchospasmogenic stimuli. Type 2 T-helper (Th2) lymphocytes play a crucial role in the initiation, progression and persistence of the disease. Initially, it was hypothesized that a disturbance in the balance between Th1- and Th2-mediated immune responses underlies aberrant Th2 reactions to harmless inhaled allergens. Nowadays, regulatory T (Treg) cells are viewed as key downregulatory cells that are capable of preventing allergic sensitisation and progression to established allergic disease, including asthma. The method of targeting T cells to treat allergic asthma is an interesting strategy that has not yet been

explored extensively. In contrast to current, rather palliative, therapies, some T-cell directed therapies harbour the potential to induce long-lasting suppression or even complete remission of disease.

In this review, we will discuss the targeting of migratory pathways that are involved in the infiltration of Th2 cells into the lung tissue and transcription factors involved in the activation and differentiation of T helper subsets, including Th1, Th2 and Treg cells, as well as the direct modulation of Th2 cells or the indirect modulation by way of antigen-presenting cells (APCs).

T-cell migration: adhesion molecules and chemokines

Chemokines orchestrate immune responses by the attraction of inflammatory cells to inflamed tissue. Chemokine receptors are expressed in different patterns on the surface of T-cell subsets. Th1 cells express the chemokine receptors CCR2, CCR5, CCR7 and CXCR3, with the latter being the most abundant type. A substantial percentage of Th2 cells express CCR7 and CCR2. One of the ligands for CCR2, monocyte chemoattractant protein (MCP)-1 (also known as C-C chemokine ligand [CCL]-2), is a potential target in asthma therapy [1]. The chemokine receptors that are preferentially expressed on Th2 cells are CCR4, CCR8, CXCR4 and (at a low level) CCR3. There is growing evidence that one of the ligands for CCR4, thymus and activation-regulated chemokine (TARC; also known as CCL17), plays an important role in the recruitment of Th2 cells to the asthmatic airway [2,3]. Although the blocking of CCR4 failed to reduce Th2 inflammation in the airways of guinea pigs [4], CCR4 deficiency and monoclonal antibodies against TARC have been demonstrated to do so in mouse models of asthma [5,6]. Increased CCR8 expression has been observed in the airways of asthmatic patients upon allergen challenge, but the CCR8 ligand I-309 was hardly detectable in bronchoalveolar lavage and in serum of asthma patients [2,3]; knockout of CCR8 did not affect allergic inflammation in mice [7]. A CXCR4 antagonist has been demonstrated to inhibit allergen-induced inflammation in a murine model of asthma [8], although increased CXCR4 expression in the asthmatic lung has only been described for eosinophils. Altogether, selective targeting of CCR4⁺ T cells might be the most attractive tool in the treatment of asthma. Anti-CCR4 and a CXCR4 antagonist are now in clinical trials for asthma; CCR3 antagonists are under investigation in murine models.

A process of slowing of lymphocyte motion and adhesion to the endothelium precedes infiltration of inflammatory

cells into tissue. Specialized integrins are involved in the adhesion of T cells to the endothelium. These include very late antigen (VLA)-4 and leukocyte function-associated antigen (LFA)-1 (also known as integrin $\alpha 4\beta 1$ and integrin $\alpha L\beta 2$, respectively), which are ligands for the adhesion molecules vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1, respectively. VLA-4 and LFA-1 are induced during antigenic activation of T cells in the lymph nodes. High affinity adhesive interactions have been described between VCAM-1 and VLA-4 that are expressed on differentiated Th2 cells, whereas VLA-4-expressing Th1 cells were less capable of sustained interactions with VCAM-1 [9]. Thus, differences in integrin activation might contribute to selective recruitment of T-cell subsets to the lung. The use of small molecule peptide inhibitors of VLA-4 has been in clinical development for the treatment of asthma but was discontinued [10].

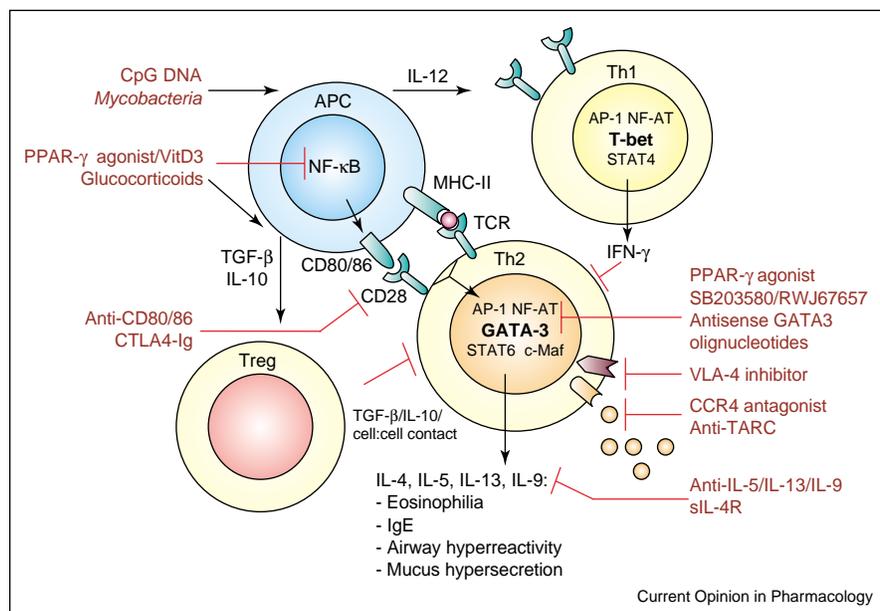
Transcription factors involved in T-cell activation and differentiation

Other therapeutic strategies that can be used to reduce Th2 responses include the administration of drugs that act on Th2-specific transcription factors. The expression of specific transcription factors is required for the development of committed Th1 and/or Th2 effector cells as well as Treg cells. The transcription factors signal transducers and activators of transcription (STAT)4 and STAT6 are specific for Th1 and Th2 cells, respectively. A transcription factor specific for naturally occurring Treg cells is FOXP3 [11], a forkhead box transcription factor

that is involved in the induction of the suppressor phenotype of these cells [12^{**}]. STAT6 is essential for the development of Th2 cells in response to interleukin 4 (IL-4) and has been described to negatively regulate a Th1-specific IL-4 silencer [13]. Other Th2-selective transcription factors are nuclear factor (NF)-IL-6 (also known as C/EBP- β), c-Maf and GATA-3 (name derived from the nucleotide sequence of the GATA consensus site). GATA-3 might be a key regulator of Th2 cytokine expression as GATA-3 is upregulated in polarized Th2 cells and is downregulated in Th1 cells. Moreover, forced expression of GATA-3 in polarized Th1 cells is sufficient to initiate Th2 cytokine expression [14]. GATA-3 is also thought to play an important role in the expression of Th2 cytokines in asthma; enhanced expression of GATA-3 has been observed in the airways of asthma patients, with a further increase occurring upon segmental allergen challenge [15,16]. A Th1-specific transcription factor is T-bet, which is crucial in the development of Th1 cells. Retroviral expression of T-bet can suppress GATA-3 expression and IL-4 and IL-5 production [17] (Figure 1).

New asthma drugs that act on Th2-specific transcription factors include dissociated steroids [18], peroxisome proliferator-activated receptor (PPAR) agonists and inhibitors of protein kinases (e.g. p38 MAP kinase inhibitors). PPAR agonists, such as cyclopentenone prostaglandins and thiazolidinediones, negatively interfere with NF- κ B, activator protein (AP)-1 and STATs [18]. In addition, PPAR agonists were shown to downregulate GATA-3 and to decrease antigen-induced airway inflammation and

Figure 1



Overview of therapeutic strategies to directly or indirectly affect Th2 activity in asthma. Asthma drugs might inhibit Th2 effector function (e.g. by neutralization of cytokines, downregulation of transcription factors and blocking of Th2-cell migration) or suppress APC function. Otherwise, asthma drugs might act to promote Th1 or Treg activities. See text for further details. Abbreviations: IFN- γ , interferon- γ .

serum levels of antigen-specific IgE in a murine model of asthma [19]. Activity of p38 can be blocked by drugs such as SB203850, SB239063 and RWJ67657 [20], which are of potential interest in the treatment of asthma as they might have a preferential inhibitory effect on Th2-type cytokines and might inhibit GATA-3 activation [21]. Treatment with GATA-3-specific antisense oligonucleotides has been shown to abrogate both infiltration of eosinophils and Th2 cytokine production, and to induce a significant reduction of AHR in ovalbumin-sensitized mice [22]. A possible therapy is to drive the immune balance towards a Th1 response; however, a risk of this is the possible development of Th1-mediated diseases, such as Crohn's disease or autoimmune diseases.

Modulation of Th2 cells or of the secreted cytokines

Different therapeutic strategies that aim to neutralize Th2-type cytokines or to restore the dysregulated Th2-dominated allergic asthmatic reactions are currently in (pre)clinical development. Blocking Th2-derived cytokines or increasing the function of counteracting Th1 cells has been an area of intense research and development. However, treatment with IL-12, soluble IL-4 receptor (sIL-4R) and anti-IL-5 have been rather disappointing to date, with only partial and transient reduction of eosinophil numbers and limited improvement of lung function [20]. Mouse models have shown that neutralization of the Th2 cytokines IL-13 or IL-9 inhibits asthma manifestations, such as AHR, eosinophilic inflammation and mucus hypersecretion, and accordingly antibodies are currently in clinical development for the treatment of asthma [20].

Asthma therapy can also be directed towards costimulation of T cells. Although interaction of the costimulatory molecule CD80 or CD86 on APCs with CLTA-4 on T cells is known to be inhibitory, the most potent costimulatory signal is provided by the interaction of CD80 or CD86 with CD28 on T cells. Stimulation of the CD3-TCR complex by the antigen presented by the class II major histocompatibility complex (MHC-II) leads to activation of mitogen-activated kinases (including p38), which results in activation of the transcription factors nuclear factor for activated T cells (NF-AT) and AP-1. Full T-cell activation requires CD28 costimulation and, in absence of a costimulatory signal, tolerance (T cell unresponsiveness; also known as anergy) is induced. Prevention of T-cell costimulation by antibodies directed to CD80 or CD86 might lead to suppressed T-cell cytokine expression. Indeed, the blocking of CD80 or CD86 inhibits allergen-induced IL-5 and IL-13 production in bronchial tissue *ex vivo* and allergen-induced IL-5 production in peripheral mononuclear blood cells of asthma patients [23,24]. In addition, blocking of CD80 or CD86 by cytotoxic T lymphocyte-associated antigen 4 (CTLA4)-Ig or by monoclonal antibodies inhibits anti-

gen-induced AHR and eosinophilic inflammation in murine models of allergic asthma and has long-term suppressive effects with regard to airway inflammation (see [25] for review). Although CTLA4-Ig is in clinical development for the treatment of rheumatoid arthritis and psoriasis and, to date, has had encouraging results, it is currently not in development for the treatment of asthma. Last but not least, other pairs of T-cell costimulatory molecules, such as the inducible costimulator (ICOS): ICOS ligand, might also be promising targets for therapeutic intervention in asthma [26,27].

Novel cellular targets of therapeutic intervention in asthma are Treg cells, which consist of naturally occurring Treg cells, type-1 Treg (Tr1) cells and Th3 cells [28]. These cells are capable of suppressing both Th1-mediated autoimmunity and Th2-mediated allergic asthma by cell-cell contact, IL-10 and transforming growth factor β (TGF- β), respectively. Recently, classical allergen immunotherapy was shown to induce Tr1- and Th3-like cells [28]. The combination of allergen immunotherapy with compounds that facilitate the generation of Tr1- and Th3-cells, such as the biologically active form of vitamin D3 (1,25(OH)₂VitD3) and glucocorticoids, might be an interesting strategy to pursue [28,29].

Modulation of aberrant Th2 responses through antigen presenting cells

Another way in which Th2-dominated asthmatic responses can be modulated is by targeting APC function, in particular that of dendritic cells (DCs). DCs play a crucial role in the generation of effector T cells and Tregs, such as Tr1 and Th3 cells, which has been reviewed in detail elsewhere [30,31]. Treg-promoting DCs are generally semi-mature cells that display lower antigen uptake capacity, reduced T-cell stimulatory capacity and defective expression of costimulatory molecules [30]. Immature DCs are also defective in the expression of costimulatory molecules and can induce tolerance during antigen presentation. During maturation, DCs upregulate expression of costimulatory surface molecules, including CD80 and CD86, which is essential in their T-cell stimulatory capacity and in their role in priming naïve T cells. Inhibition of DC maturation by inhibition of NF- κ B activation with 1,25(OH)₂VitD3, glucocorticoids or agonist of PPAR- γ receptor induces Tr1-like cells *in vitro* and tolerance in mouse models of transplantation, autoimmune diseases and asthma *in vivo* [29,32,33]. Apparently, the induction of Tr1 or Th3 cells is related to the production of the cytokines IL-10 or TGF- β , respectively, by (semi-mature or immature) DCs [31]. Many pathogens, including viruses, parasites, fungi and bacteria, as well as isolated, so-called, regulatory-type pathogen-associated molecular patterns (PAMPs) have been shown to induce the production of cytokines by DCs and to facilitate induction of Treg cells in this way [31]. However, except for treatment with CpG DNA or mycobacteria

(discussed below), strategies to use these microbes or regulatory PAMPs for the treatment of asthma have not yet been fully explored.

The Toll-like receptor (TLR)-9 agonist, CpG DNA, is a PAMP that is currently in clinical development for asthma [34]. In mouse models, CpG DNA has been shown to inhibit antigen-induced AHR, acute and persistent airway inflammation, and airway remodelling. Furthermore, CpG DNA might reduce the expression of Th2 transcription factors, such as GATA-3, by the induction of T-bet [35]. TLR-9 induces the production of the Th1-skewing cytokine IL-12 production by DCs; however, the protection against the development of asthma manifestations might not be mediated by this cytokine [34]. An interesting approach is the combination of IL-12 or CpG DNA with allergen immunotherapy, in particular when administered as a fusion protein. The latter combination is in clinical development for the treatment of allergic rhinitis and asthma. The goal is to induce allergen-specific Th1 cells that can mediate long-term suppression of allergic disease, including asthma. Treatment with inhaled CpG DNA itself (with 1018 ISS) and reliance on natural exposure to multiple allergens to reprogram allergen-specific Th2 responses into allergen-specific Th1 responses is also being tested in asthma patients.

The postulate of the hygiene hypothesis that there is an inverse relationship between the extent of exposure to microbial agents during early childhood and the prevalence of allergic diseases, including asthma, has been supported by substantial evidence. Hence, another strategy to redirect Th2-dominated allergic responses is by way of exposure to bacteria such as heat-killed or live *Mycobacteria* [36,37]. In mouse models, prophylactic treatment with *Mycobacterium Bacillus Calmette-Guerin* (BCG) or *Mycobacterium vaccae* has been shown to suppress antigen-induced asthma manifestations. Although the mechanism of action was thought to be mediated by induction of Th1 responses, recently, suppressive effects that are exhibited after exposure to heat-killed *M. vaccae* were attributed to the production of IL-10 and TGF- β by antigen-specific Treg cells [38]. To date, clinical trials that use BCG vaccination or injection of the non-pathogenic mycobacterium *M. vaccae* to treat allergic asthma have been disappointing [39,40]. Data from clinical studies on the prophylactic effects of injection with these mycobacteria, in particular in early life, are awaited.

Conclusions

Many opportunities are available for the targeting of T-cells to treat asthma. The pattern of chemokine receptors expressed by Th1- and Th2-lymphocytes is different, which offers the potential for selective intervention. However, a large redundancy exists between chemokines

and their receptors. Initial studies to target Th2 cells for the treatment of allergic asthma were focussed on the inhibition of individual cytokines implicated in the development of asthma manifestations. It remains to be seen whether the blocking of individual cytokines will offer substantial benefit to the patient. More promising approaches to limit aberrant Th2 responses are the induction of counterregulatory Th1 cells by treatment with IL-12 or CpG DNA, or the generation of Treg cells by compounds that act on DCs. The latter strategy might offer the possibility to induce long-term relief of symptoms or even complete remission of disease. However, most of these studies are established at the level of mouse models, which do not have a good reputation when it comes to predictability for the treatment of human asthma.

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