

REVIEW

Role of T cell co-stimulation in murine models of allergic asthma

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Introduction

Allergic asthma is a chronic inflammatory disorder of the lungs characterized by reversible airflow obstruction, persistent airway hyper-responsiveness, chronic airway inflammation and airway remodelling [1–3]. Allergen-specific type 2 T-helper (Th2) cells play a major role in both the initiation and progression of allergic asthma by orchestrating the inflammatory response [4, 5]. In animal models of allergic asthma, various experimental treatments have therefore been explored that target the allergen-specific T cell, including the blockade of their co-stimulatory requirements [6–8].

For optimal activation, CD4⁺ T cells require specific antigen recognition by the T cell receptor (TCR) (signal 1) and additional signals (collectively called signal 2 or co-stimulatory signals), delivered by the same antigen-presenting cell (APC) [9]. In the absence of co-stimulation, lymphocytes fail to respond effectively and are rendered anergic, or hyporesponsive to antigenic restimulation even in the presence of co-stimulation, which might be a mechanism of maintaining self-tolerance [10, 11].

This review will address the current knowledge of the role of various T cell co-stimulatory pathways in different phases of the allergic response. First, the role of these molecules in the development of the Th2-dominated allergic inflammatory responses is addressed, followed by a review of their role in ongoing and reoccurring Th2-mediated responses. In addition, the long-term effects of blockade of T cell co-stimulation in murine models of allergic asthma will be discussed. Lastly, the role of co-stimulatory receptors in the function of regulatory T cells will be addressed. The T cell co-stimulatory pathways that will be discussed are: CD28/CTLA4:B7-1/B7-2, ICOS:B7RP-1, CD40L:CD40 and OX40:OX40L.

Role of T cell co-stimulatory molecules in the development of Th2-dominated allergic inflammatory responses

The CD28/CTLA4:B7-1/B7-2 pathway

CD28 is the best-characterized co-stimulatory receptor and constitutively present on the surface of T cells (reviewed in [12–16], Table 1). Upon interaction with one of its two

ligands, B7-1 (CD80) and B7-2 (CD86) on APCs, CD28 stimulates the proliferation initiated by TCR signalling, by increasing the secretion of IL-2. In addition, CD28 promotes T cell survival by the induction of the anti-apoptotic factor Bcl-x_L. Ligation of CD28 is critical for the differentiation of T cells into Th2 cells [17, 18]. CD28 signalling contributes to the overall strength of T cell activation [19], and the development and activation of Th2 cells may require stronger signalling than Th1 cells [20, 21].

The critical role of CD28 signalling in the development of Th2-dominated allergic inflammatory responses in mice has been unequivocally demonstrated in blocking studies and, more recently, in gene targeting studies. No non-specific airway hyper-responsiveness, airway inflammation and antigen-specific IgE could be induced in CD28-deficient (CD28^{-/-}) mice [22–24] or B7-1/B7-2^{-/-} mice [25]. Blockade of the B7 ligands during antigen sensitization and/or challenge of mice strongly inhibited these manifestations of allergic asthma [26–30]. In all these studies, a decrease in Th2 cytokine production was observed in either the bronchoalveolar lavage fluid (BALF) or by antigen restimulated lung T cells *in vitro*.

B7-1 and B7-2 appear to support T cell activation equivalently [31]. On most APC populations, B7-2 is expressed constitutively at low levels and is rapidly up-regulated, whereas B7-1 is inducibly expressed later after activation. The earlier expression pattern of B7-2 suggests that B7-2 is a more important co-stimulator for initiating T cell responses. The blockade of B7-2 by mAb administration has indeed consistently been shown to inhibit the development of the various allergic airway manifestations in mice, although to a variable degree [28, 32–34]. In contrast, the contribution of B7-1 to the development of these manifestations is more controversial [22, 28, 32–35]. Comparison of mice deficient in B7-1 or B7-2 suggested that these molecules have complementary roles in the development of Th2-dominated allergic inflammatory responses [25]. For peripheral blood mononuclear cells (PBMCs) derived from atopic asthmatics, B7-2 appears to be the principal co-stimulatory ligand for allergen-induced proliferation and Th2 cytokine production [36–39].

The induced receptor for the B7 ligands, cytotoxic T lymphocyte antigen 4 (CTLA4; CD152), is expressed on activated T cells and delivers inhibitory signals (reviewed in [12, 13, 15, 16, 40]). CTLA4 reduces T cell proliferation by the inhibition of IL-2 production and progression through the cell cycle and has been implicated in Th1 differentiation. In the same way as CD28 enhances the strength of TCR signalling and hence might promote Th2 differentiation [19], engagement of CTLA4 dampens TCR signal transduction and promotes Th1 differentiation *in vitro* and *in vivo*.

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Table 1. Overview of members of the Ig and tumour necrosis factor receptor/ligand superfamilies implicated in T cell co-stimulation

Receptor(s) on T cell	Ligand(s)	Reference(s)
<i>CD28 and B7 subfamilies of the Ig superfamily</i>		
CD28/CTLA4 (CD152)/third		
B7-1/B7-2 receptor?	B7-1 (CD80)/B7-2 (CD86)	[12–16, 43, 47]
ICOS (AILIM, H4)	B7RP-1 (B7h, GL50 and LICOS (mice); B7-H2 and ICOSL (human))	[15, 16]
PD-1+unknown receptor	PD-L1 (B7-H1)/PD-L2 (B7-DC)	[15, 16, 114, 115]
BTLA	B7x	[116]
Unknown yet	B7RP-2 (B7-H3)	[117]
Unknown yet	B7-H4	[118]
Unknown yet	B7S1	[119]
<i>Tumour necrosis factor receptor/ligand superfamily</i>		
CD40L (CD154)	CD40	[55, 56]
OX40 (CD134)	OX40L	[73, 120]
4-1BB (CD137)	4-1BBL	[73, 121]
CD27	CD27L (CD70)	[73]
CD30	CD30L (CD153)	[122]
LIGHT	HVEM	[123]

Adapted from [73, 112, 113].

B7h, B7 homologue; B7RP, B7-related protein; BTLA, B and T lymphocyte attenuator; CTLA4, cytotoxic T lymphocyte antigen 4; HVEM, herpes virus entry mediator; ICOS, inducible co-stimulator; L, ligand; LIGHT, lymphotoxin-like, exhibits inducible expression, and competes with HSV glycoprotein D for HVEM, a receptor expressed by T cells; PD-1, programmed death 1.

Conversely, naïve CTLA4^{-/-} CD4⁺ cells differentiate into Th2 cells upon polyclonal stimulation, bypassing STAT-6 [41].

The blockade of CTLA4 in mice would thus be expected to aggravate asthma manifestations, whereas stimulation of CTLA4 might alleviate them. Indeed, administration of an anti-CTLA4 mAb during ovalbumin (OVA) sensitization of BALB/c mice resulted in an elevation of features of allergic airway sensitization following aerosol challenge compared with control-treated mice [42]. Enhanced Th2 cytokine production was observed both *in vitro* and *in vivo*. When OVA-sensitized BALB/c mice received anti-CTLA4 mAb solely during challenge, asthma manifestations were unaltered [42].

As mentioned earlier, blockade of the B7 ligands during antigen sensitization strongly inhibited the development of asthma manifestations in mice following aerosol challenge [27, 30], suggesting that the positive effect of blockade of CD28 predominates over the negative effect of CTLA4 blockade. The effects of stimulating CTLA4 in a murine model of allergic asthma have not been studied so far.

The existence of a third B7-1/B7-2 receptor was recently postulated in a study using a novel mouse strain lacking both CD28 and CTLA4 that demonstrated considerable B7-1/B7-2-dependent T cell co-stimulation *in vitro* and *in vivo* [43].

Although no asthma manifestations can be induced in CD28^{-/-} mice, primed T cells are observed in these mice [22–24] in contrast with B7-1/B7-2^{-/-} mice [25], suggesting that co-stimulation by the putative B7-1/B7-2 receptor may result in allergen-specific T cell activation that is not strong enough to induce the features of allergic airway sensitization.

However, failure to induce these features in CD28^{-/-} mice might also be due to the presence of CTLA4 that can signal negatively in the absence of CD28 [44–46], thus opposing potential T cell co-stimulation via the putative B7-1/B7-2 receptor. So, unmasking the possible role of co-stimulation by the supposed B7-1/B7-2 receptor in T cell activation required the absence of both CD28 and CTLA4.

However, we failed to induce any of the asthma manifestations not only in B7-1/B7-2^{-/-} mice but also in CD28/CTLA4^{-/-} mice [47]. Moreover, we were unable to demonstrate any sign of residual T cell activation in both the thoracic lymph nodes and lungs from CD28/CTLA4^{-/-} mice upon OVA-sensitization and challenge *in vivo*. So, further evidence is provided for the indispensable role of CD28 signalling in the development of Th2 responses in mice [17, 18, 22–24]. However, this does not exclude important contributions by other co-stimulatory molecules – including the supposed B7-1/B7-2 receptor – at later stages in the (re-)activation of T cells.

The ICOS:B7RP-1 pathway

Inducible co-stimulator (ICOS; also known as AILIM or H4) is a recently discovered CD28 family member that binds its own B7 family member, B7-related protein 1 (B7RP-1) (also known as B7h, B7-H2, GL50, ICOSL or LICOS) (reviewed in [15, 16]). ICOS is expressed rapidly on the surface of T cells after TCR engagement and is retained on many memory T cells, suggesting that ICOS is involved in sustaining primary and antigen-experienced (memory and effectors) T cell responses rather than initiating primary responses. Indeed, during the initial activation of naïve T cells, the effects of ICOS signals on T cell proliferation and IL-2 production are modest in comparison with those of CD28. However, ICOS co-stimulation is equivalent to that mediated by CD28 for the production of effector cytokines IFN- γ , TNF- α , IL-4 and IL-5, and is more effective in enhancing IL-10 production. ICOS has been shown to regulate both Th1- and Th2-mediated immune responses, although it appears to be more important for Th2 development perhaps by its contribution to the total strength of the signal [19, 48, 49]. In a recent study, IL-4 was shown to be critical for the maintenance of high ICOS expression, offering an explanation for the higher expression of ICOS on Th2 cells compared with Th1 cells [50].

With regard to the role of ICOS in the development of asthma manifestations, ICOS^{-/-} mice were susceptible to the influx of inflammatory cells in the BALF induced by airway challenge in primed mice, but serum OVA-specific IgE levels were strongly diminished compared with wild-type mice [51]. In contrast, several blocking studies show an inhibition of airway inflammation but no effect on serum IgE levels [52–54]. In one study, it was demonstrated that the blockade of ICOS during challenge of OVA-sensitized mice inhibited the development of airway hyper-responsiveness [52]. However, we were unable to reproduce this result with either mAb 12A8 or ICOS-Fc (D. T. Deurloo et al., unpublished observation).

The mechanism responsible for the reduced amount of BALF inflammatory cells by ICOS blockade *in vivo* is not due to a lack of T cell priming nor to a defect in Th2 differentiation as determined by unaltered proliferation [53]

and equal [53] or *augmented* Th2 cytokine production [54] upon antigen restimulation *in vitro*. However, Gonzalo et al. [52] found that the blockade of ICOS resulted in reduced mRNA levels for the chemokine receptors CCR3, CCR4 and CCR8 in the lymph nodes. Because these receptors can be found on Th2 cells and the ligands for these receptors are expressed in murine allergic lungs, the authors suggest that blockade of ICOS may hamper the trafficking of Th2 cells and thereby of other inflammatory cells to the lungs.

To date, no studies on the role of ICOS in human asthma have been reported.

Since the unravelling of the human genome, the CD28 and B7 families are rapidly growing (see Table 1), highlighting the molecular complexity of T cell co-stimulation.

The CD40L:CD40 pathway

The CD40 ligand (CD40L; CD154):CD40 pair of counter-receptors (reviewed in [55, 56]) is the best-characterized pathway of T cell co-stimulation of the TNF receptor-ligand families (Table 1).

CD40L is transiently expressed on activated CD4⁺ T cells and interacts with CD40 found on many cell types including APCs and airway [57] and bronchial epithelial cells [58, 59], airway smooth muscle cells [60] and lung fibroblasts [61] in humans. In addition to evidence for direct T cell co-stimulation via CD40L [62], triggering of CD40 contributes indirectly to T cell co-stimulation by up-regulating the expression of B7-1 and B7-2 [63, 64] on APCs, thus amplifying T cell activation through CD28-mediated signalling.

The importance of the CD40L:CD40 pathway in the induction of asthma manifestations has been investigated in mice deficient in either CD40L or CD40 [65–67]. Because ligation of CD40 on B cells, together with IL-4 [68], is critical for their activation and the induction of IgE isotype switching [69], the absence of (allergen-specific) IgE in serum was anticipated and demonstrated in all these studies. However, conflicting results were obtained regarding the involvement of the CD40L:CD40 pathway in the development of airway hyper-responsiveness and BALF eosinophilia [65–67].

The administration of anti-CD40L mAb MR1 during OVA-challenge of sensitized mice prevented the up-regulation of serum OVA-specific IgE levels, thus clearly demonstrating the success of this treatment, but did not alter the degree of OVA-induced airway hyper-responsiveness *in vivo* and BALF eosinophilia (D. T. Deurloo et al., unpublished observations). Recently, another research group obtained similar results with the same anti-CD40L mAb in a murine model of allergic asthma when administered during either OVA-sensitization or challenge [70].

Interestingly, stimulation of CD40 by an agonistic mAb markedly reduced airway eosinophilia and airway hyper-responsiveness when administered during either sensitization or challenge [70]. In keeping with these findings, CD40^{-/-} mice backcrossed with mice transgenic (Tg) for an OVA-TCR demonstrated an enhancement of these manifestations upon OVA challenge [71]. Triggering of CD40 on APCs induces the production of IL-12, a Th1 skewing factor [55, 56]. Both studies observed a correlation between CD40 deficiency/stimulation and IL-12; IL-12 levels were decreased in the BALF of the CD40^{-/-}/OVA-TCR Tg mice [71] and elevated in the

bronchi and serum of wild-type mice treated with the agonistic mAb [70]. However, anti-CD40 mAb was also effective in OVA-sensitized and challenged IL-12^{-/-} mice, suggesting that its beneficial effects in this model are at least in part independent of IL-12 [70]. Clearly, further studies *in vivo* are required to elucidate the role of the CD40L:CD40 pathway in the development of asthmatic phenomena.

Interestingly, alveolar macrophages (AMs) from atopic asthmatics demonstrated a significantly lower expression of CD40 compared with atopic non-asthmatics [72]. In both atopic groups, the addition of a blocking CD40 antibody to a co-culture of peripheral CD4⁺ T cells and AMs increased allergen-stimulated T cell IL-5 production, whereas IL-12 production by the AMs was inhibited. The addition of neutralizing mAbs to CD40L or CD40 did not have any effect on cytokine levels produced by asthmatic tissue or PBMCs (containing, however, more cell types than AMs).

The OX40:OX40L pathway

Signalling through OX40 (CD134) has been suggested to act late in the primary response after CD28 signals, in allowing effector T cells (either Th1 or Th2) to survive and continue proliferating, predominantly by the induction of anti-apoptotic factors. Consequently, OX40 regulates the number of memory CD4⁺ T cells that persist over time (reviewed in [73]).

Features of allergic airway sensitization and Th2 cytokine production are impaired in OX40^{-/-} mice [74] and OX40L^{-/-} mice [75, 76]. A blocking OX40L mAb abolished airway manifestations when administered during OVA sensitization – but not during challenge – of wild-type mice [75]. In contrast, using another mouse strain, the administration of the same antibody during the challenge phase of a fairly similar asthma model was demonstrated to reduce asthma manifestations strongly [77].

Role of T cell co-stimulatory molecules in ongoing or reoccurring Th2-dominated allergic inflammatory responses

In contrast with animal studies in which the role of T cell co-stimulatory molecules in the development of Th2-mediated asthma manifestations is examined, asthmatic patients start therapy after the development of airway symptoms, while exposure to environmental allergen mostly continues.

The CD28/CTLA4:B7-1/B7-2 pathway

Notably, studies *in vitro* have demonstrated that antigen-experienced T cells are less dependent on CD28-mediated co-stimulation in comparison with naïve T cells [78–80], whereas studies *in vivo* on the effectiveness of giving CTLA4-Ig after priming of immune responses have yielded conflicting results [81].

Recently, we investigated whether CTLA4-IgG can reverse established asthma manifestations in a novel murine model of ongoing disease, in which therapy starts after the development of Th2-dominated allergic inflammatory responses while OVA exposures are continued. In OVA-sensitized mice,

airway manifestations were induced by a first series of aerosol challenges. CTLA4-IgG was then administered followed directly by a second series of aerosols. In this ongoing murine model of allergic asthma, CTLA4-IgG appeared to have limited effectivity; airway eosinophilia and OVA-specific IgE levels could only be partially inhibited and airway hyper-responsiveness was unaffected [82].

Possibly, CTLA4-IgG inhibited established airway manifestations because newly recruited or resident naïve CD4⁺ T cells contribute to ongoing disease. Additionally, CTLA4-IgG may have inhibited antigen-experienced OVA-specific T cells to some extent in this model. In support of this latter possibility, allergen-induced proliferation and IL-5 and IL-13 production by resident T cells in bronchial tissue derived from mild atopic asthmatics were inhibited by both anti-B7-1 and anti-B7-2 mAbs [38, 83]. In addition, anti-B7-2 mAb was shown to inhibit allergen-induced proliferation of BALF T cells from atopic subjects [37]. However, whereas proliferation and Th2 cytokine production by PBMCs from atopic asthmatics is sensitive to blockade by anti-B7-2 mAb [36–39], recently activated PBMCs from the same subjects and antigen-specific T cell clones are not [36, 84].

The ICOS:B7RP-1 pathway

In the ongoing murine model of allergic asthma, antigen-experienced OVA-specific T cells predominate over newly recruited or resident naïve OVA-specific T cells at the time of intervention. Co-stimulatory molecules other than CD28 may (also) regulate these antigen-experienced T cells.

As mentioned above, the expression pattern of ICOS suggests that co-stimulation by this molecule might not only contribute to the sustenance of a primary response but also to the activation of antigen-experienced T cells. Moreover, in contrast with B7-1 and B7-2, which are expressed almost exclusively on professional APCs, B7RP-1 is expressed on both lymphoid and non-lymphoid cells [15, 16, 85], including human airway epithelial cells [86]. This might indicate a physiological role of B7RP-1 in the reactivation of memory and effector T cells in the periphery.

As discussed previously, the inhibition of airway inflammation by ICOS blockade during antigen sensitization and/or challenge of mice [52–54] was not accompanied by a defect in Th2 differentiation [53, 54], suggesting that ICOS has a role in the function of effector T cells. Interestingly, studies in murine models of allergic asthma in which effector Th2 cells dominate at the time of ICOS blockade were very successful in reducing manifestations of asthma [52, 87]. ICOS blockade during antigen challenge reduced lung inflammation and non-specific airway hyper-responsiveness following adoptive transfer of highly polarized OVA-TCR Tg Th2 effector populations to naïve mice [87]. Conversely, it was recently demonstrated that the ICOS⁺ fraction of effector OVA-TCR Tg T cells could induce airway inflammation in wild-type BALB/c mice upon OVA aerosol challenge, whereas the ICOS[−] fraction could not [88]. The administration of mAb 12A8 against ICOS solely during the last (seventh) aerosol challenge of OVA-sensitized mice significantly reduced the amount of BALF inflammatory cells and airway hyper-responsiveness, whereas ICOS blockade only at the time of

sensitization had little effect upon subsequent airway challenge [52].

Therefore, we examined the effects of ICOS blockade by ICOS-Fc in the ongoing murine model of allergic asthma. Surprisingly, in the ongoing model, the administration of ICOS-Fc had no effect on any of the final asthma manifestations. Likewise, OVA restimulation of primed lung T cells in the presence of ICOS-Fc did not affect their IL-5 production *ex vivo* (D. T. Deurloo et al., unpublished observations). Similarly, in mice in which airway inflammation was first allowed to be resolved before the second series of aerosols and administration of anti-ICOS mAb 12A8 4 weeks later, airway inflammation and serum OVA-IgE levels were unaltered [54]. Future studies may clarify the discrepant results of the various studies.

The OX40:OX40L pathway

In the experiment of Salek-Ardakani et al. [77] mice were rested for 13 weeks upon OVA-induced asthma manifestations before they received a second series of OVA aerosols together with a blocking OX40L mAb. Interestingly, the administration of an anti-OX40L mAb successfully reduced airway inflammation, suggesting that OX40 is not only important for the survival of effector CD4⁺ T cells during a primary challenge phase (see above) but also during a secondary challenge period.

Long-term effects of blockade of T cell co-stimulatory molecules

Studies *in vitro* have demonstrated that antigen binding to the TCR in the absence of co-stimulation not only fails to activate the cell but it also leads to a state of hypo-responsiveness to antigenic restimulation in the presence of co-stimulation, called anergy [10, 11]. *In vivo*, the blockade of T cell co-stimulation was shown to induce long-lasting unresponsiveness in several transplantation models [89] and in a Th2-mediated contact hypersensitivity model [90]. Short-lived treatment of asthma patients that induces tolerance to the inhalant allergen might release patients from regular intake of medicine and also, more importantly, the increased risk for infections and cancer due to continuous antigen-specific T cell suppression would be avoided. A number of studies *in vitro* and *in vivo* on the induction of antigen-specific tolerance have demonstrated that interruption of both the CD28/CTLA4:B7-1/B7-2 and the CD40L:CD40 pathway is more effective than the blockade of either pathway alone [90–93]. Therefore, the long-term effects of administration of anti-CD40L mAb MR1, CTLA4-IgG or the combination of these treatments during the aerosol challenge period of antigen-sensitized mice were investigated by rechallenge of mice 11 weeks after this challenge period, after serum clearance of experimental treatments.

In mice that had earlier received CTLA4-IgG, airway eosinophilia and OVA-specific IgE were inhibited upon rechallenge compared with control-treated mice (Fig. 1, D. T. Deurloo et al., unpublished observations). In contrast, anti-CD40L mAb had no long-term effect by itself. Moreover, in combination with CTLA4-IgG, anti-CD40L mAb

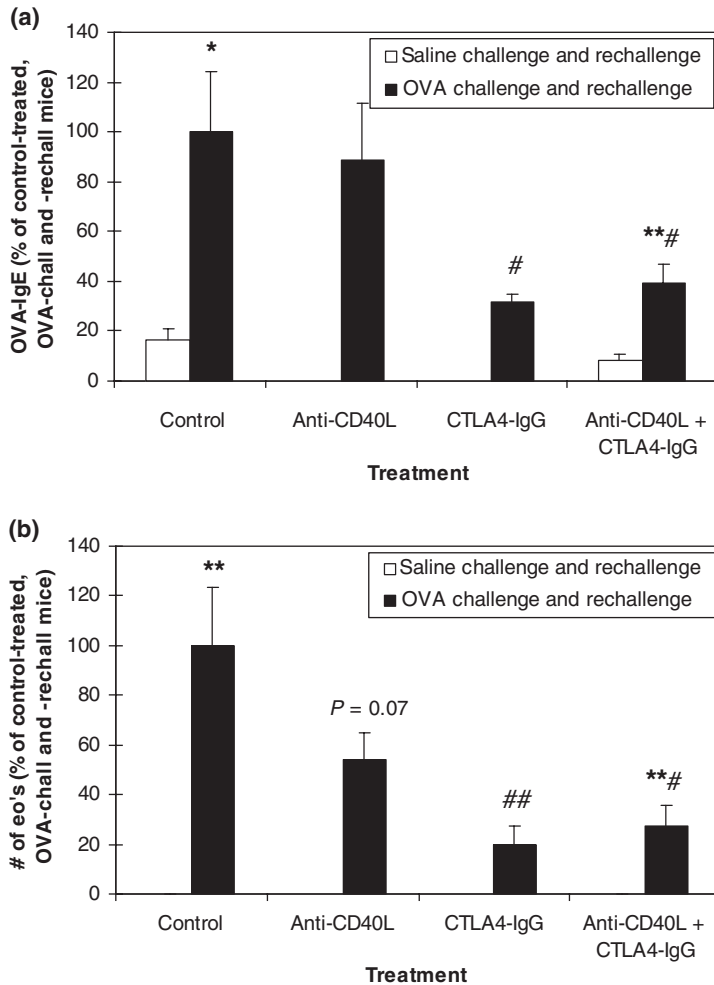


Fig. 1. Long-term effects of T cell co-stimulatory blockade-BALB/c mice were sensitized to ovalbumin (OVA) without adjuvant and challenged with eight saline aerosols or eight OVA aerosols. Shortly before the first aerosol challenge, mice received control treatment, anti-CD40L mAb, CTLA4-IgG or the combination of anti-CD40L mAb and CTLA4-IgG. Eleven weeks later, after serum clearance of experimental treatments, saline-challenged mice were rechallenged with eight saline aerosols (open bars; $n = 6$ per group) and OVA-challenged mice were rechallenged with eight OVA aerosols (closed bars; $n = 5-6$ per group). OVA-specific IgE in the sera (a) and the number of eosinophils in the BALF (b) were determined at 24 h after the last aerosol rechallenge. Values are expressed as mean $\pm$ standard error of the mean. * $P < 0.01$ and ** $P < 0.005$, as compared with saline-challenged and -rechallenged animals of the same treatment group. # $P < 0.05$ and ## $P < 0.01$, as compared with control-treated, OVA-challenged and -rechallenged animals. eo's, eosinophils; chall, challenged; rechall, rechallenged.

did not augment the CTLA4-IgG-mediated inhibition of asthma manifestations after OVA challenge nor rechallenge. Similarly, treatment of OVA-sensitized mice with anti-ICOS mAb 12A8 alone or in combination with CTLA4-Ig during the challenge period had no long-term effect by itself or added to the effects by CTLA4-IgG (D. T. Deurloo, unpublished observations). In the earlier cited study of Wiley et al. [54], in which ICOS was blocked during sensitization of mice, the significantly *augmented* OVA-stimulated Th2 cytokine production by splenocytes immediately after challenge correlated with elevated airway inflammation and serum OVA-IgE levels upon OVA rechallenge of mice 4 weeks later.

T cell co-stimulatory molecules and regulatory T cells

Interestingly, in the recent years T cell co-stimulatory receptors have also been found on the surface of the so-called regulatory T cells, subsets of lymphocytes that can inhibit harmful T cell responses directed against foreign and self-antigens (reviewed in [94–99]). The $CD4^+CD25^+$ class of 'naturally occurring' regulatory T cells constitutes 5–10% of peripheral $CD4^+$ T cells in mice and humans. The removal of these cells leads to the spontaneous development of various auto-immune diseases in otherwise normal mice [100],

demonstrating that these cells provide an additional mechanism for peripheral tolerance besides T cell anergy. The suppressive action of these $CD4^+CD25^+$ cells might be mediated by both suppressor cytokines – such as IL-10 and TGF- β – and cell-contact-dependent mechanisms.

CD28 has been shown to control the development and maintenance of $CD4^+CD25^+$ T cells [101], possibly by stimulating the expression of anti-apoptotic proteins or the production of autocrine growth and survival factors [98, 102]. However, CD28 co-stimulation is not required for the suppressive function of $CD4^+CD25^+$ regulatory T cells and might even abolish their suppressive capabilities (see [14]). $CD4^+CD25^+$ regulatory T cells also constitutively express CTLA4 on their surface [103]. However, the potential functional role of CTLA4 in $CD4^+CD25^+$ T cell function remains controversial.

In two variants of the murine asthma model, $CD4^+CD25^+$ T cells have been shown to either enhance [104] or inhibit [105] Th2 cell-mediated allergic inflammation in the airways. In human peripheral blood, the presence of $CD4^+CD25^+$ T cells was recently shown in the majority of atopic patients with allergic rhinitis that were able to suppress both Th1 and Th2 cytokine production [106].

Other types of regulatory T cells can be induced from conventional $CD4^+$ T cells [94, 96, 99, 107]. For example,

intranasal exposure to OVA has been shown to result in the induction of CD4⁺ regulatory T cells – producing primarily IL-10 and low levels of IL-4 – that inhibited the development of asthma manifestations upon subsequent rechallenge of mice with OVA [108, 109]. Interestingly, both the development and inhibitory function of CD4⁺ regulatory T cells were shown to be dependent on ICOS signalling, which had previously been shown to induce strong IL-10 production [109].

One of the explanations for the usage of co-stimulatory receptors by both T helper and T regulatory cells is that the level of ligand expression in the periphery determines which cell type will be activated [98, 102, 110, 111]. Although the role of the various regulatory T cells in murine models of allergic asthma warrants further research, it should be kept in mind that blockade of T cell co-stimulatory molecules might not only affect (the development of) Th2 cells but also these regulatory T cells.

Conclusions

Blockade of T cell co-stimulation, especially the CD28:B7 pathway, has been demonstrated to be very successful in preventing the development of features of allergic airway sensitization in mice. However, in clinically more relevant models of ongoing and reoccurring disease this intervention was shown to be insufficient to ameliorate airway manifestations. Perhaps, the blockade of the newly (to be) discovered members of the expanding families of T cell co-stimulatory molecules – alone or in combination with known members – might effectively inhibit antigen-experienced allergen-specific T cell. In addition, these new members may have a role in tolerance induction. Lastly, more detailed knowledge of the role of the various regulatory T cells in allergic asthma and their regulation by co-stimulatory molecules might provide an interesting strategy for the treatment of allergic diseases.

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