

EDITORIAL

Clinical & Experimental Allergy

As strong as an OX or as weak as a kitten?

This editorial discusses the findings of the paper in this issue by G. M. Gauvreau et al. [18], pp. 29–37.

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Current asthma therapies in children and adults improve symptoms and reduce future risk of exacerbations [1, 2]. None are truly disease modifying whereby they alter disease onset or after treatment cessation change the natural history of the underlying disease. Indeed, studies in children have failed to demonstrate that early use of corticosteroids alters disease progression [2]. Therefore, disease modifying therapies remain a goal for asthma.

Atopic asthma is classically associated with increased expression of T-helper 2 (Th2) cytokines, which are elevated in sputum [3], and bronchial biopsies [4]. A major effector axis resulting in induction of Th2 polarization is the recognition of allergen presented by dendritic cells in local lymph nodes to CD4⁺ T cell. This differentiation of naive T cells or reactivation of memory T cells depends on various costimulatory molecules primarily expressed on the surface of T cell and their cognate ligands. The OX40 receptor is preferentially expressed by T cells, and its cognate ligand OX40L is primarily expressed by antigen-presenting cells such as dendritic cells following activation by thymic stromal lymphopoietin (TSLP) [5–7]. TSLP is released by the bronchial epithelium, airway smooth muscle and some inflammatory cells in response to numerous insults such as allergen, viruses and physical damage [8–13]. OX40L plays a sentinel role in the adaptive immune response by promoting T-helper 2 (Th2) polarization of naive T cells within the lymph

node. These polarized T cells produce Th2 cytokines such as IL-4, IL-5 and IL-13. Therefore, this axis is a potential target for drug development because it orchestrates inflammation and development of an allergen-specific humoral response and the development of T and B cell memory. This approach thus presents an attractive possibility of altering the course of disease at its onset as well as modifying its progression.

Animal models have positioned both TSLP and the OX40/OX40L as critical in the development of airway inflammation and hyperresponsiveness [14–16]. In asthma studies, OX40^{-/-} and OX40L^{-/-} mice compared with wild-type mice challenged with ovalbumin showed significantly reduced Th2 response, lung inflammation, mucus secretion and marked reduction in eosinophilic inflammation, decreased goblet cell hyperplasia, and attenuated airway hyperresponsiveness. Likewise, inhibition of OX40-OX40L binding via administration of anti-OX40L mAb in wild-type mice dramatically reduced airway hyperresponsiveness compared with controls.

In human disease, there is good evidence that TSLP is up-regulated in asthma [11–13], but there is limited and conflicting data to demonstrate over-expression of OX40 or OX40L in disease [13, 17]. OX40/OX40L expression is increased in the bronchial submucosa of mild asthmatics [17], but not in moderate to severe disease [13, 17], and this was related to the degree of tissue eosinophilia and IL-4 expression.

Gauvreau and colleagues report in this edition of *Clinical & Experimental Allergy* the first human allergen challenge study to investigate the effects of OX40L blockade in mild allergic asthmatics [18]. The authors found that there was no effect upon early or late response, but OX40L blockade did result in a small reduction in total IgE and had an anti-inflammatory effect upon eosinophilic inflammation. The lack of an effect on the early or late response is disappointing, but is reminiscent of poor effects upon allergen chal-

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lenge of other antieosinophilic approaches such as anti-IL5. A number of anti-Th2 approaches are now in late-phase development including anti-IL5, anti-IL13 and anti-CRTh2 [19], and emerging evidence suggests that anti-IgE is most effective in those with eosinophilic inflammation and leads to reductions in both tissue and sputum eosinophilia. A number of antieosinophilic therapeutic strategies beyond corticosteroids are thus going to be available in the clinic. The effects described here upon eosinophilic inflammation were modest when taking into account baseline differences between the groups, and therefore, it is difficult to argue from these data that OX40L presents a profound advance in ameliorating eosinophilic inflammation. Is this end or the beginning of an OX40L blockade strategy for asthma? As with any early drug development, the study raises a number of questions such as was the duration of therapy sufficient? Is the monoclonal antibody sufficiently potent and effective? Was the best patient group selected and was the best outcome measure assessed? The effect upon eosinophilic inflammation does suggest the therapy engaged pharmacology and whether a longer duration of therapy would have been more effective remains unknown. The study focused upon mild asthma, which is appropriate for an early-phase challenge study, but whether greater effects would have been observed in more severe disease, the likeliest potential market for biological therapies or indeed a specific phenotype [20] is unknown. The effect upon eosinophilic inflammation also suggests that OX40L blockade might reduce the risk of eosinophilic driven exacerbations as observed

with anti-IL5. An impact upon exacerbation frequency would also present a clinically important effect irrespective of the lack of efficacy upon the early or late responses to allergen. What is perhaps more tantalizing is the potential that modulating the OX40/OX40L axis will affect allergic sensitization and could be disease modifying. Although this would indeed present a new therapeutic paradigm testing such a concept is not yet testable as it would require introducing therapy before or immediately at the onset of disease. Without good predictors of either disease onset or its future severity, this approach is not feasible. TSLP in addition to activating the OX40/OX40L axis and promoting allergic sensitization is intimately involved in innate immune responses. Its broader action suggests that it might be a more attractive target for asthma therapy and could have impacts beyond Th2 inflammation. Interventional studies of TSLP in asthma are underway and may help to further position the role of TSLP and the OX40/OX40L axis in asthma.

Therefore, targeting the OX40/OX40L or TSLP axis remains an exciting opportunity that may provide a step change in the treatment for asthma. Its fate will become apparent over the forthcoming years as further clinical data begins to emerge. Although the story thus far does not support the view that OX40L blockade will be as 'strong as an ox' in combating asthma, but to dismiss its role at this stage would be premature.

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