

EDITORIAL

Allergen isoforms for immunotherapy: diversity, degeneracy and promiscuity

Specificity for antigen is the hallmark of adaptive immunity and is conferred by cells of the lymphocyte lineage. Aberrant immune responses lead to disease in an antigen-specific fashion. In order to avoid the generalized immunosuppressive effects of treatments such as corticosteroids and cyclosporin, efforts have been increasingly focused on devising therapeutic strategies which are equal in specificity to the disease-initiating event.

In the early 1980s Lamb and colleagues demonstrated the induction of antigen-specific non-responsiveness following challenge of purified T-cell clones with high doses of specific peptide [1]. The concept of high dose peptide antigen for immunotherapy is attractive, particularly in the context of allergic diseases where conventional desensitizing therapy has been confounded by the presence of anaphylactogenic immunoglobulin (Ig) E antibodies.

Peptide-induced tolerance has been demonstrated in a number of animal models of disease such as experimental autoimmune encephalomyelitis (EAE) [2,3], collagen-induced arthritis [4,5], diabetes [6] and more recently, in models of allergic disease. Briner and colleagues sensitized mice to the cat allergen Fel d 1 and subsequently demonstrated the ability of allergen-derived peptides to downregulate T-cell cytokine and antibody production [7]. Hoyne and colleagues demonstrated the ability of peptides from the house dust mite allergen Der p 2 to downregulate T-cell and antibody responses to challenge with intact protein and also to prevent sensitization by prior administration [8].

More recently, attempts have been made to translate findings in animal systems into viable therapies for human disease. Norman and colleagues evaluated the ability of two peptides from Fel d 1 to downregulate allergic responses to cat in 95 sensitized individuals in a double-blind placebo-controlled trial [9]. Efficacy was demonstrated but fell below expected levels resulting in cessation of the programme.

More recently, the pendulum of future therapy for allergic diseases has swung in favour of production of recombinant allergens [10]. In particular, interest has focused on allergen isoforms and their genetically modified counterparts [11–14]. These molecules display reduced IgE binding whilst retaining T-cell epitopes and thus hold promise for safe desensitizing allergen immunotherapy. However, despite the current interest in recombinant allergen and isoform-based therapy, the immunology underlying responses to these proteins, particularly within the context of natural environmental exposure, is complex.

In the current issue of the Journal, Würtzen and colleagues [15] have investigated the epitope specificity of T-cell lines and clones reactive with the group 5 grass allergen of *Phleum pratense*. Phl p 5 has two major isoforms which share regions of profound sequence homology but also differ considerably in some areas. Within the disparate regions of the two isoforms, Würtzen and colleagues have identified isoform-specific T-cell epitopes.

The significance of this finding should be placed in the context of the large numbers of allergen proteins which have multiple isoforms. These appear particularly to be derived from plant species and are less common among animal dander and mite allergens. The authors suggest that since modulation of the specific T-cell response appears to be pivotal in successful immunotherapy, recombinant and/or isoform-based whole allergen immunotherapy will need to take such diversity into account. Unlike animal models, the human population is heterogeneous in terms of major histocompatibility complex (MHC) expression. Since the expressed MHC alleles dictate which sequences will be T-cell epitopes, the numbers of potential epitopes within a single allergen molecule is very large. Ultimately, the numbers of isoforms required for a single therapeutic preparation to be efficacious at the population level, may make this approach impractical. The same argument is brought to bear on the potential of allergen-derived peptide sequences for therapy of allergic disease mediated by allergens with multiple isoforms.

Whilst these arguments are compelling there are, at least conceptually, counter-arguments which can be applied based on some recent observations about the way in which T-cell receptors and MHC molecules interact with peptides and also the way in which tolerance induced by a region of a molecule, can effect tolerance to the entire molecule.

The binding of peptide sequences to MHC molecules is dependent upon peptide sequence and charge, and the shape of the peptide-binding groove. Individual MHC molecules clearly have the capacity to bind large numbers of different peptide sequences [16]. Equally, certain peptide sequences have the capacity to bind almost universally to MHC molecules [17]. It follows therefore that many antigen-derived peptides recognized by T cells can bind to more than one MHC molecule and are thus 'promiscuous' in this regard.

Moreover, whilst some peptides bind promiscuously to MHC molecules, it has been demonstrated that T-cell

receptors are capable of recognizing a large number of peptides in the context of multiple MHC molecules [18]. The T cell receptor may therefore be considered to be 'degenerate' in its recognition in this regard.

By measuring binding affinities *in vitro*, Sette and Sidney have recently proposed the existence of MHC 'supertypes' which are groups of MHC molecules capable of binding certain promiscuous peptides [19]. Thus peptides which bind to HLA DRB1*0101 will often be capable of also binding DRB1*0401 and 0701 [20]. Indeed data from our own work with Fel d 1 has demonstrated the presence of promiscuous Fel d 1 peptides together with degenerate T-cell recognition of individual peptides in the context of more than one MHC molecule [21].

From these observations we can deduce that in many allergen sequences there will be peptides which will be capable of binding to multiple MHC molecules and thus being presented to the immune systems of a substantial proportion of the population. Indeed, Sette and Sidney identified peptides capable of binding to extended MHC supertypes which would cover around 95% of the population. Clearly, if these peptides are derived from regions of homology between isoforms, the identification of isoform-specific epitopes may present less of an obstacle to therapy.

In addition to the concepts of supertypes, promiscuity and degeneracy in T-cell peptide interactions, Davies and colleagues have described a phenomenon termed 'linked suppression' [22]. Linked suppression is an elegant immunological trick whereby non-responsiveness induced to one epitope of a molecule can confer tolerance to the whole molecule, providing the latter is subsequently presented to the relevant T cells on the same or adjacent antigen-presenting cells. The phenomenon of linked suppression has recently been demonstrated in murine responses to house dust mite allergens by Hoyne and colleagues [23]. Furthermore, in certain systems, particularly those in which tolerance is maintained by regulatory T cells, tolerance can be passed from one generation of regulatory cell to the next, a process referred to as 'infectious tolerance' [24]. The implication therefore is that individual epitopes derived from conserved regions of an allergen protein may be sufficient in number, and promiscuous enough in binding specificity, to confer tolerance to the whole molecule (and related isoforms) in a large percentage of the population. At least conceptually.

References

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