letters

A clustered subset of MHC class II molecules

We have read with great interest the recent *Comment* by Tobes *et al.*[1] concerning major histocompatibility complex (MHC) class II 'dimers of dimers' (tetramers, superdimers). The existence of such structures, which could be of essential importance for effective T-cell activation and/or class II-mediated signal transduction in antigen-presenting cells (APCs), has been recently demonstrated[2]. Furthermore, a subset of MHC class II molecules is found in multicomponent complexes containing several tetraspan family proteins (CD37, CD53, CD81, CD82)[3,4]. Interestingly, the class II molecules present in these complexes appear to be clustered[4] and are specifically recognized by monoclonal antibodies (mAbs) to a determinant called CDw78. The CDw78 mAbs bind with low affinity to conventional MHC class II molecules (αβ heterodimers) but with relatively high avidity to the clustered subset present in the tetraspan complexes (K. Drbal, unpublished). This clustered minor subset of class II, in contrast to the unclustered majority, easily caps, becomes associated with cytoskeleton upon ligation with CDw78 mAbs, and is capable of signal transduction[5].

We propose that the clustered subset of MHC class II present in the tetraspan complexes and specifically reactive with CDw78 mAbs may be identical to the pre-formed MHC class II superdimers (tetramers). Simultaneous occupancy of the peptide binding sites by identical peptides in these superdimers/aggregates might not be so unlikely – these structures are probably already formed during intracellular biosynthesis, which is known to involve initial formation of trimers of MHC class II molecules[6]. The oligomeric class II molecules may be exposed to high concentrations of relatively few peptides in a particular vesicle of the peptide-loading compartment of the APCs; therefore the likelihood of simultaneous binding of the same peptide to the class II molecules in the complex may be quite high. Consequently, it may not be necessary to rely on an unlikely chance diffusion-based encounter of two MHC molecules carrying identical peptides on the cell surface to form a functional antigen-presenting superdimer.

In conclusion, we believe that the clustered subset of MHC class II molecules specifically targeted by the CDw78 mAbs and stabilized by interactions with tetraspan proteins may have unique antigen-presenting and signalling properties.

Václav Horejsí
Karel Drbal
Pavla Angelisová
Institute of Molecular Genetics,
Academy of Sciences of the Czech Republic,
142 20 Praha 4,
Vídenská 1083,
Czech Republic.

References

1 Tobes, R., Pareja, E., Nieto, A. and Martín, J. (1998) *Immunol. Today* 19, 192–193
2 Cherry, R.S., Wilson, K.M., Triantafilou, K. *et al.* (1998) *J. Cell Biol.* 140, 71–79
3 Angelisová, P., Hilgert, I. and Horejsí, V. (1994) *Immunogenetis* 39, 249–256
4 Szöllosi, J., Horejsí, V., Bene, L., Angelisová, P. and Damjanovich, S. (1996) *J. Immunol.* 157, 2939–2946
5 Rasmussen, A-M., Horejsí, V., Levy, F.O. *et al.* (1997) *Eur. J. Immunol.* 27, 3206–3213
6 Marks, M.S., Germain, R.N. and Bonifacino, J.S. (1995) *J. Biol. Chem.* 270, 10475–10481

Oral bacteriotherapy

In a recent article in *Immunology Today*, Strobel and Mowat suggest that digestive endogenous microflora influence the induction of oral tolerance[1]. This hypothesis appears to be reasonable as the endogenous commensal microflora has a crucial role in maintaining the integrity of the gut mucosal barrier and finely tuning the T helper 1 (Th1)/Th2 balance[2].

The presence of gut flora may affect the induction of oral tolerance[3] and allow recovery of tolerance to food antigens following gut infections[4]. Processing of proteins by endogenous microflora leads to lymphocyte hyporesponsiveness to food antigens[5] and a recent study has shown that there is a state of tolerance in normal rats that fails to develop in animals reared in the germ-free state[6]. Taken together, these observations suggest that intestinal bacteria can be beneficial in the downregulation of hypersensitivity reactions to ingested foods and reinforce the view that the maintenance of the normal ecology within endogenous digestive microflora is a crucial protective factor against allergy.

The metabolic and immunoregulating properties of endogenous digestive microflora can be altered substantially by many factors, such as the decreased frequency of breast-feeding, consumption of processed foods, substitution of artificial sweeteners for sugar, and intermittent exposure to antibiotics. It is conceivable that these factors, together with largely Th2-inducing vaccination regimens and the reduced rate of Th1-inducing childhood infections, could contribute to the increasing prevalence of allergic diseases in the Western world.

There is increasing use of probiotics and prebiotics (i.e. dietary additives that encourage the selective growth of beneficial organisms in the intestinal tract) in the general population and among allergic individuals. In addition, there is some evidence that the manipulation of endogenous digestive microflora through oral bacteriotherapy (i.e. the administration of 'probiotic' bacteria) may be of value in the treatment of allergy. For example, oral administration of probiotic bacteria has been shown to reduce intestinal inflammation in individuals allergic to cow's milk[7], to promote local IgA production[8], and to stabilize intestinal integrity[9]. Interestingly, *Lactobacillus GG*-hydrolysed casein has been shown to reduce interleukin 4 production in atopic infants with challenge-proven cow's milk allergy[10]. More importantly, probiotic bacteria, such as *Lactobacillus delbrueckii* ssp. *bulgaricus*, *Streptococcus salivarius* ssp. *thermophilus* and *Lactobacillus GG* strongly enhance the production of Th1-type cytokines[2] suggesting that the administration of highly enriched preparations of these bacteria could impact on the altered Th1/Th2 balance of allergic subjects.

In our opinion, the potential of oral bacteriotherapy to prevent and/or treat the clinical manifestations of allergy should be researched both *in vitro* and in formal clinical trials, though to date, the investigation of the claimed benefits of oral bacteriotherapy has been frequently regarded as trivial by immunologists. We believe that it is now time for