Cooperation or sabotage? Self-peptide–MHC complexes influence T-cell responses to antigens

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In their Opinion, Ge et al. [1] reviewed some recent published data on the role of self-peptide–MHC complexes in the modulation of immune responses to antigens. The authors suggest that some ‘inconsistencies’ in published findings could be attributed to potential aberrant expression of unusual MHC class II molecules (composed of Aβ and Eε chains) in MHC class II-deficient mice used by Bhandoola et al. [2]. Without debating whether the unusual MHC class II molecules were indeed expressed in the mice used in this particular study, we would like to point out that even aberrant MHC class II expression would not explain all ‘inconsistent findings’ in the field. Depending on the experimental model used, self-peptide–MHC complexes enhance [3], reduce [2,4,5] or exert no influence [6] on the responsiveness of T cells to cognate antigen. It is striking that distinct effects of self-peptide–MHC complexes were observed even when identical T-cell receptor (TCR) transgenic mice were used [3,5]. Thus, neither aberrant expression of MHC class II molecules nor the identity of the TCR can explain these discrepancies.

Identification of self-peptides and testing of their in vitro functional potential has revealed that they can act as antagonists [7,8] or weak agonists [9,10] for a given TCR. Whether a particular peptide will exhibit inhibitory function in vivo will depend on its potency (defined by relative concentrations of antagonist and agonist peptides required to observe inhibitory effects) and abundance. We have demonstrated that H-2Dβ (MHC class I allele that presents one of the antagonist self-peptides) gene dosage inversely correlates with the ability of T cells to respond to cognate antigen [4]. These findings suggest that self-peptide functionally characterized as an antagonist in vitro could also be acting in vivo to suppress the activity of T cells to antigen. There are reasons to believe that this example of in vivo antagonism might not be an isolated event [11]. Based on these findings we suggest that for each foreign antigen there might be self-peptides that can exert antagonist and/or weak agonist activity. The net result of their activities would determine the direction of their influence, which would be different for each foreign antigen. In addition, owing to differential gene expression, distinct cell types might lack some of the antagonist and/or weak agonist self-peptides. This could create a possibility that the net activity of self-peptides is different in distinct cell types. This, in turn, could explain disparate findings in experiments that used the same TCR transgenic mouse strain [3,5]. Thus, positive and negative effects of self-peptides on the strength of immune responses to cognate antigens observed in previous studies could be explained by cell type-dependent and TCR-specific events that balance the mutually opposing effects of self-peptides with antagonist and weak agonist activities.

References