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Autoreactivity of T cells selected by a single MHC/peptide ligand

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Keywords

Autoreactivity, T cell, thymus

Context

T cell development in the thymus is characterised by positive and negative selection. These processes contribute to the development of a peripheral repertoire of T cells best suited to the recognition of foreign peptides in the context of self-major histocompatability complex (MHC) molecules. Recent work has focused on the contribution a single MHC/peptide complex makes to the selection of the mature repertoire. Mouse strains have been developed that express MHC class II molecules loaded with a single peptide species. The peripheral $CD4^+$ T cell repertoire in these mice is diverse, although total numbers of $CD4^+$ T cells are reduced by up to 80%, reflecting limited positive selection. Negative selection of $CD4^+$ T cells recognising a wide array of self-peptides does not occur and so, as expected, the $CD4^+$ T cells are able to recognise self-MHC molecules expressing self-peptides. Detailed analyses of the function of these cells has not previously been reported. To investigate the function of $CD4^+$ T cells selected by a single ligand in the thymus.

Significant findings

In vitro responses: $CD4^+$ T cells from H2-M^- mice proliferated equally well in response to stimulation with syngeneic (B6) and allogeneic (bm12) APCs. However, detailed analysis revealed qualitative differences between the responses. The H2-M^- $CD4^+$ T cells secreted less interleukin (IL)-2, IL-4 and interferon (IFN)-? but comparable amounts of IL-3 in response to syngeneic APCs compared with allogeneic APCs. The responses to syngeneic APCs were more easily blocked by monoclonal antibodies to class II, CD4 and T cell receptor (TCR) molecules than were the responses to allogeneic APCs. This suggests that the affinity/avidity of the H2-M^- $CD4^+$ T cells for the syngeneic APCs is less than for the allogeneic APCs.

In vivo responses: the *in vivo* response of H2-M^- $CD4^+$ T cells to syngeneic (B6) versus allogeneic (bm12) APCs was analysed in three different models of graft versus host disease (GVHD). In two of the

models (the Simonsen assay and the induction of bone marrow aplasia) the H2-M$^-$ CD4$^+$ T cells induced disease in both syngeneic and allogeneic hosts. In the third model (lethal GVHD from gut damage) the H2-M$^-$ CD4$^+$ T cells induced disease only in the allogeneic host. Likewise H2-M$^-$.N2 mice (H2-M$^-$ mice, H2b [B6 - 129]F_2 backcrossed twice to B6) CD4$^+$ T cells were able to mediate rejection of allogeneic but not syngeneic skin grafts. Rejection of the allogeneic grafts was CD4$^+$ T cell dependent, with little contribution from the CD8$^+$ T cells.

Comments

Initial studies of the function of CD4+ T cells selected in the thymus by a single ligand suggested that these T cells were polyclonal and were both autoreactive and alloreactive. The autoreactivity was an expected consequence of lack of expression of a wide array of self-peptides by class II molecules in the single-ligand mice, and hence a deficiency in negative selection of autoreactive cells in these animals. The surprising finding in this study is that the autoreactivity is controlled by low-affinity T cells. The reasons for the curtailment of autoreactivity in the single-ligand mice remain unclear but are likely to relate to aberrant positive or negative selection by a high concentration of a single ligand. The consequence is the important and unexpected functional differences between autoreactivity and alloreactivity in these animals.

Selection pressures on the autoreactive T cells generated in this model are, however, likely to be very different from those which exist in the human thymus and the extent to which these results are relevant to autoimmunedisease in general is therefore unclear.

Methods

H2-M deficient (H2-M$^-$) mice on a C57BL/6 (B6, H2b) background were generated. Since H2-M catalyses both the release of the class II invariant chain peptide (CLIP) from newly-synthesised MHC class II molecules as well as subsequent peptide editing, the H2-M$^-$ mice expressed MHC class II (H2-Ab) molecules loaded almost exclusively with the class II invariant chain peptide (CLIP). The ability of the H2-M$^-$ CD4$^+$ T cells to respond to syngeneic (self B6) and allogeneic (foreign bm12) antigen presenting cells (APC) *in vitro* and *in vivo* was studied.

References

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