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Autoreactive T cells escape through processing

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Keywords

Antigen processing, asparagines endopeptidase, myelin basic protein, T-cell epitope

Context

The failure to delete autoreactive T cells has been attributed to two mechanisms: either the self-antigen or the pathogenic epitope is not expressed in the thymus (1), or the affinity of the T-cell receptor (TCR) for the MHC-peptide complex is insufficient to induce negative selection. The authors investigated the reasons why myelin basic protein (MBP)-specific T cells, the candidate pathogenic T cells in multiple sclerosis, avoid deletion despite the fact that MBP is expressed in the thymus and some MBP peptides bind tightly to MHC class II molecules. It should be noted, however, that MBP(Ac1-11) dissociates very rapidly from the mouse class II molecules I-Au and I-Ak and yet it is an immundominant epitope. Previously this group identified a protease, asparaginyl endopeptidase (AEP), as a critical enzyme in the generation of the T-cell epitope (2). Here they show that enzymatic destruction of an antigenic epitope in the thymus prevents autoreactive T cells from deletion.

Significant findings

MBP is sensitive to AEP proteolytic activity, since degradation of MBP can be inhibited by a short peptide competitor, AENK. Sequencing of the cleavage fragments of MBP revealed that the cleavage site is located at an Asn-Ile bond that lies in the middle of the MBP epitope(85-99) which binds to the HLA-DR2 MHC class II molecule. Interestingly, AEP could abolish the response of a T-cell hybridoma specific for MBP (85-99), whereas inhibitors of AEP enhanced presentation of this epitope. The authors propose that AEP processes and destroys this major epitope in the thymus, preventing the induction of tolerance and leading to the escape of MBP-specific T cells into the periphery. This view was corroborated by the detection of AEP in mouse thymic dendritic cells and macrophages.

Comments

Despite these elegant studies, it is still not clear how MBP-specific T cells that escape from thymus selection are maintained and activated in the periphery by the MBP epitope if there is significant AEP activity in peripheral antigen-presenting cells (APCs). The authors offered explanation is that AEP expression or its activity may be selectively downregulated, which would permit the recognition of the epitope MBP (85-99) by MBP-specific T cells. Additionally, post-translation modification of Asn to Asp by deamidation has been reported for the HEL peptide, which removes this substrate for AEP activity. Still another possibility arises from the activity of natural inhibitors of AEP in the peripheral APCs. Identification of enzymes involved in the initiation of immune responses offers potential for immunotherapy: AEP could be one such target (5). However, consideration of the bifunctional role of these enzymes should be taken into account since AEP appears to have different effects on the presentation of T-cell epitopes depending on the protein antigen, with both constructive (for tetanus toxoid) and potentially destructive (for MBP) outcomes.

Methods

Protease assay, immunoblot, FACS, transfection, T-cell proliferation assay.

Additional information

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