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GILT influences antigen processing

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Keywords

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Context

Disulfide bonds in protein antigens must be cleaved during processing for presentation by MHC class II molecules, but until recently, it has been unclear how this happens. Most class II antigen processing occurs in endosomes at mildly acidic pH, conditions not suitable for disulfide bond reduction. However, recent studies have ascribed thiol reductase enzyme activity at endosomal pH to a gamma-interferon-induced, MHC class II-associated human protein, now renamed GILT (Gamma-interferon Inducible Lysosomal Thiol reductase), which shares homology with thioredoxin and uses a similar catalytic mechanism. This study set out to clone murine GILT and to examine its role in antigen processing using a knockout approach.

Significant findings

Murine GILT cDNA was cloned and found to be about 70% identical to human GILT, with conserved active site cysteines. GILT was immunolocalized in MHC class II-containing endosomes of dendritic cells, and its maturation was similar to that of human GILT. GILT-/- mice were constructed; they showed near normal T-cell responses after immunization with proteins lacking disulfide bonds, but responses to the disulfide-containing antigens, hen egg lysozyme (HEL) and RNAse, were diminished. The GILT knockout differentially affected presentation of different HEL-derived peptides to specific T hybridomas: some were unaffected, others were presented poorly or not at all in the absence of GILT. Interestingly, one epitope with a disulfide-bonded cysteine was presented normally, but another one lacking cysteines was presented poorly in the absence of GILT. Thus, GILT seems to exert complex effects on presentation of disulfide-bonded proteins to CD4$^+$ T cells.

Comments

This work closes an important gap in our understanding of how antigens are processed for presentation to $CD4^+$ T cells. It demonstrates for the first time that GILT affects antigen presentation *in vivo* (human GILT has previously been shown to cleave disulfide bonds in model substrates) and reveals the complex impact of disulfide bond cleavage on generation of T-cell epitopes. We still lack an understanding of the rules determining which epitopes are dependent on GILT for processing - the presence or absence of cysteines in the epitope itself does not correlate with GILT-dependence. Other proteins involved in antigen processing for $CD4^+$ T-cell activation have been reported to be dysregulated in rheumatoid arthritis; it will be interesting to see if GILT follows this pattern.

Methods

Cloning, immunofluorescence, immunochemistry, T-cell stimulation assays

Additional information

References

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