T-CELL DEVELOPMENT

Identification of a thymoproteasome

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Reporting in *Science*, Murata and colleagues describe a new catalytic component of proteasomes that is expressed exclusively in the thymus.

Proteasomes are multisubunit catalytic complexes that generate peptides. The three subunits that are responsible for the proteasome catalytic activity are β1, β2 and β5. Vertebrates also have an alternative interferon-γ-inducible proteasome called the immunoproteasome, in which β1, β2 and β5 are replaced by β1i, β2i and β5i. The immunoproteasome is more efficient at generating antigenic peptides than the regular proteasome. Murata and colleagues discovered a new β5-related gene during the search of a genome database for proteasome-related genes. Northern blot and immunoblot analyses showed that the product of this gene is expressed exclusively in the thymus, so it was named β5t. β5t is part of the so-called thymoproteasome, which also includes β1i and β2i as its catalytic subunits. Having β5t rather than β5 or β5i in the thymoproteasome resulted in significantly reduced chymotrypsin activity — an interesting finding as it is this activity that is particularly important in generating high-affinity MHC class I peptides. Immunostaining experiments showed that β5t is primarily expressed in cortical thymic epithelial cells, which are the cells responsible for positive selection of immature thymocytes.

The authors next generated β5t-deficient mice. Thymic architecture and the number of $CD4^+$ T cells in these mice were virtually identical to wild-type mice, but the number of CD8 single-positive thymocytes was significantly reduced. These results show that β5t has a role in generating $CD8^+$ T cells in the thymus and suggest that in the absence of β5t, the MHC class I peptides that are generated by the thymoproteasome are of higher affinity. Because positive selection is assumed to result from low-affinity interactions between thymic epithelial cells and thymocytes, it appears that this alteration in affinity results in less positive selection of $CD8^+$ T cells.

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ORIGINAL RESEARCH PAPER Murata, S. *et al.* Regulation of $CD8^+$ T cell development by thymus-specific proteasomes. *Science* **316**, 1349–1353 (2007)