CELLULAR CYTOTOXICITY

# CTL self-defence

The granule-exocytosis cytotoxicity pathway, by which cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells secrete perforin and granzymes to kill target cells, is crucial for host defence. But, how do cytotoxic cells protect themselves from the damaging contents of their own granules? Work from Pierre Henkart's laboratory, published in *The Journal of Experimental Medicine,* indicates that granule-derived cathepsin B is crucial for the self-protection of cytotoxic lymphocytes.

Previous studies have indicated that cytotoxic lymphocytes have inherent resistance to cytotoxic mediators, including the pore-forming protein perforin, but the molecular basis for this is unknown. The authors of this study reasoned that a granule component would be a good candidate to mediate resistance as it could provide local protection during granule exocytosis. Cytotoxic granules contain perforin, granzymes (serine proteases) and lysosomal enzymes, including thiol cathepsin endoproteases, which can maintain their proteolytic activity in the extracellular environment. Before the perforin pore-forming complex is assembled, perforin passes through an intermediate membrane-associated stage that is highly susceptible to proteolysis. So, could a cathepsin that is expressed on the cytotoxic-cell surface after exocytosis cleave perforin and, in so doing, protect the effector cells?

To investigate this, Balaji *et al.* treated CTLs cultured on plate-bound anti-CD3 antibodies (to trigger degranulation) with cathepsin inhibitors. These drugs resulted in rapid T-cell suicide, which implies that cathepsins do participate in CTL self-protection. This CTL suicide does not require the Fas–FasL death pathway, as it occurred normally in CTLs from *gld* (FasL-mutant) mice, but it does require perforin, as it did not occur in CTLs from perforin-knockout mice.

Further experiments with membrane-impermeant cathepsin inhibitors and cathepsin-B-specific inhibitors showed that cathepsin-mediated protection of degranulating CTLs against perforin attack occurs in an extracellular location and that cathepsin B is required specifically. The authors also showed that CTLs express little surface cathepsin B before degranulation, but after T-cell-receptor triggering, the surface expression of this potentially protective enzyme increases rapidly. Finally, CTL surface cathepsin B was shown to be enzymatically active and to cleave perforin efficiently.

This work indicates that cytotoxic lymphocytes release granule-derived cathepsin B on degranulation, which associates with the cell surface and protects these cells against perforin attack and self-destruction. So, a long-standing question about the granule-exocytosis model seems to have been answered.

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**References and links**

**ORIGINAL RESEARCH PAPER** Balaji, K. *et al.* Surface cathepsin B protects cytotoxic lymphocytes from self-destruction after degranulation. *J. Exp. Med.* **196**, 493–503 (2002)

**FURTHER READING** Barry, M. & Bleackley, R. C. Cytotoxic T lymphocytes: all roads lead to death. *Nature Rev. Immunol.* **2**, 401–409 (2002)

**WEB SITE**

**Pierre Henkart's lab:**
http://www3.cancer.gov/intra/EIB/henkart.htm