APOPTOSIS

Death by granzyme B

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Granzyme B
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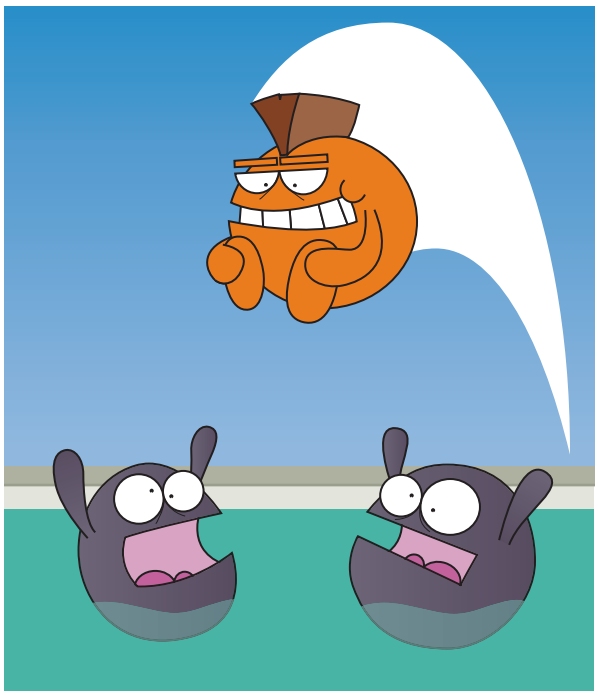
The death of effector T cells following activation is an important process in the termination of an immune response. However, the mechanisms that are involved in this activation-induced cell death (AICD) through engagement of the T-cell receptor (TCR) are not well understood. Now, new research published in *Immunity* shows that granzyme B has an important role in AICD of T helper 2 (T_H2) cells.

Examination of the kinetics of AICD, by staining for annexin V and assessing membrane permeability to propidium iodide, showed that the death of T_H1 cells occurred more rapidly than that of T_H2 cells following TCR engagement. This finding indicates that AICD is likely to involve different mechanisms in these two cell populations. Therefore, the authors examined the role of several pro-apoptotic ligands and effector molecules in AICD of T_H1 cells and T_H2 cells. Blocking the pro-apoptotic molecule CD95 ligand (also known as FAS ligand) with specific agents inhibited AICD of T_H1 cells, as previously reported. However, these agents had no effect on the death of T_H2 cells. Similarly, blocking the activity of several caspases affected only T_H1-cell death, whereas inhibition of TRAIL (tumour-necrosis-factor-related apoptosis-inducing ligand) did not affect either cell type. Therefore, none of the classic pro-apoptotic pathways seems to be involved in the death of T_H2 cells.



Granzyme B is a serine protease that is an important mediator of target-cell apoptosis by cells such as natural killer cells and cytotoxic $CD8^+$ T cells. However, granzyme B has also been shown to exert its function on certain cells that produce it, indicating that it might be involved in AICD. Interestingly, Devadas and colleagues showed that inhibition of granzyme B blocked AICD of T_H2 cells but not T_H1 cells. Cells that were isolated from granzyme-B-deficient mice and cultured in T_H2-cell-polarizing conditions before activation showed a similar resistance to AICD.

So why are T_H2 cells, but not T_H1 cells, sensitive to granzyme-B-mediated AICD? Using northern-blotting analysis and real-time PCR, the authors determined that resting and activated T_H1 cells and activated T_H2 cells express large amounts of this protease, indicating that the sensitivity of T_H2 cells to granzyme-B-mediated apoptosis is not due to preferential expression of granzyme B. The authors then examined the release of granzyme B by degranulation. Colocalization of granzyme B with lysosomal-associated membrane protein 1 (LAMP1; a marker of granules) was observed in both resting T_H1 cells and resting T_H2 cells. However, following TCR engagement, colocalization was observed only in T_H1 cells, indicating that granzyme B is released from the granules on activation of T_H2 cells but not T_H1 cells. Interestingly, the amount of SPI6, which is a protease inhibitor that specifically inhibits the activity of granzyme B, was found to be increased in activated T_H1 cells but not activated T_H2 cells. Therefore, in contrast to T_H2 cells, T_H1 cells do not release granzyme B from their granules, and they express a protein that might protect them from granzyme-B-mediated AICD.

Following restimulation *in vitro*, $CD4^+$ T cells from granzyme-B-deficient mice that had been immunized with ovalbumin formulated in alum produced large amounts of the T_H2 cytokines interleukin-4 (IL-4), IL-5 and IL-13, but interferon-γ was undetectable. In a mouse model of ovalbumin-induced allergic lung inflammation, which depends on a T_H2-cell response, mice deficient in granzyme B had considerably more cellular infiltrate in the lungs and more IL-4 and IL-5 in bronchoalveolar-lavage fluid than did granzyme-B-sufficient (control) mice.

So the data show that granzyme B is crucial for AICD of T_H2 cells but not T_H1 cells and might therefore have a role in regulating T_H2-cell responses *in vivo*.

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ORIGINAL RESEARCH PAPER Devadas, S. *et al.* Granzyme B is critical for T cell receptor-induced cell death of type 2 helper T cells. *Immunity* **25**, 237–247 (2006)