APOPTOSIS

BIM and FAS: the ultimate death squad

Two apoptotic cell-death pathways exist in mammals — a cell-intrinsic pathway and a cell-extrinsic pathway — and these distinct pathways converge with the activation of the caspase cascade. Cell death is essential for maintaining immune homeostasis and terminating an immune response but the relative contribution of these two cell-death pathways to this process is not fully understood. Now, three papers published in *Immunity* address this issue and show a cooperation between both pathways in maintaining homeostasis, preventing autoimmunity and terminating an immune response.

The cell-extrinsic pathway is initiated by ligand engagement of death receptors, such as FAS (also known as CD95) on the cell surface. Initiation of the cell-intrinsic pathway involves the activation of pro-apoptotic BCL-2 (B-cell lymphoma 2)-family members, such as BIM (BCL-2-interacting mediator of cell death), in response to developmental cues and cytotoxic stimuli including cytokine deprivation.

To examine the contributions of these two pathways, the three groups generated mice that were deficient for both BIM and FAS. They found that these double-knockout mice developed extreme lymphadenopathy compared with mice deficient for only one of these proteins, indicating a synergistic role for BIM and FAS in controlling lymphocyte homeostasis. The three groups also observed an accumulation of $CD4^+$ and $CD8^+$ memory ($CD44^{hi}$) T cells in the periphery and an accumulation of an unusual population of $CD3^+B220^+CD4^-CD8^-$ T cells. Hughes *et al.* showed that this cell population was 4–5 times bigger in the double-knockout mice compared with FAS-deficient mice, again indicating a cooperative role for BIM and FAS. In addition, Hutcheson *et al.* showed an increase in B-cell numbers and an accumulation of activated macrophages in the spleen and lymph nodes of the double-knockout mice.

Double-knockout mice also developed enhanced and accelerated autoimmunity compared with mice deficient for either BIM or FAS, as determined by elevated levels of DNA-specific autoantibodies, enhanced serum IgA antibodies and increased renal damage. Furthermore, Hutcheson *et al.* showed that double-knockout mice develop a spontaneous systemic lupus erythematosus (SLE)-like disease on a normally autoimmune-resistant background.

But what role do BIM and FAS have in terminating antiviral $CD8^+$ T-cell responses? To examine this, Hughes *et al.* infected double-knockout mice with herpes simplex virus (HSV; an acute infection) or murine gammaherpesvirus (a chronic infection). They found that BIM alone was sufficient to shutdown the antiviral $CD8^+$ T-cell response following an acute infection but that $CD8^+$ T-cell clearance following a chronic infection required the activation of both BIM and FAS. By contrast, Weant *et al.* showed that $CD8^+$ T-cell contraction following an acute lymphocytic choriomeningitis virus (LCMV) infection required the activation of both BIM and FAS, but with a more important role for BIM in the early contraction phase. The difference in the role of FAS between these two studies might reflect the level and extent of the viral infection involved — HSV was a local infection in the footpad, whereas LCMV infection was systemic.

Taken together, these studies show that BIM and FAS cooperate to regulate lymphocyte homeostasis, control lymphocyte numbers following chronic viral infection and prevent spontaneous autoimmunity.

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ORIGINAL RESEARCH PAPERS Hughes, P. D. *et al.* Apoptosis regulators Bim and Fas cooperate in shutdown of chronic immune responses and prevention of autoimmunity. *Immunity* **28**, 197–205 (2008) | Hutcheson, J. *et al.* Combined deficiency of proapoptotic regulators Bim and Fas results in the early onset of systemic autoimmunity. *Immunity* **28**, 206–217 (2008) | Weant, A. E. *et al.* Apoptosis regulators Bim and Fas function concurrently to control autoimmunity and $CD8^+$ T cell contraction. *Immunity* **28**, 218–230 (2008)
FURTHER READING Green, D. R. Fas Bim Boom! *Immunity* **28**, 141–143 (2008)