BH3-only Members of the Bcl-2 Family Are Critical Inducers of Programmed Cell Death


Apoptosis is an evolutionarily conserved mechanism for removing unwanted cells. Genetic and biochemical studies have shown that 3 classes of proteins are required for cell killing: cysteine proteases, their adaptor molecules and pro-apoptotic members of the Bcl-2 family. Anti-apoptotic Bcl-2 family members are essential for cell survival. We have cloned Bim and Bmf, two novel pro-apoptotic Bcl-2 family member which have only a BH3 domain but no other region of similarity to this family. In healthy cells Bim is sequestered to the microtubule-associated dynein motor complex by binding to DLC1/LC8 dynein light chain and Bmf is sequestered to the myosin V motor complex on the actin cytoskeleton. Different apoptotic stimuli cause release of Bim or Bmf, liberating them to relocalize to Bcl-2 and its homologs and block their anti-apoptotic activity. Bim-deficient lymphocytes, myeloid cells and neurons are resistant to certain, but not all, apoptotic stimuli that can be blocked by Bcl-2 or its homologs. These results demonstrate that distinct death stimuli activate different BH3-only proteins by freeing them to interact with anti-apoptotic family members. Bim-deficient mice have 2- to 5-fold increased numbers of all types of leukocytes, develop progressive plasmacytosis and most succumb to SLE-like autoimmune kidney disease. We have used several model systems to study thymocyte and B cell negative selection (TCR or Ig transgenic mice, super-antigens, anti-CD3 or anti-Ig antibody treatment) and found that Bim is essential for apoptotic cell death of autoreactive thymocytes and immature as well as mature B lymphocytes. These results demonstrate that the pro-apoptotic BH3-only protein Bim is essential for programmed cell death during hematopoiesis, for leukocyte homeostasis and imposes a vital barrier against autoimmunity. We are currently generating mice lacking the other BH3-only proteins to identify their essential functions in development.

Suggested reading:


