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The role of BCL-2 family members in apoptosis

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Overview

Programmed cell death or apoptosis is critical for both the development and maintenance of tissues. A distinct genetic pathway apparently shared by all multicellular organisms governs apoptosis. The BCL-2 family of proteins, which possesses both pro- and anti-apoptotic members, constitutes a decisional checkpoint within the common portion of this pathway. Another major component of the death machinery is a proteolytic system involving a family of cysteine proteases named caspases. Despite the tremendous progress in this field in the past few years we are still far from understanding the exact function of the BCL-2 family members, how these members and caspases work in concert, and the interconnection between death and survival pathways.

The importance of mitochondria in apoptosis is well established. Alterations in the mitochondrial membrane potential ($\Delta\Psi_m$) and the production of reactive oxygen species (ROS) have been noted to be early events in several apoptotic systems. In addition, it is well documented that in certain apoptotic settings cytochrome c (cyt c) redistributes from mitochondria to the cytosol leading to the activation of a downstream caspase cascade. The mitochondrial membrane location of many of the BCL-2 family members and their active role in promoting/inhibiting a mitochondrial apoptotic program implicates them as being part of the death effector mechanism based at this organelle.

The best-characterized signal transduction pathways that induce apoptosis are the cell surface receptors of the TNF family. During a survey of modifications to pro-apoptotic BCL-2 family members we noted that TNF or Fas lead to an early caspase-mediated cleavage of BID. Cleavage of cytosolic p22 BID yields a p15 carboxy-terminal fragment (tBID) that translocates to the mitochondria and is singularly required for the release of cyt c (Figure 1). The ability of tBID to cause cyt c release, might relate to its ability to form channels in artificial membranes. To determine whether BID has a critical role *in-vivo*, we generated *Bid*-deficient mice. Following administration of anti-Fas antibody, the majority of *Bid*-deficient mice survived while wild type mice died from hepatocellular apoptosis and hemorrhagic necrosis. The *Bid-deficient* mice survived with only moderate damage: caspases were activated but no mitochondrial cyt c was released. This loss of function model indicates that BID is essential for inducing the mitochondrial apoptotic program and that this program is critical for cell death to occur.

Although BID seems to be a critical molecule in the apoptotic process, its exact role is unknown. We still do not know how BID 'uses' mitochondria to kill cells. We do not know what events occur in mitochondria following its translocation and whether BID 'needs' to interact with other proteins at the mitochondrial membrane to execute its function. We also do not know how these mitochondrial events eventually contribute to the progression of the apoptotic process.

Future directions

We will use BID as a representative of the pro-apoptotic BCL-2 family members. The objective of our future studies is to define the role of BID in the apoptotic process. Identifying the proteins that interact with BID at the mitochondrial membrane is critical for understanding its mechanism of action. We will identify these proteins by using reversible protein crosslinkers. As a complimentary approach, We will use yeast as a model system to identify mammalian genes that act in the death pathway of BID. Yeast is an ideal system for this purpose since BID expressed in yeast localizes to mitochondria but does not cause cyt c release or cell death. Once, we have identified

these factors we will use them to define the mitochondrial and downstream events that are critical for the progression of the cell death process. Identifying the role of BID will also help us to define the apoptatic role of other BCL-2 family members.

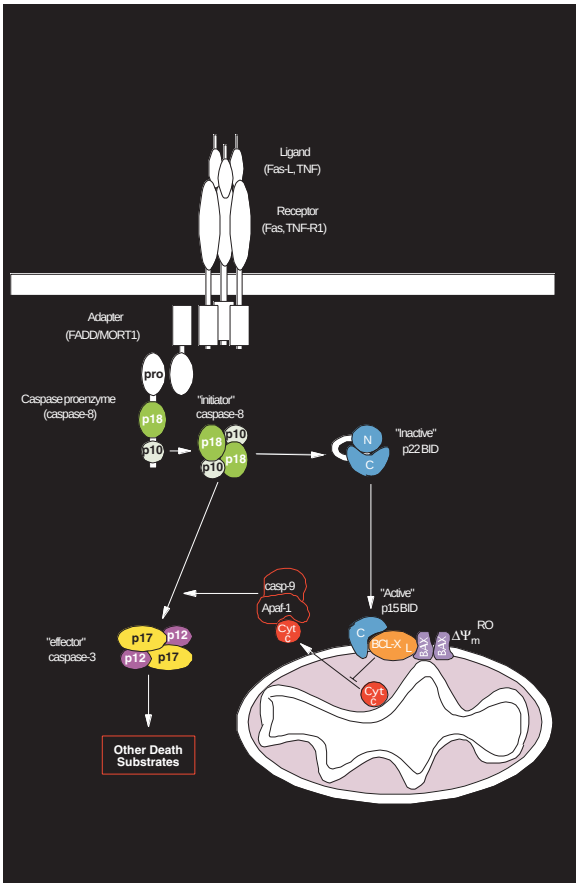

Fig 1. *Model of BID cleavage and translocation following TNF-R1/Fas engagement. Activation of TNF-R1/Fas cell surface receptor leads to activation of caspase-8. Caspase-8 cleaves cytosolic p22 BID generating a p15 carboxy-terminal fragment that translocats to the mitochondria resulting in the release of cytochrome c. Released cytochrome c activates Apaf-1, which in turn activates a downstream caspase program.*

Publications

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