Programmed cellular death can occur in all cells by highly efficient mechanisms, leading to the quiet disposal of millions of cells in the adult human each minute. This efficient execution of unwanted cells is regulated not only by cellular death signals but also by cellular survival signals. Imbalances in these signals are lethal in the development of higher organisms and likely play a major role in pathophysiological processes as diverse as atherosclerosis, cancer, heart failure, and inflammation.

As a ubiquitous multifunctional signaling system, members of the nuclear factor-κB (NF-κB) family play prominent roles in the cell death/survival balance. NF-κB proteins are homodimers or heterodimers in the cytoplasm of eukaryotic cells that share a 300 amino acid motif called the REL homology domain. The REL homology domain mediates dimer formation, nuclear localization, and interaction with inhibitory proteins (IκB proteins) that keep NF-κB proteins in the cytoplasm. Diverse cellular stimuli including mechanical forces, oxidative stress, and cytokines lead to phosphorylation of IκB proteins, allowing NF-κB dimers to enter the nucleus and activate specific target genes.

Under many circumstances, activation of NF-κB complexes is a powerful stimulus for cell survival (Figure). For example, in B lymphocytes, the cell type in which NF-κB was originally identified, engagement of cell surface IgM activates NF-κB and inhibits apoptosis. In addition, mice lacking RelA, one of the NF-κB family members, die at embryonic development day 10 of massive hepatic apoptosis. However, NF-κB activation does not always confer a clear survival advantage. For example, studies have demonstrated a proapoptotic role of NF-κB in many cell types (reviewed in Reference 1). Thus, the role of NF-κB in programmed cell death may be context sensitive.

The cell survival benefit of NF-κB is probably mediated by the specific genes transcribed after the activated complex translocates to the nucleus and binds to its consensus sequence. At least 8 different NF-κB target genes are known to regulate apoptosis. For example, A1 is a member of the bcl family of apoptosis regulatory genes that is an NF-κB target gene capable of protecting endothelial cells from programmed cell death. Another incompletely understood NF-κB target gene that protects against apoptosis is IEX-1, a growth-associated gene regulated by both NF-κB and the p53 tumor suppressor gene.

Among the NF-κB target genes, the inhibitor of apoptosis proteins (IAPs) has emerged as a critical cell survival signal. The IAP family members were initially described in baculovirus and share the baculovirus IAP repeat (BIR) domain, a 70 amino acid sequence highly conserved in eukaryotes. Six human IAP members have been described, including XIAP, survivin, cIAP1, and cIAP-2; all are proteins that can inhibit apoptosis. IAPs can directly inhibit specific caspases, and the BIR domains of IAPs appear to be both necessary and sufficient for this effect.

XIAP, so-called because the gene is on the mouse and human X chromosomes, binds to and inhibits caspase-3 and -9 and protects endothelial cells against tumor necrosis factor-α-mediated apoptosis. However, direct caspase inhibition is not the only way that XIAP can block apoptosis. In this issue of Circulation Research, Levkau et al describe two additional potential mechanisms by which XIAP may confer a survival advantage to endothelial cells. First, using a retroviral infection approach, they demonstrated that XIAP drives expression of an NF-κB–dependent reporter gene and induces a specific electrophoretic mobility shift of p50/p65 heterodimers. These experiments, together with the recently published experiments of Hofer-Warbinek et al, provide evidence for a positive feedback mechanism by which XIAP may lead to further induction of NF-κB with additional recruitment of target genes. This positive feedback is probably mediated by activation of TAK-1, a mitogen-activated protein kinase that can activate NF-κB. In fact, XIAP is not the only IAP capable of this positive feedback, as c-IAP-2 can also activate NF-κB.

The function of XIAP itself is likely carefully regulated in the cell. In addition to transcriptional control by NF-κB, the recently described protein Smac/DIABLO is released from mitochondria along with cytochrome c, leading to direct binding to and inhibition of XIAP. Furthermore, as described by Levkau et al in the present study and also by Deveraux et al, XIAP itself may be cleaved by caspases, particularly caspase-3 (although multiple caspases are capable of cleaving XIAP), and these XIAP fragments are inefficient inhibitors of caspases.

The positive feedback of XIAP in NF-κB activation contrasts with the well-described autoregulatory negative feedback mechanism of NF-κB–mediated induction of IκB. Other NF-κB target genes may provide additional negative feedback signals to NF-κB activation. For example, the zinc
benefit of the positive feedback was obtained, negative autoregulatory feedback mechanisms might be called into play, with relative inactivation of NF-κB and then cell-cycle progression with protection against apoptotic stimuli.

Thus, to optimize cell survival, IAPs may activate NF-κB complexes, and multiple, maximally induced NF-κB target genes may be necessary. This scenario agrees with experiments demonstrating that multiple IAP members are necessary to block tumor necrosis factor–induced apoptosis. These interactions remind us that despite intense attention to the roles of NF-κB and IAPs in cell survival, we are at the early stages of learning the names of the players and how they may interact. Defining the temporal relations and interactions of the proteins in the NF-κB survival pathway is a fertile area of investigation with implications not only for cardiovascular diseases but also for many other diseases.

Acknowledgments

Support for this work was provided by a grant from the National Heart, Lung, and Blood Institute (HL62943).

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Key Words: apoptosis ■ cell survival ■ caspases ■ cell cycle
Nuclear Factor-κB and Cell Survival: IAPs Call for Support
Richard T. Lee and Tucker Collins

Circ Res. 2001;88:262-264
doi: 10.1161/01.RES.88.3.262

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/88/3/262

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