Chapter 6
Overcoming Resistance to Apoptosis in Cancer Therapy

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1 Introduction

A fundamental characteristic of cancer cells is suppression of apoptosis and increased cell survival.1,2 These properties, when combined with deregulated cell proliferation, are the basic requirements for development of cancer. Increased deregulated cell proliferation by itself paradoxically may trigger cell death pathways which prevent outgrowth of the cancer cell unless the cell death pathways are inhibited.3 Another consequence of the latter may be resistance to treatments that depend on induction of apoptosis in the cancer cell. These widely held concepts have given rise to intense study of the antiapoptotic mechanisms generated in different cancer cells that are driven by different oncogenic stimuli and how these mechanisms may operate against different therapies used against cancers. The mechanisms by which different therapies induce apoptosis are in turn poorly understood and answers to both questions are needed in development of effective treatment approaches. In the following sections, we review recent information about regulation of apoptosis, how oncogenes interact with apoptotic pathways, and some of the therapeutic opportunities that are developing as a consequence of this information. Emphasis is given to studies on melanoma as a model system in these developments.

2 Recent Concepts About Regulation of Apoptosis

Although apoptosis is traditionally described in terms of intrinsic and extrinsic pathways in most instances, apoptosis induced by oncogenes proceeds via the mitochondrial “intrinsic” pathway. Much is known about this pathway and in particular the proteins involved in regulation of the pathway.

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2.1 Bcl-2 Family Proteins in Regulation of Apoptosis

Apoptosis via the mitochondrial pathway is regulated by the Bcl-2 family of proteins which share at least one conserved Bcl-2 homology (BH) domain. The prosurvival Bcl-2 proteins share four such domains and act to protect intracellular membranes associated with mitochondria, nuclei, and endoplasmic reticulum. The proapoptotic Bax and Bak proteins have three BH domains and are located in the cytosol (Bax) and mitochondrial outer membrane (Bak). They are essential for apoptosis to proceed and mice lacking both genes have a number of developmental abnormalities.1 Similarly, apoptosis of cancer cells induced by several chemotherapy agents is dependent on Bax.4-6

Once activated, Bax and Bak oligomerize and insert into the outer mitochondrial membrane and thereby cause the release of several factors from mitochondria that can trigger apoptosis. These include cytochrome-c, Smac/DIABLO, Omi, apoptosis-inducing factor (AIF), and endonuclease G. These factors are located in the membrane or intermembranous space between the outer and inner mitochondrial membranes. Two models have been proposed to explain the release of these proteins during apoptosis. In one model, an autonomous channel formed by Bax or Bak is formed and this allows the release of the factors from the intermembrane space.2 Another model depends on specific interaction of Bax or Bcl-2 with components of the permeability transition pore (PTP), which exists at sites of contact between outer and inner mitochondrial membranes. This results in opening of the PTP, swelling of the mitochondrial matrix, and rupture of the outer mitochondrial membrane.7

2.1.1 Bcl-2 Sensor Proteins

The discovery of a third group of Bcl-2 proteins which share a single BH3 domain has had a major influence on concepts regarding initiation of apoptosis.8,9 They are regarded as sensors of damage to cells and different members respond to a diverse array of damaging agents by activating the Bax/Bak proteins to damage mitochondria. Two of the members, Bid and Bim, may be able to directly cause changes in Bax and Bak, which result in their oligomerization and insertion into mitochondria.9 The other members, such as Bad, Noxa, and P53-upregulated modulator of apoptosis (PUMA), appear to function by binding to and neutralizing the antiapoptotic proteins. In addition, they may displace other BH3 proteins such as Bid, Bim, and p53, which have the ability to activate Bax and Bak.10

Bid appears to mediate apoptosis induced by tumor necrosis factor (TNF) family ligands and by granzyme B from cytotoxic T lymphocyte (CTL). Bid is cleaved by caspase-8 at Asp59 into tBid or by granzyme B at Asp75 into active (gtBid) form.11 tBid is able to cause oligomerization of cytosolic Bax or Bak associated with mitochondria which facilitates binding of the Bax/Bak oligomers to the outer mitochondrial membrane and release of aptogenic proteins as referred to above.