

Antisense Therapy

Denise M. Lapka, RN, MS, AOCN®, CCNS, and Paula J. Franson, RN, MS, OCN®

Apoptosis, or programmed cell death, is a pathway needed for embryonic development and tissue homeostasis. Apoptosis is the normal physiologic response to many stimuli, including irreparable DNA damage. The human body is composed of approximately 10^{14} cells, and each cell is capable of committing suicide by apoptosis. Various diseases, such as AIDS, neurodegenerative disorders, myelodysplastic syndromes, ischemic injury, and toxin-induced liver disease, develop because of hyperactivation of apoptosis. However, suppression of apoptosis may cause people to develop cancer, autoimmune disorders, and many viral infections.

In patients with cancer, the balance between proliferation and apoptosis is disrupted and the defects in the apoptotic pathways allow cells with genetic abnormalities to survive. Most cytotoxic and hormonal treatments, as well as radiation, ultimately kill cancer cells by causing irreparable cellular damage that triggers apoptosis. Therefore, the efficacy of cancer treatments depends not only on the cellular damage they cause but also on the cells' ability to respond to the damage by inducing apoptosis. Mutations in apoptotic pathways may result in resistance to drugs and radiation. Such mutations may serve as predictors of chemoresistance and, more importantly, as new treatment targets (Sjostrom & Bergh, 2001).

The Bcl-2 family of proteins is among the most studied molecules in the apoptotic pathway. BCL-2 first was discovered as a proto-oncogene located at the breakpoints of t(14;18) chromosomal translocations in low-grade, B cell, non-Hodgkin's lymphomas. The resulting overexpression of the BCL-2

Antisense drugs are small, chemically modified strands of DNA that are engineered in a sequence that is exactly opposite ("anti") to the coding ("sense") sequence of messenger RNA (mRNA). When an antisense drug binds to the mRNA, a duplex is formed. The duplex recruits an enzyme that degrades mRNA, thereby inhibiting the production of the intended protein. In preclinical studies, BCL-2 antisense therapy has confirmed downregulation of Bcl-2 (a protein found in the mitochondrial membrane that regulates the release of cytochrome c), demonstrated a synergistic effect between antisense and chemotherapeutic agents, and has shown a significant tumor reduction and increased survival.

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gene slows the normal course of apoptotic cell death that otherwise occurs to maintain B cell homeostasis, causing B cell accumulation and follicular lymphoma. This observation indicates that cancer does not result strictly from unrestrained cell proliferation but also could develop because of insufficient apoptotic signaling. In addition, a decrease in Bcl-2 levels or the inhibition of Bcl-2 activity may provoke apoptosis or at least sensitize cells to apoptotic death. In addition to lymphomas, Bcl-2 levels are elevated in a broad range of other human cancers, indicating that this molecule might have a role in raising the apoptotic threshold in a broad spectrum of cancerous disorders (Nicholson, 2000).

Bcl-2 acts through a unique mechanism. Prior to the discovery of the BCL-2 gene, oncogenes were believed to act by inducing uncontrolled cellular proliferation. In contrast, the BCL-2 gene was found to promote survival of cancer cells by slowing or preventing cell death. Recognition of this novel mechanism resulted in the establishment of a new oncogene class, BCL-2 (Korsmeyer, 1995).

Existing oncology therapies (e.g., cytotoxic drugs, radiation, monoclonal antibodies) work by inflicting various types of damage to cancer cell structures but converge into a final common pathway leading to apoptosis. Bcl-2 resides at the nexus between an apoptotic-triggering event (e.g., chemotherapy) and the final common pathway of cancer cell death (Genta, Inc., 2001). Bcl-2 is a normal protein found in the inner layers of the mitochondrial membrane; because Bcl-2 is not a surface protein, it is not vulnerable to attack by a monoclonal antibody. Bcl-2 regulates the release of cytochrome c from the mitochondria (Nicholson, 2000). Bcl-2 substantially delays or prevents the onset of apoptosis when a death signal is received. This delay, in turn, gives cancer cells more time to repair damage caused by chemotherapy and other cancer treatments. Therefore, Bcl-2 is an important contributing factor in the resistance of cancer cells to common types of anticancer treatments.

The proapoptotic protein Bax is the most studied member of the Bcl-2 family in cancer. Bax and Bcl-2 control a cell's decision to enter apoptosis. The ratio of these proteins appears to be the critical determinant

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