THE ROLE OF BCL-2 IN TUMORIGENESIS

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Abstract: *Apoptosis is a genetically regulated process of programmed cell death in eukaryotes, essential for normal development and the maintenance of homeostasis. As a crucial physiological mechanism, apoptosis selectively eliminates cells and regulates cell death. It occurs not only in response to damage or external stress but also during normal cell development and morphogenesis.*

Keywords: *BCL-2, BCL-XL, genetic, apoptosis, lymphoma*

Apoptosis is a form of programmed and orderly cell death, in which a cell is fragmented into apoptotic bodies and subsequently phagocytosed by macrophages or neighboring cells without triggering inflammation. In multicellular organisms, apoptosis can be initiated via two pathways:

1. The extrinsic (death receptor) pathway
2. The intrinsic (mitochondrial) pathway

In humans, apoptosis predominantly occurs through the intrinsic mitochondrial pathway, which involves the release of apoptogenic proteins into the cytoplasm. This can result from mitochondrial membrane rupture and/or increased membrane permeability. Apoptotic Bcl-2 proteins (such as Bax and Bak) play a significant role in increasing mitochondrial membrane permeability. These proteins anchor to the mitochondrial membranes and facilitate the release of apoptosis-related proteins—cytochrome c and AIF (apoptosis-inducing factor)—into the cytoplasm. In the cytoplasm, cytochrome c and APAF-1 (apoptotic protease-activating factor-1) interact to form a complex known as the apoptosome. Pro-caspase-9 then binds to this complex, resulting in the formation of a

mature apoptosome that activates caspase-9. Caspase-9, in turn, initiates a caspase cascade, leading to the activation of executioner caspases such as caspase-3, responsible for the degradation of cellular components. AIF, acting independently of caspases, also contributes to the apoptotic process. The activated caspase cascade degrades various cellular structures, including nuclear membranes, cytoskeletal proteins, and cell-to-cell junctions. Another critical function of caspases is the breakdown of proteins that inhibit apoptosis. Apoptosis is essential for morphogenesis, differentiation, and immune function in multicellular organisms. The removal of diseased or damaged cells is mediated by apoptosis. Disruptions in apoptotic mechanisms can contribute to the pathogenesis of cancer and reduce the effectiveness of conventional cytotoxic therapies. In contrast to necrosis, apoptosis preserves cell membrane integrity and prevents inflammatory responses. Apoptotic necrosis and autophagy, both regulated through mitochondrial signaling and involving BCL-2 family proteins, are closely linked. p53 can either promote or inhibit autophagy depending on the context. The interaction between autophagy, apoptosis, and necrosis signaling helps maintain T-cell homeostasis. Reactive oxygen species (ROS) and mitochondria play decisive roles in apoptosis induction under both physiological and pathological conditions. Excessive ROS activate mitochondrial permeability transition pores (PT pores), facilitating the release of calcium ions, cytochrome c, and AIF, and the subsequent activation of caspase-9 and caspases 3, 6, and 7. Research into BCL-2 family proteins has shown their significant role in cancer development. BCL-2, an anti-apoptotic protein, is encoded on chromosome 18. BCL-XL, a gene with structural similarity to BCL-2, was first cloned in vitro in 1993. It is located in the outer membranes of mitochondria and the nucleus, where it regulates transcription factor activity. High BCL-XL expression is associated with increased tumor cell proliferation, invasion, metastasis, angiogenesis, and resistance to apoptosis. The BCL-V protein, predominantly located in mitochondria, binds to the outer mitochondrial membrane and integrates into it during apoptosis. The release of pro-apoptotic proteins into the cytoplasm triggers the caspase cascade, promoting cell death. The balance of these proteins directly regulates apoptosis: increased BAX promotes apoptosis, while elevated BCL-2 levels inhibit it. Normally cytoplasmic, BAX translocates to the mitochondrial membrane upon apoptotic signaling, where it disrupts membrane integrity and facilitates cytochrome c release. Its expression is regulated by p53 and other BCL-2 family members. BAK is a transmembrane mitochondrial protein activated by apoptotic signals and plays a crucial regulatory role. It promotes apoptosis by either directly activating apoptotic pathways or inhibiting BCL-2 and BCL-XL. BAK disrupts the electron transport chain, regulates ATP production, increases Bax expression, and penetrates the mitochondrial membrane to initiate apoptosis. Overexpression of BCL-2 inhibits apoptosis, supports unchecked cell proliferation, and plays a key role in tumor formation. This gene encodes an integral outer mitochondrial membrane protein that prevents apoptosis in certain cell types like lymphocytes. A common oncogenic event is

the translocation of the BCL-2 gene to the immunoglobulin heavy chain locus, particularly in follicular lymphoma. Because tumor cells often overexpress BCL-2 compared to normal cells, BCL-2 inhibitors primarily target cancer cells with minimal effects on healthy tissues. Therefore, inhibiting BCL-2 offers a promising therapeutic strategy to reduce tumor resistance to apoptosis and limit tumor progression. Due to their multifaceted roles, BCL-2 family proteins are attractive targets for cancer therapy, as they protect tumor cells from apoptotic signals under both internal and external stress. For instance, Venetoclax (ABT-199) is a selective BCL-2 inhibitor approved for treating chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML). BCL-2 family members function as pro- or anti-apoptotic regulators and have been intensively studied over the past decade for their roles in apoptosis, oncogenesis, and cancer therapy. In healthy cells, these regulators maintain a tightly controlled balance. They can either push cells toward irreversible apoptosis or enable their survival, contributing to the formation of metastatic clones. Chromosomal translocations involving the BCL2 gene are commonly seen in B-cell leukemias and lymphomas, leading to overexpression of BCL2 protein and resistance to cell death. Lymphoma is a malignant tumor of the lymphatic system, often involving lymph nodes. During lymphoma development, B lymphocytes are exposed to various stressors (e.g., oncogene activation, DNA damage, oxygen and cytokine deficiency), enabling them to escape apoptosis.

Conclusion: BCL-2 (B-cell lymphoma 2) is a key regulator of apoptosis. It protects cells from early death caused by damaging stimuli. However, its overexpression contributes to cancer development by extending the lifespan of malignant cells. Therefore, BCL-2 plays a critical role in certain cancers. BCL-2 preserves mitochondrial membrane integrity and enhances cellular metabolism. It has neuroprotective functions and may slow neuronal death in diseases like Parkinson's and Alzheimer's. It also strengthens the i mmune system by improving lymphocyte viability and boosting immune responses. Moreover, BCL-2 supports cell regeneration and tissue repair. Nonetheless, excessive BCL-2 activity can lead to tumor development. Consequently, research is ongoing to develop cancer therapies that target and inhibit BCL-2.

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