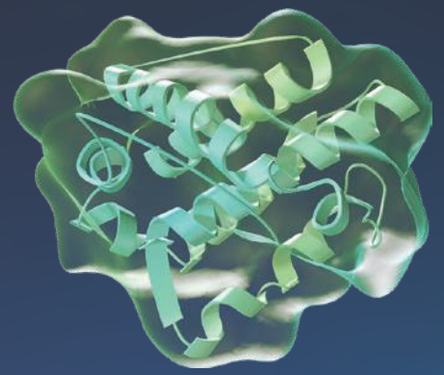
The Role of **MCL-1** (Myeloid Cell Leukemia-1) in Hematologic Malignancies

AMGEN®

Oncology

MCL-1 and its Role in Cancer



Myeloid cell leukemia-1 (MCL-1), a key regulator of apoptosis* and therapeutic target in cancer, is an antiapoptotic member of the BH3 domain-containing proteins.[1,2]

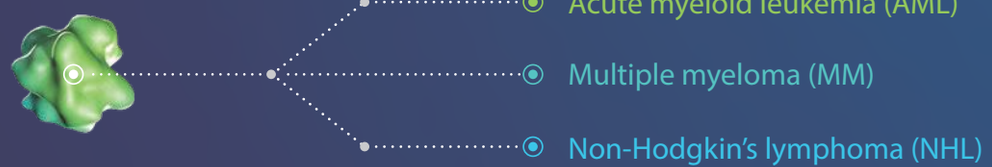
MCL-1, with other BH3 domain-containing proteins, determines cell survival or apoptosis.[1] MCL-1 plays a role in cell cycle progression and response to DNA damage.[1,3-8]

MCL-1 is structurally and functionally similar to other BH3-domain-containing proteins. Transcriptional upregulation of MCL-1 is induced by various cytokines (eg, IL-3, IL-5, and IL-6) and signaling pathways (eg, PI3K, STAT3, and MAPK).[2,9]

MCL-1 is widely expressed in human tissues and is essential for the survival of hematopoietic stem cells and multiple cell lineages including lymphocytes and neutrophils.[10-14]

Overexpression or amplification of MCL-1 is one of the most frequent alterations in cancers, including various hematologic malignancies and select solid tumors.[6]

MCL-1 is Expressed in a Variety of Hematologic Malignancies[2,15-17]



In hematologic malignancies, MCL-1 overexpression can protect cancer cells from apoptosis, and is often associated with poor prognosis and resistance to anticancer therapies.[2,16,18]

*Apoptosis: process of programmed cell death.
BCL-2, B-cell lymphoma 2; BH, BCL-2 homology; IL, interleukin; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; STAT3, signal transducer and activator of transcription 3.

MCL-1 Contributes to Drug Resistance in Cancer

In preclinical studies, MCL-1 overexpression conferred resistance to various anticancer therapies.[16,19-21] In contrast, MCL-1 downregulation or inhibition promoted apoptosis in cancer cells and increased cancer cell sensitivity to drug treatment.[19,22,23]

Targeted Therapy

MCL-1 has been implicated in innate and acquired resistance to several targeted agents, including BCL-2 inhibitors.[15,20,23] A BCL-2 inhibitor induced upregulation of MCL-1 and other BH3 domain-containing proteins in B-cell lymphoid malignancies, resulting in BCL-2 inhibitor resistance.[15] In addition, downregulation of MCL-1 increased sensitivity to a BCL-2 inhibitor in cell lines of hematologic malignancies and other cancers.[21]

Chemotherapy

MCL-1 overexpression was reported in platinum-resistant cancer cell lines. Targeting MCL-1 using a small interfering RNA (siRNA) or a small molecule inhibitor resulted in apoptosis of the platinum-resistant cancer cells.[19]

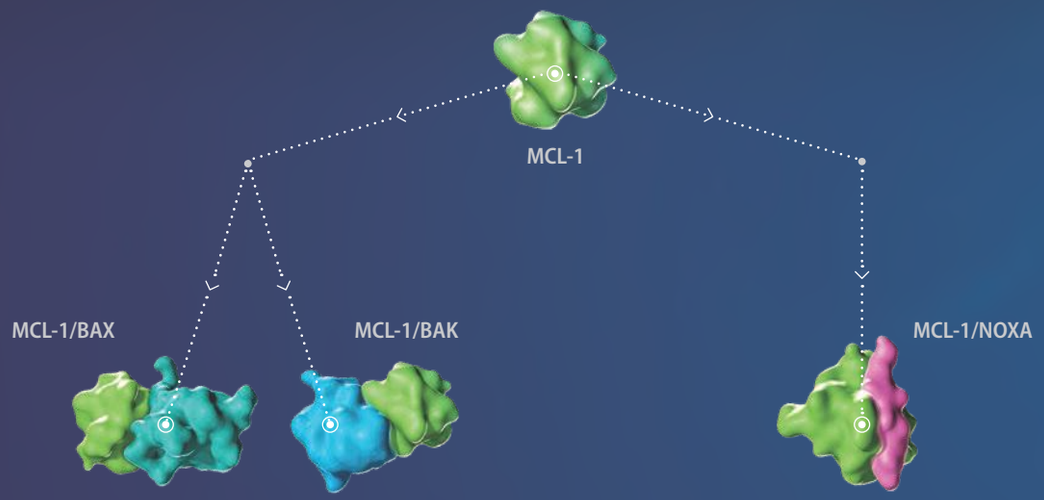
Radiotherapy

MCL-1 overexpression prevents radiation-induced apoptosis. Higher levels of MCL-1 were found in a radiation-resistant subclone compared with a radiation-sensitive parental counterpart. siRNA-induced downregulation of MCL-1 correlated with reduced levels of MCL-1 in radiation-resistant cells, indicating its role in maintenance of mitochondrial homeostasis and cell survival.[22]

MCL-1 Allows Cancer Cells to Evade Apoptosis

Antiapoptotic proteins, such as MCL-1, bind and sequester proapoptotic molecules, inhibiting apoptosis. Overexpression of MCL-1 increases sequestration of proapoptotic proteins, thus allowing cancer cells to evade apoptosis.[1,2] MCL-1 also regulates cell cycle progression via interactions with critical cyclin-dependent kinases and checkpoint inhibitors.[3-8]

MCL-1 Regulates Apoptosis Via 2 Distinct Models[2,9]



Direct Activation Model

- MCL-1 directly binds and sequesters proapoptotic BAK and BAX molecules
- Inhibits homo-oligomerization of BAK and BAX, and disrupts the intrinsic apoptotic cascade

Indirect Activation Model

- MCL-1 binds and sequesters the proapoptotic BH3-only proteins such as NOXA, BAD, BID, BIM, and PUMA
- Prevents BH3-only proteins from inducing homo-oligomerization* of BAK and BAX

*Homo-oligomerization: formation of a molecular complex with identical proteins.
BAD, BCL-2-associated agonist of cell death; BAK, BCL-2 antagonist/killer 1; BAX, BCL-2-associated x; BID, BH3 interacting domain death agonist; NOXA, phorbol-12-myristate-13-acetate-induced protein 1; PUMA, p53 upregulated modulator of apoptosis.

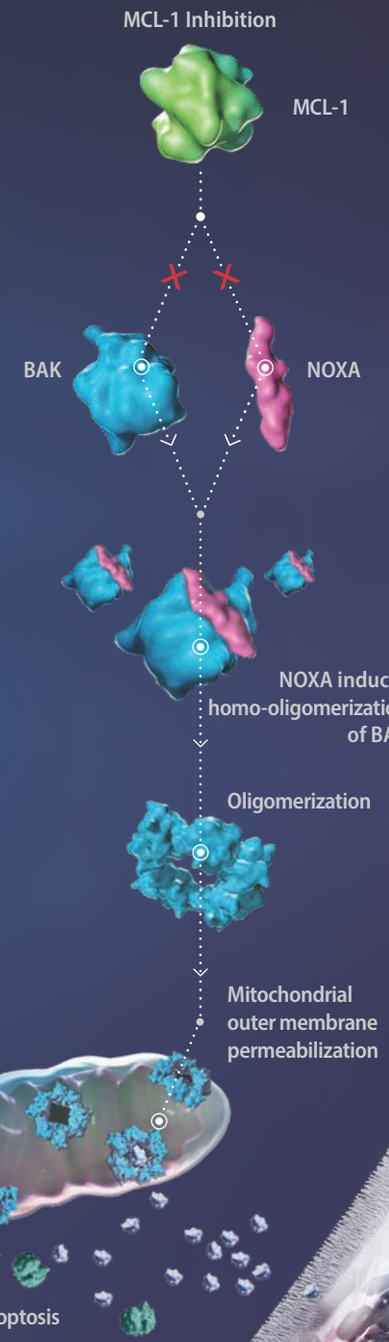
Targeting MCL-1 Is a Potential Strategy for Inducing Apoptosis in Hematologic Malignancies

MCL-1 represents a distinct target in cancer because of its role in antiapoptotic signaling, cell viability, and drug resistance.[1,2,20] In AML, MM, and NHL, MCL-1 contributes to cancer cell survival and apoptosis resistance.[1,2,15,16,24,25]

In vitro studies have established that AML and MM cells are primarily dependent on MCL-1 for survival.[16,24,26] In both MM and NHL subtypes, chromosome 1q21 amplifications enhance expression of MCL-1.[15,27]

MCL-1 inhibition has demonstrated anticancer activity in hematologic malignancies and solid tumors in preclinical studies.[1,2,24,28] MCL-1 inhibition potentially offers a new approach in clinical trials, and further research is warranted.[1,6,28]

AML cells are more susceptible to loss of MCL-1 compared to normal hematopoietic stem and progenitor cells.[26] The inhibition of MCL-1 through the disruption of the antiapoptotic complex of MCL-1 with either BAK or BAX can lead to decreased cell viability and the induction of apoptosis in various cancer cell lines.[1,24,28]

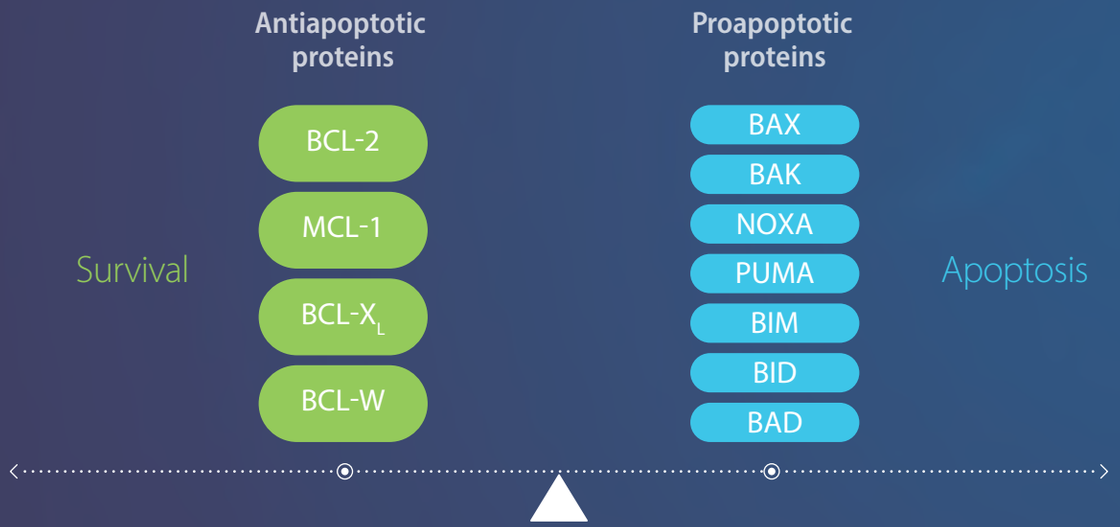


MCL-1 and Other BH3 Domain-Containing Proteins Play an Important Role in Cell Survival

Apoptosis is a highly regulated mechanism that maintains tissue homeostasis. It is dysregulated in a variety of diseases, including cancer.[2,29]

MCL-1 and other BH3 domain-containing proteins serve as primary regulators of apoptosis. These proteins are divided into 2 distinct groups depending on their effect on apoptosis.[2]

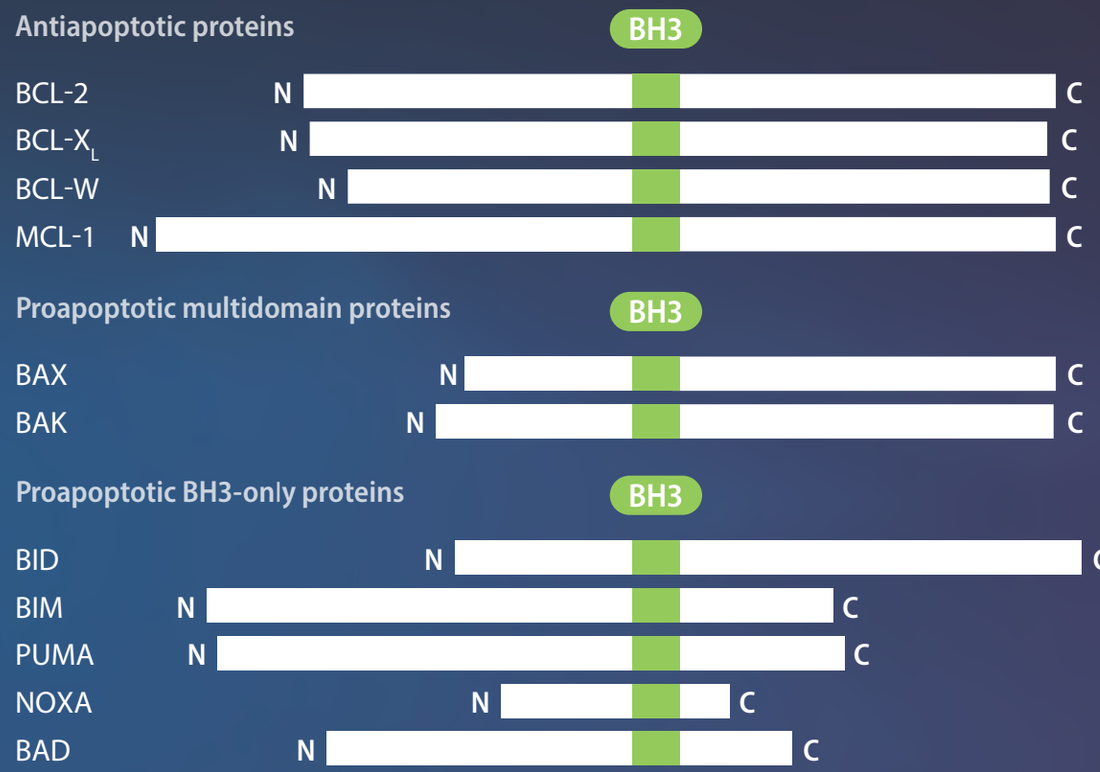
These proteins interact through a complex network of protein-protein and protein-membrane interactions. The relative levels of pro- and antiapoptotic proteins determine whether a cell will survive or undergo apoptosis.[2,9,30]



The antiapoptotic proteins differ in their binding affinity for target proteins and small molecule inhibitors due to subtle differences within the hydrophobic groove of their binding pockets.[2,15,31] As such, the antiapoptotic proteins need to be targeted individually because they bind compounds with different affinities.[32]

BCL-X_L, B-cell lymphoma extra large.

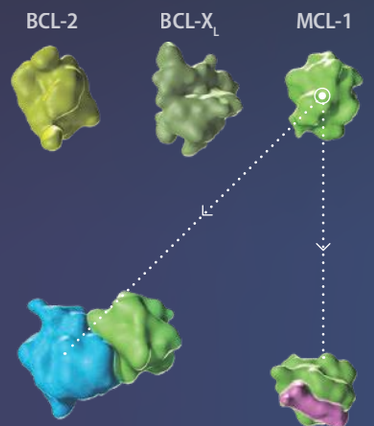
BH3 Domain-Containing Proteins Share Sequence Homology[2,30]



The BH3 domain-containing proteins function through interactions in conserved regions known as BCL-2 homology (BH) domains.[2,30] The antiapoptotic proteins are structurally different from proapoptotic proteins and have multiple BH domains. The proapoptotic proteins are further divided into 2 subcategories. BAK and BAX have multiple BH domains, while NOXA, PUMA, BIM, BID, and BAD have only the BH3 domain. The BH3-only proteins have unique functions, such as activating BAK/BAX to induce apoptosis.[2,30]

Pro- and Antiapoptotic Proteins Interact to Regulate Apoptosis[2,9]

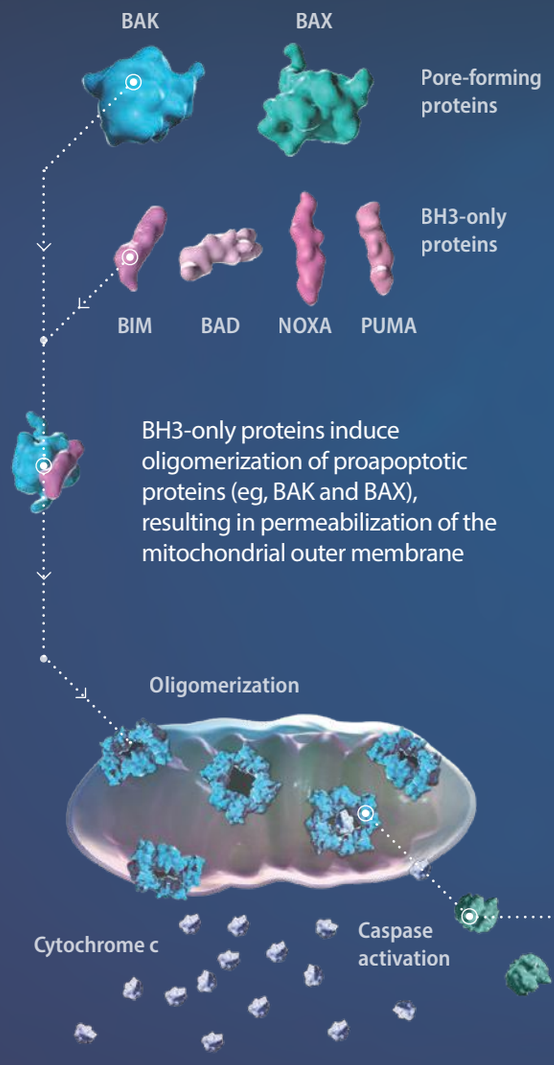
Antiapoptotic Proteins



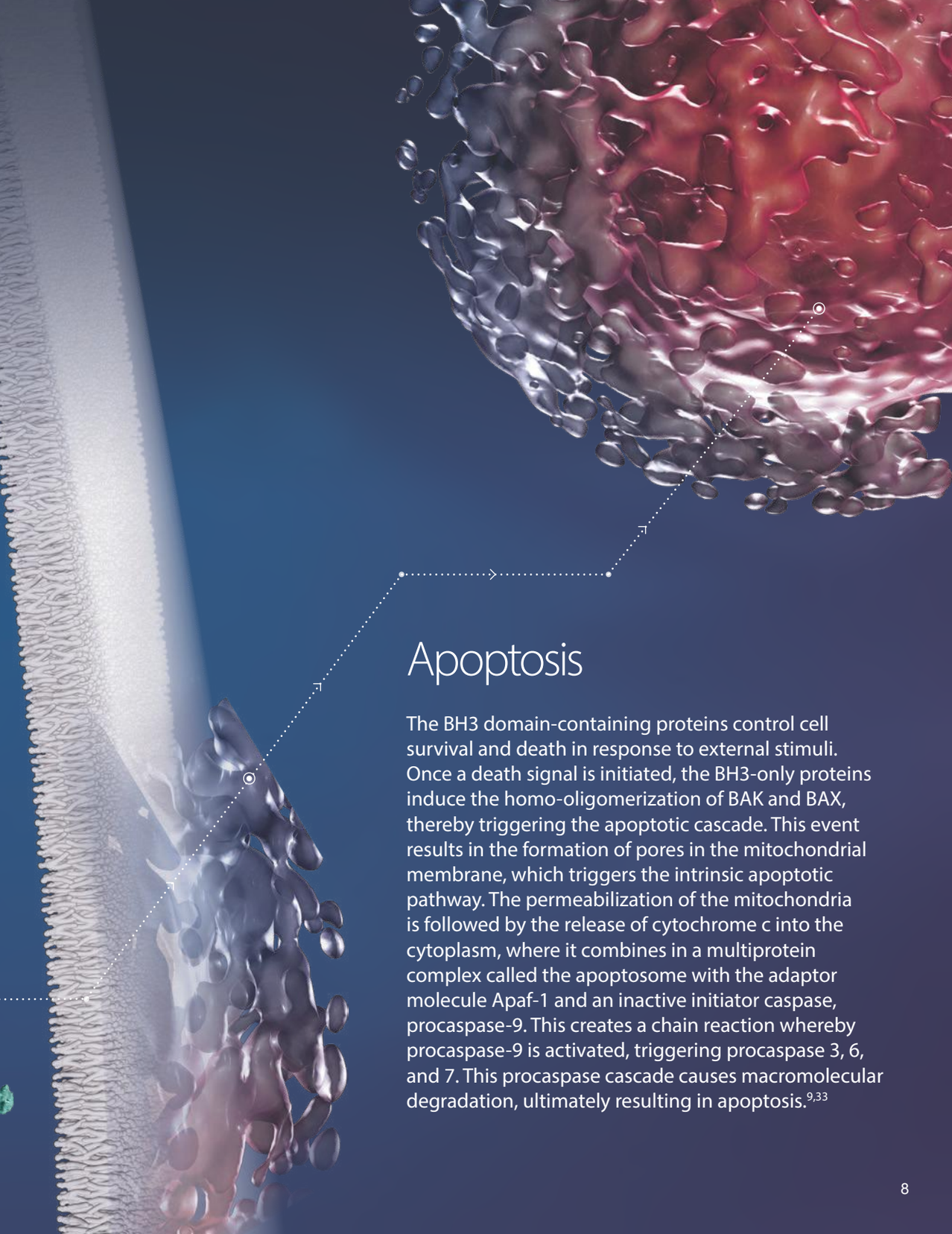
Antiapoptotic proteins inhibit cell death by binding and sequestering proapoptotic proteins

No oligomerization of proapoptotic proteins leads to cell survival

Proapoptotic Proteins



Cytochrome c is released into the cytoplasm, where it activates caspases and results in apoptosis

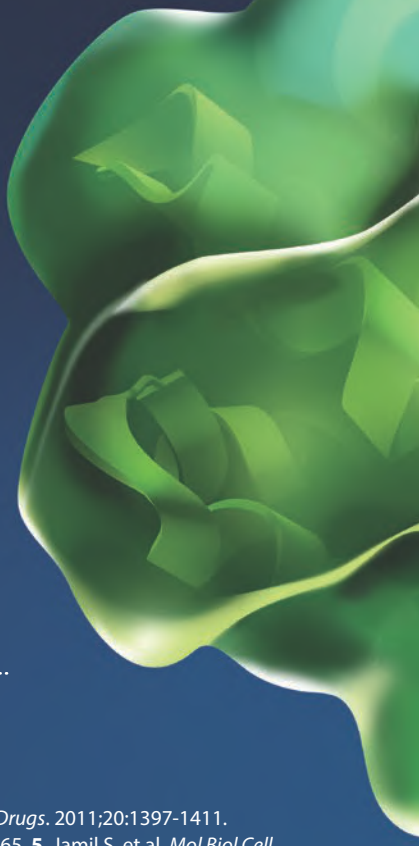


Apoptosis

The BH3 domain-containing proteins control cell survival and death in response to external stimuli. Once a death signal is initiated, the BH3-only proteins induce the homo-oligomerization of BAK and BAX, thereby triggering the apoptotic cascade. This event results in the formation of pores in the mitochondrial membrane, which triggers the intrinsic apoptotic pathway. The permeabilization of the mitochondria is followed by the release of cytochrome c into the cytoplasm, where it combines in a multiprotein complex called the apoptosome with the adaptor molecule Apaf-1 and an inactive initiator caspase, procaspase-9. This creates a chain reaction whereby procaspase-9 is activated, triggering procaspase 3, 6, and 7. This procaspase cascade causes macromolecular degradation, ultimately resulting in apoptosis.[9,33]

Summary

- MCL-1 (myeloid cell leukemia-1), a key regulator of apoptosis and therapeutic target in cancer, is an antiapoptotic member of the BH3 domain-containing proteins[1,2]
- MCL-1 is expressed in a variety of hematologic malignancies, including AML, MM, and NHL[2,15-17]
- In hematologic malignancies, MCL-1 overexpression enhances the growth and survival of cancer cells, and is often associated with poor prognosis and resistance to anticancer therapies[2,16,18]
- MCL-1 represents a distinct target in oncology because of its role in antiapoptotic signaling, cell viability, and drug resistance[1,2,20]



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