Mitochondria: gatekeepers of response to chemotherapy

Kristopher A. Sarosiek1,2, Triona Ni Chonghaile1,2, and Anthony Letai1,2

Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02215, USA
Harvard Medical School, Boston, MA 02115, USA

Mitochondria are cellular organelles that regulate commitment to and execution of apoptosis. The intrinsic apoptotic pathway culminates in the permeabilization of the mitochondrial outer membrane and dismantling of the cell. Apoptosis of cancer cells is a favorable outcome when administering chemotherapeutic treatment, yet the basis for why some cancers are sensitive to chemotherapy whereas others are not has historically been poorly understood. In this review, we present recent work that has demonstrated the importance of mitochondrial apoptotic priming, or how close a cell is to the threshold of apoptosis, in determining whether a cell will undergo apoptosis after chemotherapy treatment. Differential levels of apoptotic priming in tumors create bona fide opportunities and challenges for effective use of targeted and cytotoxic chemotherapies.

Why does chemotherapy work?
A longstanding question among not only patients but also the oncologists that are treating them is ‘why does chemotherapy work?’ This important question is asked because chemotherapy does, at times, work impressively well, leading to long-term cures of otherwise fatal neoplasms. However, despite growing understanding of how cancers arise, grow, metastasize, and eventually overcome the host, the mechanisms behind successful treatment of cancers are poorly understood [1,2]. The key determinants of response to chemotherapy are explored in this review, with a focus on how the pathway of mitochondrial apoptosis affects treatment outcome.

Chemotherapy and apoptosis
Treatment of human malignancies with chemotherapy with curative intent has been successfully conducted for over 50 years, with millions of cancer survivors enjoying long lives after treatment [3]. However, millions more have succumbed to their disease. Regardless of whether they are considered ‘cytotoxic’ or ‘targeted’, most chemotherapies function by inducing a form of irreversible programmed cell death called apoptosis [4–7,7]. Apoptosis can proceed via two distinct pathways: intrinsic and extrinsic [8]. The extrinsic apoptotic pathway is engaged on activation of cell surface death receptors and has a limited, controversial role in chemotherapy-induced apoptosis [2,4,6]. We therefore focus solely on the intrinsic, mitochondrial, apoptotic pathway in this review.

Mitochondrial apoptosis is controlled by the pro- and antiapoptotic proteins of the BCL-2 family, which can be divided into three categories based on their intracellular function and sequence homology (reviewed in [9]). One category includes the antiapoptotic proteins BCL-2, BCL-w, MCL-1, BFL-1, and BCL-XL, which contain all four BCL-2 homology domains (BH1–4). These proteins prevent apoptosis by binding and sequestering their proapoptotic counterparts. The second category, the BH3-only proteins, includes the proapoptotic proteins PUMA, BIM, BID, BAD, BIK, NOXA, and BMF, which contain only the BH3 domain. The final category, the effectors, contains BAX and BAK, which contain domains BH1–3 and can be activated by a subset of BH3-only proteins that includes BIM, BID, and, potentially, PUMA [10–16].

Activation of BAX or BAK initiates a series of steps that results in commitment to apoptotic cell death. It had been suggested that BAX and BAK are activated not by BIM and BID but instead via the inactivation of antiapoptotic BCL-2 family members [17]. However, recent studies have confirmed the direct binding and activation of BAX by BIM and BAK by BID [10,14,18]. Furthermore, although both BIM and BID are able to activate either of the effectors, BIM preferentially activates BAX while BID preferentially activates BAK [7]. On activation, BAK and BAX oligomerize and directly cause mitochondrial outer membrane permeabilization (MOMP), a critical event during apoptosis. Cytochrome c and other factors are released after MOMP and associate with several cytosolic proteins including APAF-1 to activate caspases for dismantling of the cell [8]. Even in the absence of caspase activation, post-MOMP mitochondria are progressively impaired in their ability to generate ATP and cannot maintain cellular survival except in specific, nonphysiological circumstances [8,19,20]. MOMP can thus be considered the ‘point of no return’ in mitochondrial apoptosis.

MOMP, and consequent apoptosis, is triggered clinically when a chemotherapeutic agent induces a sufficient amount of stress within a cancer cell by damaging critical

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Corresponding author: Letai, A. (Anthony.Letai@dfci.harvard.edu).
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cellular components such as microtubules, DNA, or key signaling pathways [2,4,6]. The cell responds by unleashing proapoptotic proteins or downregulating antiapoptotic members of the BCL-2 family, either of which can lead to a shift in the life/death balance in the cell irreversibly towards destruction [4,6,7]. Based on this understanding, both the state of the BCL-2 family of apoptosis-regulating proteins in the cell before encountering the stress and the magnitude of the dynamic response to the stress can have a profound impact on the eventual fate of the cell. These concepts are explored further below.

**Measuring mitochondrial apoptotic priming**

Regulation of the balance of pro- and antiapoptotic proteins within cells, and thus how close a cell is to the threshold of apoptosis, is dependent on many factors. To avoid apoptosis, a cell must express a sufficient amount of antiapoptotic proteins to bind and inactivate what proapoptotic counterparts are also present. Furthermore, most cells contain an additional amount of ‘buffering’ antiapoptotic proteins that can inactivate further pro-death signals that are encountered on a stochastic basis under normal, physiological conditions [5]. The amount of buffering that a cell may employ varies by the type of cell; many cells in the hematopoietic and immune systems maintain relatively small buffers of antiapoptotic proteins [5], probably to enable their quick and efficient elimination as the need arises [21]. Conversely, cells with a longer lifespan such as the highly specialized, fully differentiated cells that constitute vital organs are more buffered against short-term, stochastic fluctuations in cellular stress [5] that could erroneously trigger cell death in a vital cell, to the detriment of the host’s survival (reviewed in [22]). The specific factors that control the level of antiapoptotic buffering within healthy cells are unknown but may involve the epigenetic programming that maintains cell identity [23]. The varying levels of antiapoptotic buffering present within cells can affect the outcome of any event that stresses a cell, including chemotherapy treatment. For instance, a cell may express a very large reserve of unbound antiapoptotic proteins that are available for binding of their proapoptotic counterparts and therefore be protected against even a substantial amount of subsequent pro-death signaling. Alternatively, a cell may express only enough unbound antiapoptotic proteins to just barely keep the proapoptotic proteins in check and would therefore not be protected from even a small stressor. The cell that has a small reserve of unbound antiapoptotic proteins is ‘primed’ for apoptosis whereas the cell that has a large reserve is ‘unprimed’ (Figure 1). Another way to illustrate this dichotomy is to envision two cells, one close to the threshold (cliff’s edge) at which apoptosis is triggered whereas the other is far from that threshold. The one closer to the edge is considered primed whereas the other is unprimed. When these two cells are treated with equal doses of chemotherapy (pushed towards the cliff’s edge), the primed cell will be more likely to trigger apoptosis than the unprimed cell if their dynamic response to chemotherapy (strength of push towards edge) is equal (Figure 2A). Although it aids understanding to define priming in this way, priming is measured by a functional test and thus a label of primed or unprimed can be assigned only based on a given cell’s response to systematic proapoptotic stimuli as described below.

Because there may be substantial utility in knowing how close a cancer cell is to the threshold of apoptosis, an assay called BH3 profiling has been developed to measure priming in cancerous and normal cells. The basic principle is to expose mitochondria to peptides derived from the BH3 domains of pro-death BH3-only proteins and measure the resulting magnitude of MOMP (for the full methods, see [24]). Heightened sensitivity of mitochondria to BH3 peptides such as BAD BH3 or NOXA BH3, with selective

![Figure 1](image-url)
binding to antiapoptotic proteins, might indicate selective dependence on BCL-2 or MCL-1 [25–27]. Heightened sensitivity to peptides that exhibit promiscuous binding to antiapoptotic proteins, such as BIM BH3 or PUMA BH3, indicates a highly primed state, with a low reserve of unbound antiapoptotic proteins [5,27–29].

In practice, the assay is typically performed by gently permeabilizing the plasma membrane of cells and adding fixed doses of BH3 peptides derived from the BH3 domain of proapoptotic BH3-only proteins. Mitochondrial potential is then monitored for detection of MOMP, which occurs when the antiapoptotic reserve is exhausted within a cell and BAX and/or BAK are activated (Figure 1). Cells can be labeled as primed or unprimed based on the extent of mitochondrial depolarization (MOMP) that occurs in response to a fixed titration of pro-death BH3 peptides: the faster a cell is depolarized, or the lower concentration of peptide required for MOMP, the more primed it is.

Functional assays such as BH3 profiling are critical for the measurement of apoptotic priming within a cell. The activities of the BCL-2 family of proteins are regulated by a plethora of post-translational modifications and interactions with other proteins [30]. Measuring the expression level of each member of the BCL-2 family, their modifications, and the proteins they are interacting with is not a practical task and, due to additional unknown factors that may modify their activity, may not even provide an accurate assessment of priming and thus creates a need for a function-based assay. By treating a cell with fixed doses of proapoptotic signaling in BH3 profiling, it is possible to measure the integrated functional output of the BCL-2 family efficiently and meaningfully [5].

Mitochondrial apoptotic priming determines tumor response to cytotoxic chemotherapy

Using BH3 profiling to measure levels of apoptotic priming across a range of cancer types, it has been shown that primed cells readily undergo apoptosis in response to cytotoxic chemotherapy whereas unprimed cells are less likely to do so (Table 1) [5]. Notably, this holds true not only in cancer cell lines but also in primary tumors and can be predictive of how patients will respond to chemotherapy in the clinic [5,29]. In addition, cells within tumors that have undergone treatment and then recurred are frequently less primed, making them less sensitive to subsequent rounds of chemotherapy [5,29,31]. The selective pressure of chemotherapy likely culls primed cancer cells, leaving only unprimed cells to repopulate the tumor [5,29]. These unprimed relapsed tumors are frequently intractable.

Experiments measuring mitochondrial priming have also uncovered a greater understanding of apoptotic signaling in cancer cells and normal cells. A longstanding
misconception is that cancers must ‘disrupt’ or ‘disable’ apoptosis [4,32,33], which some interpret as meaning that cancer cells are inherently less sensitive to subsequent apoptotic signaling than normal cells. Disruption or disabling of apoptosis would require complete loss of signaling in the mitochondrial apoptotic pathway via, for example, total loss of BAX and BAK expression, yet this is rarely observed in cancers. Cancers commonly upregulate anti-apoptotic proteins or downregulate their proapoptotic counterparts to keep apoptosis at bay (reviewed in [30,34]), but this does not equate to disruption or disabling of the apoptotic pathway. In fact, there is little evidence that cancer cells are more refractory to apoptosis than normal cells. Although most cancers have an intact apoptotic pathway, some tumors are even highly primed for apoptosis, as demonstrated by their efficient mitochondrial depolarization in response to proapoptotic signaling in the form of BH3 peptides. This depolarization often exceeds that observed in normal somatic cells [5]. This confirms that most cancers not only express the critical effectors BAX and/or BAK and have an intact mitochondrial apoptotic pathway, but are also primed for apoptosis. The cancers that are highly primed are those that respond most favorably to chemotherapy (acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL)), whereas those that are unprimed respond poorly (endometrial and renal cell carcinomas, serous borderline tumors) [5,28,29]. The therapeutic index of conventional chemotherapy, which is directed against ubiquitous targets such as DNA and microtubules, probably derives largely from the fact that cancer cells are more ready to engage the machinery of apoptosis than normal cells, not less [5,29]. Indeed, it is unlikely that anyone would ever be cured via conventional chemotherapy, if some cancer cells were not sometimes much more primed for apoptosis than most normal cells.

Other measures of the readiness of cancer cell mitochondria to undergo cell death have been utilized to predict cellular responses to chemotherapy. For example, measuring the propensity of tumor cells to spontaneously activate caspase 3 has prognostic value for response to chemotherapy in anaplastic lymphoma [35]. In colorectal cancer, measuring and integrating the protein expression levels of several BCL-2 family members may predict how patients will respond to chemotherapy [36]. Although these other measurements are not functional tests of apoptotic priming as defined here, they nonetheless validate the importance of pretreatment apoptotic signaling in cell fate decisions.

### What determines how primed a tumor will be?

Although cancers have wide-ranging levels of mitochondrial priming that contribute to their responses to chemotherapeutic agents [5,28,29], it is unclear what determines the level of priming within a cell or tumor. At the cellular level, an attractive hypothesis is that the level of priming evident in a tumor cell is determined, at least in part, by the level of priming evident in the cell that gave rise to the tumor itself. Lending evidence to this concept is the observation that the most highly primed cancers are derived from the most highly primed normal tissues and vice versa. For instance, acute lymphoblastic leukemia cells are among the most highly primed and the most chemoresistant of cancers. They derive from the lymphocytic lineage, which is among the most highly primed lineages in the body [5,26,29] and is among the most chemoresistant [37]. Conversely, chemoresistant primary tumors, including renal cell carcinomas and endometrial cancers, are unprimed, as are the normal, healthy cells they are derived from [5]. Thus, cell lineage may be a strong determinant of the overall apoptotic priming of a tumor.

At the molecular level, the level of priming is regulated by the expression and post-translational modification state of BCL-2 family proteins – but what in turn regulates this? Most likely, priming results from the combined contributions of many signaling pathways. In normal cells, various signaling pathways can modulate BCL-2 family expression for regulation of survival. For example, the survival of mature B cells requires prosurvival B cell receptor signaling [38,39], which was recently shown to be mediated by phosphatidylinositol (PI) 3-kinase (PI3K) [40]. The PI3K prosurvival signals in these cells are controlled by Akt and the FOXO family of transcription factors that eventually modulate levels of the proapoptotic protein BIM [40].

### Table 1. Major determinants of chemotherapy success (why chemotherapy works)

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Target</th>
<th>Examples</th>
<th>Determinants of therapy success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical cytotoxic therapy</td>
<td>Ubiquitous cellular elements (microtubules, DNA, topoisomerases)</td>
<td>Paclitaxel (microtubules), topotecan (topoisomerase III), doxorubicin (DNA)</td>
<td>Pretreatment mitochondrial apoptotic priming Signalizing dynamics post-treatment</td>
</tr>
<tr>
<td>Targeted therapy</td>
<td>Cell specific targets (mutated oncogenes, differentially expressed oncogenes)</td>
<td>Erlotinib (EGFR), vemurafenib (V600E), imatinib (BCR-ABL)</td>
<td>Presence or absence of target Pretreatment mitochondrial apoptotic priming, signaling dynamics post-treatment</td>
</tr>
<tr>
<td>Antibody-based therapy</td>
<td>Cell surface markers</td>
<td>Rituximab (anti-CD20 antibody), brentuximab-vedotin (anti-CD30:MMAE antibody-drug conjugate)</td>
<td>Presence or absence of target Immune system competence</td>
</tr>
<tr>
<td>Immune modulation (reversal of immune checkpoint blockade)</td>
<td>Immune system (tumor tolerance, tumor-associated macrophages)</td>
<td>Ipilimumab (anti-CTLA4 antibody),</td>
<td>Immune system antitumor response Immune system competence Melanoma [68,89]</td>
</tr>
</tbody>
</table>

*References* [30,34,5,28,29,4,32,33,615,36,37,38,39,40].
The same pathways that modulate apoptosis in healthy cells are aberrantly expressed in cancer cells to maintain survival. PI3K, for example, is inappropriately activated in a wide range of malignancies and confers a strong enough survival advantage to cancerous cells that it is being targeted pharmacologically for cancer therapy (reviewed in [41,42]). Other common oncogenes and tumor suppressors that are deregulated in cancer have been shown to have pro- or antiapoptotic effects, including p53 [43], Notch [44], and Wnt [45] among others including the BCL-2 family. Interestingly, activation of some oncogenes, especially c-Myc, can have a strong proapoptotic effect [46–48] and thus is likely to contribute to the final overall level of priming in cancer cells.

Unsurprisingly, the tumor microenvironment is also a strong modulator of apoptotic priming. CLL, for example, is commonly treated with chemotherapy, yet cancerous cells exhibit differing levels of chemosensitivity, with a subpopulation of cells proving to be intractable and supporting relapse [28,49]. Cells residing within lymph nodes upregulate antiapoptotic BCL-XL and BCL2A1 (BFL-1) to reduce apoptotic priming, making them more likely to survive treatment [28,49]. The interactions of cancer cells with stroma can lead to chemotherapy resistance in both solid and liquid tumors (reviewed in [50]). In addition, stimulation with exogenous growth factors [48,51,52] can affect BCL-2 family protein expression and sensitivity to chemotherapy. In one such example, hepatocyte growth factor (HGF) was recently identified in a cancer cell and stroma coculture screen to induce a chemoresistant phenotype in tumor cells by activating PI3K [52], whose role in the modulation of apoptosis has already been discussed.

The pretreatment level of priming in a tumor is likely to be determined by the level of priming in the cell of origin and modulated by the microenvironment of the cell and by the pro- and antiapoptotic effects of the various perturbations that have occurred during tumorigenesis.

The chemotherapeutic window

Understanding the mitochondrial priming of the tumor alone, however, is insufficient to understanding the source of a chemotherapeutic window. The key to achieving a desirable outcome from chemotherapy is as much dependent on the lack of priming in vital organs as the priming in the tumor. When comparing apoptotic priming across healthy tissues, one can see that most healthy tissues are unprimed, which allows vital organs such as the liver, heart, brain, and kidneys to survive high doses of chemotherapy relatively unscathed [5]. The lack of priming in these vital tissues is demonstrated by their attenuated response to relatively large doses of proapoptotic BH3 peptides [5]. However, the molecular mechanisms that maintain this low level of priming in vital tissues are unknown and an active area of investigation. There are, of course, some effects of chemotherapy on these tissues, including long term pathologies such as doxorubicin-induced cardiotoxicity [53], but these organs generally continue to function during and after chemotherapy. Some healthy tissues, however, exhibit a high level of apoptotic priming, especially the hematopoietic system, which renders them sensitive to chemotherapy. A loss of the bulk of the hematopoietic system seems to be survivable, however, as evidenced by the frequent myelosuppression that accompanies chemotherapy even in those patients that are cured. In general, cells from tumors that are chemosensitive are more primed than their non-transformed counterparts, thus creating a therapeutic window for tumor response to therapy [5]. For the most broadly cytotoxic chemotherapies that target common cellular elements across all cells, successful treatment relies on a level of priming in the tumor higher than that in healthy tissues (Figure 3).

Mitochondria in targeted chemotherapies and immunochemotherapies

Mitochondrial priming also has a likely role in the cellular response to targeted chemotherapies. Although ‘classical’ cytotoxic chemotherapies can have quite specific targets (e.g., paclitaxel for microtubules, topotecan for topoisomerase II), for the purpose of this review only agents that target non-ubiquitous cellular components are considered targeted agents. Much progress has been recently made in the development of targeted agents that have the potential to be selectively toxic to cancer cells that are dependent on that target over healthy tissues that lack it (reviewed in [54]). Most of these targeted agents exert their anticancer effects by engaging the same mitochondrial apoptotic pathways as classical chemotherapies, which proposes a potential role of apoptotic priming in the response to these agents [55–57]. The largest determinant of apoptotic response to targeted agents, however, is a given cell’s dependence on the protein or signaling pathway being targeted (Figure 2B and Table 1). For example, a cell that is dependent on the epidermal growth factor receptor (EGFR) will upregulate proapoptotic BIM when EGFR signaling is inhibited, thus pushing the balance of BCL-2 family proteins towards apoptosis [57–59]. Cells lacking dependence on EGFR are unaffected by these inhibitors [57–59] and thus even a high level of mitochondrial priming in these cells is unlikely to trigger cell death (Figure 2B). Conversely, cells that are not highly primed but exhibit strong...
dependence on the targeted pathway may respond to the inhibitor with enough proapoptotic stress signaling that apoptosis is triggered (Figure 2B). Therefore, the magnitude of the response to the inhibitor is likely to be the most important factor in determining whether the cell will live or die. However, in cells that exhibit similar levels of dependence on a targeted pathway and thus similar dynamic signaling responses to the inhibition of that pathway, the level of mitochondrial priming may affect whether apoptosis will occur. A highly primed cell would need a smaller dynamic proapoptotic response to an agent to trigger apoptosis than an unprimed cell (Figure 2C and Table 1).

It is likely that using targeted agents in cells that are dependent on the target yet are unprimed may have clinical benefits even without apoptosis being induced by the targeted therapy alone. Specifically, agents targeting cancer-specific proteins or growth signaling pathways may induce a level of apoptotic stress within a cancer cell that is perhaps insufficient to trigger apoptosis but may upregulate proapoptotic proteins, thus increasing mitochondrial apoptotic priming. In this context, an additional chemotherapeutic agent, targeted or not, could provide the final bolus of proapoptotic signaling necessary to activate MOMP (Figure 2D). This has been convincingly demonstrated with many ‘priming’ agents [28,56,60–62]. These priming agents, with diverse targets including histone deacetylases and PI3K, modify levels of the BCL-2 family to improve responses to cytotoxic chemotherapy [56,61]. In addition, a novel class of agents, BH3 mimetics, has been shown to potently and specifically inhibit several antiapoptotic members of the BCL-2 family, including BCL-2, BCL-XL, and BCL-W. The administration of these agents can increase the priming of a cancer cell and thus make other, concurrently administered chemotherapies more effective [29,36,63–66].

Mitochondrial priming probably plays a smaller role in the responses of cancer cells to therapies that are based on activating an antitumor response by the immune system (Table 1). These therapies include monoclonal antibody therapies directed at cell surface markers expressed on tumor cells, immunomodulatory agents, and allogeneic stem cell transplantation. Although monoclonal antibodies targeting tumor cells can sometimes directly induce apoptosis in target cells, they most commonly rely on antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity to activate immune effector cells for maximal effectiveness [67]. In addition, agents that modulate the immune system directly, such as the anti-CTLA4 antibody (ipilimumab), enhance the antitumor responses of cytotoxic T cells [68]. Because the mitochondrial apoptotic pathway is involved in the direct antitumor cell activity of some of these therapies, priming may have a role in determining response. However, this role would probably be overshadowed by other key determinants of response and resistance including the presence or absence of the cell surface marker on the tumor cell and immune competence [67,69]. In the case of allogeneic stem cell transplantation, an adaptive immune response of the donor’s T cells against the host tumor is required. At least in acute myelogenous leukemia, the success of this strategy is not affected by the apoptotic priming of tumor mitochondria [29].

Alternative determinants of chemotherapy effectiveness

Although recent results have suggested that priming is the major determinant of chemotherapy effectiveness [5,28,29], several laboratories have provided evidence of alternatives. In mitochondria specifically, chemotherapy response has been linked to defects in mitochondrial respiratory chain complexes caused by loss of specific cytochrome c oxidase subunits [70]. The loss of these subunits was observed clinically in a subset of esophageal adenocarcinomas and was associated with increased sensitivity to chemotherapy, suggesting that mitochondrial defects can develop during tumorigenesis and may contribute to the chemotherapeutic window.

A longstanding theory of chemotherapy effectiveness has been that the proliferation rate of cancer cells determines their sensitivity to chemotherapy. However, this explanation is inadequate because clinical observations have shown that many chemosensitive cancers proliferate very slowly whereas many chemoresistant cancers proliferate quickly [71–75]. In addition, some non-proliferating healthy cells (resting B cells, for example) are extremely sensitive to DNA-damaging agents [37], thus making it less likely that proliferation alone is the basis for chemosensitivity, despite its favored place in textbooks and general opinion in oncology.

Concluding remarks

Mitochondria have a well-established and prominent role in chemotherapy effectiveness that should be exploited for cancer therapy. Specifically targeting the BCL-2 family is a strategy that has already shown promise; the BCL-2/BCL-XL/BCL-w inhibitor ABT-737 and its derivatives have activity against multiple types of blood cancer [64] and some solid tumors [76–78]. Other strategies to inhibit these proteins are also in various stages of preclinical development (reviewed in [79]). One antiapoptotic member of the BCL-2 family, MCL-1, is also a promising target in cancer therapy but has so far eluded efforts to effectively target it for cancer therapy. Other strategies to target this family, including stapled α-helices that can penetrate cells and act as inhibitors of antiapoptotic proteins, are also being pursued [80,81]. Another interesting strategy to overcome chemotherapy resistance is direct pharmacological activation of the proapoptotic effector BAX [82].

The successful use of chemotherapy to treat malignancies for over five decades is based, at least in part, on high levels of mitochondrial priming in chemosensitive tumors, a concept only recently demonstrated [5]. As we continue to broaden our understanding of apoptosis and how it is regulated, we hope to uncover critical new vulnerabilities within this pathway in cancers.

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References
10 Czabotar, P.E. et al. (2013) Bax crystal structures reveal how BH3 domains activate Bax and nucleate its oligomerization to induce apoptosis. Cell 152, 519–531
17 Willis, S.N. et al. (2007) Apoptosis initiated when BH3 ligands engage multiple Bcl-2 homologs, not Bax or Bak. Science 315, 856–859
36 Lindner, A.U. et al. (2013) Systems analysis of BCL2 protein family interactions establishes a model to predict responses to chemotherapy. Cancer Res. 73, 519–528
56 Bender et al. (2011) PI3K inhibitors prime non-hematoma cells for chemotherapy by shifting the balance towards pro-apoptotic Bcl-2 proteins and enhanced mitochondrial apoptosis. Oncogene 30, 494–503
57 Deng, J. et al. (2007) Proapoptotic BH3-only BCL-2 family protein BIM connects death signaling from epidermal growth factor receptor inhibition to the mitochondrion. Cancer Res. 67, 11867–11875
59 Cragg, M.S. et al. (2007) Gefitinib-induced killing of NSCLC cell lines expressing mutant EGFR requires BIM and can be enhanced by BH3 mimetics. PLoS Med. 4, 1681–1689 discussion 1690
73 Marcus, R. et al. (2005) CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood 105, 1417–1423