

Noxa and cancer therapy

Tuning up the mitochondrial death machinery in response to chemotherapy

Marie-Christine Albert, Kerstin Brinkmann, and Hamid Kashkar

Centre for Molecular Medicine Cologne (CMCC); Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD); and Institute for Medical Microbiology, Immunology and Hygiene (IMMIH); University of Cologne, Köln, Germany

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Abbreviations: ER, endoplasmic reticulum; HDACi, histone deacetylase inhibitor; MOMP, mitochondrial outer membrane permeabilization; ROS, reactive oxygen species; UPR, unfolded protein response

Biochemical analyses have characterized the BH3-only protein family member Noxa as a “sensitizer” with weak pro-apoptotic activity. Investigations into cancer cell responses to chemotherapeutic agents have identified Noxa as a pivotal factor mediating the cytotoxic effect of a plethora of anticancer treatments independent of its own pro-apoptotic activity. Accumulating evidence now suggests that tumor cells exert a number of strategies to counteract Noxa function by exploiting diverse cellular regulatory circuits that normally govern Noxa expression during cellular stress responses. Here, we summarize data concerning the role of Noxa in cancer chemosensitivity and highlight the potential of this enigmatic BH3-only protein family member in current and novel anticancer therapies.

expression profiles between X-ray-irradiated wild-type and interferon regulatory factor-1 (IRF-1)/p53 double deficient mouse embryonic fibroblasts (MEFs). The isolated cDNA encodes an 103-amino acid protein lacking any known motif except for 2 mutually related 9-amino acid sequences (A and B) characteristic for the Bcl-2 homology 3 (BH3) motif of the Bcl-2 protein family.³ A notable feature of murine Noxa is the presence of two BH3 regions, whereas human Noxa (and all other known BH3-only proteins) contains a single BH3 domain. Similar to murine *Noxa*, the human gene contains 3 exons but the corresponding transcript contains only sequences from exons 1 and 3, omitting exon 2.² The two BH3 regions in mouse *noxa* may have arisen by tandem duplication and fusion of the entire ancestral gene (two exons and intervening intron) producing a fusion protein comprised of 2 nearly identical *Noxa* open reading frames.⁴

Introduction

Noxa cDNA was first cloned from a human cDNA library generated by a differential plaque hybridization assay designed to identify gene products involved in leukemogenesis of adult T-cell leukemia (ATL).¹ A single cDNA clone (1,897 base pairs) consisting of a short open reading frame encoding a polypeptide of 54 amino acid residues was identified. The 2.0-kb mRNA transcript was rapidly and transiently upregulated by treatment with phorbol-12-myristate-13-acetate (PMA) and the corresponding gene was designated ATL-derived PMA-responsive gene (*APR*), although it was later given the Human Genome Organisation (HUGO) designation PMA-induced protein 1 (*PMAIP1*).² In an independent approach the *Noxa* (greek for damage) gene was identified using an mRNA differential display method comparing mRNA

BH3-Only Proteins

The Bcl-2 protein family represents the key regulatory node of mitochondrial apoptosis and consists of anti-apoptotic proteins (e.g., Bcl-2, Bcl-xl, Bcl-w, A1, Mcl-1) and two groups of pro-apoptotic proteins: multi-domain proteins (e.g., Bak, Bax) and BH3-only proteins (e.g., Bim, Bid, Puma, Bad, Noxa). The decisive event of mitochondrial apoptosis is mitochondrial outer membrane permeabilization (MOMP), which is tightly controlled by the activation and composition of pro- and anti-apoptotic Bcl-2 proteins. Upon MOMP, multiple pro-apoptotic molecules are released from the mitochondrial intermembrane space to coordinate most of the hallmark events of apoptosis such as nuclear condensation and activation of caspases, ultimately resulting in cellular self-destruction. Inefficient MOMP caused by imbalanced expression levels of Bcl-2 protein family members is considered to be one of the key determinants of therapeutic resistance to a number of anticancer regimens. Accordingly, research efforts have lately focused on the development of drugs targeting Bcl-2 proteins, which is considered a promising strategy for the treatment of human cancer.⁵

In response to cellular stress cues, BH3-only proteins regulate the activity of multidomain Bcl-2 proteins either by binding

*Correspondence to: Hamid Kashkar; Email: h.kashkar@uni-koeln.de
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to the anti-apoptotic Bcl-2 family members and thereby derepressing the pro-apoptotic proteins Bax and Bak, or by direct interaction with and activation of Bax and Bak.^{6,7} Furthermore, although BH3-only proteins were initially believed to bind indiscriminately to all anti-apoptotic Bcl-2 members, extensive biochemical analyses have revealed that their affinity and pro-apoptotic capacity varies enormously.^{5,8,9} Correspondingly, two functional classes of BH3-only proteins can be distinguished: so-called “activators” (promiscuous binders, including the BH3-only members Bim, Puma, and truncated Bid [tBid]), which are able to directly activate pro-apoptotic Bcl-2 family members, and “sensitizers” (including BH3-only proteins with weak pro-apoptotic activity such as Noxa and Bad), that initiate cell death only in conjunction with other BH3-only members.^{8,10}

Noxa: the Specific Counterpart of Mcl-1

Independent of its own inherent pro-apoptotic activity, the critical role of Noxa in regulating Mcl-1 is a unique property of this protein among other BH3-only protein family members. Myeloid leukemia cell 1 (*mcl1*) is an immediate-early gene that is activated during 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced myeloid cell differentiation and contributes both to cell viability and to the regulation of cell proliferation by interfering with a number of cellular signaling networks.^{11,12} Extensive biochemical, genome-wide, and in vivo studies identified Mcl-1 and its alteration as one of the fundamental characteristics of cancer associated with both the carcinogenic process and tumor cell response to anticancer therapy. Mcl-1 is widely expressed throughout many tissues and alterations in its expression level have been frequently observed in a variety of human cancers. As the procancer activity of Mcl-1 requires increased protein expression levels, the cancer genome adapts to ensure either high levels of synthesis, or evasion of its regulation, or both.¹³ Early biochemical studies showed that Noxa has the most restricted potential to neutralize Mcl-1, and later evidence suggests that Noxa is crucial in fine-tuning cell death decisions by specifically targeting Mcl-1.^{2,10,14} Thus, knowledge of how Noxa is regulated indirectly provides mechanistic insights into the cellular regulatory circuits governing Mcl-1 activity.

Regulatory Mechanisms Controlling Noxa Abundance and Function

Noxa was initially identified as a primary p53-responsive gene, providing the first evidence for the transcriptional regulation of *Noxa* in response to genotoxic stress.¹⁵ Complementary analyses demonstrated transcriptional upregulation of *Noxa* independent of p53 during cellular responses involving HIF-1 α , E2F1, p73, c-myc, FOXO3, and PI3K/AKT/mTOR signaling and cAMP response element-binding (CREB) protein as the responsible downstream transcription factor.¹⁶⁻²³ Furthermore, the transcriptional upregulation of *Noxa* seems to rely on post-translational modifications of IRF-1, IRF-3, and CREB in a p53-independent

manner.²⁴ Accordingly, elevated levels of *Noxa* transcript have been detected in mantle cell lymphoma (MCL) possessing a constitutively active PI3K/AKT/mTOR signaling pathway as a result of MCL-specific chronic active BCR signaling as well as cyclin D1 overexpression.²⁵

In addition to transcriptional regulation, *Noxa* function and stability is controlled by post-translational mechanisms. In particular, ubiquitylation of *Noxa* has recently been shown to be involved in the regulation of *Noxa* protein turnover and thereby influences cellular stress responses.^{26,27} Specifically, increased ubiquitylation and proteasomal degradation of *Noxa* was demonstrated as one of the central molecular mechanisms conferring resistance to genotoxic stress in a number of tumor samples.^{25,27} These data identified UCH-L1 as a *Noxa*-specific deubiquitylating enzyme that directly interacts with and stabilizes *Noxa* by removing the K48-linked polyubiquitin chains that mark *Noxa* for proteasomal degradation. Epigenetic silencing of UCH-L1 in these tumor samples reduced *Noxa* protein expression.²⁷ Further investigations revealed that *Noxa* turnover might be additionally regulated by the proteasome via an ubiquitin-independent pathway that is blocked by Mcl-1 and requires the 19S regulatory particle subunits of the 26S proteasome (Fig. 1).²⁸

In addition to tight regulation of *Noxa* protein abundance, the pro-apoptotic function of *Noxa* is controlled by its phosphorylation at position S13. This modification by glucose-dependent CDK5 blocks the pro-apoptotic function of *Noxa* at the mitochondria and also determines the cytosolic distribution of *Noxa* in Jurkat cells. This indicates that the cytosolic phosphorylated form of *Noxa* is involved in glucose uptake anticipating the involvement of *Noxa* in cellular actions other than cell death.²⁹ However, the biological significance and the physiological relevance of these findings are still to be determined.

Noxa as an Important Mediator of Cell Death in Response to Anticancer Therapy

Although the involvement of *Noxa* in carcinogenic process remains elusive, its importance as a drug target in cancer is becoming increasingly evident. *Noxa* was initially identified as a primary p53-response gene and has been repeatedly shown to be an important determinant of cell death in response to chemotherapy in cancer.^{15,30} Array-based comparative genomic hybridization (CGH) and gene-expression microarray analyses have already identified mutations or silencing of *Noxa* in cancer.³¹ Furthermore, a number of cancer cell lines have been reported to efficiently resist chemotherapy through modification of *Noxa* stability.^{25,27} Remarkably, *Noxa* was also shown to sensitize tumor cells to cytolytic immune effector cells and additional data from an RNAi-based screen revealed that *Noxa* is involved in cell death induced by tumor necrosis factor-related apoptosis-inducing ligand (TRAIL).^{32,33} Finally, there is accumulating evidence that autophagy interferes with cellular stress responses to chemotherapeutics, and *Noxa* was recently reported to mediate autophagic cell death when oncogenic H-Ras is expressed.³⁴ These studies further revealed that H-Ras-expressing cells undergo autophagic

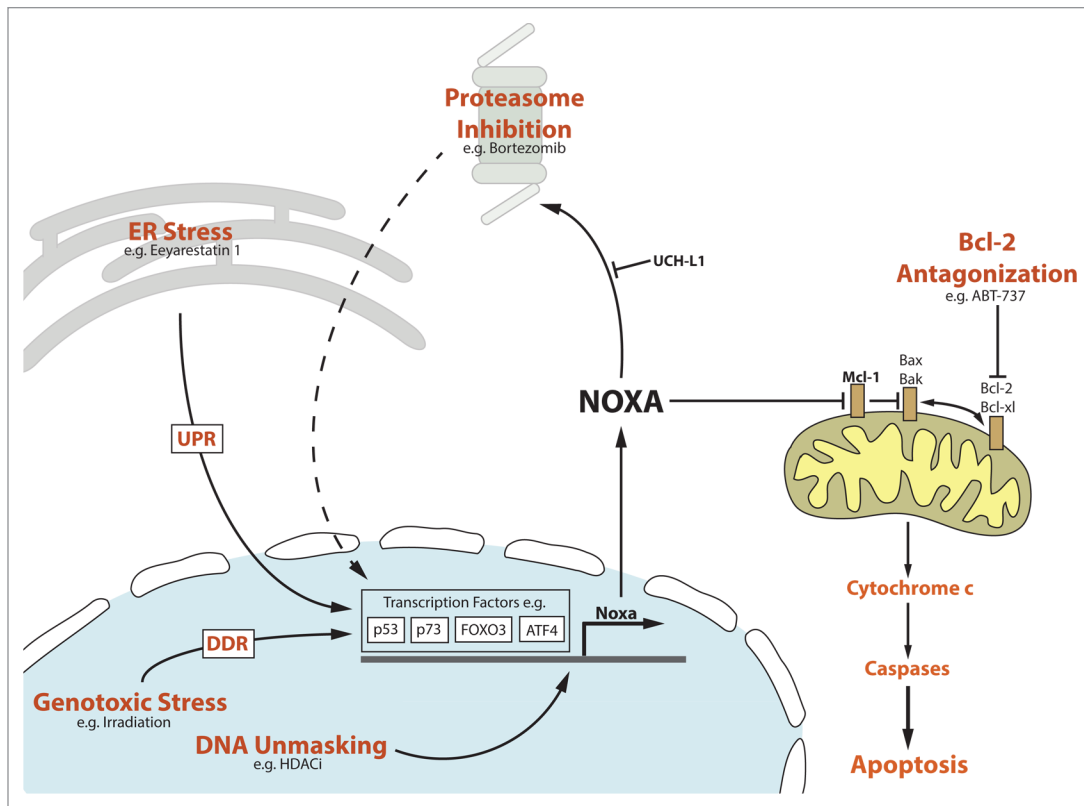


Figure 1. Regulation of Noxa during cellular stress responses to chemotherapeutic agents. Genotoxic stress activates the DNA damage response (DDR) involving transcription factors such as p53, which in turn induces transcriptional upregulation of Noxa. Endoplasmic reticulum stress (ER stress) induces Noxa transcriptional upregulation via activation of the unfolded protein response (UPR) involving transcription factors such as ATF4. Inhibition of the proteasome leads to accumulation of Noxa either post-translationally by stabilizing Noxa protein or transcriptionally by stabilizing p53. Bcl-2 antagonists primarily target Bcl-2/Bcl-xl and induce the mitochondrial apoptotic pathway. Noxa is critically required for efficient antagonism of Mcl-1, which in turn relieves the pro-apoptotic Bcl-2 members Bax and Bak, promotes the release of mitochondrial cytochrome c and activation of caspases, and ultimately induces apoptosis.

cell death as a result of Noxa-mediated displacement of Mcl-1 and Bcl-xl from Beclin 1.^{34,35}

Taken together, these data indicate that Noxa is involved in the regulation of divergent cell death pathways triggered by a plethora of cytolytic treatments in cancer (Fig. 1). Below, we will review current knowledge of how Noxa affects cellular death in response to chemotherapeutic agents (Table 1).

Genotoxic Chemotherapy

The clinical use of DNA damage-inducing agents constitutes a milestone in the treatment of cancer as it has become increasingly apparent that the response to these therapies is highly promising both in terms of anticancer activity and toxicity to noncancer cells. Noxa is transcriptionally upregulated in response to DNA damage triggered by classical anticancer agents such as etoposide or γ -irradiation, resulting in activation of the mitochondrial apoptotic pathway.¹⁵ Accordingly, downregulation of Noxa decreases the susceptibility of HeLa cells to DNA damage-mediated cell death induced by camptothecin treatment or UV irradiation (UV).³⁶ Conversely, a high expression level of

Mcl-1, the anti-apoptotic counterpart of Noxa, determines resistance of HeLa cells to UV-induced cell death.³⁷ Similarly, *Noxa*^{-/-} MEFs were shown to be resistant to DNA damage induced by etoposide or UV.³⁸ Furthermore, p53-dependent upregulation of *Noxa* transcript is required for tumor cell death in vivo in an UVB-induced skin-carcinogenesis mouse model whereas Gfi1-dependent repression of Noxa transcription is implicated in thymocyte resistance to irradiation in T cell acute lymphoblastic leukemia (T-ALL) mouse models.^{39,40} Strikingly, *Noxa*^{-/-} mice appear to be resistant to X-ray-induced gastrointestinal death.³⁸ Together, these results conclusively characterize Noxa as one of the central determinants of cell death in response to genotoxic chemotherapy.

Inhibitors of Histone Deacetylases

Accumulating recent evidence indicates a central role of epigenetic dysregulation in cancer whereby histone and DNA modifications play a critical role in tumor progression and response to anticancer treatment. Characterization of dysregulated epigenetic process in cancer has driven the rapid development of

Table 1. A list of chemotherapeutics that have been shown to induce cytotoxic effects by upregulating Noxa expression

Feature	Chemotherapeutic	Mechanism/Function	References
Genotoxic stress	Irradiation Etoposide Camptothecin	Activation of DDR and transcriptional upregulation of Noxa via transcription factors p53, p73 and FOXO3	Shibue et al., 2003 Oda et al., 2000 Saha et al., 2013 Mei et al., 2007
DNA unmasking	HDACi (LBH589) HDAC2 Vorinostat	Transcriptional upregulation of Noxa. Stabilization of Noxa protein by promoting UCH-L1 expression	Inoue et al., 2008 Fritsche et al., 2009 Xargay-Torrent et al., 2011 Brinkmann et al., 2013
Proteasome inhibition	Bortezomib	Accumulation of Noxa by stabilizing Noxa protein directly or by stabilization of transcription factors p53 and c-myc and the transactivation of <i>noxa</i> gene	Brinkmann et al., 2013 Fernández et al., 2005 Nikiforov et al., 2007
ER stress	Fenretinide Tunicamycin Tapsigargin Eeyarestatin1 Hypericin-PDT	Activation of UPR thereby activating the IRE1 α -PERK-ATF signaling cascade with AFT4 as a critical transcription factor of Noxa	Armstrong et al., 2010 Nadanaka et al., 2004 Gupta et al., 2012 Wang et al., 2008 Verfaillie et al., 2013
Bcl-2 antagonization	ABT-199 ABT-737	Induce cellular stress responses (unknown so far) and enhance the transcription of Noxa	Hauck et al., 2009 Tromp et al., 2012

small-molecule inhibitors that target the cancer epigenome.⁴¹ Histone deacetylase inhibitors (HDACi) have been repeatedly shown to induce Noxa expression, and siRNA-mediated knockdown of *Noxa* reduces HDACi-mediated cell death.⁴²⁻⁴⁴ Conversely, siRNA-mediated knockdown of *Mcl-1* potentiates HDACi-mediated apoptosis, suggesting a direct effect of HDAC inhibition on transcriptional regulation of Noxa, which in turn counteracts *Mcl-1*.⁴⁵ More strikingly, the specific deubiquitylating enzyme of Noxa, UCH-L1, was shown to be epigenetically silenced in a number of cancer entities.²⁷ HDAC inhibition results in transcriptional upregulation of UCH-L1 and stabilization of Noxa protein in tumor cells, thus identifying an additional Noxa-regulatory circuit that is epigenetically controlled. Finally, mice lacking the *Mcl-1*-specific E3-ubiquitin ligase MULE (resulting in enhanced *Mcl-1*-stability) are protected from HDACi-mediated apoptosis as a result of excessive *Mcl-1* expression.⁴⁶ In conclusion, these data indicate that the ratio of Noxa and *Mcl-1* expression is an important determinant of susceptibility to HDAC inhibitors, and that HDAC inhibition results in cell death through the antagonistic activity of Noxa against *Mcl-1*.

Proteasome Inhibition

Pharmacologic inhibitors of the proteasome have been shown to possess antitumor activity and have significant efficacy against a number of malignancies.⁴⁷ Research aiming to unravel the molecular mechanism underlying cancer-specific cytotoxicity of proteasome inhibition has identified Noxa as an essential factor. These data show that Noxa is significantly upregulated upon proteasome inhibition in a number of tumor samples and that specific downregulation of Noxa significantly reduces susceptibility to bortezomib.^{27,48-50} The majority of previous studies suggests that proteasome inhibitors induce transcriptional regulation of

Noxa.^{48,50,51} Specifically, accumulation of Noxa upon proteasome inhibition is proposed to result from stabilization of its specific transcription factors, including p53.^{48,51}

Nikiforov et al. demonstrated that accumulation of *Noxa* mRNA upon proteasome inhibition is independent of p53, HIF-1 α , and E2F1, but relies on the activity of c-myc.²² They showed that downregulation of endogenous levels of c-myc in melanoma, breast cancer, and cervical carcinoma cell lines reduces Noxa expression after bortezomib treatment. Conversely, ectopic expression of c-myc enhances Noxa accumulation and subsequently induces cell death in response to proteasome inhibition. Noxa accumulation upon proteasomal inhibition has also been reported in standard laboratory cell lines such as HEK293FT and HeLa that ectopically express Noxa as well as in tumor cell lines and primary cells from melanoma patients, indicating transcription-independent regulation of Noxa.^{26,27} Indeed, Noxa appears to be a direct target for proteasomal degradation regulated by ubiquitin-dependent and ubiquitin-independent mechanisms.^{26,27} Taken together, these data underscore the pivotal role of Noxa in potentiating cell death in response to proteasome inhibitors.

Endoplasmic Reticulum Stress

Endoplasmic reticulum (ER) stress has been shown to be induced by several anticancer treatment regimens including the DNA crosslinker cisplatin, the proteasome inhibitor bortezomib, the SERCA inhibitor tapsigargin, tunicamycin (which inhibits the UDP-HexNAc enzymes resulting in activation of the unfolded protein response [UPR]), the reactive oxygen species (ROS)-inducer hypericin-PDT, the chemotherapeutic agent fenretinide (a synthetic derivative of retinoic acid), and the specific endoplasmic reticulum-associated degradation (ERAD) inhibitor Eeyarestatin 1 (Eer-1).⁵²⁻⁵⁶ ER stress results in

the induction of the UPR with activation of the IRE1 α -PERK-ATF-signaling cascade, resulting in transcriptional activation of pro-apoptotic target proteins and ultimately triggering cell death. Noxa is a direct transcriptional target of ATF4 and has been reported to be an important mediator of ER stress-induced apoptosis in cancer therapy.^{52,57} Specifically, Noxa upregulation has been shown to be critical for effective treatment with thapsigargin and tunicamycin in MEFs and HeLa cells, fenretinide in neuroectodermal tumor cells, Eer-1 in MCL, celastrol in hepatocellular carcinoma cells, Hyp-PDT in T24 human bladder cancer cells, and the cap-translation inhibitor 4EGI-1 in multiple myeloma (MM) cell lines and primary cells.^{32,52,56-60} Remarkably, Noxa upregulation in response to ER stress does not appear to exclusively depend on the activation of PERK-signaling because increased *Noxa* mRNA expression in response to ER stress has also been observed in *PERK* knockout MEFs.⁵⁹ Nevertheless, an ATF4-dependent transcriptional upregulation in response to ER stress has been demonstrated in HeLa, neuroectodermal tumor cells, hepatocellular carcinoma cells, bladder cancer cells, and MCL.^{52,56,57,60,61} Consistent with these findings, accumulation of *Noxa* mRNA in response to ER stress is strongly reduced in *ATF4* knockout MEFs.⁵² Notably, p53-dependent upregulation of Noxa has also been reported during the treatment of melanoma cells with tunicamycin and thapsigargin.⁶² These data identify upregulation of Noxa upon ER stress as an important cellular cytotoxic response that may indirectly influence cellular stress responses when cells are exposed to conventional chemotherapy.

Oxidative Stress

Certain chemotherapeutics have been shown to induce oxidative stress, and the accumulation of ROS is frequently associated with cell death induced by anticancer treatments. Interestingly, Noxa was shown to facilitate cell death induced by oxidative stress in different cancer cell lines such as human MCL and murine medulloblastoma cells.⁶³ Furthermore, the proteasome inhibitor bortezomib was reported to induce oxidative stress, which in turn results in Noxa upregulation.^{51,64} Addition of ROS scavengers reduces the accumulation of Noxa upon proteasome inhibition and the cytotoxic effects of bortezomib. Similar results were obtained in chronic lymphocytic leukemia (CLL) treated with platinum-based compounds (e.g., cisplatin) in combination with the purine analog fludarabine.⁶⁵ The observations led to the suggestion that the cellular response to this treatment involves the generation of ROS, which induce specific transcriptional upregulation of Noxa.⁶⁵ Although ROS are associated with the cytotoxic activity of several anticancer drugs, the molecular mechanisms involving ROS or linking ROS to Noxa expression remain elusive.

Bcl-2 Antagonists

Because of their imbalanced expression levels in tumor cells and their capability to regulate MOMP, Bcl-2 proteins are considered promising anticancer therapeutic targets and research efforts have lately focused on the development of drugs targeting Bcl-2 proteins. Accordingly, several small-molecule inhibitors of Bcl-2 proteins (BH3 mimetics) have been developed and are currently under clinical evaluation.³⁰ However, none of the BH3 mimetics characterized to date efficiently targets Mcl-1.⁶⁶ The first in-human study of ABT-199, an orally bioavailable selective inhibitor of the protein Bcl-2, as monotherapy induced remissions in patients with relapsed/refractory CLL and small lymphocytic lymphoma (SLL).^{67,68} Extensive pre-clinical evaluation of Bcl-2 antagonizing protocols repeatedly showed that the susceptibility of tumor cells to Bcl-2 antagonists is substantially determined by the expression levels of Noxa, which is needed to counteract Mcl-1.⁶⁹⁻⁷⁴ Accordingly, variation in sensitivity of CLL to the BH3 mimetic ABT-737 correlates with the Mcl-1/Noxa balance.⁷⁵ Modulation of Noxa and Mcl-1 was additionally described as an effective strategy for sensitizing melanoma cells to ABT-737.⁷⁶ Furthermore, exposure to kinase inhibitors, proteasome inhibitors, ER stress, platinum compounds, caloric restriction, or vinblastine has a synergistic effect on BH3 mimetics by increasing Noxa expression.^{60,77-81} Additionally, BH3 mimetics antagonize Mcl-1 by caspase-dependent transcriptional upregulation of Noxa.⁸²

Conclusions

Through its distinctive antagonistic specificity for Mcl-1, Noxa represents a critical factor in the regulation of cell death. The high prevalence of dysregulation of Noxa in cancer, together with observations that reactivation of Noxa under diverse settings restores cytotoxic activity of a number of chemotherapeutics, strongly supports the design and evaluation of therapeutic protocols aiming to restore Noxa function or mimic Noxa action. Knowledge of how Noxa provokes a potent anticancer effect and in combination with which chemotherapeutic agents will greatly advance development of cancer therapeutic regimens.

Disclosure of Potential Conflicts of Interest

The authors declare no conflict of interest.

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