REVIEW

Molecular and Cellular Oncology 1, e29906; July 2014; © 2014 Landes Bioscience

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 (CMMC); 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

Keywords: cell death, apoptosis, bcl-2, therapy, cancer, noxa

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.

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 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]

*Correspondence to: Hamid Kashkar; Email: h.kashkar@uni-koeln.de
Submitted: 05/30/2014; Revised: 06/24/2014; Accepted: 07/02/2014; Published Online: 07/28/2014
Citation: Albert MC, Brinkmann K, Kashkar H. Noxa and cancer therapy: Tuning up the mitochondrial death machinery in response to chemotherapy. Molecular & Cellular Oncology 2014; 1:e29906; http://dx.doi.org/10.4161/mco.29906

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

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-1α, 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

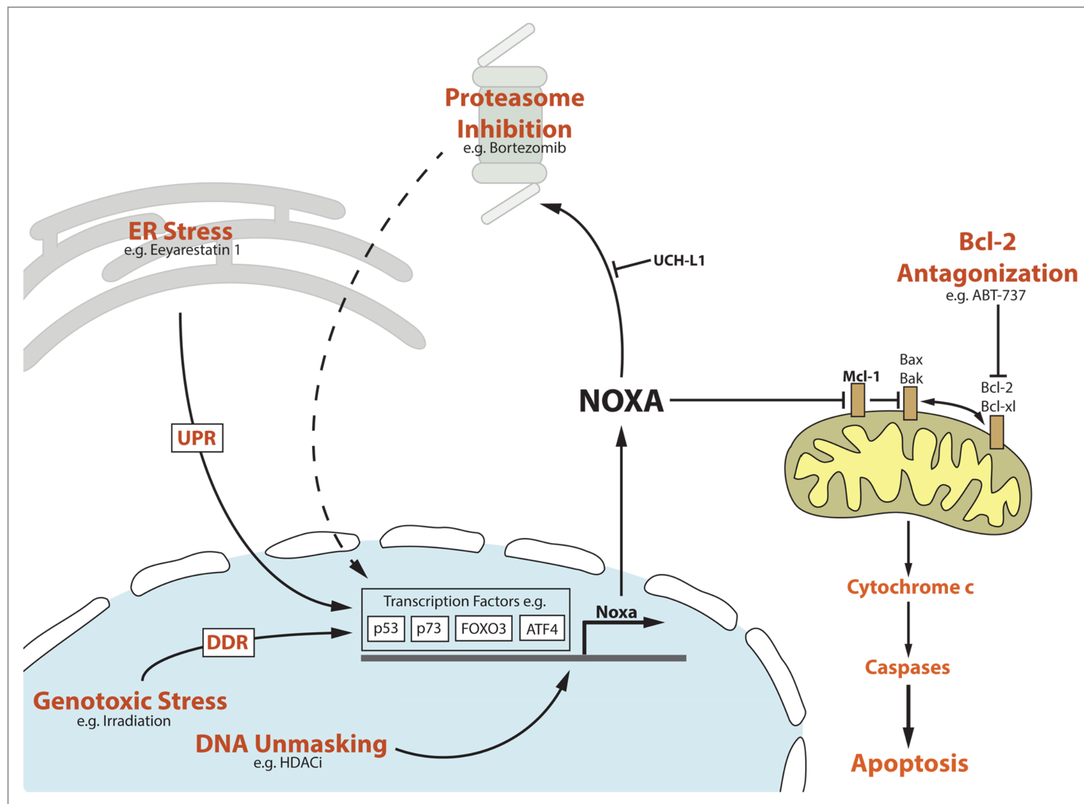

Figure 1. Regulation of Noxa during cellular stress responses to chemotherapeutic agents. Genotoxic stress activates the DNA damage response (DDR) involving transcription factors such as p53, which in turn induces transcriptional upregulation of Noxa. Endoplasmic reticulum stress (ER stress) induces 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 *noxa* 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 IRE1α-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 transcritption 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-1α, 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 IRE1α-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.

Acknowledgments

Grant support was provided by the Deutsche Forschungsgemeinschaft (DFG), KFO 286-RP3, SFB 832-A9 and Köln Fortune Program/Faculty of Medicine, University of Cologne.

References

1. Hijikata M, Kato N, Sato T, Kagami Y, Shimotohno K. Molecular cloning and characterization of a cDNA for a novel phorbol-12-myristate-13-acetate-responsive gene that is highly expressed in an adult T-cell leukemia cell line. J Virol 1990; 64:4632-9; PMID:2398525
2. Ploner C, Rainer J, Lobenwein S, Geley S, Kofler R. Repression of the BH3-only molecule PMAIP1/Noxa impairs glucocorticoid sensitivity of acute lymphoblastic leukemia cells. Apoptosis 2009; 14:821-8; PMID:19421859; http://dx.doi.org/10.1007/s10495-009-0355-5
3. Oda E, Ohki R, Murasawa H, Nemoto J, Shibue T, Yamashita T, Tokino T, Taniguchi T, Tanaka N. Noxa, a BH3-only member of the Bcl-2 family and candidate mediator of p53-induced apoptosis. Science 2000; 288:1053-8; PMID:10807576; http://dx.doi.org/10.1126/science.288.5468.1053
4. Coultas L, Huang DCS, Adams JM, Strasser A. Pro-apoptotic BH3-only Bcl-2 family members in vertebrate model organisms suitable for genetic experimentation. Cell Death Differ 2002; 9:1163-6; PMID:12404114; http://dx.doi.org/10.1038/sj.cdd.4401096
5. Adams JM, Cory S. The Bcl-2 apoptotic switch in cancer development and therapy. Oncogene 2007; 26:1324-37; PMID:17322918; http://dx.doi.org/10.1038/sj.onc.1210220
6. Willis SN, Fletcher JI, Kaufmann T, van Delft MF, Chen L, Czabotar PE, Ierino H, Lee EF, Fairlie WD, Bouillet P, et al. Apoptosis initiated when BH3 ligands engage multiple Bcl-2 homologs, not Bax or Bak. Science 2007; 315:856-9; PMID:17289999; http://dx.doi.org/10.1126/science.1133289
7. Karbowski M, Neutzner A, Youle RJ. The mitochondrial E3 ubiquitin ligase MARCH5 is required for Drp1 dependent mitochondrial division. J Cell Biol 2007; 178:71-84; PMID:17606867; http://dx.doi.org/10.1083/jcb.200611064
8. Kim H, Rafiuddin-Shah M, Tu H-C, Jeffers JR, Zambetti GP, Hsieh JJ-D, Cheng EH-Y. Hierarchical regulation of mitochondrion-dependent apoptosis by BCL-2 subfamilies. Nat Cell Biol 2006; 8:1348-58; PMID:17115033; http://dx.doi.org/10.1038/ncb1499
9. Kuwana T, Bouchier-Hayes L, Chipuk JE, Bonzon C, Sullivan BA, Green DR, Newmeyer DD. BH3 domains of BH3-only proteins differentially regulate Bax-mediated mitochondrial membrane permeabilization both directly and indirectly. Mol Cell 2005; 17:525-35; PMID:15721256; http://dx.doi.org/10.1016/j.molcel.2005.02.003
10. Chen L, Willis SN, Wei A, Smith BJ, Fletcher JI, Hinds MG, Colman PM, Day CL, Adams JM, Huang DCS. Differential targeting of prosurvival Bcl-2 proteins by their BH3-only ligands allows complementary apoptotic function. Mol Cell 2005; 17:393-403; PMID:15694340; http://dx.doi.org/10.1016/j.molcel.2004.12.030
11. Craig RW. MCL1 provides a window on the role of the BCL2 family in cell proliferation, differentiation and tumorigenesis. Leukemia 2002; 16:444-54; PMID:11960321; http://dx.doi.org/10.1038/sj.leu.2402416
12. Kozopas KM, Yang T, Buchan HL, Zhou P, Craig RW. MCL1, a gene expressed in programmed myeloid cell differentiation, has sequence similarity to BCL2. Proc Natl Acad Sci U S A 1993; 90:3516-20; PMID:7682708; http://dx.doi.org/10.1073/pnas.90.8.3516
13. Ertel F, Nguyen M, Roulston A, Shore GC. Programming cancer cells for high expression levels of Mcl1. EMBO Rep 2013; 14:328-36; PMID:23478333; http://dx.doi.org/10.1038/embor.2013.20
14. Certo M, Del Gaizo Moore V, Nishino M, Wei G, Korsmeyer S, Armstrong SA, Letai A. Mitochondria primed by death signals determine cellular addiction to antiapoptotic BCL-2 family members. Cancer Cell 2006; 9:351-65; PMID:16697956; http://dx.doi.org/10.1016/j.ccr.2006.03.027
15. Oda E, Ohki R, Murasawa H, Nemoto J, Shibue T, Yamashita T, Tokino T, Taniguchi T, Tanaka N. Noxa, a BH3-only member of the Bcl-2 family and candidate mediator of p53-induced apoptosis. Science 2000; 288:1053-8; PMID:10807576; http://dx.doi.org/10.1126/science.288.5468.1053
16. Mei Y, Xie C, Xie W, Tian X, Li M, Wu M. Noxa/Mcl-1 balance regulates susceptibility of cells to camptothecin-induced apoptosis. Neoplasia 2007; 9:871-81; PMID:17971907; http://dx.doi.org/10.1593/neo.07589
17. Qin J-Z, Stennett L, Bacon P, Bodner B, Hendrix MJC, Seftor REB, Seftor EA, Margaryan NV, Pollock PM, Curtis A, et al. p53-independent NOXA induction overcomes apoptotic resistance of malignant melanomas. Mol Cancer Ther 2004; 3:895-902; PMID:15299072
18. Kim J-Y, Ahn H-J, Ryu J-H, Suk K, Park J-H. BH3-only protein Noxa is a mediator of hypoxic cell death induced by hypoxia-inducible factor 1alpha. J Exp Med 2004; 199:113-24; PMID:14699081; http://dx.doi.org/10.1084/jem.20030613
19. Hershko T, Ginsberg D. Up-regulation of Bcl-2 homology 3 (BH3)-only proteins by E2F1 mediates apoptosis. J Biol Chem 2004; 279:8627-34; PMID:14684737; http://dx.doi.org/10.1074/jbc.M312866200
20. Flinterman M, Guelen L, Ezzati-Nik S, Killick R, Melino G, Tominaga K, Mymryk JS, Gäken J, Tavassoli M. E1A activates transcription of p73 and Noxa to induce apoptosis. J Biol Chem 2005; 280:5945-59; PMID:15572378; http://dx.doi.org/10.1074/jbc.M406661200
21. Saha MN, Jiang H, Yang Y, Reece D, Chang H. PRIMA-1Met/APR-246 displays high antitumor activity in multiple myeloma by induction of p73 and Noxa. Mol Cancer Ther 2013; 12:2331-41; PMID:24030633; http://dx.doi.org/10.1158/1535-7163.MCT-12-1166
22. Nikiforov MA, Riblett M, Tang W-H, Gratchouck V, Zhuang D, Fernandez Y, Verhaegen M, Varambally S, Chinnaiyan AM, Jakubowiak AJ, et al. Tumor cell-selective regulation of NOXA by c-MYC in response to proteasome inhibition. Proc Natl Acad Sci U S A 2007; 104:19488-93; PMID:18042711; http://dx.doi.org/10.1073/pnas.0708380104
23. Ausserlechner MJ, Salvador C, Deutschmann A, Bodner M, Viola G, Bortolozzi R, Basso G, Hagenbuchner J, Obexer P. Therapy-resistant acute lymphoblastic leukemia (ALL) cells inactivate FOXO3 to escape apoptosis induction by TRAIL and Noxa. Oncotarget 2013; 4:995-1007; PMID:23828551
24. Lallemand C, Blanchard B, Palmieri M, Lebon P, May E, Tovey MG. Single-stranded RNA viruses inactivate the transcriptional activity of p53 but induce NOXA-dependent apoptosis via post-translational modifications of IRF-1, IRF-3 and CREB. Oncogene 2007; 26:328-38; PMID:16832344; http://dx.doi.org/10.1038/sj.onc.1209795
25. Dengler MA, Weilbacher A, Gutekunst M, Staiger AM, Vöhringer MC, Horn H, Ott G, Aulitzky WE, van der Kuip H. Discrepant NOXA (PMAIP1) transcript and NOXA protein levels: a potential Achilles' heel in mantle cell lymphoma. Cell Death Dis 2014; 5:e1013; PMID:24457957; http://dx.doi.org/10.1038/cddis.2013.552
26. Baou M, Kohlhaas SL, Butterworth M, Vogler M, Dinsdale D, Walewska R, Majid A, Eldering E, Dyer MJS, Cohen GM. Role of NOXA and its ubiquitination in proteasome inhibitor-induced apoptosis in chronic lymphocytic leukemia cells. Haematologica 2010; 95:1510-8; PMID:20378569; http://dx.doi.org/10.3324/haematol.2010.022368
27. Brinkmann K, Zigrino P, Witt A, Schell M, Ackermann L, Broxtermann P, Schüll S, Andree M, Coutelle O, Yazdanpanah B, et al. Ubiquitin C-terminal hydrolase-L1 potentiates cancer chemosensitivity by stabilizing NOXA. Cell Rep 2013; 3:881-91; PMID:23499448; http://dx.doi.org/10.1016/j.celrep.2013.02.014
28. Craxton A, Butterworth M, Harper N, Fairall L, Schwabe J, Ciechanover A, Cohen GM. NOXA, a sensor of proteasome integrity, is degraded by 26S proteasomes by an ubiquitin-independent pathway that is blocked by MCL-1. Cell Death Differ 2012; 19:1424-34; PMID:22361683; http://dx.doi.org/10.1038/cdd.2012.16
29. Lowman XH, McDonnell MA, Kosloske A, Odumade OA, Jenness C, Karim CB, Jemmerson R, Kelekar A. The proapoptotic function of Noxa in human leukemia cells is regulated by the kinase Cdk5 and by glucose. Mol Cell 2010; 40:823-33; PMID:21145489; http://dx.doi.org/10.1016/j.molcel.2010.11.035
30. Brinkmann K, Kashkar H. Targeting the mitochondrial apoptotic pathway: a preferred approach in hematologic malignancies? Cell Death Dis 2014; 5:e1098; PMID:24603326; http://dx.doi.org/10.1038/cddis.2014.61
31. Mestre-Escorihuela C, Rubio-Moscardo F, Richter JA, Siebert R, Climent J, Fresquet V, Beltran E, Agirre X, Marugan I, Marín M, et al. Homozygous deletions localize novel tumor suppressor genes in B-cell lymphomas. Blood 2007; 109:271-80; PMID:16960149; http://dx.doi.org/10.1182/blood-2006-06-026500
32. Zhang L, Lopez H, George NM, Liu X, Pang X, Luo X. Selective involvement of BH3-only proteins and differential targets of Noxa in diverse apoptotic pathways. Cell Death Differ 2011; 18:864-73; PMID:21113147; http://dx.doi.org/10.1038/cdd.2010.152
33. Seeger JM, Schmidt P, Brinkmann K, Hombach AA, Coutelle O, Zigrino P, Wagner-Stippich D, Mauch C, Abken H, Krönke M, et al. The proteasome inhibitor bortezomib sensitizes melanoma cells toward adoptive CTL attack. Cancer Res 2010; 70:1825-34; PMID:20179203; http://dx.doi.org/10.1158/0008-5472.CAN-09-3175
34. Sui X, Chen R, Wang Z, Huang Z, Kong N, Zhang M, Han W, Lou F, Yang J, Zhang Q, et al. Autophagy and chemotherapy resistance: a promising therapeutic target for cancer treatment. Cell Death Dis 2013; 4:e838; PMID:24113172; http://dx.doi.org/10.1038/cddis.2013.350
35. Elgendy M, Sheridan C, Brumatti G, Martin SJ. Oncogenic Ras-induced expression of Noxa and Beclin-1 promotes autophagic cell death and limits clonogenic survival. Mol Cell 2011; 42:23-35; PMID:21353614; http://dx.doi.org/10.1016/j.molcel.2011.02.009
36. Lopez H, Zhang L, George NM, Liu X, Pang X, Evans JJD, Targy NM, Luo X. Perturbation of the Bcl-2 network and an induced Noxa/Bcl-xL interaction trigger mitochondrial dysfunction after DNA damage. J Biol Chem 2010; 285:15016-26; PMID:20223826; http://dx.doi.org/10.1074/jbc.M109.086231
37. Nijhawan D, Fang M, Traer E, Zhong Q, Gao W, Du F, Wang X. Elimination of Mcl-1 is required for the initiation of apoptosis following ultraviolet irradiation. Genes Dev 2003; 17:1475-86; PMID:12783855; http://dx.doi.org/10.1101/gad.1093903

38. Shibue T, Takeda K, Oda E, Tanaka H, Murasawa H, Takaoka A, Morishita Y, Akira S, Taniguchi T, Tanaka N. Integral role of Noxa in p53-mediated apoptotic response. Genes Dev 2003; 17:2233-8; PMID:12952892; http://dx.doi.org/10.1101/gad.1103603
39. Ming M, Soltani K, Shea CR, Li X, He YY. Dual role of SIRT1 in UVB-induced skin tumorigenesis. Oncogene 2014; In press; PMID:24441046; http://dx.doi.org/10.1038/onc.2013.583
40. Khandanpour C, Phelan JD, Vassen L, Schütte J, Chen R, Horman SR, Gaudreau M-C, Krongold J, Zhu J, Paul WE, et al. Growth factor independence 1 antagonizes a p53-induced DNA damage response pathway in lymphoblastic leukemia. Cancer Cell 2013; 23:200-14; PMID:23410974; http://dx.doi.org/10.1016/j.ccr.2013.01.011
41. Bolden JE, Peart MJ, Johnstone RW. Anticancer activities of histone deacetylase inhibitors. Nat Rev Drug Discov 2006; 5:769-84; PMID:16955068; http://dx.doi.org/10.1038/nrd2133
42. Inoue S, Riley J, Gant TW, Dyer MJS, Cohen GM. Apoptosis induced by histone deacetylase inhibitors in leukemic cells is mediated by Bim and Noxa. Leukemia 2007; 21:1773-82; PMID:17525724; http://dx.doi.org/10.1038/sj.leu.2404760
43. Xargay-Torrent S, López-Guerra M, Saborit-Villarroya I, Rosich L, Campo E, Roué G, Colomer D. Vorinostat-induced apoptosis in mantle cell lymphoma is mediated by acetylation of proapoptotic BH3-only gene promoters. Clin Cancer Res 2011; 17:3956-68; PMID:21652541; http://dx.doi.org/10.1158/1078-0432.CCR-10-3412
44. Fritsche P, Seidler B, Schüler S, Schnieke A, Göttlicher M, Schmid RM, Saur D, Schneider G. HDAC2 mediates therapeutic resistance of pancreatic cancer cells via the BH3-only protein NOXA. Gut 2009; 58:1399-409; PMID:19528037; http://dx.doi.org/10.1136/gut.2009.180711
45. Inoue S, Walewska R, Dyer MJS, Cohen GM. Downregulation of Mcl-1 potentiates HDACi-mediated apoptosis in leukemic cells. Leukemia 2008; 22:819-25; PMID:18239621; http://dx.doi.org/10.1038/leu.2008.1
46. Jing H, Kase J, Dörr JR, Milanovic M, Lenze D, Grau M, Beuster G, Ji S, Reimann M, Lenz P, et al. Opposing roles of NF-κB in anti-cancer treatment outcome unveiled by cross-species investigations. Genes Dev 2011; 25:2137-46; PMID:21979374; http://dx.doi.org/10.1101/gad.17620611
47. Adams J. The proteasome: a suitable antineoplastic target. Nat Rev Cancer 2004; 4:349-60; PMID:15122206; http://dx.doi.org/10.1038/nrc1361
48. Fernández Y, Verhaegen M, Miller TP, Rush JL, Steiner P, Opipari AW Jr., Lowe SW, Soengas MS. Differential regulation of noxa in normal melanocytes and melanoma cells by proteasome inhibition: therapeutic implications. Cancer Res 2005; 65:6294-304; PMID:16024631; http://dx.doi.org/10.1158/0008-5472.CAN-05-0686
49. Gomez-Bougie P, Wuillème-Toumi S, Ménoret E, Trichet V, Robillard N, Philippe M, Bataille R, Amiot M. Noxa up-regulation and Mcl-1 cleavage are associated to apoptosis induction by bortezomib in multiple myeloma. Cancer Res 2007; 67:5418-24; PMID:17545623; http://dx.doi.org/10.1158/0008-5472.CAN-06-4322
50. Qin JZ, Ziffra J, Stennett L, Bodner B, Bonish BK, Chaturvedi V, Bennett F, Pollock PM, Trent JM, Hendrix MJC, et al. Proteasome inhibitors trigger NOXA-mediated apoptosis in melanoma and myeloma cells. Cancer Res 2005; 65:6282-93; PMID:16024630; http://dx.doi.org/10.1158/0008-5472.CAN-05-0676
51. Pérez-Galán P, Roué G, Villamor N, Montserrat E, Campo E, Colomer D. The proteasome inhibitor bortezomib induces apoptosis in mantle-cell lymphoma through generation of ROS and Noxa activation independent of p53 status. Blood 2006; 107:257-64; PMID:16166592; http://dx.doi.org/10.1182/blood-2005-05-2091
52. Wang Q, Li L, Ye Y. Inhibition of p97-dependent protein degradation by Eeyarestatin I. J Biol Chem 2008; 283:7445-54; PMID:18199748; http://dx.doi.org/10.1074/jbc.M708347200
53. Selimovic D, Porzig BBOW, El-Khattouti A, Badura HE, Ahmad M, Ghanjati F, Santourlidis S, Haikel Y, Hassan M. Bortezomib/proteasome inhibitor triggers both apoptosis and autophagy-dependent pathways in melanoma cells. Cell Signal 2013; 25:308-18; PMID:23079083; http://dx.doi.org/10.1016/j.cellsig.2012.10.004
54. Duncan G, Wormstone IM, Liu CS, Marcantonio JM, Davies PD. Thapsigargin-coated intraocular lenses inhibit human lens cell growth. Nat Med 1997; 3:1026-8; PMID:9288732; http://dx.doi.org/10.1038/nm0997-1026
55. Nadanaka S, Yoshida H, Kano F, Murata M, Mori K. Activation of mammalian unfolded protein response is compatible with the quality control system operating in the endoplasmic reticulum. Mol Biol Cell 2004; 15:2537-48; PMID:15020717; http://dx.doi.org/10.1091/mbc.E03-09-0693
56. Verfaillie T, van Vliet A, Garg AD, Dewaele M, Rubio N, Gupta S, de Witte P, Samali A, Agostinis P. Pro-apoptotic signaling induced by photo-oxidative ER stress is amplified by Noxa, not Bim. Biochem Biophys Res Commun 2013; 438:500-6; PMID:23916707; http://dx.doi.org/10.1016/j.bbrc.2013.07.107
57. Armstrong JL, Flockhart R, Veal GJ, Lovat PE, Redfern CPF. Regulation of endoplasmic reticulum stress-induced cell death by ATF4 in neuroectodermal tumor cells. J Biol Chem 2010; 285:6091-100; PMID:20022965; http://dx.doi.org/10.1074/jbc.M109.014092
58. Descamps G, Gomez-Bougie P, Tamburini J, Green A, Bouscary D, Maïga S, Moreau P, Le Gouill S, Pellat-Deceunynck C, Amiot M. The cap-translation inhibitor 4EGI-1 induces apoptosis in multiple myeloma through Noxa induction. Br J Cancer 2012; 106:1660-7; PMID:22510748; http://dx.doi.org/10.1038/bjc.2012.139
59. Gupta S, Giricz Z, Natoni A, Donnelly N, Deegan S, Szegezdi E, Samali A. NOXA contributes to the sensitivity of PERK-deficient cells to ER stress. FEBS Lett 2012; 586:4023-30; PMID:23068609; http://dx.doi.org/10.1016/j.febslet.2012.10.002
60. Zhu H, Yang W, He LJ, Ding WJ, Zheng L, Liao SD, Huang P, Lu W, He QJ, Yang B. Upregulating Noxa by ER stress, celastrol exerts synergistic anti-cancer activity in combination with ABT-737 in human hepatocellular carcinoma cells. PLoS One 2012; 7:e52333; PMID:23284992; http://dx.doi.org/10.1371/journal.pone.0052333
61. Wang Q, Mora-Jensen H, Weniger MA, Perez-Galan P, Wolford C, Hai T, Ron D, Chen W, Trenkle W, Wiestner A, et al. ERAD inhibitors integrate ER stress with an epigenetic mechanism to activate BH3-only protein NOXA in cancer cells. Proc Natl Acad Sci U S A 2009; 106:2200-5; PMID:19164757; http://dx.doi.org/10.1073/pnas.0807611106
62. Jiang CC, Lucas K, Avery-Kiejda KA, Wade M, deBock CE, Thorne RF, Allen J, Hersey P, Zhang XD. Up-regulation of Mcl-1 is critical for survival of human melanoma cells upon endoplasmic reticulum stress. Cancer Res 2008; 68:6708-17; PMID:18701495; http://dx.doi.org/10.1158/0008-5472.CAN-08-0349
63. Ohshima-Hosoyama S, Davare MA, Hosoyama T, Nelon LD, Keller C. Bortezomib stabilizes NOXA and triggers ROS-associated apoptosis in medulloblastoma. J Neurooncol 2011; 105:475-83; PMID:21633906; http://dx.doi.org/10.1007/s11060-011-0619-0
64. Weniger MA, Rizzatti EG, Pérez-Galán P, Liu D, Wang Q, Munson PJ, Raghavachari N, White T, Tweito MM, Dunleavy K, et al. Treatment-induced oxidative stress and cellular antioxidant capacity determine response to bortezomib in mantle cell lymphoma. Clin Cancer Res 2011; 17:5101-12; PMID:21712452; http://dx.doi.org/10.1158/1078-0432.CCR-10-3367
65. Tonino SH, van Laar J, van Oers MH, Wang JY, Eldering E, Kater AP. ROS-mediated upregulation of Noxa overcomes chemoresistance in chronic lymphocytic leukemia. Oncogene 2011; 30:701-13; PMID:20935673; http://dx.doi.org/10.1038/onc.2010.441
66. Billard C. Design of novel BH3 mimetics for the treatment of chronic lymphocytic leukemia. Leukemia 2012; 26:2032-8; PMID:22453662; http://dx.doi.org/10.1038/leu.2012.88
67. BCL-2 inhibitor yields high response in CLL and SLL. Cancer Discov 2014; 4:OF5; PMID:24501317; http://dx.doi.org/10.1158/2159-8290.CD-NB2013-178
68. Souers AJ, Leverson JD, Boghaert ER, Ackler SL, Catron ND, Chen J, Dayton BD, Ding H, Enschede SH, Fairbrother WJ, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. Nat Med 2013; 19:202-8; PMID:23291630; http://dx.doi.org/10.1038/nm.3048
69. Okumura K, Huang S, Sinicrope FA. Induction of Noxa sensitizes human colorectal cancer cells expressing Mcl-1 to the small-molecule Bcl-2/Bcl-xL inhibitor, ABT-737. Clin Cancer Res 2008; 14:8132-42; PMID:19088028; http://dx.doi.org/10.1158/1078-0432.CCR-08-1665
70. Rooswinkel RW, van de Kooij B, Verheij M, Borst J. Bcl-2 is a better ABT-737 target than Bcl-xL or Bcl-w and only Noxa overcomes resistance mediated by Mcl-1, Bfl-1, or Bcl-B. Cell Death Dis 2012; 3:e366; PMID:22875003; http://dx.doi.org/10.1038/cddis.2012.109
71. Hauck P, Chao BH, Litz J, Krystal GW. Alterations in the Noxa/Mcl-1 axis determine sensitivity of small cell lung cancer to the BH3 mimetic ABT-737. Mol Cancer Ther 2009; 8:883-92; PMID:19372561; http://dx.doi.org/10.1158/1535-7163.MCT-08-1118
72. Jiang CC, Wroblewski D, Yang F, Hersey P, Zhang XD. Human melanoma cells under endoplasmic reticulum stress are more susceptible to apoptosis induced by the BH3 mimetic obatoclax. Neoplasia 2009; 11:945-55; PMID:19724688
73. Tahir SK, Yang X, Anderson MG, Morgan-Lappe SE, Sarthy AV, Chen J, Warner RB, Ng S-C, Fesik SW, Elmore SW, et al. Influence of Bcl-2 family members on the cellular response of small-cell lung cancer cell lines to ABT-737. Cancer Res 2007; 67:1176-83; PMID:17283153; http://dx.doi.org/10.1158/0008-5472.CAN-06-2203
74. Wiegmans AP, Alsop AE, Bots M, Cluse LA, Williams SP, Banks K-M, Ralli R, Scott CL, Frenzel A, Villunger A, et al. Deciphering the molecular events necessary for synergistic tumor cell apoptosis mediated by the histone deacetylase inhibitor vorinostat and the BH3 mimetic ABT-737. Cancer Res 2011; 71:3603-15; PMID:21398407; http://dx.doi.org/10.1158/0008-5472.CAN-10-3289

75. Tromp JM, Geest CR, Breij ECW, Elias JA, van Laar J, Luijks DM, Kater AP, Beaumont T, van Oers MHJ, Eldering E. Tipping the Noxa/Mcl-1 balance overcomes ABT-737 resistance in chronic lymphocytic leukemia. Clin Cancer Res 2012; 18:487-98; PMID:22128299; http://dx.doi.org/10.1158/1078-0432.CCR-11-1440
76. Lucas KM, Mohana-Kumaran N, Lau D, Zhang XD, Hersey P, Huang DC, Weninger W, Haass NK, Allen JD. Modulation of NOXA and MCL-1 as a strategy for sensitizing melanoma cells to the BH3-mimetic ABT-737. Clin Cancer Res 2012; 18:783-95; PMID:22173547; http://dx.doi.org/10.1158/1078-0432.CCR-11-1166
77. Song JH, Kraft AS. Pim kinase inhibitors sensitize prostate cancer cells to apoptosis triggered by Bcl-2 family inhibitor ABT-737. Cancer Res 2012; 72:294-303; PMID:22080570; http://dx.doi.org/10.1158/0008-5472.CAN-11-3240
78. Premkumar DR, Jane EP, DiDomenico JD, Vukmer NA, Agostino NR, Pollack IF. ABT-737 synergizes with bortezomib to induce apoptosis, mediated by Bid cleavage, Bax activation, and mitochondrial dysfunction in an Akt-dependent context in malignant human glioma cell lines. J Pharmacol Exp Ther 2012; 341:859-72; PMID:22393246; http://dx.doi.org/10.1124/jpet.112.191536
79. Simonin K, N'Diaye M, Lheureux S, Loussouarn C, Dutoit S, Briand M, Giffard F, Brotin E, Blanc-Fournier C, Poulain L. Platinum compounds sensitize ovarian carcinoma cells to ABT-737 by modulation of the Mcl-1/Noxa axis. Apoptosis 2013; 18:492-508; PMID:23344663; http://dx.doi.org/10.1007/s10495-012-0799-x
80. Meynet O, Zunino B, Happo L, Pradelli LA, Chiche J, Jacquin MA, Mondragón L, Tanti J-F, Taillan B, Garnier G, et al. Caloric restriction modulates Mcl-1 expression and sensitizes lymphomas to BH3 mimetic in mice. Blood 2013; 122:2402-11; PMID:23966420; http://dx.doi.org/10.1182/blood-2013-01-478651
81. Bates DJP, Danilov AV, Lowrey CH, Eastman A. Vinblastine rapidly induces NOXA and acutely sensitizes primary chronic lymphocytic leukemia cells to ABT-737. Mol Cancer Ther 2013; 12:1504-14; PMID:23723123; http://dx.doi.org/10.1158/1535-7163.MCT-12-1197
82. Bertin-Ciftci J, Barré B, Le Pen J, Maillet L, Couriaud C, Juin P, Braun F. pRb/E2F-1-mediated caspase-dependent induction of Noxa amplifies the apoptotic effects of the Bcl-2/Bcl-xL inhibitor ABT-737. Cell Death Differ 2013; 20:755-64; PMID:23429261; http://dx.doi.org/10.1038/cdd.2013.6

University Library

A gateway to Melbourne's research publications

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:
Albert, M-C; Brinkmann, K; Kashkar, H

Title:
Noxa and cancer therapy: Tuning up the mitochondrial death machinery in response to chemotherapy.

Date:
2014

Citation:
Albert, M. -C., Brinkmann, K. & Kashkar, H. (2014). Noxa and cancer therapy: Tuning up the mitochondrial death machinery in response to chemotherapy.. Mol Cell Oncol, 1 (1), pp.e29906-. https://doi.org/10.4161/mco.29906.

Persistent Link:
http://hdl.handle.net/11343/271122

File Description:
Published version

License:
CC BY-NC