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Dysregulation of Apoptotic Signaling in Cancer: Molecular Mechanisms and Therapeutic Opportunities

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Abstract

Apoptosis is a tightly regulated cell suicide program that plays an essential role in the maintenance of tissue homeostasis by eliminating unnecessary or harmful cells. Defects in this native defense mechanism promote malignant transformation and frequently confer chemoresistance to transformed cells. Indeed, the evasion of apoptosis has been recognized as a hallmark of cancer. Given that multiple mechanisms function at many levels to orchestrate the regulation of apoptosis, a multitude of opportunities for apoptotic dysregulation are present within the intricate signaling network of cell. Several of the molecular mechanisms by which cancer cells are protected from apoptosis have been elucidated. These advances have facilitated the development of novel apoptosis-inducing agents that have demonstrated single-agent activity against various types of cancers cells and/or sensitized resistant cancer cells to conventional cytotoxic therapies. Herein, we will highlight several of the central modes of apoptotic dysregulation found in cancer. We will also discuss several therapeutic strategies that aim to reestablish the apoptotic response, and thereby eradicate cancer cells, including those that demonstrate resistance to traditional therapies.

Keywords

evasion of apoptosis; oncogenic mutations; therapeutic targets

APOPTOSIS AND CANCER

Apoptosis is a tightly controlled cell suicide program that plays a fundamental role in development and tissue homeostasis by eliminating unnecessary and defective cells [Kerr et al., 1972; Raff, 1998]. Importantly, this evolutionary conserved form of programmed cell death eradicates potentially harmful cells, particularly genetically altered cells, and thereby serves to maintain the integrity of the organism [Ameisen, 2002]. The imperative function of appropriate apoptotic signaling in preserving the delicate balance between cell survival and cell death that is required to prevent disease is highlighted by the establishment of the evasion of apoptosis as a prominent hallmark of cancer [Hanahan and Weinberg, 2000].

Tumorigenesis requires defects in the cellular circuitry that promote uncontrolled proliferation, yet cellular proliferation mechanisms act within a complex, coordinated signaling network that serves to check aberrant proliferation by activating signaling pathways that induce cellular

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senescence or apoptosis [Lowe et al., 2004]. As a means to circumvent this protective apoptotic signaling response, cancer cells often harbor both proliferation-stimulating mutations and defects in the apoptotic circuitry, which act cooperatively to uncouple apoptosis from cellular proliferation programs [Evan and Vousden, 2001; Lowe et al., 2004]. Alternatively, cancer cells can evade apoptosis via the signaling of aberrantly active survival pathways [Kabore et al., 2004; Lowe et al., 2004]. Regardless of the mechanism, the suppression of apoptotic signaling confers an enhanced survival ability to cancer cells, which promotes their characteristic uncontrolled proliferation [Hanahan and Weinberg, 2000; Green and Evan, 2002; Lowe et al., 2004]. Furthermore, the dysregulation of apoptotic signaling is frequently implicated in drug resistance, as many anti-neoplastic agents exert their cytotoxic effects by inducing apoptosis [Lowe et al., 2004; Pommier et al., 2004; Blagosklonny, 2005; Fesik, 2005]. Given that apoptosis is regulated at several levels by multiple signaling pathways that are incorporated into an intricate cellular network, each mode of disrupted apoptotic signaling cannot be detailed in this review. Instead, we provide an overview of the key apoptotic mechanisms and highlight several of the means by which apoptosis is dysregulated in human cancers. Additionally, we briefly discuss the potential of targeting these specific apoptotic defects as novel therapeutic strategies for the treatment of cancer.

GENERAL FEATURES OF APOPTOSIS

Apoptosis is characterized by several morphological features, including blebbing of the plasma membrane, exposure of phosphatidylserine at the external surface of the cell membrane, cell shrinkage, chromatin condensation, and DNA fragmentation [Khosravi-Far and Esposti, 2004]. These distinctive alterations are triggered by the proteolytic activity of a family of cysteinyl aspartate-specific proteases, known as caspases, which dismantle the cell by cleaving critical cellular substrates, such as poly(ADP-ribose) polymerase (PARP). This cellular destruction concludes with the formation of apoptotic bodies that are subsequently eliminated by phagocytosis [Bucur et al., 2001; Khosravi-Far and Esposti, 2004].

Caspases serve as one of the principal effectors of apoptosis. As such, the activity of these proteases is stringently controlled. One aspect of this regulation involves the synthesis of caspases as inactive zymogens, each of which requires the proteolytic removal of its N-terminal prodomain to generate the mature active caspsase [Nicholson, 1999]. A subset of caspases, termed initiator caspases, interact with specific adapter molecules that facilitate their autoprocessing. Upon activation, initiator caspases process a second class of caspases, known as executioner or effector caspases, which act on key cellular proteins, resulting in the demise of the cell [Nicholson, 1999; Stennicke and Salvesen, 2000]. As depicted in Figure 1, the induction of apoptosis can be mediated by death receptor-dependent or mitochondria-dependent apoptotic pathways, known as the extrinsic and intrinsic apoptotic pathways, respectively, both of which culminate in the activation of the executioner caspases and the consequent destruction of the cell [Jin and El-Deiry, 2005].

APOPTOTIC MACHINERY

The Extrinsic (Death Receptor-Dependent) Apoptotic Pathway

The extrinsic apoptotic pathway is activated by cell surface death receptors binding their respective cytokine ligands, such as FasL, tumor necrosis factor (TNF), and TNF-related apoptosis-inducing ligand (Apo2L, TRAIL) [Khosravi-Far and Esposti, 2004]. Death receptors are members of the TNF receptor superfamily and can play a role in mediating several distinct cellular functions, nevertheless most death receptors mainly act to initiate apoptosis, with the apoptosis-inducing ability of TNF receptor-1 (TNFR1), Fas (APO-1, CD95), DR4 (TRAIL receptor 1, TRAIL R1), and DR5 (TRAIL R2) being the most extensively characterized [Ashkenazi and Dixit, 1998; Baud and Karin, 2001; Jin and El-Deiry, 2005]. Ligand binding

to the extracellular death receptor domain triggers the oligomerization of the death receptor, leading to the aggregation of a characteristic intracellular motif of death receptor family members, known as the death domain (DD). The complex of aggregated receptor domains recruits adaptor proteins containing DDs, such as FAS-associated death domain (FADD), via DD–DD interactions. These adaptor proteins function to sequester the inactive zymogen of initiator caspase-8 and/or caspase-10, resulting in the formation of the death-inducing signaling complex (DISC) [Jin and El-Deiry, 2005]. DISC formation facilitates a high local concentration of procaspase molecules and thereby promotes the auto-activation of caspase-8 [Boatright et al., 2003]. Activated initiator caspases in turn process and activate the downstream executioner caspases, including caspase-3, −6, and −7, which execute the destruction of the cell [Degterev et al., 2003].

Modification of the death receptor-dependent apoptotic signaling mechanism has been associated with several human cancers. Loss of the death-inducing activity of the Fas-FasL death receptor system [Muschen et al., 2000] and aberrant expression of cytosolic components of the death receptor-mediated apoptotic signaling pathways, including FADD [Tourneur et al., 2005], FLICE-inhibitory protein (c-FLIP) [Jin et al., 2004; Zhang et al., 2004; Kataoka, 2005], and caspases [Zhivotovsky and Orrenius, 2006], can contribute to cellular transformation. Fas-mediated apoptotic signaling has been found to be impaired in various cancer cells. Several defects that contribute to tumor cell resistance to Fas-mediated apoptosis have been observed, including the transcriptional silencing of Fas, a common oncogenic event in epithelial malignancies, and somatic mutations of Fas, which are often associated with germinal center (GC)-derived B-cell lymphomas [Muschen et al., 2002]. The loss of Fas function can promote the persistence of malignant cells by enabling these transformed cells to evade immunosurveillance and elimination mediated by FasL-expressing cytotoxic T cells [Muschen et al., 2002; Abramson and Shipp, 2005].

Deficiencies in downstream effector molecules of the death receptor signaling complexes can also play a role in carcinogenesis. In acute myelogenous leukemia (AML) cells, absent or low expression of FADD was frequently observed and predicted resistance to chemotherapy and a poor prognosis [Tourneur et al., 2004, 2005]. Furthermore, low or absent caspase-8 expression via hypermethylation of caspase-8 regulatory sequences has been reported in a number of tumor types, including neuroblastomas, medulloblastomas, and small cell lung cancer (SCLC) [Teitz et al., 2000; Shivapurkar et al., 2002; Zuzak et al., 2002]. In addition to gene silencing, the suppression of caspase-8 activity can be mediated by overexpression of c-FLIP, an anti-apoptotic protein that is recruited to the DISC and subsequently attenuates the auto-activation of caspase-8. Overexpression of c-FLIP has been reported in a variety of human cancers [Irmler et al., 1997]. Specifically, elevated levels of c-FLIP were observed in most of the colon cancer samples analyzed in a recent study [Korkolopoulou et al., 2007], and the levels c-FLIP were higher in the PC-3 and DU-145 prostate cancer cell lines compared with normal prostate stromal and epithelial cells [Voelkel-Johnson, 2003; Zhang et al., 2004]. Importantly, aberrant expression of c-FLIP has been shown to mediate resistance to cell death induced by stimulation of the TRAIL death receptors in prostate cancer cells [Zhang et al., 2004].

Considering that dysregulation of death receptor-dependent apoptotic signaling can contribute to the pathogenesis of numerous human malignancies and death receptor systems, particularly Fas-FasL, have been reported to play a role in the apoptotic response induced by anti-cancer therapy, restoring the functional activity of the death-receptor-mediated apoptotic program by targeting defects specific to certain cancer cells is a promising therapeutic approach [Fulda and Debatin, 2003]. In addition to its role in tumorigenesis, inhibition of caspase-8 activity by mechanisms involving c-FLIP [Bullani et al., 2001; Krueger et al., 2001; Kataoka, 2005] or transcriptional silencing [Fulda et al., 2001; Fulda and Debatin, 2002] has been associated with drug resistance. Consequently, therapeutic strategies that aim to induce the activation of

caspase-8 can sensitize cancer cells to apoptosis-inducing therapies. The downregulation of c-FLIP by metabolic inhibitors has been shown to sensitize a variety of cancer cells to death-receptor-induced apoptosis [Fulda et al., 2000]. Moreover, the reestablishment of caspase-8 expression by interferon-mediated transcriptional activation, demethylation, or gene transfer has been found to sensitize previously resistant caspase-8-deficient tumor cells to death receptor- and drug-induced apoptosis [Fulda et al., 2001; Fulda and Debatin, 2002].

The therapeutic value of inducing apoptosis via the extrinsic pathway extends to cancer cells with defects other than those involving components of this pathway. While some cancer cells with certain oncogenic mutations are resistant to DNA-damaging therapeutic agents, inducing apoptosis by stimulating the extrinsic apoptotic machinery can overcome this resistance since the death receptor-mediated apoptotic pathways can function in a manner independent of the p53-mediated stress response induced by these agents. For example, the TRAIL ligand has been shown to induce apoptosis in a number of cancer cell lines, including those with aberrant p53 activity, but demonstrates little or no apoptotic activity in most normal cells [Almasan and Ashkenazi, 2003]. The preferential killing of cancer cells and apparent lack of systemic toxicity mediated by TRAIL-induced apoptosis has lead to the emergence of agonistic antibodies against the TRAIL death receptors or soluble versions of TRAIL as promising tumor-specific therapeutic agents that warrant further clinical investigation [Fesik, 2005; Bucur et al., 2006] (see Table I).

The Intrinsic (Mitochondria-Dependent) Apoptotic Pathway

The intrinsic apoptotic pathway is mediated by intrinsic signals that converge at the mitochondria in response to diverse cellular stressors, including UV radiation, gamma irradiation, heat, viral virulence factors, the majority of DNA-damaging agents, and the activation of some oncogenic factors [Kroemer, 2003; Green and Kroemer, 2004; Khosravi-Far and Esposti, 2004; Bouchier-Hayes et al., 2005]. The mitochondria acts as a central regulator of the intrinsic apoptotic pathway, as mitochondrial outer membrane permeabilization (MOMP) is regarded as the critical event in the mitochondria-mediated apoptotic pathway that commits the cell to apoptosis [Bouchier-Hayes et al., 2005]. MOMP prompts the cytosolic release of various proteins that are normally confined to the mitochondrial intermembrane space (IMS). Importantly, cytochrome c leaks into the cytosol and binds to apoptosis protease-activating factor 1 (Apaf-1) in a dATP-dependent manner to form a complex that recruits procaspase-9. The formation of this complex, known as the “apoptosome,” facilitates oligomerization and activation of caspase-9 [Li et al., 1997; Boatright et al., 2003; Jin and El-Deiry, 2005]. Activated caspase-9, in turn, processes and activates the executioner caspases-3, −6, and −7, which drive the execution of the cell [Slee et al., 1999].

Alterations in the expression of components of the intrinsic apoptotic machinery or its key regulators have been associated with various human cancers. Specifically, reduced expression of Apaf-1 has been observed in numerous human melanoma samples and correlates with disease progression [Baldi et al., 2004]. The frequent transcriptional silencing of *Apaf-1* in metastatic melanomas is a result of the aberrant methylation of the promoter sequences in the gene [Soengas et al., 2001]. In addition to deficiencies in the components of the apoptosome, modulators of its formation have been implicated in the pathogenesis of cancer [Hajra and Liu, 2004]. As primary regulators of MOMP, the pivotal event in the intrinsic apoptotic pathway that enables apoptosome formation, members of the Bcl-2 family of proteins function as an apoptotic switch [Adams and Cory, 2007]. The Bcl-2 family members, each of which contains at least one of four Bcl-2 homology (BH) domains, termed BH1 to BH4, can be broadly classified into two groups: the anti-apoptotic Bcl-2 members, including Bcl-2, Bcl-xL, Mcl-1, Bcl-w, A1, and Bcl-B, and the pro-apoptotic members of the BH3-only and Bax-like subfamilies [Danial and Korsmeyer, 2004; Roset et al., 2007]. The relative levels of these

antagonistic pro- and anti-apoptotic Bcl-2 family members, which counteract the activity of one another via direct interactions, mediate the induction of apoptosis, and the disruption of this protective balancing act can contribute to carcinogenesis.

Both overexpression of anti-apoptotic members and reduced expression of pro-apoptotic members have been linked to the aberrant apoptotic signaling involved in several cellular transformation mechanisms [Adams and Cory, 2007]. Bcl-2 or Bcl-xL promote survival by binding pro-apoptotic Bax-like subfamily members, namely Bax and Bak, and thereby inhibit the induction of MOMP mediated by the homooligomerization of these proteins in the mitochondrial membrane [Hinds and Day, 2005; Jin and El-Deiry, 2005]. Bcl-2 overexpression has been reported in a variety of human malignacies, including diffuse large B-cell lymphoma (DLBCL), AML, glioblastoma, melanoma, malignant pleural mesothelioma (MPM), prostate cancer, and lung cancer [Colombel et al., 1993; Ramsay et al., 1995; Kitagawa et al., 1996; Kaufmann et al., 1998; Deininger et al., 1999; Venditti et al., 2004; Abramson and Shipp, 2005; O'Kane et al., 2006]. The overexpression of Bcl-xL is another common oncogenic event that has been observed in several types of cancer, including colorectal adenocarcinomas, Kaposi's sarcoma, and multiple myeloma (MM) [Foreman et al., 1996; Krajewska et al., 1996; Tu et al., 1998]. Additionally, in prostate cancer, Bcl-xL overexpression is associated with disease progression and the development of androgen resistance [Castilla et al., 2006]. In contrast, the BH3-only proteins, such as Bim, Bid, Puma, Bad, and Noxa, act as sensors of cellular damage and can promote apoptosis by binding the anti-apoptotic Bcl-2 family members, facilitating the release of the essential mediators of cell death, Bak and Bak, from inactive heterooligomeric complexes. The importance of the pro-apototic activity of Bax and Bak is highlighted by the high propensity of Bax/Bak-double-deficient mouse embryo fibroblasts (MEF) to undergo oncogenic transformation [Zong et al., 2001].

The BH3-only protein Bid can also serve as a link between the extrinsic and intrinsic apoptotic pathways. Upon activation of death receptor systems, the cleavage of Bid by caspase-8 generates the activated C-terminal Bid fragment, known as tBid, which translocates to the mitochondria and subsequently induces the release of cytochrome c [Khosravi-Far and Esposti, 2004]. The engagement of the mitochondria-dependent apoptotic pathway via the caspase-8-mediated cleavage of Bid is necessary to elicit a complete apoptotic response in response to the Fas/FasL system-initiated death signal in some types of cells [Wang, 2001]. Thus, the overexpression of anti-apoptotic Bcl-2 proteins can inhibit Fas-mediated apoptosis in several cell types, as demonstrated by the inhibition of anti-Fas-induced apoptosis in MCF7 breast cancer cells with elevated levels of Bcl-xL despite the activation of casapase-8 in these cells [Srinivasan et al., 1998]. Accordingly, Bcl-xL-overexpressing cells that rely on the induction of the mitochondria-dependent apoptotic pathway to amplify the extrinsic apoptotic response are resistant to certain drugs that activate Fas-mediated apoptosis, and the role of this dependence in mediating a cell type specific response to cytotoxic drugs can have important therapeutic implications [Fulda et al., 2001].

In addition to the upstream regulation of MOMP induction by the Bcl-2 proteins, the intrinsic apoptotic pathway is regulated downstream of apoptosome formation by several mediators of caspase activation [Wang, 2001; Hajra and Liu, 2004]. The inhibitor of apoptosis proteins (IAPs) are a family of caspase inhibitors that directly bind caspases-3, −7 and/or −9 and thereby impair the activity of these critical effectors of apoptosis [Schimmer, 2004]. Elevated levels of IAPs have been found in numerous types of malignant cells, and the overexpression of these anti-apoptotic proteins is associated with chemoresistance and serves as a poor prognosis marker in several types of cancer [Schimmer, 2004; Zhivotovsky and Orrenius, 2006]. The differential expression of survivin, an IAP that inhibits caspases-3 and −7, in malignant cells and normal adult cells has been demonstrated by the detection of survivin expression in each tumor cell line of the NCI 60 cell line panel, but not in untransformed cells, [Tamm et al.,

1998] and by the prominent expression of survivin in lung, colon, pancreas, prostate, and breast cancer cells, in vivo, with undetectable expression in the corresponding non-neoplastic cell types [Ambrosini et al., 1997]. Frequent overexpression of another IAP, XIAP, has also been observed in the NCI 60 tumor cell line panel [Fong et al., 2000], and in AML patients, a high level of XIAP has been associated with poor prognosis [Tamm et al., 2000]. While survivin partially inhibited Bax or Fas-induced apoptosis in cotransfection experiments using 293 cells, cell death was almost entirely blocked by XIAP under the same conditions [Tamm et al., 1998]. The potent anti-apoptotic activity of XIAP is, in part, attributable to its ability to suppress both the death receptor- and mitochondria-dependent apoptotic pathways, as XIAP acts to inhibit caspases-3, −7, and −9 [Deveraux et al., 1998].

Given that aberrant levels of key mediators of the mitochondria-dependent apoptotic pathway have been implicated in tumorigenesis and chemoresistance, these regulatory proteins can serve as specific targets for apoptosis-inducing cancer therapeutics (see Table II). Efforts that implement this approach have involved designing inhibitors of the anti-apoptotic proteins that are frequently overexpressed in tumor cells, particularly Bcl-2, Bcl-xL, and IAPs [Fulda and Debatin, 2004;Fesik, 2005]. The association of the overexpression of anti-apoptotic Bcl-2 family members, especially Bcl-2 and Bcl-xL, with resistance to various anti-cancer therapies, as demonstrated by the strong negative correlation of Bcl-xL expression levels with sensitivity of cancer cells to a panel of 122 standard chemotherapy agents [Amundson et al., 2000], makes these proteins attractive therapeutic targets [Fesik, 2005]. A promising therapeutic approach to block the action of these anti-apoptotic proteins involves the development of both peptide mimetics and small molecule inhibitors that mimic the BH3 domain of the BH3-only subfamily members and thereby bind and neutralize anti-apoptotic Bcl-2 family members [Fesik, 2005;Zhang et al., 2007]. For instance, a potent small molecule inhibitor of Bcl-2, Bcl-xL, and Bcl-w, termed ABT-737, can enhance the cytotoxicity of chemotherapeutic agents and displays single-agent activity against some cancer cells, including SCLC cells, causing complete regression of SCLC tumor xenografts in mice [Oltersdorf et al., 2005].

Similar to anti-apoptotic Bcl-2 proteins, elevated expression in most human malignancies and a role in the resistance of cancer cells to various pro-apoptotic stimuli, including chemotherapeutic agents, make IAPs promising molecular targets for the development of cancer therapeutics [Vucic and Fairbrother, 2007]. Several IAP-targeted therapies have been developed, including anti-sense oligonucleotides against XIAP and survivin and small molecule inhibitors of XIAP, and some have entered into clinical trials [Amantana et al., 2004; Schimmer, 2004; Schimmer and Dalili, 2005; Vucic and Fairbrother, 2007]. XIAP inhibitors have been shown to suppress tumor growth in xenograft mouse models and sensitize cancer cells to chemotherapeutic and radiation treatments, highlighting XIAP as a significant factor in the resistance of several types of cancer cells to apoptosis-inducing agents [Schimmer, 2004; Schimmer et al., 2004; Schimmer and Dalili, 2005]. Specifically, downregulation of XIAP by the adenoviral vector-mediated delivery of an anti-sense agent has been found to induce apoptosis in chemoresistant ovarian cancer cells [Sasaki et al., 2000] and sensitize lung cancer cells to radiation therapy [Holcik et al., 2000]. Furthermore, the inhibition of XIAP expression, using an anti-sense XIAP phosphorodiamidate morpholino oligomer (PMO), has been shown to induce apoptosis and increase caspase-3 activity as well as enhance the apoptotic effects of cisplatin and TRAIL in human androgen-insensitive DU145 prostate cancer cells [Amantana et al., 2004].

REGULATORY MECHANISMS OF THE APOPTOTIC PATHWAYS

Cellular Stress-Induced Apoptosis

The regulation of apoptosis at several levels is essential to maintain the fundamental equilibrium between cell survival and cell death that is characteristic of healthy tissues.

Disruption of this balance by alterations in the expression or function of proteins that serve as mediators of survival or apoptotic signaling pathways can lead to enhanced cellular survival, thus promoting the development and progression of cancer [Kabore et al., 2004]. Consequently, the cell has several defense mechanisms that are activated upon the introduction of cellular stressors as a means to safeguard this balance. In particular, the tumor suppressor p53 plays a key role in the prevention of aberrant cellular proliferation and the preservation of genomic integrity by inducing either DNA repair or apoptosis in response to several stress stimuli, including DNA damage and oncogene overexpression [Vogelstein et al., 2000; Fuster et al., 2007]. The activation of p53 is mediated by several post-translational modification processes, including phosphorylation, acetylation, and ubiquitination [Fuster et al., 2007]. The oncoprotein murine double minute 2 (MDM2; known as HDM2 in humans) is a critical negative regulator of p53 that acts to block the binding of the transcription machinery to p53 and to promote the proteasomal degradation of p53 through its p53-specific E3 ubiquitin ligase activity [Garcia-Echeverria et al., 2000; Fuster et al., 2007].

Apoptosis induction by p53 is a critical aspect of its tumor suppressor function. p53 can induce apoptosis by binding to DNA in a sequence specific fashion to activate the transcription of its pro-apoptotic gene targets [Yu and Zhang, 2005]. Specifically, p53 can induce the expression of several pro-apoptotic Bcl-2 proteins, including Bax and the BH3-only subfamily members Puma, Noxa, and Bid, and thereby promote the activation of the mitochondria-dependent apoptotic pathway [Schuler and Green, 2005; Yu and Zhang, 2005]. While p53-mediated apoptosis is primarily associated with the intrinsic apoptotic pathway, the transcriptional activity of p53 can also promote apoptosis by activating components of the extrinsic apoptotic pathway [Fridman and Lowe, 2003]. For example, p53 has been shown to regulate the expression of death receptor-encoding genes, including *DR4*, *DR5*, and *Fas* [Schuler and Green, 2005; Yu and Zhang, 2005]. In addition to the undeniable importance of the transcriptional regulation function of p53 in apoptosis induction, accumulating evidence supports transcriptional-independent mechanisms of p53-mediated apoptosis, whereby p53 is linked to the intrinsic apoptotic pathway through direct interactions with Bcl-2 family proteins [Schuler and Green, 2005; Yee and Vousden, 2005]. Upon initiation of p53-dependent apoptosis, but not during p53-independent apoptosis, a fraction of p53 has been found to translocate to the mitrochondria [Marchenko et al., 2000; Sansome et al., 2001]. Mitochondrial p53 has been reported to interact with both anti-apoptotic Bcl-2 family members and the pro-apoptotic Bcl-2 protein Bak, which disrupts inactive heterodimeric complexes of Bax and the anti-apoptotic BAK–MCL-1 complex, respectively, to promote the homooligomerization of Bax-like proteins, thereby triggering MOMP and apoptosis [Fuster et al., 2007].

In view of the central role of p53 in mediating several anti-proliferative processes to prevent aberrant cell proliferation, thereby earning the title “guardian of the genome,” loss of functional p53 facilitates cellular transformation by promoting the inappropriate survival of cells and the persistence and evolution of genetic defects [Fridman and Lowe, 2003]. In addition to the remarkably high incidence of p53 inactivation in human tumors, with most cancers exhibiting mutations or aberrant regulation of p53 [Hainaut et al., 1998; Momand et al., 1998], evidence of the critical function of p53 as a tumor suppressor has been provided by the generation of genetically altered mice lacking p53, as these *p53* knockout mice rapidly develop tumors at a high frequency [Attardi and Jacks, 1999]. The enhanced tumor development observed in several p53-deficient mice models has been associated with defective apoptosis, underscoring the significant role of the apoptosis-inducing activity of p53 in tumor suppression [Vousden and Lu, 2002; Fridman and Lowe, 2003].

Inactivating *p53* gene mutations have been found in an extensive number of cancers, with a high prevalence in malignancies of the lung, colon, stomach, and esophagus [Soussi, 2000]. As these mutations are most commonly point missense mutations within the region encoding

the conserved DNA binding domain (exons 5–8), mutation of the *p53* gene generally results in the generation of p53 mutants that lack the transactivation function of wild-type p53 (wt-p53) [Soussi, 2000]. Alterations in the key regulators of p53 stability and function have also been identified as a mechanism for p53 inactivation in human cancers [Fuster et al., 2007]. In particular, upregulation of MDM-2 [Momand et al., 1998], the main inhibitor of p53, or downregulation of $p14^{ARF}$ [Sato et al., 2002], a direct inhibitor of MDM-2, is fairly common in certain cancers. For example, hypermethylation of the $p14^{ARF}$ gene, resulting in the suppression of $p14^{ARF}$ expression, has been reported in sporadic [Esteller et al., 2000] and ulcerative colitis-associated colorectal carcinomas [Sato et al., 2002].

In recognition of the fact that p53 inactivation is a feature of the majority of human cancers, great efforts have been made toward developing therapeutic agents that can restore wt-p53 transcriptional activity [Fuster et al., 2007] (see Table III). The importance of this therapeutic approach is underscored by the association of loss of p53 function with increased cancer aggressiveness and resistance to anti-cancer therapies [Bossi and Sacchi, 2007]. Several strategies that aim to reinstate wt-p53 function, particularly gene transfer of wt-p53, inhibition of the MDM2-p53 interaction, and chemical restoration of wt-p53 activity, have been pursued. Despite the need for further improvements that reduce toxicity or increase anti-tumor efficiency, some p53-activating agents have shown encouraging results, supporting the continued investigation of wt-p53 reactivation as a means to develop a potent tumor-specific therapy [Bossi and Sacchi, 2007; Selivanova and Wiman, 2007].

In addition to p53, the Jun N-terminal kinases (JNKs) are activated in response to some cellular stressors and can act to mediate apoptosis [Herr and Debatin, 2001]. The JNKs are considered key modulators of diverse cellular processes, including cell proliferation, cell survival, DNA repair, and cell death [Karin and Gallagher, 2005]. While the JNK pathway has been implicated in mediating both pro-and anti-apoptotic effects that are dependent upon cellular context, JNK signaling can target several apoptotic molecules, using both transcription-dependent and transcription-independent mechanisms, to promote apoptosis [Herr and Debatin, 2001]. JNK activation results in the phosphorylation and subsequent activation of certain members of the AP-1 family of transcription factors, including c-Jun and ATF-2, thereby promoting apoptosis via triggering the expression of the pro-apoptotic c-Jun target genes, such as the death ligand-encoding genes *FasL* and *TNF* [Herr and Debatin, 2001]. JNK signaling may also play a role in the mitochondria-dependent apoptotic pathway by phosphorylating Bcl-2 and Bcl-xL, which could serve to inactivate these key anti-apoptotic proteins [Herr and Debatin, 2001].

Modification of the JNK pathway has been implicated in the pathogenesis of certain cancers. The aberrant expression of Bcl-w in gastric cancer cells has been reported to exert its pro-survival effect by suppressing the activation of JNK signaling [Lee et al., 2003]. In addition, reduced levels of the JNK effector ATF-2 have been associated with the development of mammary tumors, as $Atf\text{-}2^{-/-}$ mouse embryonic fibroblasts (MEFs) have been shown to exhibit reduced levels of apoptosis in response to some stresses and $Atf\text{-}2^{+/-}$ mice have been shown to have a high propensity for mammary tumor development [Maekawa et al., 2007, 2008]. Still, exploiting the JNK pathway as a therapeutic target for the development of apoptosis-inducing anti-cancer agents requires consideration of both its pro- and anti-apoptotic effects. While the apoptotic response of cancer cells to certain stress-inducing agents can depend on JNK activation [Singh et al., 2007; Xia et al., 2007], inhibition of JNK signaling is also being explored as a therapeutic strategy in cancer since JNK inhibitors can impair the DNA repair response in cancer cells and thereby enhance the cytotoxic effects of DNA-damaging agents [Potapova et al., 2001; Karin and Gallagher, 2005].

Survival Factor-Mediated Inhibition of Apoptosis

In addition to the induction of stress-induced apoptotic signaling, control of the promotion of cellular proliferation by survival signaling pathways is crucial for maintaining the homeostasis of healthy tissues. Because survival mechanisms, including the phosphatidylinositol 3-kinase (PI3K)-Akt, NF-κB, and Ras-Raf-MEK-ERK pathways, are dynamically linked to the apoptotic machinery in a complex cellular signaling network, activation of survival signaling can serve to block apoptotic signaling [Kabore et al., 2004]. This integration of cell survival and cell death programs is often exploited by cancer cells, using constitutive activation of survival signaling as a means of protection against the apoptotic response that would normally be elicited by various cues, including the removal of growth factors and/or genomic defects [Kabore et al., 2004].

The PI3K-Akt pathway, a downstream mediator of several cell surface receptors, particularly growth factor-stimulated receptor tyrosine kinases (RTKs), can use multiple mechanisms to exert an anti-apoptotic effect, as the activity of several key regulators of apoptosis are mediated by Akt phosphorylation [Vivanco and Sawyers, 2002]. One such class of Akt targets is the forkhead box O (FoxO) family of transcription factors, which can play an important role in controlling cellular death, proliferation, and survival through modulation of the expression of cell-cycle inhibitory genes and pro-apoptotic genes [Greer and Brunet, 2005; Lam et al., 2006; Jagani et al., 2008]. Direct phosphorylation of FoxO1 and FoxO3a by Akt serves as a key inhibitory mechanism of their transcriptional activity by promoting the nuclear exclusion and subsequent ubiquitination-mediated degradation of these transcription factors. In this manner, Akt promotes cell survival by blocking the FoxO-induced expression of pro-apoptotic gene targets such as *FasL*, *TRAIL*, and *Bim* [Greer and Brunet, 2005; Lam et al., 2006; Jagani et al., 2008]. Akt also regulates the activity of mammalian target of rapamycin (mTOR) complex 1 (mTORC1), a key mediator of cell growth, proliferation, and survival that can function to inhibit apoptosis in a cellular context-dependent manner [Castedo et al., 2002; Corradetti and Guan, 2006; Wullschleger et al., 2006]. The mTORC1 effector S6K1 may mediate the anti-apoptotic effects of mTOR by phosphorylating the BH3-only protein Bad on serine 136, resulting in the inactivation of the pro-apoptotic activity of Bad [Harada et al., 2001]. In addition, Akt itself has been shown to phosphorylate serine 136 of Bad, and this phosphorylation has been found to effectively suppress Bad-induced cell death [Datta et al., 1997].

Since Akt activation triggers multiple signaling mechanisms that inhibit both the intrinsic and extrinsic apoptotic pathways, abnormalities in the PI3K-Akt pathway can play a major role in mediating the evasion of apoptosis in cancer cells [Kabore et al., 2004]. One such aberration involves activating mutations of *PIK3CA*, the gene encoding the p110α catalytic subunit of PI3K. Somatic missense mutations of *PIK3CA* are common in several cancers, including ovarian and breast cancers [Levine et al., 2005]. The two most common types of PI3K mutants, arising from mutations of *PIK3CA* within the regions encoding the helical and kinase domains, are potent inducers of Akt activation and oncogenic transformation [Kang et al., 2005; Liu and Roberts, 2006]. In addition to PI3K mutations, several other genetic aberrations that result in the constitutive activation of Akt have been reported. The widespread prevalence of aberrant Akt activity in human cancers strongly implies that Akt activation is a key mediator of carcinogenesis [Testa and Bellacosa, 2001; Hay, 2005; Hennessy et al., 2005]. Each of the highly conserved Akt family members, Akt1, Akt2, and Akt3, has been associated with specific types of cancer. For instance, gene amplification and/or mRNA overexpression of *Akt2* has been found in a significant fraction of ovarian and pancreatic cancers, and upregulation of *Akt3* mRNA expression has been observed in hormone-insensitive breast tumors [Testa and Bellacosa, 2001]. Furthermore, a point mutation in the plekstrin homology domain (PHD) of Akt1 that leads to persistent plasma membrane localization and consequent constitutive

activation of the mutant has been found in breast, ovarian, and colorectal cancers [Carpten et al., 2008]. Moreover, the loss or downregulation of the tumor suppressor PTEN, an inhibitor of PI3K-dependent activation of Akt, is a common mechanism for constitutive Akt activation in many human cancers, especially in prostate and endometrial cancers, melanoma, and glioblastoma [Sansal and Sellers, 2004].

In light of the prominent role of aberrant Akt activation in neoplastic transformation, the PI3K-Akt pathway components, including both Akt itself [West et al., 2002] and its downstream effectors [Arden, 2006; Petroulakis et al., 2006], have emerged as potential therapeutic targets in the treatment of a variety of cancers [Hennessy et al., 2005] (see Table III). For instance, reinstating FoxO activity represents a promising therapeutic approach for a wide range of cancers, as a deficiency of functional FoxO can lead to uncontrolled cellular proliferation and accumulation of DNA damage [Arden, 2006; Lam et al., 2006]. Furthermore, inactivation of the transcriptional function of FoxO1 has been observed in PTEN-null tumor cells and restoration of FoxO activity has been found to induce cell death in a manner which parallels reconstitution with PTEN, thereby indicating that FoxOs play a key role in mediating the tumor suppressor function of PTEN [Nakamura et al., 2000]. Consequently, the preclinical development of therapeutic agents that restore the transcriptional activity of FoxO1 by inhibiting its nuclear export has been initiated [Kau et al., 2003; Schroeder et al., 2005].

In addition to the potential therapeutic effects of targeting the PI3K-Akt pathway components with monotherapeutic approaches, agents directed against elements of the PI3K-Akt pathway in combination with standard therapies have great promise to enhance the effectiveness of current therapies. In several types of cancer cells, inhibition of PI3K-Akt signaling has been shown to reverse resistance to a variety of treatments, including chemotherapy, hormone therapy, and targeted therapy [Beeram et al., 2007; Lu et al., 2007; Yu et al., 2008]. Considering that the PI3K-Akt pathway is frequently implicated in conferring therapy resistance to cancer cells, combination therapies of conventional agents with drugs aimed at re-establishing the apoptotic response by suppressing PI3K-Akt signaling may serve as a means to overcome therapy resistance in a clinical setting, particularly in cancers with genetic aberrations that activate the PI3K-Akt pathway [Hennessy et al., 2005].

The therapeutic effect of attenuating PI3K-Akt signaling is underscored by the essential role of PI3K-Akt pathway inhibition in mediating the therapeutic efficacy of a number of the drugs targeted against deregulated RTKs that aberrantly activate multiple downstream signal transduction mechanisms, including the PI3K-Akt pathway [Hennessy et al., 2005]. Given that constitutive activation of RTKs, often due to overexpression or mutational activation, plays a critical role in tumorigenesis, many agents that selectively target these cell surface receptors have been developed. Importantly, several anti-RTK therapies have demonstrated efficacy in clinical trials, both as a monotherapy and in combinational therapies [Gschwind et al., 2004; Guillemard and Saragovi, 2004]. In particular, Trastuzumab (Herceptin) is a monoclonal antibody against the extracellular domain of human epidermal growth factor receptor type 2 (HER2), an upstream RTK of PI3K that is frequently overexpressed in invasive breast cancers. Trastuzumab acts to neutralize HER2 signaling and thus prevents the pathological effects of HER2 overexpression, which includes the inhibition of apoptosis through constitutive activation of the PI3K-Akt-mTOR pathway [Yarden and Sliwkowski, 2001; Hudis, 2007]. Following the validation of its efficacy and safety, both alone and in combination with chemotherapy, by multiple clinical trials, Trastuzumab was approved by the FDA for the treatment of breast cancers with HER-2 overexpression and has since revolutionized the treatment and prognosis of women with HER2-positive breast cancer [Hudis, 2007].

Another important mediator of cell survival is NF-κB, as this transcription factor has emerged as a major player in apoptosis regulation [Dutta et al., 2006]. Activation of NF-κB by certain

TNF family members, particularly TNF, promotes the expression of anti-apoptotic proteins and consequently blocks apoptosis. Targets of NF-κB-mediated transcriptional activation include the genes that encode the IAPs, the anti-apoptotic Bcl-2 family members Bcl-xL and A1, c-FLIP, and TNF-associated factor 1 (TRAF1) and 2 (TRAF2) [Karin and Lin, 2002; Karin et al., 2002]. The anti-apoptotic activity of NF-κB can also be induced in response to DNA-damaging agents, including chemotherapeutics and radiation, thereby protecting cancer cells from death by these treatments [Dutta et al., 2006].

While NF-κB is best known as a central regulator of the inflammatory and immune responses, the importance of its more recently discovered role in controlling cell proliferation, apoptosis, and cell migration is highlighted by compelling evidence that links dysregulation of NF-κB with oncogenesis [Baldwin, 2001]. Indeed, NF-κB has been found to be constitutively activated in various malignancies and to play a role in several aspects of carcinogenesis, acting to enhance cellular proliferation, block apoptosis, and promote the angiogenic and metastatic potential of cancer cells [Basseres and Baldwin, 2006; Escarcega et al., 2007]. The significance of NF-κB activity in tumor growth and progression has been supported by studies that have demonstrated that inhibition of NF-κB activity results in decreased tumorigenicity and suppressed angiogenesis and metastasis of human melanoma and ovarian cancer cells in mice [Huang et al., 2000a,b]. In addition, reports of a mutual transcriptional antagonism between NF-κB and p53, which involves the downregulation of p53-mediated transcriptional activation by TNF-activated NF-κB, suggest that NF-κB dysregulation can also contribute to tumorogenesis by promoting the persistence and evolution of genomic defects through inhibition of the tumor suppressor function of p53 [Webster and Perkins, 1999; Ikeda et al., 2000].

The activation of NF-κB signaling not only promotes neoplastic transformation and cancer progression, but also serves as a protective mechanism used by cancer cells to escape death induced by several cancer therapies. Chemotherapy and radiation treatments have been shown to activate NF-κB in some tumor cells, and inhibition of NF-κB activity has been reported to strongly enhance the apoptosis-inducing activity of TNF, radiation, and the chemotherapeutic agents daunorubicin and CPT-11 [Wang et al., 1996, 1999]. The significant role of NF-κB activation in suppressing the apoptotic potential of chemotherapeutic agents has been further evidenced by numerous studies using various chemotherapies and a variety of strategies to block NF-κB activity [Nakanishi and Toi, 2005]. Given that NF-κB acts as a key player in carcinogenesis and chemoresistance, the NF-κB signaling pathway represents an appealing target for the development of anti-cancer agents [Nakanishi and Toi, 2005; Olivier et al., 2006]. The intense interest in targeting the NF-κB signaling pathway for pharmaceutical intervention is highlighted by the fact that over 750 inhibitors of NF-κB activity have been identified [Gilmore and Herscovitch, 2006].

While the significant progress that has been made in the development of agents that act as specific inhibitors of NF-κB provides much hope for the advancement of one such agent into clinical trials, the attenuation of the anti-apoptotic activity of NF-κB by therapeutics that target general cellular components, thereby exerting both NF-κB-dependent and -independent biological effects, has already been shown to elicit a clinical response in cancer patients [Karin et al., 2004; Olivier et al., 2006]. Notably, the anti-neoplastic activity of the proteasome inhibitor bortezomib (Velcade), an FDA-approved drug for second line treatment of MM, has been largely associated with inhibition of the NF-κB survival pathway [Adams, 2004; Olivier et al., 2006]. In addition to MM cells, bortezomib has demonstrated single-agent activity against a range of cancer cells, particularly non-Hodgkin's lymphoma (NHL) and non-small cell lung cancer (NSCLC) cells, and bortezomib has been shown to sensitize MM, NHL, and NSCLC cells to various anti-cancer agents [Leonard et al., 2006]. Based on strong preclinical evidence, a number of clinical trials investigating the efficacy of bortezomib, both as a single agent and in combination therapy, in several subtypes of NHL have been initiated, and the

clinical results thus far indicate that bortezomib-based combination therapy is a promising treatment strategy for lymphoma patients [Leonard et al., 2006].Considering that NF-κB-mediated resistance to apoptosis is a common feature of many tumor cells, this approach of using agents that block NF-κB activity to enhance the clinical activity of standard apoptosis-inducing therapies may extend to a wide range of cancers. Yet, in certain cell type- and/or stimulus-dependent contexts, NF-κB activation has also been shown to sensitize cells to apoptosis. Further investigation into the mechanisms that direct NF-κB to exert a tumor suppressor activity, as opposed to its generally anti-apoptotic activity, will provide insight into the scenarios in which NF-κB-targeted therapeutic agents, both alone and in combination with standard therapies, will offer therapeutic benefits [Dutta et al., 2006].

The small GTPase Ras functions as yet another central regulator of cellular proliferation and survival by coupling the activation of cell surface receptors, including RTKs, to downstream cytoplasmic effectors [Roberts and Der, 2007]. The stimulation of various cell surface receptors by extracellular stimuli induces the conversion of human Ras proteins, termed H-Ras, N-Ras, and K-Ras, from an inactive GDP-bound form to an active GTP-bound form. Activated Ras subsequently triggers several signaling mechanisms, including mitogen-activated protein kinase (MAPK) cascades, which are comprised of three proteins that function as a signaling relay to mediate a variety of cellular responses [Kolch, 2000; Mitin et al., 2005; Roberts and Der, 2007]. In particular, the Raf-MEK-ERK pathway is a well characterized Ras effector pathway that plays an important role in both cellular proliferation and programmed cell death [Kolch, 2000].

Once activated, ERK, the terminal serine/ threonine kinase of the Raf-MEK-ERK cascade, phosphorylates and thereby regulates the activities of a number of substrates, including 90 kDa ribosomal protein S6 kinase (RSK) and multiple transcription factors. In this manner, ERK signaling facilitates the transduction of an extracellular signal from cell surface receptors to DNA transcription factors and thus induces alterations in gene expression [Roberts and Der, 2007].

Much evidence indicates that the Raf-MEF-ERK cascade plays an important role in blocking apoptosis [Shelton et al., 2003]. Constitutively activated MEK has been shown to suppress the apoptotic response, in contrast to the promotion of apoptosis induced by a dominant negative MEK mutant, and constitutively activated ERK, as well as activated MEK, has been found to protect NIH3T3 fibroblasts against death induced by doxorubicin [von Gise et al., 2001]. Furthermore, while the Raf-MEF-ERK signaling pathway has been shown to impair apoptosis without concomitant Akt activation, this MAPK cascade has also been reported to interact with the PI3K-Akt pathway in a cooperative manner to mediate a more extensive anti-apoptotic effect [Shelton et al., 2003].

The vital role of Ras in the control of cellular growth processes is underscored by the potent transforming ability of constitutively activated Ras mutants together with the remarkable prevalence of mutationally activated Ras in human malignancies, with 30% of all human cancers harboring activating Ras mutations, including 90% of pancreatic tumors [Roberts and Der, 2007]. Mutational activation of Ras generally involves a point mutation within particular codons of one of the three Ras-encoding genes, *HRAS*, *NRAS*, and *KRAS*, resulting in the generation of Ras protein products with a single amino acid substitution at position 12, 13, or 61 [Bos, 1989]. These Ras mutants are locked in an active GTP-bound state and thus trigger the persistent activation of downstream effector pathways in a stimulus-independent manner [Roberts and Der, 2007]. Several lines of evidence indicate that the Raf-MEK-ERK cascade is a critical downstream mediator of Ras-induced oncogenesis, yet Raf-independent signaling pathways have also been shown to significantly contribute to Ras-mediated transformation in some cell types [Khosravi-Far et al., 1996; Plattner et al., 1999].

While both Raf-dependent and Raf-independent pathways appear to act as key players in Ras-induced cellular transformation, in either an independent or synergistic manner [Khosravi-Far et al., 1996], aberrant activation of Raf-MEF-ERK signaling has been directly associated with the pathogenesis of several cancers [Mercer and Pritchard, 2003]. Specifically, activating point mutations of *BRAF*, one of the three genes encoding Raf proteins, have been found in a variety of cancers, both with and without the co-occurrence of *RAS* mutations [Mercer and Pritchard, 2003; Sieben et al., 2004]. Nearly all of the known somatic mutations of *BRAF* give rise to a protein product with an enhanced kinase activity, the most common of which harbors a V600E mutation within its kinase domain [Davies et al., 2002; Sridhar et al., 2005]. The transforming activity of these activated B-Raf mutants in NIH3T3 cells and their presence in a wide range of cancers, with a particularly high incidence in malignant melanoma, highlight the significance role of aberrant Raf-MEK-ERK signaling in oncogenesis [Davies et al., 2002; Sridhar et al., 2005]. While the *BRAF* V600E mutation generally occurs independently of *RAS* muations, both types of oncogenic mutations result in similar cancer types and induce constitutive ERK signaling, suggesting that the deregulation of ERK signaling serves as a common mechanism by which Ras and B-Raf drive tumor development [Mercer and Pritchard, 2003].

In addition to activating mutations of Ras or Raf, genetically or epigenetically modified RTK signaling can trigger enhanced Raf-MEK-ERK signaling. As with the PI3K-Akt pathway, aberrant activation of upstream RTKs can result in hyperactivation of the Raf-MEK-ERK pathway and thereby promote malignant transformation and cancer progression [Paul and Mukhopadhyay, 2004]. As critical mediators of key signaling pathways that control cellular proliferation, apoptosis, and angiogenesis, RTKs are tightly regulated in normal cells and deregulation of their activity, predominantly by mutational activation or overexpression, has been found to contribute to the pathogenesis of numerous cancers [Bennasroune et al., 2004]. In particular, epidermal growth factor receptor (EGFR) is overexpressed and/or constitutively activated in many cancers, and upregulation of EGFR has been implicated in the early stages of tumor development and associated with poor prognosis [Grandis and Sok, 2004]. An elevated level of EGFR, often attributable to aberrant transcriptional activation, is common in a wide array of malignancies, including head and neck, colon, lung, breast, renal, ovarian, and prostate cancers. Mutations of EGFR that render the receptor constitutively active and consequently enable ligand-independent signaling have also been reported in a variety of cancers, with an especially high frequency in gliomas [Grandis and Sok, 2004]. For example, an EGFR mutant with a truncated extracellular domain (EGFR-vIII) is commonly found in glioblastomas, and EGFRvIII-mediated tumorogenesis has been associated with an enhanced activation of Ras and the downstream Raf-MEK-ERK cascade [Montgomery et al., 1995; Prigent et al., 1996; Feldkamp et al., 1999].

The upregulation of ERK signaling, by any of the aforementioned activating mechanisms, has been implicated in several tumor-promoting processes, including the evasion of apoptosis [Sridhar et al., 2005]. Constitutive activation of the Raf-MEK-ERK signaling pathway has been associated with resistance to apoptosis in melanoma cells, as hyperactive signaling of the ERK effector RSK has been reported to mediate the persistent phosphorylation and consequent inactivation of pro-apoptotic Bad [Eisenmann et al., 2003]. Additionally, ERK signaling can play an important role in promoting cell survival by phosphorylating several transcription factors, leading to alterations in gene transcription that result in increased levels of several proteins that inhibit apoptosis, including anti-apoptotic Bcl-2 family members and IAPs [Henson and Gibson, 2006]. Moreover, phosphorylation of Bcl-2 and Bim by ERK has been shown to play a protective role against apoptosis by blocking Bcl-2 degradation and accelerating Bim degradation [Breitschopf et al., 2000; Luciano et al., 2003].

Considering the emergence of the Raf-MEK-ERK pathway as a mechanism for apoptosis suppression in certain contexts along with the high incidence of hyperactive Raf-MEK-ERK

signaling in cancer, inhibition of Raf-MEK-ERK signaling is an attractive anti-cancer therapeutic approach [Koo et al., 2002; Sridhar et al., 2005]. Significant efforts have been made toward the development of effective therapeutic agents that specifically target components of the Raf-MEK-ERK pathway and its upstream regulators (see Table III). A number of inhibitors of Raf and MEK have been designed, and several of these agents have demonstrated antineoplastic activity against a wide range of cancers with only mild toxicity in preclinical and early clinical analysis, supporting the continued development and evaluation of Raf and MEK inhibitors [Roberts and Der, 2007]. Furthermore, since a series of post-translational modifications, including farsenylation, serves as a key mechanism that directs Ras signaling, farnesyl transferase inhibitors (FTIs) have been developed as a means to block the post-translational processing of Ras and thereby prevent its activation. While these agents fail to inactivate K- and N-Ras, FTIs inhibit the activity of H-Ras, as well as other proteins that are mediated by farsenylation, and thus have exhibited significant anti-tumor activity in preclinical and clinical studies [Basso et al., 2005, 2006]. Moreover, two strategies aimed at inhibiting EGFR signaling have been successfully developed: monoclonal antibodies against the extracellular domain of EGFR and small molecule inhibitors targeting the EGFR intracellular tyrosine kinase domain. Numerous anti-EGFR monoclonal antibodies and EGFR tyrosine kinase inhibitors have demonstrated clinical activity, as single agents and/or in combination with conventional cytotoxic therapies, with a handful of these agents already receiving FDA approval for use in various cancers, including colorectal cancer and NSCLC, and many others progressing into late-stage clinical evaluation [Dassonville et al., 2007; Overman and Hoff, 2007; Roberts and Der, 2007].

Despite the clinical success of several EGFR-targeted therapies, limitations in utilizing these agents have emerged and their optimal use has not yet been elucidated [Dassonville et al., 2007; Ho et al., 2007; Overman and Hoff, 2007]. Various mechanisms of resistance to drugs directed against EGFR have been reported [Pao et al., 2005; Dassonville et al., 2007], yet using a combination of agents to simultaneously target EGFR and the downstream Raf-MEK-ERK signaling pathway may overcome some forms of resistance [Benvenuti et al., 2007]. In addition, as acquired resistance to EGFR-targeted therapies has been associated with overproduction of vascular endothelial growth factor (VEGF), dual inhibition of EGFR and VEGF receptor (VEGFR), either by using a combination of drugs that target these RTKs separately or a single agent that acts to block both EGFR and VEGFR signaling, is a promising therapeutic strategy for several cancers, particularly NSCLC [Byers and Heymach, 2007]. The therapeutic potential of targeting multiple signaling molecules is highlighted by the significant clinical benefits provided by sorafenib [Hahn and Stadler, 2006; Rini, 2006] and sunitinib [Christensen, 2007], two targeted therapies with potent inhibitory activity against multiple tyrosine kinases, including the angiogenic RTKs platelet-derived growth factor receptor (PDGFR) and VEGFR. In addition to the demonstrated efficacy and safety of these agents in the treatment of metastatic renal cell carcinoma and gastrointestinal stromal tumors, encouraging clinical data suggest that sorafenib and sunitinib may prove to be effective therapies for NSCLC [Gridelli et al., 2007]. As strategies for the development of anticancer therapies continue to progress and evolve, the emerging role of multi-kinase inhibitors in cancer therapy has prompted a discussion regarding the advantages and disadvantages of highly selective monotherapies verses multi-targeted kinase inhibitors [Sebolt-Leopold and English, 2006].

Evasion of Apoptosis by Cancer-Specific Fusion Proteins

Distinct chromosomal translocations in leukemias and in solid tumors often result in gene fusion and consequent generation of tumor-specific chimeric oncoproteins [Rabbitts, 1994], such as NPM-ALK, the product of a fusion gene that is commonly observed in anaplastic large cell lymphoma (ALCL) [Shiota et al., 1995], and BCR-ABL, a fusion gene product that is the

causative agent of chronic myelogenous leukemia (CML) and a subset of acute lymphocytic leukemia (ALL) cases [Rowley, 1973; Melo, 1996; Deininger, 2007]. As products of genetic defects, the functional activities of various fusion proteins are inherently dysregulated, and their aberrant activities are associated with several oncogenic processes, including constitutive activation of survival pathways and suppression of apoptotic signaling [Deininger et al., 2000; Slupianek et al., 2001; Coluccia et al., 2004; Melo and Deininger, 2004; Steelman et al., 2004; Hosokawa, 2005]. In human ALCL-derived cells, the constitutive activity of NPM-ALK imparts a robust survival signal through the aberrant activation of multiple signal transduction pathways, including the Jak-Stat and PI3K-Akt pathways. In this manner, NPM-ALK exerts an anti-apoptotic effect, in part, by promoting the expression of Bcl-xL [Slupianek et al., 2001; Coluccia et al., 2004]. Similarly, the oncogenic potential of BCR-ABL, resulting from its constitutive tyrosine kinase activity, involves the activation of several survival mechanisms. In particular, the PI3K-Akt pathway has been reported to play a key role in BCR-ABL-induced leukemogenesis [Skorski et al., 1997; Van Etten, 2004; Ren, 2005]. BCR-ABL mediates the evasion of apoptosis, at least in part, by inducing the hyperactivation of Akt, thereby suppressing the FoxO-regulated expression of the pro-apoptotic factors TRAIL and Bim [Jagani et al., 2008].

The identification of the molecular pathogenesis of CML has revolutionized the core strategies employed in the development of cancer treatments by enabling the introduction of rationally designed therapies [Hehlmann et al., 2007] (see Table III). Imatinib mesylate (Gleevec, Glivec), a small molecule inhibitor of BCR-ABL, has been shown to exert an anti-proliferative effect in BCR-ABL-positive leukemia cells [Deininger and Druker, 2003] by inducing apoptosis in a caspase-dependent manner [Dan et al., 1998]. While this targeted therapy has shown a remarkable clinical response and is the standard first line treatment for all phases of CML, the emergence of imatinib resistance as a significant limitation in the treatment of CML warrants the investigation of alternative therapeutic strategies, including targeting the downstream signaling pathways of BCR-ABL that are important in the pathogenesis of CML [Ren, 2005; Deininger, 2007].

CONCLUSION

The essential role of apoptosis in preventing tumor-promoting processes, particularly aberrant cellular proliferation and the accumulation of genetic defects, has clearly been confirmed since the prospect that apoptosis serves as a barrier to cancer was initially suggested by Kerr et al. [1972]. The evasion of apoptosis is now well recognized as a prominent hallmark of cancer, and tremendous progress has been made in defining the molecular mechanisms by which cancer cells acquire resistance to apoptosis. In view of the significance of apoptosis suppression in mediating the development and progression of cancer, targeting the molecular defects responsible for the abrogation of apoptosis has emerged as a promising therapeutic approach for treating an array of cancers. While classical cancer therapies act on normal cells as well as cancer cells, thus causing adverse side effects, and fail to elicit a therapeutic response in apoptotic-deficient cells, therapeutic agents that restore apoptotic signaling are expected to selectively target and eradicate cancer cells dependent on apoptosis-suppressing oncogenic mutations for survival and to sensitize cancer cells to other anti-neoplastic agents. Indeed, the therapeutic potential of this approach has been realized, as highlighted by the clinical success of several agents directed against various identified mechanisms that act, at least in part, to protect cancer cells from apoptosis. Despite the achievements thus far, the therapeutic strategy of reinstating the apoptotic response remains an enormous challenge. This approach must be tailored to specific subsets of cancers, as various cancers cells bear distinct sets of defects. Thus, considering the high grade of heterogeneity between tumors, even of the same type, exploiting the induction of apoptosis as a means to eliminate cancer cells requires extensive efforts toward the further investigation of the specific modes of apoptotic dysregulation.

Nevertheless, the therapeutic limitations of existing drugs, often attributable to apoptosis resistance, and the encouraging results of preclinical and clinical studies clearly validate the continued search for agents aimed at reestablishing the apoptotic response.

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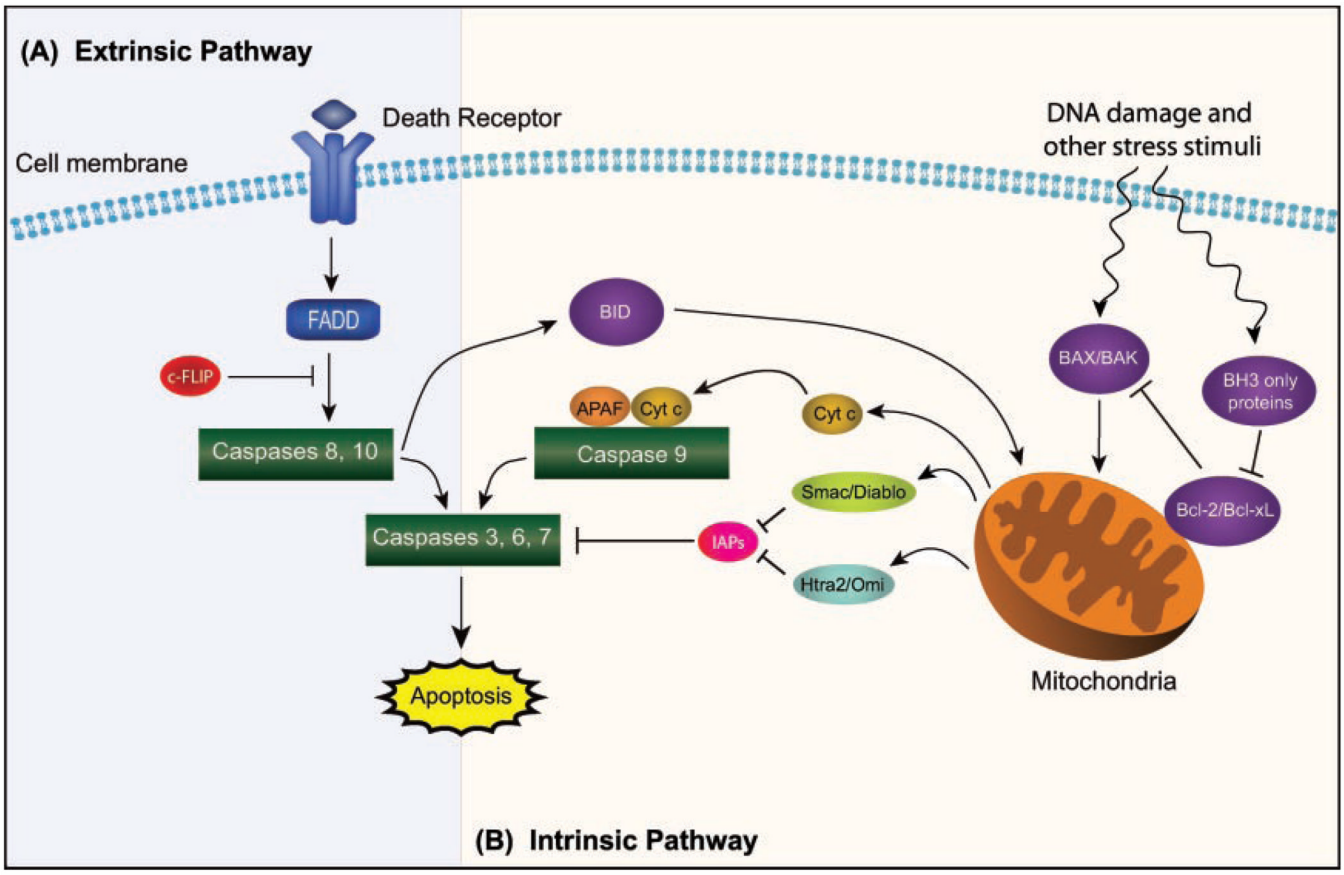

Fig. 1.
A schematic of the (A) extrinsic and (B) intrinsic apoptotic signaling pathways.

TABLE I

Therapies Targeting the Extrinsic Pathway of Apoptosis

Therapy	Target	Type of cancer (phase)	Company/reference
Agonist mAB			
Mapatumumab (HGS-ETR1)	TRAIL-R1	Non-Hodgkin's lymphoma, NSCLC and multiple myeloma (II)	Human Genome Sciences[a]/ [Tolcher et al., 2007]
Lexatumumab (HGS-ETR2)	TRAIL-R2	Various solid malignancies (I)	Human Genome Science[a]/ [Plummer et al., 2007]
CS-1008 (humanized TRA-8)	TRAIL-R2	Pancreatic cancer (II)	Daiichi Sankyo, Inc.[a]/ [DeRosier et al., 2007]
Soluble TRAIL			
AMG 951 (rhApo2L/TRAIL)	TRAIL-R1 and TRAIL-R2	NSCLC (II)	Amgen and Genentech[a]/ [Daniel et al., 2007]
TRAIL-expressing adenovirus	TRAIL-R1 and TRAIL-R2	Preclinical	Introgen Therapeutics and VirRx/[Shashkova et al., 2008]
Recombinant TNF + chemotherapy	TNF receptors	*APPROVED* in Europe in the isolated limb perfusion setting for treatment of irresectable soft tissue carcinomas and melanoma	[van Horssen et al., 2006]

NSCLC, non-small cell lug cancer.

[a] www.clinicaltrials.gov.

TABLE II

Therapies Targeting the Intrinsic Pathway of Apoptosis

Therapy	Target	Type of cancer (phase)	Company/reference
Small molecule inhibitors of Bcl-2/Bcl-xL			
Obatoclax (GX15-070)	Pan-Bcl-2 inhibitor	Hematological malignancies, NSCLC, and SCLC (I–II)	Gemin X[a]/[Perez-Galan et al., 2007]
ABT-263	Bcl-2, Bcl-xL, and Bcl-w	Lymphomas, CLL, and SCLC (I)	Abbott and Genentech[a]/[Tuma, 2007]
BH3Is	Bcl-xL	Preclinical	[Degterev et al., 2001; Ray et al., 2005]
ABT-737	Bcl-2, Bcl-xL, and Bcl-w	Preclinical	Abbott Laboratories/[Oltersdorf et al., 2005]
Bcl-2 ASOs			
Genasense (G3139)	Bcl-2	CLL, CML, melanoma, breast cancer, and colorectal cancer (I–III)	Genta Incorporated[a]/[Anon, 2007b]
SPC2996	Bcl-2	CLL (I/II)	Santaris Pharma[a]/[Tilly et al., 2007]
Peptide-based inhibitors of Bcl-2/Bcl-xL			
BH3 domain of Bak fused to a PTD	Bcl-xL	Preclinical	[Holinger et al., 1999; Brewis et al., 2003]
SAHBs	Bcl-xL	Preclinical	[Walensky et al., 2004]
MKT-077 (lipophilic cation)	Mitochondria	Solid tumors (II—discontinued trial due to toxicity)	[Bouchier-Hayes et al., 2005; Deocaris et al., 2007]
IAP inhibitors			
Gene delivery of SMAC (natural IAP inhibitor)	XIAP	Preclinical	[McNeish et al., 2003]
SMAC mimetics	XIAP	Preclinical	[Sun et al., 2004]
Capped tripeptides with unnatural amino acids	XIAP	Preclinical	[Oost et al., 2004]
Non-peptidic mimetic of SMAC	XIAP, cIAP-1 and cIAP-2	Preclinical	[Li et al., 2004]
IAP ASOs			
AEG35156 (XIAP ASO)	XIAP	Pancreatic cancer, breast cancer, NSCLC, and AML (I/II)	Aegera Therapeutics[a]/[LaCasse et al., 2006]
LY2181308 (survivin ASO)	Survivin	Hepatocellular carcinoma (I/II)	Lilly and ISIS Pharmaceuticals[a]

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; CLL, chronic lymphocytic leukemia; ASO, anti-sense oligonucleotide; CML, chronic myelogenous leukemia; PTD, protein transduction domain; SAHBs, stabilized alpha-helix of BCL-2 domains; IAP, inhibitor of apoptosis protein; SMAC, second mitochondrial-derived activator of caspase; AML, acute myelogenous leukemia.

[a]www.clinicaltrials.gov.

TABLE III

Therapies Targeting Regulatory Mechanisms of Apoptosis

Therapy	Target	Type of cancer (phase)	Company/reference
Restoration of the p53 pathway			
INGN 201 (Ad5CMV-p53)	Adenovirus-mediated delivery of wt-p53	NSCLC (I), breast cancer (II), and head and neck cancer (III)	Introgen Therapeutics[a]/[Anon, 2007a;Tolcher et al., 2006]
MDM2 inhibitors			
MI-63 and MI-147	Disruption of the MDM2-p53 interaction	Preclinical	Ascenta/http://www.ascenta.com
Nutlin-3a	Disruption of the MDM2-p53 interaction	Preclinical	[Kojima et al., 2006; Drakos et al., 2007]
p53 reactivaton			
RITA	wt-p53	Preclinical	[Issaeva et al., 2004; Krajewski et al., 2005]
CP-31398	wt-p53 and mutant p53	Preclinical	[Wischhusen et al., 2003]
PRIMA-1	Various p53 mutants	Preclinical	[Bykov et al., 2002; Rehman et al., 2005]
Inhibition of the PI3K–Akt			
PI3K inhibitors			
XL 147	PI3K	Solid tumors (I)	Exelixis[a]
XL 765	PI3K and mTOR	Solid tumors (I)	Exelixis[a]
PX-866	PI3K	Preclinical	[Howes et al., 2007]
Akt inhibitors			
GSK690693	Akt	Lymphomas and solid tumors (I)	Glaxo Smith Kline[a]
TCN-PM (VD-0002)	Akt	Metastatic cancers with activated Akt (I)	VioQuest Pharmaceuticals[a]/ [Ravandi et al., 2007]
Perifosine (KRX-0401)	Akt	Leukemias (II) and solid cancers, including NSCLC, gliomas, GIST, and renal cancer (I-II)	AOI Pharmaceuticals, NCI[a]/ [Elrod et al., 2007]
KP372-1	Akt	Preclinical	[Mandal et al., 2005]
A-443654	Akt	Preclinical	[Luo et al., 2005]
mTOR inhibitors			
Rapamycin (Sirolimus)	mTOR	*FDA APPROVED* as an immunosuppressant	Wyeth, NCI[a] [Seeliger et al., 2007]
		Clinical—many cancers (mainly I or II)	
CCI-779 (Temsirolimus, Torisel)	mTOR	*FDA APPROVED* for advanced renal cell carcinoma	Wyeth[a]/[Rini et al., 2007]
		Clinical—gynecologic malignancies (I), multiple myeloma (I/II), breast cancer (II), and MCL (III)	
RAD001 (Everolimus)	mTOR	Many cancers, including kidney cancer (I–II), breast cancer (I–II), and mCRC (II–III)	Novaritis[a]/[Lane and Lebwohl, 2006]
AP23573 (Deforolimus)	mTOR	Hematological malignancies (II), sarcomas (II–III), and other malignancies (I)	Ariad Pharmaceuticals[a]/ [Wan and Helman, 2007]
Inhibition of the Ras-Raf-MEK-ERK pathway			

Therapy	Target	Type of cancer (phase)	Company/reference
FTIs			
SCH66336 (Lonafarnib)	Ras and other targets	Many cancers (II-III)	Schering-Plough[a]/[Morgillo and Lee, 2006]
Tipifarnib (R115777)	Ras and other targets	Leukemias and solid tumors (I), including breast cancer (II)	NCI[a]/[Armand et al., 2007]
ISIS 2503 (H-Ras ASO)	H-Ras	Pancreatic cancer and colorectal cancer (II)	NCI[a]/[Adjei et al., 2003]
Raf inhibitors			
Sorafenib (BAY 43–9006, Nexavar)	B-Raf, Raf-1, VEGFR-2, VEGFR-3, PDGFR and KIT	*FDA APPROVED* for advanced renal cancer and unresectable hepatocelluar carcinoma	Bayer[a]/http://www.nexavar.com [Hahn and Stadler, 2006; Gridelli et al., 2007]
		Clinical—many cancers, including breast cancer, melanoma, and NSCLC (II–III)	
XL281	B-Raf, Raf-1, and mutant B-Raf(V600E)	Solid tumors (I)	Elexis[a]
PLX4032	Mutant B-Raf(V600E)	Melanoma with oncogenic B-Raf(V600E) (I)	Plexxikon[a]
LErafAON (Raf-1 ASO)	Raf-1	Advanced cancers (I)	Neopharm[a]/[Dritschilo et al., 2006]
MEK inhibitors			
PD325901	MEK	Colon cancer, breast cancer, and melanoma (I)	Pfizer[a]/[LoRusso et al., 2005]
AZD6244 (ARRY-142886)	MEK	NSCLC, melanoma, hepato-cellular carcinoma, mCRC, and pancreatic cancer (II)	AstraZeneca[a]/[Yeh et al., 2007]
XL518	MEK	Solid tumors (I)	Exelixis[a]
Inhibition of RTKs			
Monoclonal antibodies			
Cetuximab (Erbitux)	EGFR	*FDA APPROVED* for mCRC and advanced head and neck cancer	Bristol-Myers Squibb, ImClone Systems[a]/[Blick and Scott, 2007],
		Clinical—various solid tumors (II–III)	
Panitumumab (Vectibix, ABX-EGF)	EGFR	*FDA APPROVED* for mCRC	Amgen[a]/[Messersmith and Hidalgo, 2007]
		Clinical—NSCLC (II) and head and neck cancer (III)	
Matuzumab (EMD 72000)	EGFR	NSCLC and gastric cancer (II)	EMD Pharmaceuticals[a]/ [Yoshida et al., 2008]
Trastuzumab	HER2	*FDA APPROVED* for metastatic breast cancers with HER2 overexpression	Genentech[a]/[Hudis, 2007]
		Clinical—breast cancer (I–III)	
Tyrosine kinase inhibitors			
Gefitinib (Iressa, ZD1839)	EGFR	*RESTRICTED FDA APPROVAL* for NSCLC patients that have already received and benefited from this therapy	AstraZeneca[a]/[Blackhall et al., 2006]
		Clinical—various solid tumors (II–III)	
Erlotinib (Tarceva, OSI-774)	EGFR	*FDA APPROVED* for locally advanced or metastatic NSCLC and unresectable, locally advanced, or metastatic	Genentech, OSI Pharmaceuticals, Roche[a]/[Moore et al., 2007]

Therapy	Target	Type of cancer (phase)	Company/reference
		pancreatic cancer (in combination with gemcitabine)	
		Clinical—various solid tumors (II–III)	
EKB-569 (irreversible inhibitor)	EGFR	Colorectal cancer (II) and NSCLC (II)	Wyeth[a]/[Erlichman et al., 2006; Yoshimura et al., 2006]
HKI-272 (irreversible inhibitor)	EGFR and HER2	Preclinical studies indicated that irreversible inhibitors may be effective in patients with EGFR mutations that confer gefitinib or erlotinib resistance	Wyeth[a]/[Rabindran et al., 2004; Kwak et al., 2005]
		Clinical—breast cancer (I–II) and NSCLC (II)	
AEE788	EGFR, HER2, and VEGFR2	Glioblastoma (I/II)	Novartis, NCI[a]/[Traxler et al., 2004;Goudar et al., 2005]
Inhibition of BCR-ABL			
Imatinib Mesylate (IM, Gleevec, Glivec, STI571)	BCR-ABL (ABL kinases), PDGFR, and KIT	*FDA APPROVED for CML* and BCR-ABL-positive ALL	Novartis[a]/[Cohen et al., 2005; Deininger, 2007]
		Clinical—many cancers, including GIST (II–III)	
Dasatinib (Sprycel, BMS354825)	BCR-ABL, IM-resistant BCR-ABL mutants (except T315I), PDGFR, KIT, and SRC kinases	*FDA APPROVED* for CML and BCR-ABL-positive ALL in adult patients with resistance or intolerance to prior therapy, including IM	Bristol-Myers Squibb[a]/[Olivieri and Manzione, 2007]
		Clinical—solid tumors (I)	
Nilotinib (Tasigna, AMN107)	BCR-ABL, IM-resistant BCR-ABL mutants (except T315I), PDGFR, and KIT	*FDA APPROVED* for CML in adult patients resistant/ intolerant to prior therapy, including IM	Novartis[a]/[Kujawski and Talpaz, 2007]
		Clinical—GIST patients with resistance to both IM and sunitinib (III)	
SKI-606	BCR-ABL and SRC kinases	CML and BCR-ABL-positive ALL (I/II) and breast cancer (II)	Wyeth[a]/[Konig et al., 2008]
MK-0457 (aurora kinase inhibitor; VX-680)	BCR-ABL and IM-resistant BCR-ABL mutants, including BCR-ABL(T3151)	CML and BCR-ABL-positive ALL with T315I mutation (I/II)	Merck[a]/[Giles et al., 2007]

NSCLC, non-small cell lung cancer; TCN-PM, Triciribine Phosphate Monohydrate (TCN-PM); GIST, gastrointestinal stromal tumors; NCI, National Cancer Institute; MCL, mantle cell lymphoma; mCRC, metastatic colorectal cancer; FTIs, farnesyl transferase inhibitors; ASO, anti-sense oligonucleotide; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; RTKs, receptor tyrosine kinases; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor type 2; CML, chronic myelogenous leukemia; ALL, acute lymphocytic leukemia.

[a]www.clinicaltrials.gov.