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Signaling Pathways as Therapeutic Target in Tumor Treatment

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ABSTRACT

The treatment of tumor metastasis is an extraordinary challenge for clinicians and patients. Although the focus of the therapeutic strategy is mainly limited to that problem, a number of unsuspected adverse events are associated with the current therapies. Accordingly, the efficiency and limitation of tumor therapeutics are governed by a set of tightly regulated pattern of molecular mechanisms, whose activation or inhibition is mediated by either unique or interacting intracellular signal pathways. These signaling pathways are responsible for the modulation of various cellular functions, including cell death and survival. The imbalance between pro- and anti-survival pathways determines whether cells die or survive. Thus, the development of an efficient therapeutic approach, based on targeting the aberrant signaling pathways, is thought to be a relevant strategy for cancer treatment. In the present review, we will focus on the functional role of intracellular signaling pathways as a target for tumor therapy.

Keywords: *Signaling Pathways, Apoptosis, Autophagy, Pro-survival, Tumor, Therapeutic Target, Cancer*

Introduction

The successful eradication of any tumor requires a therapeutic approach that has the potential to kill differentiated cancer cells and to eradicate cancer initiating cells [1, 2]. Although the available therapies, which include chemotherapy, radiation therapy and immunotherapy, can successfully kill rapidly growing and differentiated tumor cells, their ability to eradicate cancer-initiating cells is obtuse [3]. Therapeutic approaches that only target differentiated cancer cells and fail to eradicate cancer initiating cells results in the development of more aggressive tumor cell populations and ultimately in a relapse [4-6]. Therefore, an efficient medicationmust have the potential to kill both differentiated cancer cell and cancer-initiating cells without impairing normal cells. Unlike normal cells, cancer cells clearly have a complex pathogenesis with the ability to reconstruct crosstalk and redundancy among the signaling pathways [7, 8]. In this context, therapeutic strategies based on targeting a single molecule or single pathway may have a limited benefit for patients. Therefore, a combination of therapies may be the best therapeutic strategy to inhibit pathways controlling tumor growth and survival. Accumulating evidence indicates that therapeutic modalites-induced phenotypic dysfunction elicit both pro- and anti-apoptotic responses that, in turn, affect the capacity of cancer cells to engage in catabolic processes such as senescence, apoptosis, postmitotic death, and autophagy [9-12].

Based on preclinical events and compared to other targeted therapeutics, therapeutic approaches targeting the aberrant signal pathways provide specific advantages to cancer patients, since these signal pathways are often upregulated in cancer cells as compared to normal cells [13]. For example, in cancer cells, the pro-apoptotic factors are inactivated and their downregulation is usually combined with upregulation of anti-apoptotic proteins, a mechanism that enables cancer cells to be

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more resistant to standard treatment [14,15]. Thus, targeting the pathways of proto-oncogenes, whose activation is tumor-specific, such as fms, a receptor tyrosine kinase, that is characteristic to leukemia [16,17], is considered a relevant target for tumor treatment. Therapeutic approaches targeting such pathways will be harmful for cancer cell rather than toxic for normal cells. Cellular factors that can selectively inhibit apoptotic pathways besides their ability to enhance the function of the pro-survival pathways, may present a promising therapeutic strartegy *via* increasing tumor sensitization to anti-cancer agents. Also, targeting factors that are implicated in the regulation of the crosstalk between pro-and anti-apoptotic pathways or even those involved in the regulation of the crosstalk between apoptotic and autophagic pathways is a relevant therapeutic strategy. Since these pathways are functionally working in tumor cells and thought to be viable target for tumor treatment.

Therapeutic Strategy Based on the Inhibition of Survival Pathways

The identification and elucidation of signaling pathways responsible for tumor growth and progression such as, RAS/RAF/MEK/ERK or PI3K/AKT/mTOR, has thrown up promising molecular targets for tumor treatment. Sseveral reports have demonstrated that the PI3K/AKT/mTOR and RAS/RAF/MEK/ERK pathways are often activated in cancer, and their components are either frequently mutated or altered [18,19]. A wide range of small-molecule inhibitors can be applied, in clinical utilization, based on their ability to block the above mentioned components of pathways and thereby inhibit their function. These observations present a significant molecular targets for the development of an expanding range of small-molecule inhibitors that can functionally block the various components of tumor associated pathways.

Anti-cancer Agents with Potential to Target MAPK/ERK Pathway

Mitogen Activated Protein Kinase (MAPK) is a signal transduction pathway, whose activation can be mediated by growth factor receptors such as, hepatocyte growth (HGF)/scatter factor (SF), insulin growth factor (IGF), and epidermal growth factor (EGF). These pathways are mainly involved in the regulation of cellular events including, cell growth and proliferation [20,21]. Accumulated evidence over the last few decades has demonstrated that MAPKs play an important role in tumor development and progression [22,23]. For example, Ras- extracellular signalling kinase (ERK) pathway is generally targeted by growth factors or activating mutations [24,25]. In different tumor types, RAS mutations is a marker for an early oncogenic events [26-28]. Thus, the dysregulation of Ras- ERK pathway can alter the expression of multiple genes regulating different cellular processes such as, cell cycle regulation, differentiation, proliferation, survival, migration, and angiogenesis [29-31]. Accordingly, the activation of ERK1/2 pathway in tumor cells in response to active mutations in the kinase domain of Ras-Raf signaling, can enhance cell proliferation, a tumor protective mechanism to escape from apoptotic cell death [32-34]. Thus, inhibition of Ras activation may increase the chemotherapeutic sensitivty of tumor cells bearing endogenous Ras mutation [35-37]. More important, the activation of ERK can increase the resistance to anti-cancer agents in different tumor types [38-40]. The activation of the MAPK signalling pathway is generally associated with the alteration of the expression of several proteins involved mainly in the regulation of different cellular functions including cell adhesion and motality, differentiation as well as proliferation.

The initial attempts to block Ras activity met with more failures rather than successes, particularly, in G1 phase malignancies. However, the inhibition of farnesylation was successful in decreasing Ras activity [41,42]. Farnesylation is a post-translational modification resulting in the addition of a 15 carbon group, a mechanism that is critical to Ras function [41,42]. Several Ras inhibitors such as, farnesyl transfer inhibitor (FTI) and Lonafarnib showed a therapeutic effects on tumor growth [43]. As reported in several studies the inhibition of farnesylation by FTI is suggested to be sufficient to block Ras-dependent cell signalling and to initiate tumor cell transformation [44]. Based on the central role of RAS/RAF/MEK/ERK pathway in tumor development and progression as reported[43], targeting RAS/RAF/MEK/ERK pathway by farnesyl transferase inhibitors is considered a therapeutic strategy for tumor treatment[43]. The combination of different FTIs with standard chemotherapy such as, Sorafenib (Bay 43-9006), small-molecule inhibitor of A-Raf, VEGF receptor (VEGFR)-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-β, Flt3, and c-KIT, has been proven in a large number of clinical studies for their therapeutic reliability [45,46].

Activation of MAP kinases ERK1/ERK2 by anti-cancer agents depends on the cell type, the expression level of growth factor receptors [47-49]. The inactivation of MEK1/2 results in the inhibition of ERK1/2 that, in turn, leades to the enhancement of the killing efficiency of anti-cancer agents [50,51]. Accumulated evidence revealed that the inhibition of ERK1/2 prior to the treatment sensitizes tumor cells to chemotherapeutic agents [38,52]. Clinical approaches like the small-molecule inhibitor of MEK1/2 (CI-1040) confirmed its potenial in suppressing MAPK phosphorylation in tumor cells [53,54]. Accordingly, several MEK inhibitors that have been investigated for their clinical relevance, these include Trametinib, Selumetinib, GDC-0973, BAY 86-9766, Pimasertib, PD325901 and CI-1040[55,56]. Also, their common toxicity including, rash and/or dermatitis acneiform, diarrhea, peripheral edema, and fatigue has been addressed [55,56]. To that end, the inhibition of cell growth by targeting MAP kinase signaling pathways is considered a promising approach for cancer treatment. Figure 1 demonstrates some of the inhibitory compounds, which have been proven to block

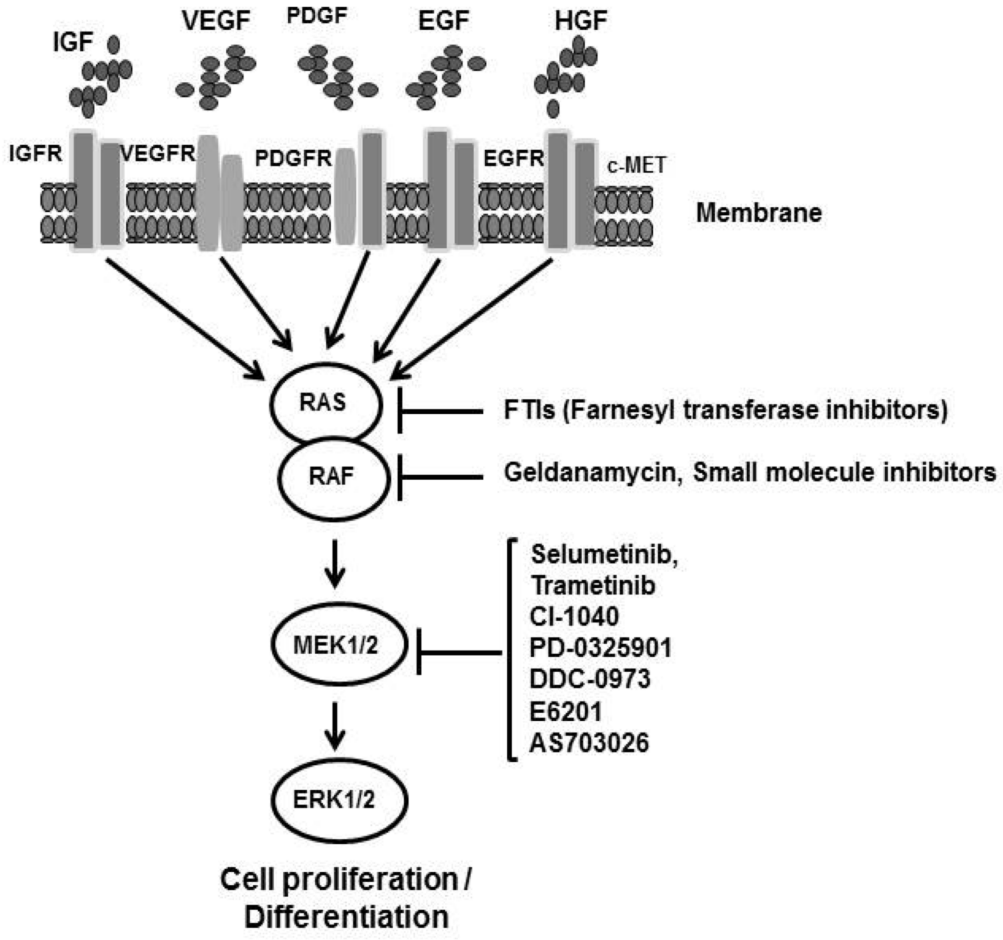

Figure 1: Targeted therapies currently available or under clinical investigation for tumor treatment, and the molecular targets on which, they are thought to be functional. EGF, epidermal growth factor; EGFR, EGF receptor; PDGFR, platelet-derived growth factor, PDGFR;, PDGF receptor; HGF, hepatocyte growth factor; hepatocyte growth factor receptor, c-Met, IGF, insulin-like growth factor; IGF receptor, IGFR; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; RAS, prototypical member of the RAS superfamily of proteins, activation of RAS signaling causes cell growth, differentiation and survival; RAF, a MAP kinase kinase kinase(MAP3K) that functions in the MAPK/ extracellular-signal regulated kinase (ERK) signal transduction pathway; a serine/threonine-specific kinase.

specific MAP kinase signaling proteins and may be relevant in a clinical application.

Anti-cancer Agents Targeting PI3K/ Akt Pathway

The activation of the PI3K pathway can be mediated *via* different extracelluar signals by the stimulation of membrane receptors such as, insulin like growth factors (IGF), estrogene receptor β (erbβ) as well as integrin receptors [57-62]. Based on its function in the modulation of cell survival, PI3K/Akt signalling cascade is target for different therapeutic agents [63-65]. The involvement of PI3K/Akt signalling pathway in the regulation of angiogenesis, cell cycle control, and G1 phase associated protein such as, cycline D and cycline- dependent kinases, such as CDK4 has been reported in several studies [66-68]. Inactivation of PI3K or Akt by small-molecule inhibitor will increase the sensitivty of tumor cells to chemotherapeutic agents. Also, the mechanistic target of Rapmycin (mTOR), the member of Akt pathway is considered a promising target for tumor therapy. Thus, the inhibition of mTOR by Rapamycin and RAD001 may enhance the efficiency of chemotherapeutic agents-induced death of tumor cells [69,70]. The inhibition of mTOR is associated with cell cycle arrest that can be mediated by the upregulation of cyclin-dependent kinase inhibitors such as, p27 leading to the downregulation of Cyclin D1 [71-73]. Thus, targeting PI3K pathway by a number of small-molecular inhibitors in cancer patients, whose tumor harbors the activated PI3K, is considered a relevant therapeutic for tumor treatment. Also, targeting the subunits of PI3K pathway such as, p110 using either specific chemical inhibitors like IC486068, LY294002, Wortmanin or by the expression of the mutant p85 can lead to the enhancement of chemotherapy-induced apoptosis of tumor

cells [74,75]. The inhibition of Akt function by either the overexpression of dominant negative Akt, glycogen synthase kinase-3 (GSK3) or by the inhibitor, ALX-349 has been reported to overcome tumor resistance to chemotherapy [76-80]. Also, clinical studies dealing with phase III trails demonstrated that the inhibition of mTOR can improve the tumor-growth delay [82-85]. Thus, targeting PI3K/Akt pathway may be a relevant strategy for tumor treatment. An outline demonstrating the components of PI3K/Akt signalling pathway in response to the activation of receptor tyrosine kinases by the corresponding ligands/agonists as well as drugs targeting mTORC1 and mTORC2 is shown (Figure 2).

Anti-cancer Agents Targeting JAK/STAT Signaling Pathway

The resistance of tumor cells to available therapetuc modalities results mainly from abnormal alterations in oncogenic signaling pathways through both genetic and epigenetic-mediated mechanisms [86,87]. These signaling pathways are implicated in the regulation of a number of nuclear transcription factors that function as final effectors, and thereby initiate a gene expression pattern leading to the promotion and progression of cancer [88-90]. The most

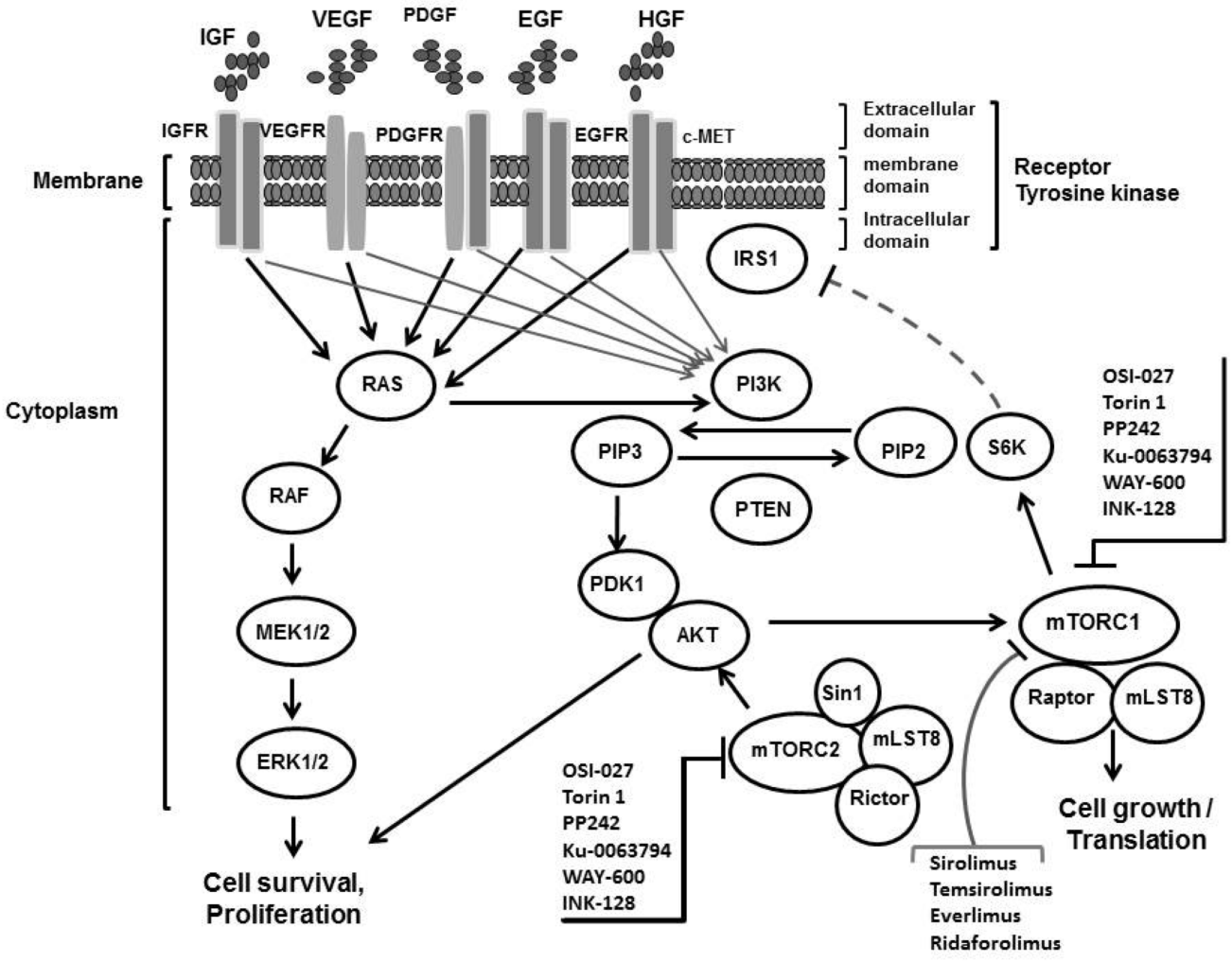

Figure 2: Targeting mTOR signaling pathway. The mTOR proteins exist in two protein complexes, namely mTOR complex1(mTORC) [mTOR, PRAS40, Deptor, and Raptor], and mTOR complex2 (mTORC2) [mTOR, mSIN1, Protor, LST8, Deptor, and Rictor]. Feedback inhibition resulting from sustained suppression of mTORC1 signaling triggers the activation of the mTORC2/AKT and ERK1/2 pathways through IRS/PI3K. Drugs targeting mTORC1, and mTORC1/mTORC2 are shown. AKT, protein kinase B; PDK1 3-phosphoinositide-dependent kinase1; PI3K, phosphoinositide 3-kinase; PIP2, phosphoinositol-2-phosphate; PIP3, phosphoinositol-3-phosphate; PTEN, phosphatase and tensin homolog; Deptor, domain containing mTOR interacting protein; Raptor, regulatory-associated protein of mTOR; Rictor, Rapamycin-insensive companion of mTOR.

discussed pathway among these is the nuclear transcriptional signal cascade JAK/STAT pathway. The main biological function of this pathway is the enhancement of cell survival through mechanism mediated by the increased expression of anti-apoptotic proteins such as, Bcl-2 and Bcl-X_L, as well as the activation of the pro-inflammatory pathways such as, NF-κB and IL-6-GP^{130}-JAK pathway that is mainly associated with tumor progression and invasion [57,91,92]. The inhibition of STAT signaling, particularly STAT3, can lead to tumor-growth delay and the increase of the sensitivity of different tumor types to chemotherapy as shown in glioblastoma [93,94] and squamous cell carcinoma [95,96]. Also, a number of chemical agents have been reported for their reliability to inhibit JAK/STAT pathway, such as AG490 [97]. These chemical agents were found to improve tumor response to the available therapeutic modalities without any abberant toxicity [98-101]. Also, the

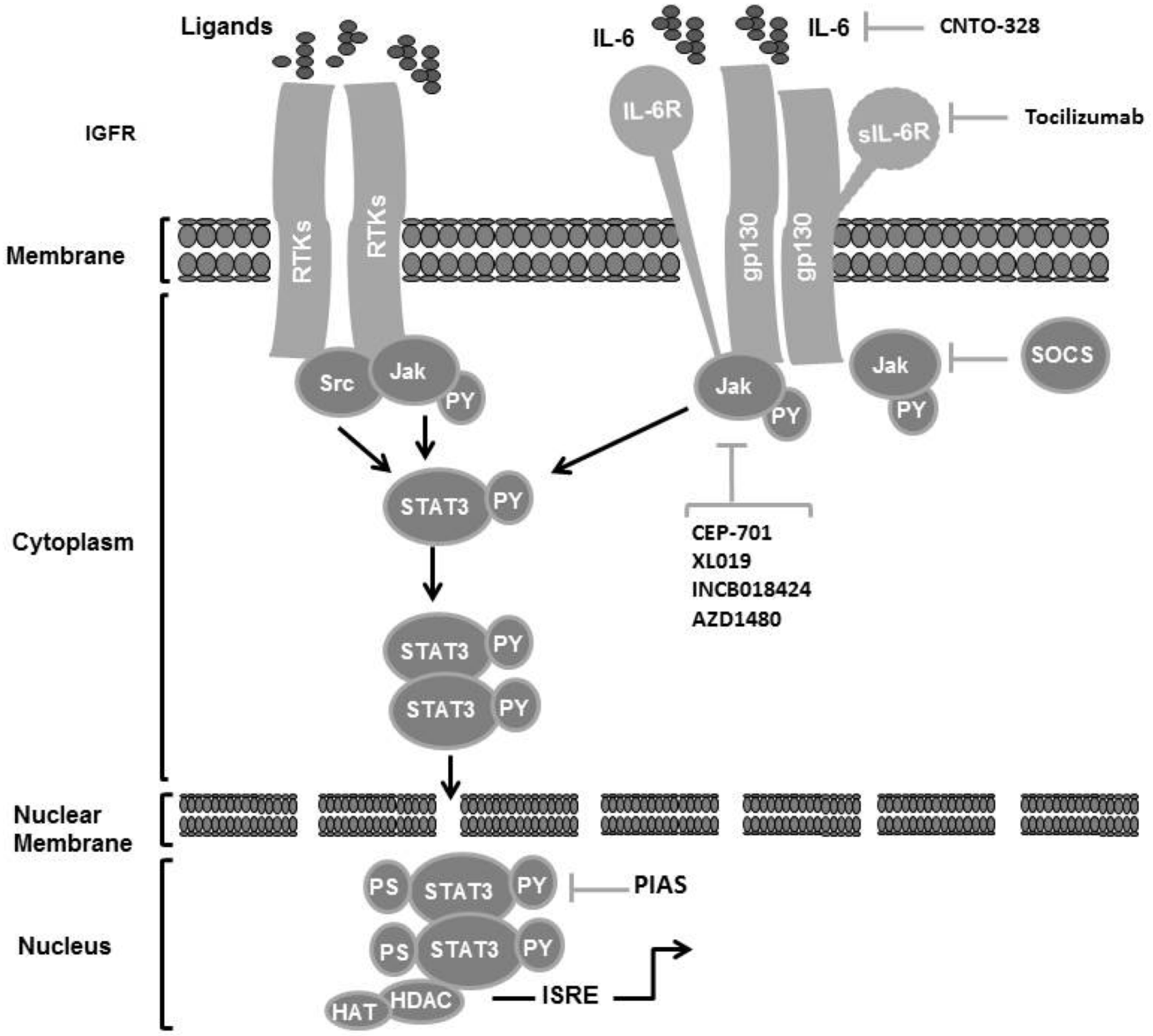

Figure 3: Signal transducer and activator of transduction 3 (STAT3) signaling. Stat3 is tyrosine phosphorylated by janus kinase (JAK) kinases in response to cytokine/growth factor activation of cell surface receptors that are known as receptor tyrosine kinases (RTKs), glycoprotein 130 (gp130) with either interleukin-6 receptor (IL-6R) or soluble IL-6R (sIL-6R). Up on tyrosine phosphorylation (PY), Stat3 dimerizes and localizes to the nucleus, where it binds to Stat3 responsive elements. Stat3 is also target for serine phosphorylation (PS). Soluble factors that activate Stat3 include, the IL-6 family of cytokines. Agents to inhibit the Stat3 canonical pathway include targeting JAK (CEP-701, XL019, INCB018424, AZD1480) and the IL-6/sIL-6R interaction (tocilizumab, CNTO-328). HAT, histone acetyltransferase; HDAC, histone deacetylase; ISRE, interferon stimulated response element.

down regulation of STAT1 and STAT2 by their specific siRNA can increase the tumor sensitivty to anti-cancer agents in different tumor types [102,103]. More importantly, the suppression of JAK/STAT signaling pathway by small-molecule inhbitors has been shown to be sufficient to trigger cell growth arrest as well as to induce apoptosis in different tumor types [104-106], an evidence for the clinical relevance of JAK/STAT signaling pathway as a target for tumor therapy. JAK/STAT signalling pathway and its small-molecules inhibitors is outlined in Figure 3.

Therapeutic Strategy Based on the promotion of Apoptotic Pathways

Apoptosis is a form of cell death, also referred to as programmed cell death, in which a 'suicide' machinery is activated within the cell leading to the fragmentation of DNA, shrinkage of the cytoplasm, membrane changes, and finally, cell death without any lysis or damage to neighboring cells [107]. The induction of apoptosis can be mediated by activation of pro-apoptotic signaling or the inhibition of the anti-apoptotic signaling. The activation of the pro-apoptotic signaling based on the stimulation of death receptors by its corresponding ligands, irrespective of p53 status of the cell, leading to the activation of effector caspases, and finally, to mitochondria-independent apoptosis, *via* mechanism mediated by the extrinsic pathway [108,109]. Whereas, the other strategy is to trigger apoptotic cell death through a non-receptor mediated pathway, namely the intrinsic pathway [110114]. The intrinsic pathway mediates the intracellular signal transduction processes that act directly on targets, within the cell, or on those associated with the mitochondrial dysregulation [111-114]. The activation of the intrinsic pathway can act in two opposing patterns. One of these patterns is mediated through the suppression of anti-apoptotic mechanisms [114], whereas the other one is mediated through the activation of pro-apoptotic mechanisms [111-114]. Thus, targeting both extrinsic and intrinsic pathways may be an attractive target for cancer treatment.

Therapeutic Modalities Targeting Extrinsic Pathway

The extrinsic apoptosis pathway transmits signals from extracellular death ligands through the appropriate death receptors to trigger the apoptotic machinery of the cell [106, 108]. The activation of the extrinsic pathway is initiated by transmembrane receptor(s) through the ligation to the corresponding ligand(s) or agonist(s) of interest [106,108]. These receptors include FasL/FasR, TNF-α/TNFR1, Apo3L/DR3, Apo2L/DR4, and Apo2L/DR5 [107]. However, one of the well-characterized receptors includes the member of the tumor necrosis factor (TNF) receptor gene superfamily [115]. These family members share similar cysteine-rich extracellular domains in addition to a cytoplasmic death domain [116]. The main function of the death domain is to transmit the external death signal from the surface of the cell to the intracellular signaling pathways. The most successful therapeutic strategy based on targeting of death receptors, is the combination of the death receptor agonist TRAIL with conventional and investigational anti-cancer agents [117,118]. Correspondingly, a significant synergy for the combination of TRAIL with several cytotoxic agents has been reported in several studies [119,120]. These include the combination of TRAIL with agents described for their cytotoxic effect such as, carboplatin, paclitaxel, doxorubicin, 5-fluorouracil, irinotecan, camptothecin [121-123]. Also, several agents such as histone deacetylase (HDAC) inhibitors, rituximab, triterpenoids, and sorafenib showed a synergistic effect when combined with TRAIL [124,125]. Furthermore, the sensitization of many human and animal cell lines by the proteasome inhibitor was found to enhance TRAIL-induced cell death [126]. More importantly, the resistance of nontransformed cells to the combination of bortezomib and TRAIL, when compared with tumor cells, suggests a therapeutic benefit without any aberrant toxicity during the course of the treatment [127]. Although the potency of bortezomib in promotion of TRAIL-induced apoptosis of tumor cells, the mechanistic role of bortezomib in the enhancement of TRAIL-mediated effects is not clear. Generally, the inhibition of proteasome has multiple biological effects on the cells, since inhibition of the proteasome results mainly in cell cycle arrest and inactivation of survival pathways such as, NF-κB [128,129]. The inhibition of proteasome inhibitor can results in the induction of the expression of death receptors DR4 and DR5 in different tumor types [130], an evidence for the contribution of bortezomib in the promotion of the extrinsic signaling pathway of apoptosis. Thus, the development of agents with the ability to promote or restore apoptosis *via* a mechanism mediated by the activation of the extrinsic pathway has emerged as important therapeutic modalities for cancer treatment [131,132]. These therapeutic agents include the recombinant human (rh) Apo2L/TRAIL, dulanermin as well as agonist antibodies directed against death receptors (DR) 4 and 5, such as conatumumab, Lexatumumab, Mapatumumab [133-135]. The death receptor agonists are considered an attractive therapeutic target for tumor treatment [136,137]. In spite of the expression of death receptors on a wide variety of normal and tumor cells, most of death receptor agonists tend to induce apoptosis of tumor cells rather than of normal cells [138]. The ability of death receptor agonists to induce apoptosis independent from the status of p53 is an advantage for death receptor agonists as therapeutic target, since p53 is frequently either inactivated or mutated in most tumor types [139, 140]. Accordingly, the crosstalk between both extrinsic and intrinsic apoptotic pathways and death receptor agonists can enhance the therapeutic efficiency when combined with conventional chemotherapeutics that target cell growth or survival pathways [141,142]. Also, the advantage of death receptor agonists has been confirmed in a large number

of preclinical studies yielding promising results [143]. Therefore, the combination of death receptor agonists and clinically-proved anti-cancer agents may be an attractive therapeutic strategy for tumor treatment. Figure 4 demonstrates the induction of apoptosis by the ligation of death receptors.

Therapeutic Modalities Targeting Intrinsic Pathway

The intrinsic pathway is a non-receptor mediated pathway and functions only *via* mitochondria associated mechanisms [144]. This pathway mediates the intracellular signals that act directly on targets, within the cell, or on those associated with the mitochondrial dysregulation [111-114]. The cell intrinsic stress sensors control the mitochondrial outer membrane permeabilization (MOMP) by a mechanism mediated through the modification of the interaction proteins of Bcl-2 family [111-114, 145]. Based on the number and the structure of their Bcl-2-homology domains (designated BH1-4), the Bcl-2 family members can be organized into three subgroups [146]. The activation of BH3-Only pro-apoptotic proteins can be mediated in response to a variable cell stress conditions. Once activated, the BH3-Only domains promote the oligomerization of the pro-apoptotic proteins Bax and Bak as well as Noxa in the mitochondrial outer membrane leading to the loss of mitochondrial membrane potential ($\Delta\Psi m$) and subsequently cell death [11-114,145]. In contrast, the other multi-BH domain proteins, such as Bcl-2, Bcl-X_L and Mcl-1 inhibit MOMP by a mechanism mediated by the neutralization of pro-apoptotic family members [147]. Thus, targeting the activation of BH3-only proteins or the inhibition of multi-BH- proteins by tumor

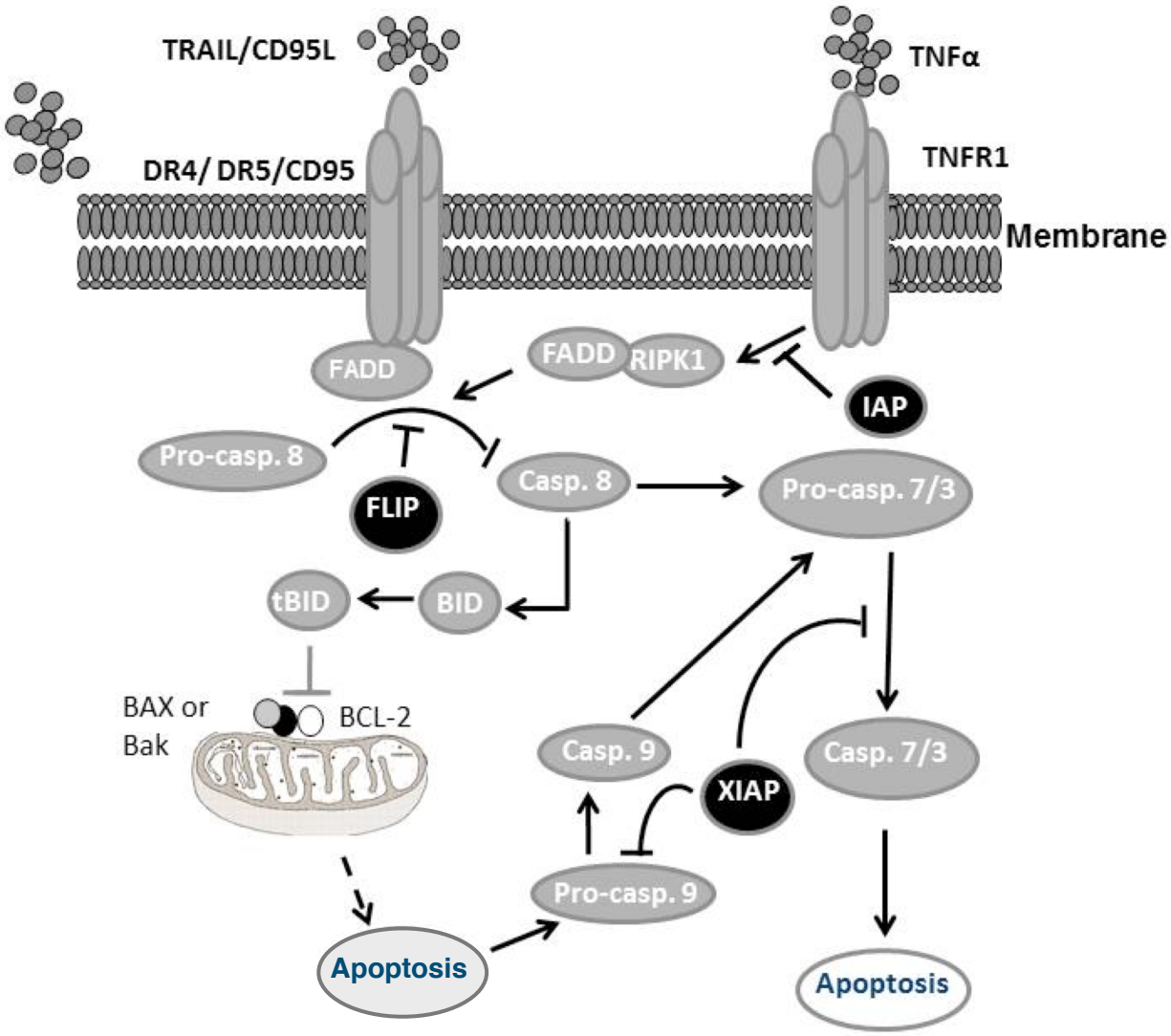

Figure 4: Apoptosis can be initiated by the death-receptor (extrinsic) pathway that acts through caspase-8 or mitochondrial (intrinsic) pathway that acts through caspase-9. Also, both extrinsic and intrinsic pathways converge to activate the effector caspase that acts mainly on the death substrates. Cell death is regulated also by the Bcl-2 and inhibitors of (IAP) protein families. Bcl2 proteins mediate apoptosis by the regulation of the mitochondria permeability transation by inhibiting (Bcl-2 and Bcl-X_L) or promoting (Bax and Bid), cytochrome c release, whereas, XIAP proteins act downstream to prevent processing of initiator caspase-9 from the apoptosome, a supramolecular caspase-activating complex that contains cytochrome c and apoptosis activating factor1.

therapeutic approaches may be a relevant strategy for tumor treatment.

Our group and others described the possible molecular mechanisms of bortezomib-induced effects in tumor cells [112]. The combination of bortezomib with the inhibitors for anti-apoptotic proteins such as, Bcl-2 or Mcl-1 or inhibitors for autophagy can improve bortezomib-induced cell death in melanoma cells [112,148]. One of the signaling pathways that thought to be a potenial target for bortezomib is the p53 signaling pathway [112]. p53 is a tumor suppressor protein that is known as a DNA damage-inducible molecule [149,150]. P53 signaling pathway is involved in the suppression of cancer progression *via* a mechanism mediated by the induction of cell-cycle arrest, apoptosis or senescence in response to various cellular stimuli [151]. The activity of p53 signaling pathway is regulated by the murine double minute 2 (MDM2) [152]. The loss of the wild-type p53 (^{wt}p53) as well as the mutation of p53 in most human tumors results in the alteration of p53 function as a positive tumor suppressor factor into a negative regulator leading to tumor progression rather than tumor suppression [153]. The ability to restore the function of p53 in tumor cells can be mediated by various strategies including the ectopic expression of functional ^{wt}p53 or the reactivation of mutant p53 in tumor cells. These suggested strategies based on the fact that p53-deficient cells undergo apoptosis or senescence in response to ^{wt}p53 gene transfer [154,155]. Also, the rescue of the mutant p53 function by Small molecules is thought to be a relevant strategy for tumor treatment. Since the reactivation of mutant p53 by the small molecules like as PRIMA-1 as well as its optimized form PRIMA-1Met were found to induce massive apoptosis in tumor cells with certain p53 mutation or those harboring various versions of mutations in the DNA-binding domain [156,157]. Thus, targeting mutant p53 by the reactivation of the mutant p53 in tumor cells may be a promising strategy for tumor treatment. Also, a tumor therapeutic strategy based on targeting p53:MDM2 interaction using several anticancer agents such as, sulphonamide compounds [158] and nutlins [159,160]. These therapeutic modalities have been early clinical trials for treatment of patients with solid tumors and haematological malignancies.

Therapeutic Strategy Based on the Crosstalk Between Pro- And Anti-Apoptotic Pathways

Despite the induction of many biological effects on both cell and tissue levels, in response to various therapeutic agents, which can be divided into pro- and anti-apoptotic effects, the signal transduction pathways in tumor cells contain multi-proteins and multi-linked pathways [161,162]. Generally, the activation of many signaling pathways demonstrates multi-interaction and cross function, an evidence for the crosstalk between pro-and anti-apoptotic pathways. The crosstalk between these controversial pathways seems to be essential for cell balance under normal physiological conditions. An example for this is the family of the proteins p53 and Bcl-2, which are involved in the regulation of apoptotic signaling pathways. These proteins can also mediate pro-survival function under certain circumstances [163-165]. Accordingly, a therapeutic strategy based on the inhibition or suppression of single pathway has shown limited success, since the inhibition of Bcl-2 by its specific siRNA in different tumor types is unable to exercise any cytotoxic activity [166,167]. A therapeutic strategy by the direct stimulation of membrane-bound anti-apoptotic or pro-apoptotic receptors, will be essential for amplifying the effects of target agents. Thus, clinical data revealed that the inhibition of endothelial growth factor receptor (EGFR) signal transduction pathway can result in an anti-tumor activity leading to tumor growth delay or cell death [168,169]. The presence of EGFR does not signify that EGFR signaling is a common pathway for different cancer types, since some tumor patients with EGFR-negative respond to EGFR inhibitors such as, Cetuximab[170,171]. The explanation for the resistance of EGFR-positive tumors may due to the presence of a significant cross-talk between PI3K/AKT and other pathways, such as those mediating opposite cellular functions like apoptosis, cell growth, and cell survival. Thus, targeting these pathways in order to interrupt this crosstalk may be a possible strategy to overcome tumor resistance to chemotherapy. Figure 5 demonstrates therapeutic modalities leading to tumor cell death via mechanism mediated by the apoptosis intrinsic pathway.

Therapeutic Strategy Based on the Modulation of Autophagic Pathways

Autophagic cell death, also known as type II cell death, is characterized by the formation of double membrane autophagic vacuoles in the cytoplasm [107]. Autophagy occurs in response to various cellular stressors differs from type I programmed cell death/apoptosis. Because the intrinsic overlapping of autophagic and cancer signaling pathways and the complexity of cancer disease, the fate of cancer cells cannot be determined by a single signaling pathway. Although the molecular mechanisms of autophagy and its functional impact in cancer, the role of autophagy varies depends on tumor type and the stage of tumor progression [172-174]. In early stage of tumor development, autophagy can act as a tumor suppressor [175-177], where as in advanced stages of tumor, the development of autophagy is more implicated in the regulation of tumor progression rather than tumor suppression [178,179]. Thus, the tumor type and stage should be taken in account by the treatment or by the development of the therapeutic modalities.

Autophagy can be induced by different forms of cancer

therapy, including conventional and novel targeted cancer therapeutics, and ionizing radiation as evidenced in several types of solid and hematological malignancies [111,180-183]. Although the involvement of the autophagic mechanisms in the modulation of the cytotoxic effects of anticancer agents, autophagy can also mediate pro-survival mechanisms in response to the toxicity withstand of the therapeutic agents [184]. In some cases, the inhibition of autophagy enhances tumor resistance to the chemotherapeutic agents [186,187], whereas in other cases the inhibition of autophagy promotes anti-cancer agents-induced apoptosis [111]. Thus, during the tumor treatment autophagy, is a only bystander so that its induction or inhibition does not influence the therapeutic status of tumor cells [187]. However, the molecular mechanisms, which are responsible for the regulation of the autophagic actions still remain to be characterized in detail. The genetic characteristics of the cancer cells seem to play a critical role in the regulation of the functional outcome of

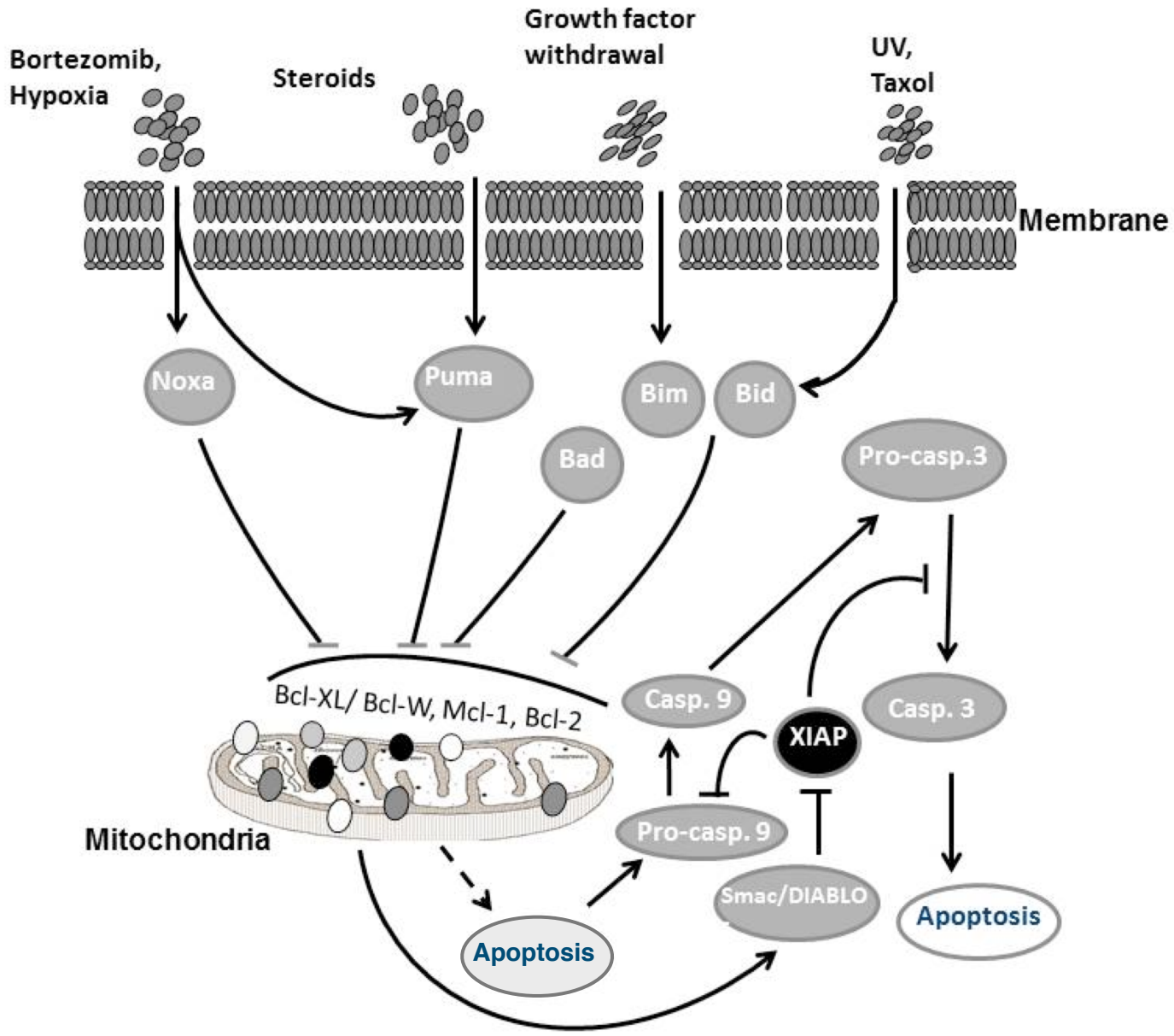

Figure 5: Targeting intrinsic pathway in cancer therapy. The intrinsic pathway can be initiated by various signals by extracellular stimuli including, anti-cancer agents (e.g. bortezomib, taxol), hypoxia, steroids, growth factor withdrawal and UV. As a consequence, the stimulation of the tumor cells by various therapeutic modalities, BH-3-only proteins (Bim, Bid, Bad, Noxa, Puma) commit with anti-apoptotic Bcl-2 family (Bcl-2, BcX_L, Mcl-1, Bcl-W) to release the inhibition of Bax and Bak to activate them. Next, Bax and Bak oligomerize and become active leading to the loss of mitochondrial membrane potential and subsequently to the release of cytochrome c, Smac/DIABLO into the cytoplasm, wherein they combine with an adaptor molecule, apoptosis protease-activating factor 1, and an inactive initiator caspase, caspase-9, within a multiprotein complex, namely apoptosome. Smac/DIABLO blocks inhibitors of apoptosis proteins to activate caspase-9 that, in turn, activates caspase-3 leading to apoptosis.

autophagy, since autophagy has been shown, to protect different tumor cells from anti-cancer agents (e.g. tunicamycin, thappsiogargin and brefeldin A)-induced cell death [188-190]. Surprisingly, the same anticancer agents were reported to trigger autophagy- mediated cell death of normal colonic epithelial cells as well as those of nontransformed murine embryonic fibroblasts [191-193]. The outcome of autophagy seems to be cell type- dependent, since the pan-Bcl-2 inhibitor was found to induce cytoprotective autophagy in the breast cancer cell MCF-7, whereas in glioma cells induced autophagic cell death [194-197]. Although the molecular mechanism underlying the opposite action of autophagy induced by pan-Bcl-2 inhibitor is not unknown, the differential expression of cellular proteins seems to control the mechanism, whereby the tumor cells decide whether the autophagic pathway mediates cell death or survival [198].

Besides the genetic composition of cancer cells, growth factors stimulation influences the mechanistic consequences of autophagy [199-201]. An evidence for this, is the rescue of tumor suppressor gene aplasia Ras homolog I (ARHI)-induced reduction of autophagy in ovarian cancer cells in response to the stimulation with various cytokines and growth factors [201]. Whereas, in some cases the deprivation of growth factor signals by itself triggers autophagy [203]. Thus, targeting of growth factors by therapeutic modalities may be a relevant strategy for

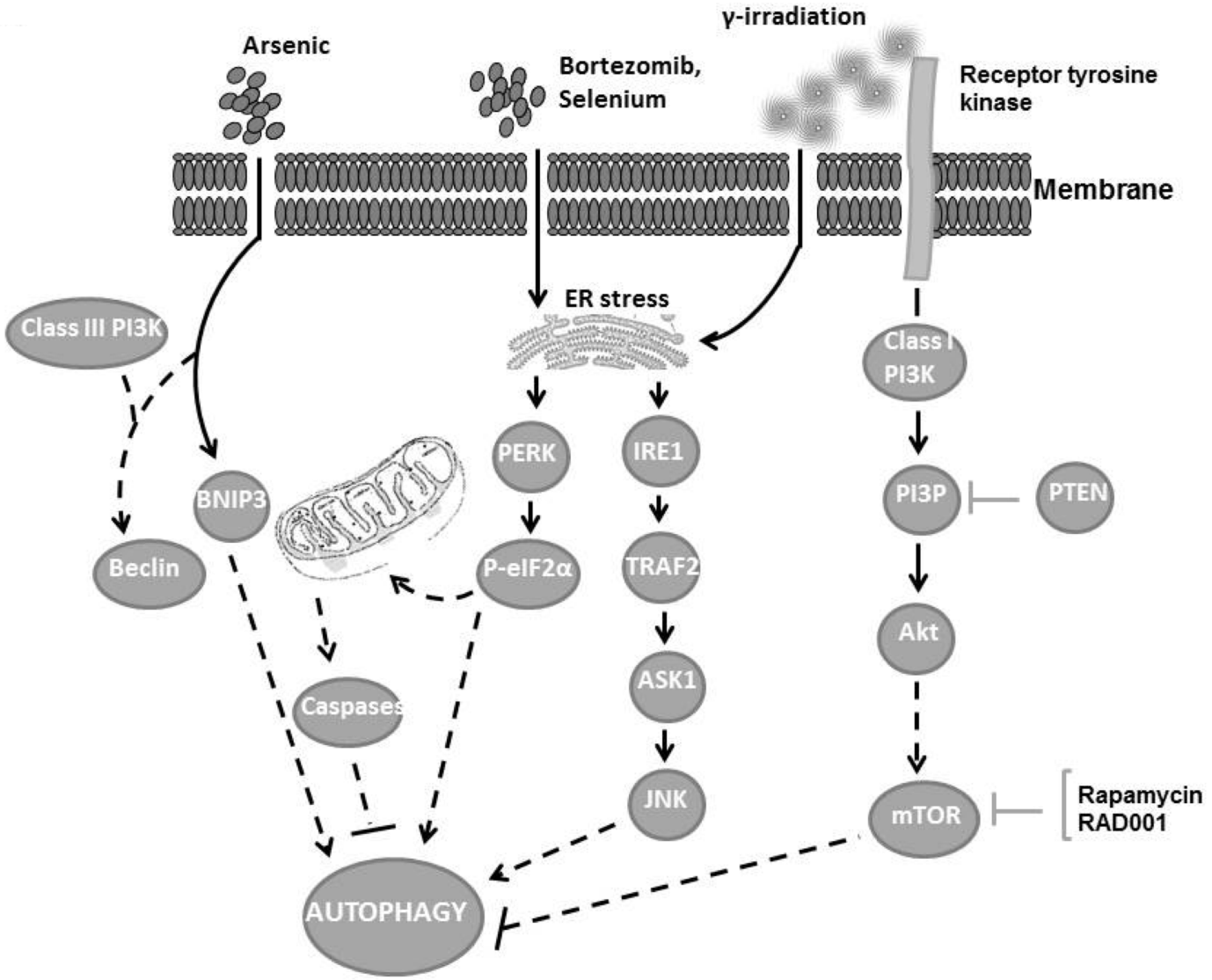

Figure 6: An overview of the autophagy signaling pathways that can be targeted for cancer therapy. Upon ionizing radiation (γ-irradiation), class III PI3K induces autophagy via mechanism mediated by endoplasmic reticulum stress, whereas, class I PI3K inhibits autophagy via mechanism-mediated by Akt/mTOR pathway. Autophagy also can be induced by PERK-eIF2α and IRE1-JNK pathways that can be initiated by ER stress. While the inhibitor of Akt/mTOR pathway has inhibitory effects on autophagy. Inhibition of pro-apoptotic proteins by small-molecules caspase inhibitors is a promising anti-cancer therapeutic strategies using autophagy promotion. Potential therapies are demonstrated in their respective pathway. Dot lines are indicative of indirect mechanism, whereas solid lines display direct pathway.

tumor therapy. The pro-survival or the pro-death nature of autophagy seem to be pathway specific, since the induction of autophagy in cancer cells by the treatment with the chemotherapeutic agents, such as curcumin is regulated by the activation of the pro-survival ERK1/ERK2 pathway and inactivation of the AKT/mTOR pathway [204,205]. Although the abrogation of curcumin-induced autophagy by the activation of Akt and inhibition of ERK pathways, only Akt pathway can attenuates curcumin-induced cytotoxicity [206,207]. Whereas, the inhibition of ERK pathway can induce apoptosis as well as autophagy [208,209]. Accordingly, the cellular outcome of autophagy seems to be determined from the pathway that is involved in the initiation of autophagy. Thus, based on the potential role of the pro-survival pathway ERK in the regulation of cell-fate decision during the processes of autophagy targeting this pathway may be a relevant approach for tumor therapy. The possible mechanisms, whereby anti-cancer agents trigger autophagic pathway in tumor cells are shown (Figure 6).

Therapeutic Strategy Based on the Crosstalk Between Pro-And Anti-Apoptotic Pathways

The decision whether the cell does survive, or die, in response to the environmental changes, depends on the cell type and the authenticity of the stress factor or stimulator [210]. Thus, the response of the cell to the environmental changes can be expressed in different forms and patterns *via* mechanisms mediated by apoptotic or/and autophagic signaling pathways. Depending on cell type and inducers, cell death can be variable in its morphology and characteristics [107]. Some anti-cancer agents can induce both apoptosis and autophagy simultaneously in different cell types [111,211]. Also, depending on the cell type, some proteins like death associated protein kinase (DAPK) can induce both apoptosis and autophagy [212].

Besides the modulation of autophagy by the apoptotic signaling

Table 1: Summary of anticancer agents and their relevant molecular targets

Anticancer agent/inhibitor	Molecular target
BKM120, BAY 80-6946, GDC-0941, PX-866, SAR245409 (XL147)	Class I PI3K
GS-1101	PI3Kδ
BYL719	PI3Kα
BEZ235, PF-04691502, PF-05212384, GDC-0980SAR245409 (XL765), GSK2126458	PI3K/mTORC1/2
Trametinib (GSK1120212), Selumetinib (AZD6244), GDC-0973 (XL518), BAY 86-9766, Pimasertib (AS703026/MSC1936369B), PD32590, CI-1040 (PD184352)	MEK1/2
PRIMA-1, CP31398, OhiKan083	Rescuing the function of mutant p53
MIRA-3, STIMA	Reactivation of p53
CP31398	Stabilization of p53
CEP-701, XL019 Jak2, INCB018424, AZD1480	JAK/Stat pathway
Trastuzumab/Herceptin,	HER2
Cetuximab/Erbitux, Erlotinib/Tarceva, Gefitinib/Iressa	EGFR
Bevacizumab/Avastin	VEGF
Imatinib/Gleevec	BCR-ABL, KIT,PDGFR
PKC412	PKC, VEGFR, PDGFR, KIT
BIBF	VEGFR, PDGFR, FGFR
BAY 43-9006/Sorafenib tosylate	VEGFR, PDGFR, KIT, FLT3, p38α, Raf
SU11248/Sunitinib malate	VEGFR, PDGFR, KIT, FLT3, RET

pathways, the modulation of apoptosis by autophagic signaling is also reported [213, 214]. The inhibition of apoptosis by autophagy is regulated by a mechanism mediated through degradation of pro-apoptotic proteins, such as caspases [215,216]. Accordingly, autophagy and apoptosis play opposite roles in cancer, since the inhibition of autophagy by chloroquine sensitize apoptosis-resistant tumor cells to anti-cancer agents [217,218]. More importantly, the role of autophagy in the modulation of tumor resistance to apoptosis induced by TRAIL has been demonstrated [219,220]. Thus, the induction of autophagy in response to TRAIL is considered a cellular strategy to protect tumor cells from TRAIL-induced cell death. Studies on the mechanism, whereby autophagy prevents TRAIL-mediated cell death revealed that following the cleavage of pro-caspase up on the treatment of tumor cells with TRAIL, active caspase 8 becomes targeted to autophagosomes and subsequently degraded in lysosomes, as a result the downstream apoptotic effectors remains inactive and subsequently increases the resistance of tumor cells to TRAIL treatment. In contrast to the negative effect of autophagy on anti-cancer agents-induced apoptosis, apoptosis can also cleavage autophagy-related proteins [221,222]. The use of autophagy, by tumor cells, as a cytoprotective strategy seems to be a common strategy independent from tumor type or the anti-cancer agent [111,223]. The mechanisms, which are thought to be involved in the regulation of the crosstalk between apoptosis and autophagy during activation death receptor signaling pathways in tumor cells, are outlined in Figure 7.

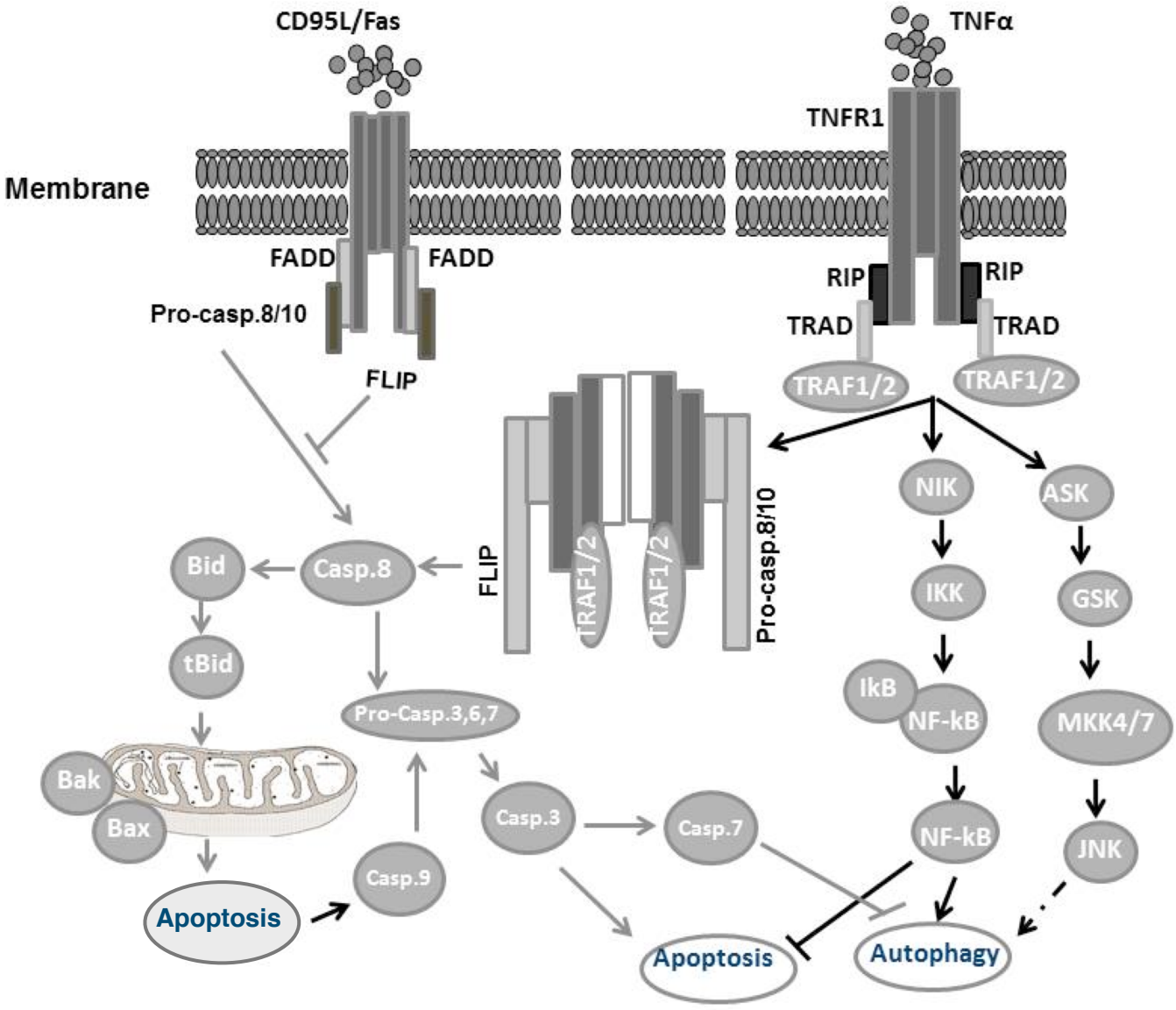

Figure 7: Anticancer agents-induced both apoptosis and autophagy in cancer cells is governed by a crosstalk mediated by both apoptosis and autophagy-associated pathways and their components. This crosstalk between apoptotic and autophagic pathways can be activated by the ligation of death receptors to their corresponding ligands/ agonists (anticancer agents). Thus, the activation of death receptor(s) in tumor cells by the treatment with anti-cancer agents can lead to the activation of autophagy- associated pathways (e.g. NF-κB), that in turn, inhibit apoptosis, or activates apoptosis -associated pathways that subsequently leads to the cleavage of caspase-7 (Casp.7), an inhibitor of autophagy.

Although the elucidation of the mechanisms, whereby autophagy counteracts apoptosis in tumor cells, the risk of the combination of cancer therapies targeting both apoptosis and autophagy is unpredictable. Thus, further analysis of the unique signaling pathways of apoptosis and autophagy may help to develop a relevant therapeutic strategy to avoid the risk of autophagy during the course of tumor treatment. Table 1 summarizes some of tumor therapeutic agents and their relevant molecular targets.

Conclusion

Targeting aberrant signaling pathways is thought to be a relevant strategy for cancer treatment. The anti-tumor efficiency of anti-cancer agents is determined by their ability to trigger cell death within tumor. Thus, the development of multifunctional agents targeting multiple components of signaling pathways in tumor cells, with an advantage over the side effects, is urgently needed for improved outcome of tumor treatment. The induction of other types of cell death such as, autophagic cell death, rather than apoptosis might occur as a result of the diversity and the mechanistic mode of chemotherapy. Although the relation between autophagic cell death and apoptosis needs more explanation, targeting alternative pathways of apoptosis and/or autophagy might overcome tumor resistance to anti-cancer agents. Alteration of apoptotic and/or autophagic signaling pathways might determine susceptibility to cell death after chemotherapy, since anti-cancer agents might trigger pathways involved in the regulation of caspase-dependent apoptosis as well as caspase-independent autophagy at the same time. Targeting therapy related to apoptosis might increase the therapeutic efficacy of anti-cancer agents by modulating signal transduction pathways, other pathways might be influenced by cross-talk between the various cell death pathways. Thus, understanding the molecular mechanism(s) involved in the regulation of autophagic cell death in response to chemotherapy might provide a new strategy to overcome tumor resistance.

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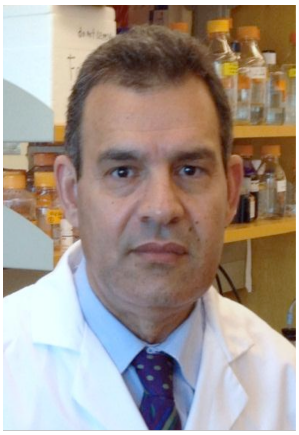

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