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Review

Broad targeting of resistance to apoptosis in cancer

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ABSTRACT

Apoptosis or programmed cell death is natural way of removing aged cells from the body. Most of the anti-cancer therapies trigger apoptosis induction and related cell death networks to eliminate malignant cells. However, in cancer, de-regulated apoptotic signaling, particularly the activation of an anti-apoptotic systems, allows cancer cells to escape this program leading to uncontrolled proliferation resulting in tumor survival, therapeutic resistance and recurrence of cancer. This resistance is a complicated phenomenon

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Autophagy
Apoptosis evasion
Nuclear transporters, natural chemopreventive agents

that emanates from the interactions of various molecules and signaling pathways. In this comprehensive review we discuss the various factors contributing to apoptosis resistance in cancers. The key resistance targets that are discussed include (1) Bcl-2 and Mcl-1 proteins; (2) autophagy processes; (3) necrosis and necroptosis; (4) heat shock protein signaling; (5) the proteasome pathway; (6) epigenetic mechanisms; and (7) aberrant nuclear export signaling. The shortcomings of current therapeutic modalities are highlighted and a broad spectrum strategy using approaches including (a) gossypol; (b) epigallocatechin-3-gallate; (c) UMI-77 (d) triptolide and (e) selinexor that can be used to overcome cell death resistance is presented. This review provides a roadmap for the design of successful anti-cancer strategies that overcome resistance to apoptosis for better therapeutic outcome in patients with cancer.

1. Introduction

According to the GLOBOCAN factsheet (http://globocan.iarc.fr/), there were approximately 14.1 million new cancer cases, 8.2 million cancer deaths and 32.6 million people living with cancer (within 5 years of diagnosis) in the year 2012 worldwide. Among these, 57% (8 million) of new cancer cases, 65% (5.3 million) of the cancer deaths and 48% (15.6 million) of the 5-year prevalent cancer cases occurred in the less/under-developed regions of the world. Cancer treatment requires a careful selection of one or more interventions, such as surgery, radiotherapy, and chemotherapy. However, despite major advances in new targeted drug development and tailored clinical trial designs, therapy resistance is commonly observed in most cancers.

Most cancers harbor significant genetic heterogeneity [1], and patterns of relapse following many therapies are due to evolved resistance to treatment. While efforts have been made to combine targeted therapies, a lack of success, rising drug costs, and significant levels of toxicity have stymied efforts to effectively treat cancer with multi-drug combinations using currently approved therapeutics [2]. Therefore, overcoming therapy resistance mechanisms is one of the most sought-after goals in cancer research.

To accomplish this goal, a non-profit organization entitled Getting to Know Cancer launched an initiative called "The Halifax Project in 2011 with the aim of producing a series of overarching reviews in each of the areas that are widely considered to be cancer hallmarks [3]. This novel approach is premised on many of the insights of genomic sequencing in cancers and it aims to target many disease-specific pathways simultaneously. This is proposed to be done by using low-cost chemistry with little to no toxicity – to address this heterogeneity (in contrast to the limited number of actionable targets that have become the norm in combination chemotherapy).

Our task in the project was to assess the many target choices that exist for resistance to cell death, and to identify up to ten important targets as well as prospective non-toxic approaches that could potentially be combined to produce a low-toxicity therapeutic approach for this area of concern. So our intent here is to discuss the inter-relationship between major mechanisms driving resistance to apoptosis in cancer and then to define a broad-spectrum therapeutic approach aimed at reaching these important targets [3]. In theory, this approach would then be combined with similar approaches being recommended for the other hallmark areas under review in this special issue.

Apoptosis or programmed cell death is evolutionarily conserved process that plays an essential role in organism development and tissue homeostasis [4]. However, in pathological conditions, particularly cancer, cells lose their ability to undergo apoptosis induced death leading to uncontrolled proliferation. Cancer cells are often found to over express many of the proteins that play important roles in resisting the activation of apoptotic cascade. Several mechanisms allow cells to escape programmed cell death and among them is the over expression of the anti-apoptotic molecules. Originally most of the research on apoptosis signaling focused on BH3 pathway proteins leading to acceptance of the Korsmeyers [5] rheostat model. This model predicted a balance between pro-survival and pro-death BH3 members. When the balance shifts toward pro-death signaling, apoptosis occurs, and in instances when pro-survival molecules outnumber pro-death proteins, survival signaling is activated leading to pathological conditions such as cancer and other diseases. With this simplistic model, the drug discovery arena moved at a rapid pace developing small molecule inhibitors (SMI) that interfere with the anti-apoptotic pathways proteins such a B-Cell Lymphoma 2 (Bcl-2), B-Cell Lymphoma extra large (Bcl-xL, Induced myeloid leukemia cell differentiation protein (Mcl-1), Bcl-2-like-protein-2 (BCL2L2/Bcl-w) and Bcl-2 related protein A1 (A1/Bfl1). Nevertheless, most of these approaches have shown little success, and in almost all instances tumor cells become resistant to such apoptosis inducing drugs [6].

Emerging evidence shows that resistance to apoptosis is multifactorial and involves many secondary players that run either parallel to Bcl-2 signaling or function in complete independence [7]. Here we review the known and emerging pathways that modulate the apoptosis signaling and discuss strategies to overcome apoptosis resistance. We anticipate that a comprehensive understanding of the resistance molecules (and the strategies to target them) will help in the design of clinically successful strategies for cancer in general and specifically in patients who show disease relapse.

2. Role of Bcl-2 family proteins in resistance to apoptosis

One of the major hallmarks of human cancers is the intrinsic or acquired resistance to apoptosis [8,9]. Evasion of apoptosis may contribute to tumor development, progression, and also to treatment resistance, since most of the anticancer therapies that are currently available include chemotherapy, and radio- and immunotherapy (which primarily act by activating cell death pathways *i.e.*, apoptosis in cancer cells). Hence, a better understanding of the molecular mechanisms underlying tumor resistance to apoptotic cell death is expected to provide the basis for a rational approach for the development of molecular targeted therapies.

There are two types of apoptosis programs *i.e.*, intrinsic and extrinsic. The Bcl-2 protein functions through hetero-dimerization with pro-apoptotic members of the BH3 family to prevent mitochondrial pore formation and prevent cytochrome *c* release and initiation of apoptosis [10] (Fig. 1). However, there is evidence suggesting that Bcl-2 may play an oncogenic role through survival pathways other than its function at the mitochondrial membrane [11]. It has been reported that Bcl-2 activates nuclear factor-κB (NF-κB) by a signaling mechanism that involves Raf-1/MEKK-1-mediated activation of inhibitor of NF-κB kinase subunit beta (IKKβ) [12]. Mortenson and colleagues [13] have shown that overexpression of Bcl-2 increases the activity of AKT and IKK as well as NF-κB transcriptional activity in cancer. While Kumar and colleagues [14] found that Bcl-2-induced tumor cell proliferation and tumor cell invasion were significantly mediated by interleukin-8.

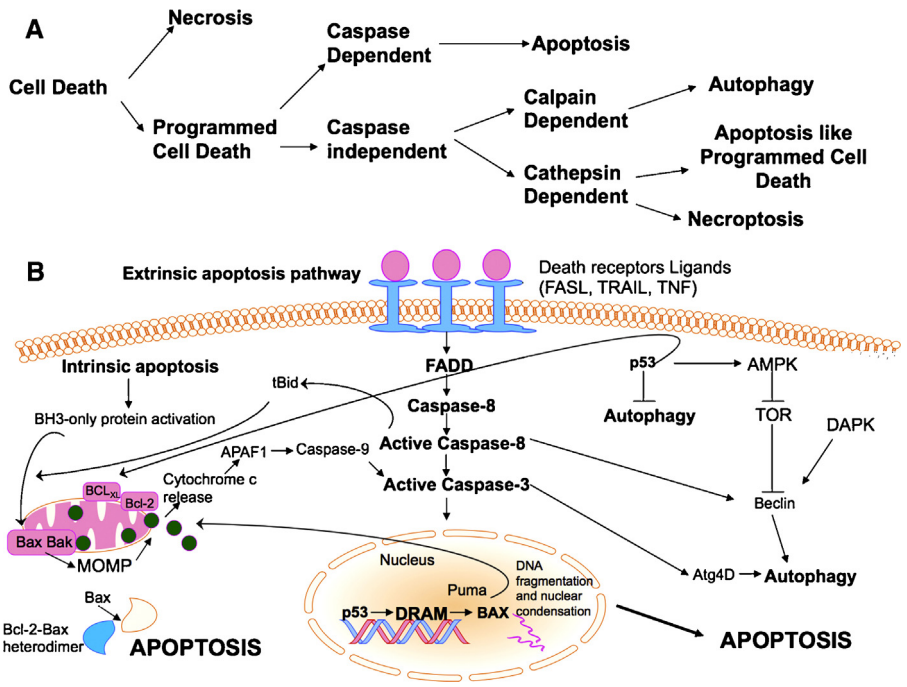

Fig. 1. The apoptosis pathway: (A) The different paths that a cell can take during the activation of cell death. (B) Apoptosis can be triggered either by external receptor-dependent stimulus (extrinsic) or through internal (intrinsic) mitochondria-mediated signaling. The extrinsic pathway is initiated by the attachment of death receptors with their death initiating ligands, such as FASL, TRAIL or TNF. Consequently, an adaptor molecule, FADD also known as FAS-associated death domain protein, couples the death receptors and this subsequently leads to the activation of caspase-8. Activated caspase-8 can either directly cleave and activate caspase-7 or caspase-3, thereby promoting apoptosis. On the other hand the intrinsic pathway is modulated by the activation of BH3-only proteins sensing different types of cell stress, such as DNA damage or ER stress, and then activating BAX/BAK at mitochondrial outer membrane (MOM). MOM permeabilization (MOMP) leads to release of different apoptosis-mediating molecules, such as cytochrome *c*, which activates caspase-9. In turn, caspase-9 cleaves and activates caspase-3 and caspase-7, thus triggering apoptotic cell death. Both pathways interface at the point of caspase-3 activation. The formation of autophagosome formation requires activation of Beclin 1 which acts as a component of a multiprotein (PI3K) complex. The crosstalk between autophagy and apoptosis is mediated at least in part by the functional and structural interaction between Beclin 1 and the anti-apoptotic proteins BCL-2 and BCL-XL. Diverse apoptotic stimuli either intrinsic or extrinsic can lead to caspase-mediated cleavage of Beclin 1 rendering it ineffective as an autophagy inducer. The master tumor suppressor p53 has essential roles in both apoptosis and autophagy. At the transcriptional level, p53 upregulates BAX, PUMA and BID or reduces the expression of BCL-2, which antagonizes BAX. In addition to apoptosis, p53 can also induce autophagy through TOR inhibition and also through transcriptional activation of DRAM.

Recently, Tucker and colleagues [15] reported that Bcl-2 over-expression leads to the maintenance of cyclin D1a expression, an activity that may occur through p38 mitogen-activated protein kinase (MAPK)-mediated signaling pathways in human lymphoma cell lines. Moreover, down-regulation of Bcl-2 could also modulate the expression of carbonic anhydrase IX (CAIX), vascular endothelial growth factor (VEGF), and pAKT in prostate cancer cell lines [16]. These studies provide evidence in support for a multi-functional role of Bcl-2 in cancer biology that extends beyond its classical role in cell survival. However, even though these early studies encouraged the application of Bcl-2 targeted drugs in a clinical setting, most of the ensuing trials have been rather disappointing [17]. Probably, the drugs are unable to target the entire set of anti-apoptotic proteins or the inhibition efficiency is not robust. Thus, new molecular targets and novel concepts of combination therapies need to gain access into clinical trials – either in neoadjuvant/adjuvant or in palliative treatments.

Apoptosis is also deliberated as a stress induced process of cellular communication [18]. In addition to intrinsic and extrinsic processes, there is another pathway that involves T-cell mediated cytotoxicity and perforin-granzyme-dependent killing of the cell where granzyme B and granzyme A proteases are responsible for inducing cell death in this pathway [19]. These intrinsic, extrinsic, and granzyme B have different modes of initiation but have the same outcome: they lead to the activation of a cascade of proteolytic enzymes, members of caspase family [20]. Granzyme A, a serine protease, causes cell death by DNA damage by single-stranded nicks, independent of caspases [21]. The mitochondrial (intrinsic) pathway is regulated by the Bcl-2 family and activated by mitochondrial disruption with subsequent cytochrome *c* release. Initiators of this pathway include UV irradiation and cytotoxic drugs. An apoptosome is formed by the interaction of cytochrome *c*, Apaf-1, d-ATP/ATP and procaspase-9 with subsequent initiation of the caspase cascade [22]. Over-expression of Bcl-2 and associated anti-apoptotic proteins Bcl-xL, Mcl-1, A1/Bf1 and Bcl-w occurs in substantial subsets of common cancer types that include pancreatic, ovarian, lymphoma, multiple myeloma, lung adenocarcinoma, prostate adenocarcinoma and others. These Bcl-2 proteins can essentially make cancer cells resistant to a variety of chemotherapeutic agents and therefore these proteins are currently important targets for the development of new anti-cancer agents [23,24].

Myeloid cell leukemia-1 (Mcl-1) is a potent anti-apoptotic protein, a member of the pro-survival Bcl-2 family, its role is emerging as a critical survival factor in a broad range of human cancers [25]. Functional studies have confirmed that Mcl-1 is capable of blocking apoptosis induced by various apoptotic stimuli, including chemotherapy and radiation [26]. Mcl-1 is highly expressed at the protein level in cancer cells and is associated with resistance to chemotherapeutic agents [27]. It has been demonstrated that down-regulation of Mcl-1 enhances the induction of apoptosis and sensitivity of cancer to chemotherapy and radiation [28]. Thus, Mcl-1 represents attractive molecular target for development of a new class of cancer therapy for treatment of cancer.

The most potent small molecule inhibitors of the Bcl-2 subfamily described to date are the Bad-like BH3 mimetics [29]. ABT-737, one of these mimetics, binds with high affinity (Ki 1 nM) to Bcl-2, Bcl-xL and Bcl-w but fails to bind to Mcl-1. It has been demonstrated that resistance to ABT-737 is linked to high expression

levels of Mcl-1 and in many instances this resistance can be overcome by treatment with agents that down-regulate, destabilize, or inactivate Mcl-1 [30]. It was also shown that knockdown of Mcl-1 sensitizes human pancreatic cancer cells to ABT-737-induced apoptosis, indicating that Mcl-1 is a relevant therapeutic target in these cancer cells [31]. Recently, a small molecule agent that is a specific inhibitor of Mcl-1 has been developed [32]. The agents showed activity against a panel of pancreatic and other cancer cell lines and works through disruption of interaction between Mcl-1-Bax and Mcl-1-Bak with remarkable activity against sub-cutaneous xenograft models of pancreatic cancer.

Highlighting the importance of apoptotic proteins, recently Stuart Schreiber's group [33] performed genomic and lineage cancer cell line (CCL) profiling to identify cancer dependencies that are targetable with small molecules and suggested combinations of compounds that mitigate apoptosis resistance. Their Cancer Therapeutic Response Portal (CTRP) suggests candidate dependencies associated with common oncogenes. The first version of the CTRP resulted from the profiling of an Informer Set of Small Molecules (ISSM), many of which target non-altered proteins that work in partnership with oncogenes. Exploiting oncogene-induced dependencies contrasts to an approach based on cancer "hallmarks" [3,34] without first linking these "nononcogene addictions" to specific genomic alterations. For example, navitoclax has been tested in phase I/II clinical trials for small-cell lung cancer [35]; however, the data suggested that navitoclax might best be targeted to patients harboring catenin cadherin-associated protein β 1 (CTNNB1) mutations, which are present in colorectal, hepatocellular, gastric, and endometrial cancers. Indeed it was demonstrated that CTNNB1 mutant CCLs are sensitive to navitoclax in several lineages, though more strongly in some (*e.g.*, gastric) than others. The same selectivity was not observed for ABT-199, a Bcl-2-specific inhibitor [36], suggesting that inhibition of other Bcl-2 family members underlies the differential response. Consistently, Rosenbluh et al. [37] recently showed that knockdown of Bcl-xL in β-catenin-active CCLs impairs proliferation, implicating Bcl-xL as a relevant target for navitoclax in CTNNB1 mutant cancers. So drug specificity and selectivity is significant, however specificity should be broad to cover secondary targets whose presence can lead to resistance to the initial compound. Such is the argument for a "pan-Bcl-2" SMI – a compound which may not bind to all of its targets in the low nanomolar range, but binds to at least Bcl-2 and Mcl-1 to disarm the pro-survival capacities of these key targets. As such, "dirty drugs" may prove useful to knock out a range of Bcl-2-family members. This is the reason why natural compound gossypol from cotton seed has attracted attention for it Bcl-2 inhibitory capacity and has been developed as an anti-cancer agent for clinical application.

3. Autophagy and resistance of cancer

Autophagy serves to maintain intracellular homeostasis through a process that involves lysosomal degradation and recycling of unnecessary or damaged cellular components, and in turn promotes cell survival. Autophagy can prevent cellular damage caused by chemotherapeutics as it attempts to maintain intracellular balance through removal of dysfunctional organelles and eliminating cellular stress. It has been suggested that this temporal survival mechanism may facilitate chemoresistance as a byproduct of its function in keeping the cancer cells alive [38]. Indeed, autophagy has been observed to guard cancer cells against apoptosis upon encountering certain anticancer drugs [39–41]. The majority of relevant preclinical studies using numerous chemotherapeutics including vorinostat, cyclophosphamide, and imatinib have demonstrated that autophagy significantly inhibits the efficacy of several classes of anticancer agents and helps to drive the acquired resistance [42–44]. Furthermore, accumulating evidence has indicated that autophagy is involved in adaptation of cancer cells to chemotherapy [45,46]. These observations suggest that under chemotherapeutic treatments, autophagy is often activated as a cytoprotective mechanism for tumor cell to survive the effects of anticancer drugs which, in turn, may drive chemoresistance. Therefore, the effects of chemotherapy might be improved by inhibiting cytoprotective autophagy to enhance the apoptosis of cancer cells in response to anticancer drugs.

In contrast to its cytoprotective role, autophagy can also lead to cell death (termed "type II programmed cell death") when induced by excessive cellular stress [47]. More importantly, autophagy-mediated cell death can participate in the upregulation of apoptosis [48,49], and the inhibition of autophagy has been observed to reduce apoptosis in some cancer cells [50]. In this regard, apoptosis and autophagic death may engage each other and share common mechanisms to polarize cellular death response. Furthermore, inhibition of caspase 8 can cause the subsequent activation of autophagy related gene (Atg) Atg6-Atg7-dependent cell death pathway [51], suggesting that autophagy-mediated cell death may serve as a backup mechanism for cell demise in the absence of apoptotic signaling. Due to its paradoxical role in both cell survival and cell death, the outcome of autophagy in cancer cells treated with chemotherapeutic drugs may therefore depend on the type of cancer and stimuli, the progress of tumorigenesis, and the apoptotic status of the cancer cells [52]. As the key mediators in the autophagic process are either products of tumor suppressor genes or oncogenes that often cross the regulatory pathways of apoptosis, clarifying their function during anticancer drug treatment may also help better understand the process of autophagy-driven chemoresistance.

Cell fate dictated by autophagy is regulated by several factors including beclin-1, PI3K, mTOR, Bcl-2, and p53, which are associated with many human disorders [53]. Beclin-1, also called Atg6, is a Bcl-2-homology domain 3 (BH3) protein, that interacts with Vps34 (a class III PI3K), Vps15 (a myristoylated kinase), and UV irradiation resistance-associated tumor suppressor gene (UVRAG) to form a multi-protein interactome that controls the initiation of autophagy, the autophagosome nucleation [54]. Negative regulators to this process include the anti-apoptotic proteins of the Bcl-2 family, which can interact with beclin-1 and inhibit the function of the Vps-UVRAG-beclin-1 multi-protein core complex [55].

It has been suggested that increased apoptosis resistance *via* anti-apoptotic Bcl-2 family members such as Bcl-2, Bcl-xL, and Mcl-1 can inhibit autophagy induced by chemotherapy, most likely in an attempt to protect cells from the autophagic cell death, and by forming inhibitory complexes with beclin-1 [56]. For example, sorafenib-activated autophagic death in hepatocellular carcinoma (HCC) cells is mediated by the reduced expression of Mcl-1. On the contrary, apogossypolone, a potent anticancer agent that inhibits Bcl-2 and Bcl-xL, has been shown to abrogate the interaction between beclin-1 and Bcl-2/xL and induces protective autophagy in HCC cells [57]. The role of beclin-1 interactome in the crosstalk between apoptosis and autophagy thus emphasizes that disturbances in beclin-1-dependent autophagy can have crucial impact on the apoptotic resistance in chemotherapy.

The ADP ribosylation factor (ARF) tumor suppressor is expressed and accumulated in response to mitogenic stimuli conveyed by oncogenic signals. The majority of ARF localizes to the nucleolus and nucleoplasm, where it antagonizes the E_3 ubiquitin ligase muring double minute 2 (MDM_2) to provoke MDM2 degradation, thereby stabilizing p53 protein [58,59]. A minor fraction of ARF (smARF) with a smaller molecular weight variant that lacks the nucleolar localization sequence and preferentially localizes to mitochondria, has been shown to induce autophagy [60,61]. Once localized to the mitochondria, smARF can bind to Bcl-xL and

disrupt the complex formation of beclin-1 with Bcl-xL, leading to an increased ability of beclin-1 to perform its autophagic functions [62,63]. Heat shock protein 70 (hsp70), a molecular chaperone that is highly expressed in tumor cells, interacts with smARF and regulates the mitochondrial trafficking of smARF, thereby acting as a critical regulator of ARF-mediated autophagy [64]. Recently, ARF has also been identified as a marker for advanced tumors and a lack of ARF function is associated with the inhibition of p53 tumor suppressor function in response to DNA damaging agents as well as ionizing radiation [65,66]. Given that smARF is tightly regulated by proteasomal degradation and preferentially stabilized by metabolic stress, it is speculated that it plays both a pro-survival role and a cytoprotective role in autophagy induced by stress.

Mounting evidence also indicates that ROS are implicated in autophagy induction in cancer therapy. Importantly, the deregulation of ROS formation during autophagic response is associated with cancer initiation, progression, and drug resistance [67,68]. ROS, especially mitochondrial ROS, serve as signaling molecules in inducing autophagy [69]. Atg4, a cysteine protease which cleaves Atg8/LC3 from the outer membrane of autophagosome, is targeted and inactivated by ROS, leading to the lipidation of autophagic process [70]. At the same time, autophagy contributes to the regulation of cellular ROS production by eliminating damaged organelles that may produce high levels of ROS which, in turn, limits chromosomal instability [71].

The selective clearance of damaged mitochondria or mitochondrial autophagy ("mitophagy") has therefore been suggested to represent an adaptive response to oxidative stress-mediated cell death in several cancer cell lines, mitigating accumulated ROS and protecting cell integrity through the removal of ROS-leaking mitochondria [72]. For instance, anticancer drugs such as 5-fluorouracil (5-FU) elicit protective autophagy against cell death, and the inhibition of autophagy could enhance apoptosis *via* ROS formation.

Suppressed expression of essential autophagic genes such as beclin-1 and ATG5 has also been observed to enhance the oxaliplatin-induced ROS production and cell death in Caco-2 cells, indicating the role of cytoprotective autophagy in eliminating ROS-induced cell death [73]. Furthermore, ROS-induced DNA damage activates the enzymatic activity of poly(ADP-ribose) polymerase-1(PARP-1), which has been demonstrated to induce protective autophagy through the AMP-activated protein kinase (AMPK) pathway and it instigates the resistance of cancer cells to ROS production by chemotherapeutic drugs [74–76]. Thus, modulating the sensitivity and regulatory mechanism of cells to ROS, such as through the use of antioxidants, could potentially serve as a strategy in chemosensitizing and reducing resistance of cancer cells by blocking ROS-mediated protective autophagy. Evidence of autophagy responding to treatments in cancer cells supports the view that this physiological process can help tumors escape drug-induced cytotoxicity (as a survival mechanism) or potentiate chemotherapeutic efficacy (as a cell death pathway). Selective inhibition or induction of autophagy may therefore help sensitize resistant tumor cells to chemotherapeutic treatments.

4. *In vitro* and *in vivo* necrotic cell death and necroptosis

Necrotic cell death is a cell death process that is morphologically characterized by a gain in cell volume, swelling of organelles, plasma membrane rupture and subsequent loss of intracellular contents. This is in contrast to programmed cell death (apoptosis), although it was long thought that necrosis is an uncontrolled cell death that is characterized by progressive loss of cytoplasmic membrane integrity, rapid influx of Na^+, Ca^{2+}, and water, resulting in cytoplasmic swelling and nuclear pyknosis [77]. However, there is now an increasing realization that necrotic cell death represents a more programmed form of necrosis, termed necroptosis [78]. The former leads to cellular fragmentation and the release of lysosomal and granular contents into the surrounding extracellular space, with subsequent inflammation. A number of toxic chemicals or physical stresses such as toxins, radiation, heat, trauma, lack of oxygen due to the blockage of blood flow, and other events can cause necrosis. When necrotic cells begin to die, cells swell and holes appear in the plasma membrane and intracellular materials spill out into the surrounding environment [79].

Necrotic cell death is believed to be a consequence of physicochemical stress, such as freeze–thawing or severe hyperthermia, and thus as accidental and uncontrolled [80]. Interestingly, necrotic cell death has emerged as an important and physiologically relevant signaling process that seems to contribute to ovulation [81,82], immune defense [83], death of chondrocytes controlling the longitudinal growth of bones [84], and cellular turnover in the intestine [85]. *In vivo* studies indicated that removal of inter-digital cells in the paws of Apaf $1^{-/-}$ mice during embryogenesis occurs by a caspase-independent necrotic-like process [86]. Noteworthy, the occurrence of necrosis in these *in vivo* models is mostly defined morphologically. Several reports also illustrate the occurrence of necrotic cell death during viral and bacterial infections. For example, HIV-1 shows to kill $CD4^+$T lymphocytes by necrosis [87] and Shigella and Salmonella can induce necrotic cell death of infected neutrophils and macrophages [88]. Although necrosis has been thought to be an unregulated process, recent research suggests that necrosis may occur in two different pathways in a living organism. The first pathway of necrosis initiation involves oncosis, where swellings of the cells occur. The cell then proceeds to blebbing, and it is followed by pyknosis, in which nuclear shrinkage transpires. In the final step of the primary necrosis, the nucleus is dissolved into the cytoplasm known as karyolysis. The second pathway of necrosis involves a secondary form of necrosis that is shown to occur after apoptosis and budding. In this case, cellular changes of necrosis occur in this secondary form of apoptosis, where the nucleus breaks into fragments, which is known as karyorrhexis.

Unlike necrosis, necroptosis is a more programmed form of necrosis that has been shown to be a defense mechanism in organisms against internal pathogens and intracellular infections [89]. Necroptosis was first recognized as a caspase-independent form of cell death that can be triggered by treatment with tumor necrosis factor (TNF) only in the presence of a pan-caspase inhibitor, such as zVAD fluoromethyl ketone. Unlike apoptosis, necroptosis requires that the function of caspase 8 be inhibited or disrupted. Several of the upstream signaling elements of apoptosis and necroptosis are shared, and sensitivity to each death pathway is regulated (sometimes in opposing ways) by an overlapping cluster of regulatory molecules, such as FLICE-like inhibitory protein (FLIP), the deubiquitinases A and cylindromatosis and the cellular inhibitors of apoptosis proteins such as the Baculoviral IAP repeat-containing protein (cIAP1 and cIAP2). At the molecular level, intracellular assembly of a highly regulated complex, the necrosome, can be triggered by death receptors (*e.g.*, tumor necrosis factor receptor 1/TNFR1), by cell-surface toll-like receptors, by DAI (which may act as a cytoplasmic viral RNA sensor). The continuing elucidation of the molecular aspects of various forms of regulated necrosis, including necroptosis, and the efficient design of combination therapies hold promise for our ability to control regulated necrosis in clinical settings.

5. The role of hsp90 on apoptosis resistance in cancer cells

Heat shock protein 90 (hsp90) is one of the most abundant proteins in eukaryotic cells. It is an enzymatic chaperone molecule with

ATPase activity that is highly active in malignant cells and tissues when compared to non-neoplastic cells. In line with its activity pattern and expression profile it has been shown to drive tumor progression by enhancing proliferation, migration and metastasis. In addition, it also confers resistance to programmed cell death by several mechanisms. By its chaperoning activity, hsp90 stabilizes a number of mutated and non-mutated kinases and several anti-apoptotic factors within the cytosol that overall favor resistance to apoptosis and mostly drive proliferation and resistance of tumor cells to various treatment regimens. These factors include, but are not limited to Akt, mutated BRAF, EGFR, JAK2 and the inhibitor of apoptosis protein survivin. Targeting cytosolic hsp90 elicits inhibition of proliferation and depending on the compound and tumor cells involved also apoptosis. The kinase, JAK2, was recently shown to be an interacting partner of hsp90 in a model of polycytemia vera [90], a myeloproliferative disorder that almost always harbors a JAK2 mutation. In line with the interaction of hsp90 and JAK2, a novel hsp90 inhibitor was shown to disrupt this interaction and depleted JAK2 protein levels *in vitro* and *in vivo*. Hsp90 signaling also appears instrumental in mediating resistance to tyrosine kinase inhibition (TKI) treatment, specifically with EGFR inhibitory molecules, such as erlotinib and gefitinib. These molecules particularly target mutated EGFR within the intracellular ATP binding domain, especially point mutations in exon 21 (L858R) and deletion located in exon 19. With respect to hsp90, Shimamura et al. [91] have elegantly shown that in several non-small cell lung cancer (NSCLC) cell lines geldanamycin (a prototype hsp90 inhibitor) preferentially elicited depletion of mutated EGFR with subsequent suppression of p-Akt, causing cell death. Moreover, 17-AAG, a derivative of geldanamycin, more efficiently suppressed mutated EGFR compared to the wild-type form. Another important aspect in lung adenocarcinomas is the fact that tumors that are initially responsive to EGFR inhibition due to selective EGFR mutation in exon 19 or exon 21 recur eventually because in the presence of EGFR sensitizing mutations, they generate secondary mutations, such as the T790M EGFR mutation, which in turn confers resistance to erlotinib/gefitinib. One option to bypass a T790M mediated resistance is the administration of so called irreversible tyrosine kinase inhibitors. However, another option appears to be the enzymatic, cytosolic inhibition of hsp90 by 17-AAG [92]. Shimamura et al. [93] have demonstrated in a murine model of lung cancer, harboring both an exon 21 (EGFR inhibitor sensitizing mutation) and the resistance mutation (T790M), that 17-DMAG (a derivative of 17-AAG with optimized *in vivo* properties) also reduced tumor growth in the presence of the T790M mutation, indicating that hsp90 inhibition may be a worthwhile strategy to combat EGFR tyrosine kinase inhibitor resistance. This was further supported by the depletion of several hsp90 chaperones/downstream molecules *in vivo*. Given the unfavorable properties of 17-AAG derived molecules, alternative molecules are being tested. One of which is Ganetespib that was recently explored in several lung cancer models, including ones harboring EGFR inhibitor resistance mediating mutations. Ganetespib behaved superiorly compared to 17-AAG and accumulated within neoplastic tissue. Due to the favorable preclinical data it was also recently assessed in a phase-II-clinical trial [94].

Most of the hsp90 functions are ascribed to its presence and function in the cytosol, but recent evidence also suggests that hsp90 is over-expressed in tumor mitochondria and organizes a mitochondrial chaperoning network that antagonizes tumor cell death. In terms of therapeutic applicability, inhibition of hsp90 elicits anticancer activity in tumor cells of various origins and therefore has emerged as a viable treatment target for cancer therapy. In 2007, Kang et al. [95] have unraveled a novel tumor chaperone network that is situated in tumor mitochondria. This network consisted of three major players, hsp90 (as referred now as mitochondrial hsp90; mHsp90), TNF receptor-associated protein 1 (TRAP1) and the cell death promoting protein Cyclophilin-D (Cyp-D). TRAP1 is a molecule that shares significant similarities to hsp90 by exhibiting both structural and enzymatic overlap with hsp90. Akin to hsp90, TRAP1 reveals ATPase activity and its ATPase activity is amenable to inhibition by geldanamycin derivatives, such as 17-AAG. Favoring TRAP1 as a suitable "druggable" target, its expression levels were increased in malignant neoplasms from lung, colon, pancreas and breast, prostate and glioblastoma, whereas in non-neoplastic counterparts expression levels were significantly lower [95]. For example, Matsuda et al. [96] have demonstrated that β-hydroxyisovalerylshikonin, a plant derivative with anti-cancer activity, depleted TRAP1 levels in mitochondria in DMS114 (lung cancer) and HL60 (leukemia) cells, respectively. In the matrix of tumor mitochondria, hsp90 and TRAP1 inhibit mitochondrial permeability transition pore (MTP)-dependent cell death initiated by Cyclophilin-D in tumor cells almost independent of their entity. Kang and colleagues also elaborated this concept further by developing two different classes of molecules to specifically inhibit the discovered chaperone network in tumor mitochondria. The first of these molecules was a modified 17-AAG (Ant-GA) molecule that harbored an Antennapedia linker sequence *(Ant)*, which allowed the molecule to accumulate in the matrix of mitochondria and inhibit both mhsp90 and TRAP1. Despite its modification Ant-GA retained its hsp90 inhibitory properties. When incubated, Ant-GA induces disruption of the mitochondrial membrane potential of tumor cells, culminating in cell death independent of their *TP53* status, suggesting that a mitochondrial chaperone-targeted treatment approach does not require presence of wild-type p53 which is amongst the most commonly mutated proteins in cancers. To further corroborate the importance of Cyclophilin-D, Kang et al., [97] also made the case that Cyclophilin-D is implicated and instrumental for the cell death elicited by Ant-GA, since cyclosporine-A, an inhibitory molecule of MPT mediated cell death mitigated Ant-GA mediated apoptosis. The second molecule that revealed inhibitory properties of the mitochondrial hsp90 chaperone network was a peptide, called shepherdin. Shepherdin was initially described as a compound that disrupted the interaction of hsp90 and survivin. This peptide induced cell death in various cancer cells with a remarkable efficacy without causing apoptosis in non-neoplastic cells, such as fibroblasts, epithelial cells or astrocytes. The initial form of shepherdin had anti-cancer activity in several skin xenograft models, including prostate cancer. Consistent with its inhibitory cytosolic properties of hsp90, shepherdin treated xenograft tumors exhibited depletion of the hsp90 chaperone client proteins, Akt, and survivin. Most notably, shepherdin was not associated with organ toxicity as provided by a necropsy analysis of shepherdin treated animals. Consistent with this notion is the finding that animals did not exhibit significant weight loss upon administration of the compound. Based on this determination, it was suggested that shepherdin appears to be a fairly safe reagent. However, one pitfall may be the fact that precise pharmacokinetics were not provided. An engineered shorter version of shepherdin showed activity against leukemia cells both *in vitro* and *in vivo* [98]. Later on, it was demonstrated that shepherdin also inhibited the mitochondrial hsp90 chaperone network by interacting directly with TRAP1 and mhsp90. Consistent with its pharmacodynamics, shepherdin induces a MPT-dependent cell death specifically in tumor cells, which akin to Ant-GA requires the functional presence of Cyclophilin-D. Along those lines, pretreatment with cyclosporine-A, an inhibitor of the MPT, attenuated shepherdin-mediated cell death. In contrast, adenoviral-mediated over-expression of Bcl-2, that at physiological levels inhibits the translocation of intermembranous cytochrome *c* into the cytosol, did not significantly suppress cell death mediated by shepherdin, suggesting that this reagent acts independent of the Bcl-2 family of proteins and mainly relies on the MPT pore in the presence of

Cyclophilin-D. All in all, shepherdin represents a prototype of a "double hit" hsp90 inhibitor with tumor specific pharmacological effects both in the cytosol and within mitochondria. Newer class of sophisticated molecules Gamitrinibs "GA-mitochondrial matrix inhibitors" have also been tested for their hsp90 inhibitory activity [99]. Gaminitribs are derived from 17-AAG and structurally contain a mitochondrial linker sequence, which enables them to efficiently accumulate in mitochondria. Two molecules have received most attention: Gamitrinib-TPP and Gamitrinib-G4. They are associated with anti-tumor activity in a number of different disease model systems, including breast cancer, lung cancer, colon cancer, prostate cancer lymphoma and glioblastoma (also reviewed in [100]). Collectively, a comprehensive understanding of how hsp90 functions promises not only to provide new avenues for therapeutic intervention, but to shed light on fundamental biological questions of apoptosis evasion.

6. The proteasome pathway and apoptosis resistance

Eukaryotic 26S proteasome is a 2.5 MDa large complex consisting of two 19S regulatory particles and one 20S catalytic core [101]. Each 19S regulatory particle is composed of the lid, which is responsible for recognition and docking of polyubiquitinylated proteins into the 20S catalytic core, and the base, which is in charge of the unfolding and linearization of large proteins. The 20S catalytic core harbors seven distinct α-subunits and β-subunits arranged in a α7β7β7α7 stacked barrel, among which mainly three sets of β-subunits, β1 (caspase-like or peptidyl-glutamyl peptide-hydrolyzing (PGPH)-like), β2 (trypsin-like), and β5 (chymotrypsin-like) are proteolytically active. Unlike common proteolytic enzymes that contain a catalytic triad, the proteasome catalytic subunits belong to a special group termed N-terminal nucleophile hydrolases, which utilizes the side chain of the N-terminal residue as the catalytic nucleophile [102–104]. All three catalytic β-subunits react with peptide bonds of substrates through their —OH group of the N-terminal threonine (Thr1), resulting in protein being degraded into small fragments of less than 10 amino acids. It has been well documented that the proteasome is required for cell cycle progression by regulating the turnover of cyclins and cyclin-dependent kinase inhibitors, and therefore inhibition of proteasome function could result in cell cycle arrest. In addition, the ubiquitin-proteasomal system can affect cell survival pathways by regulating the turnover of transcriptional factors responsible for cell survival or apoptosis such as NF-κB, p53, as well as apoptotic proteins such as the Bcl-2 family members and others [105]. Therefore, inhibition of the proteasome is linked with the induction of apoptosis.

In tumor tissues, the proteasome activity is up-regulated by intracellular oncogenic factors, which render the cancer cells more dependent on the proteasome than the normal cells. Enhanced tumor cellular proteasome activity in turn promotes the degradation of tumor suppressor proteins, resulting in cancer cell survival and proliferation as well as the development of resistance to apoptosis [106]. On the other hand, proteasome activity could be suppressed by several endogenous inhibitors as well as various exogenous inhibitors, including some synthetic compounds such as bortezomib and many natural products such as plant polyphenol epigallocatechin-3-gallate (EGCG) [107]. Although the mechanism that is involved is not clear, proteasome inhibition in cancer cells is prone to accumulate pro-apoptotic target proteins and induce cell death. The clinical efficacy of bortezomib in multiple myeloma and other hematologic malignancies lends credence to the concept that targeting the proteasome, making it a promising strategy for cancer treatment.

The proteasome also degrades IκBα, an important inhibitor of the tumor survival factor NF-κB. Many physical *(i.e.*, radiation), chemical (cancer chemotherapeutic agents), viral and biological (cytokines, growth factors) agents induce phosphorylation, ubiquitination and subsequent degradation of IκBα by the proteasome, freeing up NF-κB to translocate to the nucleus and modulate genes involved in proliferation, invasion and tumor survival [108,109]. For example, NFκB upregulates the anti-apoptotic protein Bcl-2 and downregulates the pro-apoptotic protease caspase 8. Therefore, by inhibiting the proteasome, IκBα will accumulate which will inhibit NF-κB from promoting tumor survival. The proteasome is also responsible for degrading the tumor suppressor p53. Many tumor cells inactivate p53 by over expressing p53 master regulator MDM2 [110]. In human tumors that over express MDM2, the inhibition of proteasome pathway is predicted to induce tumor cell apoptosis by accumulating p53. It has been observed that CEP1612, a dipeptidyl proteasome inhibitor, was able to rapidly induce apoptosis in different human cancer cell lines, including breast, prostate, leukemia, lung, bone, brain, and head and neck, but not in human normal fibroblasts and normal breast cells [111].

Proteasome inhibition was also sufficient to overcome apoptotic protection by Bcl-2 or Bcr-Abl oncoprotein. Proteasome inhibition accumulates Bax (but not Bcl-2) protein in mitochondria, resulting in increased ratio of Bax/Bcl-2, associated with cytochrome *c* release and apoptosis induction [112]. It has also been shown that during TNF-α-induced apoptosis, Bcl-2, but not Bax, protein is degraded through ubiquitin/proteasome-dependent pathway [113] which also increased the Bax/Bcl-2 ratio. Therefore, selectively degrading one or more Bcl-2 family proteins by the proteasome should change the ratio of pro- to anti-apoptotic proteins, which might contribute to the apoptotic commitment and result in overcoming resistance.

7. Epigenetics as a mechanism underlying drug resistance

There is uniform recognition of the importance of epigenetics (heritable non-structural changes in gene expression), as a major mechanism that can drive acquired resistance to chemotherapy [114]. For example, epigenetic mechanisms such as non-coding RNA (microRNAs) and DNA methylation are important drivers that influence the chemo-responsiveness of tumors and acquired drug resistance. Although drug resistance can be overcome using epigenetic therapies in experimental models, clinical studies of epigenetic therapies have highlighted challenges for different cancers, and there is a need to identify more targeted approaches. Here we highlight a few epigenetic mediated drug resistance mechanisms and identify strategies to overcome this challenge.

The breast and ovarian cancer cell line models have provided some of the earlier insights into the different epigenetic mechanisms underlying drug resistance. Studies have shown that taxane resistance in breast cancer may be associated with profound changes in the expression of apoptotic factors such as caspases. The gradual development of taxane resistance over a relatively small number of cell culture passages was shown to correlate with marked downregulation of caspase 9, 7 and Bcl-2 [115]. Such a shutdown of the intrinsic pathway was shown to be associated with a concomitant up regulation of autophagy. Further, low Bcl-2 expression was seen when cells develop a high level of background autophagy and this can be associated with collateral sensitivity to platinum agents, as seen for taxane resistant breast cancer. Moreover, a high level of background autophagy has also been demonstrated in breast cancer cell lines with acquired resistance to anti-endocrine agents such as tamoxifen and also faslodex (fulvestrant). Resistance to agents such as tamoxifen is a major concern

when one considers their widespread use in the management of breast cancer, both in the prophylactic and adjuvant settings.

Drug resistance in cancer in terms of changes in the entire epigenome has also been studied. Using the cDNA microarrays of several cancer cell line models made relatively resistant to cytotoxic drugs *in vitro*, candidate genes have been identified. By incorporating the use of agents that can reverse epigenetic methylation a number of drug resistant cancer cell line models have been screened and compared with their wild-type drug sensitive counterparts. In this way the major genes that we believe are subjected to silencing – generally *via* methylation of the CpG islands in the promoter region of the gene – and these changes may often be associated with the evolution of drug resistance. For example a series of epithelial ovarian cancer (EOC) cell lines with acquired resistance to paclitaxel and carboplatin and showed that resistance to paclitaxel, often with cross-resistance to carboplatin, occurred with loss of the G2 checkpoint and apoptosis [116]. Among the featured genes included the Polo Like Kinase-2 (PLK2) that was down-regulated due to acquired methylation in the CpG-island at the 5′ end of the gene. These studies demonstrated that by increasing levels of resistance to paclitaxel there was correlation with incrementally decreased expression of PLK2 and increasing CpG island methylation. Based on these studies it was proposed that exposure to chemotherapeutic stress induces methylation in the CpG island of specific "resistance" genes and this seeding effect leads to increasing methylation as the level of resistance increases, a phenomenon previously described in cells exposed to 6-mercaptopurine [117]. A study by Matthew et al. [118] looked at the influence of hypoxia on chemosensitivity in PLK2-deficient tumors. Here, complete resistance to camptothecin pointed to interplay between the tumor microenvironment and PLK2 expression, whereas in the same experiments normoxic cells showed increased drug sensitivity. The same study also showed that PLK2 can inhibit mTOR signaling under the influence of wild-type p53 control. Furthermore, it was found that the cyclin-dependent kinase inhibitor $p57^{kip2}$ appears to be down-regulated in drug resistant ovarian cancers [119]. It has also been shown that carboplatin-resistant ovarian cancer cells show promoter methylation in the CpG island of the promoter. By silencing otherwise carboplatin-sensitive cells using siRNA directed against $p57^{kip2}$, carboplatin resistance was recapitulated which was shown by a reduced apoptotic response in those cells when challenged with a sub-lethal dose of platinum agents [119]. However, these cell lines studies need validation from ovarian cancer patient tissue based expression studies to strengthen the role of low $p57^{kip2}$ and promoter methylation and its association with a poor prognosis and evidence of platinum-refractory disease.

An increasing number of genes involved in cell signaling, migration and adhesion are known to be alternatively spliced and this process appears to be altered during tumor development and progression. Different spliced forms of genes arise as a consequence of alternative pre-mRNA processing and are seen in a number of human malignancies [120,121]. Splicing processes must recognize intron and exon boundaries with accuracy – otherwise there will be changes in nucleotide sequence at the site of exon joining which shifts the reading frame with adverse consequences to the protein coding potential. Splicing is carried out by the "spliceosome" which comprises 5 small nuclear RNAs complexed with several additional proteins. Alternative splicing is one of the many cell processes that are commonly changed in the presence of cancer. These disturbances can result in the production of splice variants with neoplastic potential and could cause transformation of tumors. Alternative splicing contributes to the large number of proteins that can be produced from a much smaller number of genes in the human genome. Aberrations in alternative splicing may also affect cell proliferation, motility and susceptibility to apoptosis, which may be the result of variant mRNA that is tumor-suppressive or oncogenic and can contribute to carcinogenesis [122]. In particular, the family of splicing factors – including SC-35 (a member of the serine rich splicing factors: srsf2) – is recognized to be crucial in controlling the extent of mRNA splicing into active forms of various pro-apoptotic genes such as Bax. Head and neck cancer and ovarian cancer cell lines with acquired resistance to cisplatin have been shown to under express SC-35. Demethylation analyses have revealed that the splicing factor, arginine/serine-rich 2 (SRSF2) gene is silenced *via* methylation of CpG islands in the promoter region. Other work looking at epigenetic silencing has highlighted a number of genes that when silenced can reduce the apoptotic response of cancer cells to various anticancer agents. These studies can be used to look for biomarkers of chemo-response by detection of methylated DNA in cancer patients.

More recently, it has emerged that splicing efficiency can be affected by splicing enhancers which, in turn, interact with regulators that increase exon inclusion such as the SR family of proteins. SR proteins contain an RNA-binding domain and a characteristic SRSF2 – otherwise referred to as SC-35 – is located on chromosome 17 and contains a large CpG island. SR proteins control alternative splicing events in proto-oncogenes and tumor suppressor genes which leads to profound changes in their cellular activity. Factors such as SF2/ASF and SC35 are associated with transformation may be upregulated in some tumors [123]. In a report by Merdzhanova et al. [124] SC-35 working in conjunction with E2F1 was shown to be upregulated and required for apoptosis using a panel of lung cancer cell lines. E2F1, which is an established transcription factor, is recognized to be stabilized following treatment of cells with DNA-damaging agents such as cyclophosphamide. The upregulation accompanies SC-35 induction and there is evidence that SC-35 is a direct target of E2F1. Further, SC-35 inhibition was then shown to repress apoptosis induced by DNA damaging agents. SC-35 in its phosphorylated form is necessary for apoptosis following chemotherapy treatment with cisplatin and is up-regulated following this treatment [125,126]. These reported observations have led to the consideration that down-regulation of SC-35 – and other splicing factors – as a putative mediator of anticancer drug resistance.

More recently it has been shown that miRNA can have a significant effect on the expression of splicing factors such as SC-35. In drug resistant cell line models that carry significant upregulation of miR-221 and miR222 demonstrate marked downregulation of SC-35, a target gene for both these miRs. Further work should be focused on the influence of miR, splicing events and epigenetics on the modification of the apoptotic response in drug resistant cancers.

8. Nuclear transport in apoptosis resistance

Compartmentalization of proteins inside the eukaryotic cell is an evolutionarily conserved mechanism [127]. Each protein (especially apoptosis inducers) requires proper sub-cellular localization to mediate its specified function [128]. This is especially true for tumor suppressor proteins (TSPs) that usually reside in cell nucleus where they exert their function through sequence specific binding to DNA, modulation of gene expression, and assessment of the integrity of the genome [129]. Mislocalization of proteins has been long recognized to disrupt their function resulting in pathological conditions including cancer [130]. In eukaryotic cells, the cytosol and the nucleus intercommunicate *via* nuclear pore complexes (NPCs) present in the nuclear membrane [131]. NPCs consist of more than two dozen different proteins [132]. These nucleoporins form a channel and regulate the nucleocytoplasmic transport of various types of RNAs [133], and proteins [134]. The nuclear import and export of most proteins >40 KDa in size, including membrane

proteins, occurs through the participation of an evolutionarily conserved family of transport proteins belonging to the karyopherin-β family [135]. Karyopherins-β accomplish either nuclear import and are called importins [136] or nuclear export and are called exportins [137]. Generally, karyopherin-mediated transport occurs through the NPC, which acts as a gateway into and out of the nucleus [138]. Most of karyopherins-β interact directly with their cargoes, but may also be aided by adapter proteins [139]. Karyopherin-α, known also as importin-α, is the most-studied adapter protein [140]. All proteins are synthesized on ribosomes found in the cytoplasm. Nuclear proteins must traverse the NPC following their cytoplasmic synthesis. While nucleocytoplasmic transport is normally a highly regulated process, the aberrant expression of karyopherins has been consistently observed in different cancers and has been linked to apoptosis resistance [141]. Chromosome maintenance region 1 (CRM1) is a karyopherin that exports different protein targets from the nucleus of the cell [142]. CRM1 is the major exporter of tumor suppressor proteins (TSPs) and functions by recognizing a leucine rich nuclear exclusion signal sequences (NESs) in cargo proteins and transports them to the cytoplasm in an energy consuming process that involves RanGTP binding and hydrolysis to RanGDP [143].

It is well recognized that nuclear localization of TSPs and their DNA binding is essential for their regulatory function [144]. Mere activation of apoptosis promoting TSPs (such as FOXO3a, p27, Ikβ and prostate apoptosis response 4/Par-4) is not sufficient for their proper apoptosis induction as over-expression of CRM1 in cancer cells results in TSPs efflux and their functional inactivation. Supporting this, over-expression of CRM1 has been associated with therapy resistance, particularly resistance to apoptosis and poor survival in solid tumors [145]. The prognostic significance of CRM1 in multiple cancers has been established [146]. Its expression is increased in pancreatic ductal adenocarcinoma, renal carcinoma, non-Hodgkin's lymphomas, mantle cell lymphomas, prostate, breast, colon and other cancers. Unlike K-ras that is found mutated in >65% of cancers, these TSPs to a large extent remain wild type [147]. However, till date, there are no clinically approved drugs that broadly target the activation of TSPs. These multiple lines of evidences support the need for the development of CRM1 targeted drug for cancer treatment.

Inhibition of XPO1 is one approach to restore nuclear localization and activation of multiple TSPs, allowing them to function properly [148]. Therefore, targeted inhibition of CRM1 using specific small molecule inhibitors has been suggested to be a feasible strategy [149]. Leptomycin B (LMB) was the first natural agent identified to irreversibly inhibit XPO1 [150]. LMB is a secondary metabolite produced by *Streptomyces* spp and was originally discovered as a potent anti-fungal antibiotic [151]. LMB has been shown to be a potent and specific nuclear export inhibits XPO1 and works by alkylating and inhibiting XPO1 through glycosylation of a cysteine residue (cysteine 529) [152]. Nevertheless, LMB demonstrated marked toxicity in both preclinical studies and in a single clinical trial and its clinical development discontinued [153]. Another agent, Leptomycin A (LMA) was discovered together with LMB and showed potency twice as that of LMB [150]. However, its clinical utility has not been evaluated. A novel, small molecule, reversible inhibitor, CBS9106, with XPO1 degrading activity, was shown to have antitumor effects against multiple myeloma cells, both *in vitro* and *in vivo* [154]. The development status of this agent is not known. Recently, novel, orally bioavailable, small molecule, drug-like, selective inhibitors of XPO1 mediated nuclear (SINE) have been described [155]. SINE compounds bind irreversibly to the Cys528 NES recognizing residue in XPO1 and block its ability to bind to cargo proteins [156]. SINE have been shown to potently inhibit the growth of multiple cancer cell lines and animal tumor models such as acute myeloid leukemia [157], mantle cell lymphoma [158], and other hematological malignancies [159]. The anti-proliferative activity of SINE against pancreatic ductal adenocarcinoma and Non-Hodgkin's Lymphoma has been demonstrated [160]. Based on these multiple lines of pre-clinical evidence, the orally bioavailable SINE KPT-330 have rapidly accelerated toward clinical evaluation in solid tumors and hematological malignancies.

CRM1 carries essential roles for the normal function of non-cancerous cells as well. Therefore, the clinical feasibility of any XPO1 targeted strategy has a number of hurdles. While molecular mechanism(s) of action of the first generation XPO1 inhibitor LMB were well defined, the drug proved highly toxic in preclinical models [161] and was discontinued in the clinic, the primary reason being the incomplete understanding and validation of entire sets of pathways modulated by this master exporter. This is coupled with a lack of complete evaluation of the effects of XPO1 inhibition. As recently demonstrated by ours and independent groups, XPO1 interferes with important and complex processes such as miRNA processing [162], epithelial-to-mesenchymal transition [163]. These findings indicate that more advanced pre-clinical work in the right models is required to optimize novel XPO1 inhibitors for applications in cancer and other diseases. Systems biology, particularly mathematical modeling and network analysis, are new approaches that can be used to optimize results in areas where traditional reductionist molecular biology has failed. Mathematical modeling approaches have been utilized to individually assess the consequence of XPO1 inhibition on single pathways. Such approaches have been able to shed light on MAPK/ERK and NF-κB signaling when their nuclear export is blocked, highlighting that the technology, if used correctly, can be applied successfully in XPO1 related research. However, there are no studies to date that have evaluated the differences in the effect of XPO1 inhibition on re-alignment of proteins in cancer *versus* normal cell nuclei in any kind of global context. Major unanswered questions remain as to whether there are differences in cellular responses between cell types (cancer with aberrant genome *versus* normal cells with normal genome *versus* precancerous lesions). Performing such studies at the systems level will undoubtedly lead to the optimization of XPO1 inhibitor therapies in the clinic, as well as in the design of novel strategies targeting nuclear transport.

9. Apoptosis resistance in different cancers

9.1. Apoptosis resistance in glioblastoma

Among all brain tumors, glioblastoma multiforme (GBM) is the most prevalent brain tumor in humans [164]. It is classified as grade IV astrocytoma by the World Health Organization (WHO) [165]. Various molecular alterations are responsible for development of GBM. Apoptosis resistance plays one of the key roles in tumorigenesis and sustains malignant progression in GBM. GBM patients have a poor prognosis with a median survival of 14.6 months. Surgery, radiotherapy, and the alkylating chemotherapy with TMZ are the standard first line treatment for GBM patients [166,167]. Combination therapeutic strategy with radiotherapy and TMZ significantly improves the median survival, 2 to 5 years, compared to radiotherapy alone in patients with newly diagnosed GBM [168,169]. Therapeutic effect of TMZ on GBM cells depends on the epigenetic silencing of the O6-methylguanine-DNA-methyltransferase (MGMT) gene by promoter methylation [170]. MGMT counteracts chemotherapy-induced DNA damage by restoring the structural integrity of O6-alkylated bases. Unmethylated MGMT promoter is frequently observed in glioblastoma patients and these seem to respond poorly to TMZ treatment [171]. Until now there has been no alternative drug treatment for GBM. Thus, understanding the molecular mechanisms that mediate cellular survival and apoptosis resistance will enable us to exploit the key players to design better drug combinations for targeted therapies for GBM patients.

Erlotinib and gefitinib, which are two epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, have been evaluated for GBM treatment. The low molecular weights of these inhibitors enable them to cross the blood–brain barrier (BBB). Recent studies show that GBM patients with amplified or overexpressed EGFR responded better to erlotinib than patients with normal EGFR levels [172] and the response depended on low levels of Akt activation. So, Akt phosphorylation may be a direct result of increased EGFR activity. Thus, treatment with EGFR inhibitors can show better clinical responses. Clinical studies indicated that treatment with single tyrosine kinase inhibitor like erlotinib could not effectively inhibit survival signaling because many other RTK were co-activated in GBM cells [173,174]. Two other receptors, platelet-derived growth factor receptor (PDGFR) and c-Met or hepatocyte growth factor receptor (HGFR), are also involved in EGFR function and in maintaining downstream pathway activation [175]. This suggests that carefully designed combination of inhibitors with limited toxicity profiles and maximal additive or synergistic effects may provide more beneficial therapeutic effects [176]. TMZ causes cell cycle arrest at G2/M phase and EGFR inhibitors prevent cells from progressing beyond G1 and may therefore compromise the activity of other cell cycle-specific agents [177]. As the EGFR tyrosine kinase inhibitors show low toxicity, higher dose can be applied, but it may be difficult to predict the functionally active drug in GBM patients. However, the lack of availability of post-treatment tumor tissue for validation of target inhibition results in uncertainties regarding the sufficient inhibition of the EGFR signaling.

Many inhibitors of the anti-apoptotic members of the Bcl-2 family have been developed and several of them are under preclinical or clinical trials [178]. Although some of the inhibitors have been tested, only one compound has reached the clinical trial in GBM patients. Brain tumors that overexpress anti-apoptotic Bcl-2 and Bcl-xL proteins can be treated with their inhibitors. ABT-737, a recently developed Bcl-2 inhibitor, is known to induce apoptosis in glioblastoma cells both *in vitro* and *in vivo* by releasing the pro-apoptotic Bax protein from its binding partner Bcl-2 [179]. ABT-373 can sensitize tumor cells to the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) as well as to other anti-cancer drugs. But, cells with higher expression of Mcl-1, which is an anti-apoptotic protein of the Bcl-2 family, are found to be less responsive to ABT-737 treatment. So, combination therapy with inhibitors of Mcl-1 and Bcl-2 can be a novel strategy to treat GBM. Recent investigations indicated that the BH3-binding compound HA14-1 can enhance the sensitivity of human glioblastoma cells to both radiotherapy and chemotherapy [180]. Gossypol (AT-101), which is a multi-targeting polyphenol derived from cotton plant, is so far the only Bcl-2 targeting compound tested in clinical trials for treatment of GBMs [181]. Gossypol binds to the BH3 pocket of anti-apoptotic Bcl-2 proteins [182] as well as to other target proteins [183]. Studies suggest that administration of gossypol (20 mg/day) is well tolerated in patients and it has a low but measurable response rate. A Phase II trial of gossypol in recurrent GBM is underway to detect its efficacy against tumor progression and also its toxicity.

The inhibitors of apoptosis (IAP) family proteins like XIAP, cIAP1, cIAP2, ILP2, ML-IAP, and survivin are well known for inhibition of apoptosis in GMB [184,185]. The IAP family proteins are currently known as the baculoviral inhibitors of apoptosis repeat containing (BIRC) proteins. These BIRC proteins can inhibit apoptosis by modulating the activity of different caspases like caspase-9, caspase-7, and caspase-3, which are actively involved in intrinsic pathway of apoptosis in human glioblastoma [186]. In most GBM patients, high levels of BIRC proteins have been detected. Therefore, targeting BIRC proteins to make active caspases available for induction of apoptosis is now an established approach in developing strategy for controlling growth of human glioblastoma cells [187]. Many preclinical trials have been carried out with several small molecule inhibitors directed to BIRC proteins to identify a potential agent capable of inducing apoptosis in different cancers [188]. However, very little research has been performed with BIRC inhibitors in GBM. A recent report showed that BIRC-4 (XIAP) inhibitors synergize with radiation to increase glioblastoma cell apoptosis [189] and targeting BIRC proteins can sensitize cells to TRAIL for induction of apoptosis [190]. Recent investigations also indicated that the endogenous BIRC inhibitor Smac can significantly increase the anti-cancer efficacy of TRAIL in an intracranial glioblastoma xenograft model [191]. Also the use of inhibitors of histone deacetylase and of the proteasome in clinical trials (targeting specific, but poorly characterized aspects of apoptosis) are ongoing at the moment. The versatility and applicability of these preclinical studies will eventually contribute to elucidation of the molecular mechanisms of chemoresistance, which should ultimately result in the identification of more effective therapeutic strategies for avoiding apoptosis resistance in GBM.

9.2. Resistance to apoptosis in melanoma

Melanoma is considered the most aggressive form of skin cancer, derived from activated or genetically altered epidermal melanocytes. Human malignant melanoma is a highly metastatic cancer that is markedly resistant to conventional therapy such as dacarbazine or TMZ. The RAF/MAP kinase pathway has attracted attention because activating mutations of the BRAF serine/threonine kinase has been detected in more than 50% of melanomas. Other mutations occur in NRAS, MEK1, MEK2 as well as c-Kit. Activation of c-Kit results in the stimulation of MAPK and PI3K/AKT pathways resulting in both proliferative and survival advantage. Several other signal transduction pathways have been found to be constitutively active or mutated in other subsets of melanoma tumors including NF-κB. Raf inhibitors in general and specific BRAF inhibitors, including vemurafenib, frequently elicit therapeutic response. However, durable effects are often limited by ERK1/2 pathway reactivation *via* poorly defined mechanism. Resistance to apoptosis using BRAF specific inhibitors is mediated, in part, by the presence of NRAS mutation and required switch in activation of RAF isoform, CRAF. Furthermore, rebound melanoma growth after initial treatment with BRAF specific inhibitors is associated with elevated activation of PI3K/Akt pathway.

It has been shown that the Bcl-2 positive regulator NF-κB is a key player in human melanoma tumorigenesis. Canonical NF-κB activation in melanoma cells is associated with increased survival and proliferation. In human melanoma, a number of NF-κB-dependent chemokines are constitutively expressed at high levels including CXC ligand 8 (CXCL8 or IL8), interleukin-8 [192], CXCL1, melanoma growth stimulatory activity or MGSA [193], CCL5 (regulated on activation), normal T expressed and secreted, or RANTES [194] and CCL2 (monocyte chemotactic protein-1), or MCP1 [195]. In late stages of metastatic melanoma, hyperactivated NF-κB inhibits pro-apoptotic pathways through the upregulation of (i) tumor necrosis factor receptor-associated factor-1 (TRAF-1) and TRAF-2 [196] to inhibit the TNF-R1/caspase-8-mediated pro-apoptotic pathway TRAIL decoy receptor, inhibiting the TRAIL-mediated cell-death pathway [197,198], and (iii) Fas-associated phosphatase-1 (FAP-1) [199], which down-regulates FAS-R trafficking from cytoplasm to membrane [200]. Furthermore, in late stage metastatic melanoma, activation of NF-κB also enhances several anti-apoptotic molecules such as inhibitor of apoptosis (IAP) [201], caspase-8 (FLICE) and inhibitory protein (FLIP) [202]. NF-κB also promotes Myc activity [203] and the cell cycle regulatory proteins, cyclin D1 and cyclin dependent kinase 2 (CDK2) [204], which further contribute to melanoma tumor growth.

More than 50% of melanoma cells harbor mutations in BRAF signaling protein [205]. BRAF is part of the Raf family of

serine/threonine kinases, which are effectors of the small GTPase RAS in the ERK/MAPK pathway. This pathway is activated by several membrane-bound receptors such as receptor tyrosine kinases and G-protein-coupled receptors. BRAF transduces signals through mitogen activated protein kinase (MAPK) [206,207]. MAPK promotes regulation of cell growth, survival and differentiation [208]. Canonical activation of the MAPK pathway occurs when growth factor-growth factor receptors bind which leads to the activation of a RAS family member, any of the three isoforms H, N, and K-RAS. Activated RAS then binds and activates multiple effector proteins, including the three Raf members (ARAF, BRAF and CRAF), leading to subsequent activation of a cascade of kinases including MEK1/2 and ERK1/2. Activated ERK in turn specifically phosphorylates a number of nuclear and cytoplasmic substrates including the ETS transcription factor, which has the net effect of providing a pro-growth and pro-survival signal [209]. Concurring with these assumptions, Erk1/2 signaling has been shown to protect melanoma cells against TRAIL-induced apoptosis by inhibiting the relocation of Bax from the cytosol to mitochondria and that this may reduce TRAIL-mediated release of Smac/DIABLO and induction of apoptosis.

9.3. Apoptosis resistance in pancreatic ductal adenocarcinoma

With mortality rates almost mirroring incidence rates, pancreatic ductal adenocarcinoma (PDAC) is among the most lethal of all cancers. It causes more than 170,000 deaths worldwide and is the fourth leading cause of cancer related deaths in the United States making it a deadly disease in urgent need for newer treatment approaches [210]. PDAC tumors are very heterogeneous and carry alterations in many critical pathways (harbor a robust biological network) rendering the design of therapy against a single pathway unrealistic [211]. The major reasons for this dismal outcome include, lack of early detection markers [212], invasive behavior [213] and intrinsic resistance to therapeutic treatments [214]. Recently, several studies have identified a highly resistant subset of PDAC cancer stem cells (CSCs) with self-renewal capacity and propensity to undergo epithelial to mesenchymal transition [215]. Additionally, the low clinical efficacy of different regimens in PDAC has been attributed to the lack of drug penetrance due to the presence of high desmoplastic stroma that supports a low tumor vasculature [216]. Thus, holistic studies are needed that identify effective regimen against PDAC CSCs, and key molecules that promote desmoplastic stroma in PDAC will provide biomarkers and potential targets to overcome chemo resistance and disease recurrence.

De-regulated apoptosis signaling mechanisms have been attributed as one of the major causes for the drug resistance. Pancreatic cancer has been shown to over-express Bcl-2 and its family members. Therefore, blockade of Bcl-2 activity should become a novel therapeutic strategy for pancreatic cancer. Many groups have been working to develop anticancer drugs that block the function of Bcl-2 members. Earlier Wang and colleagues have successfully demonstrated that targeted inhibition of Bcl-2 can suppress PDAC growth *in vitro* and *in vivo* [217]. Very recently, Abulwerdi et al., [32] exploited Mcl-1 as a therapeutic target using small molecule drugs in PDAC. Both these studies collectively prove that targeted inhibition of BH3 family proteins could be a viable therapeutic strategy against PDAC.

9.4. Apoptosis resistance in colon cancer

Colorectal cancer is among the common forms of cancer worldwide and ranks third among the cancer-related deaths in the US and other Western countries. It is common to both men and women, constituting 10% of new cancer cases in men and 11% in women. Despite recent advancement in therapeutics, the survival rates from metastatic are less than 5%. Growing evidence supports the contention that epithelial cancers including colorectal cancer, the incidence of which increases with aging, are diseases driven by the pluripotent, self-renewing cancer stem cells (CSCs). Dysregulation of Wnt, Notch, Hedgehog and/or TGF-β signaling pathways that are involved in proliferation and maintenance of CSCs leads to the development therapy resistance.

The loss of heterozygosity (LOH) at the bcl-2 gene locus and the expression of the bcl-2 gene has been examined in colorectal carcinoma cell lines and carcinoma tissues. LOH at the bcl-2 locus was detected in 60% (6/10) of colonic carcinomas, all of which were well differentiated adenocarcinomas, whereas LOH was not seen in poorly differentiated ones. Further, tree colorectal carcinoma cell lines, all of which were derived from poorly differentiated adenocarcinomas, expressed considerable levels of bcl-2 mRNA and protein. These results suggest that LOH at the bcl-2 locus is frequently associated with well differentiated adenocarcinomas of colon, and bcl-2 overexpression has implications for the development of poorly differentiated adenocarcinomas of the gastrointestinal tract.

Colon tumors have been shown to exploit the lymphocyte death program by expressing FasL [218]. This may enable colon tumors to mount a “Fas counterattack” against antitumor lymphocytes, impairing antitumor immune responses. FasL-expressing colon tumor-derived cell lines can trigger Fas-mediated apoptosis of co-cultured T cells *in vitro*. FasL expressed in esophageal cancer has been significantly associated with apoptosis and depletion of tumor-infiltrating lymphocytes (TIL) *in vivo*. FasL may also facilitate metastatic colonization of Fas-sensitive organs such as the liver, by inducing apoptosis of target organ cells. Normal colonic epithelial cells express Fas and are relatively sensitive to Fas-mediated apoptosis. By contrast, colon tumor-derived cell lines are usually resistant to induction of Fas-mediated apoptosis, and colon cancer cells frequently coexpress Fas and FasL. The mechanisms allowing resistance to Fas-mediated apoptosis are complex, and defects have been identified at several levels of Fas signal transduction. The “Bcl-2 rheostat” may be pitched against apoptosis in colon cancer, in as much as over-expression of Bcl-2, downregulation of Bak, and mutation of Bax are common defects in colon tumors. Caspase-1 is also downregulated in colon cancer. The high frequency of p53 mutations in late-stage cancers may also inhibit Fas signaling. Fundamental defects in apoptosis signaling may contribute to both immuno- and chemoresistance in colon cancer and allow expression of FasL to counterattack antitumor lymphocytes.

9.5. Apoptosis resistance in prostate cancer

With an estimated 233,000 new cases diagnosed and 29,480 deaths, prostate cancer is considered as the top major cause for cancer related deaths in the United States. Hormone ablation therapy is used to manage early stage disease, however, in majority of cases, prostate cancer becomes castrate resistant [219]. The disturbance in apoptosis pathway activation in prostate cancer therapy resistance has been clearly defined [220]. More specifically, Bcl-2 over-expression has been shown to promote androgen ablation resistance [221]. Aside from disturbed apoptotic machinery, a number of studies have demonstrated that lack of autophagy activation may also contribute to chemo- and hormone therapy resistance in prostate tumors [222,223]. Nevertheless, there are reports showing that autophagy pathway activation may even promote apoptosis resistance and this has been linked to therapy resistance of prostate cancer [224,225]. Therefore, it is needless to say that autophagy modulators have been shown to resensitize prostate cancer cells to radiation or chemotherapy [226,227]. Similarly, a number of Bcl-2 inhibitors have shown to reverse prostate cancer

chemoresistance [228,229]. Mcl-1 inhibition has also been shown to re-sensitize prostate cancer cells to different chemotherapeutics and targeted therapies [230–232]. Besides Bcl-2 and Mcl-1 over-expression, TRAIL induced apoptosis resistance in prostate cancer has also been reported [233]. The development of TRAIL resistance is both genetic and epigenetic [234] that manifests in apoptosis resistance. Collectively, these studies clearly prove that sensitivity to therapeutics (chemo-, hormone, radio- or targeted) is directly correlated to the presence of functional apoptotic machinery.

9.6. Apoptosis resistance in breast cancer

Breast cancer is the major cause for female cancer mortality in the western world (GLOBACON). Despite the advances in early detection and the greater understanding of the molecular pathways underlying breast cancer biology, a major fraction of patients have recurrent disease that becomes refractory to most of the available therapies [235]. Systemic therapies include the use of cytotoxic, hormonal, and immunotherapy is usually used in the adjuvant, neoadjuvant, and metastatic settings. While these systemic agents are active in the majority of primary breast cancers and also to a great extent in metastatic cases, nevertheless, after a variable period of time, progression occurs. Resistance to therapeutics in breast cancer is multi-factorial. It involves disturbances in the apoptotic machinery, p-glycoprotein and the multidrug resistance protein family, HER-2/neu gene amplification and protein expression, along with the expression of additional members of the epithelial growth factor receptor family, DNA ploidy, p53 gene mutations, cyclin E and p27 dysregulation that cumulatively drive the development of cancer stem cells [236]. A number of studies have linked breast cancer drug resistance to disturbed or over-expression of pro-survival factors including Bcl-1, Mcl-1 and other BH3 family members [237]. This is confirmed from the observation that BH3 mimetic ABT-737 can sensitize BH3 protein over-expressing breast cancer cells [238]. Studies have also linked disturbed proteasome signaling to breast cancer chemo and radio resistance [239]. These findings become particularly relevant as proteasome inhibitor bortezomib treatment causes suppression of MDRs leading to induction of apoptosis in breast tumor models [240]. In summary these studies prove that the inherent resistant traits of breast cancer are associated with malfunctioning of the apoptosis signaling. Targeting the different pathways that either induce apoptosis or suppress the pro-survival signaling is expected to resulting in overcoming drug resistance to various therapies.

9.7. Apoptosis resistance in leukemia's (focus on chronic lymphocytic leukemia and acute promyelocytic leukemia)

Chronic lymphocytic leukemia (CLL) is the most common B-cell malignancy in the Western world and is characterized by the accumulation of mature CD5 positive B lymphocytes in peripheral blood, bone marrow, and lymphoid organs [241]. CLL disease is generally associated to apoptosis resistance. A combination of alterations in the apoptotic machinery as well as micro-environmental survival signals within the CLL cells cause a cell death resistance. Recent studies suggest that most CLL clones include activated cells that proliferate at appreciable rates [242,243]. Thus, the balance between proliferation and cell death is extremely within patients and reflects the different disease progression [244].

In CLL, defects in the intrinsic and extrinsic apoptotic pathways have been described. B-cells can be resistant to both CD95/Fas [245] and TRAIL death receptors induction [246]. The intrinsic, or mitochondrial, pathway is regulated by the Bcl-2 family proteins, classified into anti-apoptotic (Bcl-2, Bcl-XL, Bcl-w, Mcl-1, A1) and pro-apoptotic (Bax, Bak, Bim, Bad, Bid, Hrk, Noxa, Puma) members [247]. In CLL the overexpression of anti-apoptotic proteins has implicated in resistance to apoptosis [248]. Aberrant expression of Bcl-2 is common in CLL patients and is associated with poor response to chemotherapy and decreased overall survival [249]. Moreover, Mcl-1 protein expression was correlated with adverse prognostic factors, such as disease stage, IgVH mutation status, ZAP-70 positivity and CD38 expression [250] and, was found to be predictive of the clinical outcomes of CLL patients [251,252]. In B-cells, several signals are involved in regulation of Bcl-2 family proteins, including BCR, cytokine signaling and microRNA. CD40 signaling has been suggested to trigger up-regulation of the anti-apoptotic proteins Mcl-1, A1 and Bcl-xL [253,254]. BCR signaling has been reported to be able to regulate Mcl-1, through hyper-activation of Akt [255] which also contributes to maintain cell survival by phosphorylating and inactivating the pro-apoptotic factor proteins Bad and Bim [256,257]. Given the key role that anti-apoptotic proteins play in CLL, they became an attractive target for the creation of novel therapeutic agents, such as anti-sense methodology [258], small molecules mimicking the action of BH3 domain [259], and microRNAs (mainly miRNA-15a and miRNA-16-1) [260]. For several decades, front-line therapy for CLL has been represented by treatment with alkylating agents and purine analogs [261]. Recently, significant clinical outcomes have been achieved using chemo-immunotherapy, such as rituximab, a chimeric monoclonal antibody against CD20, administrated in combination with fludarabine or fludarabine plus cyclophosphamide [262,263]. Nevertheless, the relapse remains problematic, particularly in older patients, thus the identification of innovative and specific agents against CLL remains of high interest [264].

Very interesting is the use of a cottonseed extract derivative, gossypol, which acts as a BH3-mimetic, interfering with the functions of Mcl-1, Bcl-2 and Bcl-xL proteins (from highest to lowest affinity) and displacing pro-death partners to induce apoptosis [265–267]. However, despite this encouraging data and the abundant literature describing the molecular mechanisms triggered by phytochemicals to inhibit cell growth and induce apoptosis in cancer cells, only few of them entered clinical trials [268].

Acute promyelocytic leukemia (APML or APL for short) is a subtype of acute myelogenous leukemia (AML). APL is characterized by an abnormal accumulation of immature granulocytes. The disease harbors chromosomal translocation involving the retinoic acid receptor alpha (*RARα* or *RARA*) gene and is distinguished from other forms of AML by its responsiveness to all-*trans* retinoic acid therapy. The role of Bcl-2 proteins in apoptosis resistance to retinoic acid therapy has been intensively investigated. It has been shown that the ability of retinoid-induced cells to undergo apoptosis depends on the level of expression and the functional interaction between Bcl-2 and Bax [269]. Highlighting its significance, autophagy and Beclin 1, an autophagic protein, were shown to be upregulated during the course of all trans retinoic acid (ATRA)-induced neutrophil/granulocyte differentiation of an APL-derived cell line. This induction of autophagy is associated with downregulation of Bcl-2 and inhibition of mTOR activity. Further, other studies have shown that a BH3 domain mimetic, JY-1-106, which antagonizes the anti-apoptotic BCL-2 family members B-cell lymphoma-extra large (BCL-xL) and myeloid cell leukemia-1 (MCL-1) alone and in combination with retinoids reduced cell viability in HL-60 APL cells alone and in combination with retinoids. The combination had the greatest impact on cell viability by stimulating apoptosis. These studies indicate that dual BCL-xL/MCL-1 inhibitors and retinoids could work cooperatively in APL.

10. Role of different natural compounds (phytochemicals) against apoptosis resistance

Since the early eighties, when apoptotic cell death appeared on the stage of molecular cancer field, scientists understood that

bypassing apoptotic resistance resulted in novel therapeutic solutions against cancer. These efforts successfully involved novel and canonical anticancer drugs, but also stimulated the interest to explore the possibility that natural compounds may re-sensitize tumor cells to pro-apoptotic drugs. However, many of the studies that followed have been limited to preclinical laboratory experiments (largely confined to cell lines). More importantly, it is difficult to figure out how molecules that are structurally and functionally different (*i.e.*, stability, bioavailability, biotransformation *etc.*) can behave similarly, and remove the resistance occurring in cancer cells to apoptotic induction.

It must be imagined that a unique mechanism, common to many phytochemicals, is responsible for their ability to re-establish the lost sensitivity to apoptosis. The well-known antioxidant capacity shared by the large majority of these compounds has been evoked to explain the experimental evidence. However, the "antioxidant hypothesis" is weakened by paradoxes and contradictions. In fact, the scavenging activity of the phytochemicals against ROS chemically converts them into oxidative products which display a high reactivity toward thiols and can lead to the loss of protein function. Therefore, paradoxically, the net result between protection offered by many phytochemicals and damage caused by its toxic products may weigh in favor of the latter. As an example, in lung cells, quercetin efficiently protects against H_2O_2-induced DNA damage, but this positive effect is counteracted by the reduction in GSH level, an increase in LDH leakage and cytosolic-free calcium concentration [270]. Quercetin may also form quercetin–quinone (QQ) species when the molecule is employed as an antioxidant. QQ, like other semiquinone radicals and quinones, is toxic because of its ability to arylate protein thiols. Protection against QQ may arise from GSH which, when present at the right concentration, quickly traps QQ [271]. Accordingly with this example, a pivotal review from Ursini's group explains how the major mechanism of action for nutritional antioxidants is the paradoxical oxidative activation of the Nrf2-Keap1 (nuclear factor erythroid 2-related factor 2-Kelch-like ECH associated protein 1) signaling pathway, since kinetic constraints indicate that *in vivo* scavenging of radicals by these compounds is ineffective in antioxidant defense [272].

Nonetheless, although this preamble illustrate a critical challenge in this area of research, recent studies have demonstrated that treatment with phytochemicals may represent an applicable therapeutic strategy to bypass apoptotic resistance in specific types of cancers [273,274].

Pleiotropy"' and "synergism" are two terms often associated to the effects of natural compounds to explain their multiple biological activities. The former refers to their ability to bind and interfere with the activity of several effectors that insist on one or more pathways, converging on the same cellular process, for example apoptosis, cell cycle arrest, autophagy. The latter indicates the property to enhance the efficacy of chemotherapeutic drugs in co-treatment protocols with the advantage to limit toxicity for patients. Both features, pleiotropy and synergism, find rationale applications in the physiopathology of cancer and is highly relevant to some specific diseases such as CLL, a form leukemia which remains indolent for decades. In fact, patients with CLL may survive for many years without any treatment because of the relatively slow progression rate of the disease. This feature makes CLL patients ideal models to test the pleiotropic properties of natural chemo-preventers possessing limited toxicity. In fact, in the temporal window during which patient's remains asymptomatic, chronic administration of a specific phytochemical may retard disease onset. Moreover, when the disease progresses to clinically relevant forms and requires pharmacological interventions, the same compound can be introduced in the therapeutic protocol as adjuvant to synergistically improve the efficacy of the therapy. Supplementation with biologically active phytochemicals or phytochemicals-enriched food may represent an important approach to modify the clinical progression of cancers. However, to move from speculation to clinical application, further fundamental steps are required, such as well designed, randomized, control clinical trials.

10.1. EGCG

Mechanistic studies suggest that polyphenols have multiple intracellular targets, one of which is the proteasome complex [275,276]. Several botanically derived agents such as green tea catechins, isoflavones, anthocyanins, anthocyanidins, quercetin (3,3′,4 5,7-pentahydroxyflavone), apigenin and curcumin have been identified as potent proteasome inhibitors, with a more favorable toxicity profile compared to velcade and bortezomib and may be ideal candidates for therapeutic applicability in cancer chemoprevention and treatment. The goal of this section is to focus on providing a model of a botanically derived agent green tea polyphenol that has been demonstrated to induce apoptosis through targeting of the ubiquitin/proteasome pathway.

Among the constituents of green tea extracts (GTE), laboratory studies have identified EGCG as the most potent chemopreventive agent which appears to affect a number of molecular processes including induction of apoptosis and inhibition of tumor growth and angiogenesis [277–280]. More recently EGCG has been found to affect several cancer-related proteins including p27, Bcl-2 or Bcr-Abl oncoproteins, Bax, matrix metalloproteinases (MMP-2 and MMP-9) [281], the androgen receptor, EGF receptor, activator proteins 1(AP1), and some cell cycle regulators [282–284]. Based on their studies of GTE in cell culture systems, Adhami et al. [285] were able to demonstrate that EGCG (in GTE) induces apoptosis, cell growth inhibition and cyclin kinase inhibitor WAF-1/p21-mediated cell cycle-dysregulation. Using cDNA microarrays, they also observed the EGCG treatment of prostate cancer cells results in induction of genes that functionally exhibit growth-inhibitory effects and repression of genes that belong to the G-protein signaling network. These data confirm that GTEs exert potent and selective *in vitro* and *in vivo* pro-apoptotic activity on prostate cancer cells. Although there are several mechanisms by which EGCG may operate in prostate carcinogenesis, EGCG has been demonstrated to potently and selectively inhibit the proteasome activity in intact human cells leading to the accumulation of IkB-α and p27 proteins, and growth arrest [286]. This inhibition of proteasome activity by EGCG occurred at or near physiological concentrations similar to that found in the body fluids of green tea drinkers. Other studies have shown that a mixture of green tea polyphenols (polyphenon E) is equally potent inhibiting the proteasome activity as purified EGCG [287]. Polyphenon E preferentially inhibits the proteasomal chymotrypsin-like activities over other activities; b. Polyphenon E inhibits proteasome activity in intact cells in a concentration-dependent manner. Treatment of polyphenon E, at all used concentrations in both cell lines, increased accumulation of the proteasome target protein p27Kip1 in human multiple myeloma and prostate cancer cells. Similar to purified EGCG, using a cell-free proteasome assay it has been shown that Polyphenon E significantly inhibits the chymotrypsin-like activity of the purified rabbit 20S proteasome with an IC_{50} value of 0.88 μM. To investigate whether polyphenon E specifically inhibits the proteasomal chymotrypsin-like activity, its effects on the PGPH-like and trypsin-like activities of the purified 20S proteasome were determined. Polyphenon E inhibited PGPH-like activity of the purified rabbit 20S proteasome with an IC_{50} value of 7 μM. The IC_{50} value for trypsin-like activity was above 100 μM, thus demonstrating that polyphenon E preferentially inhibits the proteasomal chymotrypsin-like activities over other activities. The most significant study analyzed the effect of 2 mg/diet of Polyphenon E

in a phase I/II clinical trial on asymptomatic CLL patients (Rai stage 0 to II). The results of the study indicated that in 69% of patients a substantial decline in absolute lymphocyte count (>20%) and/or reduction of lymphadenopathy (>30%) during the 6 months of active treatment [288,289]. Also flavopiridol, a semisynthetic flavonoidal alkaloid, originated from an Indian plant and known for its ability to inhibit cyclin-dependent kinases, achieved significant clinical activity in patients with relapsed CLL, including those with high-risk genomic features and bulky lymphadenopathy [290,291].

These data strongly suggest that the proteasome, an important large multi subunit protease complex in the cell, is a cancer-related molecular target of green tea catechins and that inhibition of the proteasome activity by EGCG may be the primary pathway by which tea catechins, specifically EGCG, induce prostate epithelial cell apoptosis. This appears to be accomplished *via* the proteasome inhibition pathway *i.e.*, IκB-α protein expression, accumulation of p27 proteins and decreasing NFκB DNA-binding activity, and resulting in the inhibition of prostate cell survival and the induction of apoptosis, thereby decreasing progression from HGPIN to prostate [292,293] – similar to the effects of bortezomib and velcade (PS-341) [294–296].

The proteasome has been proven to be an excellent target for developing anticancer drugs, but several side effects (including nausea, fatigue, diarrhea, peripheral neuropathy, rapidly reversible reduction in platelets, and reversible thrombocytopenia) have been observed with bortezomib. Therefore, it is necessary to identify less toxic proteasome inhibitors with similar potency to bortezomib or different novel proteasome inhibitors, as we have proposed in this study. Additionally, although it is clear that the ester carbon of EGCG is important for mediating the proteasome-inhibitory activity, EGCG is very unstable under physiological conditions. Therefore, a series of EGCG analogs are evolving that are aimed at improving stability and bioavailability of EGCG. Among them, peracetate-protected or the pro-drug of EGCG was found to have increased bioavailability, stability, and proteasome-inhibitory activities against various human cancer cells and tumors compared to EGCG, suggesting its potential use for cancer prevention and treatment [297]. The early laboratory and Phase I trials have demonstrated GTPs, specifically EGCG, have a completely different chemical structure from bortezomib. Most importantly, (−)-EGCG and other catechin mixtures at varying doses has been found to be relatively better tolerated in clinical trials, in contrast to the observed AEs seen in the bortezomib trials, and thus appear to have significant potential to be tested in clinical trials.

In green tea, the catechin EGCG has been extensively studied for the biological activities and cellular targets, among which the proteasome attracts more attention [277]. Both naturally-occurring (−)-EGCG and synthetic enantiomer (+)-EGCG are able to potently and specifically inhibit the chymotrypsin-like activity of proteasome β5 subunit in an irreversible way with IC_{50} range 86–194 nM *in vitro* and 1–10 μM *in vivo* [280]. Of note, EGCG is able to interact with not only the β5 subunit in constitutive proteasome but also the β5i subunit in interferon-γ inducible immunoproteasome (referring to as BrAAP activity) with even higher affinity [298]. Preclinical studies have demonstrated the chemosensitizing effect of EGCG and other catechins *in vitro* and *in vivo*. It has also been shown that EGCG reversed drug resistance by inhibiting the drug efflux transporter P-gp. For example, Kitagawa et al. [299] reported that catechins increased the cellular accumulation of P-gp substrates in human cervical epidermal carcinoma cells. The chemosensitization by EGCG through the inhibition of P-gp expression/activity has also been validated in Caco-2 human intestinal adenocarcinoma cells (which are often used as a model for intestinal transport studies mediated by P-gp) [300] and tamoxifen-resistant MCF-7 human breast cancer cells [301], as well as in the xenograft mouse models using doxorubicin-resistant KB-A1 cells [302] or doxorubicin-resistant BEL-7404/DOX hepatocarcinoma cells [303]. The study with tamoxifen-resistant MCF-7 cells also found that EGCG was able to inhibit the activity of the BCRP transporter [304]. EGCG was also reported to enhance the sensitivity of glioblastoma to temozolomide, and of prostate carcinoma to doxorubicin [305], and of breast carcinoma to paclitaxel [306] in corresponding ectopic or orthotopic xenograft mouse models. Furthermore, the peracetate-protected prodrug of EGCG also exhibited a chemosensitizing effect in the treatment of leukemia cells by augmenting the efficacy of conventional chemotherapy daunorubicin and cytosine arabinoside [307]. A very recent study reported that polymer-based nanoparticle of polyphenols EGCG and theaflavin retained biological effectiveness with over 20-fold dose advantage than EGCG/theaflavin in exerting anti-cancer effects and also enhanced the potential of cisplatin in several different tumor cell types [308].

Encouraged by the preclinical results, a few studies were conducted using green tea extract (GTE) as monotherapy or a complementary/alternative medicine (CAM) in cancer patients. Although its anticancer activity was unsatisfactory, the oral consumption of GTE was well tolerated in these studies [309–311]. After a temporary suspension of EGCG in clinical trials by the US Food and Drug Administration (FDA) for additional review of toxicity, a tea extract named polyphenon E further proved the safety of tea polyphenols. In a polyphenon E phase I clinical trial in patients with asymptomatic Rai stage 0 to II chronic lymphocytic leukemia, most patients showed declines in absolute lymphocyte count and/or lymphadenopathy after daily oral consumption of Polyphenon E. A phase II trial using 2 g polyphenon E twice a day to evaluate its efficacy showed that it was well tolerated by patients with CLL and durable declines in the absolute lymphocyte count and/or lymphadenopathy were observed in the majority of patients [288]. Furthermore, two clinical studies using polyphenon E in combination with erlotinib are currently ongoing in patients with advanced non-small cell lung cancer and premalignant lesions of the head and neck, respectively. The chemosensitizing effect of polyphenon E in clinical settings remains to be determined. The *in vitro* and *in vivo* studies suggest that tea polyphenols (especially EGCG) may serve as powerful agents for reversing tumor drug resistance and enhancing the efficacy of chemotherapy.

10.2. Resveratrol

Isolated from the skin of red grapes, resveratrol received much attention due to its association with the French Paradox (*i.e.*, the observation of low coronary disease incidence in high fat diet consuming French population who consume Red Wine-a supposedly major source of resveratrol). Later on a number of laboratories have demonstrated the anti-cancer activity of resveratrol in multiple tumor models. Studies have since shown that resveratrol can reverse apoptosis resistance and also sensitize cancer cells to different apoptosis inducing agents (chemotherapeutics). For example, Sprouse and Herbert [312] very recently demonstrated that resveratrol can augment paclitaxel treatment in paclitaxel resistant breast cancer cell line models. In another study Huq and colleagues [313] showed that resveratrol can overcome chemoresistance in ovarian cancer. In nasophyrangeal carcinoma, resveratrol has been shown to cause expansion of ER, and ER caspase mediated apoptosis [314]. Similarly, it was demonstrated that resveratrol sensitizes tamoxifen in estrogen receptor resistance breast cancer models that show epithelial-to-mesenchymal transition [315]. In a glioma model, resveratrol was shown to suppress X linked inhibitor of apoptotic proteins [316]. While Díaz-Chávez [317] utilized a proteomic approach to investigate the mechanism of resveratrol mediated chemosensitization and highlighted the role of hsp27 (at least in the model they tested).

Other studies support the apoptosis and necrosis inducing effects of resveratrol in different cancer models. Aside from resveratrol, studies have also focused on its biological analog piceatannol as well. For example, Farrand and colleagues [318] demonstrated that piceatannol enhances cisplatin sensitivity in ovarian cancer *via* modulation of p53, X-linked inhibitor of apoptosis protein (XIAP), and mitochondrial fission. Several natural compounds have been employed to assess their anti-apoptotic effects in *in vitro* models of CLL. For example, resveratrol (3,4′,5-trihydroxystilbene), a phytoalexin well known for its healthy properties, induced apoptosis in WSU-CLL cells (derived from a CLL patient resistant to fludarabine) and in B cells isolated from CLL patients; instead, normal peripheral blood mononuclear cells were slightly affected. The effect of this compound, used at 10–50 μM concentration, was correlated to a down-regulation of two anti-apoptotic proteins, inducible nitric oxide synthase and Bcl-2 [319,320]. Recently, it has been reported that oral administration of resveratrol (5 g/day) for 4 weeks, to three CLL patients, decreased circulating white blood cell counts and directly lowered O-linked β-N-acetylglucosamine (O-GlcNAc) levels in leukemic cells through proteasomal activation; this is an interesting result considering that CLL cells are characterized by high levels of proteins that are post-translationally modified by O-GlcNAc moieties [321]. Resveratrol, in combination with quercetin, induced apoptosis and cell cycle arrest in G0/G1 in human 232B4 cell line derived from CLL [322]. Collectively, these studies very clearly demonstrate that grape derivative resveratrol and its analogs can either induce apoptosis by themselves or can sensitize resistant cells to apoptosis inducers.

10.3. Curcumin

Curcumin, which is the major component of turmeric has been used in folklore medicine for centuries. The first reports on anticancer activity of curcumin were reported in 1985 [323]. Since then more than 3000 studies have been reported on the different anti-cancer mechanisms of curcumin and related analogs (numbers from PubMed search). Numerous studies have shown the apoptotis inducing effects of curcumin and analogs in cancer cell lines (the readers are referred to several outstanding reviews in the literature [324]).

In primary B-CLL cells curcumin induced apoptosis with a mean EC_{50} of 5.5 μM, fourfold lower than the EC_{50} observed in normal mononuclear cells (21.8 μM). The molecule blocks NF-κB signaling, probably through inhibition of IκB [325]. Some authors observed an induction of apoptosis in primary B-cells using curcumin in association with other natural compounds, such as rapamycin and EGCG. In the former case, the effect was associated with a decreased expression of Bcl-2 and an increased level of the pro-apoptotic factor Bax [326]. Sequential administration of curcumin and EGCG led to a substantial increase in B-cells death, overcoming stromal protection [327,328]. These are some examples showing the potency of curcumin in overcoming resistance to apoptosis. The synergism shown by curcumin with other natural compounds need to be examined in greater details in order to move these combinations in clinical studies.

10.4. Quercetin

Quercetin a phytochemical found in a broad range of fruits, vegetables and beverage, is widely known for its antioxidant, anti-inflammatory, anti-proliferative and apoptotic effects both in cell culture and animal models [329,330]. Quercetin at relatively low concentrations (10–20 μM) is able to down-regulate Mcl-1 and thus sensitize to apoptosis the B-cells isolated from CLL patients [331,332], with the maximal effect observed in combined treatments with apoptotic inducers (see below). Moreover, recent studies have reported that quercetin affects Hh, Wnt, as well as Notch signaling, emphasizing the potential efficacy of the molecule against CLL [333].

10.5. Isothiocyanates

Several studies have documented the cancer-preventive activity of many isothiocyanates (ITCs), occurring in cruciferous vegetables. They produce their anticancer effects through distinct but interconnected signaling pathways [334]. Sulforaphane, a well-studied ITC, restored chemosensitivity to DOX in mouse fibroblasts with p53 mutated at codon 220 [335]. The clinical pattern observed for the above reported mutation sustains a strong oncogenic potential and a lack of chemotherapy response. Sulforaphane was able to increase the efficacy of DOX, allowing its administration at levels within the concentration range clinically achievable [336]. The mechanism by which Sulforaphane reversed DOX resistance involves a rapid depletion of glutathione that renders cells more susceptible to DOX-induced oxidative stress, stress-induced damage, and apoptosis induction. The same study has shown that, pre-treatment with *N*-acetyl-cysteine, a glutathione precursor, prevented Sulforaphane plus DOX-induced apoptosis. Since the clinical doses of DOX currently being used during therapy are associated with severe cardiotoxicity [337], Gupta et al. [338] analyzed the ability of phenylethyl ITC (PEITC) to enhance the cytotoxic effects of low (sub-toxic) concentrations of DOX in human breast carcinoma cells stably transfected with the oncogene HER2. PEITC increased the cytotoxicity of DOX. Moreover, DOX treatment suppressed HER2 expression modestly, whereas the combination of PEITC with DOX markedly decreased the expression of HER2 and the phosphorylation of STAT3, known to play a critical role in the expression of cell proliferative pathways [339]. Consistently, combination treatment showed increased cleavage of caspase 3 and PARP as compared to individual treatment indicating apoptosis. In colorectal cancer cells, co-administration of Sulforaphane potentiated the growth inhibition activity of oxaliplatin through a reduction of intracellular ATP levels, activation of caspase-3, DNA fragmentation, and PARP cleavage [340]. Cisplatin was also tested in combination with PEITC in endometrial cancer cells [341] or with BITC in leukemia cells [342]. The combination therapy induced an increase in caspase-3 activity and increased levels of cleaved PARP. Such effects were not cell-specific since these results could also be observed in breast cancer cells. The sensitization induced by ITCs was partly mediated by ERK and Noxa activation. Interestingly, no effect was found in normal breast cells or lymphocytes.

ITCs also enhanced the efficacy of cisplatin when used against human non-small cell lung cancer cells [343]. Neither cellular platinum accumulation nor DNA platination accounts for this effect. Protein binding is important for the induction of apoptosis by ITCs [344]. ITCs covalently modify cysteine residues in tubulin, resulting in tubulin conformational changes, disruption of microtubule polymerization, and ultimately apoptosis. Tubulin-binding agents such as paclitaxel are commonly used in combination with platinum drugs to treat non-small cell lung cancer [345]. Thus, β-tubulin depletion may correlate and be important for sensitization to platinum compounds by ITCs.

Taken together, the evidence reported above indicates that EGCG and ITCs have an enormous potential for enhancing tumor cell sensitivity to therapy. However, some recent results sound a cautionary note. EGCG and ITCs are able to increase Nrf2 expression [346], a key transcription factor inducing a cytoprotective gene array. Since many standard chemotherapeutic agents are cytotoxic, their cytotoxic effects can be abrogated by tumor cells by upregulation of Nrf2 signaling, thereby yielding a more aggressive tumor [347]. Even if pharmacologic induction of Keap1–Nrf2-signaling axis allows for pulsed rather than permanent induction [348],

further studies are necessary before suggesting the use of EGCG or ITCs in patients with established cancers who are undergoing chemotherapy treatment.

10.6. Marine derived agents with apoptosis inducing properties

Aside from different plant derived natural products, nature has bestowed many other types of anti-cancer compounds from marine sources as well. A key word search on 'Marine anticancer agents' reveals more than 3000 hits in PubMed. Many of these studies directly point to the apoptotic inducing potential of marine derived compounds in cancer cell lines and animal xenograft models [349–358]. For those seeking additional detail in this area, we refer the reader to an excellent literature review on the topic [359].

In summary, there is ample laboratory and early phase clinical evidence demonstrating that natural agents (both plant and marine derived) can impact important signaling pathways associated with apoptosis. However, a lot remains to be learned on their exact mechanism of action especially in relation to overcoming resistance to apoptosis. Further studies on these agents are anticipated to enhance our knowledge that in turn will drive their rapid clinical use in combination with standard chemotherapeutics or targeted therapies against therapy resistant cancers.

11. Broad spectrum approach to obtain synergies between various different approaches

Given that the heterogeneity that is present in most cancers, it is our assumption that the complete arrest of the various subpopulations of immortalized cells in any given cancer will require simultaneous actions on mechanisms that are important for several aspects of cancer's biology. We therefore believe that it is important to be able to anticipate synergies that might be achieved by acting on specific targets and with specific approaches (*i.e.*, when contemplating an approach aimed at a broad-spectrum of targets). Accordingly, in this review, we also explored cross-hallmark relationships that have been found between the prioritized target sites and the approaches that we identified in this review.

Specifically, when evidence in the literature showed that the targets and approaches that we identified as relevant for apoptosis resistance were also therapeutically relevant for other aspects of cancer's biology (*i.e.*, anti-carcinogenic) we noted them as having "complementary" cross-hallmark effects. While those that were found to have pro-carcinogenic actions were noted as having "contrary" effects. In instances where reports on relevant actions in other aspects of cancer biology were mixed (*i.e.*, reports showing both pro-carcinogenic potential and anti-carcinogenic potential), the term "controversial" was used. Finally, in instances where no literature support was found to document the relevance of a target site or approach in a particular aspect of cancer's biology, we documented this as "no known relationship". These validation results are shown below in tabular form in Tables 1 and 2.

It is predicted that future cancer therapeutics will be based on network pharmacology strategies that will likely involve empirical testing of mixtures of constituents. Therefore, we wanted to create a starting point for other researchers who might be considering translational projects. We anticipated interest in approaches reported to exhibit a large number of anti-carcinogenic actions across the hallmarks and we anticipated that a lack of pro-carcinogenic potential might be important to identify in advance (since targets or approaches that have been shown to exert pro-carcinogenic actions would potentially represent a confounding and unwanted influence/factor in empirical research).

Our cross validation exercise showed that in some instances, the underlying evidence used to support the indication of a

Table 1
Relationships between resistance to apoptosis targets and cancer hallmarks.

Targets related to resistance to apoptosis	Inhibit Bcl-2	Inhibit Mcl-1	Activate tumor autophagy	Activate tumor necrosis	Inhibit hsp90	Inhibit proteasome	Inhibit nuclear exporter CRM1
Other cancer hallmarks							
Genomic instability	0	0	0	0	0	0	0
Sustained proliferative signaling	+ [360,361]	+ [32,362]	+/– [363,364]	+/– [365,366]	+ [367,368]	+ [369,370]	+ [141]
Tumor promoting inflammation	+ [371,372]	+ [373,374]	– [375,376]	+/– [377,378]	+ [379,380]	+ [381–383]	0
Evasion of Anti–growth Signaling	+ [384–386]	+ [237,387]	+ [388]	+ [389]	+ [390,391]	+ [392,393]	+ [394]
Replicative immortality	+/–[395,396]	+ [362]	+/– [397–399]	+/– [400]	+ [401,402]	+ [403,404]	0
Dysregulated metabolism	+ [405–407]	+ [408–410]	+ [411–413]	+ [414–417]	+ [418–420]	+ [421]	0
Immune system evasion	+ [422]	+ [423]	0	+ [424]	0	+ [425–427]	0
Angiogenesis	+ [428]	+ [429]	+/– [430]	– [431]	+ [432]	+ [433]	+ [434]
Tissue invasion and metastasis	+ [435]	+ [436]	+ [437,438]	+ [439]	– [440,441]	+ [442]	+ [443]
Tumor microenvironment	+ [444,445]	+ [444]	+/– [446,447]	– [448]	+ [449]	+ [450]	+ [451]

Prioritized targets were evaluated for known effects in other cancer hallmark areas. Targets that were found to have complementary, anti-carcinogenic actions reported in another hallmark area were indicated with "+", while targets that were found to have pro-carcinogenic actions in another hallmark area were indicated with "–". In instances where reports on relevant actions in other hallmark areas were mixed (*i.e.*, reports showing both anti-carcinogenic potential and pro-carcinogenic potential), the symbol "+/-" was used. Finally, in instances where no literature support was found to document the relevance of a target in a particular aspect of cancer's biology, we documented this as "0". These cross-hallmark relationships are reported in the upper rows of the table.

Table 2
Relationships of the approaches to different cancer hallmarks.

Approaches	Gossypol	EGCG	UMI-77	Triptolide	Selinexor
Other cancer hallmarks					
Genomic instability					
Sustained proliferative signaling	0	+[452,453]	0	0	0
Tumor promoting inflammation	+[454,455]	+[456,457]	+ [32]	+[458,459]	0
Evasion of anti-growth signaling	+[460,461]	+[462,463]	0	+[464,465]	0
Replicative immortality	+[466,467]	+[468–470]	+ [32]	+ [471]	0
Dysregulated metabolism	+[472,473]	+[474,475]	0	+ [476]	0
Immune system evasion	+ [477]	+ [478]	0	+[479–481]	0
Angiogenesis	0	+[482,483]	0	– [484]	0
Tissue invasion and metastasis	+ [454]	+ [485]	0	+ [486]	0
Tumor microenvironment	+ [487]	+ [488]	+ [32]	+[489,490]	+[491,492]
	+ [493]	+[483,494]	+ [32]	+[495,496]	+ [497]

Selected approaches were evaluated for reported actions in other cancer hallmark areas. Approaches that were found to have complementary, anti-carcinogenic actions in a particular hallmark area were were indicated with "+", while approaches that were found to have pro-carcinogenic actions in a particular hallmark area were indicated with "–". In instances where reports on relevant actions in other hallmarks were mixed (*i.e.*, reports showing both anti-carcinogenic and pro-carcinogenic potential), the symbol "+/-" was used. Finally, in instances where no literature support was found to document the relevance of an approach in a particular aspect of cancer's biology, we documented this as "0". These cross-hallmark relationships are reported in the upper rows of the table.

cross-hallmark relationship was robust, consisting of multiple studies involving detailed *in vitro* and *in vivo* findings. In other instances, however, the underlying evidence that was used to report the existence of a cross-hallmark relationship was quite weak (*e.g.*, consisting of only a single *in vitro* study involving a single cell-type). Additionally, there are examples of approaches that are known to exert different effects at different dose levels and in different tissues but dose-levels and cell/tissue types were not used to discriminate when gathering together these reported actions. Nonetheless, given that the overarching goal in this project was to create a foundation that would allow researchers to look systematically across the literature in each of these areas, the tables should serve as a useful starting point as long as they are approached with caveats in mind and a degree of caution. Essentially, we believe that this heuristic should be useful to consider synergies that might be anticipated in testing that involves certain targets and/or mixtures of chemical constituents that are being considered for therapeutic effects.

12. Conclusions and future directions

Resistance to apoptosis is multi-factorial involving the interaction of various signaling pathways at multiple levels. Therefore, the use of single pathway targeted agents to commit cancer cells to undergo apoptosis is not a feasible strategy (except in isolated cases). Hence, this requires a careful selection of treatment strategies that are based on a comprehensive understanding of the biological networks involved in resistance. This article presents some of the major genetic and epigenetic drivers of apoptosis resistance and provides a list of prioritized targets and the approaches that can be utilized against them to overcome *de novo* or acquired resistance. In this review, first we discussed how Bcl-2 family proteins play critical role in the biology of apoptosis activation/resistance. We presented knowledge on the development of agents such as gossypol and synthetic compounds particularly ABT-737 that have entered clinical trials. Additionally, we also highlighted problems associated with Bcl-2 inhibition and the development of resistance by one of its family member Mcl-1 making it an attractive target. In this direction, specific drugs against Mcl-1 are being investigated in the pre-clinical setting and some of these agents are expected to enter clinical evaluation in the near future. Additional cell death mechanisms such as autophagy and necrosis were also discussed and strategies, particularly the use of natural agents such EGCG were highlighted. The role of chaperone protein hsp70 in apoptosis resistance was evaluated and suggestions to overcome this critical protein marker using natural products were presented. The article also discusses the molecular mechanisms that support the resistance to apoptosis in different cancers such as glioblastoma, multiple myeloma, CLL, prostate cancer, breast cancer, colon cancer and pancreatic cancer. The role of epigenetic players, particularly miRNAs, in the development of apoptosis resistance was also highlighted. The cross-validation tables (Tables 1 and 2) are offered here as a simple heuristic framework that is intended to help researchers approach the topic of anticipated synergies. Although, these attempts do not represent a homogenous set of underlying data, it is hoped that it can serve as a starting point for the translational research that will be needed for the design of effective natural product based therapies. Rigorous experimentation will obviously be needed to determine whether or not actual synergies between the identified approaches emerge that can be predicted and clinically applied. A much broader range of targets overall may be the only chance we will have to address cancer associate heterogeneity. It is a promising approach, but a considerable amount of encompassing research needs to follow to determine methodological validity. Collectively, these unique targets and specific strategies may bring forward a broad form of therapy to overcome resistance to apoptosis resulting in better treatment outcome in patients suffering from cancer.

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