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REVIEW

Disruptive environmental chemicals and cellular mechanisms that confer resistance to cell death

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Abstract

Cell death is a process of dying within biological cells that are ceasing to function. This process is essential in regulating organism development, tissue homeostasis, and to eliminate cells in the body that are irreparably damaged. In general, dysfunction in normal cellular death is tightly linked to cancer progression. Specifically, the up-regulation of pro-survival factors, including oncogenic factors and antiapoptotic signaling pathways, and the down-regulation of pro-apoptotic factors, including tumor suppressive factors, confers resistance to cell death in tumor cells, which supports the emergence of a fully immortalized cellular phenotype. This review considers the potential relevance of ubiquitous environmental chemical exposures that have been shown to disrupt key pathways and mechanisms associated with this sort of dysfunction. Specifically, bisphenol A, chlorothalonil, dibutyl phthalate, dichlorvos, lindane, linuron, methoxychlor and oxyfluorfen are discussed as prototypical chemical disruptors; as their effects relate to resistance to cell death, as constituents within environmental mixtures and as potential contributors to environmental carcinogenesis.

Abbreviations

AIF	apoptosis-inducing factor
APAF	apoptosis-activating factor-1
BH	BCL-2 homology
BPA	bisphenol A
CAR	constitutive androstane receptor
CDK	cyclin-dependent kinase
CSCs	cancer stem cells
DBP	dibutyl phthalate
DD	death domain
DDT	dichlorodiphenyltrichloroethane
DEHP	diethylhexyl phthalate
DISC	death-inducing signaling complex
4EBP1	4E binding protein 1
EGFR	epidermal growth factor receptor;
ERK	extracellular signal-regulated kinase
FADD	Fas-associated death domain protein
FLIP	FADD-like apoptosis regulator
GJIC	gap junctional intracellular communication
IAP	inhibitor of apoptosis protein
JNK	C-Jun N-terminal kinase
LH	luteinizing hormone
MDM2	murine double minute 2
mRNA	messenger RNA
mtDNA	mitochondrial DNA
mTOR	mammalian target of rapamycin
MXC	methoxychlor
NADPH	nicotinamide adenine dinucleotide phosphate
NF- κ B	nuclear factor- κ B
PI3K	phosphoinositide 3-kinase;
PIDD	TP53-induced protein with death domain
PP	peroxisome proliferators
PPAR- α	peroxisome proliferator-activated receptor- α
PTEN	phosphatase and tensin homolog
PXR	pregnane X receptor
RAIDD	RIP-associated Ich-1/Ced-3-homologue protein with a death domain
RB	retinoblastoma
RIP	receptor-interacting protein
ROS	reactive oxygen species
RTK	receptor tyrosine kinase
SMAC	second mitochondrial activator of caspases
TGF- β	transforming growth factor- β
TNF	tumor necrosis factor
TP	tumor protein
TRADD	TNF receptor-1-associated death domain
TRAIL	TNF-related apoptosis inducing ligand receptor
XIAP	X-linked inhibitor of apoptosis protein

Introduction

Cancer death is one of the major causes of mortality worldwide. According to the World Health Organization, there were ~32.6 million cancer patients in the world in 2012 (http://www.iarc.fr/en/media-centre/pr/2013/pdfs/pr223_E.pdf). The projected figures show that this year alone >14 million new cancer cases will be diagnosed and ~8.2 million cancer estimated deaths within 5 years of diagnosis 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 (http://www.iarc.fr/en/media-centre/pr/2013/pdfs/pr223_E.pdf). In all cancers, an abnormal and ongoing division of damaged/dysfunctional cells initially leads to the formation of a tumor (initiation), where the immortalized cells that have avoided cell death continue to proliferate in an unregulated manner (progression) and then ultimately invade other tissues at later stages in the disease (metastasis).

The immortalized cellular phenotypes that emerge in most cancers have largely avoided cell death, which can be defined as a terminal failure of a cell to maintain essential life functions, and can be classified according to its morphological appearance, as apoptosis, necrosis, autophagy or mitotic catastrophe. During cell death, numerous enzymes and signaling pathways are modulated [nucleases, distinct classes of proteases (e.g. caspases, calpains, cathepsins and transglutaminases, protein binding signaling intermediates and so on)], which can exhibit immunogenic or non-immunogenic responses (1). Tumor cells are genetically programmed to undergo apoptotic and non-apoptotic death pathways (e.g. necrosis, autophagy, senescence and mitotic catastrophe). Normally, apoptotic resistance is rendered by the up-regulation of antiapoptotic molecules and the down-regulation, inactivation or alteration of pro-apoptotic molecules. However, dysfunction in these cell-death pathways is associated with initiation and progression of tumorigenesis. An increased resistance to apoptotic cell death (involving the inhibition of both intrinsic and extrinsic apoptotic pathways) is therefore an important hallmark for cancer cells.

Several tumor suppressor proteins, such as TP53, recognize DNA damage and activate DNA repair processes. Irreparable DNA damage can induce apoptosis and prevent neoplastic transformation (2) and can also trigger cellular senescence of transformed cells. Regulation of apoptosis is influenced by BCL-2 family members of pro-apoptotic and antiapoptotic factors, death receptors and the caspase network. Alterations of proto-oncogenes, tumor suppressor genes and de-regulation in epigenetic factors such as microRNAs are potent causes of cancer growth. Proto-oncogenes encode proteins that stimulate cell proliferation, inhibit apoptosis or both. They are classified

into six broad groups: transcription factors, chromatin remodelers, growth factors, growth factor receptors, signal transducers and apoptosis regulators. Normally, they are activated by genetic alterations (e.g. mutations or gene fusions, amplification during tumor progression or by juxtaposition to enhancer elements into an oncogene) (3–5). These genetic changes can alter oncogene structure or increase/decrease its expression. Similarly, tumor suppressor genes, which are involved in DNA repair, regulation of cell division (cell cycle arrest) and apoptosis, when mutated or inactivated by epigenetic mechanisms can cause cancer (4,5).

In this review, we discuss these mechanisms, their relationship to resistance to apoptosis and the importance of this hallmark characteristic of cancer as a potential enabler of environmental carcinogenesis. In 2011, a non-profit organization called Getting to Know Cancer launched an initiative called 'The Halifax Project' with the aim of producing a series of overarching reviews to assess the relevance of biologically disruptive chemicals (i.e. chemicals that are known to have the ability to act in an adverse manner on important cancer-related mechanisms) for carcinogenesis. To that end, our team was specifically tasked to review the hallmark of cancer 'resistance to cell death' and its relationships to other hallmarks of cancer. We were also tasked to identify a list of important, prototypical target sites for chemical disruption and a corresponding list of environmental chemicals that have been shown to have the potential to act on these targets. Ultimately, this review was not intended as a means to implicate specific chemicals in environmental carcinogenesis. Rather we undertook this review to explore what is known on this topic to provide a basis for further discussion of this idea and to help us identify future research needs.

To begin, we offer a brief review of several key mechanisms and pathways that are related to resistance to cell death. Specifically, we highlight apoptotic pathways, necrosis and necroptosis, the role of autophagy and the relationship that these mechanisms and pathways have with cancer (Table 1). For those who are seeking more in-depth treatment of these topics, several recent reviews can provide additional information (6,7). In doing so, we also focus on a number of important mechanisms and pathways that are relevant for disruption [i.e. binding to estrogen receptor α (ER α), P53, ErbB-2/HER-2 tyrosine kinase, extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK), MAP kinase, P16/P53, BCL-2/P53, peroxisome proliferator-activated receptor- α (PPAR- α), gap junctional intracellular communication (GJIC), hypersecretion of luteinizing hormone (LH) by gonadotroph cells in pituitary gland]. This list of target sites is not intended to be comprehensive. Other targets exist, including well-known mechanisms such as ALK, CD20/22/79b, MDM2, PD-L1, VEGF, HER receptors, BRAF, Rho-associated protein kinase, fibroblast growth factor-9, cathepsins, cyclooxygenases, prostaglandins and so on. We selected these targets because each of them are actively involved in resistance to cell death and all of them have been shown to be of considerable importance.

Apoptotic pathways

The extrinsic pathway: death receptor-mediated apoptosis

Receptor-mediated pathways are initiated by death ligands that bind to their specific death receptors, which include TNF-receptor 1, Fas/CD95 and TNF-related apoptosis-inducing ligand (TRAIL) receptor (8). All of these receptors contain the death domain, which is essential for the transduction of an apoptotic signal. After death ligands bind to their receptors, adapter molecules including Fas-associated death domain (FADD) or TNF receptor-1-associated death domain (TRADD) recruit the procaspase-8 for forming the death-inducing signaling complex. This

leads to the initiation of the caspase cascade through activation of CASP-8 or -10, followed by subsequent activation of executive caspases such as CASP-3 and -7, and an irreversible commitment to apoptosis (9).

The intrinsic pathway: mitochondria-mediated apoptosis

Mitochondria play a pivotal role in cell survival as well as in apoptotic cell death, and defects in mitochondrial function might contribute to cancer initiation and progression. The mitochondria-mediated intrinsic pathway is initiated by various stimuli, such as high cytoplasmic Ca²⁺ levels, reactive oxygen species (ROS), ultraviolet irradiation, viral infections or xenobiotics (10). Mitochondrial control of apoptosis is evolutionary conserved and tightly regulated by the BCL-2 proteins divided into 20 pro-apoptotic and antiapoptotic members, which share conserved BCL-2 homology (BH) domains. The antiapoptotic members (BCL-2, BCL-X_L, BCL-w, MCL-1, BCL-B) exhibit four BH domains (BH1-4). The pro-apoptotic members are categorized as BH3-only proteins (BAX, BAK, BIK, BAD, BIM, HRK, BCL-G HRK/DP5, NOXA and PUMA/BPC3), as reviewed in ref. 11. In normally proliferating cells, the pro-apoptotic BH3-only proteins are sequestered away from the antiapoptotic BCL-2 proteins. Although the antiapoptotic members such as BCL-2, BCL-X_L or BCL-w are integral proteins of the outer mitochondrial membrane, the pro-apoptotic BCL-2 members are located predominantly in the cytoplasm. After an apoptotic signal, the free pro-apoptotic BH3-only proteins associate with BCL-2 on mitochondria. Additionally, pro-apoptotic BAX and BAK undergo conformational changes leading to homo- or oligo-merization at the mitochondrial outer membrane (12). Consequently, this leads to a mitochondrial outer membrane permeabilization, the decisive event that delimits the frontier between survival and death. Upon apoptosis induction, the voltage-dependent anion channel protein plays a critical role in the dissipation of mitochondrial transmembrane potential (13,14). After mitochondrial membrane disruption followed by osmotic swelling, soluble pro-apoptotic mitochondrial intermembrane space proteins like cytochrome c, apoptosis-inducing factor, endonuclease G, second mitochondrial activator of caspases (SMAC/DIABLO) and OMI/HTRA2 are released into cytosol resulting in activation of intrinsic apoptotic signaling cascades. The released cytochrome c, along with apoptosis-activating factor-1 (APAF-1) and procaspase-9, form the cytosolic apoptosome complex, which leads to the activation of CASP9, and in turn triggers the caspase cascade, resulting in apoptotic cell death (15,16). However, inhibitor of apoptosis proteins (IAPs) can directly bind to CASP-3, -6 and -7 and antagonize their proteolytic activities. In contrast, IAPs are inactivated, and caspase activity restored by proteins released from the mitochondria, such as SMAC/DIABLO or HTRA2/OMI (17). The intrinsic pathway might also operate independently of the caspase cascade by utilizing the release of the apoptosis-inducing factor and endonuclease G from mitochondria, and their translocation to the nucleus. Apoptosis-inducing factor is linked to chromatin condensation and the high-molecular-mass chromatin fragments, and after nuclear translocation, endonuclease G elicits DNA fragmentation (15). Because mitochondria-mediated apoptosis plays a critical role in cancer development and in the cellular response to anticancer agents, the significance of mitochondrial DNA mutations in cancer is currently an important area of investigation (18) (Figure 1).

The novel PIDDosome-mediated apoptotic pathway

CASP2 was identified as the first apoptotic and the most conserved caspase (19). CASP2 was detected at various compartments in the cell including the nucleus, the Golgi apparatus,

Table 1. Characteristics of apoptosis, autophagy and necrosis pathways

	Morphological and biochemical features and modulators of cell death	Methods of detection
Apoptosis	Morphological features: cellular shrinking, condensation and margination of chromatin, nuclear fragmentation and DNA laddering, plasma membrane budding and formation of apoptotic bodies in cytoplasm. Not surrounded by tissue injury of inflammation. Biochemical features: caspase-dependent cell death pathway. Activation: activation of intrinsic apoptotic pathway; BCL-2, c-FLIP, survivin IAP-antisense mRNA technology; recombinant TRAIL for DR4 and/or DR5 receptor; E2F-1 gene therapy; TWEAK (tumor necrosis factor-related weak inducer of apoptosis) is a cytokine belonging to TNF-ligand family for Tweak-receptor inducing apoptosis. Inhibition: natural and synthetic inhibitors of caspases; nitrosylation of caspase 9 or 3; c-Jun-mRNA antisense technology; CEP 1347-inhibitor of JNK signaling blocks A β -induced cortical neuron apoptosis.	Microscopic techniques: cellular features by light microscopy, nuclear DNA analysis by fluorescent stains (annexin V), confocal laser microscopy and electron microscopy. Assessment of DNA fragmentation: enzyme-linked immunosorbent assay, terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling assay, comet method, DNA diffusion, immunohistochemistry for single-stranded DNA and gel electrophoresis. Flow cytometry: cell cycle. Laser scanning cytometry: DNA content, phosphatidylserine translocation, inner mitochondrial transmembrane potential and caspase activity. Gene expression: northern blot, RNA protection assay, reverse transcription-polymerase chain reaction and immunohistochemistry. Evaluation of apoptosis-associated proteins: enzyme-linked immunosorbent assay, western blot and electrophoretic mobility shift assay.
Autophagy	Morphological features: partial chromatin condensation, no DNA laddering, cell membrane blebbing and formation of more autophagosome. Biochemical features: caspase-independent cell death pathway. Activators: conventional cytotoxic drugs and irradiation; BCR-ABL tyrosine kinase inhibitor-imatinib; anti-EGFR-cetuximab; proteasome inhibitors; TRAIL and histone deacetylase inhibitors; mTOR inhibitors and its analogs; ATP-competitive inhibitors of mTORC1 and mTORC2; dual PI3K-mTOR inhibitor; antidiabetic drug-metformin; serotonin reuptake inhibitor-fluoxetine; norepinephrine reuptake inhibitor-maprotiline; antiepileptic drug-valproic. Inhibitors: antibody against EGFR-cetuximab; Class III PI3K inhibitors-3-methyadenine, wortmannin and LY294002; antimalarial drugs-hydroxychloroquine; vacuolar ATPase-bafilomycin A1; lysosomotropic drug-monomensin; microtubule-disrupting agents-taxanes, nocodazole, colchicine, vinca alkaloids; antidepressant drug-clomipramine; antischistosome agent-lucanthone (autophagosome degradation).	Electron microscopy, immunohistochemical staining of microtubule-associated protein 1 light chain 3 (LC3) as a general marker for autophagic membranes, monodansylcadaverine staining of autophagic vacuoles and protein degradation assays.
Necrosis	Morphological features: cell size increases, clumping and random degradation of nuclear DNA, cell membrane swelling and rupture, swelling of organelles, gain in cell volume (oncosis), organelle degeneration mitochondrial swelling and increased vacuolation. Activation: hyperactivation of poly(ADP-ribose) polymerase 1 (PARP1) enzyme with depletion of β -nicotinamide adenine dinucleotide and of ATP, hypoxic injury and oxidative stress (ROS/reactive nitrogen species); chetomin-inhibitor of tumor growth by inducing necrosis <i>in vivo</i> ; dimethoxy-naphthoquinone-generation of ROS and induces apoptosis or necrosis; myristoleic acid methyl ester-induces apoptosis and necrosis in prostate cancer cells; sterigmatocystin-a mycotoxin inhibits DNA synthesis and causes necrosis. Inhibition: necrox-2 [5-(1,1-dioxo-thiomorpholin-4-ylmethyl)-2-phenyl-1H-indol-7-yl]-(1-methanesulfonyl-piperidin-4-yl)-amine] and necrox-5 [5-(1,1-dioxo-thiomorpholin-4-ylmethyl)-2-phenyl-1H-indol-7-yl]-(tetrahydro-pyran-4-ylmethyl)-amine]-is a cell-permeable necrosis inhibitor selectively locks oxidative stress-induced necrosis with antioxidant property; tyrphostin AG 126-reduces LPS-induced tyrosine phosphorylation of p42 ^{MAPK} ; cyclosporin A-inhibitor of the mitochondrial permeability transition pore (MPTP) and prevents necrosis; IM-54 (indolylmaleimide derivative)-inhibits necrotic cell death induced by H ₂ O ₂ in promyelocytic leukemia HL-60 cells; PARP inhibitor VIII, PJ34 [2-(dimethylamino)-N-(6-oxo-5,6-dihydrophenanthridin-2-yl)acetamide hydrochloride]-inhibitor of PARP-1 and PARP-2 and inhibits necrosis; IM-54 [2-(1H-indol-3-yl)-3-pentylamino-maleimide]-a selective inhibitor of oxidative stress-induced necrosis.	Electron microscopy; nuclear negative staining; ethidium homodimer III DNA assay; detection of inflammation and damage in surrounding tissues.

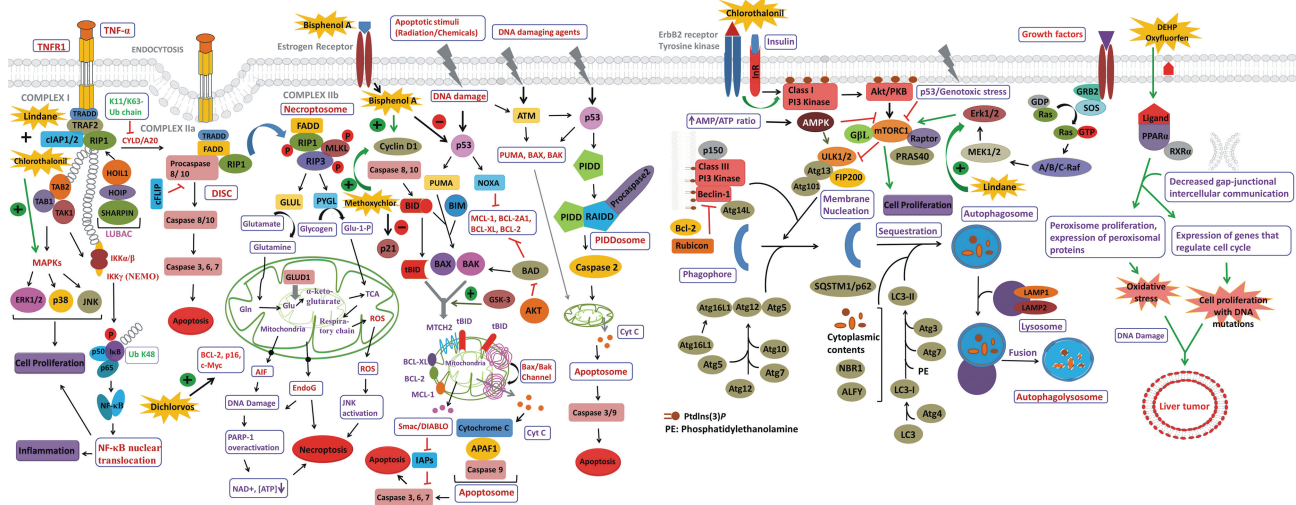


Figure 1. Apoptotic and non-apoptotic signaling pathways and the involvement of anthropogenic chemicals.

endoplasmic reticulum and cytoplasm. Previous studies have shown that CASP2 can be activated by DNA damage induced by anticancer drugs, such as cisplatin and etoposide, or by ultraviolet and γ -irradiation, and it is a critically involved in genotoxic stress-induced apoptosis (19). CASP2 activation leads to the release of cytochrome c, indicating that CASP2 acts upstream of mitochondria-mediated intrinsic pathway (20). Moreover, the treatment of cells with the CASP2 inhibitor and/or small interfering RNA to block CASP2 from inducing the release of cytochrome c is followed by the activation of CASP9 and 3. Similar to other initiator caspases, pro-caspase-2 contains a Caspase Activation and Recruitment Domain at the N-terminus. CASP2 recognizes a pentapeptide VDVAD for cleavage of target proteins, and its known target proteins are BID, PARP, Plakin, Huntingtin and DNA fragmentation factor 45. Because CASP2 is activated by a proximity-induced self-cleavage mechanism, it obtains proximity by forming a PIDDosome, which is composed of three protein components, PIDD (TP53-induced protein with death domain), RAIDD (RIP-associated Ich-1/Ced-3-homolog protein with a death domain) and CASP2, whose interaction supported by their respective death domains. PIDD death domain can also interact with the death domain of receptor-interacting protein-1 kinase implicated in the nuclear factor- κ B (NF- κ B) activation (21). PIDD appears to act as a molecular switch, controlling the balance between life and death upon DNA damage (Figure 1).

Necrosis and necroptosis

In contrast with apoptosis, necrosis is a genetically controlled process; necrosis involves an uncontrolled and progressive loss of cytoplasmic membrane integrity, a rapid influx of Na^+ , Ca^{2+} and water, resulting in cytoplasmic swelling, nuclear pyknosis and the release of lysosomal and granular contents into the surrounding extracellular space (22). Although the molecular mechanisms underlying apoptosis are better understood, little is known about the molecular events leading to necrosis. Necrosis has recently emerged as an important and physiologically relevant signaling process contributing to ovulation, immune defense, death of chondrocytes controlling the longitudinal growth of bones and cellular turnover in the intestine (23). *In vivo* studies indicated that removal of interdigital cells in the paws of *Apaf1*^{-/-} mice during embryogenesis occurs by a caspase-independent necrotic-like process (24). However, accumulating evidence by many researchers suggests that necrosis is not just an unregulated and uncontrollable process. Rather, it involves a programmed and actively

regulated process (aptly named necroptosis), which is regulated by the kinase activity of RIPK1 and RIPK3 that form the necrosome complex (25). This leads to the plasma membrane permeabilization, release of cell contents and exposure of damage/danger-associated molecular patterns (DAMPs), such as HMGB1, S100 protein, IL33 and mitochondrial DNA. Under normal physiological conditions, autophagy and the caspase-8-FLIP_L-FADD platform are apparently gatekeepers preventing necroptosis (26).

The paradoxical role of autophagy in cancer

Autophagy is the basic catabolic mechanism in response to starvation or other stressful conditions whereby unnecessary or dysfunctional misfolded or aggregated proteins and cellular components (e.g. mitochondria, endoplasmic reticulum and peroxisomes) are engulfed within double-membrane vesicles called autophagosomes and are eventually digested by lysosomal enzymes to sustain cellular metabolism (27,28). During macroautophagy, a cytoplasmic cargo is delivered to the lysosome through an autophagosome, which fuses with the lysosome to form an autolysosome. Microautophagy involves the inward folding of the lysosomal membrane, which delivers a small portion of cytoplasm into the lysosomal lumen. Both macro- and micro-autophagy can be either non-selective or selective in the removal of large cellular components and protein aggregates (29). Autophagy involves several key steps for the final degradation of cellular components in lysosomes: (i) initiation and nucleation of phagophore; (ii) expansion and maturation of autophagosomes; (iii) fusion of the autophagosome with the lysosome to form the autolysosome and (iv) execution of autophagy (degradation). These steps are tightly regulated by highly conserved *Atg* genes and non-*Atg* genes (30).

Disorders in autophagic signaling pathways are frequently observed in cancer patients. Autophagy has been referred to as a 'double-edged sword' because it acts as an activator of tumor cell death (tumor suppression) as well as it plays a part in tumor cell survival during tumor development and in cancer therapy. Impaired autophagy was shown leading to failure of removing damaged protein and organelles, and exerting genomic instability and aneuploidy, which promotes tumorigenesis (31-33). The loss of *BECN1* was found in human breast and ovarian cancers (34), whereas *Becn1* null mice were shown to be tumor prone (35). In contrast, the *BECN1* forced expression can inhibit tumor development. Additionally, sustained p62 (SQSTM1) expression, which results from autophagy defects, was found to be

important in the promotion of tumorigenesis through de-regulation of NF- κ B expression (33). Tumor cells experience elevated cytotoxic and metabolic stresses (e.g. hypoxia and deprivation of growth factor and oxygen), which can activate autophagy to maintain cellular biosynthesis and survival (28). Recent data indicate that suppression of autophagic proteins inhibited cell growth and conferred or potentiated the induction of cell death, indicating that autophagy contributes to cell survival in human cancer cells, as well as plays a role in adaptive response of tumor cells to anticancer therapies (36). A careful examination of the literature shows that an increased level of autophagic markers in the dying cell might not be the result of increased autophagic flux but due to a blockage of autophagy at its maturation. Therefore, the simple determination of numbers of autophagosomes is insufficient for an overall estimation of autophagic activity. It is necessary to distinguish by performing 'autophagic flux' assays whether autophagosome accumulation is due to autophagy induction or, alternatively, a blockade of steps in the downstream of autophagosome formation. Now, it is agreed that the true meaning of 'autophagic cell death' should be cell death by autophagy, not cell death with autophagy (Figure 1).

Dysfunctional apoptosis in cancers

The fundamental link between malignancy and apoptosis is exemplified by the ability of oncogenes, such as MYC and RAS, and tumor suppressors, such as TP53 and RB (Retinoblastoma), to actively engage apoptosis as well as the aberrant alterations of apoptosis regulatory proteins such as BCL-2 and c-FLIP in various solid tumors (37–39). Acquired apoptosis resistance is a hallmark of most human cancers. With regard to apoptosis triggers, a variety of signals (irradiation, growth/survival factor depletion, hypoxia, oxidative stress, DNA damage, cell cycle checkpoints defects, telomere malfunction and oncogenic mutations, chemotherapeutic agents and heavy metals) appear to provide the selective pressure needed to alter apoptotic programs during tumor development in support of tumor evolution (40–42). The ability of tumor cells to acquire resistance to apoptosis is a compensatory mechanism, which gives tumor cells a distinct (survival) advantage over normal cells. Defects in apoptosis have been implicated in many events relevant to tumorigenesis: (i) cell accumulation from the imbalance of cell proliferation and cell death or a failure of normal turnover process; (ii) permissive cell survival in the face of antigrowth signals, for example, hypoxia in tumor mass, cell-matrix and cell-cell adherence or contact inhibition; (iii) promoting resistance to the killing mechanisms of immune cell attack and (iv) fostering tumor metastasis by promoting cell survival in the circulation under detachment conditions, also known as *anoikis* resistance (43). The importance of this sort of dysfunction is underscored by the fact that tumor cells that possess alterations in proteins involved in apoptosis are often resistant to chemotherapy and are more difficult to treat (because anticancer drugs primarily work by inducing apoptosis). Tumor cell survival, unlike the survival of normal cells, is therefore highly dependent on aberrations of apoptosis signaling pathways (37).

Emerging evidence indicates that cancer stem cells (CSCs), the rare subpopulation of undifferentiated tumorigenic cells, are potential driving force for tumor growth and maintenance (44). To date, CSCs have been identified and isolated from various solid tumors including the lung, brain, breast, colon and skin. These CSCs are highly capable of self-renewal and are able to generate a progeny of differentiated cells that constitute a large majority of cells in the tumors (45). Most importantly, CSCs are apoptosis resistant and very likely responsible for tumor resistance to chemotherapy and irradiation (46). This can be attributed to the undifferentiated status of CSCs and to the extrinsic

factors such as the tumor microenvironment and adhesion-based interactions, which also support their apoptotic resistance (47). Furthermore, the epithelial/mesenchymal transition (EMT) mechanism has been found to underlie the CSC characteristics that are linked to *anoikis* resistance (48). Accumulating evidence also suggests that this inherent resistance in CSCs shares similar extrinsic and intrinsic apoptotic pathway as normal stem cells and differentiated cancer cells (49,50).

Regulation of apoptosis in cancer

Evasion of apoptotic pathways allows cells to sustain chronic proliferation, which is a hallmark of cancer. Recently, two working models of apoptosis (both regulated by BCL-2 family and BH3-only proteins) were reviewed (51). The direct model proposes that the activator BH3-only proteins (BIM, BID and PUMA) can directly activate BAX and/or BAK oligomerization in addition to neutralizing BCL-2-like proteins, whereas the sensitizer BH3-only proteins (BAD and NOXA) release activator from activator/pro-survival protein complex. The indirect model suggests that BAX is primed in normal cells by BH3-only protein and bound with BCL-2. In excess of pro-apoptotic signaling, BH3-only proteins compete with BCL-2 allowing oligomerization of BAX and BAK leading to apoptosis (52). The BAX/BAK oligomerization loosens the integrity of mitochondria and culminates with mitochondrial outer membrane permeabilization facilitating the release of cytochrome c into the cytoplasm, which interacts with APAF-1, and leads to the ATP-dependent formation of apoptosome, and the recruitment and activation of the CASP-9, -3 and -7. In the absence of APAF-1 and CASP-9, cytochrome c release itself is not sufficient to induce apoptosis (53–55). Cytochrome c diffusion and death receptor signaling mediates modulation of XIAP by SMAC/DIABLO and OMI/HTRA2, and activation of caspases (56) (Figure 1). Up-regulation of XIAP, survivin and down-regulation of APAF-1 has been observed in several tumors.

Cellular stress and DNA damage are regulated through two tumor suppressor genes TP53, which induces expression of NOXA, PUMA and RB upon various environmental and chemical stresses. Recently, a bona fide tumor suppressor gene neurofibromin 2 (NF2/Merlin) was shown to regulate apoptosis through the Hippo pathway (57). RB integrates outside inhibitory signals, whereas TP53 senses irreparable damage in genomic integrity, intracellular organelles and nucleotides, as well as suboptimal level of glucose, and growth inhibitory signals (58). TP53 activities are tightly regulated by a network of protein-protein interactions, microRNAs and a range of post-translational modifications, including phosphorylation, acetylation, methylation and ubiquitination (59,60). TP53 activity is suppressed by a direct binding of TP53 to murine double minute 2 (MDM2), which targets TP53 for proteasomal degradation. NOXA also induces apoptosis in TP53/TP73-dependent manner in response to DNA damage, whereas PUMA, the most potent pro-apoptotic regulator, induces apoptosis both in a TP53-dependent and -independent fashion (61–63).

Cellular metabolism is a key for the survival of cells, whereas altered metabolism in cells induces either apoptosis or resistance to apoptotic stimuli. Metabolic enzymes and its intermediates from glycolysis, pentose phosphate pathway and tricarboxylic acid cycle have shown deregulated in many cancer types to provide nicotinamide adenine dinucleotide phosphate (NADPH), citrate, acetyl CoA and various other metabolites for high demand of biosynthesis and proliferation (64). Chronic proliferating cells short circuit their metabolic pathways and mostly depend on aerobic glycolysis to sustain the massive biosynthesis of intracellular structures. Various post-translational modification regulates cellular growth especially phosphorylation

and acetylation and increase apoptotic sensitivity. Metabolic intermediates also regulate pro- and anti-apoptotic regulators (BCL-2 family protein). Perturbations in acetyl-CoA production may extend to other oncogenic contexts beyond that of BCL-xL (65–67). Redox status of tissues/cells affects their sensitivity to cytochrome c. Reduced glutathione mostly produced by NADPH inactivates cytochrome c, whereas apoptotic agents produce ROS to activate cytochrome C and apoptosis (68). Key regulatory metabolic enzymes, which affect apoptosis (e.g. hexokinase, fructose 2,6-bisphosphate kinase, lactate dehydrogenase M and pyruvate dehydrogenase kinase), are also implicated in cancer (55). Growth factors/cytokines regulate pro-survival signaling by RAS- and PI3K-AKT pathways through cognate receptor tyrosine kinase (RTK). Most human cancers harbor mutations in AKT and PTEN, which leads to AKT activation and resistance to apoptosis (69,70). Death receptor signaling triggers the recruitment of FADD and TRADD adapter proteins to induce dimerization of CASP-8 and subsequent activation of CASP-3 and -7. In some cell types, CASP-8 directly cleaves BH3-only protein BID to localize it to the mitochondria and activate BAX (71).

Additionally, 'anoikis', the detachment of cells, is another major regulator of apoptosis. The detachment of adherent cells (loss of critical interaction between the cell and the extracellular cell matrix) leads to apoptosis due to the loss of integrin α -5 or β -5 signaling and the loss of focal adhesion kinase, a reduction of talin-integrin interaction, and of c-Jun N-terminal kinase signaling (72).

Oncogenes, tumor suppressor genes and apoptosis

Human health is continuously challenged by exposure to a wide range of environmental chemicals that affect DNA integrity (73). When DNA repair capacity is exhausted, DNA damage accumulates in cells at a higher level, and this excess damage causes an increased frequency of mutation and/or epigenetic alterations of specific genes (oncogenes and tumor suppressors) resulting in the disruption of the cellular networking that controls cellular homeostasis and leads to cellular transformation and cancer development (74). The inactivation of expression of tumor suppressor genes via genetic and epigenetic changes (DNA hypermethylation, histone deacetylation/methylation and microRNA targeting) often leads to tumor initiation and progression, whereas amplification and overexpression of oncogenes result in the similar tumorigenic phenotype (75). Tumor suppressor 'driver' genes include: genes for retinoblastoma protein (RB), tumor protein TP53 (TP53), BRCA1 and 2, PTEN, VHL, APC, CD95, ST5, 7 and 14, YPEL3, whereas 'driver' oncogenes include: growth factors (e.g. C-SIS, WNT), RTKs (EGFR, PDGFR, VEGFR, TRK, ERBB2), cytoplasmic tyrosine (SRC, ABL and BTK) and serine/threonine (ATM, MTOR, ERK, PI3KCA, AKT1, 2 and 3, LKB1 and RAF) kinases, transcriptional factors (MYC and E2F), GTP-ases (RAS) and others (CCND1), as reviewed by Lee et al. (74). Discovery of microRNA genes added new members to both tumor suppressor (e.g. miR-34a) and oncogene (e.g. miR-17–92) families (76).

As part of the DNA damage response to genotoxic stress, apoptosis is triggered by chemical-induced DNA lesions and represents a first line of defense allowing the organism to eliminate damaged cells. Notably, cells respond to stress-induced DNA damage by increasing their levels of TP53 (77). The wild-type TP53 prevents cancer formation through the activation of cell cycle arrest or apoptosis via transcriptional regulation of hundreds of specific gene targets or via multiple protein-protein interactions. TP53 and its evolutionary older relatives, TP63 and TP73, exhibit a similar modular structure and share significant structural and functional homologies; however, their tumor suppressive role is not as straightforward as TP53. Genes for all

TP53 family members produce proteins with the transactivation domain displaying a tumor suppressive function and proteins without transactivation domain acting as oncoproteins (78). TP53 is mutated in >50% of human cancers, whereas in other cancers, its function is compromised by de-regulation of the TP53 pathway. Both TP63 and TP73 are rarely mutated or epigenetically altered in human cancers. *tp53*^{-/-} mice develop tumors with short latency and 100% penetrance (77). Tumor suppressive function for TP73 was confirmed using *tp73*^{-/-} mice (79). *tp53*^{+/-} and *tp63*^{+/-} mice are less cancer prone than *tp53*^{-/-} and *tp63*^{+/-} mice, respectively.

The synergistic effects of the TP53 family members in tumor suppression were highlighted using mice heterozygous for mutations in both TP53 and TP63, or TP53 and TP73 displaying higher tumor burden and metastasis, compared with *tp53*^{+/-} mice (80). Accumulating data show that TP53 family proteins can regulate cell survival via cell cycle arrest, senescence and apoptosis and are abnormally expressed in different cancer types (breast tumors, acute myeloid leukemia, head and neck tumors, melanoma, renal cell carcinoma, colon, ovarian and lung tumors) suggesting that their differential expression may disrupt the TP53 response and contribute to tumor initiation/progression and linked to cancer prognosis and treatment (78).

Although mutations of TP63 mutations are almost non-existent in human cancers, >80% of primary head and neck squamous cell carcinomas, other squamous cell epithelial malignancies and non-small cell lung cancer retain TP63 expression, where it is often over-expressed and occasionally amplified. The TP63 expression strongly influences the tumor cell response to genotoxic stress (81). TP63 activates death domain receptor- and mitochondria-mediated apoptosis pathways, which are clearly reinforced by concomitant treatment with genotoxic stress. However, Δ Np63 α confers resistance to apoptosis via a transcriptional regulation of AKT1, as well as via down-regulation of several microRNAs (miR-181a, -519a and -374a) and up-regulation of miR-630, which targets proteins involved in cell cycle arrest and apoptosis for down-regulation, hence conferring tumor cell chemoresistance (82,83). It is likely that apoptosis sensitivity to genotoxic agents may be determined not only by TP53 but also by TP73 and TP63 function, and its isoforms (84).

The disruption of normal cell death

From a disruption standpoint, the inactivation or attenuation of the TP53 apoptotic response, achieved by mutations or epigenetic alterations, is known to promote cell transformation (77). For example, non-polycyclic aromatic hydrocarbon components present in tobacco smoke condensate are able to attenuate the TP53 apoptotic response, as suggested by studies in mouse epidermal cells (78). The transcription factor C/EBP β , which is induced by cigarette smoke has also been involved in TP53 repression (85,86). Following a prolonged exposure to environmental chemicals, bulky DNA adducts may not be removed by DNA repair mechanisms but converted into mutations. Subsequent DNA replication cycles may lead to hot spot mutations in key growth regulatory genes, thereby resulting in malfunction of tumor suppressor genes and amplification/overexpression of oncogenes (74).

Similarly, mutated RAS oncogenes were found in the experimental tumors of rodents that had been exposed to chemical or physical compounds, as well as in many human cancers (87). For example, exposure to hydrocarbon solvents has been associated with an increased risk of exocrine pancreatic cancer, the human tumor with the highest prevalence of K-RAS mutations (88). And heterocyclic amines have been implicated in both initiation and maintenance of breast tumorigenesis mediated by upregulated

H-RAS expression, ERK pathway activation, NOX1 expression and elevation of ROS (89). Although the sustained activation of the NF- κ B transcription factor is another important element involved in chemical tumorigenesis, tobacco, alcohol, high-fat diet, environment pollutants, cancer-causing viruses (human papillomavirus, hepatitis B and C viruses, human immunodeficiency virus and bacteria (*Helicobacter pylori*), ultraviolet light, ionizing radiation, obesity and oxidative stress are all potent NF- κ B stimuli (90,91). The following proteins: pro-inflammatory proteins (cyclooxygenase-2, inducible nitric oxide synthase, TNF, interleukin-8); proliferative/pro-survival factors (bone morphogenetic proteins, stem cell factor, vascular endothelial growth factor, granulocyte-monocyte colony stimulating factor) and antiapoptotic proteins [TRAF-1 and -2, the CASP-8 inhibitor (FLIP), IAPs, XIAP, BCL2 and its homologues and matrix metalloproteinases] are overall involved in tumor promotion, initiation and progression (92).

The critical research gaps for a clear understanding of chemical carcinogenesis include the following:

1. Understanding how genetic modifications by low-dose environmental mixtures can disrupt/overcome normal cell death.
2. Understanding the molecular processes and pathways activated/blocked by individual chemicals and mixture of chemicals with disruptive potential.
3. Understanding the low-dose effects of environmental chemicals (single and mixtures) on cell death within different tissues and organs of human.
4. Clearly distinguishing the differences between the contributions of both carcinogenic and non-carcinogenic chemicals (individually and in mixtures) in environmental carcinogenesis by experimental methods.

Key target sites for disruption

In this review, we wanted to look at several key target sites that disrupt normal cell death and potentially have relevance for environmental carcinogenesis. It is generally agreed that many cancers arise from a single cell that has accumulated genetic and epigenetic mutations of a few crucial genes of proto-oncogenes and tumor suppressors, and that this is caused by random errors in DNA replication or a reaction of the DNA with free radicals or other chemical species of endogenous or exogenous origin (93). However, we also know that chemicals with disruptive potential are capable of a wide range of additional cellular level effects that are relevant to cancer (94), and the general population now faces ongoing exposures to thousands of environmental chemicals that are present in consumer products, our food, our water and in the air (95). At the same time, regulators worldwide have remained largely focused on the effects of single chemicals while placing very little emphasis on the effects of exposures to mixtures of chemicals in the environment (96). Accordingly, in this review, we emphasize the pivotal and enabling role that resistance to cell death plays in carcinogenesis and we highlight some of the key mechanisms and pathways that can be chemically disrupted (i.e. in a manner that results in dysfunction of normal cell death routines) and that have the potential to be supportive of the emergence of an immortalized cellular phenotype.

To that end, we first identify and review a number of key targets of this nature that have been shown to be active sites for chemical disruption in the past as follows:

Binding to ER α

Given that many anthropogenic agents are xenoestrogens, a considerable amount of environmental health research has

focused on ER level disturbances (97). Many xenoestrogens binds to ER and either activates it or inhibits it. ER α activation stimulates cell proliferation and initiates cancer through tumor promotion, whereas the activation of ER β stimulates terminal cell differentiation and disrupts cancer progression, which is an anticancer effect. For example, many of the organochlorine (OC) pesticides such as lindane or their metabolites fall into the category of xenoestrogens that disrupt endocrine processes by acting as agonists of ER α and/or antagonists of ER β and by exerting antiandrogenic effects (by binding to androgen receptors). ER α and tumor suppressor protein p53 exert opposing effects on cellular proliferation. ER α 's repression of p53-mediated cell death has been widely investigated, especially in breast cancer (98), but emerging evidence suggests a much more complex role for ER α -controlled pathways in other tumor-related phenomena. ER α interacts with p53 bound to promoters of *Survivin* and *multidrug resistance gene 1* (MDR1), and inhibits p53-mediated transcriptional repression of these genes in human cancer cells *in vivo*. It was found that p53 is necessary for ER α to access the promoters and there is cross-talk between the pathways mediated by ER α and p53 (99). It has been also been shown that an increase of ER α messenger RNA (mRNA) level in ER α -positive breast cancer is associated with de-regulation of metabolism, which produce a complementary effect on cell differentiation and proliferation (100). On the other hand, evidence of ER α 's role in the EMT has also been reported. In endometrial carcinomas and breast cancer, ER α 's activity is negatively associated with the activation of EMT via the Wnt, Sonic Hedgehog and transforming growth factor- β (TGF- β) signaling (101,102). EMT involves the loss of cell-cell adhesion and a consequent increase in mobility and invasiveness. It has been proposed that ER α acts to promote invasive growth in breast cancer cells by a direct, ER α -dependent expression of metastasis-associated genes, such as the MTA-3 protein. It is important to note that a physiological feedback mechanism regulates the efficiency of ER α activation through the state of cell-cell interactions that are mediated by E-cadherin (103). Although EMT promotes a decrease in cellular contacts, it also inhibits ER α transcription thus limiting its own ER α -dependent activation. Although no effects on genetic instability and immune system evasion of systematic ER α activation have been reported, the synergy of action involved in these different (deregulated) pathways may be very important for cancer onset and progression.

Gap junctional intracellular communication

In addition to tumor promotion ability, some environmental chemicals directly or indirectly cause DNA mutations through free radical production (ROS/reactive nitrogen species) and may cause both tumor initiation and tumor promotion by inhibiting GJICs and connexins (Cx) (104,105). Blockage of GJIC between the normal and the pre-neoplastic cells creates an intra-tissue microenvironment in which tumor-initiated pre-neoplastic cells are isolated from growth controlling factors of normal surrounding cells resulting in clonal expansion (106). Gap junction channels and Cxs control cell apoptosis by facilitating the influx and flux of apoptotic signals between adjacent cells and hemi-channels between the intracellular and extracellular environments. Recently, it has also been demonstrated that Cx proteins in conjunction with their intracytoplasmic localization, may act as signaling effectors that are able to activate the canonical mitochondrial apoptotic pathway (107). Tumor-promoting chemicals such as phenobarbital, dichlorodiphenyltrichloroethane (DDT) and 12-O-tetradecanoylphorbol 13-acetate block apoptosis and also block GJIC, whereas several antitumor chemicals, such

as retinoids and dexamethasone, increase GJIC and increase apoptosis. So, it has been hypothesized that GJIC is necessary for apoptosis and blockage of apoptosis with chemicals/carcinogens could therefore promote the initiation of premalignant cells in tumorigenesis (108). For example, knockdown of connexin 43 (Cx43) had an inhibitory effect on GJIC and resulted in a reduction of cell death after treatment with cisplatin and *Salmonella* (109), and Kang et al. (105) reported on the inhibition of GJICs in normal human breast epithelial cells by pesticides, polychlorinated biphenyls, polybrominated biphenyls and halogenated hydrocarbons (when given as single compounds or as mixtures), and suggested that they may contribute to carcinogenesis through this mechanism.

Peroxisome proliferator-activated receptor- α

PPAR- α receptors are mainly found in the liver and belong to the steroid hormone receptor superfamily that functions as a transcription factor for genes involved in glucose, lipid and amino acid metabolism, and that also induces enzymes involved in the metabolism of xenobiotics. Upon ligand binding, PPARs heterodimerize with the retinoid X receptor and bind to the specific promoter sequence and trigger the expression of target genes (110). A variety of chemicals including certain herbicides and plasticizers induce peroxisome proliferation with increased replicative DNA synthesis, suppression of apoptosis and increased expression of peroxisomal acyl-CoA oxidase in rodent liver and other tissues. In rodents, these peroxisome proliferating chemicals act as non-genotoxic carcinogens that promote the development of tumors (111). Chemicals of industrial importance such as diethylhydroxylamine and chlorinated solvents are peroxisome proliferators (PP) that induce elevated S-phase in rat and mouse and play an important role in hepatocarcinogenicity. The molecular mechanisms of altered expression of cell cycle regulatory proteins resulting in the elevation of S-phase, and suppression of apoptotic cell death and induction of proliferation are evidenced by the activation of PPAR- α and survival signaling by p38 MAPK in hepatocellular carcinomas (112).

Hypersecretion of LH by gonadotroph cells in pituitary gland

Neuroendocrine disruptors are environmental pollutants that are agonists/antagonists or modulators of the synthesis and/or metabolism of neurohormones, neuropeptides and neurotransmitters. Sustained hypersecretion of LH occurs following the disruption of the hypothalamic-pituitary-testicular axis. The tumorigenic response to a chemical in an endocrine tumor is generally dose responsive. As the dose of environmental chemical increases, the extent of perturbation of normal endocrine homeostasis increases resulting in a stronger trophic stimulus to the target cell (113). LH up-regulates the expression of apoptotic inhibitor, survivin in a dose-dependent manner via ERK1/2 signaling pathway and inhibits apoptosis in ovarian epithelial tumors *in vitro* (114).

p53

As noted previously, p53 is a tumor suppressor gene and has been described as the 'guardian of the genome'. p53 is a transcriptional activator regulating the expression of Mdm2 (negative regulator of p53) and genes involved in growth arrest (p21, Gadd45 and stratifin), DNA repair (p53R2) and apoptosis (Bax, Apaf-1, PUMA and NoxA). Its activity disrupts the formation of tumors by arresting growth and inducing apoptosis. This 53kDa phosphoprotein induces apoptosis by stimulating BAX and FAS antigen expression, or by repression of BCL-2 expression. p53 mutations are found in most of the tumors and contribute to the

complex molecular network events leading to tumor formation. Notably, the progression of cancers which overcome cell death [via the inactivation of tumor suppressor genes (p53) and activation of oncogenes (c-Ha-ras)] after exposures to organophosphorus pesticides is also associated with an increase in genome instability (115). Accordingly, one of the most important candidates, as a key regulator of malignant transformation, is P53. Somatic mutations of this gene or perturbations in its pathways are among the most frequent alterations in human cancers (116). Arguably, the most important decision maker in cellular process that unfold in response to every kind of stress and harm, P53 is involved in cell cycle arrest, apoptosis, regulation of metabolism, DNA repair and every pathway connected to them. Its action is therefore opposed to evasion from growth control, genetic instability, sustained proliferative signaling and cellular motility, whereas it can be an important promoter of metabolic changes and even replicative immortality. Cross-talk between P53 pathways and most molecular mechanisms that transduce external signals (to promote or inhibit cell proliferation) is branched and efficient so chemical disruptors that systematically impair P53 can readily produce harmful effects on almost all of the hallmarks involved in malignant transformation.

p16/p53

p16^{INK4A} (p16) and p53 are tumor suppressor genes (antioncogenes). p16 is known as cyclin-dependent kinase (CDK) inhibitor and specifically blocks the activity of CDK4 and CDK6. The binding of 16kDa protein p16^{INK4A} to CDK4 inhibits the phosphorylation of retinoblastoma protein (pRB) and subsequently inhibits the transcription factor (E2F), the release and arrest of the G₁ phase of cell cycle and the suppression of cellular proliferation. p16 also inhibits the growth of breast cancer cells by inhibiting the VEGF signaling pathway and angiogenesis. And recently, it has been demonstrated that the anticancerous ability of p16 is additionally attributed to its ability to induce tumor cells to enter senescence. It also induces apoptosis both *in vitro* and *in vivo* (117). The functional or structural loss of p16^{INK4A} therefore leads to the cell cycle propagation of genetically damaged/mutated cells and increases the subsequent risk of tumor development. p16 is encoded by *INK4a* gene and an alternative reading frame of *INK4a* transcribes to p14^{ARF}, which mediates the link between p16 and p53 pathways. So, loss of the *INK4a* gene disrupts p16^{INK4A}/CDK4/6/pRB and p14^{ARF}/MDM2/p53 pathways, which controls cell proliferation (118). Notably, the p16 locus was found to be inactivated in many cancers such as lung, breast, melanoma, pancreatic, brain and >80% of squamous cell carcinoma of the head and neck tumors (119). Thus, p16^{INK4A}, p14^{ARF} and p53 genes involved in cell cycle pathways are major targets of inactivation in carcinogenesis. Occupational exposure to chemicals and metal dusts form ROS and reactive nitrogen species in humans through oxidant-mediated responses, which causes hypermethylation of p16^{INK4A} and p53 along with the activation of MAP kinase to induce carcinogenesis.

BCL-2/p53

BCL-2 is a proto-oncogene, which regulates cell cycle progression and apoptosis (antiapoptotic), whereas p53 is a tumor suppressor gene. BCL-2 constitutively suppresses p53-dependent apoptosis. The BCL-2/p53 axis requires pro-apoptotic protein (Bax) and the effector molecule (CASP-2) as essential apoptotic mediators following the silencing of Bcl-2 or Bcl-x_L. p53 possesses pro-apoptotic properties that appear to be constitutively active despite its suppression by Bcl-2 (120). Both p53 and Bcl-2 are strong predictors of recurrence and survival in rectal

cancer (121). And the chemical 7,12-dimethyl benz-(a)-anthracene induces tumor growth in breast cancer that is apparently due to the inactivation of p53 aided by the absence of Bcl-2 (122).

ErbB-2/HER-2 tyrosine kinase

The human epidermal growth factor receptor (EGFR/HER) family consists of ErbB/HER lineage of receptor proteins (ErbB1–4) as it shows similarity to the *v-ErbB* oncogene of avian erythroblastosis virus (123). The ErbB-2/HER protein tyrosine kinase receptor contains an extracellular domain followed by a single transmembrane segment and intracellular tyrosine kinase activity, which regulates cell growth and differentiation particularly during embryogenesis (124). Overexpression of ErbB2/HER2 is related with cancer. Binding of epidermal growth factor ligands to their cognate ErbB receptors induces homo- or hetero-dimerization of ErbB2 and autophosphorylation of phosphotyrosine residues in the cytoplasmic domain, which serve as docking sites for adaptor proteins to downstream signals for growth and survival. Up-regulation of PI3K/AKT signaling pathway is found in ErbB2+ breast cancers, where it exerts pro-survival effects overcoming cell death (125).

The PI3K/AKT/mammalian target of rapamycin (mTOR) pathway is important for cell growth and survival, and it is also frequently activated in cancer. PI3Ks are a family of intracellular signal transducer enzymes involved in many cellular functions such as cellular growth, proliferation, differentiation and survival playing an important role in tumorigenesis (126). Upon activation of the RTKs by growth factors, PI3Ks convert phosphatidylinositol-4,5-bisphosphate into phosphatidylinositol-3,4,5-triphosphate, which provides docking sites for pleckstrin homology domain containing proteins, including phosphoinositide-dependent kinase-1 and protein kinase B. This conversion is mainly controlled by the phosphatase and tensin homolog (PTEN), which dephosphorylates PIP₃ into phosphatidylinositol-4,5-bisphosphate, thereby regulating the uncontrolled activation of AKT pathway. Loss of PTEN tumor suppressor is common in malignancies and correlates with increased AKT activity. AKT is activated by phosphorylation of Thr308 by phosphoinositide-dependent kinase-1 (PDK1) and Ser473 by the mammalian target of rapamycin complex 2 (mTORC2). Activated AKT phosphorylates glycogen synthase kinase 3, forkhead box transcription factors, BCL-2 family members and the tuberous sclerosis complex (TSC1/2) thereby regulating a range of pathways involved in protein synthesis, proliferation, metabolism and apoptosis (127).

The mTOR pathway is the main target of the rapamycin, a natural compound produced by the *Streptomyces hygroscopicus*, which displays potent immunosuppressant and antiproliferative properties. The mTOR pathway integrates stimuli from diverse upstream pathways including the PI3K/AKT pathway and is responsible for the synthesis of a wide range of proteins involved in cell growth, proliferation, survival and tumorigenesis. mTOR can act in complex with Raptor (mTORC1) or Rictor (mTORC2) and these complexes regulate entirely different programs in the cell. When activated, mTORC2 activates and stabilizes AKT by its phosphorylation at Ser473, and controls actin cytoskeleton organization and cell migration, whereas mTORC1 increases mRNA translation by phosphorylation of the downstream molecules p70S6K (S6K) and 4E binding protein 1 (4EBP1). Phosphorylation of p70S6K leads to mRNA biogenesis, translation of ribosomal proteins and cellular proliferation. 4EBP1, in the hypophosphorylated state, binds the eukaryotic initiation factor 4E preventing its binding to eIF4G, and thereby to form the translational initiation complex eIF4F. Once phosphorylated,

4EBP1 is unable to bind to eukaryotic initiation factor 4E, which results in increase of translation of proteins related to cell proliferation and viability (128,129).

AKT activation affects components of the apoptosis regulatory machinery, including the BCL-2 family, the caspase family or the function of death domain receptors. AKT directly phosphorylates the BAD protein, which is a pro-apoptotic member of the BCL-2 family, whereas the dephosphorylated BAD promotes apoptosis (130,131). AKT might also prevent apoptosis by phosphorylation and inactivation of glycogen synthase kinase-3, CASP-9 and indirect activation of NF- κ B leading to the altered transcription of pro-survival genes (e.g. IAP1, IAP2), as reviewed in refs 132–134. The mTOR pathway has also been linked by several studies to play a role in cell death by apoptosis and autophagy (135). One of the proposed pathways by which mTOR regulates autophagy was discovered in studies from yeast essential autophagy genes (Atgs), as reviewed in ref. 136. Atg1/Atg13/Atg17 complex is required for maximal catalytic activity of mTOR leading to Atg13 phosphorylation, subsequently destabilizing the complex and inactivating Atg1. In the mammalian cells, unc-51-like kinase 1 (ULK1) and focal adhesion kinase interacting protein of 200 kD (FIP200) form the complex with mammalian ATG13. mTORC1 activation correlates with the phosphorylation of ULK1-ATG13-FIP200 complex and inhibition of autophagy. Activation of P70S6k by mTOR may block apoptosis by increasing antiapoptotic BCL-2/BCL-xL protein expression and inactivating the pro-apoptotic protein BAD (137). In human prostate cancer cell lines, ErbB-2 kinase activity was increased by OC insecticides such as lindane, DDT and fungicide chlorothalonil. DDT induces cellular proliferation of the androgen-dependent human prostate cancer cell line LNCaP by phosphorylation of MAP kinase. However, no proliferative effect was induced in androgen-independent PC-3 cell line (138).

Mitogen-activated protein kinase

MAPK are serine/threonine kinases that transduce extracellular signals from a diverse range of stimuli and elicit cellular responses such as proliferation, differentiation, survival, migration, development, inflammatory responses and apoptosis. In mammalian cells, three MAPK families have been characterized namely classical MAPK (ERK), C-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK) and p38 kinase. MAPK pathways involve a series of protein kinase cascades, and each cascade consists of more than three enzymes that are activated in a series: a MAPK kinase kinase (MAPKKK/MAP3K), a MAPK kinase (MAPKK/MAP2K/MEK) and a MAP kinase (MAPK) (139). MAPK has a pleiotropic role in cancer, especially p38 and JNK MAPK pathways that are involved in the cross-talk between autophagy and apoptosis induced by genotoxic stress. p38 MAPK plays a dual role in genotoxic stress-induced apoptosis. Rottlerin-induced apoptosis of HT29 colon carcinoma cells was contributed by the up-regulation of non-steroidal anti-inflammatory drug activated gene-1 (NAG-1) via a p38 MAPK-dependent mechanism (140). However, under certain circumstances, it also involved in mediating resistance to apoptosis. The phosphorylation of p38 significantly increased the resistance to docetaxel-induced apoptosis in prostate cancer cells (141). And the suppression of p38 MAPK reversed the overexpression of micro RNA-214, which is linked to the radiotherapy resistance of non-small-cell lung carcinoma cells (142). It also regulates autophagy both as a positive and negative regulator. Platinum compounds such as E-platinum induced autophagic cell death in gastric carcinoma BGC-823 cells via suppression of mTOR by decreasing phosphorylation of p38 MAPK (143). On the other hand,

suppression of the p38 signaling pathway induced autophagic and necroptotic cell death in TNF α -treated L929 cells. JNK MAPK promotes the phosphorylation of c-Jun and activating transcription factor-2 (ATF-2) resulting in the activation of AP-1 and the expression of Fas/FasL signaling pathway proteins, which subsequently activate effector caspase 3 and trigger apoptosis (144). JNK activation is associated with transformation in many oncogene and growth-factor-mediated pathways, whereas p38 MAPK activation involves in cell differentiation processes such as adipocytes, erythroblasts, myoblasts, cardiomyocytes and neurons. Regulation of the cell cycle is critical in cellular proliferation and development of multicellular organisms, and abnormalities in MAPK signaling play a critical role in the development and progression of cancer. MAP kinases are reported to be involved in several pathological conditions such as cancer and other diseases. MEK4/MKK4 is involved in stress-activated pathways such as JNK, and p38 is consistently inactivated by mutation in many cancers including cancers of the ovary, breast, pancreas, bile duct, lung, colon and testes (145).

ERK/MAPK

ERK pathway is a well-characterized MAPK signaling cascade with the Raf-MEK-ERK pathway. The stimulation of RTKs initiates the multistep cascade process resulting in the phosphorylation of p44MAPK (ERK1) and p42MAPK (ERK2) and increasing its enzymatic activity. The activated ERKs translocate into the nucleus and transactivate many transcription factors and regulate expression of genes to promote cell growth, differentiation or mitosis (139). It also regulates post-translational regulation of the assembly of cyclin D-cdk4/6 complexes, which subsequently phosphorylates the RB protein causing the activation of transcription factor E2F and regulates the genes involved in G₁/S progression of cell cycle. In human hepatocytes, TGF- β induces apoptosis by the up-regulation of Rac-independent NADPH oxidase NOX4 mediating the production of ROS, which precedes the loss of mitochondrial transmembrane potential, cytochrome c release and caspase activation, for an efficient mitochondrial-dependent apoptosis (146). However, NOX4 up-regulation was inhibited by intracellular antiapoptotic signals such as PI3K and ERK/MAPK pathways. The overactivation of the MEK/ERK pathway in hepatocellular carcinoma HCC cell line confers resistance to TGF- β -induced apoptosis by impairing the up-regulation of the NADPH oxidase NOX4 expression (147). De-regulation of ERK activity is common in cancer leading to proliferation, migration, resistance to apoptosis and loss of differentiated phenotypes. In particular, cancerous mutations are mostly affecting Ras and B-Raf along with the overexpression of EGFR and ERBB2 in the ERK-signaling pathway. ERK signaling also plays a crucial role in disrupting the antiproliferative effects of ligands such as TGF- β (145). OC pesticides or their metabolites (endosulfan, dieldrin and DDE) and *p*-nonylphenol, a detergent by-product from plastic manufacturing, all produced dose-dependent ERK-1/2 phosphorylation in a pituitary tumor cell line GH₃/B6/F10, which expresses high levels of membrane receptors for ER- α (148).

Environmental chemicals that confer resistance to cell death

In this review, we wanted to further consider the possibility that low-dose exposures to combination of environmental chemicals might have a role to play in environmental carcinogenesis. To that end, we developed a list of environmental chemicals that had been shown to act disruptively on the key target sites mentioned previously. Specifically, we sought to identify chemicals

that were ubiquitous in the environment and not known to be carcinogenic, or classified as carcinogenic to humans. We focused on bisphenol A (BPA), chlorothalonil, dibutyl phthalate (DBP), diethylhexyl phthalate (DEHP), dichlorvos (DDVP), lindane, methoxychlor (MXC), linuron, and oxyfluorfen. These reported actions of these chemicals on these important target sites are described below.

Bisphenol A

Ubiquitous environmental anthropogenic chemicals such as BPA (4,4'-(propane-2,2-diyl)diphenol) and phthalates are commonly found in consumer products, and act as obesogens by disrupting the metabolic homeostasis pathway. This involves the activation of PPAR γ , which is a critical regulator of fat formation and also regulates lipid, glucose and energy in humans. BPA in particular is an estrogenic mimic which does not cause mutations *per se*, but increases breast cancer incidence (149–151). BPA-exposed to HRBEC cell lines and T47D breast cancer cells showed markedly reduced pro-apoptotic negative regulators of the cell cycle (p53, p21WAF1 and BAX) with concomitant increases in proliferation initiating gene products (proliferating cell nuclear antigen, cyclins, CDKs and phosphorylated pRB). It also induced an increase in the ER α : ER β ratio (152). In addition, TP53 loss of function promoted activation of mTOR pathway, together with PI3K, AKT and 4EBP1 and, concurrently, PTEN was suppressed which resulted in enhanced cell growth and proliferation, and ultimately breast tumorigenesis (153). Besides increasing the risk of breast cancer, BPA neutralizes the effects of tamoxifen, undermining a widely used preventive measure to control disease. It has been shown that BPA affects the P53 pathway, inducing a prominent evasion of apoptosis coupled by an increased proliferation (152), and the GPER/EGFR/ERK pathway influencing proliferation and migration (154). This action seems to be delivered mainly through a substantial activation of mTOR pathways and a negative regulation of pro-apoptotic proteins like P53, P21 and BAX. In a number of cases, this BPA-induced cellular misbehavior persists even after BPA has been removed thus providing additional evidences of the chronic potential of this chemical disruptor. BPA has also been shown to disrupt double-strand break repair machinery *in vivo* suggesting that consistent environmental exposure to BPA may severely and dangerously affect the stability of DNA in mammalian cells (155). And BPA exerts a pro-metastatic influence in at least one mouse model of mammary carcinogenesis (156).

Chlorothalonil

Chlorothalonil (2,4,5,6-tetrachloroisophthalonitrile) is a broad-spectrum, non-systemic, OC pesticide (fungicide). It is used to control pathogenic fungi that attack vegetables, fruits, trees and agricultural crops. It is predominantly used on peanuts, potatoes and tomatoes and as an antifungal additive in paints, emulsion and resin. The carcinogenicity of chlorothalonil was evaluated in rodents, and the studies have shown evidence of renal tubular carcinomas and adenomas, and stomach tumors (157). Chlorothalonil up-regulates the expression of ErbB-2 tyrosine kinase and MAP kinase leading to cell proliferation in a prostate cancer cell line (138). Chlorothalonil readily reacts and conjugates with glutathione in the liver, and chlorothalonil metabolites consist of a mixture of di- and tri-glutathione conjugates, cysteine S-conjugates and mercapturic acids. In the proximal tubules of kidney, glutathione conjugates are completely cleaved by enzymes γ -glutamyl transpeptidase and dipeptidases to the cysteine S-conjugates, which are further cleaved by enzyme β -lyases to the corresponding thiol derivatives. The production

of thiol derivatives is thought to be responsible for the toxicity seen in the kidneys (158). In a eukaryotic system, chlorothalonil reacted with proteins and decreased cell viability by formation of substituted chlorothalonil-reduced glutathione (GSH) derivatives and inhibition of specific NAD thiol-dependent glycolytic and respiratory enzymes (159). Caspases (cysteine-dependent proteases) and transglutaminase are some of the thiol-dependent enzymes involved in apoptosis. So, inhibition of these thiol-dependent enzymes in tumor-initiated cells (by chlorothalonil) may disrupt apoptotic cell death and aid in tumor survival. Chlorothalonil is considered to be non-genotoxic but classified as 'likely' to be a human carcinogen by all routes of exposure (95). It may also act as cytochrome P-450 inducer with the formation of ROS and peroxisome proliferation, which increases the subsequent risk of tumor development (160).

DBP and DEHP

Diesters of phthalic acid are commonly referred to as phthalates. These man-made chemicals are widely used in consumer products, food processing and medical applications. They are measured in residential indoor environments (indoor air and house dust) and also in foods, milk and drinking water. High-molecular-weight phthalates are used as plasticizers in the manufacturing of polyvinyl chloride and low-molecular-weight phthalates are used in making varnishes, lacquers and personal-care products. All of the phthalates have been shown to disrupt reproductive tract development in male rodents in an antiandrogenic manner (161). Phthalate compounds such as DBP, butyl benzyl phthalate and DEHP mimic the function or activity of the endogenous estrogen 17 β -estradiol (E2) and bind to ERs. Interestingly, phthalates can mimic estrogen in the inhibition of tamoxifen-induced apoptosis in human breast cancer cell lines by increasing intracellular BCL-2/BAX ratio, which promotes drug resistance to the ER antagonist tamoxifen in breast cancer (162). DEHP also up-regulates the expression of antiapoptotic activating transcription factor-3 (ATF-3) and down-regulates the pro-apoptotic P53 transcription and thereby suppresses apoptotic cell death in fetal mouse genital tubercle (163). It also inhibited apoptosis of Syrian hamster embryo cells (164). DBP induces proliferation and invasiveness of ER-negative breast cancer through AhR/HDAC6/c-Myc signaling pathway (165) and induces cell proliferation of ovarian cancer cells by inducing the expression of cyclin D and cdk-4 (166), whereas butyl benzyl phthalate promotes breast cancer progression by inducing the expression of lymphoid enhancer-binding factor 1 (165). DEHP induces hepatocarcinogenesis in rodents by activating PPAR α and peroxisomal genes or cell proliferation and also decreases GJIC with enhanced replicative DNA synthesis (167,168), whereas DEHP and its main metabolite mono(2-ethylhexyl) phthalate induce ROS species and activate nuclear p53 and p21 in a human prostate adenocarcinoma cell line (169).

DDVP

DDVP (2,2-dichlorovinyl dimethyl phosphate) is an organophosphate insecticide used on crops and animals, and to control household pests. It is effective as an external insecticide against flies, aphids, spider mites and caterpillar, and also as anthelmintic in the treatment of parasitic worm infections in dogs, livestock and humans (170). It acts as a cholinesterase inhibitor on the nervous systems of insects. The United States Environmental Protection Agency (USEPA) has classified DDVP as a probable carcinogen, and DDVP administration induced adenomas of the pancreatic acinar in male rats, mononuclear cell leukemia in male rats, mammary gland fibroadenomas in

female rats and squamous cell papilloma of the forestomach in both male and female mice (171). DDVP is also both mutagenic and clastogenic, actions that probably involve the alkylation of DNA or protein (172,173), and it generates ROS species, which induce oxidative stress in human erythrocytes *in vitro* (174). It also significantly induced the levels of DNA repair enzyme, ataxia telangiectasia mutated in primary rat microglial cells (175), and it has been shown to cause cancer in mouse gastric tissues by upregulating the expression of p16, Bcl-2 and c-myc genes. DDVP induces DNA methylation in multiple tissues in an animal toxicity study. Pro-apoptotic gene silencing mediated by DNA hypermethylation causes apoptosis resistance (176) and it is the link between DDVP and cancer risk observed in some epidemiology studies (177). However, its impact on resistance to apoptosis is not entirely clear. For example, it was also reported to cause an increase in the expression of caspase-1 and TNF- α in brain tissues and intracellular caspase-3 in natural killer cells (in a dose- and time-dependent manner) inducing apoptosis (178).

Lindane

Lindane (γ -hexachlorocyclohexane) is a pesticide that has been used heavily in the past. Its long-term use and the dumping of its production waste have resulted in a widespread and persistent environmental presence. Recently, the effects of lindane, as an activator of ER α and a promoter of angiogenesis, have been investigated both *in vitro* and *in vivo* (179). It has been demonstrated that this pesticide positively influences endothelial cell proliferation and migration. Lindane strongly potentiates metalloprotease activity and nitric oxide production through the enhancement of eNOS. Lindane also exerts a cytotoxic effect on human peripheral blood lymphocytes (180) and disrupts the autophagic pathway by activating MAPK/ERK pathway. This high constitutive induction of MAPK/ERK pathways impedes the tumor suppressive function and provides a malignant advantage to tumors. Lindane disrupts the autophagic process evidenced by enlarged acidic vesicles labeled with specific autophagic vacuole maturation markers LC3, Rab7 and LAMP1, the conversion of cytosolic form of LC3-I into membrane-bound LC3-II and enhanced formation of the Bcl-xL/Beclin 1 complex.

Lindane also inhibits mitochondrial apoptotic cell death by the up-regulation of Bcl-xL, Bax down-expression, prevention of cytochrome c release and inhibition of caspase-3 and -9 activities in rat hepatocytes. So, the disruption of two pro-survival mechanisms (autophagic and apoptotic pathways) occurs in parallel with necrosis induction (181). Lindane also up-regulates antiapoptotic isoforms of protein kinase C in rat hepatocytes by increasing oxidative stress in a cytochrome P-450 (CYP)-dependent manner. Overall, these events clearly demonstrate that the acute and chronic effects of lindane *in vivo* with the induction of necrotic cell death and tumor promotion, respectively (182). *In vivo* studies demonstrated a decline in the activity of tricarboxylic acid cycle dehydrogenase enzymes with the modulation of acid phosphatase and lactic dehydrogenase in hepatocarcinogenesis induced by lindane in mice (179,180). Lindane also activates ERK1/2 and c-Jun cascades in human HaCaT keratinocytes cells, but had no effect on p38 MAPK activation. The activation of ERK1/2 results in the activation of Raf and MEK1/2 as well as activation of protein kinase C. It also stimulated ROS generation, which activated ERK and JNK cascades through ROS-dependent mechanism with no effect on MEK1/2 phosphorylation.

Linuron

Linuron (3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea) is a wide-spectrum herbicide and applied to soils to control pre-emergent

and post-emergent broad-leaved and annual grasses amongst cultivated crops and vegetables. It enters humans either through contaminated food or drinking water, or by dermal contact. It is an endocrine disruptor structurally related to the non-steroidal antiandrogen (androgen receptor antagonist), flutamide, which inhibits 5 α -reductase enzyme. It produces Leydig cell tumors via an antiandrogenic mechanism, where sustained hypersecretion of LH and increased serum estradiol follow the disruption of hypothalamic-pituitary-testicular axis, and appears to be responsible for the development of dose-dependent increase in Leydig cell hyperplasia and adenomas (113). Linuron showed *in vitro* influence on the cell growth rate and GJIC on the endothelial cell line F-BAE GM 7373 and demonstrated tumor-promoting activity. The inhibition of GJIC by linuron (between the normal and pre-neoplastic cells) creates an environment in which tumor-initiated pre-neoplastic cells are isolated from several growth regulators and results in clonal expansion. Several tumor-promoting chemicals have been reported to block GJIC and thereby disrupt apoptosis (108). The loss of lymphocytes after exposure to the pesticide may also lead to a severely impaired immunological function (183).

Methoxychlor

MXC (1,1,1-trichloro-2,2-bis(4-methoxyphenyl)ethane) is a DDT-derivative OC pesticide that was developed after the ban of DDT and exhibits antiandrogenic and estrogenic activity. It disrupts prolactin secretion by inhibition of dopamine in the hypothalamus and decreases circulatory LH. MXC blocks the surge in LH and follicle-stimulating hormone secretion during the female reproductive cycle (184). MXC stimulates proliferation and human breast cancer cell growth by the up-regulation of genes that involve cell cycle (*cyclin D1*), and the down-regulation of genes *p21* and *Bax* affecting G₁/S transition and apoptosis, respectively, through ER α signaling (185). MXC reduces fertility in female rodents by causing ovarian atrophy and antral follicle atresia (apoptotic cell death) by inducing oxidative stress through mitochondrial production of ROS (186). MXC induced premature nuclear expression of ER gene in neonatal uterine epithelium of mice (187). MXC itself exhibits ER binding potential and the metabolism of MXC forms monohydroxy and dihydroxy metabolites exhibiting estrogenic activity. Another MXC metabolite 2,2-bis(p-hydroxyphenyl)-1,1,1-trichloroethane exhibits reproductive toxicity by binding to ER α receptor and acts as an AR antagonist (188). Chronic exposure to estrogenic chemicals such as MXC leads to persistent cell proliferation causing the formation of neoplastic lesions. MXC interact with nuclear receptors and activates either pregnane X receptor (PXR) or both PXR and constitutive androstane receptor (CAR) (189). In recent years, researches have revealed most unsuspected roles for PXR and CAR in modulating hormone, lipid and energy homeostasis as well as cancer (190). Activation of both PXR and CAR induces CYP3A, and there is a positive association between CYP3A activity, breast cancer disease genesis and lymph node metastasis (191).

Oxyfluorfen

Oxyfluorfen (2-chloro- α,α,α -trifluoro-p-tolyl 3-ethoxy-4-nitrophenyl ether) is a diphenyl-ether herbicide used to control pre-emergent and post-emergent broadleaf and grass weeds in agriculture. Mostly, handlers (mixers, loaders and applicators) are exposed during the use of liquid or granular formulations of oxyfluorfen. It is rapidly absorbed and excreted unchanged in feces and urine with little remaining in the tissues of humans. The primary toxic effects of oxyfluorfen are related to blood and liver disorders. In rodents, it inhibits protoporphyrinogen

IX oxidase enzyme resulting in the inhibition of heme biosynthesis and also induces the symptoms consistent with the expression of human variegate porphyria. The USEPA has classified it as a possible human carcinogen (as an increased incidence of combined hepatocellular adenomas and carcinomas was observed in mice treated with oxyfluorfen). It has also been demonstrated to have the potential to induce mouse liver tumors by non-genotoxic means, but it is not predicted to be carcinogenic in humans (192). Toxicological studies in male mice showed expression of *Cyp2b10* and *Cyp4a10* transcripts, markers of CAR and PPAR α nuclear receptor activation (192). PPs cause hepatomegaly, peroxisome proliferation and increased fatty acid catabolism. Chronic administration of PPs causes liver tumors in rodents (193). Chemicals that interact with PPAR α are known to induce or facilitate liver tumors (194). Though the molecular mechanisms involved in PPAR α -induced hepatocarcinogenesis has not been fully uncovered, recently, it has been demonstrated that PPs may induce severe liver toxicity causing mortality in mice with hepatocyte-restricted PPAR α activation in the absence of ligand (VP16PPAR α). Long-term exposure to PPs results in hepatocellular carcinomas in VP16PPAR α mice by modulating DNA damage response signaling network especially Chk1 and its checkpoint signaling cascade causing increase in DNA synthesis, cell proliferation and apoptosis suppression (195) (Figure 1).

Cross-hallmark relationships

Given that the carcinogenicity of low-dose exposures to chemical mixtures in any given tissue will likely depend upon simultaneous instigation of several important tumor promotion mechanisms and the disruption of several important defense mechanisms, it was felt that one way of visualizing the potential synergies of combinations of chemicals could involve a thorough review of disruptive actions of each chemical across the full range of mechanisms that are known to be relevant in cancer biology. Accordingly, we undertook a cross-validation activity to illustrate the cross-hallmark relationships that are known for the target sites that we identified and to illustrate the extent that these chemicals are also known to disrupt other mechanisms that are also relevant to carcinogenesis.

These relationships are depicted in Tables 2 and 3. Target sites and chemicals that were not only relevant for resistance to cell death but also known to be relevant for other areas of cancer biology were noted as pro-carcinogenic in the areas where evidence existed. Targets and chemicals that were found to have anticarcinogenic potential in other areas of cancer biology were also highlighted where supporting evidence could be found. In instances where reports on relevant actions in other aspects of cancer biology were mixed (i.e. reports showing both pro-carcinogenic potential and anticarcinogenic potential), this was also noted. Finally, in instances where no literature support was found to document the relevance of a target site or chemical in a particular aspect of cancer's biology, this was documented as well.

Perspective

Cell death is intrinsically connected to different kinds of biological damage caused by environmental pollutants. For example, chemicals that promote genetic instability usually trigger apoptosis (a defensive mechanism intended to prevent functionally compromised cells from harming the system). So, hypothetically speaking, exogenous exposures to combinations of disruptive chemicals that act on the mechanisms described previously

Table 2. Cross-validation of target pathways

Target pathways	Deregulated metabolism	Evasion of anti-growth signaling	Angiogenesis	Genetic instability	Immune system evasion	Replicative immortality	Sustained proliferative signaling	Tissue invasion and metastasis	Tumor promoting inflammation	Tumor micro-environment
Binding to ER α	+(100)	-(196)	0	0	0	+(197,198)	+(199-201)	+/- (101-103,202,203)	+(204,205)	+(206)
P53	+(207)	-(208)	-(209)	-(210,211)	+(212,213)	+(214-217)	-(218)	-(219-222)	+(223-225)	+(226)
ErbB-2/HER-2 tyrosine kinase	0	-(227)	0	+(138,228)	0	+(229,230)	+(216)	+(231-234)	+(235,236)	+(237)
ERK/MAPK	+(196,238,239)	+(240,241)	+(242)	-(243,244)	-(245,246)	+(247)	+(154)	+(248-252)	+(253)	+(254)
MAP kinase	+(255)	+(240,241,256)	+(257)	+(138,258)	+/- (246,259)	+(260-262)	+(138)	+(248-250)	+(263,264)	+(254)
P16/p53	0	0	-(265)	-(266,267)	+(268,269)	+(214,270)	-(271)	-(267,272-275)	+(276)	+(277)
Bcl-2/p53	0	+/- (278-287)	+(288,289)	-(290)	+(291-293)	+(229,294)	-(271)	+(289,295,296)	+(297)	+(298)
PPAR- α	+(299,300)	-(301-303)	-(304)	0	0	-(301)	+/- (167,192)	0	+(305,306)	+(307)
GJIC	0	0	0	0	0	0	-(308)	+/- (309-311)	+(312)	+(313)
Hypersecretion of LH by gonadotroph cells in pituitary gland	0	0	0	0	0	0	-(314)	+(315,316)	+(317,318)	0

Target pathways resistance to cell death were cross-validated for effects in other cancer hallmark pathways. Targets that were found to have opposing actions in a particular hallmark (i.e. anticarcinogenic) were denoted using '-'. whereas targets that were found to have promoting actions in a particular hallmark (i.e. carcinogenic) were denoted using '+'. In instances where reports on relevant actions in other hallmarks were mixed (i.e. reports showing both pro-carcinogenic potential and anticarcinogenic potential), the symbols '+/-' were 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 denoted using '0'.

Table 3. Cross-validation of disruptors

Prototypical disruptors	Deregulated metabolism	Evasion of antigrowth signaling	Angiogenesis	Genetic instability	Immune system evasion	Replicative immortality	Sustained proliferative signaling	Tissue invasion and metastasis	Tumor promoting inflammation	Tumor micro-environment
BPA	+(319-322)	+(152)	+(323)	+(155,324,325)	0	+	+(154)	+(326-328)	+(329)	0
DBP	All via hormone disruption	0	+(165)	+(330)	0	0	+(165,166)	0	+(331)	0
Chloroethalonil	0	+(332)	0	+(138,333)	0	0	+(138)	0	+(158)	0
Lindane	+(179,180,334)	0	+(335)	+(243,336)	0	0	+(199,200)	0	+(155)	0
DDVP	+(337)	+(338)	0	+(339,340)	0	0	0	0	+(338,341)	0
MXC	0	0	0	+(342,343)	0	0	+(201)	0	+(344,345)	0
Oxyfluorfen	+(192)	0	+	0	0	0	+(192)	0	+(192)	0
DEHP	+(168,346)	+(169)	0	0	0	0	+(167)	0	+(347)	0
Linuronx	+(348)	0	0	0	0	0	0	0	+(349,350)	0

Disruptors of resistance to cell death were cross-validated for effects in other cancer hallmark pathways. Disruptors that were found to have opposing actions in a particular hallmark (i.e. anticarcinogenic) were denoted using '-'. whereas disruptors that were found to have promoting actions in a particular hallmark (i.e. carcinogenic) were denoted using '+'. In instances where reports on relevant actions in other hallmarks were mixed (i.e. reports showing both pro-carcinogenic potential and anticarcinogenic potential), the symbol '+/-' were used. Finally, in instances where no literature support was found to document the relevance of a chemical in a particular aspect of cancer's biology, were denoted using '0'.

(conferring resistance to cell death) could exacerbate the effects of unrepaired cellular damage. The potential for dysfunction in this key safeguard is therefore an important consideration because this sort of genetic instability increases the overall probability of damage and mutations that could support the emergence of a fully immortalized cellular phenotype.

Past studies have indicated that several cancer hallmark processes are impacted by a variety of chemical carcinogens and oncogenes (95,96), and there are various agencies worldwide such as USEPA and International Agency for Research on Cancer working on classifying the environmental chemicals based on the carcinogenic potential with the purpose of protecting human health. However, the effects of environmental chemical mixtures have had much less attention, and in this project, we have looked specifically at a number of prototypical chemicals with disruptive potential that is relevant to apoptosis. The concern that we have relates to the possibility that individual chemicals that are disruptive of these key mechanisms and pathways may have the potential to contribute to environmental carcinogenesis without being carcinogenic *per se*.

For example, as we noted previously, BPA strikingly impairs TP53 activity and its downstream targets, cell cycle regulators, p21WAF1 and RB, or pro-apoptotic BAX, thereby enhancing the threshold for apoptosis (152). BPA activates mTOR pathway and enhances cell growth and proliferation (351). It also activates PPAR- α (which suppresses apoptosis and enhances cell proliferation), and it inhibits GJIC through a modulation of the gating of gap junction channels, which contributes to tumor formation by increasing intracellular signaling and enhancing proliferation (352). And BPA influences cell proliferation and migration by GPER/EGFR/ERK pathway. But despite a significant and growing body of literature that has documented all of these mechanistic contributions, researchers and regulators have had considerable difficulty proving whether or not BPA has carcinogenic effects in humans (319).

From this perspective, it seems that the longstanding focus on the carcinogenic potential of individual chemicals is really too narrow (given the wide range of environmental chemical exposures that we now face). Instead, it would seem more prudent to focus on mechanistic contributions and anticipated synergies of mixtures of individual constituents that have been shown to individually exert disruptive effects on hallmark cancer processes (at dose levels that are environmentally relevant). In this case, BPA is a good example because it is ubiquitous in the environment and it has also been shown to exert its effects on TP53 at low-dose levels (353). So, even if it cannot be definitively categorized as a human carcinogen, it appears to have potential to play a contributing role in environmental carcinogenesis. Future research will therefore need to illustrate how chemicals that have the potential to produce this sort of a disruptive effect can be experimentally combined with other environmental chemicals that disrupt other hallmark processes to enable carcinogenesis.

We fully recognize that much of the evidence in the toxicological literature that documents the disruptive actions of these chemicals has been produced under a wide range of differing experimental circumstances, and it is not our intent to jump to conclusions about the role that aggregated exposures to mixtures of these chemicals might play in environmental carcinogenesis. But it is our contention that the ubiquitous presence of these (and other) chemicals with disruptive potential needs to be carefully considered, even if these chemicals are not individually carcinogenic. Moreover, researchers who investigate this possibility will also need to consider other mechanisms that are affected by these individual chemicals as well (see Tables 2 and

3). In some cases, dose–response research may reveal thresholds that make these actions unlikely at levels of exposure that are seen in the environment, but to the extent that low-dose effects can be found, these additional disruptive effects may also be important factors to consider.

Conclusions

The disruption of the mechanisms that regulate cell death is fundamentally important to our understanding of environmental carcinogenesis. The enablement of an immortalized cellular phenotype can only occur when many important safeguards have been bypassed. It therefore appears reasonable to consider the effects of ubiquitous environmental chemicals that have been shown to disrupt cell death as it is a very important safeguard. Although a considerable amount of research has been done to characterize the effects that many chemicals have on the mechanisms that are relevant for normal cell death, very little attention has been given to the combined effects of these chemicals on this hallmark of cancer, or the role that these sorts of disruptions at the mechanistic level might serve to contribute to environmental carcinogenesis. In this review, we have identified a number of important targets that are highly relevant for cell death and we have identified a number of ubiquitous environmental chemicals that have been shown to act disruptively on these targets. Future research is needed that looks carefully the role of these prototypical disruptors and other disruptive chemicals that can act on these same mechanisms at levels of exposure that are commonly seen in the environment. Regulators who now focus solely on determining the carcinogenic potential of individual chemicals would be well served to additionally consider the synergies that might occur when chemicals that are disruptive at the mechanistic level are combined with other disruptive chemicals (i.e. those that can enable other complementary processes that are similarly instrumental and enabling in carcinogenesis). To anticipate the sorts of synergies that might be produced, the pleiotropic nature of these chemicals will need to be considered as well. Individual chemicals may produce a range of disruptive effects that are relevant for a multitude of mechanisms, yet individual constituents in any given combination of exposures may not need to be carcinogenic *per se*. Combinations of these chemicals may produce foundational effects that enable carcinogenesis, so progress in our understanding of this potential will help us to refine our approach to cancer risk assessment.

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