Role of Xenobiotic in Autophagy Inflection in Cell Death and Carcinogenesis

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Durgesh Nandini Das and Prashanta Kumar Panda

Abstract

Macro-autophagy (herein referred to as autophagy) is considered a major degradation pathway for damaged organelles, aggregate-prone proteins, and pathogens. There is substantial evidence stating that dysfunctional autophagy is the cause of the manifestation of multifarious degenerative diseases and cancer. Xenobiotics (here, the known group I carcinogens), substances considered foreign to the human body, are associated with inciting multiple stresses such as the endoplasmic reticulum (ER) stress, mitochondrial stress, and dysfunctional lysosome. Furthermore, autophagy exhibits a dichotomous role in cancer, although a detailed description of the modulation of autophagy by the known important carcinogens is provided only by a limited number of reports. The pro-tumorigenic role of carcinogen-induced autophagy/mitophagy has been explored which maintains homeostasis in cancer. On the contrary, the association of carcinogens with the induction of autophagic cell death has been reported. In addition, certain xenobiotics for protecting cells through dampening of necrosis, inflammation, and maintenance of genome integrity have been proposed. So far, only a few

Both authors contributed equally to this work.

D. N. Das (✉)
Department of Life Science, National Institute of Technology Rourkela, Rourkela, Odisha, India

Department of Medicine, Texas Lung Injury Institute, University of Texas Health Science Centre at Tyler, Tyler, TX, USA
e-mail: dasd@wustl.edu

P. K. Panda
Department of Life Science, National Institute of Technology Rourkela, Rourkela, Odisha, India

Division of Medical Oncology, Department of Internal Medicine, Washington University School of Medicine, St. Louis, MO, USA
e-mail: prashantakpanda@wustl.edu

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studies exploring the xenobiotic-associated autophagy modulation, both in vitro and in vivo, have been reported. The synergistic effect of environmental carcinogens in relation to autophagy has been explored, although quite little was discovered. Besides describing autophagy modulation by xenobiotics in the normal cells, there are reports illuminating how autophagy modulation could be utilized as an effective therapeutic approach for the impediment of carcinogenesis and to rescue cells from cytotoxicity. In addition, the application of chemopreventive compounds for autophagy modulation mitigating cellular toxicity and carcinogenesis have been described to achieve a safer and healthier human life.

Keywords

Carcinogenesis · Xenobiotic compounds (XCs) · Autophagy · Mitophagy · Group-1 carcinogen · Cytotoxicity

1.1 Introduction

Macro-autophagy (hereafter referred to as autophagy) is a process of lysosomal degradation in which intracellular cargo such as damaged organelles and aggregate-prone proteins are sequestered in the double-membrane vesicles known as autophagosomes, which subsequently fuse with the lysosome to form the autolysosome. The autolysosome is the organelle that ultimately degrades and recycles the autophagic cargo recycled (Levine and Klionsky 2004; Bhutia et al. 2013; Panda et al. 2015). Autophagy maintains homeostasis in a cell and saves the cell from various stressors such as amino acid starvation, genotoxic stress, hypoxia, and chemotherapeutics (Kimmelman and White 2017). Principally, there are three different types of autophagy—(a) microautophagy, (b) macroautophagy, and (c) chaperone-mediated autophagy (CMA) (Yim and Mizushima 2020). The dysregulation of autophagy is associated with the development of several diseases, including cancer. The role of autophagy in cancer is quite complicated while it plays a tumor-suppressive role during tumor initiation; it induces tumor promotion in the stages of tumor progression (Mathew and White 2011; Kimmelman and White 2017). The process of autophagy comprises five steps: (a) Nucleation of phagophore, (b) Expansion of phagophore, (c) Closure of phagophore to form autophagosome, (d) Fusion of the autophagosome with the lysosome, and (e) Degradation of the autophagic cargo (Galluzzi et al. 2015) (Fig. 1.1).

The International Agency for Research on Cancer (IARC) (Soto and Sonnenschein 2010) lists 107 agents, most of which are chemicals, as known human carcinogens (Group 1), 59 agents as probable human carcinogens (Group 2A), and 267 agents as possible human carcinogens (Group 2B). Most of the agents in Groups 2A and 2B are reported to be carcinogenic in animals, although there is no

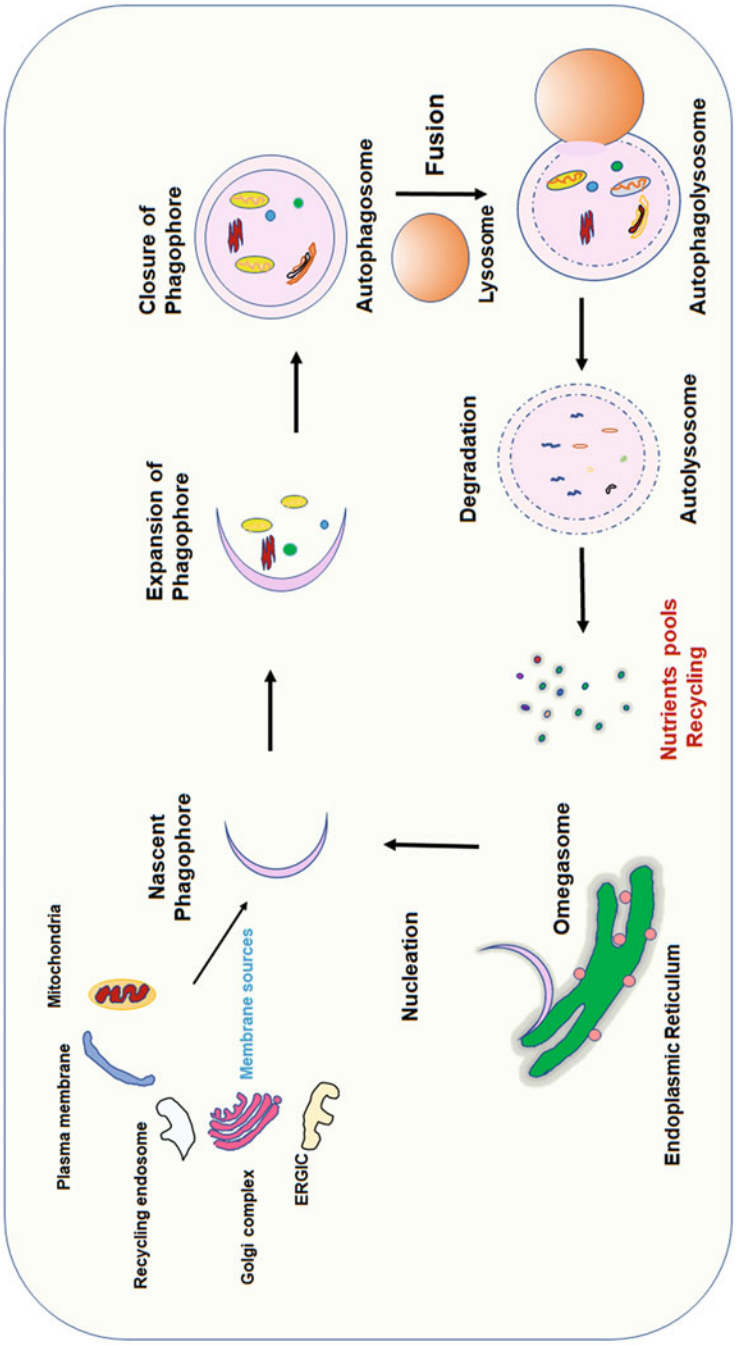

Fig. 1.1 A general schematic for mammalian autophagy process. The nucleation of phagophore begins de novo from the omegasome. However, several other membrane sources, ER–Golgi intermediate compartment (ERGIC), the Golgi, the plasma membrane, mitochondria, and the recycling endosomes, provide inputs for the elongation of phagophore or the isolation membrane. The expansion of phagophore is followed by complete sealing to form the autophagosome. The autophagosome then fuses with the lysosome to create autolysosomes, where the ultimate degradation of the autophagic cargo occurs. Subsequently, the degraded material is recycled back into the cytoplasm for the maintenance of homeostasis in the cell

definitive evidence regarding these being carcinogenic in humans as well. The present article focuses on certain Group 1 xenobiotic compounds (XCs), such as polycyclic aromatic hydrocarbons (PAHs), including Benzo[a]pyrene (B[a]P), 2,3,7,8-Tetrachlorodibenzodioxin (TCDD), dibenzofuran, and certain other inorganic compounds such as cadmium, arsenic, chromium, and nickel (Birkett et al. 2019).

Emerging evidence indicates that alteration in the autophagic pathway could be correlated to the onset of cytotoxicity resulting from chronic exposure to the aforestated XCs. These XCs contain several aryl hydrocarbon receptor (AhR) agonists, which upon activation lead to the induction of cytochrome P450 enzymes capable of converting procarcinogens into the carcinogens, which is a crucial event triggered in an individual for vulnerable to metastatic growth (Androutsopoulos et al. 2009; Hankinson 2016; Das et al. 2017a, b, c).

More importantly, the present article explores the consequences of autophagy modulation by XCs regarding cytotoxicity and carcinogenesis. In addition, autophagy, as well as autophagy-mediated cell death induced by known Group 1 carcinogens, are highlighted. Interestingly, the role of chemopreventive compounds in modulating autophagy and how these compounds could be utilized to rescue cells from toxicity and carcinogenesis as a complementary approach is discussed.

1.2 Aryl Hydrocarbon Receptor and Cytochrome P450 Regulates the Development of Carcinogenesis

The Aryl hydrocarbon receptor (AhR) is an intensively reported ligand-activated transcription factor that is adequately expressed in multiple organs and tissues. AhR contributes to the detoxification process for numerous xenobiotic substances and initiates phase I and phase II detoxification pathways. The XCs toxins that serve as the activators of AhR disrupt several cellular functions to extend the perception regarding the toxic and carcinogenic effects. The toxic compounds activate AhR, which may exhibit acute or chronic toxicity depending on the kind of toxin, its dose, and the health and age of the individual (Jaishankar et al. 2014; Arenas-Huertero et al. 2019). AhR plays an important role in xenobiotic-induced carcinogenesis. Several in vivo studies have demonstrated a substantial connection between the induction of aryl hydrocarbon hydroxylase activity and the carcinogenesis induced by XCs. Exposure to XCs is a major concern because once the XCs have entered the body, they can conveniently cross the cell membrane due to lipophilic in nature. In the cytoplasm, the XCs binds to the AhR, and the resulting system forms a complex with the chaperone proteins, namely, heat shock protein 90 (HSP90), co-chaperone protein X-associated protein 2 (XAP2), and p23 (Reyes et al. 1992; Tsai et al. 2015; Kudo et al. 2018). Binding of XCs to AhR indicates that the activation of the complex and its translocation to the nucleus has begun.

After forming a heterodimeric complex with the AhR nuclear translocator (ARNT), the complex again binds with the 5'-TNGCGTG-3′ consensus sequence of the xenobiotic-responsive element (XRE) present in the promoter region of

several genes, such as cytochrome P450 (CYP450), GST, UDP-GT, and quinine oxidoreductase (Gelboin 1980; Das et al. 2017a). Consequently, it induces the expression of various genes that are involved in XCs metabolism, including the CYP isoforms 1A1 and 1B1. Moreover, binding of XCs to AhR indicates the activation of a transcription factor that augments the expression of various genes, including those encoding the CYP450 enzymes, which metabolize XCs into mutagenic intermediates, ultimately leading to carcinogenesis (Fig. 1.2) (Das et al. 2017a, b, c). Interestingly, AhR is generally known to mediate cancer initiation via DNA damage, attributed to its role in the induction of CYP450 enzymes. The key findings regarding multiple cancer sites have elucidated that exposure to several of these persistent AhR ligands leads to an upsurge in cancer progression through the enhancement of tissue invasion and metastasis.

In AhR-stimulated human lung carcinoma A549 cells it has been demonstrated there is increased expression of E2F1 target genes such as RFC38 and PCNA, which are associated with cell cycle regulation (Watabe et al. 2010). Moreover, Ahr displays a central role for facilitating tumorigenesis, characterized by forming DNA adduct, reducing cell–cell adhesion, and increasing cellular proliferation in cigarette smoke-induced lung carcinogenesis (Tsay et al. 2013). It has been demonstrated that exposure to environmental carcinogen TCDD, activates AhR dependent pathway specifically by increasing expression of matrix metalloproteinases (MMPs), which are involved with increased invasive potential for generating melanoma tumorigenesis. (Villano et al. 2006). TCDD has also been demonstrated to augment MMP10 expression in keratinocytes (De Abrew et al. 2014). The carcinogenicity prospective of XCs is associated with their ability to bind to the DNA, thereby enhancing DNA cross-linking, leading to a series of disrupting effects, which may ultimately result in tumor initiation. These XCs increase cellular toxicity by regulating the generation of reactive oxygen species (ROS), which mediate apoptosis. Similarly, AhR-dependent tumor promoters may serve as significant tumorigenic agents as they possess the capability to enhance the repair of any DNA damage and the development of the initiated cells ultimately driving tumor progression (Dietrich and Kaina 2010).

Cellular toxicity results due to XCs, disturb the homeostasis in the cell by modulating autophagy, which results in unusual proliferation and leading to carcinogenesis. A previous study demonstrated that particulate matter stimulated AhR regulates autophagy in keratinocytes (Jang et al. 2019). Conversely, AhR activation by TCDD led to repressed autophagy in HaCaT cells and normal human epidermal keratinocytes (NHEKs) (Kim et al. 2020). The cellular mechanisms contributing to the manifestation of toxicities are examined by comparing a series of events that begin with exposure, involve a multitude of interactions between the invading toxicant and the host, and culminate in a toxic effect.

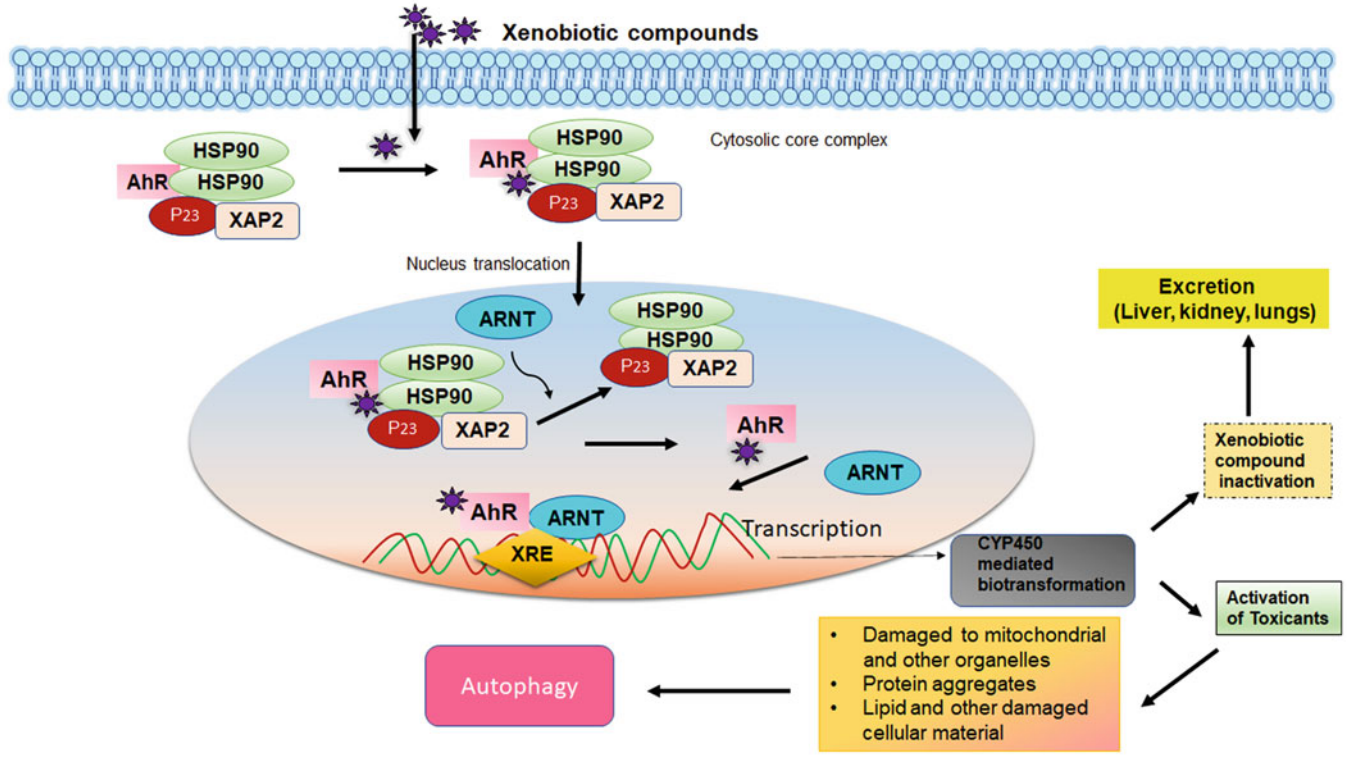

Fig. 1.2 Molecular representation of the biotransformation of a xenobiotic compounds. The schematic diagram illustrates the molecular events that occur following the entry of an aryl hydrocarbon receptor (AhR) ligand-activated transcription regulator for binding to xenobiotic compounds. In the absence of a ligand, the AhR exists within the cytosol as a complex with the dimer of the molecular chaperone named heat shock protein 90 (HSP90), the HSP90-interacting

protein p23, and the co-chaperone protein X-associated protein 2 (XAP2). Molecular chaperone HSP90 is abundant in eukaryotic cells and performs the function of regulating more than 300 target substrates. HSP90 also regulates AhR to maintain the stability of the AhR complex in a ligand-free state within the cytoplasm. In the presence of a ligand, the AhR forms a heterodimer with the aryl hydrocarbon receptor nuclear translocator (Arnt) and translocates into the nucleus, where it binds with the xenobiotic responsible element (XRE) to act as a transcription factor that induces the toxicant-metabolizing enzyme cytochrome P450. The activated xenobiotic compound causes damage to cellular components through, for example, protein aggregates, mitochondrial damage, or other stress

1.3 Cellular Mechanisms Underlying Xenobiotic Compound-Induced Toxicity and Carcinogenesis

Xenobiotic metabolic enzymes are divided into phases I and II that are required for metabolizing of xenobiotics compounds including environmental carcinogens, drugs, and pesticides. Phase I xenobiotic-metabolizing enzymes like Cytochrome P450 (CYPs) are linked with the biotransformation of environmental pollutants and associated with the development of cancer. On the contrary phase II xenobiotic-metabolizing enzymes are linked to biotransformation of xenobiotics to more excretable form while the inability to detoxify ends with the formation of carcinogens which lead to cancer (Nebert and Dalton 2006; Jancova et al. 2010).

Autophagy is stimulated in response to distinct cellular stresses caused by XCs, such as the ER stress, oxidative stress, lysosomal damage, and DNA damage (Lafleur et al. 2013; El-Demerdash et al. 2018; Ashoor et al. 2013; Kvitko et al. 2012) (Fig. 1.3). Interestingly, autophagy operates as a cytoprotective mechanism, degrading the damaged cellular proteins and organelles, which could be toxic to the cell, thereby restoring cellular equilibrium in the cell (Ogata et al. 2006; Moreau et al. 2010). It is noteworthy that autophagy is a catabolic pathway activated in response to various cellular stressors, such as damaged organelles, ER stress, ROS, DNA damage, and the accumulation of misfolded or unfolded proteins. The high levels of ROS in the early stage of XCs related carcinogenesis or cell transformation are oncogenic and cause DNA damage, inhibition of DNA repair, and alterations in normal signal transduction, ultimately leading to malignant transformation.

1.3.1 Endoplasmic Reticulum (ER) Stress Regulates Xenobiotic Compounds Associated Toxicity and Carcinogenesis

ER is considered as an important organelle for containing enzymes needed for xenobiotic biotransformation. The endoplasmic reticulum plays an important role in protein folding and when the load of the unfolded protein dominates it exerts ER stress. Moreover, ER maintains homeostasis in the cell by protein folding (Xu et al. 2005). Modulation of the ER stress signaling pathways is an important concern for protecting against the cellular damage induced by xenotoxicants.

In this context, XCs, such as cadmium, induce the expression of Grp78 through the phosphorylation of eIF2 alpha, which increased the translational activity of ATF4 resulting in ER stress response, which displays a protective role against cadmium-induced cytotoxicity (Liu et al. 2006). In addition, ER stress and change in calcium homeostasis are associated with cadmium triggered apoptosis (Biagioli et al. 2008). Furthermore, cadmium induces ER stress and autophagy in proximal convoluted tubule cells (Chargui et al. 2011). Moreover, cadmium-tempted cytotoxicity by accelerating ER stress and autophagy in retinal pigment epithelial cells (Zhang et al. 2019a).

According to a previous report, cigarette smoke induces protracted ER stress and autophagic cell death in human umbilical vein endothelial cells (Csordas et al. 2011).

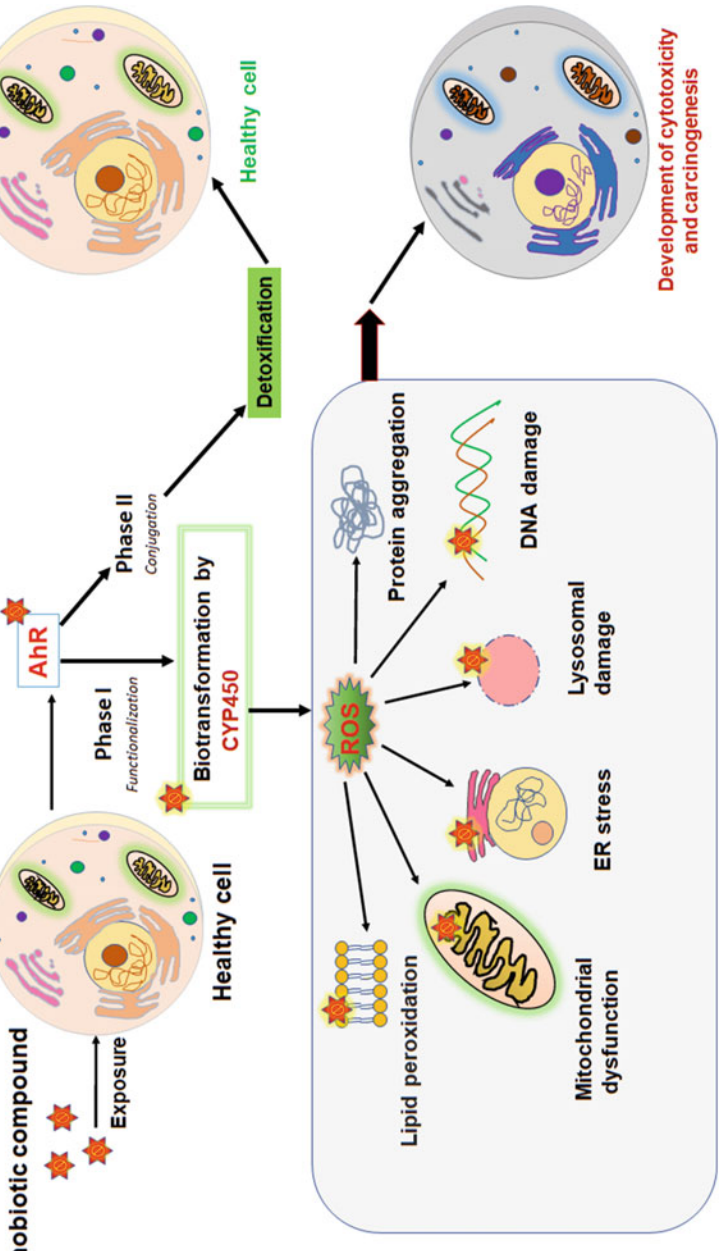

Fig. 1.3 The metabolism Xenobiotic compounds (XCs) regulated by xenobiotic metabolizing enzymes (XMEs). There are two types of XMEs which are classified as phase I (functionalization) and phase II (conjugation) reaction. The CYP450 enzymes play a dominant role in phase I Reaction for the biotransformation of most of the xenobiotic compounds. The complex of the xenobiotic compound with AhRdimerizes with ARNT and recognizes the XRE sequence, which transcribes the enzymes that modulate different cellular processes such as lipid peroxidation, mitochondrial damage, ER stress, lysosomal damage, DNA damage, protein aggregate leading to carcinogenesis. However, some of the XCs bypass the phase I enzymes and follows phase II reaction for detoxification and excreted. However, it is not rigid for the exclusive division of phase I and phase II reactions which need more precise study

Similarly, the elevation of autophagy by arsenic is associated with ER stress, initiation of UPR, and the deposition of protein aggregates in human lymphoblastoid cells (Bolt et al. 2012). In addition, TCDD is reported to induce ER stress in PC12 cells via the PERK-eIF2α signaling pathway (Duan et al. 2014a). However, it has been elucidated that lead compound-induced toxicity stimulates the mTORC1 pathway of autophagy in cardio fibroblasts to ensure survival under ER stress conditions (Sui et al. 2015). Furthermore, B[a]P was reported to induce cell cycle arrest and apoptosis in human choriocarcinoma cancer cells via the ROS-induced ER stress pathway (Kim et al. 2017). Recent findings revealed that the mutual communication between autophagy and ER stress in response to cigarette smoke extract (CSE) exposure stimulates apoptosis in human bronchial epithelial cells (He et al. 2019).

1.3.2 Mitochondrial Dysfunction and Xenobiotic Compounds Triggered Toxicity and Carcinogenesis

In recent decades, there has been an increase in the reports describing the toxic effects of pollutants on the mitochondria. Mitochondria are the major locations for energy production and the execution of oxidative reactions within the cells (Hamanaka and Chandel 2010). Xenotoxicants induce mitochondrial impairment via multiple mechanisms; therefore, several methods are required to evaluate mitotoxicity. Previous studies have reported that mitochondrial dysfunctions lead to increased levels of ROS, mainly to activate autophagy. Moreover, the majority of the ROS are produced in mitochondria. Another factor influencing the generation of mtROS is calcium signaling, in which calcium ions are transferred from the ER to the mitochondria "quasi-synaptically," that is, through closely placed mitochondria-associated ER membranes (Marchi et al. 2017). Calcium encourages ATP synthesis by exhilarating ATP synthase and the enzymes involved in the tricarboxylic acid cycle (Rizzuto et al. 2000), which suggest increased mitochondrial metabolic rate, oxygen consumption, and mitochondrial ROS generation. Calcium accrual in mitochondria results in augmented mitochondrial ROS (Hansson et al. 2008).

B[a]P induces abnormal mitochondria and cellular demise in Hep3B cells (Jiang et al. 2011). Furthermore, PM2.5 stimulates oxidative stress, which triggers the autophagy pathway in A549 human lung epithelial cells (Deng et al. 2013). Cadmium-based quantum dots increase the intracellular ROS levels, affect mitochondrial function, and induce autophagy, leading to apoptosis in mouse renal adenocarcinoma cells (Luo et al. 2013). Studies evaluating the toxicity of zinc oxide nanoparticles (NPs) revealed that these NPs induced cell death in normal skin cells through autophagic vacuole accumulation and damage to mitochondria via ROS production (Yu et al. 2013).

Cigarette smoke exposure induces the stimulation of autophagy and dysregulation of mitochondrial repair machinery resulting in cell death in granulosa cells (Gannon et al. 2013). In accordance with this, another report suggests persistent exposure to cigarette smoke alters mitochondrial structure and function in airway epithelial cells leading to COPD pathogenesis (Hoffmann et al. 2013).

Mitochondrial targeting of CYP1B1 and its role in PAH-induced mitochondrial dysfunction has also been elucidated previously (Bansal et al. 2014). Cadmium also activates ROS induced PINK1/Parkin dependent mitophagy in mice kidneys (Wei et al. 2014). Silica nanoparticles exposure causes ROS-triggered autophagy in MRC-5 cells, which could be a mechanism for cell survival (Petrache Voicu et al. 2015). Similarly, exposure to amorphous silica nanoparticles induces vascular endothelial cell injury following both apoptosis and autophagy via ROS-facilitated MAPK/Bcl-2 and PI3K/Akt/mTOR signaling axis (Guo et al. 2016). Interestingly, TCDD-induced toxicity mediated by mitoAhR localized to the intermembrane space (IMS) influences mitochondrial dysfunction (Hwang et al. 2016). Exposure to particulate matter (PM) induces autophagy in macrophages through the oxidative stress intermediated PI3K/Akt/mTOR signaling pathway (Su et al. 2017). Our group has recently deciphered that the exclusion of dysfunctional mitochondria through mitophagy represses B[a]P-triggered apoptosis in HaCaT cells (Das et al. 2017c). Furthermore, the use of electronic cigarettes induces mitochondrial stress in neural stem cells (Zahedi et al. 2019).

1.3.3 Lysosomal Disruption and Xenobiotic Compounds Prompted Toxicity and Carcinogenesis

Lysosomes play a central role in cellular catabolism, trafficking, and processing of foreign particles. Lysosomes facilitate detoxification and cell survival through the storage and degradation of genotoxic materials. Lysosome pathology may imply cytotoxicity, conceivably leading to cell death, and should, therefore, be considered adverse for cellular injury and dysfunction. Mechanistic investigations may involve the evaluation of cell or tissue-specific clearance pathways and mitochondrial toxicity. Similarly, an impaired lysosomal function may have an impact on autophagy and ultimately lead to an increase in oxidative stress, mitochondrial dysfunction, inflammation, and cell death (Boya et al. 2005; Martini-Stoica et al. 2016).

Moreover, defects in lysosomal capacity result from a modification in the lumen pH and/or altering in lysosomal membrane permeabilization which interrupts the autophagosome and lysosomal fusion. Prevalent variations in membrane permeability may cause acidified cytosol and cellular necrosis (Martini-Stoica et al. 2016). Agricultural insecticide lindane disrupts the maturation of an autophagosome into an autolysosome following aberrant activation of the ERK pathway found in several types of cancer (Corelle et al. 2006). Ji et al. observed that graphene oxide quantum dots blocked the autophagic flux by decreasing the activity of cathepsin B and obstructing the lysosome proteolytic potential in GC-2 and TM4 cells (Ji et al. 2016). Similarly, in hepatocytes silica nanoparticles induced dysfunctional autophagy through lysosomal impairment leading to inhibition of autophagosome and lysosome fusion (Wang et al. 2017a). Likewise, lead disrupts autophagic flux by impeding the formation and activity of lysosomes in the neural cells

(Gu et al. 2019). Furthermore, arsenic nanoparticles induce apoptosis and impairment of mitochondria and lysosomes in isolated rat hepatocytes (Jahangirnejad et al. 2020).

1.3.4 Induction of DNA Damage in Response to Xenobiotic Compounds

Autophagy and DNA damage response (DDR) are two important biological processes that are crucial for cellular and organismal homeostasis. DNA damage activates autophagy, while autophagy is essential for several functional consequences of DDR signaling, including senescence, cell death, the repair of DNA lesions, and cytokine release. DNA damage is the initial crucial step during the process of carcinogenesis. Chemical carcinogens are capable of causing the formation of carcinogen DNA adducts or encouraging other modifications to the DNA, such as oxidative damage and amendments to the DNA ultrastructure (e.g., DNA strand breakage, strand cross-linking, chromosomal rearrangements, and deletions). Prolonged exposure to low levels of arsenic or cadmium leads to cell transformation in the target tissues. Although the mechanism of this cell transformation is not completely understood yet, it is supposed that defective autophagy leading to the accumulation of genomic mutations and epigenetic alterations is a contributor (Mathew et al. 2007). Cigarette smoke induces oxidative stress and DNA damage, and it is more severe as a carcinogen in mice exposed to the chemical from birth (Micale et al. 2013). In A549 cells particulate matter 2.5 (PM2.5) enhanced autophagy, elevated oxidative stress, and activated the tumor necrosis factor-alpha (TNF-α) causing cytotoxicity (Deng et al. 2014). Similarly, particulate matter 10 (PM10) exposure resulted in an elevation in the ROS levels, inflammatory cytokines, DNA damage, and autophagy in human lung cells (de Oliveira Alves et al. 2017). PM2.5 induced oxidative stress via ROS generation, which led to DNA damage, lipid peroxidation, and protein carbonylation; consequently tempted ER stress, depolarized mitochondria, and autophagy, ultimately causing apoptosis in both in vitro and in vivo (Piao et al. 2018). Similarly, cadmium exerts toxic molecular effects and consequently increases DNA strand breaks, elevates the ER stress, increases ROS production, and disturbs the calcium homeostasis. Different signaling pathways such as calcium-ERK and PERK-eIF2α have been implicated in cadmium-activated autophagy (Messner et al. 2016). Arsenic induces the production of ROS/RNS, which may generate a mechanism for the disruptions of DNA repair (Tam et al. 2020).

1.4 Autophagy Plays a Dual Role in Cellular Stress Response: Cell Survival or Cell Death

Increasing evidence has been indicating that several xenobiotic compounds modulate autophagy. Since autophagy plays a dual role, there is an incessant debate on whether autophagy acts as a cell death mechanism or conversely as a cytoprotecting one in the presence of XCs.

1.4.1 Triggering Autophagy/Mitophagy Rescues from Xenobiotic Compounds Triggered Cytotoxicity

There is extensive evidence that autophagy protects against XCs-induced cytotoxicity. Defective mitophagy leads to cigarette smoke-induced lung cellular senescence in chronic airway diseases (Ahmad et al. 2015). For instance, TCDD exposure induced protective autophagy mechanism to ameliorate ROS-induced cytotoxic effects in human SH-SY5Y neuronal cells (Zhao et al. 2016). A study by our research group revealed that B[a]P-induced mitophagy in HaCaT cells as a cytoprotective mechanism to resist cell death (Das et al. 2017c). Moreover, cadmium-initiated autophagy in rat renal mesangial cells has been reported to assist in rescuing against apoptosis- and necrosis-mediated cell death (Fig. 1.4) (Fujishiro et al. 2018).

Bisphenol A (BPA) is a chemical used commonly in the production of polycarbonate plastics and epoxy resins. BPA enters the human body via different routes such as food and drinking water. The current literature reports that autophagy inhibition because of the disruption of autophagosome–lysosome fusion is the main cause underlying the deposition of toxic lipids in the liver. Furthermore, facilitating autophagy by using mTOR inhibitor Torin2 is reported to increase the degradation of toxic lipids, suggesting that autophagy could be used for therapeutic benefit to reduce toxic lipid deposition in the liver (Song et al. 2019).

Recently, it was established that heme-induced toxicity was enhanced upon the inhibition of autophagy in H9c2 cardiomyoblast cells, further corroborating that the differential role of autophagy inhibition depends on the cellular context, dose, and time (Gyongyosi et al. 2019).

Furthermore, it was observed that cadmium triggered cytotoxicity in mouse liver cells which is liknked with the disruption of autophagic flux due to inhibition of autophagosome-lysosome fusion (Zou et al. 2020) (Fig. 1.4).

1.4.2 Autophagic Cell Death Induced by Xenobiotic Compounds

Morphologically, autophagic cell death is characterized by huge autophagic vacuolization of the cytoplasm in deficiency of chromatin condensation (Kroemer et al. 2009). In fact, there is a paucity of established reports where autophagy inhibition completely inhibited cell death induced by xenobiotics. Delayed cell

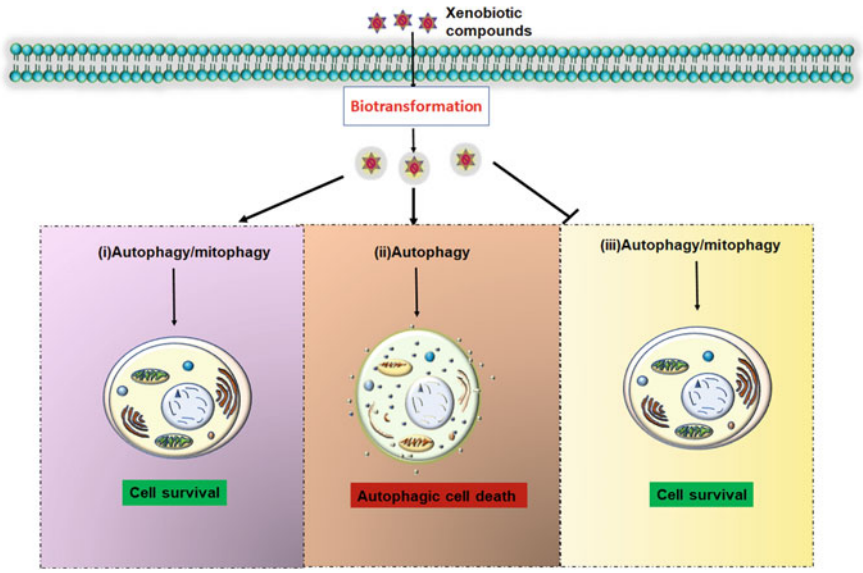

Fig. 1.4 Toxicity and autophagy modulation by xenobiotic compounds. (i) Benzo[a]pyrene and TCDD protect cells by inducing autophagy, whereas bisphenol A, cadmium, cigarette smoke, and heme induced toxicity could be alleviated by stimulating autophagy. (ii) Cigarette smoke extract (CSE) and TCDD-triggered autophagic cell death. (iii) Mitigating autophagy protect cells from cigarette smoke and particulate matter triggered cytotoxicity

death was demonstrated in 3-methyladenine (3-MA) treated or ATG5 knockdown human umbilical vein endothelial cells (HUVECs) which were exposed with cigarette smoke extract. On the contrary, cell death was unaltered after treating with apoptosis inhibitor BCL-XL suggesting manifestation of autophagic cell death induced by CSE is independent of apoptosis (Csordas et al. 2011). Furthermore, TCDD activates cell death through the induction of autophagy in bovine kidney cells (MDBK cells) (Fiorito et al. 2011). Similarly, nuclear receptor 77 (Nur77) was found to promote cigarette smoke-induced autophagic cell death by increasing the dissociation of B-cell lymphoma 2 (Bcl2) from Beclin-1 in lung cells (Qin et al. 2019) (Fig. 1.4).

1.4.3 Mitigating Autophagy/Mitophagy Protects Xenobiotic Compounds Induced Cytotoxicity

In addition to evaluating the effects of autophagy by inducing autophagy, it is equally important to analyze in what way autophagy inhibition regulates the XCs-induced cytotoxicity. Previous studies have reported substantially reduced levels of apoptosis in the lungs of $LC3B^{-/-}$ mice compared to wild type mice, and enhanced resistance to emphysema upon cigarette smoke exposure (Chen et al. 2010). The treatment with autophagy inhibitors, like 3-methyladenine (3-MA) or

spautin-1, reduced the airway injury in particulate matter (PM)-treated mice (Xu et al. 2017). In addition, mice with knocked-down autophagy-related gene Beclin1 or LC3B exhibited reduced airway inflammation and mucus hypersecretion in response to PM exposure (Chen et al. 2019a). Cigarette smoke-induced Nix/BNIP3L-dependent mitophagy triggers airway epithelial cell and mitochondria injury and causes COPD pathogenesis (Zhang et al. 2019b). This result further corroborates that the use of autophagy inhibitors could serve as a therapeutic strategy for inhibiting PM-induced airway inflammation (Fig. 1.4).

1.5 Molecular and Cellular Signaling Responsible for Causing Carcinogenesis upon Exposure to Xenobiotic Compounds

Cancer initiation, promotion, and progression are exceptionally complex processes. XCs induced carcinogenesis may occur via multiple mechanisms (Barrett 1993; Patterson et al. 2018). Evidence suggests that chemical toxicants may operate through genotoxic, cytotoxic, as well as epigenetics pathways, which further complicates the pursuit of alleviating chemical toxicant-associated diseases and cancers. It is also suggested that XCs may induce carcinogenic effects through the disruption of important signal transduction pathways.

1.5.1 PI3K/Akt/mTOR Signaling Pathway

Phosphatidylinositol 3-kinase (PI3K), protein kinase B(Akt), and mammalian target of rapamycin (mTOR), the components of PI3K/Akt/mTOR signaling pathway, play important functions in a cell, such as pathologic changes, cellular physiology, and cell survival. Therefore, disruptions of this pathway result in different types of cancer (Levine 2007; Bartholomeusz and Gonzalez-Angulo 2012; Kandoth et al. 2013; Tai et al. 2017). Chemical toxicants, such as all the members of Group I carcinogens, are capable of inducing malignant cell transformation via PI3K/Akt/mTOR pathway. PI3K/Akt and mTOR signaling pathways are crucial to several aspects of cellular growth and survival in normal physiological conditions as well as during carcinogenesis.

PI3K/Akt/mTOR pathway plays a critical role in multiple cellular functions and is a major regulator of autophagy (McAuliffe et al. 2010). Various growth factor receptors and oncogenes activate PI3K. In fact, elevation in PI3K signaling is regarded as a distinct marker of cancer (Fruman et al. 2017). Members of protein kinase B (Akt)-serine/threonine kinase family mainly exist in three isoforms (Akt1, Akt2, and Akt3) and are common downstream effectors of the PI3K signaling pathway (Fresno Vara et al. 2004). Akt is the master regulator of tumor cell invasion, migration, and metastasis. Current evidence suggests that mTOR is associated with a myriad of functions including lipid generation, nucleotide precursors biosynthesis, metabolic alteration, and metastasis (Yecies and Manning 2011; Ben-Sahra et al. 2013; Valvezan et al. 2017).

Tobacco smoke (TS) is reported to induce lung tumorigenesis through the upregulation of the Akt/mTOR pathway (Memmott and Dennis 2010). Slug induced by B[a]P is involved in the regulation of the invasive properties of fibroblast-like synoviocytes (FLS) in rheumatoid arthritis following PI3K/Akt/mTOR pathway (Lee et al. 2013). Similarly, silica nanoparticles are reported to suppress phosphorylated PI3K, Akt, and mTOR in endothelial cells in a dose-dependent manner (Duan et al. 2014b). Roy et al. reported that zinc oxide nanoparticles induced apoptosis through enhancement of autophagy via PI3K/Akt/mTOR inhibition. The levels of phosphorylated PI3K, Akt, and mTOR were significantly decreased in macrophages upon exposure to zinc oxide nanoparticles (Roy et al. 2014).

Furthermore, PM2.5 stimulates autophagy in human bronchial epithelial cells through suppression of the PI3K/Akt/mTOR pathway (Liu et al. 2015a). In addition, PM2.5 exposure induces autophagy in lung macrophages through the oxidative stress-mediated PI3K/Akt/mTOR pathway (Su et al. 2017). Moreover, inactivating mTOR augments autophagy-mediated epithelial injury in airway inflammation caused by particulate matter (Wu et al. 2020a).

Wang et al. reported that arsenic disulfide attenuates the Akt/mTOR signaling pathway, thereby prompting both autophagy and apoptosis in osteosarcoma (Wang et al. 2017b). B[a]P, a known carcinogen, induces pyroptotic and autophagic cell death in HL-7702 human normal liver cells through the inhibition of the PI3K/Akt signaling pathway (Li et al. 2019a).

1.5.2 MAPK/ERK Signaling Pathway

Mitogen-activated protein kinases (MAPKs) involve extracellular signaling-regulated kinase. Sustained activation of the MAPK/ERK pathway by carcinogens causes a selective alteration in autophagy at the maturation step, resulting in the giant defective autolysosomes accumulation (Corelle et al. 2006). Studies suggest that the activation of extracellular signal-regulated kinases (ERK) could be a contributor to the autophagic effects and promote cell survival (Ogier-Denis et al. 2000; Cagnol and Chambard 2010). B[a]P exposure to HepG2 cells is reported to induce p53-dependent cell death, under the regulation of p38 MAPK and ERK pathway (Lin et al. 2008). Similarly, arsenic is reported to stimulate cell proliferation through enhanced ROS generation, ERK signaling, and Cyclin A expression in HaCaT and Int407 cells (Chowdhury et al. 2010). Furthermore, iron oxide nanoparticles are reported to induce autophagy in RAW 264.7 macrophage in a dose-dependent manner together with phosphorylated ERK (Park et al. 2014). Copper oxide nanoparticle-induced cytotoxicity in human keratinocytes and mouse embryonic fibroblasts mediated via p53 and ERK activation (Luo et al. 2014). In addition, ERK activation plays an important role in enhancing the radiosensitivity of silver nanoparticles; while the inhibition of ERK reduces autophagy, the ERK levels triggered by silver nanoparticles could reduce apoptosis in glioma cells (Wu et al. 2015). Rinna et al. explored the effects of silver nanoparticles on MAPK activation

and confirmed the role of ROS in DNA damage during silver nanoparticles-elevated toxicity in human embryonic epithelial cells (Rinna et al. 2015). In lung cancer cells cadmium induces cell migration and invasion through the activation of the ERK pathway (Zhai et al. 2019).

1.5.3 Hypoxia-Inducible Factor (HIF)

Hypoxia-inducible factor-1 is a heterodimer encompassing α and β subunits. It is a transcription factor that mediates the adaptive mechanism to hypoxia. Hypoxia-inducible factor-1 is regulated mainly by oxygen-dependent changes and could be responsible for regulating autophagy and other hypoxia-related responses (Bruick and McKnight 2001). Studies have reported that nicotine encourages the accumulation of hypoxia-inducible factor-1α protein and vascular endothelial growth factor (VEGF) expression in human lung cancer cells via nicotinic acetylcholine receptors (Zhang et al. 2007). In addition, in human non-small cell lung cancer cells mitochondrial reactive oxygen species facilitate nicotine in elevating the expression of hypoxia-inducible factor-1α (Guo et al. 2012). TCDD is reported to induce hypoxia-inducible factor-1α pathway, oxidative stress, and metabolic stress, contributing to trophoblastic toxicity (Liao et al. 2014). Zinc oxide nanoparticles are reported to enhance ROS generation, apoptosis, autophagy, and hypoxia-inducible factor-1α signaling pathway in HEK-293 cells and mouse kidney tissues (Lin et al. 2016). Hypoxia-inducible factor-1α inhibits the mitochondria-mediated apoptosis induced by silver nanoparticles in human lung cancer cells through the regulation of autophagic flux via ATG5, LC3-II, and p62 regulation (Jeong et al. 2016).

1.5.4 NF-κB Signaling Pathway

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is an inducible transcription factor regulated by signal activation cascades. NF-κB modulates the expression of several genes involved in diverse cellular processes such as cell proliferation and apoptosis and the stress responses to a variety of noxious stimuli, thereby promoting carcinogenesis and cancer progression. It has been reported that PAHs exposure activates the NF-κB transcription factor in the hepatoma cell line (Volkov and Kobliakov 2011). In addition, B[a]P stimulates oxidative stress and endothelial progenitor cell dysfunction by activating the NF-κB pathway (Ji et al. 2013). Moreover, it has been investigated activation of the NF-κB pathway takes place during chronic exposure of B[a]P in hepatocellular carcinoma (Ba et al. 2015). Furthermore, cadmium induces nephrotoxicity through an elevation in the levels of ROS involved in NF-κB -mediated apoptosis (Ansari et al. 2017), while PM2.5 induces apoptosis by upregulating NF-κB signaling in Chinese hamster ovary cells (Peng et al. 2017). Similarly, arsenic induces apoptosis in p53-proficient (p53+/+)

and p53-deficient (p53−/−) cells via differential alteration of the NF-κB pathway (Yin and Yu 2018). Intriguingly, cigarette smoke encourages HMGB1 translocation and release, contributing to migration and NF-κB stimulation through the induction of autophagy in lung macrophages (Le et al. 2020).

1.5.5 p53 Signaling Pathway

The "cellular gatekeeper" p53 acts through transcription-dependent as well as transcription-independent mechanisms which transmits a type of stress-inducing signals for various antiproliferative cellular responses (Zilfou and Lowe 2009). A previous study reported that B[a]P-induced toxicity related to DNA damage and p53 modulation in HepG2 cells (Park et al. 2006). p53 regulates autophagy in an ambiguous manner such as p53 stimulated autophagy leads to cell death or shows protective response depending upon the different cellular contexts (Crighton et al. 2007; Amaravadi et al. 2007). Moreover, B[a]P-induced DNA damage instigates p53-independent necroptotic cell death via a Bax/Bcl-2-dependent mitochondrial pathway in human non-small cell lung carcinoma cell line (Jiang et al. 2013). Besides, B[a]P 7,8-diol-9,10-epoxide promotes p53-independent necrosis following the mitochondria-linked pathway involving Bak and Bax activation (Zhang et al. 2015). In addition, TCDD was reported to induce cell death through autophagy in bovine cells with decreased Mdm2 and increased p53 levels (Fiorito et al. 2011). A study by our research group deciphered that TCDD instigates p53-regulated apoptosis through the activation of cytochrome P450/aryl hydrocarbon receptors in the HaCaT cell line (Das et al. 2017b).

1.6 Xenobiotic Compounds (Group I Carcinogens) Induce Carcinogenesis In Vitro and In Vivo

Carcinogenic compounds may cause cancer either by directly inducing DNA damage or through indirect cellular or physiological effects. Disruptive XCs may contribute to multiple stages of tumor development by influencing the tumor microenvironment. The tumor microenvironment involves intricate interactions among the blood vessels that supply nutrient pool to tumor cells (Casey et al. 2015).

Fibroblast growth factor 9 (FGF9) that plays a substantial role in B[a]P-induced lung adenocarcinoma CL5 cell invasion as well as the progression of human lung adenocarcinoma (Ueng et al. 2010). It has been demonstrated that B[a]P upsurges breast cancer cell migration and invasion through upregulation of the ROS-stimulated ERK pathway and promotes the activation of matrix metalloproteinase-9 (Guo et al. 2015). B[a]P was demonstrated to promote A549 cell migration, invasion, and EMT through the up-regulation of linc00673 expression in an AhR-dependent manner (Wu et al. 2020b). Moreover, the study of the

effects of B[a]P on cancer metastasis and progression reported the NF-κB pathway as a potential target. Increased aggressiveness of B[a]P-triggered squamous carcinomas were observed in PACE4 overexpressed transgenic mice (Bassi et al. 2015). Furthermore, it was also found B[a]P activates the ERK pathway, as well as its downstream partner phosphorylated checkpoint kinase-1 (Chk1), is involved with cellular proliferation in human lung cancer cells (Wang et al. 2015). B[a]P promotes migration, invasion, and metastasis in lung adenocarcinoma cells through the upregulation of the TG-interacting factor (Yang et al. 2018). Moreover, the p38 MAPK pathway is reported to be intricately involved in B[a]P-induced migration and invasion in hepatoma cells (Wang et al. 2019a). Similarly, AhR mediates cell proliferation enhanced by B[a]P in human lung cancer 3D spheroids (Jimma et al. 2019).

The carcinogen nitrosamine 4-(methylnitrosamino)-1-butanone (NNK) found in the cigarette smoke that induces migration and invasion via the activation of a c-Src/PKCι/FAK loop, which may promote the development of human lung cancer (Shen et al. 2012). Electronic-cigarette smoke is reported to induce lung adenocarcinoma and urothelial hyperplasia in FVB/N mice (Tang et al. 2019). Equally increasing evidence suggests that CSE is also found to modulate the expression of Claudin-1, E-Cadherin, and miR-21, which might be associated with increased migration of cancer cells (Dino et al. 2019).

Cadmium is classified as a Group 1 carcinogen and has been demonstrated to be directly associated with tumors of the lung, breast, and prostate (Person et al. 2013; Divekar et al. 2019; Zimta et al. 2019). Similarly, arsenic and cadmium exhibit estrogen-like activity that contributes to the risk of developing mammary tumorigenesis (Divekar et al. 2019). The interaction between Atg4B and Bcl-2 plays an important role in cadmium-induced cross-talk between apoptosis and autophagy through the disassociation of Bcl-2 from Beclin1 in A549 cells (Li et al. 2019b).

Substantial report suggests that TCDD exposure causes disruption of mitochondria changing the mitochondrial membrane potential ($\Delta\Psi m$) and engrosses with mitochondria to nucleus stress signaling (Biswas et al. 2008). TCDD also promotes lung tumors through attenuation of apoptosis via Akt and ERK1/2 signaling pathways activation in female A/J mice (Chen et al. 2014). Moreover, Vk*Myc mouse exposure to TCDD provokes splenomegaly, blood cell abnormalities, and plasma cell carcinoma resembling multiple myeloma (Wang et al. 2019b).

Assessment of the carcinogenic effect of TCDD in vivo using mouse embryonic stem cells revealed the formation of teratoma (Yang et al. 2019). Activated macrophages were reported to be crucial during acute PM2.5-persuaded angiogenesis in lung cancer in a mouse model (Li et al. 2020).

1.7 Autophagy Modulation Induced by Xenobiotic Compounds Regulates Carcinogenesis

Accumulating evidence indicates that autophagy modulation could serve as an effective therapeutic strategy for combating cancer. Studies concerning XCs and autophagy modulation in relation to carcinogenesis are gaining increasing interest from a therapeutic perspective. Evidence suggests that cigarette smoke-induced autophagy in head and neck squamous cell carcinoma (HNSCC) cells and oral keratinocytes (OKF6/TERT2) cells result in the upregulation of ΔNp63α protein expression and a consequent increase in the NOS2 expression. Conversely, downregulation of ΔNp63α, IRF6, or NOS2 mitigates the autophagic process, which further suggests a relationship between smoke-induced autophagy and ΔNp63α/IRF6/NOS2 signaling and corroborates that modulation of ΔNp63α/IRF6/NOS2 signaling and consequently autophagy could serve as an effective therapeutic strategy against cigarette smoke-induced carcinogenesis (Ratovitski 2011). It is also known that cigarette smoke exposure induces cancer-associated fibroblast phenotype through the induction of autophagy, mitophagy, and DNA damage. Moreover, stromal fibroblasts secrete lactate and ketone bodies as a stress response strategy by fueling the oxidative mitochondrial metabolism (OXPHOS) in neighboring epithelial cells (Salem et al. 2013). On the contrary, nicotine, which is one of the active components in cigarette smoke, exhibits protective effects in ulcerative colitis (UC) patients through autophagy induction (Pelissier-Rota et al. 2015). CSE and B[a]P diol epoxide (BPDE) were observed to be involved in the transformation of human bronchial epithelial cells (HBECs) through the upregulation of vasorin expression. Vasorin-induced lung carcinogenesis was enhanced upon inhibition of autophagy-mediated apoptosis in the cigarette smoke treated cells (Chen et al. 2019b).

The study on the mechanism underlying metal-induced carcinogenesis is receiving increasing interest as metals are considered pollutants for several organisms. Only a few reports have investigated the role of autophagy in metal-induced carcinogenesis. Cadmium, which is considered one of the most hazardous materials, affects different organs and organisms. Increasing evidence suggests that cadmium-induced carcinogenesis is associated with the inhibition of autophagy, indicated by the accumulation of autophagosomes and the adaptor protein p62 (Wang et al. 2018; Ashrafizadeh et al. 2019). Inhibition of autophagic flux in cadmium-exposed oral squamous cell carcinoma (OSCC) CAL27 cells results in reduced migration and invasion, suggesting that autophagy plays a crucial role in cadmium-exposed carcinogenesis (Fan et al. 2019). In addition, Psoralidin (Pso), a nontoxic natural compound, inhibits autophagic flux and induces apoptosis in prostate cancer, demonstrating that autophagy inhibition could serve as an effective therapy in cadmium-induced carcinogenesis (Pal et al. 2017).

Besides autophagy modulation in response to exposure to several known carcinogens, some reports demonstrate selective autophagy, such as mitophagy, playing a master role in carcinogenesis (Chang et al. 2017). It is well established that the presence of damaged mitochondria is associated with the initiation of both

central and peripheral COPD-associated non-small cell lung cancer (NSCLC). Excessive dysfunctional mitochondria, which lead to oxidative stress, are observed in COPD patients, and evidence suggests that increased oxidative stress leads to carcinogenesis (Ryter et al. 2018; Ng Kee Kwong et al. 2017). Moreover, COPD and NSCLC are connected through a common mechanistic linkage (Houghton 2013; Ng Kee Kwong et al. 2017). Accumulating evidence display that aberrant lung function upsurges the occurrence of lung cancer pathogenesis (Mannino et al. 2003; Purdue et al. 2007). More importantly, it has been demonstrated that excessive mitophagy is the cause of COPD pathogenesis (Mizumura et al. 2014). Surprisingly, it is important to know the role of autophagy/mitophagy which plays a crucial role in pulmonary diseases (Aggarwal et al. 2016). Furthermore, more mechanistic demonstration of autophagy/mitophagy is required when connecting COPD associated carcinogenesis. There are also reports describing autophagy effect in response to environmental carcinogens such as nickel, which is a Group 1 carcinogen. According to one study, nickel-induced carcinogenesis occurs in human bronchial epithelial cells via a novel SQSTM1 regulatory network (Huang et al. 2016). Another report demonstrated nickel-induced carcinogenesis in human bronchial epithelial cells via increased hexokinase 2 (HK2) expression (Kang et al. 2017). Furthermore, particulate matter (PM) with an aerodynamic diameter of less than 2.5 μm (PM2.5) induces oxidative stress-mediated autophagy in A549 cells. In addition, PM2.5 is considered a novel player for epithelial-to-mesenchymal transition, which contributes to several malignant characteristics observed in cancer (Xu et al. 2019).

The combination of two persistent organic pollutants TCDD and endosulfan disturbs mitochondrial homeostasis and ultimately leads to cell death through the induction of mitochondrial apoptosis associated with an early onset of autophagy (Rainey et al. 2017). Although a few reports regard autophagy as a biomarker for metal-induced toxicity (Di Gioacchino et al. 2008), several studies have established that metal exposure induces autophagic cell death in several cancers. Arsenic, an important carcinogen, is reported to induce autophagy or autophagic cell death, depending on the cellular context. It has been demonstrated that increased SnoN facilitates Beclin-1-independent protective autophagy against arsenic trioxide (As_2O_3)-induced cell death in ovarian carcinoma cells (Smith et al. 2010). Arsenic sulfide (As_2S_2)-induced cell death is promoted upon treatment with autophagy inhibitor 3-MA, suggesting the protective role of autophagy in human osteosarcoma cells (Wang et al. 2017b). According to a report, reduced autophagic flux due to disrupted autophagosome-lysosome fusion was observed in human keratinocytes in response to acute arsenic exposure, which resulted in skin carcinogenesis (Wu et al. 2019). This report delineated that the p62/Nrf2 feedback loop regulates arsenic-induced carcinogenesis. Recent reports suggest that arsenic trioxide is also involved in autophagic degradation in several cancers such as glioma, non-small cell lung cancer (NSCLC), and myeloid leukemia (Kanzawa et al. 2005; Mao et al. 2018; Liu et al. 2020).

1.8 Autophagy Induced by the Synergistic Effect of Cigarette Smoke and PM2.5 Regulates Carcinogenesis

Several reports confirm the association of cigarette smoke exposure and carcinogenesis. However, only a few reports describe the relationship between combinatorial exposure-induced autophagy and carcinogenesis. For instance, combinatorial exposure to cigarette smoke and PM2.5 was reported to increase the levels of autophagy proteins (ATG5, Beclin1, and LC3-II), demonstrating the association of autophagy induction with lung cancer progression. Furthermore, autophagy involved with cell invasion, migration, and EMT was observed in response to combinatorial treatment with cigarette smoke and PM2.5, as evidenced by the siRNA study of the autophagy gene Atg5. Together, these findings suggest that autophagy inhibition could be applied in a therapeutic intervention (Fig. 1.5) (Lin et al. 2018). The mechanisms underlying Group 1 carcinogen-induced autophagy modulation and carcinogenesis remain unexplored to date, and further mechanistic investigations on the role of autophagy and selective autophagy are required for precise therapeutic intervention.

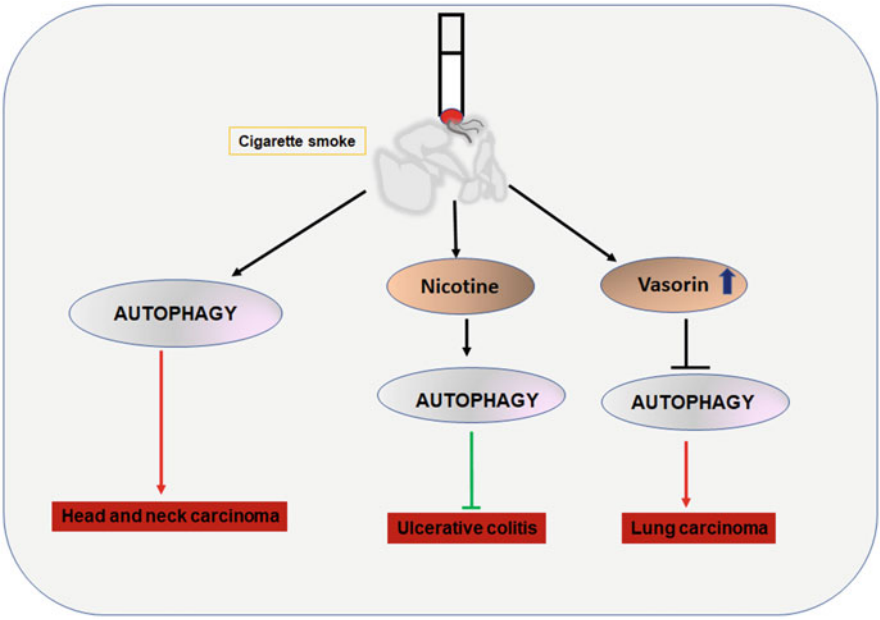

Fig. 1.5 Carcinogenesis and autophagy modulation by xenobiotic compounds. Xenobiotic compounds for example cigarette smoke regulate carcinogenesis via context-dependent regulation of autophagy. Cigarette smoke exposure leads to Head and Neck carcinoma via autophagy induction, while nicotine, one of the active components of cigarette smoke, rescues the cells from ulcerative colitis through autophagy induction. Vasorin upregulation in response to cigarette smoke exposure associated with the inhibition of autophagy which stimulates lung carcinogenesis

1.9 Impact of Chemopreventive Compounds on Xenobiotic Compounds-Induced Toxicity and Carcinogenesis

The chemopreventive compounds exhibited beneficial effects for the prevention of the inhibition of XCs induced cytotoxicity and carcinogenesis. Most of the existing studies on chemopreventive compounds capable of suppressing xenobiotic-induced toxicity have been investigated. For example, capsaicin was reported to modulate the pulmonary antioxidant defense system in B[a]P-induced lung cancer in Swiss albino mice. Moreover, capsaicin also mitigated lysosomal damage in B[a]P-induced lung cancer proliferation (Anandakumar et al. 2008). Another compound baicalein was reported to mitigate the levels of lysosomal enzymes and xenobiotic-metabolizing enzymes in B[a]P-induced lung carcinogenesis in Swiss albino mice (Naveenkumar et al. 2014). Fascinatingly, combination therapy of curcumin and resveratrol was reported to modulate drug-metabolizing enzymes as well as antioxidant indices during lung carcinogenesis in mice (Liu et al. 2015b). Eicosapentaenoic acid inhibits TCDD-induced upstream events of MAPK phosphorylation, the increase in the $[Ca^{2+}]_i$ levels, and the cell surface changes in the microvilli of HepG2 cells (Palanisamy et al. 2015). Likewise, S-Allylcysteine acts as an inhibitor of B[a]P-induced precancerous carcinogenesis in human lung cells by inhibiting the activation of NF-κB (Wang et al. 2019c).

Remarkably, B[a]P-trigger apoptosis was rescued by *Bacopa monnieri* treatment, which provided cytoprotection through Beclin-1-dependent autophagy (Das et al. 2016). Similarly, antidiabetic drug metformin could suppress nickel-induced autophagy and apoptosis by alleviating hexokinase-2 expression and activating lipocalin-2 expression in lung cancer (Kang et al. 2017). Nowadays the precipitous interest has been focused on citrus peel polymethoxy flavones as it prevents B[a]P/dextran sodium sulfate-induced colorectal carcinogenesis by modulating xenobiotic metabolism and ameliorating autophagic defect in ICR mice (Wu et al. 2018). Sulforaphane, a natural dietary compound generally found in the cruciferous vegetables such as broccoli, prevents cadmium-induced carcinogenesis by restoring autophagy, diminishing Nrf2, and reducing apoptosis resistance (Wang et al. 2018). Recently another group investigated natural flavonoid iso-orientin, attenuates benzo [a]pyrene-induced liver injury in vitro, and in vivo through the inhibition of autophagy and pyroptosis (Xueyi et al. 2019).

1.10 Conclusion

The present article discusses the role of the important Group 1 carcinogens in modulating autophagy. Although it is well established that autophagy plays an important role in cancer cell maintenance, increasing evidence has been suggesting that autophagy inhibition or dysfunctional autophagy is also associated with the induction of carcinogenesis. Several studies have reported the association of carcinogens with cancer development, the literature concerning the regulation of carcinogenesis by XCs-induced autophagy is scanty. Moreover, little research has

been conducted to decipher the roles of selective autophagy, such as mitophagy, ER-phagy, pexophagy, lysophagy, and ciliophagy, for the regulation of carcinogenesis induced by Group 1 carcinogens; this area of research requires exploration for precise dissection of autophagy in search of better therapeutics. The study of XCs-induced toxicity and carcinogenesis is required for planning and implementing better therapeutic strategies in the future. The study of the combinatorial effect of important carcinogens in relation to autophagy represents another research area to be explored in the future to discover possible therapeutic benefits. Moreover, it is imperative to understand the mechanism underlying the carcinogenesis regulated by XCs stimulated autophagy. It is vital to search for potent autophagy inhibitors, only a few of which are reported in the literature so far. The currently available data regarding metal-induced carcinogenesis has also been discussed, with special emphasis on autophagy. The current research on XCs induced autophagy and metabolism alteration in relation to carcinogenesis is at a stage of infancy which should be addressed. In summary, delineating the complicated interrelationship between xenobiotics and autophagy modulation will attract autophagy scientists for investigating autophagy intonation could be effective therapeutics in the case of cytotoxicity and carcinogenesis.

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