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Review Article

Particulate matter induced cell death: Current understanding of molecular drivers that lead to lung damage

Durgesh N. Das [a,b,1], Dhruv Mitroo [a,b,*]

[a] The Veterans Research and Education Foundation of St. Louis, St. Louis, MO 63103, USA
[b] John Cochran Division, Veterans Affairs Medical Center, 915 N. Grand Blvd., St. Louis, MO 63106, USA

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ABSTRACT

Particulate matter (PM), ubiquitous in indoor and outdoor air parcels, is an environmental hazard and poses a risk to human health. The proclivity for PM to be continuously inhaled is what leads to adverse human outcomes. This is because often if not always, PM is chemically laden with toxins. The scientific literature is impressively growing with studies in vitro and in vivo that probe PM-induced cellular deaths, resulting in improved knowledge of disease onset. New cell death mechanisms are being proposed, including revisions of canonical definitions (e.g., necrosis). It is helpful in our view if the current knowledge of the processes within a cell initiated by PM insults and leading to cell death are summarized and supplemented to the literature. Such a summary should highlight proteins that act as death activators or gatekeepers in a given affected transduction pathway. Additionally, this summary should discern how PM dose can promote cell death versus lead to signaling that restores cell function. The result should underscore cell resiliency and provide insight on therapeutic strategies. To this end, the objective of this review is to present reception, transduction, and the response of a cell to PM exposure. We emphasize cellular transduction pathways that have been reported by the literature as impacted significantly by PM uptake (that would otherwise occur during homeostasis in a well-regulated manner) and the resulting defined cell deaths: autophagy, apoptosis, necrosis, and cuproptosis. We find that while reactive oxygen species (ROS) and subsequent inflammatory cytokine release are commonly studied and subject to therapeutic research, damage to organelles such as the mitochondrion (and leading to mitophagy) is receiving equivalent attention as attractive research targets. We conclude the review by scaling cell death to organ or organism pathophysiology and the importance of a genetic mutations for burden of PM-induced disease. That is, while air pollution or PM might not directly cause mutations, it can be a driver by creating an environment within the cell that favors the growth and progression of cells with these mutations.

1. Introduction

1.1. Background and human context

As of 2016, air pollution is the second highest risk factor for non-communicable diseases with cardiovascular diseases being the leading driver followed by chronic respiratory diseases [1]. Particulate matter (PM) refers to airborne particles ranging from solid to liquid typically no larger than a few tens of micrometers, thus remaining airborne long enough to become a component of the surrounding air parcel, that significantly contribute to air pollution. As such, PM represents a very mobile environmental component and often times an inhalation hazard. From a regulatory or exposure monitoring metric, PM is classified into three categories based on aerodynamic diameter: < 10 μm (PM_{10}), < 2.5 μm ($PM_{2.5}$), and < 1 μm (PM_1). However, when consdiering inhalation hazards, it is common to re-classify the three catgories as coarse (10 μm - 2.5 μm), fine (2.5 μm - 0.01 μm), and ultrafine (< 0.01 μm). Perhaps the most widely recognized category is $PM_{2.5}$ for its measurement feasibility and calculable mortality burden, latter for which ranges from approximately 1 to 5 million annual premature deaths according to recent estimates [2–4]. The noncommunicable diseases (that eventually lead to these premature deaths) associated with $PM_{2.5}$ exposure include cardiovascular diseases, strokes, chronic obstructive pulmonary disease (COPD), lower respiratory diseases, and lung cancer [5].

* Corresponding author at: John Cochran Division, Veterans Affairs Medical Center, Building 7A, Room 101, 915 N. Grand Blvd., St. Louis, MO 63106, USA.
E-mail address: dhruv.mitroo@va.gov (D. Mitroo).
[1] Present address: Department of Medicine, Division of Pulmonary & Critical Care Medicine, Washington University in St. Louis, St. Louis, Missouri, 63110, USA.

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At the cellular level, the cytotoxic effects of PM can be divided into long- and short-term depending on symptoms, impairment of lung function, and need for hospitalization. Unresolved though is etiology of PM-related diseases, largely, due to the multitude of sources, complex flux of PM formation, chemical and physical alteration (such as atmospheric aging or aggregation through coagulation), and loss from circulation. The challenge associated with relating a component of PM to a specific disease is further complicated by climate change, changing societal behavior, and large-scale anthropogenic activity such as mining and agriculture. This underscores the importance for research on specific at-risk populations [6–10].

Inhalable PM is defined as the fraction of total suspended PM that enters the nasal and oral cavities and deposit in the pulmonary system [11]. Each individual particulate then, depending on its size, either deposits in different regions of the lung or is exhaled. The fraction that ultimately deposits is called the deposition fraction. Taken together, this narrows the set of PM that is relevant to inhalation exposure. This relevant set can then be segregated into subsets. Three such subsets are typically discussed when modeling regional or local deposition: the fractions that deposits in the head region, conducting airways, and gas exchange region [12–14]. Each region has an associated dominant aerosol deposition mechanism, not discussed further in this review. Relevant to this review is that the local or regional deposition along the respiratory tract affects disease progression within the host species. Lung deposition models suggest very large (PM_{10}) and very small ($<PM_{0.01}$) aerosols are lost to the head region, implying that $PM_{2.5}$ and PM_1 are the PM sets that pose significant risk to lung function [15]. Once in the alveolar region, some constituents can translocate across the gas-blood barrier and enter systemic circulation [16,17]. Translocation mechanisms range from diffusion of constituents the size of large biomolecules to tight junction disruption, and are beyond the scope of this review. Although alveolar deposition has far-reaching consequences to pathogenesis beyond the pulmonary system, recent work suggests the largest deposition site of inhaled $PM_{2.5}$ and PM_1 in the acinar region is the small airways [17–20]. Thus, distal airway insults become a relevant injury mechanism for lung disease.

The airway epithelium is the first location of interaction between PM and the human body. As such, the development of advanced in vitro models using pulmonary epithelial cells is gaining traction [21]. The airway epithelium is pseudostratified, highly differentiated, known for tight junctions, and the respective makeup of cell types (including epithelial, goblet, basal, club, and others to a minor extent) changes in each region of the respiratory system, from the nose to the alveoli [22]. Importantly, the upper airway contains mucus and cartilage whereas the lower airway contains smooth muscle and macrophages [23,24]. This distinction is important as PM removal mechanisms differ. In proximal airways, mucus, a sticky, viscous fluid containing mucins and highly glycosylated proteins, lines the airway epithelium and in conjunction with ciliary beating has the function to protect the human body by trapping, moving, and ejecting (through breathing, coughing, or sneezing) PM. This process is called mucociliary clearance [25]. In the distal airway epithelium, such as alveolar ducts, alveolar macrophages engulf PM during phagocytosis, and if the immune response activated thereafter is adequate, PM is metabolized and excreted [26]. A problem arises when the dose or component of PM frustrates any two of these physiological processes thereby initiating disease.

1.2. Purpose of this review

A limiting factor in our current knowledge of lung pathogenesis stemming from PM exposure is the biological response leading to cytotoxicity: from the activation of cellular response pathways, to cellular homeostasis disruption, and ultimately cell death. The purpose of this review is to summarize the current knowledge of the biological response at the cellular level resulting from a PM insult and briefly scaling that to what occurs when PM resides in the lung and ultimately leads to a diseased state of the pulmonary system. We place special emphasis on pathways towards cell death including recent discoveries and proposed cell death mechanisms that might become relevant to clinical outcomes and significantly supplement our knowledge of pathogenesis and pathophysiology as it stands currently. To provide context within the signaling pathway, we discuss also reception and transduction. The inclusion criteria for studies that support this purpose are recency and administration of a substance beyond pure compound (i.e., real PM, lab-generated PM, or commercially available nanoparticles). The inclusion criteria for previous reviews are historical context, updates, and supplemental reading for topics of interest related but beyond the purpose of this review. We hope this review increases the visibility of such pathways to the scientific community.

The scope of this review is limited to cell death, not cell survival, therefore we limit discussion on immune responses and multi-tissue signaling. However, we believe it is important to include discussion on inflammation and provide the reader with understanding that, generally, PM-induced inflammation (systemic or local) is inevitable at the organism scale. We do so from a toxicology perspective and not an immunology one, that is, how exposure to PM can induce an inflammatory response, and not what that response looks like. Therefore, the inclusion criteria for studies that support this scope are an explicitly stated nominal PM dose, a measurable endpoint of cell death, a measurable inflammatory response, and an explicit reference to a signal transduction pathway.

The structure of this review is based on direct and indirect effects. We begin by addressing the paradigm that PM is spatially and temporally uniform. This section is relevant in our view as it brings the aerosol and medical communities together on common misnomers. We then provide an overview of how a cell recognizes a foreign body and begins the process of metabolism and excretion. Because modern PM contains compounds novel to the human body, their metabolism ultimately leads to unintended consequences including organelle damage, stasis disruption, inflammation, and epigenetic alterations. It is, as we present, during metabolism that an abnormal process begins; as cells try to survive, they eventually fail, and through different avenues reach the same fate, death. These are avenues that go beyond autophagy and apoptosis. We conclude the review with a brief summary of known (pulmonary) clinical outcomes of PM exposures, including lung cancer, with emphasis on the relevance of Kirsten rat sarcoma virus (KRAS) and Epidermal Growth Factor Receptor (EGFR) oncogenes in the context of random mutations versus those induced by air pollution.

2. On the heterogeneity of PM

Reviews already exist that highlight heterogeneity of PM [27–31]. Reading of these reviews can be supplemented with the reading of the many case studies, available in the literature and not listed herein, that associate health outcomes with ambient PM, emphasizing its spatial and temporal variability. An acceptable conclusion from reading the reviews is that atmospheric PM is complex. An acceptable conclusion from reading case studies is that PM complexity is tied to health outcomes. To keep in line with our scope, in this review, we limit modeling PM as an abiotic mixture.

Physically, PM can present itself with a range of fractal structures, glassiness/viscosity, and porosity. Chemically, it can be comprised in equal parts by myriad species (e.g., urban aerosols) or one (e.g., industrial manufacturing), as either a core-shell or uniform mixture. Optically, it ranges from very scattering to very absorbing. As a population, it can be classified as internally or externally mixed, a topic that has gained recent attention by aerosol scientists when reconciling measurements to models [32]. It can originate from biogenic (natural), anthropogenic (manmade) sources, or both. Components that make up atmospheric PM include water, microorganisms (we don't discuss this further to remain within the scope of this review), carbonaceous compounds (both organic and elemental), inorganic compounds, metals, and

minerals [33].

Owing to this complexity, PM induces a response in cells, and in tissue more broadly, by more than one route. Perhaps the most widely studied route/response is oxidative stress (OS) induced by sustained overproduction of reactive oxygen species (ROS). However, other routes exist such as by cell membrane disruption [34] or modification to DNA either directly or by changes to the epigenome [35–37], and these routes may be specific to cell types (e.g., epithelial versus endothelial cells or even macrophages). Following OS, the corresponding responses include organelle stress and inflammation (discussed in Section 6). Inflammation is a more complex outcome compared to organelle stress and cell membrane disruption because it involves a whole tissue, organ, system, or even the whole organism's coordinated response; this can result in cell or tissue survival through pathogenesis rather than direct cell death. Ultimately, cell death ensues by increased autophagy and apoptosis rates (discussed further in Section 7), by necrosis (discussed further in Section 7), or in the case of inflammation, by an immune response from either the myeloid or lymphoid system [38–40] that results in dispatching affected cells (e.g., phagocytosis by alveolar macrophages; [41]). These represent abnormal death routs distinct from well-regulated autophagy (main catabolic route of the cell) and apoptosis (programmed cell death). To clarify, apoptosis is a normal process during homeostasis; it is the increased instances of apoptosis that are abnormal and driven by PM exposure. Other abnormal, PM-induced death routes for the cell beyond these two are being discovered or proposed, and are presented in Section 7. Such abnormal death routs are worth exploring in this review for two main reasons. First, because to date we do not fully understand said mechanisms, nor whether they are induced by specific atmospheric or industrially manufactured (that is, highly pure, therefore interacting with the human cell in a very specific way and evoking a unique response) nanoparticles. Second, because climate change and deforestation exacerbate PM burden with increased sources from conflagrations [42–45] and aridification of endorheic basins [46–49]. With the likelihood that PM exposure becomes more complex to quantify, research with the aim of developing protective, prophylactic, and therapeutic strategies is needed and the intent of Section 7 is to help increase awareness of emerging PM-induced abnormal death routes to the scientific community. Sections 3 – 6 are the sequence of events inside the cell, that we believe are of value to the reader, leading up to said death routes.

3. Activation: role of the aryl hydrocarbon receptor, a transcription factor, in PM-induced cytotoxicity

The human cell has many ways of detecting and responding to changes in the extracellular environment, including ion channels and other surface proteins collectively known as receptors [50]. When a foreign body is introduced in this environment, cellular receptors have evolved to kickstart signaling. This process is best described by three stages. Reception, the first stage, is when such body, referred to as the ligand, binds to a receptor. Transduction, the second stage, occurs shortly after because the now activated receptor engages in a signal-transduction pathway. The response, which is the third and final stage, is the outcome [51]. PM often presents itself as an abiotic mixture. This implies that the immune system may not be immediately activated because the mixture does not contain viruses, bacteria, or other microorganisms, and is instead triggered by a slower inflammatory response. A ligand-activated receptor exists in many human cells whose function includes sensing xenobiotic molecules: the aryl hydrocarbon receptor (AhR; [52]), which is highly expressed in the human lung [53]. Unlike most receptors, the AhR (in its inactive state, that is, prior to ligand binding) is not found on cell surfaces. It is found in the cytoplasm.

Many reviews address the importance of this receptor, and over the past three decades its role and function(s) have been re-evaluated [52, 54–65,]. It resides in the cytoplasm as a part of a larger protein complex which includes chaperone proteins [61] that help prevent its degradation [66]. Ligands that activate the AhR are varied, however well-recognized ones include polycyclic aromatic hydrocarbons (PAHs), such as benzo[a]pyrene, and halogenated aromatic hydrocarbons (HAHs), such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) [8,67]. The activated complex then translocates to the nucleus where the AhR dissociates from its chaperone proteins to heterodimerize with the AhR nuclear translocator (ARNT), forming a new complex that induces transcription of targeted genes [61,68]. Such genes are preceded by a nucleotide sequence known as xenobiotic response elements, where the AhR binds to [69,70]. The genes that code for Cytochrome P450s (Cyp450s) are perhaps the most widely-recognized genes activated by the AhR-ARNT complex upon binding to DNA, likely due to their role in metabolism (see Section 4) and thus early signal transduction. The literature is filling with evidence that Cyp450 gene upregulation is associated with PM exposure, specifically, in response to the organic fraction of PM [71–79]. Other upregulated genes of interest however include those coding for glutathione S-transferases [80–82], quinone oxidoreductases [72,83,84], interleukins [73,74,85–87], cyclooxygenase-2 (COX-2; [65,79,86,88–91]), and nuclear factor erythroid 2-related factor 2 (Nrf2; [76]). Several signaling pathways and cascade reactions exist involving these genes, such as the Nrf2-antioxidant response element (ARE) in response to OS, or the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) to invoke an immune response, which are discussed later in this review.

4. PM metabolism: the most widely studied of xenobiotic-metabolizing enzymes, Cytochrome P450s

4.1. Overview of xenobiotic-metabolizing enzymes

Cyp450s are a superfamily of monooxygenase enzymes whose primary function is catalyzing electron transfer that leads to oxidation reactions with substrates [92–95]. Structurally, Cyp450s have an iron cofactor in their active site that binds to molecular oxygen, transferring an oxygen atom to a substrate (with the other being reduced to water) [96,97]. 57 genes within the human genome are known to encode for over 50 Cyp450 isozymes [98,95]. While these enzymes were first discovered in the late 1950s / early 1960s [99–103], in recent decades they have been studied for their role in bioactivation: metabolism of drugs and other xenobiotics [104–106]. Recent literature suggests there are about 15 such isozymes that are actively involved in drug / xenobiotic compound metabolism [95,107,108]. While Cyp450s are found in highest concentration in the liver, they are found elsewhere, including in the lung, likely to start metabolizing inhaled xenobiotic compounds.

Metabolism by Cyp450s has historically been modeled as a two-step process: activation by oxidation (phase I) and conjugation to render the xenobiotic of interest hydrophilic (phase II, sometimes considered "detoxification") [8,109–111]. However, some reviews model this metabolism process as four steps, namely, translocation inside the cell (phase 0), phase I, phase II, and liver processing for excretion (phase III) [112,113]. For the sake of this review, we will limit our discussion to phases I and II, treating them as parallel rather than series processes. We do this to engage the reader on the problem xenobiotics metabolism poses, which is that the initial functionalization that takes place in phase I can lead to toxicity [8].

Other important xenobiotic-metabolizing enzymes (XMEs) exist in mammals beyond Cyp450s. These include glycosyltransferase such as uridine 5′-diphospho-glucuronosyltransferase (UGTs; [114–117]), flavin-containing monooxygenases (FMOs; a different family of monooxygenases than Cyp450s) found in the endoplasmic reticulum (ER; [118–123]), epoxide hydrolases (EHs; [124–127]), sulfotransferases (SULTs; [128–130]), and glutathione S-transferases (GSTs; [131–133]). These XMEs have both membrane-bound and cytosolic forms. To the best of our knowledge, there is no evidence of existence of intranuclear XMEs.

Much like some drugs that need to be activated to induce a biological

response, PM components such as PAHs induce a biological response only after activation. The effect of PAH-containing PM, and model molecule benzo[a]pyrene (BAP), on the human body are studied due to phase I leading to carcinogenic products [8]. The problematic step in phase I is formation of oxidized products (such as epoxides and quinones) from Cyp450s, which are hydrophilic and electrophilic. This leads to downstream aberrant reactions including DNA binding and thus alteration of DNA function without the DNA structure itself altered (i.e., epigenetic changes). Metabolomics best addresses this topic, and such information is available elsewhere in the literature [134]. Therefore, excretion does not take place (or at least, not as efficiently), and the "detoxification" cycle does not complete.

4.2. Studies on Cyp450s

To date, 18 mammalian Cyp450 families are known, and convention labels such families as "Cyp1", "Cyp2", "Cyp3", and so on [98]. Eight enzymes in the Cyp1-3 families account for most drug metabolism, probably because they contain significantly more genes than the other families [135,136]. The literature associated with PM-induced expression is ripening, demonstrating such families also account for PM metabolism. To summarize all studies associated with PM's effect on Cyp450s expression is beyond the scope of this review. Within the scope is to list the known isozymes detected in response to organic and metallic compounds commonly found in PM, as these two constituents have been proposed in a recent review by Salana and Verma [29] to be important contributors towards PM toxicity. For familiarity with the Cyp450 enzyme family prior to reading Subsections 4.2.1 and 4.2.2, we recommend reading either the full chapter or the specific section on the Cyp450 enzyme family of Perry and Collard [111].

Of note is the ongoing discovery of how, and to what extent, Nrf2 (like the AhR, Nrf2 is also a transcription factor) regulates Cyp450s expression through DNA methylation. For context, the 5′-C-phosphate-G-3′ (CpG) sites are DNA regions where methylation can occur. We know methylation is typically done by DNA methyltransferases (DNMTs; [137]). However, to our knowledge, we do not know if xenobiotic-induced methylation, which is one of several types of epigenetic change resulting from PM exposure [8], occurs directly at this site or by alteration of DNMTs. Given this context, the way Nrf2 alters Cyp450s expression is hypothesized to be by regulating DNA methylation of the CpG units. This hypothesis comes from recent studies comparing the response between $Nrf2^{-/-}$ (KO) and wild-type (WT) mice to $PM_{2.5}$ [138], and drugs [139]. These are important discoveries in understanding how Nrf2 helps cells adapt to OS, in these cases, by inducing expression of cytoprotective genes (such as those coding for Cyp450s).

4.2.1. Organic compounds

While organics such as PAHs, dioxins, furans, and biphenyls in the bloodstream tend to be metabolized by the liver, lung cells, probably owing to their high AhR expression, can metabolize them also as shown by in vitro studies using model compounds [140–142]. PAH metabolites include hydroxylated PAHs and dihydrodiols, which are used as biomarkers in urine specimen for PAH exposure [143,144]. CYP1A1 and CYP1B1 proteins (enzymes) are perhaps the most important Cyp450s involved in the metabolic activation of PAHs [145]. However, the extent to which enzyme is more important is unclear and dependent on the relevance of the in vitro model; for example, CYP1A1, CYP1A2, and CYP1B1 protein expression in response to benzo[a]pyrene differs for human liver cells when cultured as 2D monolayer versus 3D spheroids [146]. Dioxins do not appear to be metabolized as extensively as PAHs, however studies in animal cells are scant and dated [147,148]. CYP1A1, CYP1A2, and CYP1B1 proteins are reported to be the most important Cyp450s involved in the metabolism of dioxins [149,150]. Extraction of the organic fraction from diesel PM induces a higher CYP1A1 protein expression compared to the elemental carbon core [73].

4.2.2. Metallic compounds

Although transition metals are subject of investigation due to their potential to induce ROS inside the cell [151], we did not find evidence or a mechanism by which Cyp450s metabolize metallic compounds. Rather, and besides ROS production, metallic compounds exert effects on enzymes by inhibition [152].

5. Oxidative stress and related damage to the human airway

In the context of the human body, free radicals are potent, short-lived oxidizers due to their unpaired electron, and are important components of ROS. However, other less potent but longer-lived ROS exist, such as hydrogen peroxide (H_2O_2), which can dominate the ROS makeup within a cell or tissue. A balanced concentration of ROS is important to homeostasis; it is the elevated and sustained production that induces OS in cells. OS occurs precisely because unbalanced ROS concentration, accumulating (ROS overproduction), overwhelms the antioxidant "defenses" of the cell, and causes tissue damage [153,154]. A redox imbalance is another way to call OS [155,156]. Excluding inflammation followed by immune responses, there is not a set primary mechanism that leads directly to tissue damage following OS, rather, in our opinion, it is the damage to different organelles. The series of cellular events covered so far in response to PM, from AhR-mediated activation to XME-induced metabolism, can elicit OS due to the sudden unmanaged production of ROS. Our understanding is that this production results from either the activation phase (phase I) during xenobiotic metabolism [157–159], or bioavailable transition metals in PM that can generate high concentrations of ROS due to their low affinity of outer (d-orbital) electrons [151], donating those to molecular oxygen. The extent to which a component of PM can generate ROS is known as the oxidative potential (OP; [160–162]), and is a currently accepted general indicator of PM toxicity [163,164]. A figure of all the steps described thus far from inhalation to eliciting OS is presented in Fig. 1.

For literature on PM-induced OS in the trachea, bronchi, small airways, and alveoli, we direct the reader to the following reviews: Albano et al. [21], Mudway et al. [165], and Mazzoli-Rocha et al. [166]. Important highlights from these reviews include inflammation mediators nicotinamide adenine dinucleotide phosphate (NADPH) and duox oxidase 1 (DUOX1), the mitogen-activated protein kinase (MAPK) and NF-κB (a transcription factor that, like the AhR, exists in the cytosol, but that unlike the AhR isn't directly activated by PM) pathways, role of COX-2, and role of interleukins.

6. Endoplasmic reticulum and mitochondrial stress

Cyp450s are predominantly found in the ER membrane alongside other XMEs, as mentioned in Section 4.1. However, in animals they are also present in the mitochondrial membrane [167,168]. The ER's primary function is protein synthesis, including protein folding, whereas the mitochondrion's primary function is energy production for the cell [169].

6.1. Endoplasmic reticulum stress

Of the cellular processes calcium is involved in, metabolism and cell death are of interest to us in the context of both ER stress and communication between the ER and the mitochondrion. The ER is the organelle with the highest concentration of calcium [170,171]. Depletion of calcium can lead to accumulation of improperly folded or unfolded proteins; this is the definition of ER stress as we currently know it [172,173]. The proteome of a healthy cell is maintained by the ER quality control (ERQC) system, which includes removal of misfolded polypeptides by either ER-associated degradation (ERAD) or autophagic degradation [174,175]. ERAD includes maintaining functional turnover of Cyp450s in the human liver [176], and recently was found important also in the human lung for bronchopulmonary dysplasia [47,177–179].

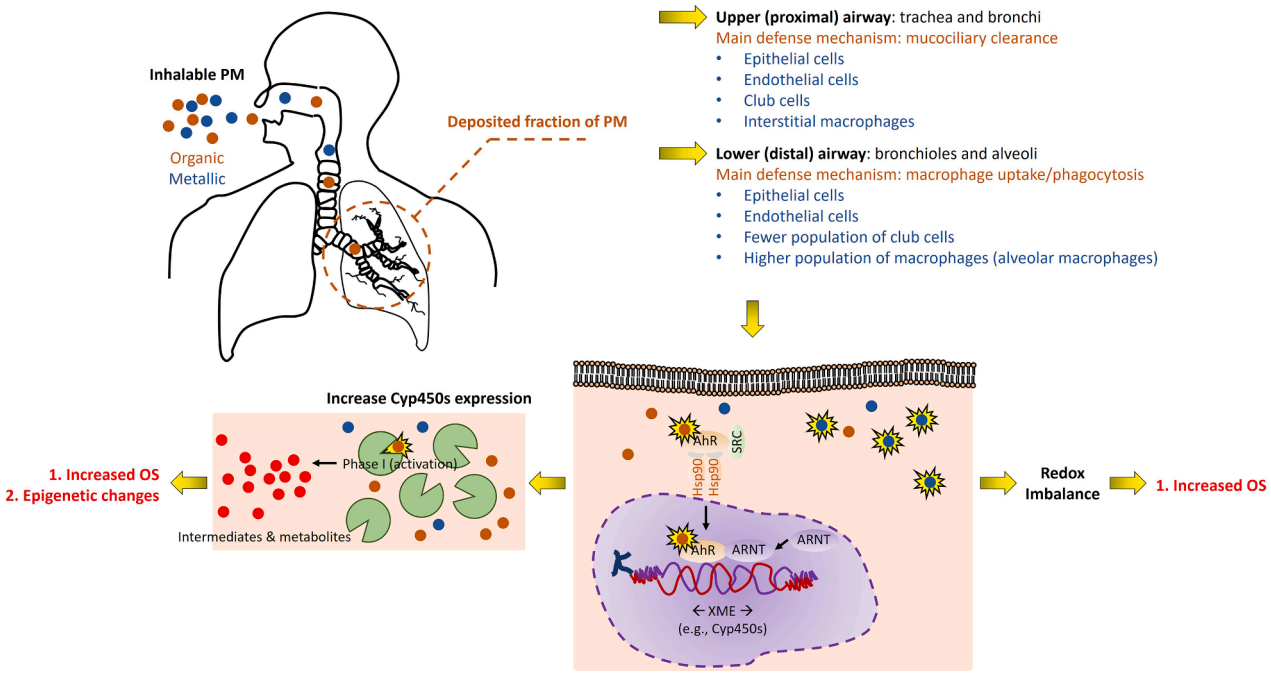

Fig. 1. A schematic of how inhaled PM leads to OS in human airway cells.

It is possible that the ERAD process is also likely tied to the propensity of Cyp450s to produce ROS.

Globally, for secretory pathways beyond just the impact on Cyp450 production, we look at ER stress through the lens of calcium signaling, emphasizing the influence of calcium's concentration gradient on protein folding, proteostasis, mitochondrial energy use, and ultimately apoptosis. The signaling pathway known as the unfolded protein response (UPR) best describes the series of events leading to cell death by apoptosis resulting from ER stress, where if ER stress is sustained, the ER homeostasis breaks, and signaling shifts towards pro-apoptotic pathways. Summarizing work by Shore et al. [180] and Urra et al. [181], proteins inositol-requiring enzyme 1α (IRE1α), protein kinase RNA-like endoplasmic reticulum kinase (PERK), and activating transcription factor 6 (ATF6) located in the ER membrane initiate UPR signaling as an adaptive response. Under prolonged ER stress, this adaptive response is insufficient hence the UPR switches signaling that aims to dispatch, i.e., suicide, the cell: apoptosis. This apoptotic mechanism occurs because the gene coding for B-cell leukemia/lymphoma 2 (Bcl-2; an anti-apoptotic protein) becomes downregulated while the gene coding for endoplasmic reticulum oxidoreductase 1α (ERO1α; an oxidase) becomes upregulated. Unfolded protein accumulation leads to IRE1α oligomerization and activation of apoptosis signal-regulating kinase 1 (ASK1) and c-Jun NH2-terminal kinase (JNK). This signaling pathway alters microRNA (miRNA) expression and affects ER permeability, releasing pro-apoptotic proteins to the cytosol promoting apoptosis. While this may not be the only mechanism in action, it is our interpretation as a simplistic overview of what Shore et al. [180] and Urra et al. [181] present as accepted knowledge.

To our best knowledge, the role of PM on the UPR is unclear. Studies in mice models, both in vivo and in vitro, provide evidence that $PM_{2.5}$ induces ER stress. The data suggests apoptosis in lung and liver tissue via the PERK-activated UPR branch [182], fibrosis [183] including via a newly proposed ROS-ER stress-TGFβ/SMADs (transforming growth factor beta/suppressor of mothers against decapentaplegic; the reader is encouraged to review the literature for the latter's nomenclature) axis [184], damage by ROS mediated by Nrf2 during metabolism phase I [76], and for the case of titanium dioxide (TiO_2), inflammation [185]. Studies on human pulmonary cell lines are scant and only imply a general toxicity mechanism derived by ER stress [186,187]. Studies of ER stress in other cell lines exist that we do not list here. Clinical/observational studies involving participants with preexisting conditions such as asthma that contain evidence of ER stress are similarly not listed here as they do not provide evidence it is PM-induced. We conclude that in the listed studies, the overarching mechanism was ROS production, which we hypothesize must imbalance the calcium concentration in the ER of cells of both organs. While ER stress can also activate the NF-κB pathway [188], an important pathway in immune and inflammatory responses discussed towards the end of this review, and other inflammasomes, we do not find compelling evidence of how PM triggers or affects this pathway, thus exclude discussion from this review. So, relating to ER stress, a clear axis, pathway, set of pathways, cascade, or activation of an immune response in the lung remain elusive that we believe provides an important knowledge gap to fill by both in vivo and in vitro studies. To this end we agree with and bring attention to an editorial by Velasco [189] that although over a decade old remains relevant.

6.2. *Mitochondrial stress*

Likewise to ER stress, the downstream transduction branches can involve and stress other organelles. The mitochondrion is one such organelle that can be stressed from PM exposure. According to a recent review by Rodríguez-González and Gutiérrez-Kobeh [190], it is conceptually possible to divide the apoptotic pathway, between initiation and execution, into three distinct ones: extrinsic, perforin/granzyme, and intrinsic (mitochondrial). A key event in the intrinsic pathways is mitochondrial outer membrane permeabilization (MOMP; [191]), leading lower mitochondrial membrane potential ($\Delta\Psi_m$), lower ATP synthesis, and the release of pro-apoptotic proteins including Cytochrome C, second mitochondria-derived activator of caspases/direct inhibitor of apoptosis-binding protein with low pI (Smac/DIABLO), serine proteinase omi/high temperature requiring protein A2 (Omi/HtrA2), apoptosis-inducing factor (AIF), and endonuclease G (EndoG). For detail and elucidation of this mechanism in vertebrates we suggest the reviews by Wang and Youle [192] and Rodríguez-González and Gutiérrez-Kobeh [190]. Here, in the following sections, we aim to shed light on how PM affects or promotes the intrinsic apoptotic pathway by two mitochondrial-mediated mechanisms. The unifying theme is that

any effect of PM on $\Delta\Psi_m$ (or MOMP) is a key activator of this intrinsic apoptotic pathway. We expand discussion on apoptosis in Section 7.1. We note that the other apoptotic pathways can be triggered by PM exposure, and direct the reader to other reviews available in the literature [193,194].

6.2.1. *Damage to mitochondrial-associated membranes*

Mitochondrial-associated (or mitochondrial-associated ER) membranes (MAMs), the interface between the ER and mitochondria, are important in interorganelle communication, including between UPR signaling and mitochondria [170]. During tethering between the two organelles, calcium transport is likely the most important process [195]. Therefore, the discovery of tethering proteins including mitofusin 2 (Mfn2; [196]), the vesicle-associated membrane protein-associated protein B- protein tyrosine phosphatase-interacting protein 51 (VAPB-PTPIP51) complex [197], and the inositol 1,4,5-trisphosphate receptor- glucose-regulated protein 75- voltage-dependent anion channel 1 (IP_3R-GRP75-VDAC1) complex [198] becomes an important first target for PM constituents to potentially alter. Considering the importance of MAMs and tethering proteins, any effect of PM on them is likely implicated in disruption of $\Delta\Psi_m$ in the intrinsic apoptotic pathway. Depending on cell type, mitochondria can take different morphologies such as fragmented, tubular, or elongated. How, or to which propensity, do these morphologies influence the interaction with PM constituents we do not know.

In Sprague Dawley rats, urban $PM_{2.5}$ has been shown to decrease gene expression and protein concentration of mitofusin 1 (Mfn1) and optic atrophy 1 (OPA1), both proteins associated with mitochondrial fusion, and increase gene expression and protein concentration of Mfn2 (associated with mitochondrial fusion), and dynamin-related protein 1 (Drp1) and fission protein 1 (Fis1) associated with mitochondrial fission [199]. In a separate study employing Sprague Dawley rats, very high (>1000 μg/m^3) concentrations of urban/coastal $PM_{2.5}$ also increased gene expression and protein concentration of Drp1 and Fis1 in a dose-dependent manner [200]. In the same study, Mfn1 and OPA1 first increased then decreased with PM concentration. In C57 black 6 (C57BL/6) mice, commercially available diesel $PM_{2.5}$ decreased Mfn1 and Mfn2, and increased Drp1 [201]. However, the same study showed that in vitro in alveolar type 2 (AT2) cells, "long-term" (i.e., 25 μg/mL kept for 30 px) exposure to the same diesel $PM_{2.5}$ decreased Mfn1, and increased Mfn2 and Drp1. A separate study in C57BL/6 mice validates only some of these trends using Drp1-KD and OPA1-OE models, concluding that inhibiting mitochondrial fission and promoting mitochondrial fusion can help restore PM-induced damage [202]. Contributing to the evidence in vitro, urban $PM_{2.5}$ has been shown to decrease Mfn2 and increase Fis1 [203]; however, the cell model was not pulmonary in that study. Based on these few studies, evidence suggests tethering proteins are important in PM-induced damage, but neither a defined role of these proteins is confirmed nor is the contribution towards this based on PM properties evaluated.

6.2.2. *Mitochondrial ROS overproduction*

Mitochondrial ROS overproduction is, based on our survey of the literature, the most widely studied of the three mechanisms proposed in Section 6.2 that lead to the intrinsic apoptotic pathway. Before we examine this pathway solely in the context of apoptosis, we wish to note that, besides apoptosis, mitochondrial ROS overproduction can also lead to other cell fates including survival through inflammation (and therefore with an immune response). Several studies suggest that, in organs beyond just the lung, a way this PM-induced inflammation and immune response are modulated is by mitochondrial stress [204–208]. It is our understanding that excessive ROS overproduction leads to cell death (e.g., by apoptosis), whereas moderate ROS overproduction leads to cell survival (e.g., through inflammation) [209]. A schematic of this is

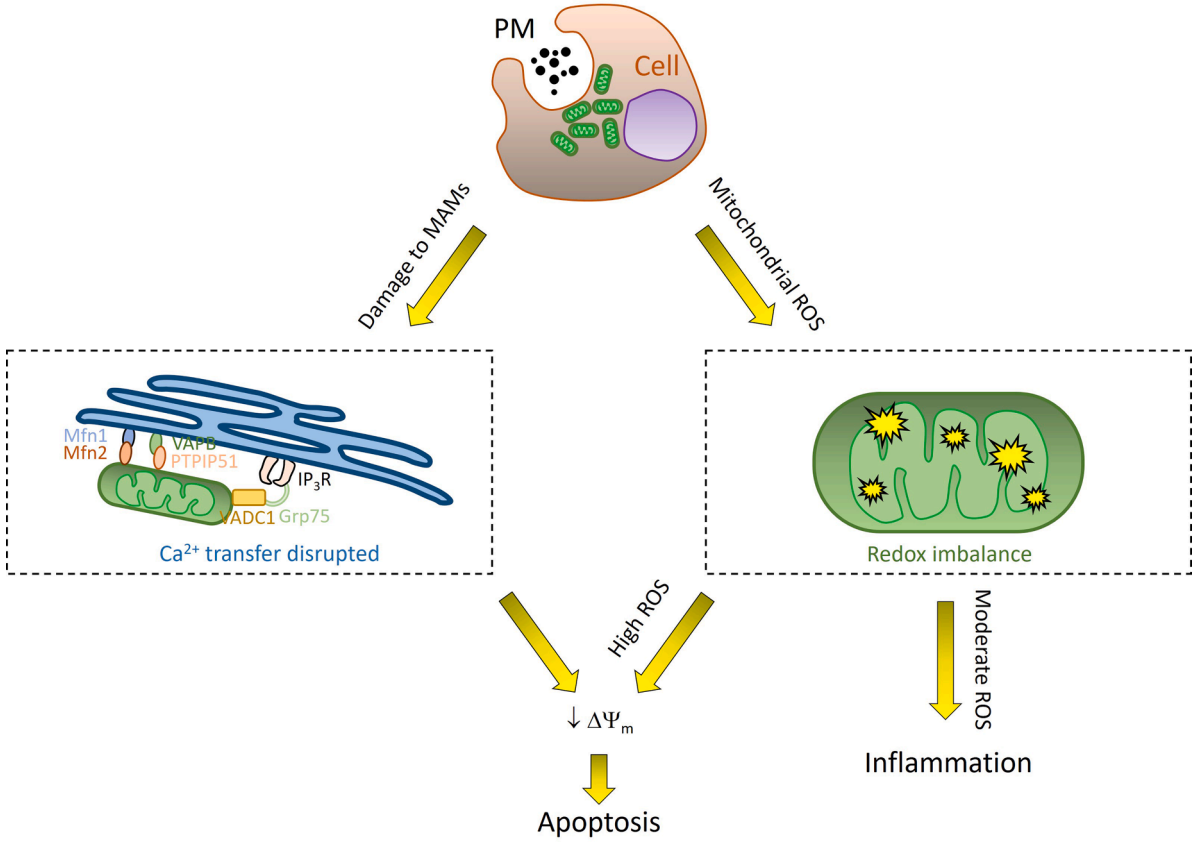

Fig. 2. Two proposed mechanisms of PM-induced mitochondrial stress with corresponding outcomes.

presented in Fig. 2.

As mentioned in Section 5, excessive ROS inside a cell can be caused either by phase II metabolism of PM components or by the redox activity of metals present in PM. Studies specific to the lung highlight the role of mitochondria and mitochondrial stress following PM-induced OS. Upon review of the literature, we made a selection of articles that advanced the mechanistic understanding of PM-induced mitochondrial ROS and thus warrant individual highlight, proposed as follows. In primary human nasal epithelial (HNE) and bronchial epithelial (HBE) cells, commercially available diesel $PM_{2.5}$ induced both a statistically significant and dose-dependent ROS increase when compared to carbon black nanoparticles [210]. In the same study, an increase in expression of Cyp450 1A1 (CYP1A1; a phase I XME) and NADPH quinone oxidoreductase-1 (NQO-1; a Phase II XME) was measured. In HBEC, chronic obstructive pulmonary disease (COPD)-diseased human bronchial epithelial (DHBE), and BEAS-2B cells, urban $PM_{2.5}$ induced OS, as revealed by multiple assays [205]. In that study several results are worth noting: (i) PM increased expression of Nrf2 and pro-inflammatory cytokines tumor necrosis factor α (TNFα) and interleukin-6 (IL-6) in all three cell lines in a dose-dependent manner, (ii) PM increased mitochondrial ROS and decreased $\Delta\Psi_m$ (assayed by MitoSOX and MitoTracker® Deep Red FM) in BEAS-2B cells in a dose-dependent manner, and (iii) that PM concentrations were chosen, to our interpretation, at low enough concentrations so as not to induce cell death via the intrinsic apoptotic pathway, instead only induce mitochondrial metabolism dysfunction (but still ends in cell survival). In L-132 cells, urban/coastal PM collected on the 5-μm stage of a cascade impactor (we interpret it as PM_{10}) caused an increase in cytosolic to mitochondrial Cytochrome C for three endpoints at 24, 48, and 72 h, at both a 10% lethal concentration (LC_{10}) and 50% lethal concentration (LC_{50}), that was statistically significant from the control cells [211]. This was coupled with a statistically significant increase in Caspase 9, a pro-apoptotic protein (caspases are proteases, but are highly regulated during apoptosis to target specific proteins). While ROS was not explicitly assayed in this study, it was in a previous study (in conjunction with an inflammatory response) utilizing the same cell line and PM [212]. The only issue we note with potentially interpreting Dagher et al. [211], however, is that the L-132 cell line may not be representative of any pulmonary cell line according to the supplier, American Type Culture Collection (ATCC). It is our view that in spite of this issue, this study is worth highlighting in this section for its clever investigation at two low cytotoxicity doses of PM and its induction of mitochondrial stress and activation of the intrinsic apoptotic pathway. Results from this study, Dagher et al. [212], and Leclercq et al. [205] align with the review by Redza-Dutordoir and Averill-Bates [209], reinforcing our interpretation that excessive ROS overproduction leads to cell death whereas moderate ROS overproduction activates adaptive signaling pathways that may lead to cell survival. In BEAS-2B and mouse alveolar macrophage RAW 264.7 cell lines, urban PM (segregated into three size ranges) induced OS as measured by heme oxygenase-1 (HO-1) concentration as well as the canonical acellular dithiothreitol (DTT) assay [213] (the DTT assay is an indicator of OP, and can be used as a proxy for OS). This was strongly correlated with PAH content, and electron microscopy images in the same work qualitatively suggested that not only was PM found in high concentration in mitochondria, but that it was the smallest of the three sizes, coincidentally highest laden with PAHs, that was mostly found in the mitochondria. This tendency of PAHs to reside in mitochondria is consistent with independently-derived suggestions that the high lipid content of mitochondria makes this organelle prone to accumulation of organics such as PAHs [214–216]. In rat alveolar macrophage NR8383 cells, commercially available PM (<4 μm) led to mitochondrial dysfunction by decreased $\Delta\Psi_m$, increase in caspases, increase in TNFα and IL-6 release, increase in NF-κB, and decrease in inhibitor of NF-κB α (IκBα) concentration [217]. In Sprague Dawley rat alveolar macrophages, urban $PM_{2.5}$ induced ROS overproduction, implicated by mitochondrial damage [199]. In Wistar rat alveolar macrophages, urban $PM_{2.5}$ (collected on the same university campus as Li et al. [199] but during a different time) induced ROS overproduction and elevated intracellular calcium, indicative of mitochondrial stress [218]. Of note in that study was a dose-dependent decrease in Bcl-2, an increase in Bcl-2-associated X protein (Bax; a pro-apoptotic protein and part of the Bcl-2 family), and an increase in pro-apoptotic caspases concentrations, which we speculate may imply ER stress as well, especially when coupled with elevated intracellular calcium.

As noted at the beginning of the previous paragraph, many studies on PM-induced mitochondrial ROS and subsequent dysfunction do exist, and we encourage the community to read them. Additionally, we suggest the reviews by Chew et al. [219] and An et al. [220] for more evidence of PM-induced mitochondrial-mediated cytotoxicity. Some studies cited by these reviews include results from A549 cells, but we do not interpret results from this cell model in our review beyond Section 5.

The mitochondrion's role in ROS overproduction and activating the Nrf2 and NF-κB signaling pathways is important in inflammatory processes, so we revisit the importance of these two pathways in Section 8.

7. Cell deaths

If survival mechanisms, such as inflammation, fail, then PM cytotoxicity leads to cell death. So far, we mentioned three cellular death mechanisms: autophagy (normal), apoptosis (normal but can be increased to abnormal rates), and necrosis (abnormal). In light of recent evidence, we wish to explore additional abnormal cell death mechanisms to conclude this review. Prior to exploring those, we briefly review autophagy and apoptosis both during homeostasis and following PM exposure.

7.1. Autophagy and apoptosis

Another way to conceptualize autophagy and apoptosis is to consider them as programmed. While both autophagy and apoptosis are normal (endogenous, self-regulating) cellular processes and are both important for homeostasis and tissue regeneration, the rates at which these processes occur can be affected by external stimuli, such as PM exposure.

In the case of autophagy, PM can increase its rates, disrupt the process, or trigger an immune response generally, to our knowledge, by OS. For example, in Sprague Dawley rats and RAW 264.7 cells, urban seasonal (winter and summer) $PM_{2.5}$ increased microtubule-associated protein light chain 3 (LC3; both LC3-I and LC3-II, both autophagic markers) gene expression while decreasing sequestosome 1 (SQSTM1; commonly known as p62, a receptor of autophagy) expression in a dose-dependent manner [221]. In that study, the authors concluded that OS was mediated by the phosphoinositide 3-kinase (PI3K)/ protein kinase B (Akt)/ mammalian target of rapamycin (mTOR) (collectively: PAM) signaling pathway, a pathways involved in autophagy [222,223] (there is an important role of autophagy in some cancers, but discussion on this topic is beyond both the scope and purpose of this review). In a recent study comparing the effect of urban $PM_{2.5}$ on BEAS-2B and NIH-3T3 cell lines, the authors found that PM-induced cell death in BEAS-2B was due to inhibited mitophagy (via parkin) whereas in NIH-3T3 it was due to increased autophagy [224]. In that work, for BEAS-2B cells, LC3-II decreased with PM dose whereas p62 increased, but for NIH-3T3 cells, LC3-II increased with PM exposure whereas p62 decreased. Also in that work, both cellular ROS and mitochondrial ROS (assayed by MitoSOX) increased in BEAS-2B cells with increasing PM dose. Thus for lung diseases, the role of autophagy can be helpful or harmful, and in the context of PM-induced cytotoxicity, outcomes appear to be cell-specific.

In the case of apoptosis, its increased occurrence could be as a defense mechanism to remove damaged cells thus preserving the overall tissue or the organism [225]. PM increases instances of apoptosis to abnormal rates, and this deregulation can ultimately lead to a pathology [193]. According to Aghaei-Zarch et al. [193], the corresponding signaling pathways affected include NF-κB, ER stress, and Janus Kinase /

Signal Transducer and Activator of Transcription (JAK/STAT; involved in many cellular processes including cell survival). Both the NF-κB and JAK/STAT signaling pathways activated by PM exposure can lead to inflammation which ultimately is the likely avenue by which a pathology arises. An interesting question is whether PM-induced NF-κB signaling exerts pro-apoptotic or anti-apoptotic effects: if transcription is suppressed (e.g., by nucleolar sequestration of v-rel avian reticuloendotheliosis viral oncogene homolog A, commonly abbreviated as either RelA, or p65) or Cytochrome C is released, it would induce apoptosis [226,227] whereas if the affected mechanism upregulates anti-apoptotic genes such as Bcl-2, the caspase cascade is inhibited and apoptosis is downregulated. Baichwal and Baeuerle [226] suggest this is cell type-dependent. Again, according to Aghaei-Zarch et al. [193], PM increases apoptotic rates, so PM likely affects NF-κB to act as a pro-apoptotic factor. Cytochrome C, normally a part of the electron transport chain inside the mitochondrion, upon release into the cytoplasm following MOMP (Section 6.2), acts as a pro-apoptotic protein, further suggesting that increased rates of apoptosis can come from other mechanism too (MAM disruption and ER stress) and not only by any effect on the NF-κB signaling pathway or other potentially inflammatory processes. Additionally, we bring attention to the reader of the relationship between the larger Bcl-2 family of proteins not discussed in this review, which can be pro-apoptotic, pro-apoptotic BH3-only, or anti-apoptotic, and their relationship with MOMP as discussed elsewhere for their role in apoptosis [228,229]. The differential expression of all or part of this family of proteins in response to PM insults is important because of how they govern whether a cell commits to apoptosis.

Considering the importance of the mitochondrion in autophagy and apoptosis, we wish to bring to light an important process during increased apoptosis: mitophagy. Like autophagy, mitophagy, a type of autophagy where dysfunctional mitochondria are removed, is an important process in homeostasis [230]. We provide a schematic of this process in Fig. 3a. The sequence of events during either normal or slightly increased mitophagy (e.g., resulting from moderate exposure to PM) begins with phagophore formation, followed by the phagophore engulfing damaged mitochondria to form an autophagosome, and finally the fusion of the autophagosome with lysosomes to digest the autophagosome contents. Of interest in this process is the role of mitochondrial-associated proteins, such as histone deacetylase 6 (HDAC6). The function of HDAC6, at the time of discovery over two decades ago, was associated with microtubule formation [231]. Recently, HDAC6 has been found to repress transcription via histone deacetylation and is identified as a key protein in the "autophagy-cilia" axis [232–234] for its role in autophagy-mediated cilia disassembly, otherwise known as "ciliophagy". Very recently, HDAC6 has emerged as a promising candidate to selectively inhibit and combat several types of cancers [235,236]. Although literature suggests HDAC6 is important in ciliogenesis of lung tissue and implicated in diseases such as COPD and idiopathic pulmonary fibrosis (IPF), we are not aware of studies examining expression of HDAC6 and its role in the autophagy-cilia axis on pulmonary ciliated epithelial cells.

Fig. 3b and 3c are transmission electron microscopy snapshots of mitophagy taking place in primary human small airway epithelial cells (HSAECs) for healthy control cells (Fig. 3b) compared to cells dosed with 50 μg/mL of flame-generated soot and that have internalized the soot after 48 h of incubation (Fig. 3c). To obtain the images, after ~48 h of incubation with or without soot, cells were fixed overnight at +4°C with a solution of 2.5% glutaraldehyde and 2.0% paraformaldehyde in 0.15 M cacodylate buffer at pH 7.4 with 2 mM calcium chloride. Samples were then analyzed using a JEM1400plus (Japan Electron Optics Ltd., Tokyo, Japan) operated at 120 kV. From Fig. 3c, there is evidence that the soot induced stress signaling in the cell: compared to the healthy control cell, the stressed cell shows a dramatic increase in damaged mitochondria and increased presence of vesicles, suggesting mitophagy is increased to restore cellular function. Concurrently to that experiment, we monitored cell attachment behavior in real-time utilizing electric cell-substrate impedance sensing (ECIS; model ZΘ, Applied Biophysics, USA) as a previously validated proxy of cell proliferation in response to soot/PM exposure [237]. Briefly, ECIS leverages

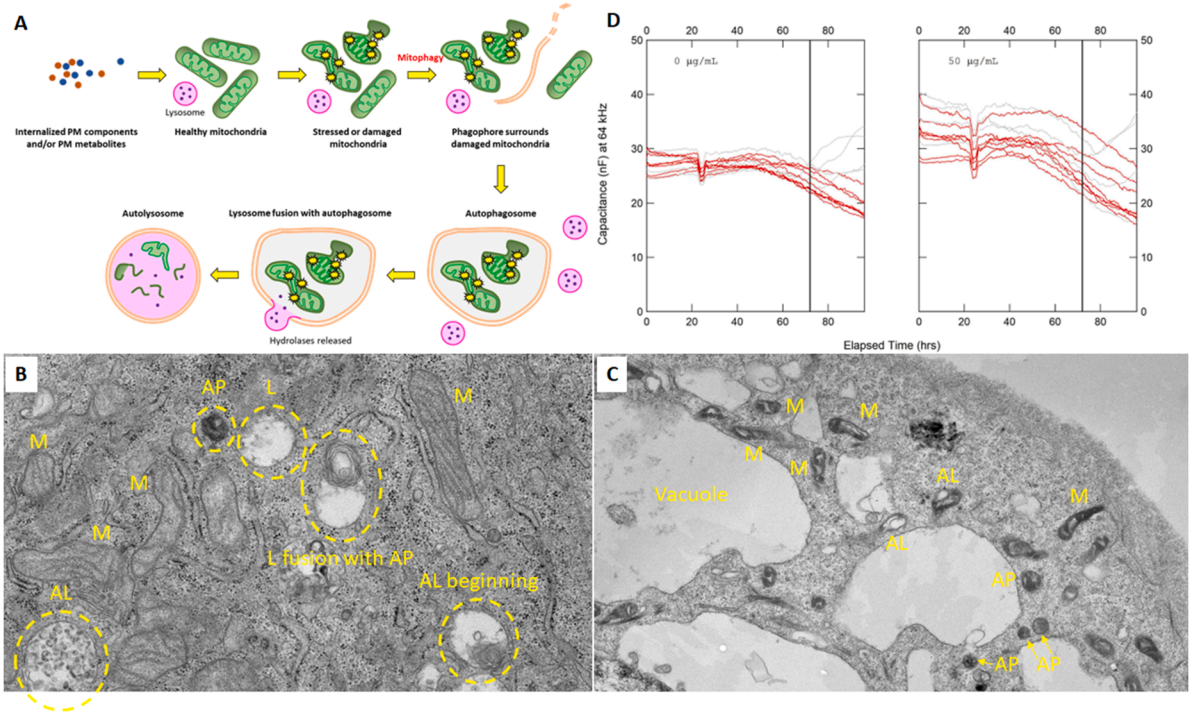

Fig. 3. The process of mitophagy. (A) conceptual diagram resulting from PM exposure, (B) TEM image of normal mitophagy taken in a healthy (control) HSAEC, and (C) TEM image of increased mitophagy and increased mitochondrial damage (noted by swollen and misshapen mitochondria) taken in a HSAEC treated with soot. Ultrastructures are as follows: AP autophagosome, AL autolysosome, L lysosome, and M mitochondrion. Note increased vacuolization in (C).

electrophysiological properties of a cell when attached to gold electrodes subject to alternating current (AC) over a range of frequencies [238,239]. The purpose of employing ECIS is the same as during the experimental design of Dagher et al. [211] in Section 6.2.2, whereby we target processes during low cytotoxicity and induction of mitochondrial stress. As such, ECIS is in our view an extremely powerful non-invasive technique to help determine complementary assay doses and choose assay endpoints following in vitro PM exposures. The comparison between control and treated cells is shown in Fig. 3d. A mild decrease in confluency coupled with larger spread across wells at the 48 h endpoint gave us confidence that the mechanism in action, mitophagy, was playing a role before increased cell death, leading to cell survival (although stressed), rather than cell death by other avenues, such as increased apoptosis or necrosis. This is also consistent with previously published work by Das et al. [240], where benzo[a]pyrene-induced cell death is suppressed by mitophagy. Improved understanding of mitophagy in relation to apoptosis and other biological processes induced by PM exposure may be warranted.

7.2. Necrosis

According to the Nomenclature Committee on Cell Death (NCCD), a cell is defined as dead following any one of three criteria: loss of cell membrane integrity, presence of apoptotic bodies, and phagocytosis of cell fragments by adjacent cells [241]. Necrosis is different from autophagy and apoptosis in that it is an abnormal process. Ardon-Dryer et al. [242] provide live-cell imaging of mineral dust PM's effect on pulmonary cells that perhaps best illustrates the difference between the two processes. While apoptosis' morphological features include cell shrinkage and cell membrane blebbing resulting in the formation of apoptotic bodies (that are eventually engulfed by phagocytes), necrosis' morphological feature is characterized by a self-destruction followed by release of cell contents directly to the extracellular matrix (or bloodstream), resulting in inflammation [242]. This means that unlike apoptosis, necrosis does not involve a proper clearing mechanism for the leaked contents of the dead cell. Interestingly, in the study by Ardon-Dryer et al. [242], while dose-dependency appears to switch cell death mechanism from apoptosis to necrosis, it was the intermediate concentration of dust PM that led to highest cell death, suggesting that lower viability at higher dust concentrations was due to inhibition of cell proliferation rather than increased cellular death instances. This reinforces the importance of, similar to studies cited in Section 6.2., in vitro studies that take into account dose-dependency of PM exposure beyond its effect on cell proliferation. These studies can be extended beyond PM effects on lung cells, for example, evidence from one of our recent studies suggests flame-generated soot induces epithelial-mesenchymal transitions (EMTs) in ARPE-19 ocular cells at high doses and is dependent on soot physicochemical properties, as not all types of soots employed in that study induced EMTs in our cells even at high doses [237].

Around two decades ago a paradigm shift occurred suggesting that while necrosis remained accepted as an abnormal process, it could be regulated or programmed [243,244]. This implied a correction to the traditional view of necrosis that it can therefore occur during normal physiology, not only during pathophysiological processes (such as those resulting from a PM insult). At the cellular level, perhaps the defining feature of programmed necrosis is that, unlike apoptosis, it is caspase-independent [245]. Recently, several of the programmed necrotic processes have been identified. To our knowledge, these are necroptosis, pyroptosis, ferroptosis, and NETosis. We review how PM affects these processes, the role of damage-associated molecular patterns (DAMPs), and the inflammatory responses in the following subsections.

7.2.1. Necroptosis

An update to the NCCD definitions presented in the previous section is to include necrosis [246]. This likely resulted from several highly impactful articles published a few years prior providing evidence of a necrotic cell death that was dependent on the receptor-interacting protein kinase 3 (RIPK3): necroptosis [247–250]. Necroptosis is initiated by a ligand binding to receptors known as death receptors, members of the tumor necrosis factor (TNF) superfamily of cell surface receptors, which include TNFα, tumor necrosis factor receptor 1 (TNFR1), Fas (otherwise known as cluster of differentiation 95, abbreviated to CD95), and Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL; [251–253]). Summarizing the reviews by Hanson [252], Grootjans et al. [251], and Wu et al. [253], the signal transduction pathway that follows, activated by phosphorylation, leads a checkpoint. A protein complex known as Complex I forms, which includes proteins such as TNFR1-associated death domain protein (TRADD), Fas-associated protein with death domain (FADD), receptor-interacting protein kinase 1 (RIPK1), TNF receptor associated factor (TRAF) family proteins, and cellular inhibitor of apoptosis proteins 1 and 2 (cIAP1 and cIAP2, respectively) and is intended to lead the cell to survival. Complex I then transitions to Complex II, which can be further distinguished in Complex IIa and Complex IIb. If Caspase 8 is absent, then Complex IIb can be referred to as a necrosome and cell death occurs by necroptosis and is followed by DAMP release. The accepted mechanism is that the necrosome leads to mixed lineage kinase domain like pseudokinase (MLKL) phosphorylation by RIPK3, which oligomerizes inserting itself into the cell membrane, causing rupture. The inflammation that follows necroptosis is implicated in several diseases [254,255] including cancer [256].

7.2.2. Pyroptosis

A cell's cytoplasm naturally contains inflammasomes. These are protein complexes that activate upon stress or an insult and lead to inflammation, mediated by Caspase 1, following release of pro-inflammatory cytokines such as interleukin-1β (IL-1β; [257–259]). Cell death mediated by abnormally high inflammasome activation is known as pyroptosis [245]. Like necroptosis, this mechanism is viewed as programmed, having NOD-like receptor containing a Pyrin (NLRP, including NLRP1 and NLRP3) activation as a key trigger and Gasdermin D (GSDMD) as executioner causing pores to form in the plasma membrane that lead to cell lysis [260].

Although generally recent, the literature is quickly expanding with studies linking PM exposure to pyroptosis. In BALB/c mice, urban $PM_{2.5}$ induced inflammation and alteration of lung tissue potentially as a result of pyroptosis [261] considering the increase in mRNA expression immunohistochemistry staining of Caspase 1, NLRP3 and GSDMD following PM exposure. In that study, the role of pyroptosis was further evidenced by a cohort of exposed mice receiving intraperitoneal doses of a caspase inhibitor demonstrating statistically significant lower lactate dehydrogenase (LDH) release, total proteins in bronchoalveolar lavage fluid, and interleukin-18 (IL-18), although the decrease in IL-1β was not statistically significant. Similar results, with a similar proposed pathway, were observed in allergic rhinitis female C57BL/6 mice models using urban $PM_{2.5}$ (collected in the same city as [261] but during a different period), exacerbating damage to the nasal mucosa [262]. In another study, BALB/c mice and RAW 264.7 cells exposed to urban/-coastal $PM_{2.5}$ demonstrated, among other mechanisms, pyroptosis as a cell death fate but in a ROS-dependent way [263]. In 16-HBE cells, wood smoke $PM_{2.5}$ extracts were shown to induce pyroptosis by two mechanisms: the aforementioned Caspase 1-dependant and a newly proposed ATP-receptor pathway, as confirmed by the knocked-down cell counterparts [264]. In RPMI-2650 cells, commercially available PM (<4 μm) led to pyroptosis-mediated cell death as evidenced by the dose-dependent decrease in viability coupled with an increased protein expression of Caspase 1, NLRP3, GSDMD, IL-1β, and IL-18 [265]. In that study, the role of pyroptosis was further evidenced by inhibition of NLRP3 leading to a statistically significant lower protein expression of the inflammasomes. We note that other in vitro studies exist probing pyroptosis in ocular cells.

7.2.3. Ferroptosis

Ferroptosis, perhaps unlike the name suggests, is not a mechanism directly induced by iron present in PM. Ferroptosis is considered as another programmed cell death characterized by lipid ROS accumulation, dependent on iron availability, and without apoptotic and necrotic features of membrane blebbing or rupture [245,266]. Examples of lipid ROS are lipid peroxides, resulting from oxidation and/or normal metabolism. Polyunsaturated fatty acids (PUFAs) are perhaps the most well-known example of lipids that undergo oxidation during ferroptosis [267]. Because ferroptosis depletes glutathione, a well-known antioxidant, ROS accumulation and lipid peroxidation leads to cell death, for example, by reacting with proteins and nucleic acids [268–270].

In BEAS-2B cells, certified reference material for urban fine dust decreased cell viability in a dose-dependent manner while concurrently increasing cellular and mitochondrial ROS, and increased lipid peroxidation (as shown by using lipophilic fluorescent dye 4,4-difluoro-5-(4-phenyl-1,3-butadienyl)-4-bora-3a,4a-diaza-s-indacene-3-undecanoic acid; BODIPY 581/591 C11) [271]. In that study, ferroptosis was suggested following the differential mRNA expression and protein quantification of several ferroptosis biomarkers. In mouse alveolar macrophage J 774A.1 and RAW 264.7 cell lines, exposure to $PM_{2.5}$ yielded similar results but with detection of increased inflammasomes, proposing a connection between the two by ROS [272]. In BALB/c mice, exposure to urban $PM_{2.5}$ resulted in elevated concentrations of inflammatory cytokines in collected bronchoalveolar lavage fluid and blood samples, as well as a qualitative decrease in glutathione peroxidase 4 (GPX4; a biomarker for ferroptosis, as shown by Western blot images) [273]. In the same study, MLE-12 cells exposed to urban $PM_{2.5}$ decreased in viability to a larger extent compared to cells exposed to carbon black or a reference PM, over the same 72 h incubation period. The cell viability increased with statistical significance upon treatment with Vitamin C and Coumarin. These results correlated with a decrease of glutathione and GPX4, and an increase in BODIPY 581/591 C11 and Acyl-CoA synthetase long-chain family member 4 (ACSL4; important in activation of fatty acids such as PUFAs) measurements. The importance of this study was a first attempt at correlating PM physicochemical properties to cell death fates by one metric: OP.

Several candidate drugs, not mentioned in this review but available in the literature, are being proposed to alleviate PM-induced lung injury by suppressing ferroptosis.

7.2.4. NETosis

With an apt acronym, neutrophil extracellular traps (NETs; [274]) are web-like structures deployed by neutrophils to trap foreign bodies such as pathogens. This action results from the neutrophil death, releasing its contents to the extracellular matrix and is thus known as NETosis. This action can stimulate a larger immune response as well [245]. While NETosis may be more canonically associated with microorganism infections (which could still result from inhalation of PM), even abiotic PM has shown to induce NETosis in vivo and in vitro.

In summary for Section 7.2, we hope the chosen studies have highlighted the cellular mechanisms between different cell fates, and how PM affect these mechanisms and fates. For a detailed review focused solely on elucidating programmed necrosis including diagrams comparing necroptosis, pyroptosis, ferroptosis, and NETosis, we recommend the review by Kim et al. [245].

7.3. Cuproptosis

In Section 2, we alluded to the possibility that one specific chemical entity, such as a compound or an ion, can interact with the human cell in a very specific way and evoking a very unique response. Copper, for example, can be found in high concentrations in particulate matter with sources ranging from vehicle emissions (both exhaust and non-exhaust, e.g., brake wear; [275]), mineral dust [276], and mining or smelting processes [277,278]. The effect on the cell of copper present in PM may become of importance: cuproptosis [279] is the newest form of cell death reported in the literature at the time of this review. This process is rather specific to the mitochondrion as an excess of Cu^{2+} ions can bind to lipoylated proteins in the tricarboxylic acid (TCA; commonly known as the Krebs) cycle. This is a distinct mechanism than general OS-induced cell deaths, and is referred to as proteotoxic stress, similar to ER stress discussed in Section 6.1. considering it's due to accumulation of misfolded or damaged proteins. While the initial discovery was not in pulmonary cell lines, there is evidence of cuproptosis occurring in such cells. According to Tsvetkov et al. [279], cuproptosis primarily occurs in cells that use oxidative phosphorylation as the main metabolic pathway, and such is the case for pulmonary cells [280]. To date, we know of one study exposing copper oxide (CuO) nanoparticles to C57BL/6J mice and MH-S alveolar macrophage cell line, with specific goal of quantifying indicators for cuproptosis ferredoxin (FDX1), dihydrolipoamide succinyltransferase (DLST), dihydrolipoamide acetyltransferase (DLAT) and Cu transporter 1 (CTR1) [281]. Two important conclusions from that study were the mediation of cuproptosis by FDX1 utilizing a knock-down model of MH-S cells and that interleukin-17a (IL-17a) was found to be the indicator of inflammation from this process. The only other study we are aware of exposed CuO nanoparticles to C57BL/6 mice and RAW 264.7 cells: in that study, they found evidence of cuproptosis in both models, however for the in vivo model, although copper accumulation was found in the lung, cuproptosis was evaluated for the liver [282]. Considering the recent discovery and few studies on cuproptosis resulting from a PM insult, and we believe the time is ripe for more studies in vitro and in vivo considering the wide range of copper sources presented.

Fig. 4 illustrates the cell deaths resulting from PM exposure discussed in Section 7 of this review.

8. Cell survival and effects beyond the cell to a full tissue or organ: inflammation and immune responses, and cancer

Upon PM exposure, following reception and transduction (Section 3), the biological response at the tissue or organism scale alluded to thus far in this review is most often inflammation. Inflammation can either be local or systemic, and either acute or chronic. Several PM-induced signal transduction pathways mentioned have the potential of leading the human body to systemic inflammation: OS, Nrf2, NF-κB (including activated from ER stress), MAPK, and JAK/STAT. Targeting these pathways for therapy options is dependent on our knowledge of how insults affect them. For example, a review by Pardo et al. [283] examined the role of Nrf2 in preventing PM-induced toxicity by protection against OS and inflammation [283]. Dissimilar to Nrf2's role in drug/PM metabolism and antioxidant defenses, NF-κB instead acts as a regulator more downstream during inflammation and the ensuing immune responses [284]. As elaborated in Section 7, the potential for systemic inflammation is not limited to activation or modification of these pathways, but can also follow cell death, specifically, dysregulated apoptosis, necrosis (abnormal and programmed), and cuproptosis. We summarize the role of important proteins in all cell death mechanisms in Table 1, including potential for tissue-level outcomes.

We note that the effect of inflammation on disease onset should be studied beyond a single cell type, and generally showcases the superiority of in vivo models compared to in vitro models, because at the organism scale, the molecules (proteins) that signal a whole-body response across organs are released into the bloodstream. These are known as cytokines [287] and, while they can be redundant due to overlapping functions [288], are a hallmark of paracrine and endocrine signaling in our immune system. Considering we emphasized discussion on cytotoxicity and autocrine signaling thus far, we did want to mention paracrine and endocrine signaling in this section, because examples of cytokines mentioned in this review included several interleukins and TNFα. The pathologies that arise as a result of elevated acute or chronic inflammation are varied for several reasons: the redox imbalance

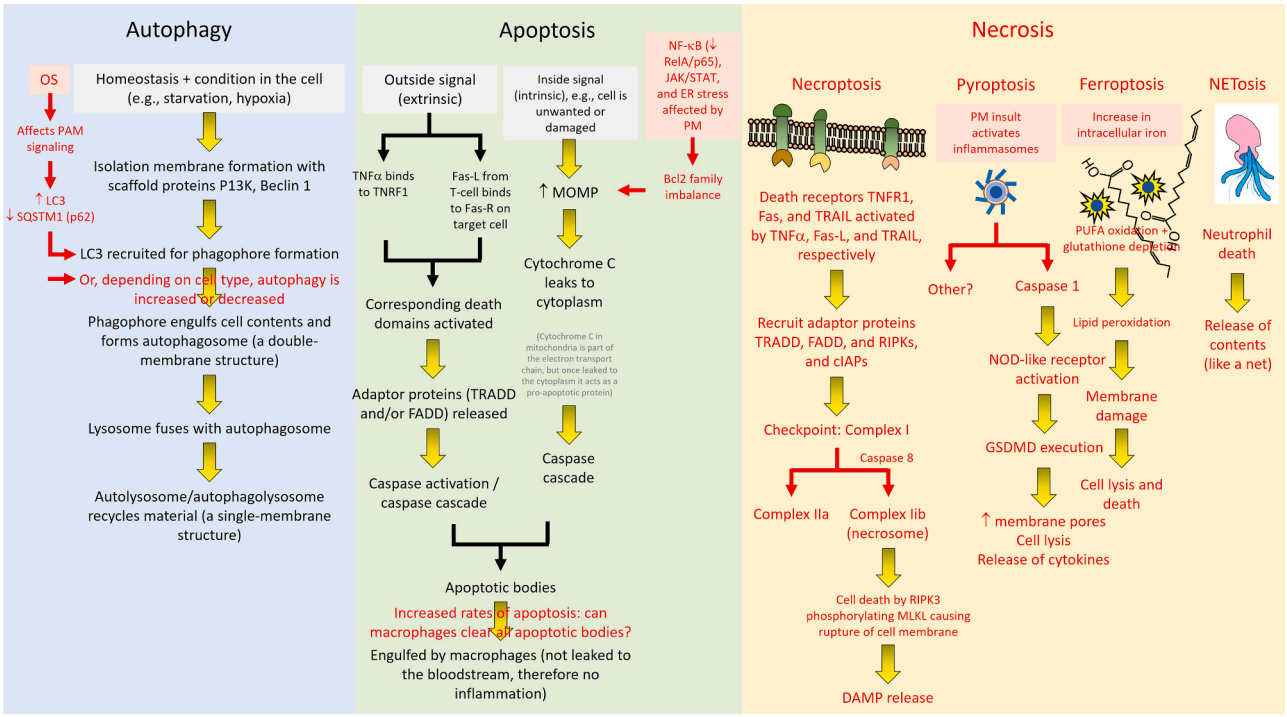

Fig. 4. Three major cell death pathways. Black text indicates normally occurring cell death (e.g., during homeostasis) whereas red text indicates abnormal cell death resulting from PM insults. Cuproptosis is not shown in this figure.

resulting in OS now triggers a cascade of inflammatory responses, inflammation can be localized to a specific tissue of a specific organ, or the affected pathway is cell-specific. For example, cytokines TNFα and interleukin-13 (IL-13) lead to inflammation that triggers asthma [285, 286]. Interestingly, it is proposed that inhibitor of apoptosis (IAP) proteins, such as cIAP1 and cIAP2 mentioned in Section 7.2.1., determine whether a cell dies with or without an inflammatory response [289]. As a result, IAP inhibitors offer an attractive avenue in the pursuit of cancer therapies with clinical trials underway [290].

Aside from inflammation, another biological response is the formation of tumors, which may progress to become malignant (i.e., cancer). The relevance of PM in cancer has recently been re-evaluated for lung cancer specifically. This is because, although globally decreasing, lung cancer is increasing in the non-smoking population and PM exposure is the likely cause [291–294]. A 2013 study reported that an increase of 10 $\mu g/m^3$ of PM_{10} increased lung cancer risk by 22% and lung adenocarcinoma risk by 51%, whereas an increase of 5 $\mu g/m^3$ of $PM_{2.5}$ increased lung cancer risk by 18% and lung adenocarcinoma risk by 55% [295]. A newer 2020 study based on a cohort in a different continent instead reported that an increase of 10 $\mu g/m^3$ of $PM_{2.5}$, during a 3-year exposure, increased lung cancer risk by 12% [296]. Both studies report 95% confidence intervals in their data. Elucidating the effect of PM on lung cancer rates may not be as straightforward due to person-to-person genetics and random mutations coming to play. Random mutations in genes that code for enzymes that regulate apoptosis, such as caspases or more commonly p53, are a cause of cancer [297,298]. If an enzyme cannot carry out regulated self-destruction of the cell, the cell proliferates until a tumor forms. Notably and fairly recently, the canonical initiation-promotion model for tumorigenesis [299] has been reevaluated partly due to the influence of environmental toxins (such as PM) to the random mutation [300]. Notably are the oncogenic mutations in KRAS and EGFR occurring in healthy lung tissue. Similar to the AhR, EGFR is a receptor. However, unlike the AhR, EGFR is not involved in xenobiotic sensing; rather, it is involved in normal cell growth and regeneration with a pathway that ultimately affects transcription. We believe public health policy and lung cancer therapy could benefit from EGFR research considering a recent impactful study association PM exposure to EGFR-driven lung cancer [301]. Other recent impactful cancer therapy options arise from PANoptosis (which encapsulates pyroptosis, apoptosis, and necrosis) [302], and cuproptosis [303]. For hereditable traits, AhR-mediated PAH and HAH metabolism leads to epigenetic changes.

9. Conclusion

The cell signaling process following PM detection that leads to its metabolism is mediated by the AhR; downstream processes from signal transduction to the cellular response result in either cell survival by inflammation, or cell death. Signal transduction can take many avenues and is likely dependent on the physicochemical properties of PM; this is an area we believe benefits from further research. Generally, if natural defenses such as mucociliary clearance don't suffice and PM resides long enough and in high enough concentrations, at the cellular level, it elicits OS. We highlight two types of PM components, organic and metallic. Metallic PM elicits OS by direct redox imbalance whereas organic PM does so mediated by the AhR that induces increased expression of XMEs such as Cyp450s; the metabolites of this enzyme then elicit OS (or even epigenetic changes to DNA). Following OS can be several processes, but generally involve organelle damage as first step and a subsequent energy imbalance in the cell. We highlighted two important organelles whose PM-induced damage leads to cell death or inflammation: the ER and the mitochondrion. In terms of cell death, PM alters endogenous processes such as autophagy and apoptosis, or induces abnormal processes, known as necrosis and very recently (and very specifically to copper) cuproptosis. We discussed these latter two in some detail as they are fairly recent discoveries and important in our view for future research in PM-induced damage. Importantly, throughout this review, we list proteins that are important in the many signaling pathways mentioned and involved (from a lesser to pivotal extent) both in homeostasis and dysregulated by PM exposure. This list may be extensive, but we believe is important for both aerosol scientists and clinicians because most avenues to cell death are very well regulated, and knowledge of cascades

Table 1
Important proteins and genes mentioned in this review that are measurably affected by PM. Note that the functions, pathways, etc. implicated are in response to PM or drugs, specifically, in this table.

Full name	Abbreviation	Gene or Protein	Cell Signaling	Function	Pathway(s) Affected	Cellular-level Outcome	Tissue-level Outcome	Knowledge	Citations
Aryl Hydrocarbon Receptor	AhR	Protein	Reception	Binds to exogenous compounds (PM or PM components)	NF-κB; others	Many	Many	High	[88,8,90,67]
Cytochrome P450s	Cyp450s	Protein	Early Transduction	Xenobiotic metabolizing enzymes (metabolize PM)	None intrinsically	Many	Many	High	[8,71–79, 145,146, 149,150,]
Epoxide hydrolases	EHs	Protein	Early Transduction	Xenobiotic metabolizing enzymes (metabolize PM)	None intrinsically	Many	Many	Medium-high	[8,127]
Flavin-containing monooxygenases	FMOs	Protein	Early Transduction	Xenobiotic metabolizing enzymes (metabolize PM)	None intrinsically	Many	Many	Medium	[118,121]
Glycosyltransfarases	Gtfs	Protein	Early Transduction	Xenobiotic metabolizing enzymes (metabolize PM)	None intrinsically	Many	Many	Medium-high	[115,116]
Glutathione S-transferases	GSTs	Protein	Early Transduction	Xenobiotic metabolizing enzymes (metabolize PM)	None intrinsically	Many	Many	Medium-high	[80,132, 127,82]
(NADPH) Quinone oxidoreductases	NQOs	Protein	Early Transduction	"Detoxifying" / "Phase II" (metabolize PM)	None intrinsically	Many	Many	Medium	[210,83,84]
Inositol-requiring enzyme 1α	IRE1α	Protein	Transduction: ER stress	Initiate unfolded protein response signaling	UPR signaling	Apoptosis	Many	Medium	[180] (and references therein); [181] (and references therein)
Protein kinase RNA-like endoplasmic reticulum kinase	PERK	Protein	Transduction: ER stress	Initiate unfolded protein response signaling	UPR signaling	Apoptosis	Many	Medium	[180] (and references therein); [181] (and references therein)
Activating transcription factor 6	ATF6	Protein	Transduction: ER stress	Initiate unfolded protein response signaling	UPR signaling	Apoptosis	Many	Medium	[180] (and references therein); [181] (and references therein)
c-Jun NH2-terminal kinase	JNK	Protein	Transduction: ER stress	affects ER permeability (releasing pro-apoptotic proteins)	NF-kB?	Apoptosis	Many	Medium	[180] (and references therein); [181] (and references therein)
B-cell leukemia/ lymphoma 2	Bcl-2	Protein	Transduction	Pro-apoptotic or anti-apoptotic protein; affects MOMP	NF-kB?	Apoptosis	Many	Unclear, may depend on PM concentration	[228,229]
Bcl-2-associated X protein	Bax	Protein	Transduction	Pro-apoptotic or anti-apoptotic protein; affects MOMP	NF-kB?	Apoptosis	Many	Unclear, may depend on PM concentration	[228,229]
Cytochrome C	-	Protein	Transduction	Pro-apoptotic	NF-kB; Intrinsic apoptotic pathway	Apoptosis	Many	High	[193,226, 211,212, 227] (and references therein)
second mitochondria-derived activator of caspases/direct inhibitor of apoptosis-binding protein with low pI	Smac/ DIABLO	Protein	Transduction	Pro-apoptotic	Intrinsic apoptotic pathway	Apoptosis	Many	Medium-high	[192] (and references therein); [190] (and references therein)

(*continued on next page*)

Table 1 (*continued*)

Full name	Abbreviation	Gene or Protein	Cell Signaling	Function	Pathway(s) Affected	Cellular-level Outcome	Tissue-level Outcome	Knowledge	Citations
Mitofusins	Mfns	Protein	Transduction	MAM teathering protein	Intrinsic apoptotic pathway (specifically, MOMP)	Apoptosis	Many	Low	[201,200, 199,203]
vesicle-associated membrane protein-associated protein B-protein tyrosine phosphatase-interacting protein 51 comlex	VAPB-PTPIP51	Protein	Transduction	MAM teathering protein	Intrinsic apoptotic pathway (specifically, MOMP)	Apoptosis	Many	None	None specific to PM exposure
inositol 1,4,5-trisphosphate receptor-glucose-regulated protein 75- voltage-dependent anion channel 1 complex	IP_3R-GRP75-VDAC1	Protein	Transduction	MAM teathering protein	Intrinsic apoptotic pathway (specifically, MOMP)	Apoptosis	Many	None	None specific to PM exposure
Caspases	-	Protein	Transduction	Regulators of inflammatory responses	Many	Apoptosis, Pyroptosis	Inflammation	High	[226,257, 227,258, 259]; [261, 263][265, 264]
microtubule-associated protein light chain 3s	LC3s	Protein	Transduction	Autophagic marker; PAM signaling	NF-κB; ER stress; JAK/STAT)	Autophagy	Unclear	Medium-low	[224,221]
sequestosome 1	(also known as p62)	Protein	Transduction	Receptor of autophagy; PAM signaling	NF-κB; ER stress; JAK/STAT)	Autophagy	Unclear	Medium-low	[224,221]
Nuclear Factor kappa-light-chain-enhancer of activated B cells	NF-κB	Protein	Transduction	Transcription factor	NF-κB	Apoptosis	Many	Medium-high	Many
Histone deacetylase 6	HDAC6	Protein	Transduction	Cilia formation; mitochondiral-associated proteins?	Unclear	Unclear	Ciliopathies	Low	[232,233, 234]
Qualitative decrease in glutathione peroxidase 4	GPX4	Protein	Transduction	Biomarker for ferroptosis	Unclear	Ferroptosis	Unclear	Low	[273]
Ferredoxin / Ferredoxin 1 gene	FDX1	Gene	Transduction	Biomarker for cuproptosis	Unclear	Cuproptosis	Unclear	Low	[281]
dihydrolipoamide succinyltransferase gene	DLST	Gene	Transduction	Biomarker for cuproptosis	Unclear	Cuproptosis	Unclear	Low	[281]
dihydrolipoamide acetyltransferase gene	DLAT	Gene	Transduction	Biomarker for cuproptosis	Unclear	Cuproptosis	Unclear	Low	[281]
Cu transporter 1 gene	CTR1	Gene	Transduction	Biomarker for cuproptosis	Unclear	Cuproptosis	Unclear	Low	[281]
Interleukins	Ils	Protein	Transduction: cytokine signaling	Communicate with other cells or tissues to initiate immune response	Many	Many	Inflammation	High	Many, including [85,73,74, 257,205, 258,285,86, 259,286, 87]; [261, 281]

and checkpoints offer valuable targets for therapeutic interventions. Finally, we briefly scale up the effect of a PM insult from the cellular scale to the tissue scale and discuss survival mechanisms such as inflammation and cancer. Where beyond the scope or purpose of this review, we attempted to leave the reader with cited literature for in-depth reading, based on our survey of the literature, of what we found most helpful. We would like to mention that the physical uptake of PM prior to even AhR reception is not discussed in this review.

Conflicts of interest

The authors declare they have no conflicts of interest related to this work to disclose.

CRediT authorship contribution statement

Durgesh N. Das: Writing – review & editing, Writing – original draft, Validation, Methodology, Conceptualization. **Dhruv Mitroo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Durgesh Nandini Das reports financial support was provided by US Department of Veterans Affairs and a relationship with US Department of Veterans Affairs that includes employment, Dhruv Mitroo reports financial support was provided by US Department of Veterans Affairs and by US Department of Defense. Both authors have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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