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Environmental $PM_{2.5}$-triggered stress responses in digestive diseases

Kezhong Zhang

Center for Molecular Medicine and Genetics, Department of Biochemistry, Microbiology, and Immunology, Wayne State University School of Medicine, Detroit, Michigan, USA

Abstract

Airborne particulate matter in fine and ultrafine ranges (aerodynamic diameter less than 2.5 μm, $PM_{2.5}$) is a primary air pollutant that poses a serious threat to public health. Accumulating evidence has pointed to a close association between inhalation exposure to $PM_{2.5}$ and increased morbidity and mortality associated with modern human complex diseases. The adverse health effect of inhalation exposure to $PM_{2.5}$ pollutants is systemic, involving multiple organs, different cell types and various molecular mediators. Organelle damages and oxidative stress appear to play a major role in the cytotoxic effects of $PM_{2.5}$ by mediating stress response pathways related to inflammation, metabolic alteration and cell death programmes. The organs or tissues in the digestive tract, such as the liver, pancreas and small intestines, are susceptible to $PM_{2.5}$ exposure. This review underscores $PM_{2.5}$-induced inflammatory stress responses and their involvement in digestive diseases caused by $PM_{2.5}$ exposure.

INTRODUCTION

Epidemiological studies and biomedical research have consistently linked real-world airborne pollutants to the increase of mortality and morbidity associated with modern human complex diseases.[1-5] In particular, environmental airborne particulate matter in fine and ultrafine ranges (aerodynamic diameter <2.5 μm, $PM_{2.5}$) is strongly associated with the development of air pollution-associated systemic diseases (figure 1).[1 5 6] There exist linear dose-risk relationships between $PM_{2.5}$ concentrations and the occurrence of cardiovascular and metabolic diseases, as a 3% increase in cardiovascular disease incidence or a 1% increase in diabetes prevalence was observed in populations under 10 $\mu g/m^3$ increase in $PM_{2.5}$ exposure.[4 5] This relationship remained consistent even for countries within the guidelines for US Environmental Protection Agency (EPA) $PM_{2.5}$ exposure limits, such as Europe and USA. Chronic $PM_{2.5}$ exposure increases the danger of cardiovascular and

Correspondence to Dr Kezhong Zhang; kzhang@med.wayne.edu.

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metabolic diseases to an even greater degree and effects may be more pronounced in susceptible populations such as older adults, lower socioeconomic status and individuals with pre-existing conditions.[4] Short-term exposure to polluted air at levels generally considered ‘acceptable’ may impair mental ability in elderly people in the USA.[7]

In most cases, airborne $PM_{2.5}$ is a complex mixture of particles and gases from gasoline and diesel engines, mixed with dust from wear of road surfaces and tires.[8 9] Airborne $PM_{2.5}$ particles have an incremental capacity to penetrate the distal airway units and the systemic circulation.[10] Under inhalation exposure to $PM_{2.5}$, fine $PM_{2.5}$ nanoparticles can reach the terminal bronchioles, pass through the air–blood barrier and enter the blood circulation (figure 1).[11 12] Both transmission electron microscopy (TEM) and in vivo real-time visualisation of $PM_{2.5}$-simulating fluorescent dyed nanoparticles revealed the deposition of $PM_{2.5}$ particles in the extrapulmonary organs.[13 14] While ultrafine PM particles, such as $PM_{0.2}$, have a more uniform deposition pattern in acinar regions through endocytosis or diffusion, ambient $PM_{2.5}$ particles of various sizes can enter into the gastrointestinal tract and the lymphatic system and be retained in the liver and kidney.[13 15-18] One of the possible mechanisms through which $PM_{2.5}$ is retained in extrapulmonary organs/tissues is internalisation of particles by macrophages.[13 14 19]

It has been demonstrated that the cytotoxic effects of $PM_{2.5}$ are more associated with $PM_{2.5}$ as a complex rather than single or a few components of $PM_{2.5}$ particles.[20] The specialised cell types of inflammatory and metabolic nature are exquisitely sensitive to $PM_{2.5}$ particles and play major roles in promoting air pollution-associated systemic diseases.[9 19 21] At the molecular level, $PM_{2.5}$ particles appear to be highly effective in triggering inflammatory stress responses in inflammatory and/or metabolic cell types. Emerging evidence suggests that intracellular stress responses originated from the endoplasmic reticulum (ER), mitochondria or lysosome, which are targeted by $PM_{2.5}$, interact with inflammatory signalling pathways to modulate inflammatory equilibrium and metabolic homeostasis in multiple organs/tissues.[14 22-25] $PM_{2.5}$-induced, integrated inflammatory stress responses play major roles in driving the pathogenesis of complex diseases associated with air pollution.

During the past two decades, the research community has been using both in vivo and in vitro $PM_{2.5}$ exposure systems, genetically engineered animal models, molecular and cellular approaches, as well as bioinformatics to determine the cytotoxic effects and stress mechanisms through which environmental $PM_{2.5}$ causes systemic diseases. Towards this direction, a large amount of published information and data repositories in public domains have been accumulated. In this review, the recently reported studies on $PM_{2.5}$-induced inflammatory stress responses in the digestive system are summarised and interpreted, with the intention to help the understanding, prevention and treatment of air pollution-associated diseases.

THE RESPONSES TO $PM_{2.5}$: ORGANELLE STRESS, INFLAMMATION AND METABOLISM

Maintenance of inflammatory equilibrium and metabolic homeostasis is among the most fundamental requirements for survival and well-being. In response to environmental challenges, nutritional signals or pathological conditions, inflammatory response and metabolic regulation interact and are highly integrated, and the proper function of each is dependent on the other.[26] This interface serves as a central homeostatic mechanism, and its dysregulation critically contributes to the development of modern human complex diseases, such as cardiovascular disease, metabolic syndrome, neurodegenerative disease and cancer. Accumulating evidence has established that stress signalling originated from intracellular organelles, particularly from the ER, mitochondria and lysosome, acts as a major driving force that facilitates inflammatory and metabolic responses.[23 24 26 27] Research from our group and others have identified that chronic inflammation, altered organelle stress responses and dysregulated energy metabolism in major inflammatory metabolic organs/tissues represent the major driving forces of $PM_{2.5}$-caused pathogenesis.

$PM_{2.5}$-induced ER stress response

ER stress response, also known as unfolded protein response (UPR), is an intracellular stress signalling from the ER to protect cells from stress caused by the accumulation of unfolded or misfolded proteins in the ER.[28 29] As a protein-folding compartment and a dynamic calcium store, the ER is delicately sensitive to intracellular and extracellular stimuli. Environmental stressors, pharmacological stimuli and pathological conditions, such as chronic disease, viral infection, oxidative stress and inflammatory challenges, can directly or indirectly cause ER stress and induce UPR in specialised cells or organs/tissues.[23 24 30] The basic UPR pathways in mammalian cells are composed of three main signalling cascades mediated by three ER membrane-localised transducers: inositol-requiring 1 (IRE1α), double-strand RNA-activated protein kinase-like ER kinase (PERK) and activating transcription factor 6 (ATF6). In response to ER stress, PERK phosphorylates eukaryotic translation initiation factor 2α (eIF2α) to attenuate general protein translation to limit newly synthesised proteins entering the ER lumen, which is saturated by unfolded or misfolded proteins. However, under prolonged ER stress, phosphorylated eIF2α can recognise the unique 5'-untranslated regions and initiate translation of select mRNAs to encode proteins involved in amino acid metabolism, oxidative stress response and cell death programmes. On activation of the UPR, IRE1α functions as an RNase to splice the mRNA encoding X-box binding protein 1 (XBP1), leading to transcriptional reprogramming of the stressed cells. As an RNase, IRE1α can also process select mRNAs or microRNAs, leading to their degradation under pathophysiological ER stress, a pathway called 'Regulated IRE1α-dependent decay (RIDD)'.[31-36] Additionally, under ER stress, ATF6 is activated to function as a transcription factor to induce expression of the UPR genes encoding functions aiding ER recovery from the stress.[37-39] The UPR pathways are orchestrated to help the cells adapt to and survive stress conditions. However, when ER stress gets prolonged or too severe to handle, the UPR will initiate a cell death programme to eliminate the stressed cells. Under pathophysiological conditions, the UPR can modulate cell metabolism, inflammation

and programmed cell death, engaging the pathogenesis of a variety of diseases, such as metabolic disease, cardiovascular disease, neurodegenerative disease, and cancer.[23]

The macrophage cell type is susceptible to environmentally relevant $PM_{2.5}$ in inducing ER stress and activation of the UPR.[14] Inhalation exposure of wild-type mice of C57BL/6 strain background to concentrated environmental $PM_{2.5}$ (mean concentration 74.6 $\mu g/m^3$) for 10 weeks induced ER stress and selective activation of UPR pathways in the lung and liver tissues.[14] Ambient $PM_{2.5}$ exposure activates PERK, leading to phosphorylation of eIF2α and induction of C/EBP homologous transcription factor CHOP/GADD153 (figure 2). Activation of PERK-mediated UPR pathway relies on the production of reactive oxygen species (ROS) and is critical for $PM_{2.5}$-induced, ER stress-associated apoptosis.[14] $PM_{2.5}$ exposure exerts discernable effects on the primary UPR transducer IRE1α. Interestingly, $PM_{2.5}$ decreased the activity of IRE1α RNase in splicing the *Xbp1* mRNA, while it elevated IRE1α protein levels and phosphorylation state in mouse livers (figure 2).[14] Because functional XBP1 plays an essential role in cell metabolism, inflammation and secretory pathways,[40-42] $PM_{2.5}$ may elicit its cytotoxicity by inhibiting *Xbp1* mRNA splicing and thus XBP1 maturation. Furthermore, IRE1α is known to activate the c-Jun N-terminal kinase (JNK)-mediated or tumour necrosis factor receptor associated factor (TRAF)-mediated pathway to promote inflammatory or apoptotic responses under ER stress conditions.[24 43-45] In the liver tissue of mice exposed to $PM_{2.5}$ for 10 weeks, levels of phosphorylated JNK were increased, coinciding with the increased expression and phosphorylation of IRE1α as well as hepatic inflammation and injuries triggered by $PM_{2.5}$ (figure 2).[14] Moreover, the levels of several mRNA targets of RIDD were also decreased in the $PM_{2.5}$-exposed mouse livers.[14] However, it remains to be validated whether the $PM_{2.5}$-triggered suppression of these mRNAs was through the IRE1α-mediated RIDD pathway, given that IRE1α RNase activity was repressed by $PM_{2.5}$. Additionally, $PM_{2.5}$ exposure can activate the ATF6-mediated UPR branch in the liver,[14] with its pathophysiological significance yet to be determined.

$PM_{2.5}$-induced ER stress response and toxic health effects can differ with the exposure scenarios. Acute exposure to high-dose $PM_{2.5}$ (96 $\mu g/cm^2$) for 10 days induced ROS burst, DNA damage, activation of the three major UPR pathways, autophagy and necrotic cell death in human bronchial epithelial cells.[46] In comparison, low-dose $PM_{2.5}$ exposure (6 $\mu g/cm^2$) led to low-grade ROS accumulation, milder DNA damage, ER stress response, cell cycle arrest, apoptosis and autophagy. In rats that were intratracheally instilled with $PM_{2.5}$, the $PM_{2.5}$ challenge induced IRE1α/XBP1 branch of UPR, which depended on the assembly of XBP1/hypoxia-inducible factor 1α (HIF1α) transcriptional complex, in the vascular endothelium.[47] Associated with the development of metabolic syndrome, chronic inhalation exposure to $PM_{2.5}$ for 10 months induced macrophage infiltration and UPR in mouse white adipose tissue.[48] $PM_{2.5}$ exposure induced two distinct UPR pathways mediated through IRE1α: ER-associated degradation and RIDD of mRNAs. Correlated with the induction of the UPR and macrophage infiltration, expression of genes involved in lipogenesis, adipocyte differentiation and lipid droplet formation were increased in the adipose tissue of the $PM_{2.5}$-exposed mice,[47 48] implicating a pathophysiological role of the UPR in $PM_{2.5}$-induced metabolic disorders. Consistently, in humans, maternal exposure to $PM_{2.5}$ increased adiposity in infants.[49 50]

In summary, the current literature illustrates that inhalation exposure to $PM_{2.5}$ selectively activates the UPR pathways in the liver, the major digestive organ, in an ROS-dependent manner. $PM_{2.5}$-induced hepatic UPR pathways include ER stress-associated pro-apoptotic response mediated through PERK-eIF2α-CHOP and proinflammatory response mediated through IRE1α-JNK However, $PM_{2.5}$ exposure represses IRE1α RNase activity in splicing *Xbp1* mRNA, although it increases expression and phosphorylation of hepatic IRE1α protein.[14] How the UPR pathways are selectively activated by $PM_{2.5}$ exposure remains to be further elucidated.

$PM_{2.5}$-induced mitochondrial stress response

$PM_{2.5}$ exposure has a major impact on mitochondrial homeostasis and function. Depending on the exposure scenarios, $PM_{2.5}$ can stimulate mitochondrial ROS release, activate mitophagy, cause mitochondrial damage and decrease mitochondria numbers in multiple organs/tissues. Mitochondria are exquisitely sensitive to $PM_{2.5}$ stimulation in releasing ROS. This has been evidenced in $PM_{2.5}$-exposed macrophages[14 51] and in the lung,[14 52] liver,[14] heart,[53] adipose tissue[54 55] and blood vessels[56 57] of mice or rats exposed to $PM_{2.5}$. With mouse primary hepatic stellate cells and human hepatic stellate cell line LX-2, Qiu *et al*[22] demonstrated that $PM_{2.5}$ exposure triggered the mitophagy process by activating the PINK1/Parkin pathway in a manner depending on mitochondrial ROS release. The $PM_{2.5}$-induced mitophagy was concomitant with the activities of mitochondrial fission and cytochrome c release in hepatic stellate cells. Interestingly, inhibition of mitophagy diminished hepatic fibrosis induced by $PM_{2.5}$.[22] The $PM_{2.5}$-induced mitophagy and redox imbalance were confirmed by an in vivo study with mice exposed to $PM_{2.5}$.[58]

Studies with animal models confirmed that $PM_{2.5}$ exposure caused mitochondrial damage, characterised by a decline in mitochondrial membrane potential, fragmented mitochondria and increased mitochondrial ROS released in the lung, liver and adipose tissues.[22 52 54 59] $PM_{2.5}$-caused mitochondrial damage appears to be responsible, at least partially, for the development of pulmonary fibrosis,[52] non-alcoholic steatohepatitis (NASH)[19 21 22] and type 2 diabetes (T2D)[19 21] under air pollution. Exposure to $PM_{2.5}$ can also modulate mitochondrial UPR (UPR^{mt}), a mitochondria-originated stress signalling required to maintain mitochondrial proteostasis and function,[60] in spermatogenic cells of prepubertal rats.[61] Intratracheal instillation of low-dose $PM_{2.5}$ (5 mg/kg) to prepubertal rats induced UPR^{mt}, reflected by induction of the master UPR^{mt} regulators ATF5 and ATF4 in spermatogenic cells. However, the instillation of high-dose $PM_{2.5}$ (10 mg/kg) to the rats suppressed UPR^{mt}, which was correlated with the declined spermatogenic cell numbers and conception rates. Interestingly, supplementation of vitamin C and vitamin E (100 mg/kg of vitamin C and 50 mg/kg of vitamin E) can attenuate the effect of high-dose $PM_{2.5}$ (10 mg/kg) on suppressing UPR^{mt} in spermatogenic cells, and the vitamin intervention promoted conception rate recovery, alleviated mitochondrial damage and reduced spermatogenic cell apoptosis in rats under high-dose $PM_{2.5}$ exposure.[61]

$PM_{2.5}$-induced lysosomal stress response

$PM_{2.5}$ exposure elicits strong effects on the autophagic response by activating lysosome-associated pathways. Macroautophagy or autophagy was induced in human bronchial

epithelial cells on exposure to environmental $PM_{2.5}$ particles.[62] $PM_{2.5}$-induced autophagy, which requires tumour protein p53 (TP53) activation and expression of its downstream target DNA damage-regulated autophagy modulator 1 (DRAM1), led to upregulation of vascular endothelial growth factor A by activating the SRC (SRC proto-oncogene, non-receptor tyrosine kinase)-signal transducer and activator of transcription 3 pathway. This signalling network extended the role of TP53-DRAM1-dependent autophagy beyond cell fate determination to the control of proinflammatory response in bronchial epithelial cells under $PM_{2.5}$ exposure.[62] However, a study by Wang and Tang[63] showed that $PM_{2.5}$ induced both autophagy and apoptosis through ER stress response pathways in human endothelial cells, where autophagy protected against $PM_{2.5}$-induced apoptosis.

Intriguingly, our studies with animal models showed that inhalation exposure to environmental $PM_{2.5}$ induced autophagy in the liver that counteracted hepatic steatosis induced by a high-fat diet (figure 3).[64] $PM_{2.5}$ exhibited a strong effect on triggering hepatic autophagy programme in a manner depending on the inflammatory pathway mediated through Toll-like receptor-myeloid differentiation primary response 88 (MyD88).[64] In contrast to a ‘two-hits’ hypothesis that $PM_{2.5}$ exposure may interact with a high-fat diet or obese condition to exacerbate metabolic disorders, $PM_{2.5}$ exposure counteracted hepatic steatosis and hyperlipidaemia of obese mice under the high-fat diet through stimulating hepatic autophagy. Under normal chow, $PM_{2.5}$ exposure triggers hepatic autophagy, but meanwhile represses PPARα, PPARγ SIRT1 and CREBH, the key regulators of fatty acid oxidation and lipolysis (figure 3A).[64] Because $PM_{2.5}$-caused repression of fatty acid oxidation and lipolysis outweighed the effect of hepatic autophagy, the normal chow-fed animals exhibited hepatic steatosis and hypertriglyceridaemia under $PM_{2.5}$ exposure. Under the high-fat diet or obese condition, however, overnutrition-caused hepatic steatosis and hypertriglyceridaemia were alleviated by hepatic autophagy triggered by $PM_{2.5}$ (figure 3B).[64-66] Apparently, the steatosis-relieving effect of $PM_{2.5}$-induced hepatic autophagy overrides the repressive effect of lipid mobilisation caused by $PM_{2.5}$ exposure, and thereby, $PM_{2.5}$ stimulation displays discernable effects on mitigating hepatic steatosis, liver injuries and hyperlipidaemia in the obese animals under the high-fat diet.[64] The identification of the ‘beneficial’ effect of $PM_{2.5}$ on activating hepatic autophagy provides new insights into the complex effects of airborne $PM_{2.5}$ pollution and the mechanistic basis by which multiple stressors interact to modulate pathophysiology in complex diseases. This also changes our view on the ‘two-hits’ hypothesis that two stressors or insults act in synergy to promote pathogenesis. The second hit, $PM_{2.5}$ exposure, could mitigate the detrimental effect of the first ‘hit’, obesity or high-fat diets, in driving liver steatosis.

$PM_{2.5}$-INDUCED STRESS RESPONSES IN THE DIGESTIVE SYSTEM AND DISEASES

Inflammatory stress responses and dysregulated energy metabolism in major inflammatory metabolic organs/tissues have been identified as the driving force of $PM_{2.5}$-caused pathogenesis.[67-71] Increasing evidence showed that inhalation exposure to environmentally relevant $PM_{2.5}$ induces integrated inflammatory stress responses in the digestive system that contribute to the progression of complex diseases. Among the organs/tissues of the digestive

tract, the liver, pancreas and small intestine are particularly susceptible to $PM_{2.5}$ exposure in promoting pathological stress responses and metabolic or digestive diseases (figure 1).

$PM_{2.5}$-induced stress responses in the liver

Chronic or subchronic exposure to concentrated $PM_{2.5}$ causes injuries to the liver, the major detoxification and metabolic organ. Inhalation exposure to $PM_{2.5}$ may impose stress on the liver through three major paths[13 21 72]: (1) systemic effects of circulating proinflammatory cytokines or chemokines from pulmonary inflammation triggered by $PM_{2.5}$ exposure, (2) retention of activated neutrophils and monocytes to the liver tissues under $PM_{2.5}$ exposure and (3) $PM_{2.5}$ nanoparticles reach to and are deposited in the liver. In the past 15 years, we and others demonstrated that inhalation exposure to $PM_{2.5}$ caused liver-associated diseases by exaggerating hepatic inflammation, inducing organelle stress and oxidative damage, and disrupting energy homeostasis. On a normal chow diet, wild-type C57BL/6 mice exposed to environmentally relevant $PM_{2.5}$ at a concentration of approximately 80 $\mu g/m^3$ or higher for 10 weeks developed NASH-like and T2D-like phenotypes.[19 21 67 73] After $PM_{2.5}$ exposure, the mice displayed hepatic steatosis, inflammation and fibrosis, coincided with impaired hepatic glycogen storage, glucose intolerance and insulin resistance.[19 21] Interestingly, these phenotypes were accompanied by significant loss of body weight of the mice. Linked to the $PM_{2.5}$-induced liver-associated phenotypes, the livers of $PM_{2.5}$-exposed mice exhibited: (1) activation of inflammatory responses mediated through JNK, nuclear factor kappa B (NF-κB) and Toll-like receptor 4 (TLR4) in Kupffer cells[14 19 21 67]; (2) selective activation of the UPR,[14] oxidative stress[14 19] and autophagy[22 64]; and (3) suppression of the insulin receptor substrate 1 (IRS1)-mediated signalling.[21] Moreover, $PM_{2.5}$ exposure repressed the major metabolic regulators PPARα, SIRT1, CREBH and Farnesoid X receptor (FXR) as well as the anti-inflammatory regulator PPARα in the liver.[19 21 64 74] Consistent with the repression of metabolic regulators by $PM_{2.5}$, hepatic circadian oscillation and lipid metabolism were disrupted in mice exposed to $PM_{2.5}$.[75-77] Specific to liver fibrogenesis, $PM_{2.5}$ exposure stimulated the transforming growth factor β (TGFβ)-SMAD3 signalling and promoted the production of collagens by hepatic stellate cells.[19] Importantly, $PM_{2.5}$-induced TGFβ signalling, collagen production and hepatic fibrogenesis as well as suppression of PPARγ relied on NADPH oxidase-dependent ROS production.[19]

A variety of studies have confirmed that $PM_{2.5}$-triggered ROS or oxidative stress is the root of inflammatory stress responses and tissue injuries,[14 78 79] and the reduction of nuclear factor erythroid-derived 2-related factor 2 (NRF2), a master regulator of anti-oxidative stress response, is heavily involved in air pollution-associated complex diseases.[80 81] Interestingly, AMPK activators, monounsaturated fatty acids (MUFAs) (eg, oleanolic acid) and melatonin can mitigate $PM_{2.5}$-caused oxidative stress as well as hepatic inflammation, fibrosis and liver injuries in animal models.[82-84] Additionally, a meta-analysis of epidemiological evidence suggested that exposure to airborne $PM_{2.5}$ pollution increased the risk of gastrointestinal cancers.[85] The impact of $PM_{2.5}$ on the risk of hepatocellular carcinoma (HCC) has been observed in East Asia, Europe and USA.[86-90] Ambient $PM_{2.5}$ pollution was associated with increased mortality in patients with HCC[91]. $PM_{2.5}$-induced NASH activities may be associated with the progression of HCC under air pollution; however, the mechanistic basis by which $PM_{2.5}$ pollutant is involved in HCC remains to be elucidated.

$PM_{2.5}$-induced stress responses in the pancreas

The association between exposure to $PM_{2.5}$ and type 1 or T2D mellitus has been confirmed in population studies.[92 93] Exposure to $PM_{2.5}$ reduced pancreatic homogenate glutathione peroxidase (GSH-Px), increased methane dicarboxylic aldehyde and decreased pancreas glucose transporter 2 expression in a rat model of gestational diabetes mellitus.[94] $PM_{2.5}$-induced oxidative response and inflammation in the pancreas are responsible for the increased risk of pancreatic impairment and glycaemic consequences under $PM_{2.5}$ exposure. In a mouse model of streptozotocin-induced type 1 diabetes, $PM_{2.5}$ promoted pancreatic β cell damage by stimulating interleukin 1β (IL1β) and tumour necrosis factor α (TNFα) production in macrophages and β cells.[95] $PM_{2.5}$ exposure can also attenuate insulin secretion from β cells in a dose-dependent manner.[95]

$PM_{2.5}$-induced stress responses in small intestines

In mice exposed to real-world $PM_{2.5}$ at a concentration of approximately 90 $\mu g/m^3$, the intestines displayed oedema and discrete epithelial lesions (loss of crypts) after 3 weeks of PM exposure.[96] Sporadic inflammatory cell infiltration was observed in mouse intestines after 6 weeks of exposure. At the 12th week post PM exposure, the epithelial lesions and confluence of inflammatory cell infiltration were profound in mouse intestines.[96] In human small intestinal cells, treatment of $PM_{2.5}$ particles increased ROS production, iron accumulation, lipid peroxidation and ferroptosis.[97] Like the scenarios in the lung and liver tissues, $PM_{2.5}$-caused damage to small intestines is through oxidative stress and inflammatory challenges.[96 97] Direct administration of high-dose $PM_{2.5}$ (200 μg/mice) via gavage caused intestinal epithelial cell death, tight junction damage and increased intestinal permeability in a manner depending on oxidative stress and inflammatory response.[98] Additionally, chronic inhalation exposure to concentrated ambient $PM_{2.5}$ can alter the composition of intestinal microbiota and modulate metabolic profiles in mice.[99-102] Interestingly, in spontaneously hypertensive rats, exposure to ambient $PM_{2.5}$ pollutants led to alterations of intestine microbiota that are associated with cardiovascular diseases.[103]

PERSPECTIVE

Inhalation exposure to environmentally relevant $PM_{2.5}$ exerts systemic adverse health effects, causing injuries to multiple organs/tissues. At the molecular level, $PM_{2.5}$ nanoparticles directly or indirectly target intracellular organelles, particularly the ER, mitochondria and lysosome, inducing integrated inflammatory stress responses. At the organ/tissue level, $PM_{2.5}$-caused oxidative damage and inflammatory challenge represent the major cytotoxic consequence caused by $PM_{2.5}$ exposure that drives the pathogenesis of complex diseases, including those that are associated with the digestive system. In the past decade, the pathological impact, cytotoxic effects and mechanistic basis by which $PM_{2.5}$ inhalation causes liver-associated diseases have been well studied. $PM_{2.5}$ exposure causes mitochondrial damage, oxidative stress, selective activation of the UPR pathways, autophagy and mitophagy, coinciding with the inflammatory responses mediated through TLR, JNK and NF-κB in the liver. These inflammatory stress response pathways are orchestrated to promote the development of NASH and obesity-independent T2D. While the progress is intriguing, some open questions remain. First, as the ER, mitochondria and

lysosome are sensitive to $PM_{2.5}$ exposure in activating organelle stress responses, what are the mechanisms by which the cells sense $PM_{2.5}$ and how $PM_{2.5}$ exposure can differentially induce stress response pathways in different organs or tissues? Second, inhalation exposure to $PM_{2.5}$ adversely affects the functions of the liver, pancreas and intestine. Does $PM_{2.5}$ exposure disrupt the interorgan communication among the major digestive organs? For example, does the $PM_{2.5}$-induced pancreatic damage worsen hepatic insulin resistance? Are intestinal injuries or microbiota dysregulation caused by $PM_{2.5}$ pollution contributing to liver pathogenesis? Additionally, is there any nutritional or pharmaceutical intervention to prevent or mitigate the cytotoxic effects caused by $PM_{2.5}$ exposure? This seems a trivial question, as air pollution and the relevant problems cannot be resolved unless the industrialised, resource-exhausting lifestyle is changed. However, multiple studies have shed light that MUFAs, vitamin C plus E or melatonin can mitigate $PM_{2.5}$-caused oxidative stress, inflammation, mitochondrial damage and tissue/cell injuries in animal models.[61 83 84] For future research, it is interesting to test whether MUFAs or vitamins, as a nutritional supplement, can prevent or alleviate the systemic diseases caused by $PM_{2.5}$.

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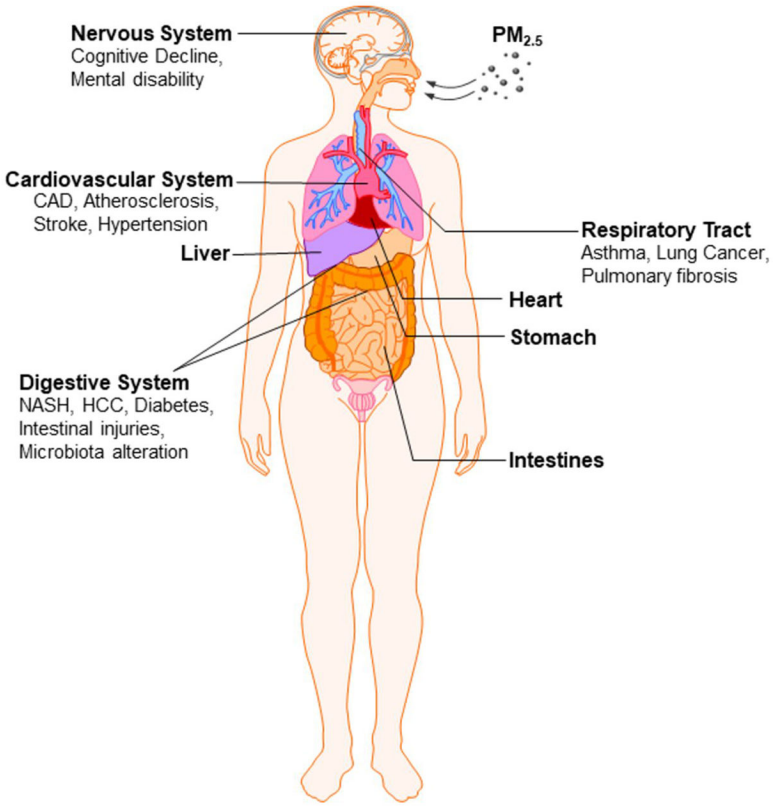

Figure 1.

The systemic effects of inhalation exposure to $PM_{2.5}$. The diseases caused by $PM_{2.5}$ pollution in different systems are shown. CAD, coronary artery disease; HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis.

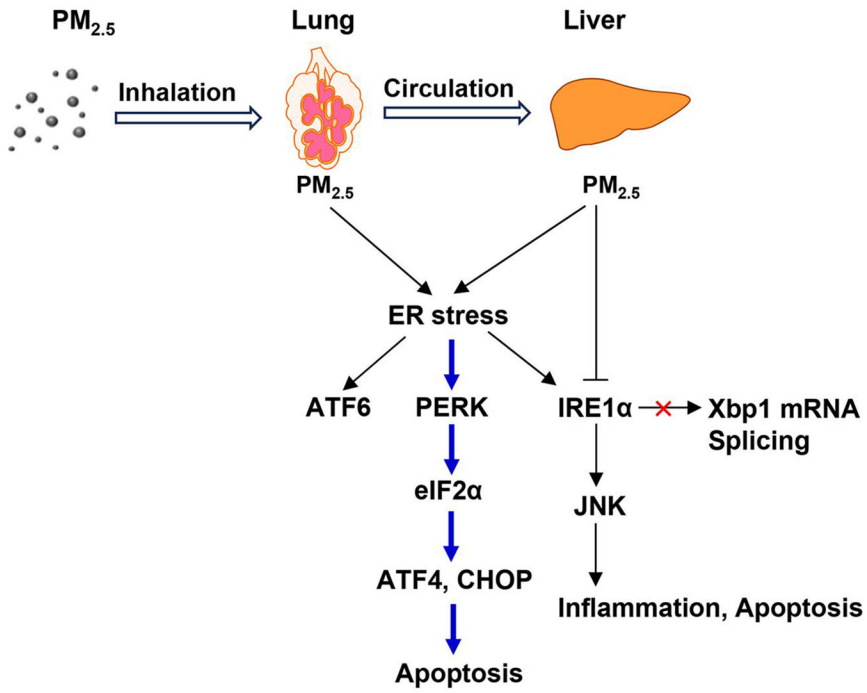

Figure 2.

Illustration of endoplasmic reticulum (ER) stress and unfolded protein response (UPR) in mouse lung and liver tissues induced by $PM_{2.5}$ exposure. ATF6, activating transcription factor 6; IRE1α, inositol-requiring 1; JNK, c-Jun N-terminal kinase; PERK, protein kinase-like ER kinase.

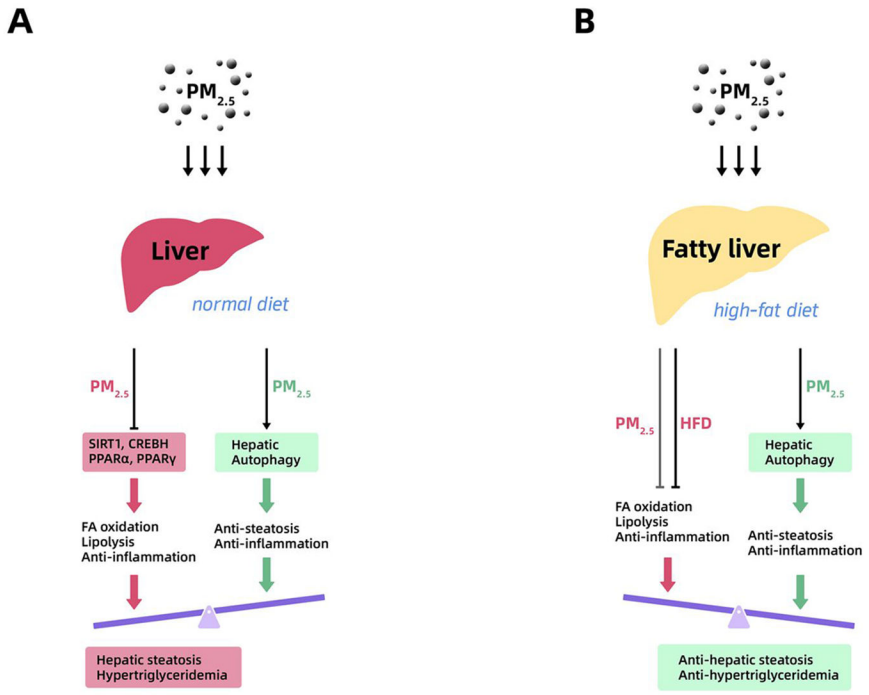

Figure 3.

The effects and pathways by which $PM_{2.5}$ exposure promotes or mitigates hepatic steatosis and hypertriglyceridaemia in mice under normal chow or a high-fat diet (HFD). (A) The effects and pathways by which $PM_{2.5}$ represses lipid metabolic and anti-inflammatory pathways and induces hepatic autophagy in the livers of mice under normal chow. (B) The effects and pathways by which $PM_{2.5}$ and HFD repress or promote hepatic autophagy as well as lipid metabolic and anti-inflammatory pathways in the fatty livers of HFD-fed mice. FA, fatty acid.