


# eGastroenterology Environmental PM<sub>2.5</sub>-triggered stress responses in digestive diseases

Kezhong Zhang 

**To cite:** Zhang K. Environmental PM<sub>2.5</sub>-triggered stress responses in digestive diseases. *eGastroenterology* 2024;2:e100063. doi:10.1136/egastro-2024-100063

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<https://doi.org/10.1136/egastro-2024-100063>).

Received 08 January 2024  
Accepted 07 February 2024

## ABSTRACT

Airborne particulate matter in fine and ultrafine ranges (aerodynamic diameter less than 2.5 µm, PM<sub>2.5</sub>) 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<sub>2.5</sub> and increased morbidity and mortality associated with modern human complex diseases. The adverse health effect of inhalation exposure to PM<sub>2.5</sub> 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<sub>2.5</sub> 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<sub>2.5</sub> exposure. This review underscores PM<sub>2.5</sub>-induced inflammatory stress responses and their involvement in digestive diseases caused by PM<sub>2.5</sub> 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.<sup>1–5</sup> In particular, environmental airborne particulate matter in fine and ultrafine ranges (aerodynamic diameter <2.5 µm, PM<sub>2.5</sub>) is strongly associated with the development of air pollution-associated systemic diseases (figure 1).<sup>1–5–6</sup> There exist linear dose-risk relationships between PM<sub>2.5</sub> 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 µg/m<sup>3</sup> increase in PM<sub>2.5</sub> exposure.<sup>4–5</sup> This relationship remained consistent even for countries within the guidelines for US Environmental Protection Agency (EPA) PM<sub>2.5</sub> exposure limits, such as Europe and USA. Chronic PM<sub>2.5</sub> exposure increases the danger of cardiovascular and 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.<sup>4</sup>

Short-term exposure to polluted air at levels generally considered ‘acceptable’ may impair mental ability in elderly people in the USA.<sup>7</sup>

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

It has been demonstrated that the cytotoxic effects of PM<sub>2.5</sub> are more associated with PM<sub>2.5</sub> as a complex rather than single or a few components of PM<sub>2.5</sub> particles.<sup>20</sup> The specialised cell types of inflammatory and metabolic nature are exquisitely sensitive to PM<sub>2.5</sub> particles and play major roles in promoting air pollution-associated systemic diseases.<sup>9–19–21</sup> At the molecular level, PM<sub>2.5</sub> 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<sub>2.5</sub>, interact with inflammatory signalling pathways to modulate inflammatory equilibrium and metabolic homeostasis in multiple organs/tissues.<sup>14–22–25</sup> PM<sub>2.5</sub>-induced,

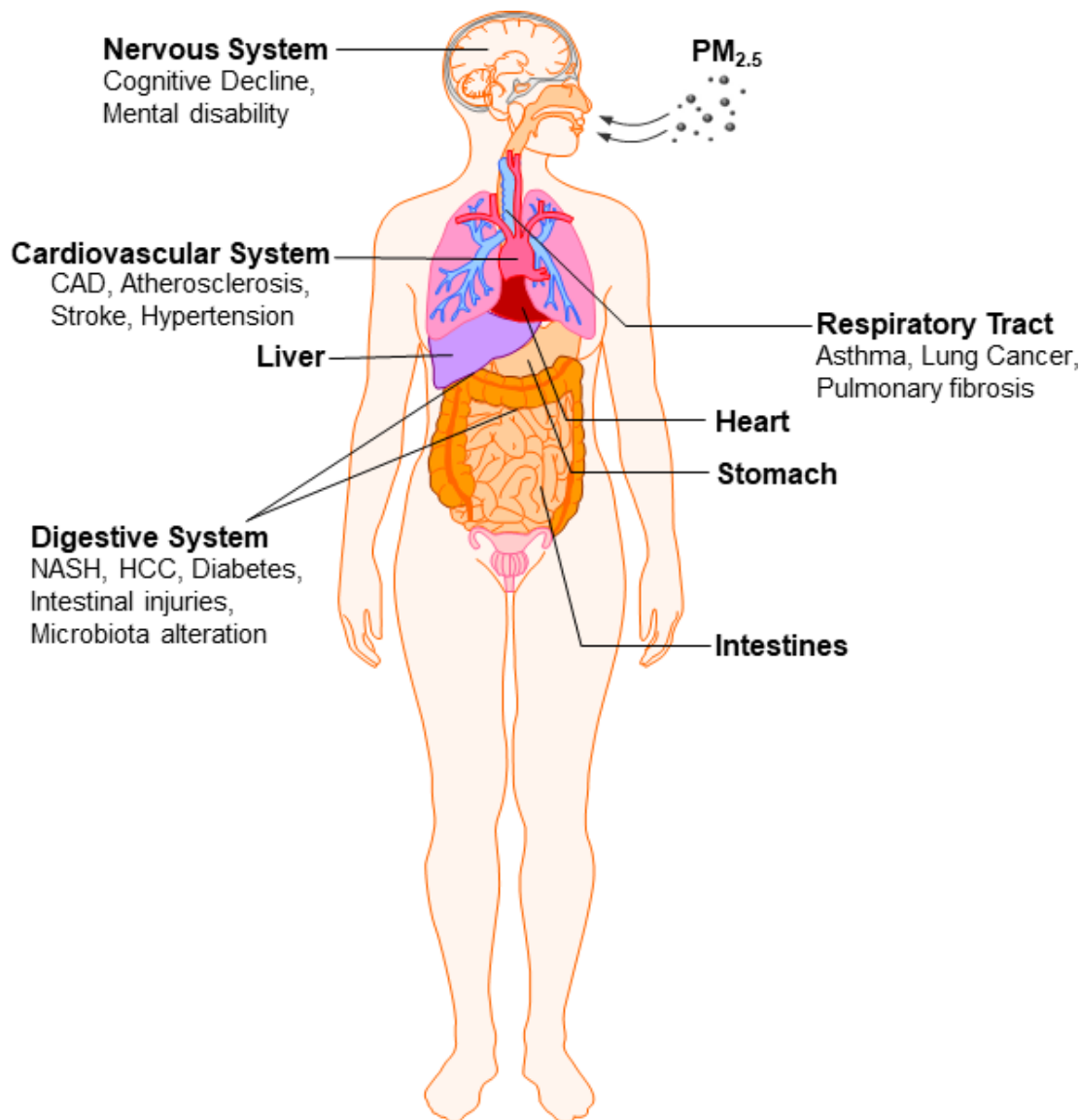


© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

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

## Correspondence to

Dr Kezhong Zhang;  
kzhang@med.wayne.edu



**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.

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.<sup>26</sup> 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.<sup>23 24 26 27</sup> 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<sub>2.5</sub>-caused pathogenesis.

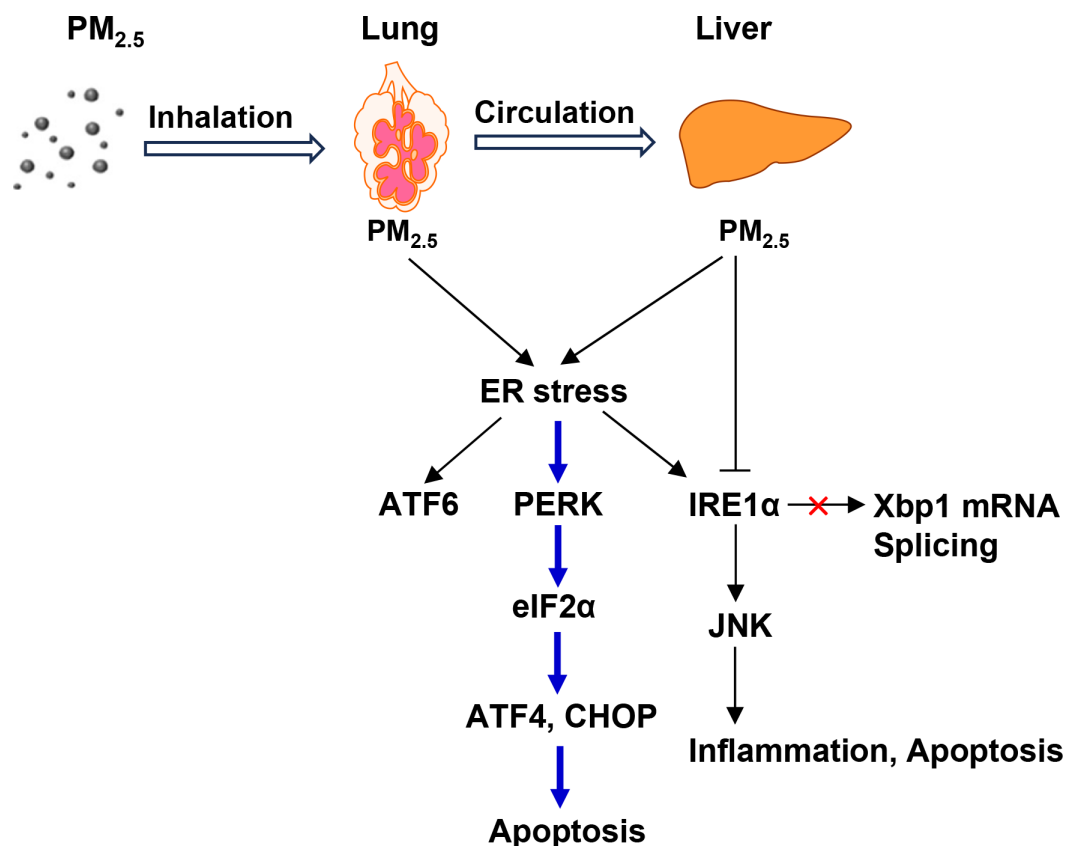
### PM<sub>2.5</sub>-induced ER stress response

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.<sup>28–29</sup> 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.<sup>23–24–30</sup> The basic UPR pathways in mammalian cells are composed of three main signalling cascades mediated by three ER membrane-localised transducers: inositol-requiring 1 (IRE1 $\alpha$ ), 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 2 $\alpha$  (eIF2 $\alpha$ ) 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 eIF2 $\alpha$  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, IRE1 $\alpha$  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, IRE1 $\alpha$  can also process select mRNAs or microRNAs, leading to their degradation under pathophysiological ER stress, a pathway called 'Regulated IRE1 $\alpha$ -dependent decay (RIDD)'.<sup>31–36</sup> 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.<sup>37–39</sup> 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.<sup>23</sup>

The macrophage cell type is susceptible to environmentally relevant PM<sub>2.5</sub> in inducing ER stress and activation of the UPR.<sup>14</sup> Inhalation exposure of wild-type mice of C57BL/6 strain background to concentrated environmental PM<sub>2.5</sub> (mean concentration 74.6  $\mu\text{g}/\text{m}^3$ ) for 10 weeks induced ER stress and selective activation of UPR

pathways in the lung and liver tissues.<sup>14</sup> Ambient PM<sub>2.5</sub> exposure activates PERK, leading to phosphorylation of eIF2 $\alpha$  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<sub>2.5</sub>-induced, ER stress-associated apoptosis.<sup>14</sup> PM<sub>2.5</sub> exposure exerts discernable effects on the primary UPR transducer IRE1 $\alpha$ . Interestingly, PM<sub>2.5</sub> decreased the activity of IRE1 $\alpha$  RNase in splicing the *Xbp1* mRNA, while it elevated IRE1 $\alpha$  protein levels and phosphorylation state in mouse livers (figure 2).<sup>14</sup> Because functional XBP1 plays an essential role in cell metabolism, inflammation and secretory pathways,<sup>40–42</sup> PM<sub>2.5</sub> may elicit its cytotoxicity by inhibiting *Xbp1* mRNA splicing and thus XBP1 maturation. Furthermore, IRE1 $\alpha$  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.<sup>24–43–45</sup> In the liver tissue of mice exposed to PM<sub>2.5</sub> for 10 weeks, levels of phosphorylated JNK were increased, coinciding with the increased expression and phosphorylation of IRE1 $\alpha$  as well as hepatic inflammation and injuries triggered by PM<sub>2.5</sub> (figure 2).<sup>14</sup> Moreover, the levels of several mRNA targets of RIDD were also decreased in the PM<sub>2.5</sub>-exposed mouse livers.<sup>14</sup> However, it remains to be validated whether the PM<sub>2.5</sub>-triggered suppression of these mRNAs was through the IRE1 $\alpha$ -mediated RIDD pathway, given that IRE1 $\alpha$  RNase activity was repressed by PM<sub>2.5</sub>. Additionally, PM<sub>2.5</sub> exposure can activate the ATF6-mediated UPR branch in the liver,<sup>14</sup> with its pathophysiological significance yet to be determined.

PM<sub>2.5</sub>-induced ER stress response and toxic health effects can differ with the exposure scenarios. Acute exposure to high-dose PM<sub>2.5</sub> (96  $\mu\text{g}/\text{cm}^2$ ) 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.<sup>46</sup> In comparison, low-dose PM<sub>2.5</sub> exposure (6  $\mu\text{g}/\text{cm}^2$ ) 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<sub>2.5</sub>, the PM<sub>2.5</sub> challenge induced IRE1 $\alpha$ /XBP1 branch of UPR, which depended on the assembly of XBP1/hypoxia-inducible factor 1 $\alpha$  (HIF1 $\alpha$ ) transcriptional complex, in the vascular endothelium.<sup>47</sup> Associated with the development of metabolic syndrome, chronic inhalation exposure to PM<sub>2.5</sub> for 10 months induced macrophage infiltration and UPR in mouse white adipose tissue.<sup>48</sup> PM<sub>2.5</sub> exposure induced two distinct UPR pathways mediated through IRE1 $\alpha$ : 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<sub>2.5</sub>-exposed mice,<sup>47–48</sup> implicating a pathophysiological role of the UPR in PM<sub>2.5</sub>-induced metabolic disorders. Consistently, in humans, maternal exposure to PM<sub>2.5</sub> increased adiposity in infants.<sup>49–50</sup>



**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; IRE1 $\alpha$ , inositol-requiring 1; JNK, c-Jun N-terminal kinase; PERK, protein kinase-like ER kinase.

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-eIF2 $\alpha$ -CHOP and proinflammatory response mediated through IRE1 $\alpha$ -JNK. However,  $PM_{2.5}$  exposure represses IRE1 $\alpha$  RNase activity in splicing *Xbp1* mRNA, although it increases expression and phosphorylation of hepatic IRE1 $\alpha$  protein.<sup>14</sup> 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<sup>14 51</sup> and in the lung,<sup>14 52</sup> liver,<sup>14</sup> heart,<sup>53</sup> adipose tissue<sup>54 55</sup> and blood vessels<sup>56 57</sup> 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*<sup>22</sup> 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  $PM_{2.5}$ .<sup>22</sup> The  $PM_{2.5}$ -induced mitophagy and redox imbalance were confirmed by an *in vivo* study with mice exposed to  $PM_{2.5}$ .<sup>58</sup>

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.<sup>22 52 54 59</sup>  $PM_{2.5}$ -caused mitochondrial damage appears to be responsible, at least partially, for the development of pulmonary fibrosis,<sup>52</sup> non-alcoholic steatohepatitis (NASH)<sup>19 21 22</sup> and type 2 diabetes (T2D)<sup>19 21</sup> under air pollution. Exposure to  $PM_{2.5}$  can also modulate mitochondrial UPR (UPR<sup>mt</sup>), a mitochondria-originated stress signalling required to maintain mitochondrial proteostasis and function,<sup>60</sup> in spermatogenic cells of prepubertal rats.<sup>61</sup> Intratracheal instillation of low-dose  $PM_{2.5}$  (5 mg/kg) to prepubertal rats induced UPR<sup>mt</sup>, reflected by induction of the master UPR<sup>mt</sup> regulators ATF5 and ATF4 in spermatogenic cells. However, the instillation of high-dose  $PM_{2.5}$  (10 mg/kg) to the rats suppressed UPR<sup>mt</sup>, which was correlated with the declined spermatogenic cell numbers and conception rates. Interestingly, supplementation of vitamin C



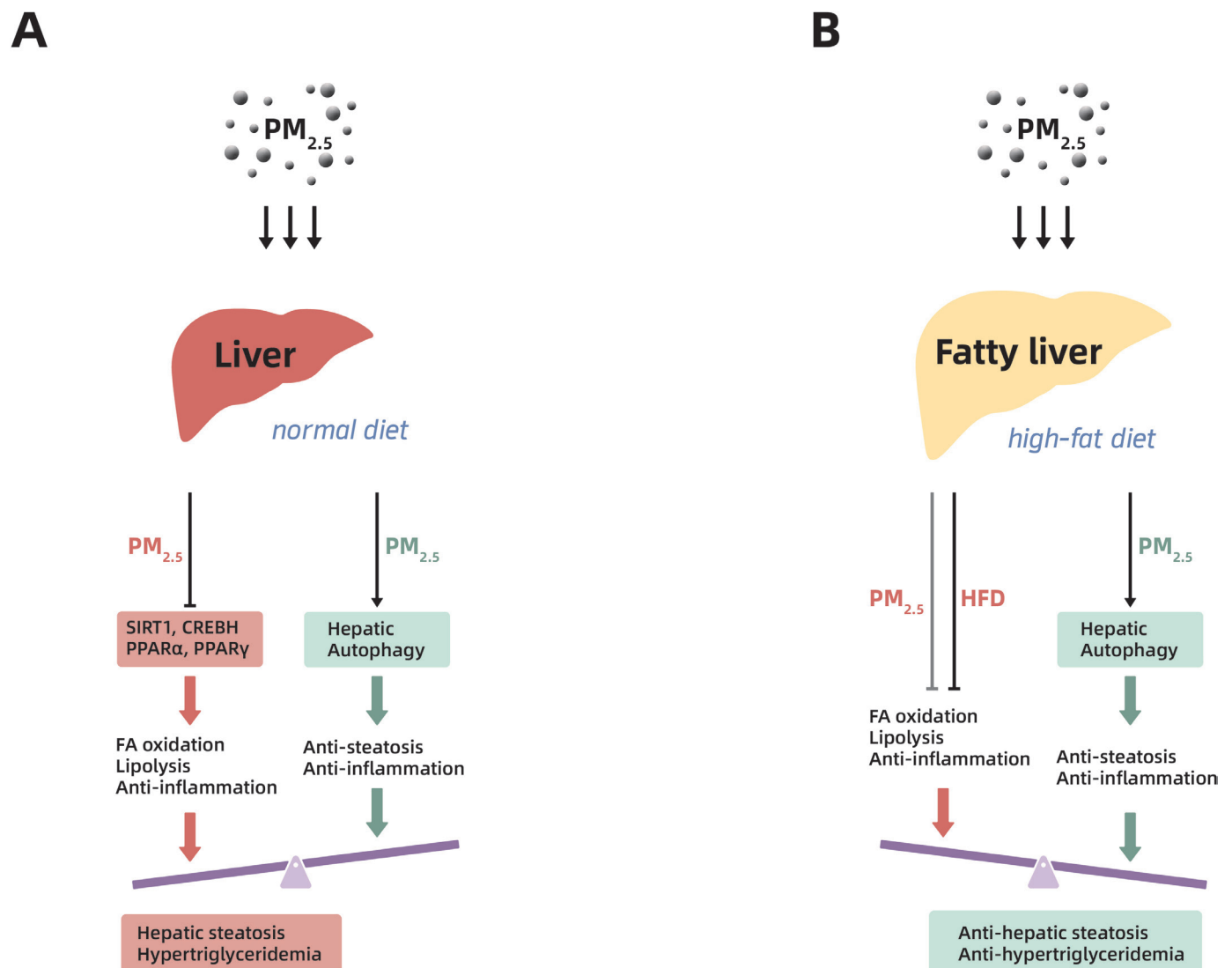
and vitamin E (100 mg/kg of vitamin C and 50 mg/kg of vitamin E) can attenuate the effect of high-dose PM<sub>2.5</sub> (10 mg/kg) on suppressing UPR<sup>mt</sup> in spermatogenic cells, and the vitamin intervention promoted conception rate recovery, alleviated mitochondrial damage and reduced spermatogenic cell apoptosis in rats under high-dose PM<sub>2.5</sub> exposure.<sup>61</sup>

### PM<sub>2.5</sub>-induced lysosomal stress response

PM<sub>2.5</sub> 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<sub>2.5</sub> particles.<sup>62</sup> PM<sub>2.5</sub>-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<sub>2.5</sub> exposure.<sup>62</sup> However, a study by Wang and Tang<sup>63</sup> showed that PM<sub>2.5</sub> induced both autophagy and apoptosis through ER stress response pathways in human endothelial cells, where autophagy protected against PM<sub>2.5</sub>-induced apoptosis.

Intriguingly, our studies with animal models showed that inhalation exposure to environmental PM<sub>2.5</sub> induced autophagy in the liver that counteracted hepatic steatosis induced by a high-fat diet (figure 3).<sup>64</sup> PM<sub>2.5</sub> exhibited a strong effect on triggering hepatic autophagy programme



**Figure 3** The effects and pathways by which PM<sub>2.5</sub> 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<sub>2.5</sub> 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<sub>2.5</sub> 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.

in a manner depending on the inflammatory pathway mediated through Toll-like receptor-myeloid differentiation primary response 88 (MyD88).<sup>64</sup> In contrast to a ‘two-hits’ hypothesis that PM<sub>2.5</sub> exposure may interact with a high-fat diet or obese condition to exacerbate metabolic disorders, PM<sub>2.5</sub> exposure counteracted hepatic steatosis and hyperlipidaemia of obese mice under the high-fat diet through stimulating hepatic autophagy. Under normal chow, PM<sub>2.5</sub> exposure triggers hepatic autophagy, but meanwhile represses PPAR $\alpha$ , PPAR $\gamma$ , SIRT1 and CREBH, the key regulators of fatty acid oxidation and lipolysis (figure 3A).<sup>64</sup> Because PM<sub>2.5</sub>-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<sub>2.5</sub> exposure. Under the high-fat diet or obese condition, however, overnutrition-caused hepatic steatosis and hypertriglyceridaemia were alleviated by hepatic autophagy triggered by PM<sub>2.5</sub> (figure 3B).<sup>64–66</sup> Apparently, the steatosis-relieving effect of PM<sub>2.5</sub>-induced hepatic autophagy overrides the repressive effect of lipid mobilisation caused by PM<sub>2.5</sub> exposure, and thereby, PM<sub>2.5</sub> stimulation displays discernable effects on mitigating hepatic steatosis, liver injuries and hyperlipidaemia in the obese animals under the high-fat diet.<sup>64</sup> The identification of the ‘beneficial’ effect of PM<sub>2.5</sub> on activating hepatic autophagy provides new insights into the complex effects of airborne PM<sub>2.5</sub> 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<sub>2.5</sub> exposure, could mitigate the detrimental effect of the first ‘hit’, obesity or high-fat diets, in driving liver steatosis.

### PM<sub>2.5</sub>-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<sub>2.5</sub>-caused pathogenesis.<sup>67–71</sup> Increasing evidence showed that inhalation exposure to environmentally relevant PM<sub>2.5</sub> 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<sub>2.5</sub> exposure in promoting pathological stress responses and metabolic or digestive diseases (figure 1).

#### PM<sub>2.5</sub>-induced stress responses in the liver

Chronic or subchronic exposure to concentrated PM<sub>2.5</sub> causes injuries to the liver, the major detoxification and metabolic organ. Inhalation exposure to PM<sub>2.5</sub> may impose stress on the liver through three major paths<sup>13 21 72</sup>: (1) systemic effects of circulating proinflammatory cytokines or chemokines from pulmonary inflammation triggered

by PM<sub>2.5</sub> exposure, (2) retention of activated neutrophils and monocytes to the liver tissues under PM<sub>2.5</sub> exposure and (3) PM<sub>2.5</sub> nanoparticles reach to and are deposited in the liver. In the past 15 years, we and others demonstrated that inhalation exposure to PM<sub>2.5</sub> 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<sub>2.5</sub> at a concentration of approximately 80  $\mu\text{g}/\text{m}^3$  or higher for 10 weeks developed NASH-like and T2D-like phenotypes.<sup>19 21 67 73</sup> After PM<sub>2.5</sub> exposure, the mice displayed hepatic steatosis, inflammation and fibrosis, coincided with impaired hepatic glycogen storage, glucose intolerance and insulin resistance.<sup>19 21</sup> Interestingly, these phenotypes were accompanied by significant loss of body weight of the mice. Linked to the PM<sub>2.5</sub>-induced liver-associated phenotypes, the livers of PM<sub>2.5</sub>-exposed mice exhibited: (1) activation of inflammatory responses mediated through JNK, nuclear factor kappa B (NF- $\kappa$ B) and Toll-like receptor 4 (TLR4) in Kupffer cells<sup>14 19 21 67</sup>; (2) selective activation of the UPR,<sup>14</sup> oxidative stress<sup>14 19</sup> and autophagy<sup>22 64</sup>; and (3) suppression of the insulin receptor substrate 1 (IRS1)-mediated signalling.<sup>21</sup> Moreover, PM<sub>2.5</sub> exposure repressed the major metabolic regulators PPAR $\alpha$ , SIRT1, CREBH and Farnesoid X receptor (FXR) as well as the anti-inflammatory regulator PPAR $\gamma$  in the liver.<sup>19 21 64 74</sup> Consistent with the repression of metabolic regulators by PM<sub>2.5</sub>, hepatic circadian oscillation and lipid metabolism were disrupted in mice exposed to PM<sub>2.5</sub>.<sup>75–77</sup> Specific to liver fibrogenesis, PM<sub>2.5</sub> exposure stimulated the transforming growth factor  $\beta$  (TGF $\beta$ )-SMAD3 signalling and promoted the production of collagens by hepatic stellate cells.<sup>19</sup> Importantly, PM<sub>2.5</sub>-induced TGF $\beta$  signalling, collagen production and hepatic fibrogenesis as well as suppression of PPAR $\gamma$  relied on NADPH oxidase-dependent ROS production.<sup>19</sup>

A variety of studies have confirmed that PM<sub>2.5</sub>-triggered ROS or oxidative stress is the root of inflammatory stress responses and tissue injuries,<sup>14 78 79</sup> 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.<sup>80 81</sup> Interestingly, AMPK activators, monounsaturated fatty acids (MUFAs) (eg, oleonic acid) and melatonin can mitigate PM<sub>2.5</sub>-caused oxidative stress as well as hepatic inflammation, fibrosis and liver injuries in animal models.<sup>82–84</sup> Additionally, a meta-analysis of epidemiological evidence suggested that exposure to airborne PM<sub>2.5</sub> pollution increased the risk of gastrointestinal cancers.<sup>85</sup> The impact of PM<sub>2.5</sub> on the risk of hepatocellular carcinoma (HCC) has been observed in East Asia, Europe and USA.<sup>86–90</sup> Ambient PM<sub>2.5</sub> pollution was associated with increased mortality in patients with HCC.<sup>91</sup> PM<sub>2.5</sub>-induced NASH activities may be associated with the progression of HCC under air pollution; however, the mechanistic basis by which PM<sub>2.5</sub> pollutant is involved in HCC remains to be elucidated.

### PM<sub>2.5</sub>-induced stress responses in the pancreas

The association between exposure to PM<sub>2.5</sub> and type 1 or T2D mellitus has been confirmed in population studies.<sup>92,93</sup> Exposure to PM<sub>2.5</sub> 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.<sup>94</sup> PM<sub>2.5</sub>-induced oxidative response and inflammation in the pancreas are responsible for the increased risk of pancreatic impairment and glycaemic consequences under PM<sub>2.5</sub> exposure. In a mouse model of streptozotocin-induced type 1 diabetes, PM<sub>2.5</sub> promoted pancreatic  $\beta$  cell damage by stimulating interleukin 1 $\beta$  (IL1 $\beta$ ) and tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) production in macrophages and  $\beta$  cells.<sup>95</sup> PM<sub>2.5</sub> exposure can also attenuate insulin secretion from  $\beta$  cells in a dose-dependent manner.<sup>95</sup>

### PM<sub>2.5</sub>-induced stress responses in small intestines

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

### PERSPECTIVE

Inhalation exposure to environmentally relevant PM<sub>2.5</sub> exerts systemic adverse health effects, causing injuries to multiple organs/tissues. At the molecular level, PM<sub>2.5</sub> nanoparticles directly or indirectly target intracellular organelles, particularly the ER, mitochondria and lysosome, inducing integrated inflammatory stress responses. At the organ/tissue level, PM<sub>2.5</sub>-caused oxidative damage and inflammatory challenge represent the major cytotoxic consequence caused by PM<sub>2.5</sub> 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<sub>2.5</sub> inhalation causes liver-associated diseases have been well studied. PM<sub>2.5</sub> 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- $\kappa$ B 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<sub>2.5</sub> exposure in activating organelle stress responses, what are the mechanisms by which the cells sense PM<sub>2.5</sub> and how PM<sub>2.5</sub> exposure can differentially induce stress response pathways in different organs or tissues? Second, inhalation exposure to PM<sub>2.5</sub> adversely affects the functions of the liver, pancreas and intestine. Does PM<sub>2.5</sub> exposure disrupt the interorgan communication among the major digestive organs? For example, does the PM<sub>2.5</sub>-induced pancreatic damage worsen hepatic insulin resistance? Are intestinal injuries or microbiota dysregulation caused by PM<sub>2.5</sub> pollution contributing to liver pathogenesis? Additionally, is there any nutritional or pharmaceutical intervention to prevent or mitigate the cytotoxic effects caused by PM<sub>2.5</sub> 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<sub>2.5</sub>-caused oxidative stress, inflammation, mitochondrial damage and tissue/cell injuries in animal models.<sup>61,83,84</sup> 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<sub>2.5</sub>.

**Contributors** The author (KZ) conceived the idea and wrote the paper.

**Funding** The research work in the Zhang lab is partially supported by National Institutes of Health (NIH) grants DK126908, DK132065, and DK134361.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

### ORCID iD

Kezhong Zhang <http://orcid.org/0000-0002-6062-235X>

### REFERENCES

- Chen JC, Schwartz J. Metabolic syndrome and inflammatory responses to long-term particulate air Pollutants. *Environ Health Perspect* 2008;116:612–7.



- 2 Raaschou-Nielsen O, Sørensen M, Ketzler M, *et al.* Long-term exposure to traffic-related air pollution and diabetes-associated mortality: a cohort study. *Diabetologia* 2013;56:36–46.
- 3 Gandotra S, Zhang K. Environmental Pm2.5 in the USA: A national health risk factor *Environ Dis* 2023;8:83–5.
- 4 Shamsa EH, Song Z, Kim H, *et al.* n.d. The links of fine airborne particulate matter exposure to occurrence of cardiovascular and metabolic diseases in. *PLOS Glob Public Health*;2:e0000707.
- 5 Pearson JF, Bachireddy C, Shyamprasad S, *et al.* Association between fine particulate matter and diabetes prevalence in the U.S. *Diabetes Care* 2010;33:2196–201.
- 6 Krämer U, Herder C, Sugiri D, *et al.* Traffic-related air pollution and incident type 2 diabetes: results from the SALIA cohort study. *Environ Health Perspect* 2010;118:1273–9.
- 7 Gao X, Coull B, Lin X, *et al.* Short-term air pollution, cognitive performance, and nonsteroidal anti-inflammatory drug use in the veterans affairs normative aging study. *Nat Aging* 2021;1:430–7.
- 8 Alfaro-Moreno E, Martínez L, García-Cuellar C, *et al.* Biologic effects induced in vitro by Pm10 from three different zones of Mexico city. *Environ Health Perspect* 2002;110:715–20.
- 9 Soukup JM, Becker S. Human alveolar macrophage responses to air pollution Particulates are associated with insoluble components of coarse material, including particulate endotoxin. *Toxicol Appl Pharmacol* 2001;171:20–6.
- 10 Nemmar A, Hoylaerts MF, Hoet PHM, *et al.* Ultrafine particles affect experimental thrombosis in an in vivo Hamster model. *Am J Respir Crit Care Med* 2002;166:998–1004.
- 11 Kreyling WG, Hirn S, Möller W, *et al.* Air-blood barrier translocation of tracheally instilled gold nanoparticles inversely depends on particle size. *ACS Nano* 2014;8:222–33.
- 12 Roberts S, Martin MA. Methods for bias reduction in time-series studies of particulate matter air pollution and mortality. *J Toxicol Environ Health A* 2007;70:665–75.
- 13 Li D, Li Y, Li G, *et al.* Fluorescent reconstitution on deposition of PM(2.5) in lung and extrapulmonary organs. *Proc Natl Acad Sci U S A* 2019;116:2488–93.
- 14 Laing S, Wang G, Briazova T, *et al.* Airborne particulate matter selectively activates endoplasmic reticulum stress response in the lung and liver tissues. *Am J Physiol Cell Physiol* 2010;299:C736–49.
- 15 Kwon J-T, Hwang S-K, Jin H, *et al.* Body distribution of inhaled fluorescent magnetic nanoparticles in the mice. *J Occup Health* 2008;50:1–6.
- 16 Sarlo K, Blackburn KL, Clark ED, *et al.* Tissue distribution of 20 nM, 100 nM and 1000 nM fluorescent polystyrene latex nanospheres following acute systemic or acute and repeat airway exposure in the rat. *Toxicology* 2009;263:117–26.
- 17 Murugan K, Choonara YE, Kumar P, *et al.* Parameters and characteristics governing cellular Internalization and trans-barrier trafficking of nanostructures. *Int J Nanomedicine* 2015;10:2191–206.
- 18 Heyder J, Gebhart J, Rudolf G, *et al.* Deposition of particles in the human respiratory tract in the size range 0.005–15 Mm. *Journal of Aerosol Science* 1986;17:811–25.
- 19 Zheng Z, Zhang X, Wang J, *et al.* Exposure to fine airborne particulate matters induces hepatic fibrosis in murine models. *J Hepatol* 2015;63:1397–404.
- 20 Brook RD, Franklin B, Cascio W, *et al.* Air pollution and cardiovascular disease: a statement for Healthcare professionals from the expert panel on population and prevention science of the American heart Association. *Circulation* 2004;109:2655–71.
- 21 Zheng Z, Xu X, Zhang X, *et al.* Exposure to ambient particulate matter induces a NASH-like phenotype and impairs hepatic glucose metabolism in an animal model. *J Hepatol* 2013;58:148–54.
- 22 Qiu Y-N, Wang G-H, Zhou F, *et al.* Pm2.5 induces liver fibrosis via triggering ROS-mediated mitophagy. *Ecotoxicol Environ Saf* 2019;167:178–87.
- 23 Hetz C, Zhang K, Kaufman RJ. Mechanisms, regulation and functions of the unfolded protein response. *Nat Rev Mol Cell Biol* 2020;21:421–38.
- 24 Zhang K, Kaufman RJ. From endoplasmic-reticulum stress to the inflammatory response. *Nature* 2008;454:455–62.
- 25 Zhang X, Zhang K. Endoplasmic reticulum stress-associated lipid droplet formation and type II diabetes. *Biochem Res Int* 2012;2012:247275.
- 26 Hotamisligil GS. Inflammation and metabolic disorders. *Nature* 2006;444:860–7.
- 27 Hotamisligil GS. Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. *Cell* 2010;140:900–17.
- 28 Zhang K, Kaufman RJ. Signaling the unfolded protein response from the endoplasmic reticulum. *J Biol Chem* 2004;279:25935–8.
- 29 Ron D, Walter P. Signal integration in the endoplasmic reticulum unfolded protein response. *Nat Rev Mol Cell Biol* 2007;8:519–29.
- 30 Walter P, Ron D. The unfolded protein response: from stress pathway to homeostatic regulation. *Science* 2011;334:1081–6.
- 31 Hollien J, Weissman JS. Decay of Endoplasmic Reticulum-localized mRNAs during the unfolded protein response. *Science* 2006;313:104–7.
- 32 Hollien J, Lin JH, Li H, *et al.* Regulated Ire1-dependent decay of messenger Rnas in mammalian cells. *J Cell Biol* 2009;186:323–31.
- 33 Upton J-P, Wang L, Han D, *et al.* Ire1Alpha cleaves select microRNAs during ER stress to derepress translation of proapoptotic caspase-2. *Science* 2012;338:818–22.
- 34 Wang J-M, Qiu Y, Yang Z, *et al.* Inositol-requiring enzyme 1 facilitates diabetic wound healing through modulating micrornas. *Diabetes* 2017;66:177–92.
- 35 Wang J-M, Qiu Y, Yang Z, *et al.* Ire1Alpha prevents hepatic steatosis by processing and promoting the degradation of select microRNAs. *Sci Signal* 2018;11.
- 36 Zhang K, Liu H, Song Z, *et al.* The UPR transducer Ire1 promotes breast cancer malignancy by degrading tumor suppressor microRNAs. *iScience* 2020;23:101503.
- 37 Adachi Y, Yamamoto K, Okada T, *et al.* Atf6 is a transcription factor specializing in the regulation of quality control proteins in the endoplasmic reticulum. *Cell Struct Funct* 2008;33:75–89.
- 38 Yamamoto K, Sato T, Matsui T, *et al.* Transcriptional induction of mammalian ER quality control proteins is mediated by single or combined action of Atf6Alpha and Xbp1. *Dev Cell* 2007;13:365–76.
- 39 Nadanaka S, Yoshida H, Kano F, *et al.* Activation of mammalian unfolded protein response is compatible with the quality control system operating in the endoplasmic reticulum. *Mol Biol Cell* 2004;15:2537–48.
- 40 Lee A-H, Chu GC, Iwakoshi NN, *et al.* XBP-1 is required for biogenesis of cellular secretory machinery of exocrine glands. *EMBO J* 2005;24:4368–80.
- 41 Martinon F, Chen X, Lee A-H, *et al.* TLR activation of the transcription factor Xbp1 regulates innate immune responses in macrophages. *Nat Immunol* 2010;11:411–8.
- 42 Madhavan A, Kok BP, Rius B, *et al.* Pharmacologic Ire1/Xbp1S activation promotes systemic adaptive remodeling in obesity. *Nat Commun* 2022;13:608.
- 43 Urano F, Wang X, Bertolotti A, *et al.* Coupling of stress in the ER to activation of JNK protein kinases by transmembrane protein kinase Ire1. *Science* 2000;287:664–6.
- 44 Nishitoh H, Matsuzawa A, Tobiume K, *et al.* Ask1 is essential for endoplasmic reticulum stress-induced neuronal cell death triggered by expanded polyglutamine repeats. *Genes Dev* 2002;16:1345–55.
- 45 Qiu Q, Zheng Z, Chang L, *et al.* Toll-like receptor-mediated Ire1Alpha activation as a therapeutic target for inflammatory arthritis. *EMBO J* 2013;32:2477–90.
- 46 Zhou W, Tian D, He J, *et al.* Exposure scenario: another important factor determining the toxic effects of Pm2.5 and possible mechanisms involved. *Environ Pollut* 2017;226:412–25.
- 47 Xu X, qimuge A, Wang H, *et al.* Ire1Alpha/Xbp1S branch of UPR links Hif1Alpha activation to mediate ANGII-dependent endothelial dysfunction under particulate matter (PM) 2.5 exposure. *Sci Rep* 2017;7:13507.
- 48 Mendez R, Zheng Z, Fan Z, *et al.* Exposure to fine airborne particulate matter induces macrophage infiltration, Unfolded protein response, and lipid deposition in white Adipose tissue. *Am J Transl Res* 2013;5:224–34.
- 49 Alderete TL, Song AY, Bastain T, *et al.* Prenatal traffic-related air pollution exposures, cord blood adipokines and infant weight. *Pediatr Obes* 2018;13:348–56.
- 50 Zhou S, Lin L, Bao Z, *et al.* The association of prenatal exposure to particulate matter with infant growth: a birth cohort study in Beijing, China. *Environ Pollut* 2021;277:116792.
- 51 Zhao Q, Chen H, Yang T, *et al.* Direct effects of airborne Pm2.5 exposure on macrophage polarizations. *Biochim Biophys Acta* 2016;1860:2835–43.
- 52 Chang EM, Chao CC, Wang MT, *et al.* PM(2.5) promotes pulmonary fibrosis by mitochondrial dysfunction. *Environ Toxicol* 2023;38:1905–13.
- 53 Li R, Kou X, Geng H, *et al.* Mitochondrial damage: an important mechanism of ambient Pm2.5 exposure-induced acute heart injury in rats. *J Hazard Mater* 2015;287:392–401.
- 54 Xu Z, Xu X, Zhong M, *et al.* Ambient particulate air pollution induces oxidative stress and alterations of mitochondria and gene expression in brown and white adipose tissues. *Part Fibre Toxicol* 2011;8:20.
- 55 Si H, Gao T, Yang J, *et al.* Multi-Omics reveals hypertrophy of adipose tissue and lipid metabolism disorder via mitochondria in



- young mice under real-ambient exposure to air pollution. *Front Pharmacol* 2023;14:1122615.
- 56 Guan L, Geng X, Stone C, et al. PM(2.5) exposure induces systemic inflammation and oxidative stress in an intracranial atherosclerosis rat model. *Environ Toxicol* 2019;34:530–8.
  - 57 Zhang L-M, Lv S-S, Fu S-R, et al. Procyanidins inhibit fine particulate matter-induced vascular smooth muscle cells apoptosis via the activation of the Nrf2 signaling pathway. *Ecotoxicol Environ Saf* 2021;223:112586.
  - 58 Fan X, Dong T, Yan K, et al. Pm2.5 increases susceptibility to acute exacerbation of COPD via Nox4/Nrf2 redox imbalance-mediated mitophagy. *Redox Biol* 2023;59:102587.
  - 59 Xu X, Liu C, Xu Z, et al. Long-term exposure to ambient fine particulate pollution induces insulin resistance and mitochondrial alteration in adipose tissue. *Toxicol Sci* 2011;124:88–98.
  - 60 Shpilka T, Haynes CM. The mitochondrial UPR: mechanisms, physiological functions and implications in ageing. *Nat Rev Mol Cell Biol* 2018;19:109–20.
  - 61 Wang C, Liu X, Shu Z, et al. Exposure to automobile exhaust-derived Pm2.5 induces spermatogenesis dysfunction by damaging UPR(Mt) of Prepubertal rats. *Ecotoxicol Environ Saf* 2022;245:114087.
  - 62 Xu X, Wang H, Liu S, et al. Tp53-dependent autophagy links the ATR-Chek1 axis activation to proinflammatory VEGFA production in human bronchial epithelial cells exposed to fine particulate matter (Pm2.5). *Autophagy* 2016;12:1832–48.
  - 63 Wang Y, Tang M. Pm2.5 induces autophagy and apoptosis through endoplasmic reticulum stress in human endothelial cells. *Sci Total Environ* 2020;710:136397.
  - 64 Qiu Y, Zheng Z, Kim H, et al. Inhalation exposure to PM(2.5) counteracts hepatic steatosis in mice fed high-fat diet by stimulating hepatic autophagy. *Sci Rep* 2017;7:16286.
  - 65 Singh R, Kaushik S, Wang Y, et al. Autophagy regulates lipid metabolism. *Nature* 2009;458:1131–5.
  - 66 Yang L, Li P, Fu S, et al. Defective hepatic autophagy in obesity promotes ER stress and causes insulin resistance. *Cell Metab* 2010;11:467–78.
  - 67 Tan H-H, Fiel MI, Sun Q, et al. Kupffer cell activation by ambient air particulate matter exposure may exacerbate non-alcoholic fatty liver disease. *J Immunotoxicol* 2009;6:266–75.
  - 68 Liu C, Xu X, Bai Y, et al. Air pollution-mediated susceptibility to inflammation and insulin resistance: influence of Ccr2 pathways in mice. *Environ Health Perspect* 2014;122:17–26.
  - 69 Rajagopalan S, Park B, Palanivel R, et al. Metabolic effects of air pollution exposure and reversibility. *J Clin Invest* 2020;130:137315:6034–40.:
  - 70 Liu C, Bai Y, Xu X, et al. Exaggerated effects of particulate matter air pollution in genetic type II diabetes mellitus. *Part Fibre Toxicol* 2014;11:27.
  - 71 Hu R, Zhang L, Qin L, et al. Airborne PM(2.5) pollution: a double-edged sword Modulating hepatic lipid metabolism in middle-aged male mice. *Environ Pollut* 2023;324:121347.
  - 72 Jeong S, Park SA, Park I, et al. Pm2.5 exposure in the respiratory system induces distinct inflammatory signaling in the lung and the liver of mice. *J Immunol Res* 2019;2019:3486841.
  - 73 Li R, Sun Q, Lam SM, et al. Sex-dependent effects of ambient PM(2.5) pollution on insulin sensitivity and hepatic lipid metabolism in mice. *Part Fibre Toxicol* 2020;17:14.
  - 74 Wang M, Tan J, Zhou J, et al. Farnesoid X receptor mediates hepatic steatosis induced by PM(2.5). *Environ Sci Pollut Res* 2020;27:34412–20.
  - 75 Li R, Wang Y, Chen R, et al. Ambient fine particulate matter disrupts hepatic circadian oscillation and lipid metabolism in a mouse model. *Environmental Pollution* 2020;262:114179.
  - 76 Wang Y, Li R, Chen R, et al. Ambient fine particulate matter exposure perturbed circadian rhythm and oscillations of lipid metabolism in adipose tissues. *Chemosphere* 2020;251:126392.
  - 77 Palanivel R, Vinayachandran V, Biswal S, et al. Exposure to air pollution disrupts circadian rhythm through alterations in chromatin dynamics. *iScience* 2020;23:101728.
  - 78 Xu M-X, Ge C-X, Qin Y-T, et al. Prolonged Pm2.5 exposure elevates risk of oxidative stress-driven nonalcoholic fatty liver disease by triggering increase of dyslipidemia. *Free Radic Biol Med* 2019;130:542–56.
  - 79 Somayajulu M, Ekanayaka S, McClellan SA, et al. Airborne particulates affect corneal homeostasis and immunity. *Invest Ophthalmol Vis Sci* 2020;61:23.
  - 80 Ge C, Tan J, Zhong S, et al. Nrf2 mitigates prolonged Pm2.5 exposure-triggered liver inflammation by positively regulating SIKE activity: protection by Juglanin. *Redox Biol* 2020;36:101645.
  - 81 Somayajulu M, McClellan SA, Wright R, et al. Airborne exposure of the Cornea to PM(10) induces oxidative stress and disrupts Nrf2 mediated anti-oxidant defenses. *Int J Mol Sci* 2023;24:3911.
  - 82 Song L, Jiang S, Pan K, et al. AMPK activation ameliorates fine particulate matter-induced hepatic injury. *Environ Sci Pollut Res Int* 2020;27:21311–9.
  - 83 Wei C-T, Wang Y-W, Wu Y-C, et al. Reparative efficacy of liposome-encapsulated oleanolic acid against liver inflammation induced by fine ambient particulate matter and alcohol in mice. *Pharmaceutics* 2022;14:1108.
  - 84 Zhu L, Zhang Q, Hua C, et al. Melatonin alleviates particulate matter-induced liver fibrosis by inhibiting ROS-mediated mitophagy and inflammation via Nrf2 activation. *Ecotoxicol Environ Saf* 2023;268:115717.
  - 85 Pritchett N, Spangler EC, Gray GM, et al. Exposure to outdoor particulate matter air pollution and risk of gastrointestinal cancers in adults: a systematic review and meta-analysis of epidemiologic evidence. *Environ Health Perspect* 2022;130:36001.
  - 86 Sun M, Gao M, Luo M, et al. Association between air pollution and primary liver cancer in European and East Asian populations: a Mendelian randomization study. *Front Public Health* 2023;11:1212301.
  - 87 Wu Z-H, Zhao M, Yu H, et al. The impact of particulate matter 2.5 on the risk of hepatocellular carcinoma: a meta-analysis. *Int Arch Occup Environ Health* 2022;95:677–83.
  - 88 VoPham T, Bertrand KA, Tamimi RM, et al. Ambient PM(2.5) air pollution exposure and hepatocellular carcinoma incidence in the United States. *Cancer Causes Control* 2018;29:563–72.
  - 89 Cui H, Qi Y, Guo C, et al. The effect of PM(2.5) exposure on the mortality of patients with hepatocellular carcinoma in Tianjin, China. *Environ Sci Pollut Res* 2023;30:78632–40.
  - 90 VoPham T, Jones RR. State of the science on outdoor air pollution exposure and liver cancer risk. *Environ Adv* 2023;11:100354.
  - 91 Lee C-H, Hsieh S-Y, Huang W-H, et al. Association between ambient particulate matter 2.5 exposure and mortality in patients with hepatocellular carcinoma. *Int J Environ Res Public Health* 2019;16:2490.
  - 92 Mozafarian N, Hashemipour M, Yazdi M, et al. The association between exposure to air pollution and type 1 diabetes mellitus: A systematic review and meta-analysis. *Adv Biomed Res* 2022;11:103.
  - 93 Tong Y, Pei L, Luo K, et al. The mediated role of complement C3 in PM(2.5) exposure and type 2 diabetes mellitus: an elderly panel study in Beijing, China. *Environ Sci Pollut Res Int* 2019;26:34479–86.
  - 94 Yi L, Wei C, Fan W. Fine-particulate matter (Pm2.5), a risk factor for rat gestational diabetes with altered blood glucose and Pancreatic Glut2 expression. *Gynecol Endocrinol* 2017;33:611–6.
  - 95 Zhang B, Yin R, Lang J, et al. PM(2.5) promotes beta cell damage by increasing inflammatory factors in mice with streptozotocin. *Exp Ther Med* 2021;22:832.
  - 96 Li D, Zhang R, Cui L, et al. Multiple organ injury in male C57Bl/6J mice exposed to ambient particulate matter in a real-ambient PM exposure system in Shijiazhuang, China. *Environ Pollut* 2019;248:874–87.
  - 97 Park M, Cho Y-L, Choi Y, et al. Particulate matter induces Ferroptosis by accumulating iron and dysregulating the antioxidant system. *BMB Rep* 2023;56:96–101.
  - 98 Mutlu EA, Engen PA, Soberanes S, et al. Particulate matter air pollution causes oxidant-mediated increase in gut permeability in mice. *Part Fibre Toxicol* 2011;8:19.
  - 99 Shan S, Xiong Y, Guo J, et al. Effect of an inulin-type fructan from platycodon grandiflorum on the intestinal microbiota in rats exposed to Pm2.5. *Carbohydr Polym* 2022;283:119147.
  - 100 Ran Z, An Y, Zhou J, et al. Subchronic exposure to concentrated ambient Pm2.5 Perturbs gut and lung microbiota as well as metabolic profiles in mice. *Environ Pollut* 2021;272:115987.
  - 101 Wang W, Zhou J, Chen M, et al. Exposure to concentrated ambient PM(2.5) alters the composition of gut Microbiota in a murine model. *Part Fibre Toxicol* 2018;15:17.
  - 102 Mutlu EA, Comba IY, Cho T, et al. Inhalational exposure to particulate matter air pollution alters the composition of the gut microbiome. *Environ Pollut* 2018;240:817–30.
  - 103 Chen D, Xiao C, Jin H, et al. Exposure to atmospheric pollutants is associated with alterations of gut microbiota in spontaneously hypertensive rats. *Exp Ther Med* 2019;18:3484–92.