

# Cell Death Pathways: The Variable Mechanisms Underlying Fine Particulate Matter-Induced Cytotoxicity

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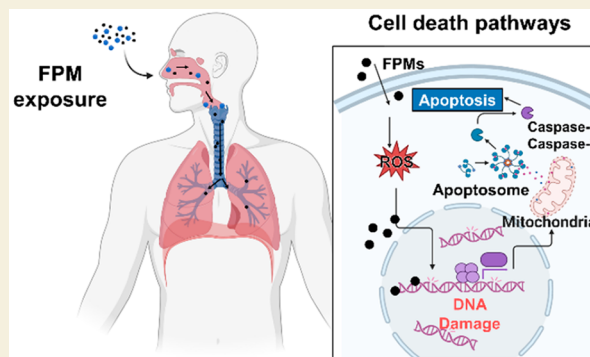
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**ABSTRACT:** Recently, the advent of health risks due to the cytotoxicity of fine particulate matter (FPM) is concerning. Numerous studies have reported abundant data elucidating the FPM-induced cell death pathways. However, several challenges and knowledge gaps are still confronted nowadays. On one hand, the undefined components of FPM (such as heavy metals, polycyclic aromatic hydrocarbons, and pathogens) are all responsible for detrimental effects, thus rendering it difficult to delineate the specific roles of these copollutants. On the other hand, owing to the crosstalk and interplay among different cell death signaling pathways, precisely determining the threats and risks posed by FPM is difficult. Herein, we recapitulate the current knowledge gaps present in the recent studies regarding FPM-induced cell death, and propose future research directions for policy-making to prevent FPM-induced diseases and improve knowledge concerning the adverse outcome pathways and public health risks of FPM.

**KEYWORDS:** Air pollution, Fine particulate matter, Cytotoxicity, Cell death pathway, Apoptosis, Autophagy, Inflammation, Health risks



Recently, health issues due to air pollution are becoming increasingly prominent. Particulate matter (PM), a major contributor of air pollution, has gained global attention. Several epidemiological studies have correlated PM pollution with various detrimental health issues, including respiratory diseases, cardiovascular diseases, reproductive system disorders, and even neurological disorders.<sup>1–4</sup> Although the harmful effects of heavy PM pollution have been recognized, the adverse outcome pathways (AOPs) involved remain controversial. PM exhibits variable compositions depending on the source of generation and atmospheric conditions.<sup>5</sup> The complex physicochemical properties of PM render it difficult to elucidate its cytotoxic mechanisms. In addition, PM, especially fine PM (FPM, such as PM<sub>2.5</sub>) and ultrafine PM, can enter the respiratory tract and lungs and even cross the air–blood barrier, causing long-term toxicity in secondary organs, such as the heart, liver, kidneys, and brain.<sup>6</sup> Thus, the cytotoxicity of FPM is inevitable regardless of the exposure pathway and biodistribution patterns, which warrant further investigation.

Cell death is a distinct genetic and biochemical pathway that is essential for nearly all living organisms. It is not only involved in the developmental processes of multicellular organisms but also critical for immune responses against various diseases, such as infections and cellular dysfunction. In recent years, various forms of cell death patterns, such as apoptosis,<sup>7</sup> autophagy,<sup>8</sup> pyroptosis,<sup>9</sup> ferroptosis,<sup>10</sup> necroptosis,<sup>11</sup> and cuproptosis,<sup>12</sup> have been described in detail. To date, numerous studies have focused on the toxic effects and related mechanisms of FPM.

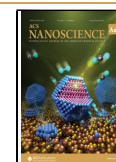
Furthermore, cell death pathways induced by engineered nanoparticles have helped understand FPM-induced cytotoxicity.<sup>13–15</sup> Although the corresponding body of knowledge is expanding (Table 1), several questions remain unanswered, particularly questions regarding the cell death pathways and related mechanisms induced by FPM. Owing to the complex network of interacting genes implicated in cell death, specific FPM-related cell death pathways need to be elucidated. Consequently, understanding the FPM-induced cell death pathways may provide further clues that can help modulate these pathways to treat related diseases. Herein, we summarized the current stage of understanding regarding FPM-induced cell death pathways and elaborated the existing knowledge gaps. We expect that a deeper understanding of the physiological and mechanistic aspects of FPM-induced cell death signaling will yield further knowledge regarding AOPs and public health risks.

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**Table 1. Summary of Studies on Cell Death Pathways upon FPM Exposure**

cell death process	cell death signaling	cell types	ref	
apoptosis	bax/bcl-2/caspase-3	Mouse primary cortical neuron cells	89	
	miR-194-3p/caspase-3/DAPK1	HBEpiCs	90	
	JNK/P53 pathway	Rat cardiomyocyte	91	
	TNF- $\alpha$ signaling pathway	A549 cells	43	
	MAPK 2/STAT1 signaling pathway	A550 cells	43	
	COX-2/PGES/PGE2 inflammatory pathway	MAEC	45	
	p53-bax-caspase pathway	HUVECs	46	
	$\beta$ 2AR/PI3K/Akt pathway	AC16	47	
	Nrf2 pathway	hESCs	51	
	RIPK1 apoptotic signaling pathway	GC-2spd cells	52	
	ROS-JNK/ERK apoptotic pathway	Rat embryonic cells	53	
	autophagy	AMPK signaling pathway	A549	57
		NOS2 signaling pathway	BEAS-2B	92
ATR-CHEK1/CHK1 inflammatory response axis		BEAS-2B	60	
ROS-AKT-mTOR axis		HUVECs	61	
NF- $\kappa$ B/p38/Akt signaling pathways		MAECs	62	
MyD88-mediated inflammatory pathway		Mouse liver cells	63	
pyroptosis		ROS-NLRP3-caspase-1 pathway	RAW 264.7	69
	NLRP3-caspase-1 pathway	Mouse cardiomyocytes	93	
	NLRP3-caspase-1 pathway	BV-2 and HMC-3 microglial cell	71	
	NLRP3-caspase-1 pathway	Mouse brain tissue	94	
	NLRP3-caspase-1 pathway	Mouse microglia	95	
ferroptosis	iron overload/redox imbalance	EA.hy 926 and HUVECs	76	
	ERK/CREB pathway	Neuro-2a (N2A) and SH-SY5Y cells	78	
necroptosis	ATP synthesis	BEAS-2B	79	

## MAJOR TOXIC COMPONENTS OF FINE PARTICULATE MATTER

Due to the emission sources and generation patterns, FPM might exhibit significantly different components. Typically, the cytotoxicity of FPM is attributable to its constituent harmful substances (e.g., heavy metals, polycyclic aromatic hydrocarbons (PAHs), and pathogens) (Figure 1).<sup>16,17</sup> These components are deemed to be the determining causes of a range of detrimental effects.

The heavy metals on FPM originate from a diverse variety of generation sources, such as fuel combustion, geogenic sources, metallurgy, and resuspended dust, leading to various profiles and amounts.<sup>18</sup> For example, in the FPM samples collected from Beijing, China during 2013–2019, Pb, Mn, Cd, Sb, Sr, Ni, and other heavy metals were detected,<sup>19</sup> and in the FPM samples extracted in Los Angeles between 2005 and 2018, Al, Ba, Cd, Co, Cr, Cu, Pb, Zn etc. were detected.<sup>20</sup> Similar heavy metals were also observed on FPM in other countries such as Japan and Poland.<sup>21,22</sup> Notably, some heavy metals on the FPM are known to be highly carcinogenic, such as As, Pb, Cd, and Co, and thus, needed to be carefully incorporated into the health risk assessment of FPM.

Another type of toxic components on FPM is PAHs. Contrary to heavy metals, PAHs might be generated through incomplete combustion processes from biomass burning, coal burning, and vehicle emissions.<sup>23</sup> Typical species of PAHs on FPM were variable, including but not limited to acenaphthylene, anthracene, acenaphthene, chrysene, fluorene, fluoranthene, pyrene, phenanthrene, naphthalene, benzo[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, benzo[*a*]pyrene, benzo[*ghi*]perylene, dibenzo[*a,h*]anthracene, and indeno[123-*cd*]pyrene.<sup>24</sup> Mounting studies have pointed out that long-term exposure to PAHs loading on FPM may impair lung function and increase the risk of lung cancer.<sup>25</sup> For example, loading with benzo[*a*]pyrene (B[*a*]P), a well-known human carcinogen categorized by the International Agency for Research on Cancer (IARC),<sup>26</sup> the fine biochar particles would incur severe phospholipid membrane disruption in macrophages and impair the innate immune defenses.<sup>27</sup>

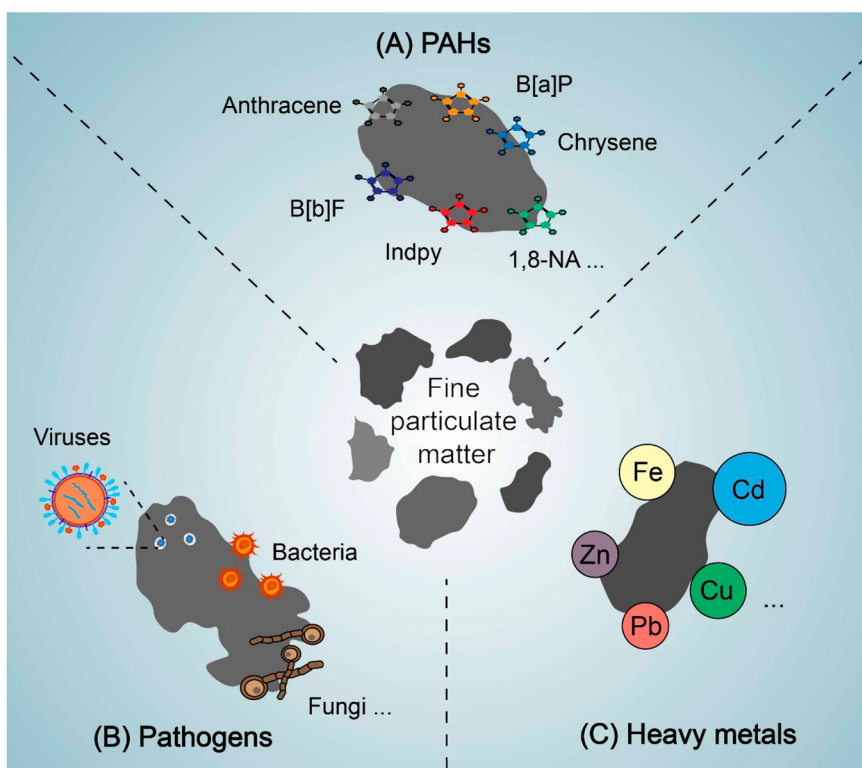
Apart from the heavy metals and PAHs, pathogen (e.g., fungi, bacteria, and viruses) loadings on the FPM have gained attention. Based on the epidemiological studies showing the positive relationship between FPM pollution and pathogen transmission, many studies have documented the hitchhiking of pathogens on the FPM and the possible health risks.<sup>28–30</sup> The FPM-induced damage to the respiratory system would cause inflammation of cells, thereby increasing susceptibility to free pathogens through various mechanisms, such as reactive oxygen species (ROS) generation.<sup>31,32</sup> In addition, the coexposure of FPM and pathogens could significantly increase both the transmission of and infection by pathogens. For instance, Liu et al. demonstrated that the coexposure of FPM and *Pseudomonas aeruginosa* would increase the transmission of *P. aeruginosa*, which induces structural damage in the upper respiratory tract associated with systematic inflammatory reactions.<sup>33</sup>

Meanwhile, the attached copollutants, namely, the components, are all responsible for the toxicity of FPM. The different components involve a range of physical and biochemical mechanisms. For example, size is a critical property in determining the cytotoxicity. In addition, the biotransformation of particles *in vivo* is a critical factor as it considerably alters the physiochemical properties and related cytotoxicity of FPM. Therefore, regarding the overall adverse health outcomes of FPM, increasing efforts should be invested to shed light on the contributions and roles of the complex components and *in vivo* fate of FPM in causing overall cytotoxicity.

## MAJOR CELL DEATH PATHWAYS INDUCED BY FINE PARTICULATE MATTER

### Apoptosis

As a major cell death pathway, apoptosis plays an important role in the biological maintenance of homeostasis and has been widely studied.<sup>34</sup> Aberrant apoptosis of cells would give rise to cardiovascular disease, immune disease, neurodegenerative diseases and osteoporosis.<sup>35–37</sup> Apoptosis could be visualized through multiple characteristics, including shrinkage of the cytoplasm, condensation of nuclei, detachment from the surrounding tissue, and convolution of outlines.<sup>7</sup> Two apoptotic pathways have been proposed: intrinsic and extrinsic pathways.<sup>38</sup> The intrinsic pathway is controlled by the B-cell lymphoma 2 (bcl-2) family proteins, while the extrinsic pathway involves the members of the tumor necrosis factor (TNF) and resultant deadly signaling cascade, which will occur upon FPM exposure.<sup>39</sup>



**Figure 1.** Proposed primary components that are responsible for the cytotoxicity of various FPM, including PAHs, pathogens, and heavy metals.

Typically, the apoptotic pathway induced by FPM exposure is regulated by a set of well-defined signaling pathways, and caspase-3 molecule can be regarded as one important marker.<sup>7</sup> Generally, FPM exposure could induce apoptosis in various cell types (Figure 2). For example, Chen et al. found that the collected FPM samples could alter the protein expression of apoptosis-related markers (*i.e.*, BCL2-Associated X (bax) and B-cell lymphoma-2 (bcl-2)) and subsequently activate caspase-3, leading to apoptosis of neurons.<sup>40</sup> It has been also uncovered that exposure of real FPM could induce activation of caspase-3 by downregulating miR-194-3p and upregulating death associated protein kinase 1 (DAPK1) expression in human bronchial epithelial cells.<sup>41</sup> In addition to the *in vitro* studies above, Wang et al. found that FPM exposure promoted inflammation and oxidative stress in hyperlipidemic rats, by triggering caspase-3 in cardiomyocytes via the JNK/P53 pathway.<sup>42</sup>

Although the outcome (namely, caspase-3 activation) has been clarified, several pathways have been implicated for the FPM exposure (Table 1). One important pathway is mitogen-activated protein kinase (MAPK) induced by inflammation and ROS generation.<sup>34</sup> For instance, many studies have found that FPM could sensitize lung epithelial cells to apoptosis via nuclear factor kappa-B (NF- $\kappa$ B), TNF- $\alpha$ , and signal transducer and activator of transcription 1 (STAT1) signaling pathways, leading to the inflammation in the respiratory system.<sup>43</sup> This pathway has also been validated after silica nanoparticle (one typical model FPM) exposure to the lung epithelial cells, that the cells would be primed to undergo apoptosis.<sup>44</sup> Not limited to the epithelial cells, numerous pathways, such as cyclooxygenase-2 (COX-2)/prostaglandin E synthase (PGES)/prostaglandin E2 (PGE2) inflammatory pathway and p53-bax-caspase pathway, and  $\beta$ 2-adrenergic receptor ( $\beta$ 2AR)/ phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway, were verified in the

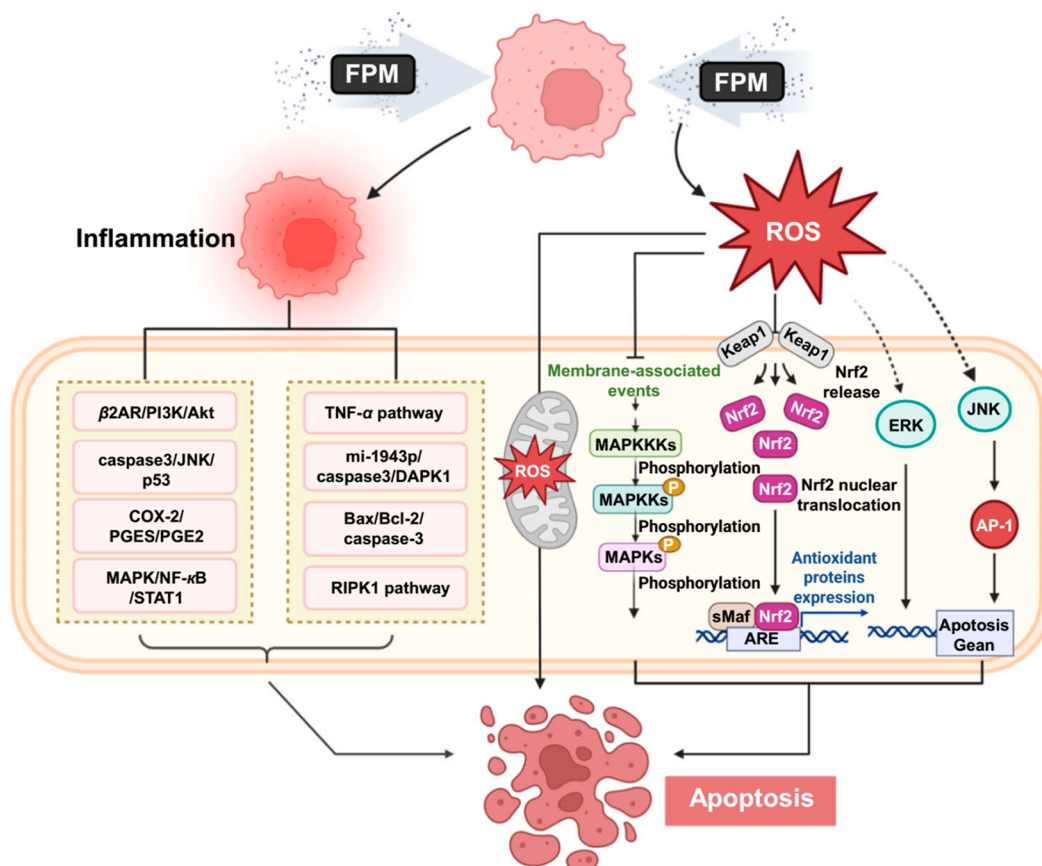
endothelial cells and cardiomyocytes, corresponding to the cardiology disorders, *e.g.*, plaque progression and/or acute coronary syndromes.<sup>45–47</sup> Similar pathways are also reportedly activated in endothelial cells upon exposure to other nanoparticles, such as titanium oxide (TiO<sub>2</sub>), zinc oxide (ZnO), and copper oxide (CuO), inducing apoptosis.<sup>48–50</sup>

Remarkably, FPM induced similar apoptosis pathways with metal-based nanoparticles. Since many metal species are found on FPM, the cytotoxicity might be attributed to the metal ion release via cell membrane damage and ROS generation. However, unlike the liquid matrix *in vivo*, other pathways, including nuclear factor erythroid 2-related factor (Nrf2) pathway, receptor-interacting protein kinase 1 (RIPK1) apoptotic signaling pathway and ROS- c-Jun N-terminal kinases (JNK)/extracellular signal-regulated kinases (ERK) apoptotic pathway, were revealed in various epidermal cells, in response to the dermal exposure of FPM.<sup>51–53</sup> For comparison, exposure of nano-ZnO would also induce apoptosis in human keratinocytes through the Nrf2 pathway.<sup>54</sup> Thus, it could be deduced that the metal ion release may occur after endocytosis or within the lysosomes.

Since unexpected apoptosis links to structural damages and disorders, even diseases, clarifying FPM-induced cell death pathways may help understand its cytotoxic mechanisms. Thereby, the different signaling pathways occur in various cell types, and these differences appear to be largely dependent on the biotransformation of FPM both *in vivo* and *in vitro*.

### Autophagy

Autophagy is defined as a crucial pathway for cells to retain cellular equilibrium and respond to external stress, as a process where the cellular components or even whole organelles are sequestered into lysosomes for degradation. The lysosomes then digest these substrates and create new cellular structures.<sup>8</sup> In



**Figure 2.** Illustration of the mechanisms of apoptosis induced by FPM. Apoptosis induced by FPM can be induced by inflammation and ROS generation. FPM-induced inflammation further activates the bax/bcl-2/caspase-3, TNF- $\alpha$ , and miR-194-3p/caspase-3/DAPK1 signaling pathways and etc. FPM-induced ROS generation triggers pathways, such as the Nrf2 and RIPK1 apoptotic signaling pathways.

general, autophagy is triggered when cells are stressed and is characterized by isolated membranes, autophagic vesicles, and autophagic lysosomes.<sup>8</sup> In addition, autophagy has also been reported to be involved in both the adaptive and the innate immune system.<sup>8</sup> Although autophagy is a normal process during the cell cycle, the reactions of autophagy may cause metabolic stress, cell death, and even cancer and neurodegenerative diseases.<sup>55</sup>

Normally, autophagy involves numerous proteins, which can be used as markers, e.g., autophagy related 5 (Atg5), autophagy related 12 (Atg12), Beclin1, and microtubule-associated protein 1 light chain 3 (MAP1LC3) (Figure 3).<sup>8</sup> For example, it has been reported that metal-based nanoparticles could mediate autophagy by upregulating these proteins.<sup>56</sup> Similar to apoptosis, autophagy could be induced by ROS generation upon FPM exposure in some model cell lines, via adenosine 5'-monophosphate-activated protein kinase (AMPK) signaling and nitric oxide synthase 2 (NOS2) signaling pathways.<sup>57,58</sup> These signaling pathways have been also assessed in cytotoxicity studies of nanoparticles, as reflected by the induction of autophagy via inhibition of the mammalian target of rapamycin (mTOR) pathway.<sup>59</sup>

In addition to ROS generation, the FPM-induced inflammatory reactions could promote cellular autophagy through ATR-CHEK1/CHK1 inflammatory response axis, ROS-AKT-mTOR axis, NF- $\kappa$ B/p38/Akt signaling pathways and MyD88-mediated inflammatory pathway.<sup>60–63</sup> Accordingly, it has been found that silica nanoparticles could induce autophagy in bronchial

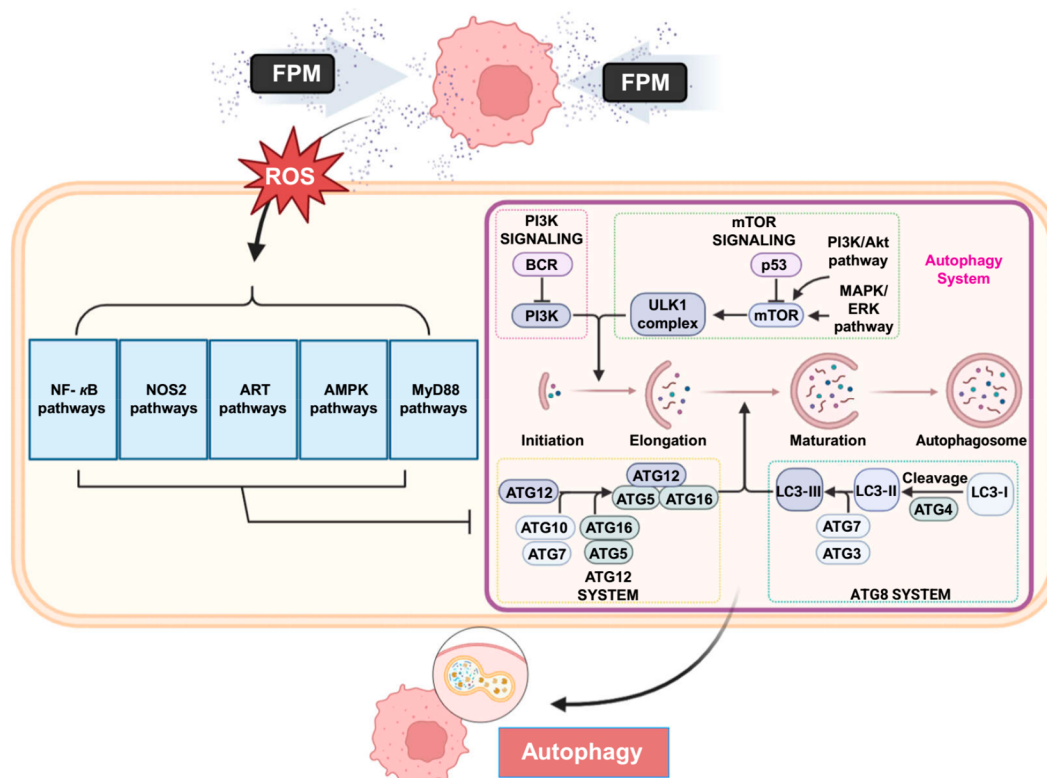
epithelial cells by inhibiting PI3K/AKT/mTOR expression,<sup>64</sup> and ZnO nanoparticles would lead to autophagy in macrophages via the PI3K/mTOR/AKT cascade.<sup>49</sup>

Apoptotic and autophagic pathways can intercross at various levels. In fact, both cell death pathways could be induced via FPM-induced ROS generation; however, apoptosis is always the preferred pathway. Apoptosis and autophagy are strongly correlated as they share similar stimuli associated with different downstream signaling pathways. In some points of view, autophagy blocks the trigger of apoptosis, and apoptosis-associated caspase activation reversely inhibits the autophagic process. The dialogue between autophagy and apoptosis will significantly affects both cell death pathways as well as immune reactions.<sup>65</sup>

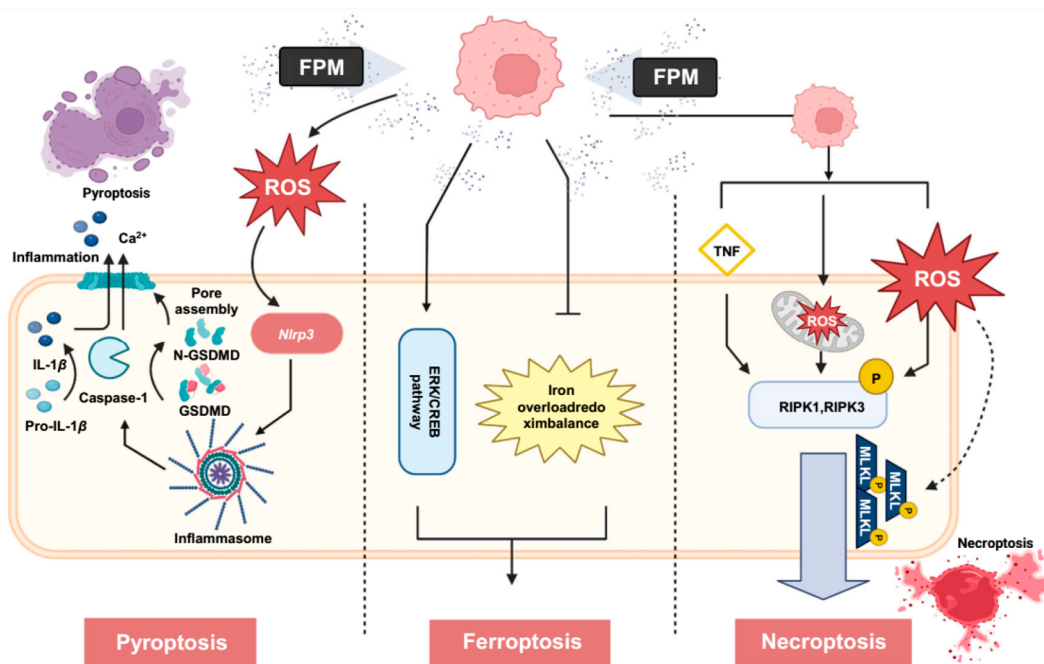
### Pyroptosis

Pyroptosis, also referred to as cellular inflammatory necrosis, is another programmed cell death pathway.<sup>66</sup> It is characterized by constant cell growth until the cell membrane ruptures, expelling the contents and inducing severe inflammatory responses. Recently, pyroptosis has received great attention owing to its association with innate immunity and disease, such as neurological disorders, infections and atherosclerosis.<sup>66</sup>

Cellular pyroptosis has been demonstrated to rely on the activation of NOD-like receptor thermal protein domain associated protein 3 (NLRP3), NLR family CARD domain containing 4 (NLRC4), and absent in melanoma 2 (AIM2) inflammasomes, and caspase-1 signaling.<sup>67</sup> Therefore, most



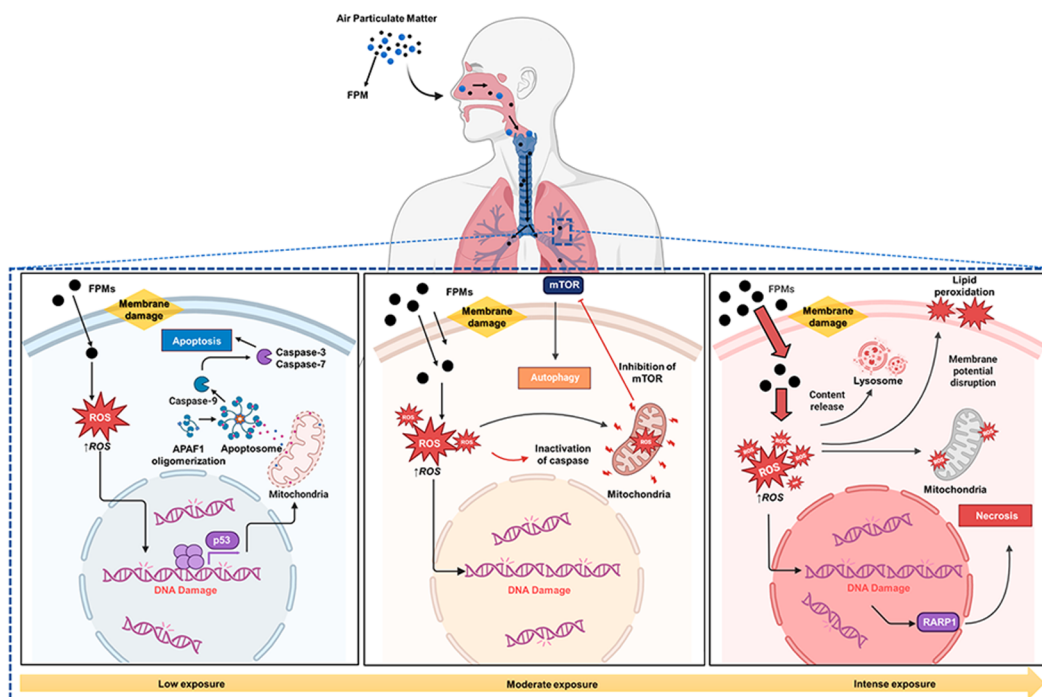
**Figure 3.** Illustration of the mechanisms of autophagy induced by FPM. Autophagy induced by FPM can be induced via ROS generation through diverse signaling, e.g., NF- $\kappa$ B, NOS2 and ART pathways.



**Figure 4.** Illustration of the mechanisms of pyroptosis, ferroptosis, and necroptosis induced by FPM. The three cell death patterns are mainly induced by FPM through ROS generation.

studies on FPM-induced pyroptosis are centered on these pathways (Figure 4). For example, Jia et al. found that FPM could disrupt the alveolar–capillary barrier by upregulating oxidative stress levels, which further induced cellular pyroptosis via caspase-1 signaling pathways.<sup>68</sup> Ren et al. reported that FPM could upregulate the ROS–NLRP3-mediated pathway and cause

pyroptosis.<sup>69</sup> Compared to the previous studies showing that ROS generated by ZnO nanoparticles would activate NF- $\kappa$ B-mediated NLRP3 inflammasomes in A549 cells,<sup>70</sup> the pyroptosis induced by FPM appeared to be attributed to the metal ion release. In addition, the activation of NLRP3 and the consequent cellular pyroptosis following FPM exposure have been observed



**Figure 5.** Proposed schematic of cell death pathways caused by ROS generation upon FPM exposure. Overview of regulated cell death pathways due to ROS, highlighting FPM as a stimulus with different exposure doses.

both *in vitro* (such as BV-2 and HMC-3 microglial cell lines) and *in vivo*.<sup>71–73</sup>

Pyroptosis is regarded as an alternative form of apoptosis, which is a proinflammatory state coupled to inflammatory cytokine release in the surrounding tissues. Caspase-1 is a major marker of pyroptosis, which is often accompanied by apoptosis. Thus, it is difficult to differentiate pyroptosis and apoptosis within a single cell, however, pyroptosis is more likely to occur when cells contain high amounts of gasdermin D (GSDMD) protein. Notably, pyroptosis is often observed in the central nervous system and has been correlated with brain disorders. Considering the possible translocation of FPM into the brain, the pyroptosis induced by FPM and the mechanisms involved in the central nervous system should be further explored.

### Ferroptosis and Necroptosis

Ferroptosis is a recently defined regulated programmed cell death.<sup>74</sup> During ferroptosis, cellular cysteine transport proteins are blocked and glutathione peroxidase (GPX4) is inhibited, resulting in the depletion of intracellular glutathione (GSH).<sup>74</sup> Consequently, lipid peroxidation is intensified to extent of cell death, which is also caused by GPX4 enzyme suppression.<sup>74</sup> The susceptibility to ferroptosis is closely correlated with the metabolism of amino acids, iron, and polyunsaturated fatty acids, as well as the production of GSH, phospholipids, NADPH, and coenzyme Q10.<sup>75</sup>

To date, the correlation between FPM and ferroptosis has been rarely reported (Figure 4). For example, Wang and Tang found that FPM could induce ferroptosis in human endothelial cells via inducing iron overload and redox imbalance.<sup>76</sup> Remarkably, many studies unveiled that heavy metals, *e.g.*, As, Pb and Cd, could induce imbalances in redox systems, thereby causing ferroptosis.<sup>77</sup> In another study, FPM exposure would lead to ferroptosis in neuronal cells by inhibiting the extracellular regulated protein kinases (ERK)/cAMP-response element binding protein (CREB) pathway.<sup>78</sup>

Necroptosis is a form of regulated cell death that critically relies on RIPK3 and mixed lineage kinase domain-like (MLKL).<sup>11</sup> Necroptosis occurs when cells are exposed to extreme threats, such as high-dose of toxicants (Figure 4). Duan et al. found that high-dose FPM would induce BEAS-2B cell necroptosis by downregulating the enzymes responsible for adenosine triphosphate (ATP) synthesis.<sup>79</sup> Similar to ferroptosis, necroptosis could be induced by heavy metals, however, studies regarding FPM-induced necroptosis are scarcely known.<sup>80,81</sup>

Collectively, both ferroptosis and necroptosis can be triggered by ROS stimuli, which might be generated by copollutants or the particle itself. However, these pathways induced by FPM warrant further study for better understanding of cytotoxicity mechanisms. For instance, it has been proposed that there is crosstalk between ferroptosis and apoptosis upon polystyrene microplastics exposure; however, the complex relationships between the two pathways need to be elucidated.<sup>82</sup>

### CONCLUSIONS AND PERSPECTIVES

As air pollution is becoming a serious problem globally, the health risks posed by FPM are gradually coming into focus. Epidemiological and toxicological studies have shown that FPM is associated with various diseases and disorders, however, the molecular mechanisms underlying these associations remain unclear. One reason for this is that the cell death pathways (*i.e.*, autophagy, apoptosis, pyroptosis, ferroptosis, and necroptosis) are complex, which indicates an intertwined crosstalk and correlation with each other. For example, it has been demonstrated that FPM would induce apoptosis through different pathways, such as the NF- $\kappa$ B/STAT1 signaling pathway. In another occasion, FPM would also trigger cell autophagy through the NF- $\kappa$ B pathway. Although the two pathways involve NF- $\kappa$ B, the downstream pathways and outcomes are starkly different.

Although the findings of the studies regarding the cytotoxicity of engineered nanoparticles with controllable physicochemical properties have helped understand the underlying molecular mechanisms of FPM, the complex components of FPM, namely, heavy metals, PAHs, and even pathogens, would lead to more complicated cytotoxicity profiles. Apparently, the different pathways summarized here are largely attributable to the characteristics of collected FPM. For example, Cd-induced cytotoxicity is often considered to be because of ROS generation, and whether Cd loading on FPM contributes to inducing cell death needs to be further studied. Some essential trace elements, such as Fe, should be also considered in inducing inflammatory reactions.<sup>83</sup> It seems that ROS generation is a major trigger for different cell death pathways, especially programmed cell death. Many stresses, such as exotic invaders (namely fine particles), pathogens, heavy metals and PAHs, which disrupt the cellular homeostasis, essentially enhance the production of ROS (Figure 5). Thus, whether the heavy metals and PAHs attached to or released from FPM should be clarified, that is, understanding the bioaccessibility of the copollutants on FPM.

Another important factor determined the cytotoxicity pathways is the cell type. According to previous studies, inhaled particles could pass the air–blood barrier and then translocate to other organs,<sup>84</sup> e.g., heart,<sup>85</sup> brain, and even knee joint.<sup>82,86,87</sup> Thus, the target cells of FPM vary in diverse studies and the reported mechanisms are different. For example, the FPM could sensitize lung epithelial cells to apoptosis via the NF- $\kappa$ B pathway and induce apoptosis on endothelial cells through the COX-2/PGE2 pathway. In addition, the cytotoxicity profiles of FPM highly depend on the uptake of different cells. For instance, macrophages would undergo autophagy after endocytosis of carbon-based FPM, while epithelial cells would be affected by the pollutants loading on FPM without apparent endocytosis of particles.<sup>27,88</sup> Collectively, the whole picture in the cytotoxicity profiles of FPM should be further teased out.

Therefore, the current knowledge gaps on the cell death pathway caused by FPM should be filled by future studies. The following points are a few recommendations for future studies.

- (i) Although recent studies have comprehensively delineated certain cell death pathways, such as apoptosis and autophagy, novel FPM-induced cell death pathways (e.g., ferroptosis and cuproptosis) warrant further exploration. In addition, owing to the complex relationships between these cell death pathways, a more specific and detailed network and crosstalk among the different pathways should be pictured after FPM exposure.
- (ii) It should be noted that the pathways caused by FPM appeared differently in various organs or tissues. For instance, the death pathways induced by FPM are different in various cells, such as epithelial and endothelial cells (Table 1). Considering the translocation of inhaled FPM to secondary organs (i.e., direct toxicity) and secretion of cytokines upon FPM exposure (i.e., indirect toxicity), the different cell death patterns and signaling pathways on various organs should be differentiated clearly.
- (iii) Owing to the “Trojan horse” effects of FPM, some trace elements, such as Fe, Cu, and Mn, could be transferred into cells, inducing cell metabolism disorders. For example, a large amount of Fe in cells would induce change of redox potential and further ferroptosis. Thus,

the influences on cell metabolism and the resulting cytotoxicity of FPM should be clarified in future studies.

- (iv) Mounting data have evidenced the implications of airborne particles in pathogen (e.g., fungi, bacteria, and viruses) transmission and epidemic spreading. The roles of pathogens on FPM should be further investigated. For example, whether the pathogens loaded on FPM would increase their accessibility and invasion is hardly understood so far. Thus, the cell death pathways caused by complex FPM and associated pathogens need to be elucidated.

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CRediT: **Yue Wu** writing-original draft (supporting).

### Notes

The authors declare no competing financial interest.

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