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REVIEW ARTICLE

$PM_{2.5}$ exposure inducing ATP alteration links with NLRP3 inflammasome activation

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Abstract

Fine particulate matter ($PM_{2.5}$) has been the primary air pollutant and the fourth leading risk factor for disease and death in the world. Exposure to $PM_{2.5}$ is related to activation of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, but the mechanism of $PM_{2.5}$ affecting the NLRP3 inflammasome is still unclear. Previous studies have shown that $PM_{2.5}$ can cause alterations in adenosine triphosphate (ATP), and an increase in extracellular ATP and a decrease in intracellular ATP can trigger the activation process of the NLRP3 inflammasome. Therefore, we emphasize that ATP changes may be the central link and key mechanism of $PM_{2.5}$ exposure that activates the NLRP3 inflammasome. This review briefly elucidates and summarizes how $PM_{2.5}$ acts on ATP and subsequently further impacts the NLRP3 inflammasome. Investigation of ATP changes due to exposure to $PM_{2.5}$ may be essential to regulate NLRP3 inflammasome activation and treat inflammation-related diseases such as coronavirus disease 2019 (COVID-19).

Keywords $PM_{2.5}$ · ATP · Energy metabolism · NLRP3 inflammasome · COVID-19

Abbreviations

$PM_{2.5}$	fine particulate matter
NLRP3	NOD-like receptor family pyrin domain containing 3
ATP	adenosine triphosphate
COVID-19	coronavirus disease 2019
PAHs	polycyclic aromatic hydrocarbons
ASC	apoptosis-associated speck-like protein
K^+	potassium
Ca^{2+}	calcium
Na^+	sodium
IL-1β	interleukin-1β
IL-18	interleukin-18
TCA	tricarboxylic acid
ROS	reactive oxygen species
NADPH	nicotinamide adenine dinucleotide phosphate
DNA	deoxyribonucleic acid

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Introduction

Fine particulate ($PM_{2.5}$) has become the main contributor to air pollution and the fourth leading risk factor for death and disability in the world (GBD C 2020; WHO 2016; Xu et al. 2020). $PM_{2.5}$ compositions mainly include inorganic salts, carbon-containing substances such as persistent organic pollutants, metal elements, including lead and cadmium, which are adsorbed and adhered to the surface (Samek et al. 2017; Xie et al. 2019; Zhang et al. 2013); Zhao et al. 2019). The proportion of each component in $PM_{2.5}$ is related to factors such as source, region, climate, season, and formation pattern (Samek et al. 2017; Xie et al. 2019; Zhang et al. 2013); Zhao et al. 2019). Furthermore, they can absorb a large number of toxic and harmful substances, such as heavy metals and persistent organic pollutants due to their large specific surface

area and deposit in the respiratory tract and pass through the alveoli into the blood system due to their small size, and subsequently disperse and accumulate in various tissues and organs of the human body through the circulatory system (Shou et al. 2019; Sun et al. 2020; Wei and Tang 2018). Therefore, the toxicity and health effects of $PM_{2.5}$ depend not only on the components and concentrations, but also on their unique physical and chemical properties, such as a Fenton reaction of heavy metals that can produce intracellular reactive oxygen species (ROS), and population susceptibility (Zeng et al. 2020).

The NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome is a complex composed of NLRP3, apoptosis-associated speck-like protein (ASC) and inactive caspase-1 precursor, which can be activated by a series of substances such as $PM_{2.5}$ and adenosine triphosphate (ATP, an intracellular basic energy unit), and biological processes including potassium (K^+) efflux, calcium (Ca^{2+}) and sodium (Na^+) influx, mitochondrial damage, and lysosome destabilization and rupture, etc. (Liu et al. 2020). Activation of the NLRP3 inflammasome is the key innate immune pathway responsible for producing active caspase-1 and interleukin-1β(IL-1β) involved in the sterile inflammatory response (Liu et al. 2018a). Mitochondria as the center of biological energy of cells plays an important role in airborne particulate matter-induced immunotoxicity (Sharma et al. 2021). Although several studies have suggested that there is an association between $PM_{2.5}$ exposure and NLRP3 inflammasome activation, the underlying mechanisms are still unknown (Cheng et al. 2020; Duan et al. 2019; Jia et al. 2021; Niu et al. 2021; Wang et al. 2020a). Furthermore, several reports showed that there is an association between $PM_{2.5}$ exposure and decreased intracellular ATP (Duan et al. 2019; Jin et al. 2019a; Jin et al. 2019b; Ning et al. 2019). In addition, extracellular ATP has been confirmed as an activator of the NLRP3 inflammasome (Hudson et al. 2019; Jiang et al. 2017; Wang et al. 2013). Therefore, ATP may mediate the relationship between $PM_{2.5}$ exposure and activation of the NLRP3 inflammasome. However, there is a critical gap in understanding the mechanism referring to $PM_{2.5}$ exposure and activation of the NLRP3 inflammasome.

In this review, we briefly summarize the essential potential role of ATP in the NLRP3 inflammasome activation process triggered by exposure to $PM_{2.5}$(Fig. 1 and Table 1). This study may shed light on the strategy to treat $PM_{2.5}$-induced ATP-dependent NLRP3 inflammasome-related inflammatory response and diseases (Fig. 2).

$PM_{2.5}$ exposure and ATP alteration

Previous studies have shown that $PM_{2.5}$ can lead to intracellular mitochondrial dysfunction and subsequently weaken mitochondrial respiration and reduce ATP production (Ku et al. 2016; Miao et al. 2019; Park et al. 2021). For example, exposure to haze, the dose of $PM_{2.5}$ can reduce ATP production in the lungs of rats, decrease the activity of malate dehydrogenase and citrate synthase [critical enzymes in the tricarboxylic acid (TCA) cycle], and attenuate the expression of mitochondrial respiration chain genes such as *UQCRI1* and *NDUFS2*(Jin et al. 2019a). ATP levels decrease significantly with increasing seasonal exposure to $PM_{2.5}$, which is regulated by *PPARa* in a dose-dependent manner and is accompanied by cardiac damage in Sprague Dawley rats (Jin et al. 2019b). $PM_{2.5}$ exposure can cause mitochondrial damage, such as mitochondrial vacuolation and rupture of the mitochondrial membrane in type II alveolar epithelial cells, and accompany a decrease in ATP levels as evidence of energy metabolism disorders (Ning et al. 2019). Li et al. reported that exposure to $PM_{2.5}$ led to a decrease in Na^+/K^+-ATPase and Ca^{2+}-ATPase, which can inhibit the catalysis and decomposition process of ATP and subsequently suppress the influx of K^+ and the efflux of Ca^{2+}, respectively (Li et al. 2015a). Fu et al. reported that exposure to $PM_{2.5}$ can up-regulate ATP citrate lyase (ACLY), which will inevitably decrease the level of ATP (Li et al. 2015a). A recent study demonstrated that $PM_{2.5}$ exposure inhibited sATP synthesis in BEAS-2B cells and down-regulated four enzymes responsible for ATP production, including *ATP5F*, *COX7A*, *NDUF*, and *UQCR*(Duan et al. 2020). Taken together, exposure to $PM_{2.5}$ will cause a decrease in cellular ATP.

ATP alteration and NLRP3 inflammasome activation

It is well-known that ATP stores energy in the form of high-energy phosphate bonds and the hydrolysis of the bonds provides a large amount of free energy to drive the metabolic reaction of various cells. ATP can be synthesized during cellular respiration, either in the cytoplasm during glycolysis or in the mitochondria via the TCA cycle and the electron transport system in the presence of oxygen. The biological effect of ATP on the NLRP3 inflammasome depends on its intracellular and extracellular flow (Fig. 3). Specifically, ATP release from intracellular to extracellular can activate the NLRP3 inflammasome (Asgari et al. 2013). In other words, elevated extracellular ATP (ATP exposure) or decreased intracellular ATP (ATP efflux) may be the key step to ultimately activate the NLRP3 inflammasome (Nomura et al. 2015; Wang et al. 2013).

It should be noted that extracellular ATP can trigger the P2X7 membrane receptor to activate the NLRP3 inflammasome and subsequently secrete mature caspase-1 and IL-1β (Amores-Iniesta et al. 2017; Baron et al. 2015; Chen et al. 2013; Di Virgilio et al. 2017; Hudson et al. 2019; Jiang

Table 1 A brief summary of the relationship among $PM_{2.5}$, ATP, NLRP3, and COVID-19

Variables	Patterns	References
$PM_{2.5}$ and ATP	Particulate mediate NLRP3 inflamamsome activation via phagosomal destabilization	(Hornung et al. 2008)
	$PM_{2.5}$ inhibit Na^+K^+-ATPase and Ca^{2+}-ATPase and induce ROS and lung injury	(Li et al. 2015b)
	$PM_{2.5}$ exposure causes abnormal energy metabolism and ATP decrease in lung tissues	(Jin et al. 2019a)
	$PM_{2.5}$ exposure causes cardiac ATP reduction by regulating PPARa selection	(Jin et al. 2019b)
	$PM_{2.5}$ causes lung injuries and coupled energy metabolic disorder as a decrease in ATP levels	(Ning et al. 2019)
	Inhibition of ATP citrate lyase protects $PM_{2.5}$-induced epithelial-mesenchymal transition	(Fu et al. 2019)
ATP and NLRP3 inflammasome	Extracellular ATP activate P2X7 receptor and function in the ATP-mediated lysis of antigen-presenting cells.	(Surprenant et al. 1996)
	ATP activate the P2X7 receptor to trigger NLRP3 dependent inflammasome activation	(Mariathasan et al. 2006)
	Pannexin-1 is required for releasing mature IL-1β induced by activating P2X7 receptors that are ATP-gated cation channels	(Pelegrin and Surprenant 2006)
	ATP is a major endogenous danger signal that engages the P2X7 receptor/pannexin-1 axis, leading to NLRP3 inflammasome activation, IL-1β maturation and lung fibrosis.	(Riteau et al. 2012)
	The NLRP3 inflammasome is activated through ATP-dependent lysosomal cathepsin B release	(Hoegen et al. 2011)
	Extracellular ATP release triggering subsequent purinergic receptors results in NLRP3 inflammasome activation in response to PAMPs and DAMPs	(Gombault et al. 2012)
	The assembly of the NLRP3 inflammasome requires a signal derived from extracellular ATP, pore-forming toxins, or crystalline materials	(Juliana et al. 2012)
	Intestinal inflammation activation is mediated by ATP-reactive P2X7 purinoceptors	(Kurashima et al. 2012)
	Downregulation of the Na/K-ATPase pump activates the NLRP3 inflammasome	(Lacroix-Lamande et al. 2012)
	ATP release and purinergic signaling is a common pathway for particle-mediated inflammasome activation	(Riteau et al. 2012)
	C3a modulates IL-1β secretion by regulating ATP efflux and subsequent NLRP3 inflammasome activation	(Asgari et al. 2013)
	ATP-P2X4 signaling mediates NLRP3 inflammasome activation: a novel pathway of diabetic nephropathy	(Chen et al. 2013)
	ATP stimulation trigger the universal localization of ASC pyroptosome within the cytoplasm	(Wang et al. 2013)
	Ethanol, ATP and LPS treatments up-regulates NLRP3 expression, and causes caspase-1 cleavage and the release of IL-1β and IL-18 in astrocytes supernatant	(Alfonso-Loeches et al. 2014)
	ATP activates the NLRP3 inflammasome in a ROS-dependent manner	(Zhang et al. 2015)
	Intracellular ATP decrease mediates NLRP3 inflammasome activation upon nigericin and crystal stimulation	(Nomura et al. 2015)
	Nanoparticles activated the NLRP3 inflammasome through ATP, ADP and adenosine	(Baron et al. 2015)
	Inflammatory sites contain high (hundred micromolar) extracellular ATP concentrations	(Di Virgilio et al. 2017)
	Blocking ATP-sensitive K channel alleviates morphine tolerance by inhibiting NLRP3-mediated neuroinflammation	(Qu et al. 2017)
	Mitochondrial function is required for extracellular ATP-induced NLRP3 inflammasome activation	(Sadatomi et al. 2017)
	The ATPase activity of NLRP3 has pivotal role in infammasome activation	(Shim et al. 2017)
	Extracellular ATP activates the NLRP3 inflammasome and is an early danger signal of skin allograft rejection	(Amores-Iniesta et al. 2017)
	P2X7R-mediated NLRP3 inflammasome activation is dependent on extracellular ATP	(Jiang et al. 2017)
	Connexin43 hemichannel-mediated ATP release link with inflammasome pathway activation	(Mugisho et al. 2018)
	LPS-ATP-induced endothelial cell pyroptosis is regulated by ROS/NLRP3/Caspase-1 signaling pathway	(Tang et al. 2019a)
	NLRP3 ATP-hydrolysis motif is targeted by MCC950 for inflammasome inhibition	(Coll et al. 2019)
	Pregnane X receptor activating ATP release mediates NLRP3 inflammasome activation	(Hudson et al. 2019)
	ATP directly activates membrane channel P2X7 receptor, K+ efflux, and NLRP3 inflammasome	(Wang et al. 2020b)

Table 1 (continued)

Variables	Patterns	References
$PM_{2.5}$ and NLRP3 inflammasome		
	K+ efflux is the common step for NLRP3 inflammasome activation triggered by bacterial toxins and $PM_{2.5}$	(Munoz-Planillo et al. 2013)
	$PM_{2.5}$ cause NLRP3 inflammasome activation and lung fibrosis through cathepsin B release, ROS production, and potassium efflux	(Zheng et al. 2018)
	$PM_{2.5}$ exposure aggravated oAβ-induced inflammation and microglia was possibly dependent on NLRP3 inflammasome activation	(Wang et al. 2018)
	$PM_{2.5}$-related cardiac injury is mediated by macrophages polarization and NLRP3 inflammasome activation	(Du et al. 2019)
	$PM_{2.5}$ induce immune response by activating TLR4/MAPK/NF-κB pathway and NLRP3 inflammasome in alveolar macrophages	(Tang et al. 2019b)
	$PM_{2.5}$ change blood vessel formation through ROS-mediated NLRP3 inflammasome pathway	(Shen et al. 2019)
	$PM_{2.5}$ exposure cause depressive-like responses through Nrf2/NLRP3 signaling pathway	(Chu et al. 2019)
	$PM_{2.5}$-induced cardiac injury is associated with NLRP3 inflammasome activation	(Duan et al. 2019)
	$PM_{2.5}$ compromises antiviral immunity in influenza infection by inhibiting activation of NLRP3 inflammasome and expression of interferon-β	(Tao et al. 2020)
	NLRP3 Inflammasome is associated with $PM_{2.5}$-induced neuroinflammation in Alzheimer's disease	(Shi et al. 2020)
	$PM_{2.5}$-induced oxidative stress activates the TRPM2-Ca^{2+}-NLRP3 axis to promote lung injury	(Wang et al. 2020)
	$PM_{2.5}$ induce acute allergic airway inflammation via the TLR2/NF-κB/NLRP3 signaling pathway	(Dai et al. 2020)
	$PM_{2.5}$ triggers cornea inflammation and pyroptosis via NLRP3 inflammasome activation	(Niu et al. 2021)
	$PM_{2.5}$-induced lung inflammation via activating of the NLRP3/caspase-1 signaling pathway	(Jia et al. 2021)
	PM2.5-induced lung injury is attenuated in macrophage-specific NLRP3 deficient mice	(Xiong et al. 2021)
	PM2.5 activated the NLRP3 inflammasome in human umbilical vein endothelial cells	(Hu et al. 2021)
$PM_{2.5}$ and COVID-19	There is an association between short-term exposure to $PM_{2.5}$ and COVID-19 infection	(Zhu et al. 2020)
	A small increase in long-term exposure to $PM_{2.5}$ leads to a large increase in the COVID-19 death rate	(Wu et al. 2020)
	Both the short- and long-term $PM_{2.5}$ exposures contribute to a higher motality of COVID-19	(Mehmood et al. 2020)
	Short-term or chronic $PM_{2.5}$ exposure has a significant negative impact of the human immune system	(Zoran et al. 2020)
NLRP3 inflammasome and COVID-19	SARS-CoV-2 might directly activate NLRP3 inflammasome, and severe COVID-19 patients can demonstrate a dysregulated NLRP3 inflammasome activity and a cytokine storm	(van den Berg and Te 2020)
	There is a link between the pathogenesis of severe COVID-19 and NLRP3 activation	(Freeman and Swartz 2020)
	Emerging role of IL-6 and NLRP3 inflammasome as potential therapeutic targets to combat COVID-19	(Paniri and Akhavan-Niaki2020)
	The role of NLRP3 inflammasome in obesity-related COVID-19 exacerbations	(Bertocchi et al. 2020)
	The NLRP3 inflammasome activation is a potential drug target fighting COVID-19	(Shah 2020)

et al. 2017; Liu et al. 2018a; Pelegrin and Surprenant 2006). Blocking ATP hydrolysis by MCC950 can inhibit the activation and formation of the NLRP3 inflammasome (Coll et al. 2019). The P2X7 receptor, pannexin-1, and connexin-43 hemichannels function as ATP-gated ion channels to permeate and transfer Na^+, K^+, and Ca^{2+}, and further influence NLRP3 inflammasome activation (Cymer et al. 2020; Huang et al. 2019; Karmakar et al. 2016; Mugisho et al. 2018; Mugisho et al. 2019; Parzych et al. 2017; Tonkin et al. 2018; Wang et al. 2020b; Yang et al. 2019). Activated P2X7 receptors triggered by extracellular ATP can recruit the pannexin-1 gap junction protein to form a larger pore channel, subsequently accelerating K^+ efflux and Ca^{2+} influx, and further activating the NLRP3 inflammasome (Chakfe et al. 2002; Dubyak 2007; He et al. 2016; Hudson et al. 2019; Liu et al. 2018a; Mariathasan et al. 2006; Riteau et al. 2012; Surprenant et al. 1996). Down-regulation of the Na^+/K^+-ATPase and Ca^{2+}-ATPase pump by stimuli such as $PM_{2.5}$ and leptospiral glycolipoprotein activates the NLRP3 inflammasome (Geng et al. 2006; Guo et al. 2017; Lacroix-Lamande et al. 2012; Li

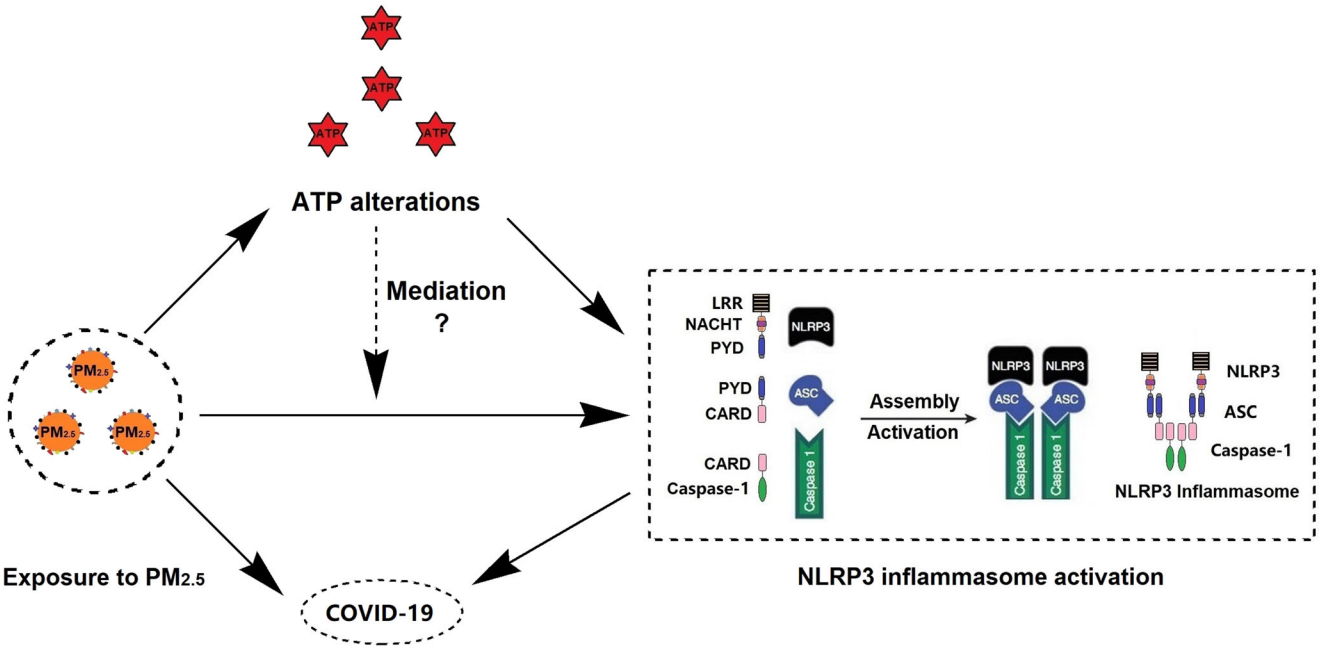

Fig. 1 The mediation role of ATP alterations in the association between exposure to $PM_{2.5}$ and activation of the NLRP3 inflammasome. Exposure to $PM_{2.5}$ can induce ATP alterations. In addition, both $PM_{2.5}$ exposure and ATP alteration can activate the NLRP3 inflammasome. Both exposure to $PM_{2.5}$ and activation of NLRP3 inflammasome are related to COVID-19. Therefore, the review explores the mediation role of ATP alteration in the association of $PM_{2.5}$ exposure, the NLRP3 inflammasome activation, and their related COVID-19

et al. 2015a). Several studies confirm that both K^+ efflux (low intracellular K^+) and Ca^{2+} influx (high intracellular Ca^{2+}) can trigger the NLRP3 inflammasome activated by various stimuli such as particulate matter and bacterial toxins (Liu et al. 2020; Munoz-Planillo et al. 2013; Petrilli et al. 2007; Suadicani et al. 2006).

There are a variety of additional ways, such as ROS over generation, mitochondrial deoxyribonucleic acid (DNA) damage, lysosome rupture, and endoplasmic reticulum stress, mediating the process of activation of NLRP3 inflammasomes with ATP. For example, Zhang et al. demonstrated that ATP activates the NLRP3 inflammasome in a ROS-dependent manner (Zhang et al. 2015). Macrophage treatment with ATP leads to the rapid generation of ROS, while the application of the diphenyleneiodonium nicotinamide adenine dinucleotide phosphate (NADPH) oxidase inhibitor can effectively inhibit the activation of the caspase 1-related NLRP3 inflammasome mediated by ATP (Martinon 2010). Extracellular macrophages treated with ATP induce ROS production and subsequently process and secrete pro-inflammatory cytokines, including IL-1β and interleukin-18(IL-18)(Cruz et al. 2007). Additionally, ATP treatments stimulate the generation of mitochondrial ROS (mROS), cause caspase-1 cleavage, and trigger activation of the NLRP3 inflammasome to release IL-1β and IL-18 in astrocytes (Alfonso-Loeches et al. 2014). Excessive levels of ATP acting on the cell membrane increase ROS as NADPH oxidase-dependent $O_2^{\bullet-}$ production in cells and trigger activation of the NLRP3 inflammasome (Abais et al. 2015). Inhibition of LPS-ATP-induced ROS production and endothelial cell pyroptosis by neferine can block the ROS/NLRP3/Caspase-1 signaling pathway (Tang et al. 2019a).

ATP plays a pivotal role in maintaining the cellular powerhouse position of mitochondria (Yu and Bennett 2016). The imbalance of intracellular and extracellular ATP will seriously impact the normal physical function of cells and the body. In other words, mitochondrial homeostasis is indispensable for normal metabolic circuits and signaling pathways based on mitochondrial metabolism. Extracellular ATP-induced mitochondrial dysfunction and disruption, such as loss of mitochondrial membrane potential and mitochondrial fragmentation, which can result in mitochondrial DNA damage and trigger activation of the extracellular ATP-induced NLRP3 inflammasome (Shimada et al. 2012; Sutterwala et al. 2014; Zhong et al. 2018).

In addition, ATP-driven destabilization or rupture of the lysosome leads to the release of the lysosome content to the cytoplasm through cathepsin B, which participates in the activation process of the NLRP3 inflammasome. For example, the activation of the NLRP3 inflammasome in the pathology of pneumococcal meningitis depends on the production of ATP, the destabilization of lysosome, and the activation of cathepsin B (Hoegen et al. 2011). Nigericin, an activator of the NLRP3 inflammasome, results in decreased cellular ATP and subsequently causes membrane permeabilization of the lysosome and activation of the NLRP3 inflammasome (Heid et al. 2013). Uptake of particulates such as silica crystals and aluminum salt leads to acidification, swelling, and rupture of the lysosome, and subsequent activation of the NLRP3

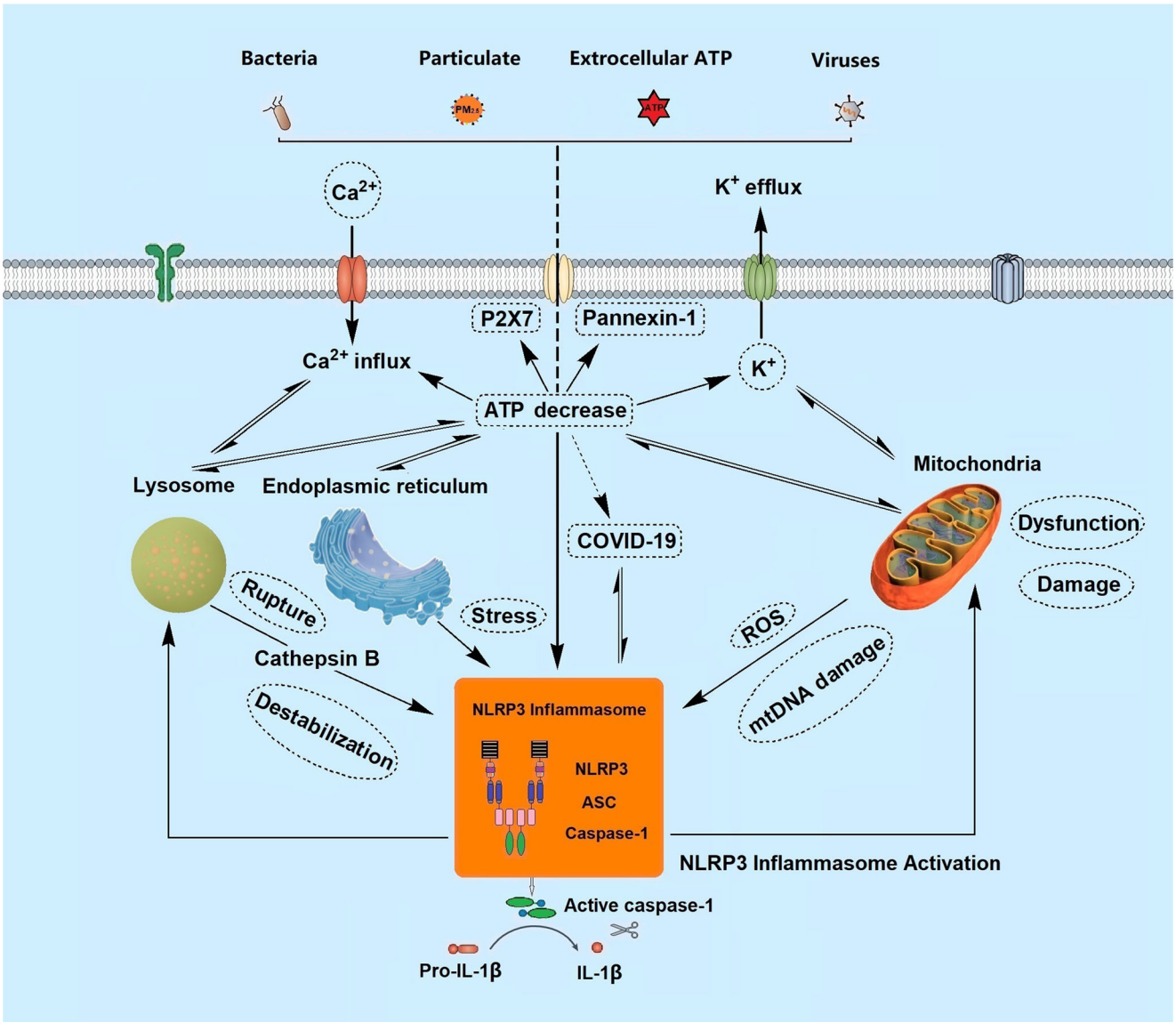

Fig. 2 The potential ATP mediated pathway of $PM_{2.5}$ exposure on NLRP3 inflammasome activation. Exposure to $PM_{2.5}$ induce intracellular ATP decrease, which is linked with K^+ efflux, Ca^{2+} influx, lysosome rupture, mitochondria disfunction, endoplasmic reticulum stress, and subsequently activate NLRP3 inflammasome

inflammasome (Hornung et al. 2008). While inhibition of phagosomal acidification or cathepsin B alters NLRP3 activation, indicating that lysosome destabilization plays a role in regulating NLRP3 inflammasome activation.

$PM_{2.5}$ exposure and NLRP3 inflammasome activation

The potential molecular mechanisms of $PM_{2.5}$ exposure on human health include the inflammatory response, oxidative stress, and genotoxicity (Byun et al. 2016; Chen et al. 2020; Guan et al. 2016). Additionally, oxidative stress is closely related to the inflammatory response and plays an important role in inflammatory processes (Lugrin et al. 2014). Several studies found that exposure to $PM_{2.5}$ can initiate the process of NLRP3 inflammasome activation and associated inflammation-related diseases (Hu et al. 2021; Xiong et al. 2021). $PM_{2.5}$ exposure may lead to increased endogenous carbon dioxide (CO_2), suicidal death of erythrocytes (accompanied by loss of circulating red blood cells, hypoxia, anemia, and dysfunction of the vascular endothelium), and activated NF-kB through ligands for toll-like receptors and, subsequently, the NLRP3 inflammasome (Liu et al. 2018b; Nguyen et al. 2009; Zappulla 2008). A recent study indicated that $PM_{2.5}$ promotes the NLRP3/caspase-1 pathway to further induce

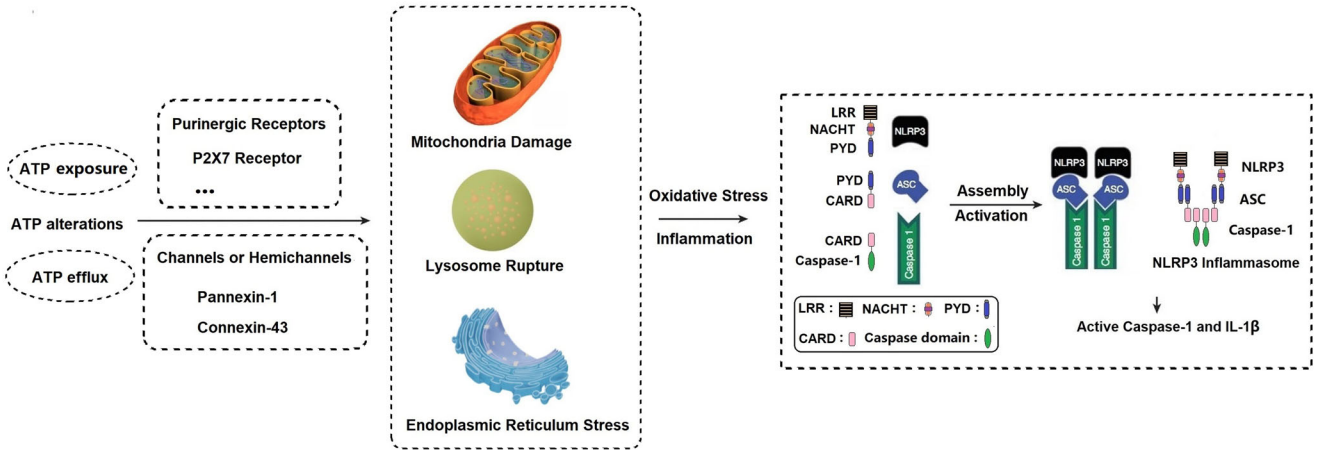

Fig. 3 The process of ATP alteration activating the NLRP3 inflammasome. Both elevated extracellular ATP (ATP exposure) or decreased intracellular ATP (ATP efflux) can activate P2X7 receptor and open hemichannels such as pannexin-1 and connexin-43 in the cellular membrane, which result in various biological processes including mitochondria damage, lysosome rupture, and endoplasmic reticulum stress, and subsequently oxidative stress and inflammatory response, and finally activate the NLRP3 inflammasome

pulmonary inflammation (Jia et al. 2021). Furthermore, $PM_{2.5}$ induces intracellular ROS and subsequently triggers lung injury such as lung inflammation and fibrosis, inhibition of blood vessel formation, and cornea inflammation by activating the NLRP3 inflammasome (Niu et al. 2021; Shen et al. 2019; Wang et al. 2020a; Zheng et al. 2018). In addition, exposure to $PM_{2.5}$ leads to cardiac dysfunction and injury, which are mediated by macrophage polarization and activation of the NLRP3 inflammasome in mice with apolipoprotein $E^{-/-}$ (Du et al. 2019). Exposure to $PM_{2.5}$ induces abnormal electrocardiogram alteration (ECG) and increased inflammatory cell and fibrosis, which may be due to activation of the NLRP3 inflammasome (Duan et al. 2019). $PM_{2.5}$ from the pig house activates the TLR4/MyD88 pathway to induce ROS production and further trigger the NLRP3 inflammasome in alveolar macrophages (Tang et al. 2019b). After exposure to $PM_{2.5}$ from $Nrf2^{-/-}$ and WT mice for 9 weeks, there were obvious depressive-like responses and the NLRP3 signaling pathway was more activated in $Nrf2^{-/-}$ mice than in WT mice (Chu et al. 2019). There were many activators, such as $PM_{2.5}$, ATP, bacteria, and viruses, that trigger the activation of the NLRP3 inflammasome (Kelley et al. 2019; Liu et al. 2020; Liu et al. 2018b). However, the underlying mechanism of $PM_{2.5}$ exposure to activation of the NLRP3 inflammasome is still unclear.

Mediation of ATP in PM2.5 exposure and NLRP3 inflammasome activation

Cellular stimulation driven by environmental or endogenous particles such as $PM_{2.5}$, silica, and uric acid can trigger extracellular delivery of intracellular ATP (intracellular ATP decrease) and subsequent activation of the ligand (ATP)-gated/sensitive ionotropic P2X7 membrane receptor at the cell surface (Baron et al. 2015; Gombault et al. 2012; Riteau et al. 2012). Previous studies demonstrated that exposure to $PM_{2.5}$ can inhibit Na^+/K^+-ATPase and Ca^{2+}-ATPase activities and induce alveolar macrophages to produce ROS, which may indicate that ATP mediates the process of generation of ROS induced by $PM_{2.5}$ and then activates the NLRP3 inflammasome (Li et al. 2015b). Additionally, extracellular ATP triggers the activation of the NLRP3 inflammasome and subsequently the maturation of IL-1β, which is consistent with the decrease in intracellular ATP driven by exposure to $PM_{2.5}$ and complications of activation of the NLRP3 inflammasome (Amores-Iniesta et al. 2017; Jiang et al. 2017; Ning et al. 2019; Niu et al. 2021; Jia et al. 2021). Although some of the participants, such as the $PM_{2.5}$, ATP, and NLRP3 inflammasomes, presented in different previous different studies, did not highlight the mediated and pivotal role of ATP in the association between $PM_{2.5}$ exposure and activation of the NLRP3 inflammasome. Taken together, although ATP is related to several activators and regulators of the NLRP3 inflammasome, its direct key role in the process of exposure to $PM_{2.5}$ activating the NLRP3 inflammasome needs further confirmation.

Association among $PM_{2.5}$, NLRP3 inflammasome, and COVID-19

The great interest in the link between $PM_{2.5}$, the NLRP3 inflammasome and COVID-19 arises with the COVID-19 pandemic in the world. A recent study demonstrated that $PM_{2.5}$ and the air quality index were positively related to daily new

cases of COVID-19 in Milan, Italy (Zoran et al. 2020). Each 1μg/m^3 increase in $PM_{2.5}$ is related to a 15% increase in COVID-19 death in the USA (Wu et al. 2020). A 10 μg/m^3 elevation in $PM_{2.5}$ was associated with a 2.24% (95% CI: 1.02 to 3.46) increase in daily confirmed cases in China (Zhu et al. 2020). In addition, both short- and long-term exposure to $PM_{2.5}$ causes an increase in the incidence of lethal COVID-19(Mehmood et al. 2020). What is more, the NLRP3 inflammasome plays an important role in the pathogenesis of COVID-19 infection (Freeman and Swartz 2020; Shah 2020; van den Berg and Te 2020). An increase in diabetes complications in patients with COVID-19 is partly attributed to overactivation of the NLRP3 inflammasome (Bertocchi et al. 2020). NLRP3 inflammasome blocker drugs, such as MCC950 and Colchicine, may provide a promising treatment strategy for patients with COVID-19 infection (Paniri and Akhavan-Niaki2020). These studies may indicate that ATP-regulating drugs may be a potential treatment for patients with COVID-19.

Conclusion and future perspectives

In summary, exposure to $PM_{2.5}$ can lead to decreased intracellular ATP (ATP efflux). Both elevated extracellular ATP and decreased intracellular ATP derived from particles such as $PM_{2.5}$ and crystals can activate the NLRP3 inflammasome through several approaches such as K^+ efflux, Ca^{2+} influx, ROS, mitochondrial DNA damage, lysosome destabilization and rupture. Meanwhile, exposure to $PM_{2.5}$ can trigger the activation process of the NLRP3 inflammasome. However, the critical and central role of ATP in the procedure of environmental stimuli such as exposure to $PM_{2.5}$ and activation of the NLRP3 inflammasome was ignored in previous studies. Understanding the roles and regulatory mechanisms of ATP alteration initiated by exposure to particulate substances in the effect of activation of the NLRP3 inflammasome is essential to develop potential treatment approaches against NLRP3-related inflammatory symptoms and diseases such as COVID-19.

This study serves as a catalyst for the role of ATP in future studies, which remain inadequate molecular mechanisms of $PM_{2.5}$-driven ATP transfer and regulation and subsequent activation of the NLRP3 inflammasome. ATP-associated ion channels in the cellular membrane, such as P2X7 receptors, pannexin-1, and connexin-43, play an important role in various biological processes such as the inflammatory response, oxidative stress, and genotoxicity. Exploring the underlying molecular mechanisms of ATP transfer and regulation at the cellular level is crucial to maintaining body homeostasis and biological function. Identifying specific drugs or candidate genes for ATP-related disorders may provide novel strategies to prevent and treat a host of inflammatory diseases driven by ATP alterations.

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Declarations

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