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Effects of fine particulate matter on bone marrow-conserved hematopoietic and mesenchymal stem cells: a systematic review

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The harmful effects of fine particulate matter ≤2.5 μm in size ($PM_{2.5}$) on human health have received considerable attention. However, while the impact of $PM_{2.5}$ on the respiratory and cardiovascular systems has been well studied, less is known about the effects on stem cells in the bone marrow (BM). With an emphasis on the invasive characteristics of $PM_{2.5}$, this review examines the current knowledge of the health effects of $PM_{2.5}$ exposure on BM-residing stem cells. Recent studies have shown that $PM_{2.5}$ enters the circulation and then travels to distant organs, including the BM, to induce oxidative stress, systemic inflammation and epigenetic changes, resulting in the reduction of BM-residing stem cell survival and function. Understanding the broader health effects of air pollution thus requires an understanding of the invasive characteristics of $PM_{2.5}$ and its direct influence on stem cells in the BM. As noted in this review, further studies are needed to elucidate the underlying processes by which $PM_{2.5}$ disturbs the BM microenvironment and inhibits stem cell functionality. Strategies to prevent or ameliorate the negative effects of $PM_{2.5}$ exposure on BM-residing stem cells and to maintain the regenerative capacity of those cells must also be investigated. By focusing on the complex relationship between $PM_{2.5}$ and BM-resident stem cells, this review highlights the importance of specific measures directed at safeguarding human health in the face of rising air pollution.

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INTRODUCTION

Particulate matter (PM) is a complex mixture of solid and liquid microscopic particles that enter the atmosphere as a result of natural environmental processes or human activities[1]. PM with aerodynamic diameters ≤10 μm cannot be filtered by the cilia and mucus of the nose and human respiratory tract, and instead infiltrate tracheobronchial and alveolar tissues, eventually entering the circulatory system and causing illness[2]. Fine particulate matter ≤2.5 μm in size ($PM_{2.5}$) is especially harmful to human health[3].

$PM_{2.5}$ is generated from both natural environmental and human sources. The former include dust, soil particles, pollen, and sea salt aerosols, while the latter are primarily the products of combustion processes, such as fossil fuel combustion in power plants, industrial emissions, residential heating and cooking, and vehicle exhaust emissions[4]. The annual average concentration of $PM_{2.5}$ measured in the Seoul Metropolitan area from November 2005 to March 2012 was 27 μg/m^3,[5], and it was 25 μg/m^3 in 2017[6], which is nearly three times the WHO standard. $PM_{10\text{-}2.5}$ is less of a concern, although these particles can irritate the eyes, nose, and throat. The substantial health risk of $PM_{2.5}$ is related to its ability to enter the circulation and infiltrate the lungs. PM deposition in the lungs triggers airway inflammation, compromising normal immune responses and rendering this vital organ vulnerable to infection[7]. Damage to the bronchial mucociliary system induced by $PM_{2.5}$ can impede the effective clearance of bacteria[8]. Other adverse effects of $PM_{2.5}$ include increased inflammatory cytokine release, which triggers lung fibroblast and epithelial cell death, interference with gap junctions and thus intercellular communication, and increased permeability of the epithelial barrier, impairing its function as a physical constraint and its role in innate pulmonary immunity[9]. Following the inhalation of $PM_{2.5}$, the particles pass through the epithelial barrier and successively cross the basement membrane, subepithelial connective tissue layer, and endothelial cells to finally enter the bloodstream[10,11]. Ambient particles are toxic to cytochrome P450s, a ubiquitous superfamily of enzymes responsible for eliminating most hydrophobic compounds in tissues throughout the body[12]. $PM_{2.5}$ and other foreign substances can also be transferred from the circulation through pores and fenestrate in the vascular endothelium to interact with the mononuclear phagocyte system in reticular connective tissues and thereby reach potentially sensitive target sites such as the bone marrow (BM)[13,14], where they alter the activity of stem cells. Through its direct transfer via the blood circulation to major organs, $PM_{2.5}$ has been implicated in cardiopulmonary[15], respiratory[16], and cardiovascular diseases[17], lung cancer[18], and an increased risk of death[19,20]. $PM_{2.5}$ is also a risk factor for asthma[21] and, in children, for cough variant asthma by reducing immune regulation and ventilatory function[22].

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Table 1. Key findings of studies on the effects of $PM_{2.5}$.

Studies	Key findings	References
Mice (in vivo)	$PM_{2.5}$ exposure induces reactive oxygen species (ROS) production and oxidative stress in BM-derived endothelial progenitor cells (EPCs) and BM.	79,160
Mice (in vivo, in vitro)	Ni nanoparticle exposure diminishes the number and functions of EPCs in BM.	161
Mice (in vivo, ex-vivo)	Exposure to $PM_{2.5}$ alters the mobilization of endothelial progenitor cells from the BM.	162
Adult humans, mice (in vivo)	Exposure to $PM_{2.5}$ dramatically decreases the number of BM-derived EPCs and their activity.	163
Mice (in vivo, in vitro)	$PM_{2.5}$ exposure inhibits the proliferation of BMSCs and induces apoptosis by inhibiting Akt phosphorylation, increasing ROS production, and elevating serum tumor necrosis factor (TNF)-α and interleukin (IL)-1β levels.	68
$Nrf2^{-/-}$ mice (in vivo)	In wild-type mice exposed to $PM_{2.5}$, the proportions of HSPCs, granulocyte monocyte progenitor cells (GMPs), megakaryocyte-erythrocyte progenitor cells (MEPs), and megakaryocyte progenitors (MkPs) are significantly increased. Conversely, only the proportion of HSPCs is decreased in the BM of $Nrf2^{-/-}$ mice.	77
$Nrf2^{-/-}$ mice (in vivo)	Nuclear factor erythroid-2-related Factor 2 (NRF2) controls HSPC proliferation, differentiation, and survival, plays a crucial role in myeloid formation from HSCs, and regulates HSPC retention and migration in the BM niche.	87
Mice (in vivo, ex vivo)	Neonates exposed to $PM_{2.5}$ induces senescence of HSCs.	76
Mice (in vivo, ex vivo)	Superoxide dismutase (SOD) activity, IL-1β, IL-6, TNF-α, nuclear factor kappa light chain enhancer of activated B cells (NF-κB), and p65 increase DNA injury, and connexin 43 (Cx43) decreases DNA injury in the BM of $PM_{2.5}$-exposed mice.	79
Mice (in vivo, ex vivo)	NRF2 antioxidant response genes undergo epigenetic reprogramming in the sinonasal mucosa in response to exposure to $PM_{2.5}$.	86
Human placental/umbilical cord blood samples (in vitro)	Survival, proliferation, and differentiation of HSPCs are controlled by intracellular ROS levels, which are essential for preserving HSPC homeostasis.	164
$Nrf2^{-/-}$ mice (in vivo)	Without controlling the quantity of ROS in the hypoxic milieu of the BM, NRF2 enhances the survival rate of HSPCs in the BM of $Nrf2^{-/-}$ mice by preventing their apoptosis.	165
Mice (in vivo, in vitro)	ROS controls the self-renewal, migration, and development of HSCs and the BM microenvironment.	166,167
Mice (in vivo, in vitro)	NADPH oxidase 4 (NOX4) controls HSC function and is downregulated upon HSC differentiation.	89
Mice (in vivo, in vitro)	Pregnancy-related maternal exposure to fine $PM_{2.5}$ causes HSC senescence with preferential disruption of the BM microenvironment, which facilitates the onset of myeloproliferative illness.	52
Duck (in vivo, in vitro)	Cadmium treatment significantly decreases the differentiation of BMSCs and BMMs into osteoblasts and osteoclasts and accelerates apoptosis in vitro via P2X7/PI3K/AKT signaling and the RANKL/OPG pathway, respectively.	93
Blood isolated from human (ex vivo)	Prolonged exposure to biomass smoke increases the risks of osteoporosis and bone resorption in premenopausal women.	94
Human; cohort study	Higher air pollution levels are associated with reduced bone mineral density (BMD) and a greater likelihood of osteoporosis.	151
BM isolated from human (in vitro)	$PM_{2.5}$ decreases the number of BM-MSCs and increases cell death via stress-related cell shrinkage, membrane disruption, and upregulation of inflammatory markers such as TNF-α and IL-6.	95
Human BMSCs, human bronchial epithelial cells, and SD rats	Conditioned medium from $PM_{2.5}$-treated 16HBE (human bronchial epithelial) cells promotes BMSC differentiation into cancer-associated fibroblasts and endothelial-like cells.	101
Rats (in vivo)	Repeated exposure to $PM_{2.5}$ causes disseminated intravascular coagulation.	120
Human; cohort study	Short- and long-term $PM_{2.5}$ exposure cause deep venous thrombosis and hypercoagulability.	119
Human; case-crossover study	Short-term exposure to $PM_{2.5}$ induces venous thromboembolism.	168
Human; crossover study	Diesel exhaust inhalation increases the levels of blood markers of inflammation.	169
Middle-aged mice (time course study)	$PM_{2.5}$ induces local and systemic inflammatory responses, resulting in decreased alveolar area in the lung, and an increased IL-6 level and decreased PON 1 activity in blood.	170
Mice (in vivo, in vitro)	BMD and bone volume decrease after prolonged exposure to organic dust, whereas trabecular spacing, serum IL-6 levels, and number of osteoclasts increase.	158
Human endometrial stem cells (in vitro), mice (in vivo)	$PM_{2.5}$ exposure inhibits self-renewal, transdifferentiation, and migration in vitro and in vivo via the SERPINB2 gene.	171

Exposure to $PM_{2.5}$ and some of its constituents is associated with a reduced hemoglobin level during the third trimester in multiparous pregnancy[23]. The BM is the major source of adult stem cells, mainly hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). This review particularly focuses on the impact of exposure to $PM_{2.5}$ on BM-residing stem cells, especially HSCs and MSCs, and the underlying mechanisms.

HSCs

HSCs are multipotent, self-renewing cells with the ability to differentiate into functional blood cells[24]. Disruption of HSC function can affect hematopoiesis, immune function, and overall health[25]. As multipotent primitive cells, HSCs can develop into all types of blood cells, including myeloid- and lymphoid-lineage cells[26]. Their maintenance is facilitated by a highly specialized niche microenvironment hosting mesenchymal stromal cells, endothelial cells, and megakaryocytes[27]. Blood cells have a high turnover rate and thus form a highly regenerative tissue. HSCs can be divided into long-term (LT)-HSCs, short-term (ST)-HSCs, and multipotent progenitor (MPP) cells. Under normal physiological conditions, LT-HSCs are in a resting state, but in response to stress, they are activated to develop into all lineage blood cells[28,29], ensuring the long-term survival and lifelong hematopoietic function of HSCs.

HSCs undergo self-renewal, replication, and multilineage differentiation. Self-renewal is maintained by asymmetric mitosis[30], in which one of the two daughter cells is an early progenitor cell and the other retains all of the stem cell characteristics. As a result, the number of HSCs remains constant regardless of the number of replication cycles, generating progenitor cells to meet an organism's normal differentiation needs[31,32]. HSCs differentiate into two branches: lymphoid cells and myeloid progenitor cells. Lymphoid progenitor cells further differentiate into T cells, B cells, natural killer (NK) cells, and myeloid progenitor cells can further differentiate into red blood cells, platelets, granulocytes, macrophages, and dendritic cells[33,34]. Given the short lifespan of blood cells, HSCs must continuously differentiate to maintain their populations.

MSCs

MSCs have self-renewal potential and tri-lineage plasticity[35]. The regulation of HSCs is mediated by MSCs, which modulate the BM microenvironment in addition to providing an osteoblastic niche. MSCs express a particular set of markers on their surface, including cluster of differentiation (CD)73, CD90, and CD105, but not CD14, CD34, CD45, and human leukocyte antigen-DR (HLA-DR)[35]. The main sources of MSCs are the BM[36], adipose tissue[37,38], and umbilical cord tissue[39]. BM-MSCs undergo self-renewal and multilineage differentiation[40] into osteocytes, chondrocytes, adipocytes[37,41–44], hepatocytes[45], cardiomyocytes[46], pancreatic cells[47–49], and neuronal cells[50,51]. This differentiation potential of BM-MSCs contributes to modulation of the BM microenvironment, which can affect HSCs in a noncell-autonomous manner. Maternal exposure to $PM_{2.5}$ during pregnancy disrupts the BM microenvironment and causes MSC senescence, followed by the senescence of HSCs and the development of myeloproliferative disease[52].

Mechanism of $PM_{2.5}$ toxicity

The composition and characteristics of $PM_{2.5}$ vary geographically and temporally depending on the source and atmospheric conditions. $PM_{2.5}$ is mainly composed of black carbon[53], polycyclic aromatic hydrocarbons[54,55], aryl hydrocarbons[56], volatile organic hydrocarbons[57], heavy metals[58], organic compounds[59], minerals[60], inorganic ions[61], and biological materials[62]. Elements such as Al, As, Br, Ca, Cl, Cr, Fr, K, Mg, Mn, Na, Pb, Ti, and Zn, as well as sulfate, nitrate, and ammonium ions, are also commonly present in $PM_{2.5}$[63].

There is a relationship between exposure to airborne pollutants and poor human health[52]. In humans, the initial phase of angiohematopoiesis occurs outside of the embryo, in the yolk sac, from approximately 16 days of development[64]. Hematopoiesis is next transiently relayed in the liver before it shifts to the BM. During maternal exposure to $PM_{2.5}$ in pregnancy, the particles directly enter the alveoli of the lungs and penetrate the blood–gas and placental barriers[65], potentially causing premature birth and increasing the risk of mortality of preterm infants[66].

$PM_{2.5}$ can interfere with normal hematopoiesis and has been implicated in leukemia and other hematopoiesis-associated diseases[67]. In mice receiving an intranasal instillation of $PM_{2.5}$ over a period of months, the number of stem cells in the BM decreased[68]. Exposure to $PM_{2.5}$ for 2 weeks was sufficient to impair hematopoiesis in the BM of mice[69]. A summary of investigational studies on the effects of $PM_{2.5}$ is provided in Table 1.

The mechanisms by which $PM_{2.5}$ affect HSPCs and HSCs

Hematopoietic stem and progenitor cells (HSPCs), the progenitors of HSCs in the BM, have the capacity for self-renewal and multilineage differentiation[70]. The regulation of survival, proliferation, differentiation, and migration of HSPCs is essential for hematopoietic hemostasis and therefore the maintenance of mature immune cell generation[71–73].

PM exposure induces the production of ROS and oxidative stress[74,75]. Both oxidative stress and inflammasome activation are enhanced in the BM of $PM_{2.5}$-exposed mice (Fig. 1). In newborn mice, inflammasome activation can be detected in the BM for up to 12 months following $PM_{2.5}$ inhalation, indicating that the particles enter not only the peripheral blood but also the BM[76]. Mice born after maternal $PM_{2.5}$ exposure exhibited a similar number of lineage$^-$Sca-1$^+$c-Kit$^+$ (LSK) cells and HSCs as control mice at 6 months of age, but at 12 months of age, the number of HSCs, but not LSK cells, was significantly increased[76]. LSK cells were highly enriched in HSPCs. In the BM, $PM_{2.5}$ significantly increased the number of HSPCs (1.2-fold), GMPs (2.8-fold), MEPs (1.3-fold), and MkPs (1.7-fold) in wild-type mice but significantly decreased the number of HSPCs (0.8-fold) in Nrf2$^{-/-}$ mice, suggesting that NRF2 regulates HSPC differentiation to myeloid lineages and is involved in the proliferation or survival of HSPCs[77]. The numbers of GMPs, common myeloid progenitor cells (CMPs), MEPs, and common lymphoid progenitor cells (CLPs) in the BM did not differ significantly between newborn $PM_{2.5}$-exposed mice and control mice at 6 months[76]. However, at 12 months, the proportion of myeloid lineage cells was increased, and the proportion of lymphoid lineage cells was reduced[76]. Similarly, tertiary transplanted $PM_{2.5}$-exposed LSK cells in the peripheral blood were shown to consist of a higher proportion of myeloid lineage cells and a lower proportion of lymphoid lineage cells[76]. A similar hematopoietic skewing toward the myeloid lineage occurs in organs repopulated by myeloid-biased (My-bi) HSCs, while skewing toward a lymphoid lineage was observed in the blood, BM, and spleen after repopulation by lymphoid-biased (Ly-bi) HSCs[78]. In another study, mice with low- and high-dose $PM_{2.5}$ exposure exhibited pathological changes in their BM[79]. $PM_{2.5}$ exposure was shown to decrease the proliferation of BM-derived stromal cells by inhibiting the phosphorylation of Akt (without changing apoptosis) and increasing ROS production, both of which were reversed by treatment with N-acetyl-L-cysteine (NAC) (Fig. 1)[80]. However, offspring born from NAC-treated mice showed growth retardation and had a low body weight[52]. A model simulating respiratory tract lining fluid was used to demonstrate the depletion of antioxidants in response to PM exposure[81]. In fetal mice consecutively exposed to 50 μg/m^3 $PM_{2.5}$ during the first 12.5 days of gestation, an increase in the levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG), a major biomarker of oxidative stress, cyclooxygenase-2 (COX-2), and TNF-α, a marker of inflammation, was observed in the lungs at E16.5d. In contrast, there was no increase in mitochondrial ROS levels in the liver-derived HSCs of $PM_{2.5}$-exposed fetal mice because $PM_{2.5}$ inhaled

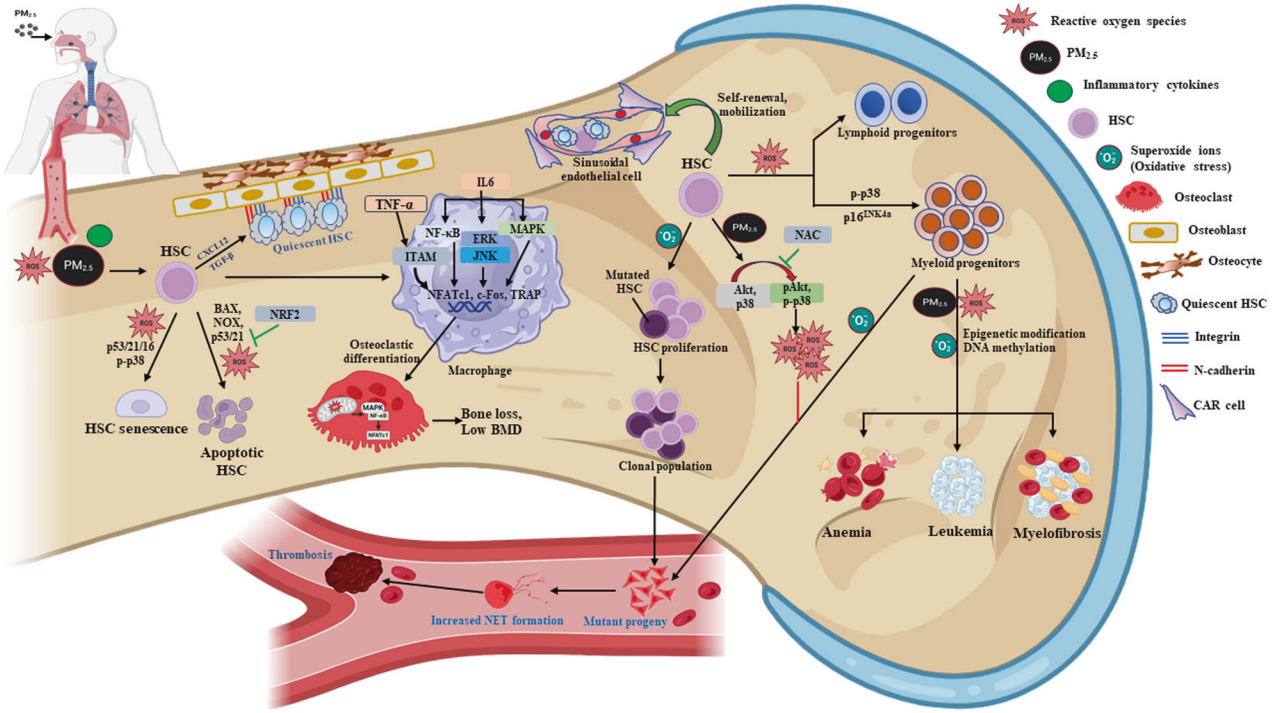

Fig. 1 Mechanism of $PM_{2.5}$ toxicity in BM-conserved HSCs. Inflammatory cytokines, including IL-1β, IL-6, IL-8, and TNF-α, are secreted by bronchial epithelial cells and alveolar macrophages in response to $PM_{2.5}$ exposure. Systemic inflammatory responses are caused by the spread of these inflammatory factors from the lungs to the BM. The concentrations of $PM_{2.5}$ and inflammatory cytokines are increased in the BM. $PM_{2.5}$ inhibits the proliferation of HSCs, causing senescence and apoptosis. The proportion of quiescent HSCs in the BM is ~ 75%. The majority of cells are in G0 phase, and anchoring proteins on the surface of the bone, such as integrin and N-cadherin, as well as cytokines from myeloid stromal cells, such as CXCL12 and TGF-β, control the quiescence of HSCs. ROS, p53, p21, and p-p38 trigger the senescence of HSCs, whereas BAX, NOX, ROS, and p21 trigger their apoptosis. NRF2 inhibits the apoptosis of HSCs caused by $PM_{2.5}$. In the differentiation of HSCs to macrophages, IL-6 promotes osteoclast formation in response to a low level of RANKL by controlling NF-κB, extracellular signal-regulated protein kinase/Jun N-terminal kinase, and mitogen-activated protein kinase signaling pathways, as well as transcription factors downstream of these pathways—nuclear factor-activated T-cell 1 (NFATc1), c-Fos, and tartrate resistance acid phosphatase (TRAP). TNF-α stimulates immunoreceptor tyrosine-based activation motif adaptor protein (ITAM), which promotes the transcription of NFATc1, c-Fos, and TRAP, thereby enhancing osteoclast formation and function in bone resorption. Sinusoidal endothelial (SER) cells supported by CXCL12-abundant reticular (CAR) cells in the BM regulate the proliferation, differentiation, homing, mobilization, and quiescence of HSCs. $PM_{2.5}$ disrupts the function of sinusoid endothelial cells, resulting in a decrease in the self-renewal and proliferation abilities of HSCs and an increase in the number of quiescent HSCs. SER facilitates the differentiation of HSCs into lymphoid and myeloid progenitors. $PM_{2.5}$ disrupts the differentiation of HSCs by decreasing the number of lymphoid progenitors and increasing the number of myeloid progenitors. Few lymphoid progenitors further differentiate into NK, T, and B cells, leading to the failure of immune functions. $PM_{2.5}$ phosphorylates Akt and p38 in HSCs, stimulating the production of ROS and increasing oxidative stress. The increased ROS levels caused by $PM_{2.5}$ exposure promote the excessive proliferation of myeloid progenitors, resulting in leukemia, anemia, and myelofibrosis. Superoxide ions produced by BMSCs cause mutations in HSCs, leading to the production of mutant progeny, which increases neutrophil extracellular trap (NET) formation and causes thromboses in blood vessels.

during pregnancy did not directly affect these cells in the fetus[52]. BM cellularity and the mitochondrial ROS levels of BM HSCs were not significantly altered between control and $PM_{2.5}$-exposed offspring at 2 months, but at 6 months, the BM HSCs in $PM_{2.5}$-exposed offspring had significantly increased levels of mitochondrial ROS and senescence-associated factors, such as senescence-associated beta-galactosidase (SA-β-gal), phospho-p38, and $p16^{INK4a}$, and increased myeloid lineage-biased differentiation, leading to functional defects in clonogenic formation and donor cell-derived repopulation, engraftment, and self-renewal potentials in transplantation experiments. The fact that the senescent phenotype of HSCs induced by maternal $PM_{2.5}$ exposure can be reversed by NAC treatment indicates that it is triggered mainly by oxidative stress[52]. NAC is an antioxidant that reduces the levels of ROS, produces cysteine by deacetylation, and increases glutathione levels, thereby promoting the scavenging of free radicals[82]. Treatment with NAC may reduce the telomere attrition rate associated with senescence, decrease lipid peroxidation, and activate the catalytic subunit of telomerase, thereby preventing the senescence of HSCs[83]. Similar to HSCs from maternal $PM_{2.5}$-exposed offspring, those from newborn $PM_{2.5}$-exposed middle-aged mice showed enhanced levels of mitochondrial ROS and senescence-related functional defects, as evidenced following serial transplantation and irradiation stress[76]. The mechanism is thought to involve a deficiency of telomerase activity, leading to telomere shortening and a reduction in the reconstitution potential of HSCs during transplantation[84]. In human lung epithelial cells, $PM_{2.5}$ causes telomerase shortening and increases the levels of senescence markers[85]. While newborn control LSK cell-transplanted recipient-derived BM cells exhibited radioprotective effects and short-term repopulation of cells and thus almost rescued all of the lethally irradiated recipient mice, newborn $PM_{2.5}$-exposed LSK cell-transplanted recipient-derived BM cells did not exert radioprotective effects on recipient mice, and all of these mice died within 9 weeks of transplantation[76].

Exposure to $PM_{2.5}$ activates the NRF2 pathway[86], a regulator of HSPCs that induces their expansion in response to stress. NRF2 modulates HSPC retention and migration in the BM microenvironment; regulates the proliferation, differentiation, and survival of HSPCs and other progenitors[87]; and plays a role in the

development of myeloid cells from HSCs[88]. The level of NRF2 is increased in the BM HSCs of $PM_{2.5}$-exposed mice and in their offspring at 6 months[52] but is significantly decreased in NRF2-knockout mice[77]. Intracellular ROS levels regulate the survival, proliferation, and differentiation of HSPCs and are critical for maintaining their homeostasis[87,88]. NRF2 increases the survival rate of HSPCs by inhibiting their apoptosis in the BM without changing the level of ROS in the hypoxic microenvironment of the BM[88].

NADPH oxidase (NOX)1, 2, and 4 are expressed in mouse BM LSK cells, whereas HPCs, Lin^- cells, and mononuclear cells from mouse BM express NOX1 and 2, but not NOX4, suggesting that the expression of NOX4 is downregulated upon HSC differentiation and that NOX4 plays an important role in regulating HSC function[89]. The expression levels of NOX4 and the NOX-associated subunits ^{p67phox}, $p47^{phox}$, and $p22^{phox}$ are increased in the heart tissue of $PM_{2.5}$-exposed mice[90]. Elevated ROS levels modulate HSC-specific phosphorylation of p38, limiting the function of HSCs[91]. In maternal $PM_{2.5}$-exposed offspring, p38 expression in HSCs is upregulated. Activation of the p38 pathway contributes to the induction of p16 and cellular senescence in response to other stimuli, including DNA damage resulting from exposure to genotoxic and oxidative stress and telomere shortening due to extensive replication[92]. Compared to the BM cells from control mice, BM cells from newborn $PM_{2.5}$-exposed 12-month-old mice exhibit reduced clonogenicity, involving colony-forming unit (CFU)- induced granulocytes/monocytes, burst-forming-unit-erythrocytes, and CFU-induced erythrocytes/macrophages/megakaryocytes. Maternal exposure to $PM_{2.5}$ during pregnancy selectively affects the BM microenvironment, causing premature aging, with BM HSCs gradually becoming senescent via a noncell autonomous pathway. The mechanisms by which $PM_{2.5}$ affects HSCs are shown in Fig. 1.

The above studies indicate that the effects of $PM_{2.5}$ on mice depend on the age at exposure, with more harmful effects during the embryonic stage than the adult stage. This finding was also shown in a mouse study in which 9 of 25 (36%) 1-year-old maternal $PM_{2.5}$-exposed offspring had a higher propensity to develop a myeloproliferative illness, with enhanced SA-gal activity in MSCs and HSCs observed over time[52].

The mechanisms by which $PM_{2.5}$ affects MSCs

$PM_{2.5}$ changes the BM microenvironment with subsequent effects on HSCs, including the induction of osteoclastogenesis and adipogenesis. The expression levels of runt-related transcription Factor 2 and osteopontin are lower in the BM cells of $PM_{2.5}$-exposed mice than in those of control mice[76]. $PM_{2.5}$-exposed BM cells have low bone mineralization ability and primarily differentiate into osteoclasts, both of which are closely associated with an increase in receptor activator of nuclear factor κB ligand (RANKL) levels and a decrease in osteoprotegerin (OPG) levels[76]. Exposure to cadmium significantly inhibits the differentiation of BMSCs and bone marrow macrophages (BMMs) into osteoblasts and osteoclasts and promotes apoptosis in vitro via P2X7/PI3K/AKT signaling and the RANKL/OPG system[93]. In humans, the serum level of RANKL was increased by 41% and that of OPG was

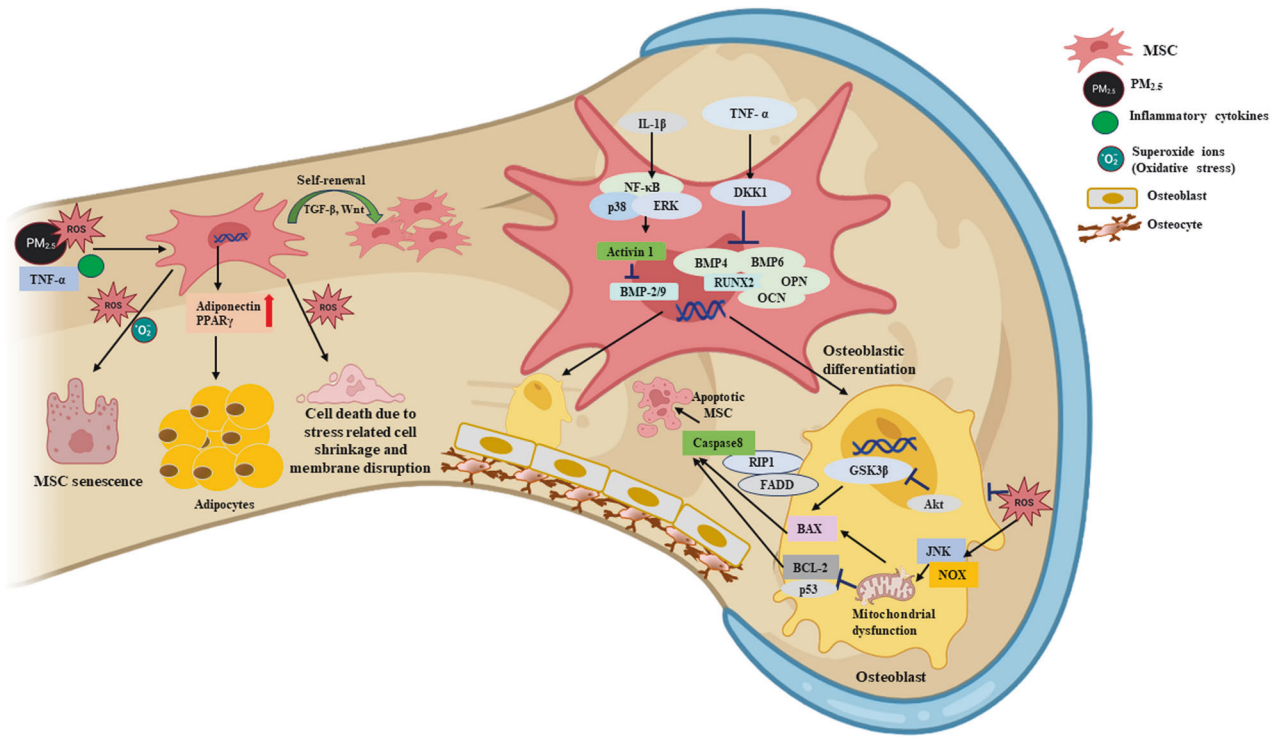

Fig. 2 Mechanism of $PM_{2.5}$ toxicity in BM-conserved MSCs. $PM_{2.5}$ and inflammatory cytokines in bronchial epithelial cells enter the BM via blood vessels. $PM_{2.5}$, inflammatory cytokines, and ROS inhibit the self-renewal and proliferation abilities of MSCs. Under normal conditions, TGF-β and Wnt facilitate the self-renewal of MSCs. ROS and oxidative stress cause the senescence of MSCs and increase their shrinkage and membrane disruption, resulting in MSC death. The production of IL-1β triggered by $PM_{2.5}$ activates NF-κB, p38, and ERK, finally activating the Active 1 protein, which inhibits the transcription of bone morphogenic protein (BMP)-2, BMP-4, and BMP-9. These proteins are essential for the maturation of osteoblasts. TNF-α inhibits the osteogenic differentiation of MSCs by stimulating the production of Dickkopf-related protein 1 (DKK1), thereby inhibiting the transcription of osteocalcin, BMP-4, BMP-6, RUNX-2, and OPN. Furthermore, the ROS produced by MSCs after exposure to $PM_{2.5}$ cause mitochondrial dysfunction via the Jun N-terminal kinase (JNK) and NOX pathways, leading to release of the apoptosis-promoting protein BAX and inhibition of BCL-2 production and the apoptosis of mature osteoblasts via PI3K/Akt/GSK3β signaling. TNF-α may activate FADD and bind to RIP, thereby activating caspase-8 and inducing the apoptosis of MSCs. Exposure of MSCs to $PM_{2.5}$ stimulates the production of adiponectin and PPARγ, thereby increasing the differentiation of MSCs to adipocytes rather than osteocytes.

reduced by 22% among 79 premenopausal women constantly exposed to $PM_{10-2.5}$ biomass compared with control women, suggesting that chronic exposure to biomass smoke increases the risk of bone resorption and osteoporosis[94].

BM-MSCs from $PM_{2.5}$-exposed mice show increased adipogenesis (adiponectin and peroxisome proliferator-activated receptor γ) and senescence[76]. A low concentration of $PM_{2.5}$ increases the proliferation of BM-MSCs in vitro, but an increase in the $PM_{2.5}$ concentration decreases the number of BM-MSCs, induces cellular morphological changes, and increases cell death caused by stress-related cell shrinkage and membrane disruption[95]. In C10 alveolar epithelial cells exposed to 50 μg $PM_{2.5}/cm^3$, the sub-G0/G1 phase is prolonged, indicative of both apoptotic and necrotic cell death[96]. Receptor interacting protein (RIP) and the fas-associated death domain (FADD) complex act in concert with caspase-8 and have been implicated in $PM_{2.5}$-induced apoptosis[96]. Inflammatory markers such as TNF-α and IL-6 are upregulated in response to $PM_{2.5}$[95]. TNF-α and FADD interact with RIP to induce apoptosis[97]. In BM-MSCs treated with 150 μg $PM_{2.5}$/ml, antiapoptotic BCL2 is upregulated, while proapoptotic BAX and the tumor suppressor gene p53 are downregulated[95]. Exposure to $PM_{2.5}$ promotes the secretion of inflammatory cytokines in the respiratory tract[98,99] and promotes BM-MSC differentiation[100] into endothelial-like cells and cancer-associated fibroblasts[101]. The levels of IL-1β, IL-6, and COX-2 mRNAs are increased in $PM_{2.5}$-exposed 16HBE cells. IL-6 is important for inducing the expression of markers of differentiation, such as CD31, von Willebrand factor, α-smooth muscle actin (α-SMA), and fibroblast activation protein (FAP), whereas IL-1β and COX-2 induce the expression of α-SMA and FAP[101]. $PM_{2.5}$ elevates ROS levels via NOX, a key factor in ROS generation[102] that is also elevated in mitochondrial disorders[103]. The mechanisms by which $PM_{2.5}$ affects MSCs are summarized in Fig. 2.

Hematopoiesis and blood disorders related to $PM_{2.5}$

Mesodermal progenitor cells (MPCs) differentiate into CMPs, GMPs, and other oligo-potent or unipotent progenitor cells, which in turn give rise to mature blood cells[104,105]. The effects of $PM_{2.5}$ that have reached the BM affect BM-conserved stem cells. Children in areas with high 24 h $PM_{2.5}$ concentrations (mean 25−50 μg/m^3) have a higher rate of mild to moderate anemia[106], and those in areas with very high 24 h $PM_{2.5}$ (>50 μg/m^3) have a higher rate of moderate to severe anemia[95]. In animal models, $PM_{2.5}$ exposure causes more harmful effects, including BM microenvironment impairment, in young mice than in adolescent mice[68,95]. $PM_{2.5}$ increases ROS production and thus the cellular levels of inflammatory cytokines (TNF-α, IL-1β, and IL-6), which in turn inhibit the differentiation and proliferation of erythroid precursor cells and promote an erythropoietin-resistant state[52,68,95]. Inflammatory cytokines also cause the breakdown of ferroportin by upregulating hepcidin synthesis, thereby reducing iron absorption in the gastrointestinal tract[107,108]. Murine erythrocytes are reportedly deformed in a mice after $PM_{2.5}$ exposure[109]. As in humans, mice exposed to air pollution have an increased risk of anemia, depending on the $PM_{2.5}$ dose and exposure time[95]. Mice exposed to $PM_{2.5}$ for 100 s/day for eight consecutive days have increased erythrocyte distortion, leading to hemolytic anemia (Fig. 1)[109]. Leukemia is a malignant clonal disease characterized by abnormal proliferation and impaired differentiation of HSCs. Exposure to $PM_{2.5}$ injures HSCs in the BM[52] and has been implicated in adult leukemia and childhood hematological malignancy[110,111]. Among the effects of long-term exposure to $PM_{2.5}$ is the alteration of DNA methylation[112]. Molecular epidemiologic studies indicate that DNA methylation of the genes associated with leukemia positively correlates with exposure to environmental toxins[113,114]. DNA methylation involves incorporation of a methyl group at the fifth carbon of cytosine to produce 5-methylcytosine, which is oxidized to 5-hydroxymethylcytosine, a suppressor of gene expression[115,116], which prevents cellular differentiation and thus promotes the development of leukemia. $PM_{2.5}$ is also linked to platelet function[117,118], and deep venous thrombosis and hypercoagulability are associated with long-term (~8 years) exposure to $PM_{2.5}$[119]. The mechanism of $PM_{2.5}$-associated thrombosis involves increases in the levels of inflammatory cytokines, oxidative stress, and platelet activation as well as stimulation of coagulation pathways and reduced fibrinolysis[120–122]. The increased expression levels of inflammatory cytokines, such as IL-6 and IL-1β, in rats exposed to $PM_{2.5}$ induces disseminated intravascular

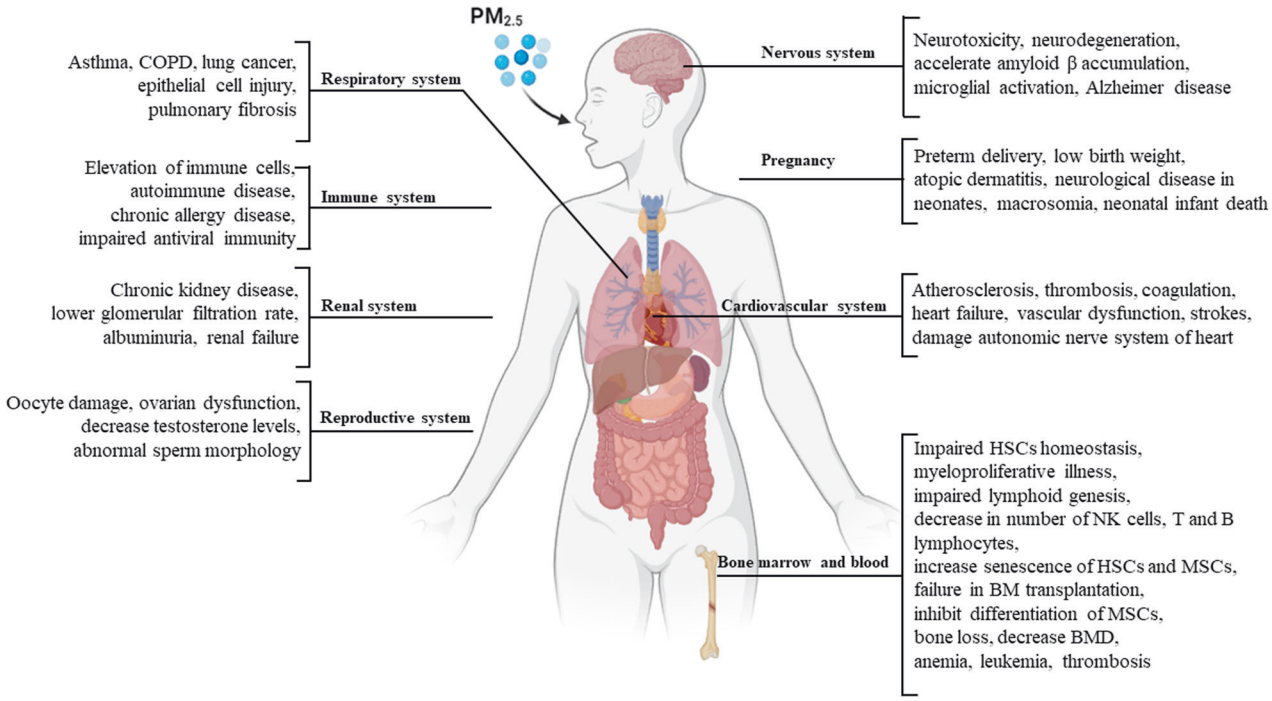

Fig. 3 Effects of $PM_{2.5}$ in humans. Schematic of the effects of $PM_{2.5}$ in humans.

coagulation[120]. The effects of moderate to high doses of $PM_{2.5}$ include the activation of tissue-factor-dependent extrinsic pathways, coagulation, and the upregulation of adhesion molecules, such as vascular cell adhesion molecule 1 and intracellular adhesion molecule 1[118].

Health implications and clinical outcomes

An increase in the incidence and mortality of certain illnesses has been linked to exposure to ambient $PM_{2.5}$. Several studies have reported a high risk of $PM_{2.5}$-related mortality in patients with lung cancer, ischemic heart disease, stroke, chronic obstructive pulmonary disease (COPD), and other disorders worldwide (Fig. 3)[123–128]. One of the main targets of $PM_{2.5}$-induced toxicity is the lung, the first site of $PM_{2.5}$ deposition in the airway. $PM_{2.5}$ causes inflammation in the airways, impairs normal immunological responses in the lung, and increases their susceptibility to several respiratory diseases[7]. First, injury to the bronchial mucociliary system caused by $PM_{2.5}$ suppresses the clearance of foreign particles[8]. Next, lung epithelial cells and fibroblasts undergo apoptosis due to $PM_{2.5}$ exposure, resulting in the disruption of inflammatory cytokine networks, rendering them incapable of communicating through gap junctions. This impairment in cellular communication leads to increased permeability of the lung epithelial barrier, ultimately diminishing its efficacy as a physical component of pulmonary innate immunity[9]. $PM_{2.5}$ reaches the lungs by inhalation and activates immune cells, such as macrophages and neutrophils, which release inflammatory mediators. Fine-tuned regulation of the survival, proliferation, differentiation, and migration of HSPCs is essential for hematopoietic homeostasis, including the normal generation of mature immune cells[71–73]. Excessive exposure to $PM_{2.5}$ causes inflammation and the release of cytokines that act on HSPCs. Type I interferons (e.g., IFN-α) and type II interferons (e.g., IFN-γ) are important for the adaptation of HSPCs to inflammation and drive the proliferation of quiescent HSCs; however, their chronic administration impairs the self-renewal ability of HSCs[129]. This is a result of the induction of DNA damage in HSCs entering the cell cycle, which is linked to an increased mitochondrial membrane potential and mitochondrial production of ROS[130]. IL-1β is also a central mediator of innate immunity and acts directly on HSCs in vitro, promoting their proliferation and differentiation into myeloid lineage cells by activating the transcription factor PU.1. Chronic administration of IL-1β diminished the self-renewal ability of HSCs in a mouse model[131]. HSCs also respond to TNF, which induces their proliferation and directs myeloid lineage differentation in HSCs, thus compromising the repopulation of these cells[132]. The $PM_{2.5}$-induced disruption of HSC maintenance limits the differentiation of HSCs to lymphoid-lineage progenitor cells, leading to deficiencies in NK cells and T and B lymphocytes and thus to an inability to combat infection[133]. $PM_{2.5}$ also disrupts macrophage phagocytosis, increasing susceptibility to infection and inducing chronic lung injury[117]. Air pollution, including $PM_{2.5}$, causes a T-cell imbalance, proinflammatory cytokine production, local pulmonary inflammation, oxidative stress, and methylation changes, all of which underlie the pathogenesis of autoimmune diseases[56]. For example, chronic exposure to $PM_{2.5}$ causes several[134,135] abnormalities linked to the development of type 2 diabetes mellitus (T2DM), adipose inflammation, insulin resistance (IR), and hepatic endoplasmic reticulum (ER) stress. $PM_{2.5}$ has been suggested to modulate ER stress and inflammatory pathways, leading to IR and the development of T2DM[136]. In addition, exposure to $PM_{2.5}$ not only causes subclinical alterations in cardiovascular function but also damages the heart's autonomic nervous system (ANS), which decreases heart rate variability and is inextricably linked to cardiovascular morbidity and mortality[137]. Additionally, $PM_{2.5}$ is linked to the prevalence and development of chronic kidney disease (CKD) and decreases the glomerular filtration rate (GFR)[138]. Maternal prenatal exposure to $PM_{2.5}$ is linked to poor birth outcomes, such as preterm delivery, low birth weight, and neonatal infant death[139–141]. Furthermore, $PM_{2.5}$ influences several other harmful health outcomes, including impaired antiviral immunity, bone loss, liver fibrosis, lung cancer, macrosomia, Alzheimer's disease, and ovarian dysfunction (Fig. 3)[142–148].

Epidemiological and experimental studies

$PM_{2.5}$ has several implications for human health, mainly related to cardiovascular and respiratory diseases and cancer[149]. Long-term exposure to $PM_{2.5}$ was associated with a decline in bone strength among adults in Southwest China[150] and with a decrease in BMD and an increase in the likelihood of osteoporosis[151]. $PM_{2.5}$ at 1 μg/m^3 increased the risk of osteoporosis by 14.6% in 8033 rural residents of Henan Province, China, between July 2015 and September 2017[152]. In several cities in Brazil from 2010 to 2018, long-term exposure to $PM_{2.5}$ was linked to an increase in the mortality rates of a variety of cancers, including bone cancer, and persons older than 60 years had a higher risk of succumbing to bone cancer[153]. Morales-Ancajima et al. evaluated the association between hemoglobin and air pollution in a residential area among 139,368 children (ages 6–35 months). Anemia was detected in 30.8% of the exposed children, and moderate to severe anemia was detected in 8.8%[154]. Honda et al. performed a study involving 4121 older persons with anemia (34.9%) who lived in areas with high annual mean $PM_{2.5}$ levels (>11.1 ± 2.8 μg/m^3). Individuals with 2–5 years of exposure to $PM_{2.5}$ pollution had a mean decline in hemoglobin levels of 0.81 ± 0.06 g/dL[155]. The $PM_{2.5}$ levels in blood samples from adult patients (age 20–71 years) were higher in those with acute myeloid leukemia than in healthy individuals[156]. Exposure of newborn mice to $PM_{2.5}$ induced HSC senescence by causing chronic oxidative stress and inflammasome activation in the BM[76]. Exposure of pregnant mice to $PM_{2.5}$ caused progressive senescence of HSCs as a result of the continuous impairment of the BM microenvironment[52]. $PM_{2.5}$ increases the numbers of systematic inflammatory cells and the risks of associated diseases in adult mice by regulating NRF2-dependent myeloid-biased hematopoiesis[77]. The proliferation of BMSCs is inhibited by $PM_{2.5}$ exposure, leading to their degeneration and death and increasing IL-6 and TNF-α production. The osteoblastic development of BMSCs is suppressed, as is the deposition of extracellular matrix, and TNF-α, IL-6, and IL-11 mRNA levels are elevated upon coculture of chronic lymphoblastic leukemia cells with BMSCs[157]. Continuous exposure to organic dust lowered the bone density and bone volume fraction in mice and increased bone trabecular spacing and the serum IL-6 concentration and number of osteoclasts. The lung-inflammatory-bone axis, which encompasses the systemic IL-6 effector pathway, is involved in inhaled organic dust extract-mediated bone damage in mice[158]. According to Calderon et al., 6-year-old children who lived in locations with high $PM_{2.5}$ pollution levels had decreased bone density and increased IL-6 production compared with those who resided in areas with low $PM_{2.5}$ and air pollution levels[159]. An analysis of 175,959 men and 186,437 women showed that for each 10 μg/m^3 increase in $PM_{2.5}$, men and women had 17% and 14%, respectively, greater likelihoods of an increased platelet count (≥90th percentile)[117].

FUTURE RESEARCH

The effect of $PM_{2.5}$ on the functional integrity of HSCs in the BM is a new avenue of investigation in research on immune disorders and blood cancers induced by $PM_{2.5}$ exposure. However, such studies are complicated by the geographical and temporal variability of $PM_{2.5}$ levels, which makes it difficult to determine individual exposure. Developing strategies for accurate exposure assessment, such as exposure modeling or personal monitoring approaches, would be beneficial. Among the methods through which $PM_{2.5}$ impacts HSCs, inflammation, oxidative stress, and

epigenetic alterations have been examined using cutting-edge experimental methods and molecular investigations. The identification of reliable biomarkers of $PM_{2.5}$-induced adverse effects on HSCs is crucial for monitoring $PM_{2.5}$ exposure in at-risk populations, analyzing $PM_{2.5}$-derived health consequences, and evaluating therapeutic efficacy. The effects of $PM_{2.5}$ on HSCs can be facilitated by animal models that appropriately represent human responses and by in vitro systems that accurately mimic the HSC milieu.

How long-term exposure to $PM_{2.5}$ affects HSCs is another important area of research. Elucidating the impact of $PM_{2.5}$ on the function, self-renewal, and differentiation potential of HSCs and thus on hematopoiesis can provide insights into the mechanism by which blood-related illnesses arise from $PM_{2.5}$ exposure. The epigenetic changes induced by exposure to $PM_{2.5}$ can be examined by studying DNA methylation patterns, histone modifications, and noncoding RNA expression. Epidemiological studies on the relationship between $PM_{2.5}$ exposure and hematological diseases or anomalies in sizable populations are also essential to determine the potential hazards of $PM_{2.5}$ and guide the development of preventative measures. All these areas of investigation should be accompanied by research on therapies and tactics that lessen the harmful effects of $PM_{2.5}$ on HSCs, such as by determining the efficacy of protective agents, therapeutic intervention options, and air pollution reduction initiatives. Identifying susceptible groups, such as people with blood diseases or genetic predispositions, will be essential to develop focused preventative and intervention strategies.

CONCLUSIONS

Studies on the effects of $PM_{2.5}$ on BM-conserved MSCs and HSCs have revealed that exposure alters the BM microenvironment and causes oxidative stress, inflammation, and DNA damage in HSCs, reducing their ability to self-renew and differentiate, thereby leading to abnormal hematopoietic development. The $PM_{2.5}$-mediated functional changes in HSCs impact the immune system and have been implicated in hematological diseases. Similar effects on BM-conserved MSCs, a cell population essential for BM microenvironment maintenance, immunological control, and tissue healing, have been linked to exposure to $PM_{2.5}$. MSC equilibrium can be disrupted by $PM_{2.5}$-induced oxidative stress and inflammation, resulting in decreased proliferation and poor differentiation of these cells together with weakened immunomodulatory capabilities. These results have important ramifications for MSC-mediated tissue regeneration and repair processes. The negative effects of $PM_{2.5}$ on BM-conserved HSCs and MSCs are well established and include disturbances in hematopoiesis, the immune system, and tissue healing mechanisms. The findings summarized in this review highlight the urgent need for mitigation measures aimed at reducing $PM_{2.5}$ pollution, the benefits of which will safeguard the structural and functional integrity of BM stem cells, including their regenerative capability. In addition to elucidating the molecular mechanisms by which $PM_{2.5}$ exerts its detrimental effects on HSCs and MSCs, potential therapeutic interventions, such as antioxidant strategies or anti-inflammatory treatments, require increased research attention. The ability to determine the effects of $PM_{2.5}$ on BM-conserved HSCs and MSCs in humans will encourage the development of strategies to mitigate $PM_{2.5}$ pollution, protect human health, and advance well-being in the face of mounting environmental problems.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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