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REVIEW

Etiology and Pathophysiology

Fine particulate matter induces adipose tissue expansion and weight gain: Pathophysiology

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Summary

Dysregulations in energy balance represent a major driver of obesity. Recent evidence suggests that environmental factors also play a pivotal role in inducing weight gain. Chronic exposure to fine particulate matter ($PM_{2.5}$) is associated with white adipose tissue (WAT) expansion in animals and higher rates of obesity in humans.

This review discusses metabolic adaptions in central and peripheral tissues that promote energy storage and WAT accumulation in $PM_{2.5}$-exposed animals and humans. Chronic $PM_{2.5}$ exposure produces inflammation and leptin resistance in the hypothalamus, decreasing energy expenditure and increasing food intake. $PM_{2.5}$ promotes the conversion of brown adipocytes toward the white phenotype, resulting in decreased energy expenditure. The development of inflammation in WAT can stimulate adipogenesis and hampers catecholamine-induced lipolysis. $PM_{2.5}$ exposure affects the thyroid, reducing the release of thyroxine and tetraiodothyronine. In addition, $PM_{2.5}$ exposure compromises skeletal muscle fitness by inhibiting Nitric oxide (NO)-dependent microvessel dilation and impairing mitochondrial oxidative capacity, with negative effects on energy expenditure.

This evidence suggests that pathological alterations in the hypothalamus, brown adipose tissue, WAT, thyroid, and skeletal muscle can alter energy homeostasis, increasing lipid storage and weight gain in $PM_{2.5}$-exposed animals and humans. Further studies will enrich this pathophysiological model.

KEYWORDS
adipocyte hypertrophy, air pollution, metabolism, obesity

1 | INTRODUCTION

The increasing rates of obesity represent a global health concern.[1] Obesity is a chronic disease caused by genetic, environmental, and psychosocial factors.[2] In the last years, more attention has been focused on the role of environmental factors, such as airborne particulate matter (PM), in altering energy metabolism and promoting weight gain.[3–6]

PM is composed of a mixture of organic and inorganic chemicals, generated from human and natural sources.[7] Fine PM ($PM_{2.5}$; diameter of particles: ≤2.5) represents a large majority of PM in the atmosphere.[8,9] Long-term exposure to $PM_{2.5}$ has a profound impact on health and disrupts metabolic homeostasis.[10] In humans and animals, chronic inhalation of $PM_{2.5}$ triggers insulin resistance, metabolic syndrome, and diabetes.[3,6] In rodent models, exposure to high $PM_{2.5}$

levels induces adipocyte hypertrophy and WAT mass expansion.[11–14] Epidemiological studies demonstrate that individuals chronically exposed to high $PM_{2.5}$ concentrations have higher abdominal adiposity and present an increased risk of developing obesity.[15–17] Recent evidence has highlighted that $PM_{2.5}$ exposure affects central and peripheral tissues involved in regulating energy metabolism.[6,18] Such metabolic adaptions can affect systemic energy balance, redirecting energy substrate toward storage.[18,19]

This review analyzes the detrimental effects of $PM_{2.5}$ on central and peripheral organs that regulate energy homeostasis, in the effort to explain WAT expansion and weight gain in $PM_{2.5}$-exposed animals and humans,

2 | $PM_{2.5}$: COMPOSITION AND TOXICITY

$PM_{2.5}$ consists of carbonaceous nuclei with adsorbed polycyclic aromatic hydrocarbons, endotoxins, and transition metals.[20] In the lungs, $PM_{2.5}$ induces the activation of alveolar macrophages,[21] producing an intense inflammatory response.[6,7] The finest fraction of $PM_{2.5}$ (~0.2 μm) can migrate into the bloodstream by crossing the epithelium–capillary lining; circulating particles are then internalized into peripheral tissues via endocytosis.[6,22] Larger particles (~2 μm) can accumulate in central/peripheral tissues, transported by alveolar macrophages.[23] Organic/inorganic molecules adsorbed to $PM_{2.5}$ surfaces can independently migrate into circulation. In cells, $PM_{2.5}$ directly oxidizes organic molecules and triggers the production of reactive oxygen species (ROS)[7] by interfering with the mitochondrial respiratory chain.[24] ROS activate cellular stress-apoptotic/inflammatory pathways in central and peripheral tissues, augmenting tissue inflammation and causing functional deficit.[6]

3 | ADIPOSE TISSUE AND ENERGY METABOLISM

Adipocytes and immune, stromal, and vascular cells are components of adipose tissue.[25] Adipocytes are plastic cells, which are able to respond to nutritional and body–environment variations by modifying their biological signature.[25,26] Nutritional excess, inflammation, and toxic substances drive adipocytes toward a pro-inflammatory/dysfunctional phenotype.[6,25] A tight cross talk between adipose tissue and central/peripheral organs regulates whole-body metabolic homeostasis.[5,25,27]

White adipocytes are the most abundant cells in WAT, in which they store energy in the form of triglycerides (TGs). A positive energy balance stimulates adipocyte hypertrophy and hyperplasia, producing WAT expansion.[28] Conversely, brown adipocytes can convert TGs into heat[28] through the activation of the uncoupled protein (UCP)-1, increasing whole-body energy expenditure.[28,29] Although brown adipose tissue (BAT) deposits are limited in humans, mitochondria-rich adipocytes (beige) are largely represented in WAT.[29] White and brown/beige adipocytes can mutually switch phenotypes to meet variable body energy needs.[30] Higher energy demands stimulate adipocyte browning,[28] whereas energy excess promotes the conversion of brown adipocytes toward the white phenotype (i.e., whitening).[28,29] Additionally, inflammation can trigger the whitening of brown adipocytes,[6,28,31] compromising the oxidative capacity of BAT.[28,31]

4 | $PM_{2.5}$ EXPOSURE TRIGGERS WAT MASS EXPANSION IN ANIMAL MODELS

Epidemiological evidence suggests that long-term $PM_{2.5}$ exposure is associated with abdominal adiposity and increased risk of obesity.[17,32] In lean and obese mice, chronic $PM_{2.5}$ exposure stimulates adipocyte hypertrophy and WAT accumulation in both subcutaneous and visceral deposits.[11–14,33–35] In WAT of $PM_{2.5}$-exposed rodents, Mendez et al. demonstrated an increased expression of the key lipogenetic markers acetyl-CoA carboxylase (ACC) and diglyceride acyltransferase-2 (DGAT2).[33] Similarly, in $PM_{2.5}$-exposed pair-fed mice, adipocyte hypertrophy and WAT mass expansion occurred along with an increased expression of the pro-adipogenic factors peroxisome proliferator-activated receptor (PPAR)-γ and cAMP response element-binding protein-α (CREB-α).[14]

One hypothesis is that $PM_{2.5}$-associated WAT accumulation results from anxiety-driven overeating.[19,36] Mice exposed to diesel-derived $PM_{2.5}$ in utero show microglial activation, increased anxiety, and higher body weight in adult life, compared with littermate controls.[36] This suggests that prolonged exposure to PM can remodulate the circuits that regulate feeding behavior and energy balance. However, in $PM_{2.5}$-exposed animals, WAT expansion occurred independently to changes in energy intake[12,14,37] and was associated to decreased energy expenditure and inflammation in the hypothalamus, BAT, and WAT.[12,19,38] This provides evidence that $PM_{2.5}$-induced tissue adaptions can contribute to energy balance disruption, WAT accumulation, and weight gain.

5 | $PM_{2.5}$-INDUCED HYPOTHALAMIC INFLAMMATION IMPACTS ENERGY METABOLISM

5.1 | The role of the hypothalamus in regulating energy balance

The hypothalamus regulates systemic energy balance and metabolic efficiency by integrating hormonal, environmental, and neurological signals.[39] Within the medio-basal hypothalamus, specific neuronal populations in the arcuate nucleus (ARC), i.e., pro-opiomelanocortin (POMC) and agouti-related protein (AgRP) neurons, control food intake, with opposite activities.[39] AgRP neurons release neuropeptide Y and stimulate the secretion of orexin and melanin-concentrating hormone, resulting in orexigenic activity/anti-thermogenic effects.[39] By contrast, POMC neurons have anorectic/thermogenic effects. POMC neuronal projections toward the paraventricular nucleus

induce the release of thyrotropin-releasing hormone and corticotrophin-releasing hormone, both with anorectic and thermogenetic properties.[39] The paraventricular nucleus is also important for the activation of BAT thermogenesis.[39] In addition, the ARC controls locomotor activity,[39] and dysfunction in this brain hub can compromise voluntary physical activity in mice.[39] The adipose tissue-derived hormone leptin exerts a central anorectic effect by activating the Janus-activated kinase signal transducer—activator of transcription-3 (JAK-STAT3) signaling in POMC neurons. Similarly, insulin suppresses AgRP and activates POMC neurons, promoting satiety and increasing energy expenditure.[40] Thereby, a proper insulin/leptin sensitivity in the ARC is pivotal for maintaining a proper systemic energy balance.[40]

5.2 | Hypothalamic inflammation disrupts energy homeostasis

Hypothalamic inflammation triggers leptin and insulin resistance,[41,42] suppresses adaptive thermogenesis and energy expenditure,[43] and promotes weight gain.[19,41] In rodents, the activation of the pro-inflammatory factors—inhibitor of nuclear factor kappa-B kinase subunit-β (IKK-β) and nuclear factor kappa-light-chain-enhancer of activated β cells (NF-κβ)—significantly increased food intake and decreased energy expenditure, resulting in weight gain.[44,45] By contrast, the inhibition of the toll-like receptor 4/MyD88 pathway and IKK-β restored leptin signaling and energy expenditure[45,46] and improved metabolic health in obese rodents.[47] Similarly, reversing microglia-induced inflammation in the ARC is sufficient to restore leptin sensitivity, decrease food intake, and reduce WAT mass expansion in high-fat diet-fed rodents.[48] Together, these data show that hypothalamic inflammation can stimulate energy storage and weight gain.

5.3 | $PM_{2.5}$ triggers hypothalamic inflammation

$PM_{2.5}$ exposure triggers inflammation in multiple brain areas.[6,49] Although nanoscale particles can directly cross the blood–brain barrier,[50] $PM_{2.5}$ is thought to cause brain inflammation by (i) inducing inflammation of the olfactory bulb/tract,[51] (ii) altering gut microbiota composition and the gut–brain axis,[51,52] and (iii) upregulating circulating pro-inflammatory mediators[51] (Figure 1). The increased permeability of the blood–brain barrier resulting from systemic inflammation facilitates the migration of antigens and pro-inflammatory molecules into the neuroglial *milieu*.[53] In the hypothalamus, $PM_{2.5}$ induces membrane peroxidation and activates the microglia response.[49,52] $PM_{2.5}$ can also stimulate the expression of tumor necrosis factor (TNF)-α and IKK-β[19] in the hypothalamus and NF-κB in the paraventricular nucleus.[49,54]

5.4 | $PM_{2.5}$-induced hypothalamic inflammation affects energy balance and body weight

$PM_{2.5}$-induced hypothalamic inflammation is associated with leptin resistance, WAT accumulation, and decreased energy expenditure.[19,49] Central leptin resistance increases food intake[19] and decreases BAT-induced thermogenesis in $PM_{2.5}$-exposed rodents.[19,55] Of note, hypothalamic inflammation and leptin resistance preceded WAT accumulation and the decline in energy expenditure,[19] suggesting that hypothalamic inflammation plays a causal role. In addition, $PM_{2.5}$-induced hypothalamic dysfunction can reduce locomotory activity in exposed animals, contributing to the decrease in energy expenditure.[19] Finally, the $PM_{2.5}$-induced increase in cortisol levels[56] can stimulate the differentiation of pre-adipocytes into mature adipocytes, promoting WAT adipogenesis.[57,58]

6 | $PM_{2.5}$-DRIVEN ADIPOSE TISSUE DYSFUNCTION CAN ALTER ENERGY HOMEOSTASIS

$PM_{2.5}$ exposure triggers inflammation and metabolic dysfunction in WAT and BAT.[6] $PM_{2.5}$ can reach the adipose tissue via the bloodstream, although further evidence is needed to explain the mechanism.[6] In addition, pro-inflammatory molecules originating from

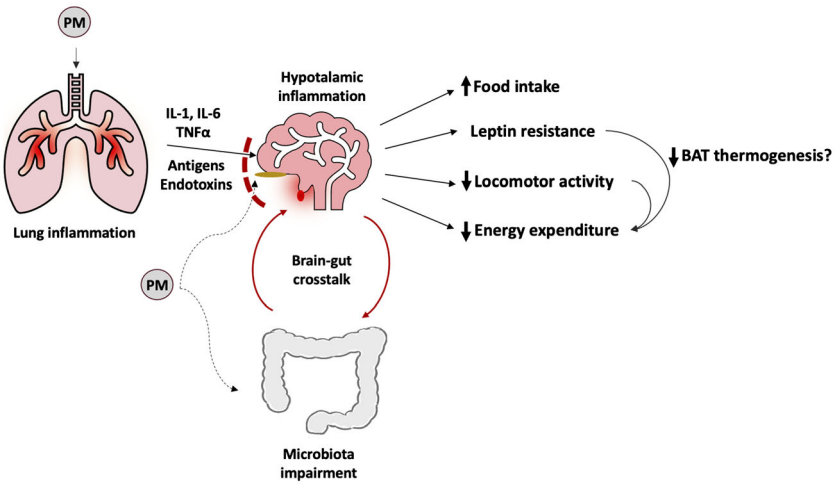

FIGURE 1 $PM_{2.5}$-induced hypothalamic inflammation affects energy balance. BAT, brown adipose tissue; IL, interleukin; PM, particulate matter; TNFα, tumor necrosis factor-α.

central/peripheral tissues can impair WAT and BAT health.[6] $PM_{2.5}$ increases gut permeability,[59,60] allowing the migration of bacterial lipopolysaccharide (LPS) and other pro-inflammatory molecules that stimulate WAT inflammation, adipogenesis, and the whitening of BAT.[61,62] Likewise, pro-inflammatory mediators, ROS, and organic by-products (e.g., oxidized lipids) originating from the airways can enhance inflammation and metabolic dysfunction in WAT and BAT.[6,63]

6.1 | Inflammation in adipose tissue

$PM_{2.5}$ increases oxidative stress and inflammation in adipose tissue[14,64] (Figure 2). Chronic $PM_{2.5}$ exposure induces monocyte infiltration[11,13,65] and macrophage accumulation in both WAT and BAT,[12,13,33,65–68] along with activating the pro-inflammatory pathways: c-Jun n-terminal kinase (JNK) and NF-kB.[6,12,65,69]

The development of inflammation in WAT can modify lipogenetic/lipolytic balance in adipocytes. Oxidative stress and inflammation suppress oxygen consumption, impair lipid metabolism,[70] and stimulate TG storage in white adipocytes.[71] In WAT, increased levels of pro-inflammatory mediators (e.g., TNFα and LPS) can induce mitochondrial dysfunction and increase adipogenesis.[72,73] Chronic inflammation in WAT is associated with impaired lipolysis and decreased energy expenditure.[74] In line with this evidence, pro-inflammatory cytokines such as TNFα have been shown to induce resistance to catecholamine-stimulated lipolysis in white adipocytes.[75] Lastly, chronic inflammation can trigger the whitening of brown/beige adipocytes, with potential negative effects on systemic energy expenditure.[76,77] Of note, in $PM_{2.5}$-exposed mice, the inhibition of the antioxidant transcription factor—nuclear factor erythroid 2-related factor 2 (Nrf-2)—was shown to exacerbate adipocyte hypertrophy,[34] whereas antioxidant administration effectively reverted the process.[14] This suggests a potential role of oxidative stress/inflammation in WAT mass expansion in animals undergoing chronic $PM_{2.5}$ exposure.

6.2 | Mitochondrial impairment

$PM_{2.5}$ exposure has been shown to alter mitochondrial functionality in endothelial cells,[78] cardiomyocytes,[79] skeletal muscle,[80] WAT, and BAT.[81] Reactive constituents of $PM_{2.5}$, ROS, and pro-inflammatory mediators affect mitochondria and respiratory chain complexes.[24,64] $PM_{2.5}$ organic components (e.g., nitrates and aromatic polycycles) disrupt membrane integrity,[82] mitochondrial DNA strands,[83] and mitochondrial fusion/fission processes.[84]

Chronic $PM_{2.5}$ exposure leads to a significant reduction in mitochondrial number and size in WAT and BAT.[7,24,85] $PM_{2.5}$ also suppresses—proliferator-activated receptor gamma coactivator-1-α (PGC-1α) and UCP-1—in both adipose tissues.[12,14,69,81,86] These changes are associated with increased superoxide anions and the upregulation of Nrf-2,[81,86] suggesting a causal role of oxidative stress.

In $PM_{2.5}$-exposed mice, mitochondrial impairment was associated with adipocyte hypertrophy and WAT accumulation.[12,14] The development of mitochondrial dysfunction in WAT and BAT can reroute energy substrates toward accumulation. Mitochondrial dysfunction impairs glucose and lipid oxidation, stimulating TG storage and adipocyte hypertrophy, independently from changes in energy balance.[24,28,33,87] Recent studies show that, in adipocytes treated with a $PM_{2.5}$-rich solution, increased TG storage is associated with impaired β-oxidation in mitochondria[88] and upregulated CREB-α.[89] Importantly, the latter protein was shown to be necessary for the activation of enzymes involved in lipogenesis and TG synthesis in $PM_{2.5}$-treated adipocytes[88,89] (Figure 2).

6.3 | Whitening of brown adipocytes

In $PM_{2.5}$-exposed mice, mitochondrial impairment and the downregulation of UCP-1 and PGC-1α suggest the whitening of brown adipocytes.[14,38,68,81,86,90,91] The switch toward the white phenotype is further corroborated by the decrease in BAT volume and the

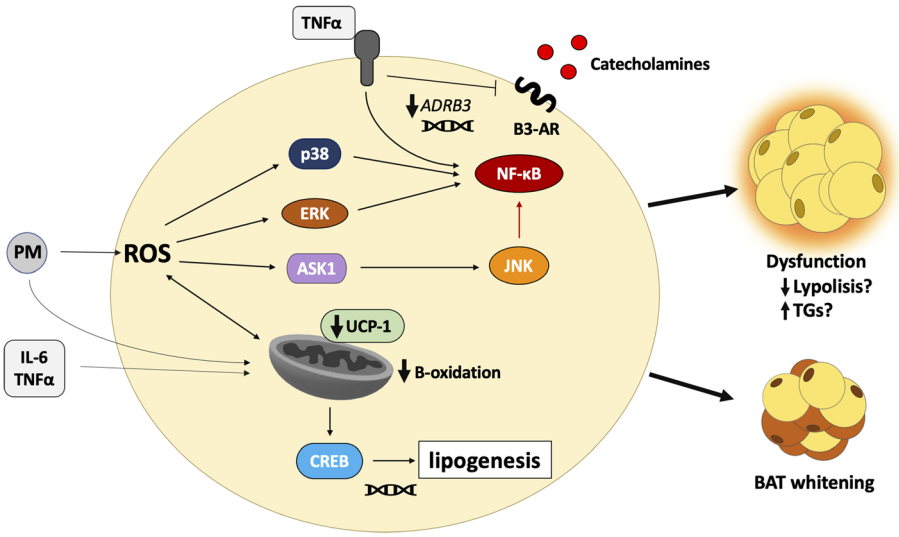

FIGURE 2 Molecular pathways activated in adipose tissue under $PM_{2.5}$ exposure. ROS activate inflammatory pathways and impair mitochondria, stimulating the whitening of BAT. In WAT, increased oxidative stress and inflammation potentially enhance TG synthesis and suppress lipolysis. ADRB3, adrenal receptor B3; ASK, apoptosis signal-regulating kinase 1; B3-AR, B-3 adrenal receptor; BAT, brown adipose tissue; IL-6, interleukin 6; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; p38, p38 mitogen-activated protein kinase; PM, particulate matter; ROS, reactive oxygen species; TGs, triglycerides; TNFα, tumor necrosis factor-α; UCP-1, uncoupling protein-1.

expression of white-specific markers in brown adipocytes.[81,86,91] The whitening of brown adipocytes is probably secondary to increased inflammation in BAT.[6,68,77,90,92] Activated macrophages, TNFα, and the chemokine C-C motif ligand 2 (CCL-2) suppress the browning of adipocyte precursors[93] and downregulate UCP-1 and PGC-1α.[6,94] In addition, thyroid dysfunction and decreased production of thyroxine (T3) and tetraiodothyronine (T4) can drive the whitening of brown adipocytes under chronic $PM_{2.5}$ exposure.[95]

BAT plays a crucial role in regulating energy expenditure and body weight.[96,97] Thus, BAT dysfunction can cause TG accumulation in WAT and weight gain.[28] Brown adipocytes oxidize plasma glucose and fatty free acids (FFAs),[28,29,98,99] opposing diet-induced obesity.[28,98] BAT is also necessary for satiation and diet-induced thermogenesis; catecholamines and several gut-derived hormones participate in the postprandial activation of BAT.[100,101] In addition, beige adipocytes are important for substrate oxidation and contribute to regulating body weight.[28] In line with this evidence, Rajagopalan et al.[38] showed that the reduction of metabolic activity and glucose uptake in BAT was associated with lower energy expenditure rates in chronically $PM_{2.5}$-exposed mice, suggesting a potential role of $PM_{2.5}$-induced BAT dysfunction in weight gain.

7 | $PM_{2.5}$ INHIBITS THYROID FUNCTION

The thyroid is pivotal in regulating energy expenditure and thermoregulation.[39,102] Thyroid dysfunction and decreased T3 and T4 synthesis/release dramatically impact energy expenditure rates, promoting body weight gain and obesity.[39,102]

Epidemiological studies indicate that chronic exposure to high $PM_{2.5}$ levels is associated with altered thyroid functions and reduced T3 and T4 plasma concentrations.[103–107] In rodents, $PM_{2.5}$ exposure has been shown to increase ROS/oxidative stress, stimulating NF-κB expression and producing pathological changes in the thyroid (e.g., augmented follicular cavity size and reduced follicular epithelial cells).[107] Notably, these histopathological alterations were associated with decreased thyroid peroxidase expression and T3 and T4 biosynthesis and release.[107]

8 | $PM_{2.5}$ IMPAIRS SKELETAL MUSCLE FITNESS

Skeletal muscles are major determinants of body energy expenditure,[108] and variations in their metabolic activity play a critical role in the pathogenesis of obesity.[108] Recent studies have shown that chronic $PM_{2.5}$ exposure has detrimental effects on muscle mass and physical performance, especially among the elderly.[109,110] Chronic inflammation and oxidative stress stimulate proteolysis and mitochondrial dysfunction in skeletal muscle.[111–114] Pro-inflammatory mediators (e.g., TNFα) and WAT dysfunction can decrease muscle insulin resistance,[3,111,112,115] which can contribute to myofiber atrophy.[114,115] Finally, $PM_{2.5}$ has been shown to increase sedentary behavior by inducing neurological and cardiorespiratory conditions.[18] The consequential lack of physical activity, in turn, worsens muscle mass/fitness, generating a detrimental cycle.

Available experimental evidence[80,109,116,117] indicates that (i) microvascular alterations and (ii) mitochondrial dysfunction represent key causal factors for the functional impairment of muscles in $PM_{2.5}$-exposed animals and humans.

8.1 | Microvascular alterations

Animal and human studies suggest that both acute and chronic $PM_{2.5}$ exposure impairs muscle microvessel dilation.[109,116,117] $PM_{2.5}$ exposure induces inflammation in endothelial and perivascular smooth muscle cells, stimulating their shift toward a dysfunctional/prothrombotic phenotype.[78,118–120] The $PM_{2.5}$-induced vasodilatory deficit is associated with increased leukocyte adhesion and the expression of markers of oxidative stress and inflammation in microvessels.[117] Endothelial inflammation and the resulting reduction in nitric oxide production[78,118] are likely responsible for the vasodilatory deficit.[78,109] The lack of an effective vasodilatory response to meet increased energy needs affects physical fitness in exposed subjects.[110,116,121–123] Additionally, the long-term vasodilatory deficit and impaired perfusion can contribute to mitochondrial dysfunction, muscle fitness decline,[110,124] and muscle atrophy[110] (Figure 3).

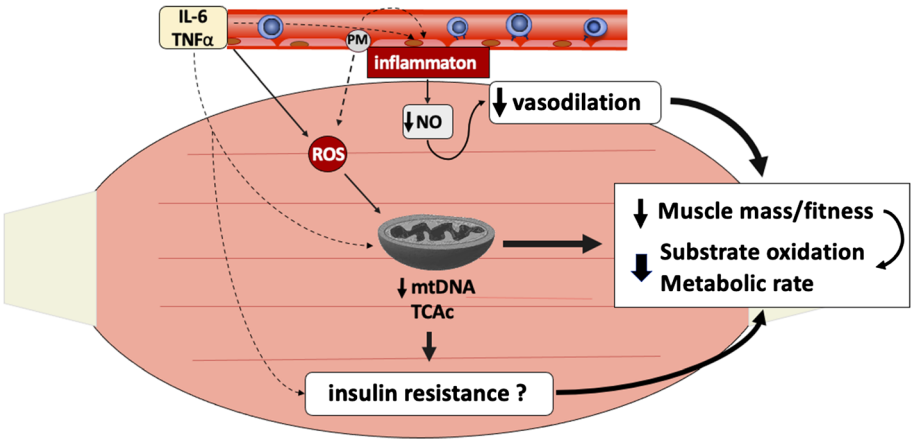

FIGURE 3 $PM_{2.5}$-induced metabolic alterations in skeletal muscle. IL-6, interleukin 6; MtDNA, mitochondrial DNA; NO, nitric oxide; PM, particulate matter; ROS, reactive oxygen species; TCAc, tricarboxylic acid cycle; TNFα, tumor necrosis factor-α.

8.2 | Mitochondrial dysfunction

Efficient mitochondria in skeletal muscle are important for maintaining higher energy expenditure rates.[125,126] Chronic $PM_{2.5}$ exposure induces permanent functional changes in muscle mitochondria.[80] Mice exposed to high $PM_{2.5}$ levels in utero show significantly decreased energy expenditure and levels of mitochondrial DNA, mRNA transcripts, and tricarboxylic acid cycle intermediates during adult life.[80] There is no clear evidence indicating that $PM_{2.5}$ has direct effects on skeletal muscle. In muscle, $PM_{2.5}$-induced mitochondrial dysfunction can be attributed to increased ROS and/or chronic inflammatory status. In line with this hypothesis, some authors have shown that increased oxidative stress impairs muscle oxidative efficiency and inhibits oxidative phosphorylation in mice.[127] In addition, the development of dysfunction in muscle microvasculature can further decrease mitochondrial oxidative capacity.[124,128] The decline in physical activity, under chronic $PM_{2.5}$ exposure, can further affect mitochondrial fitness.[80] Conversely, the reduced oxidative capacity in muscle[108] contributes to decreased physical activity in $PM_{2.5}$-exposed individuals, generating a detrimental cycle.

9 | CONCLUSIONS

The findings discussed show that $PM_{2.5}$-induced pathological alterations in the hypothalamus, thyroid, skeletal muscle, WAT, and BAT can result in increased TG storage and WAT mass expansion in exposed animals and humans (Figure 4). However, the relationship between $PM_{2.5}$ and obesity is still poorly explored. The effects of $PM_{2.5}$ exposure on single organs and the dynamics of hormones and molecular mediators implicated in the control of energy balance still need to be fully elucidated. Further mechanistic insights will enrich this pathophysiological model.

Lifestyle interventions can ameliorate the whole-body inflammatory status, mitigating the negative effects of $PM_{2.5}$ on adipose tissue and metabolic health. The administration of high doses of antioxidant/anti-inflammatory compounds, e.g., hydroxytyrosol and quercetin, effectively reduce adipocyte hypertrophy,[14] WAT mass expansion,[14,129] and weight gain[129] in $PM_{2.5}$-exposed rodents. Antioxidant supplements also decrease WAT inflammation and increase UCP-1 expression in BAT,[14] improving whole-body metabolic homeostasis.[14,129] Further evidence also shows that regular training is effective in decreasing visceral WAT mass and improving inflammation in $PM_{2.5}$-exposed rodents.[130] Future studies should assess the regulatory effect of exercise on WAT under $PM_{2.5}$ exposure because the negative consequences of exercising in highly polluted areas could possibly outweigh the health benefits. The epidemic of obesity and the alarming levels of air pollution worldwide warrant further investigations on the relationships between $PM_{2.5}$ and obesity.

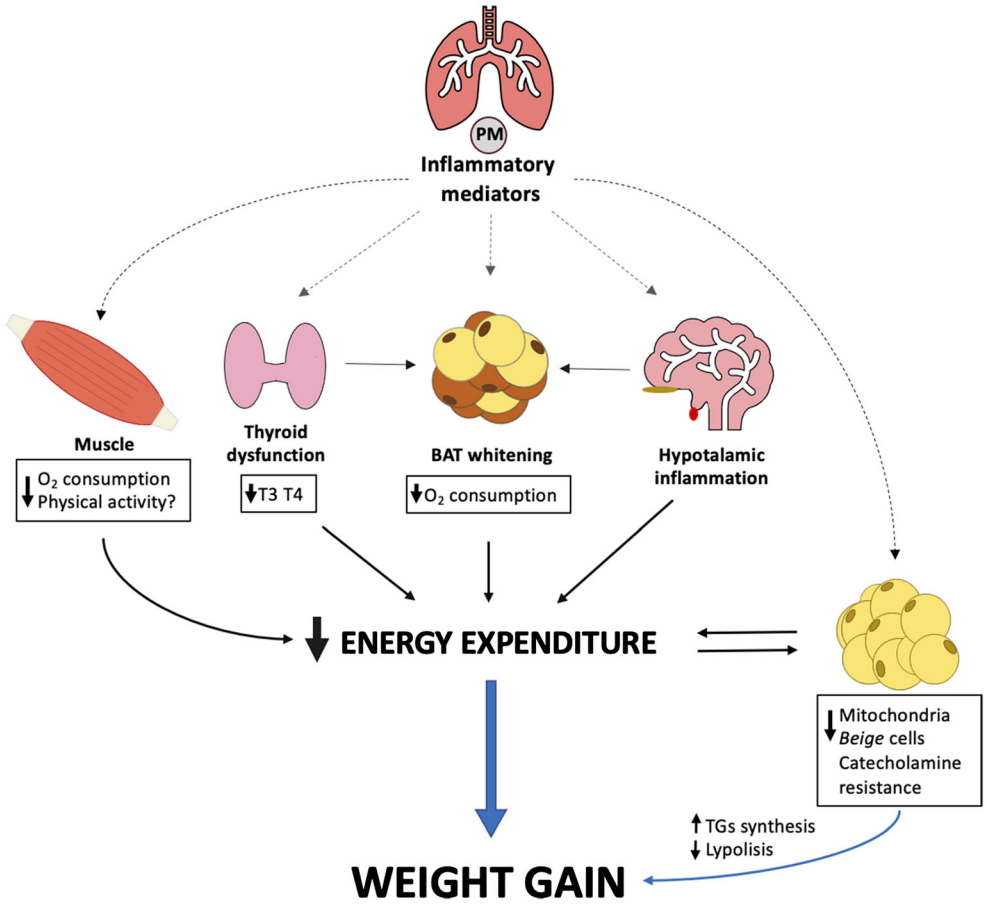

FIGURE 4 Synoptical scheme showing the pathophysiological mechanisms discussed. BAT, brown adipose tissue; T3, thyroxine; T4, tetraiodothyronine; TGs, triglycerides.

10 | RESEARCH STRATEGY

An extensive search was carried out on Medline, Scopus, Embase, and Web of Science to identify eligible articles to discuss. The language was restricted to English. The search strategy was assessed by alternatively combining the keywords "adipose tissue," "adipocytes," "obesity," "metabolism," "weight gain," "overweight," "obesity," "body mass index," "energy expenditure," "hypothalamus," "skeletal muscle," "thyroid," "organs," "tissues," "mitochondria," "waist circumference," "inflammation," "PM," "particulate matter," "air pollution," and "pollutants." Full text articles of studies reporting appropriate methodologies were considered. To elucidate the mechanisms, experimental data investigating the effects of fine PM (diameter of particles: ≤2.5 μm) in rodents have been discussed. Data from controlled human studies were considered to elucidate the effects of $PM_{2.5}$ on cortisol and skeletal muscle vasculature.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Lucio Della Guardia conceived the work, collected data, and drafted the manuscript. Ling Wang revised and edited the manuscript.

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