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大气颗粒物对呼吸系统的毒性作用和致病机制研究进展

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摘　要

大气颗粒物是空气污染的重要组成部分，可导致各类呼吸系统疾病，研究表明颗粒物能够通过减弱呼吸系统防御功能、引起氧化应激和炎症、改变表观遗传等方式致病。本文就大气颗粒物对呼吸系统的毒性作用及致病机制方面的研究进展作一综述。

关键词

大气颗粒物，呼吸系统，防御功能，氧化应激，炎症，表观遗传

Research Progress on the Toxic Effect and Pathogenic Mechanism of Atmospheric Particulate Matter on Respiratory System

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Abstract

Atmospheric particulate matter is an important part of air pollution and can lead to various

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respiratory diseases. Studies have shown that particulate matter can cause disease by weakening the defense function of respiratory system, causing oxidative stress and inflammation, changing epigenetics and so on. This paper reviews the research progress of toxic effect and pathogenic mechanism of atmospheric particulate matter on respiratory system.

Keywords

Atmospheric Particulate Matter, Respiratory System, Defense Function, Oxidative Stress, Inflammation, Epigenetics

1. 引言

空气污染使人类许多疾病的发病率和死亡率增加，颗粒物(Particulate Matter, PM)作为空气污染的主要成分对疾病的影响格外突出，根据 2019 年全球疾病负担研究结果，颗粒物污染是世界前五的死亡风险因素之一[1]。悬浮于大气中的液态或固态颗粒统称为大气颗粒物，可由工业或家用燃料燃烧、交通工具运行、采矿、建筑施工等人类活动产生，或由土壤、海浪、沙尘暴、火山、森林大火等自然来源产生。多种气态污染物(氮氧化物、硫氧化物、氨和挥发性有机物等)在大气中经过一系列光化学反应可成为颗粒物的二次来源[2]。颗粒物的成分复杂，包含碳质组分、硝酸盐、硫酸盐、金属(如铁、铜、镍、锌和钒)、多环芳烃和内毒素等物质[3]。一般按照颗粒物的直径对其进行分类：直径 < 10 μm 为 PM10；直径 < 2.5 μm 为 PM2.5；直径 < 0.1 μm 为 PM0.1。粗颗粒的直径在 2.5 μm 到 10 μm，通常沉积于上呼吸道引起咳嗽和黏液分泌增加。细颗粒的直径小于 2.5 μm，容易避开气管纤毛的过滤机制进入肺泡，而超细颗粒即 PM0.1 能够穿过肺泡－毛细血管膜，通过血液循环引起全身毒性[4]。颗粒物与多种呼吸系统疾病如哮喘、慢性阻塞性肺疾病(COPD)、肺肿瘤等的发生及恶化息息相关[5]。本文着重总结了颗粒物对呼吸系统防御结构的毒性作用，从氧化应激、炎症、表观遗传三方面梳理了近些年颗粒物致病机制方面的进展，旨在提高对颗粒物健康危害性的全面认识，并探讨亟待研究的科学问题。

2. 颗粒物与呼吸系统疾病

大量流行病学证据表明，暴露于大气颗粒物的人群易患呼吸系统疾病。一项横断面研究发现，在上海市成年永久居民人群中，长期高浓度颗粒物暴露与肺功能下降相关，年平均 PM2.5 暴露量每增加 10 μg/m^3，用力肺活量(FVC)降低 45.83 mL (95% CI: −82.59, −9.07)，肺活量(VC)降低 89.12 mL (95% CI: −124.94, −53.3) [6]。Tian, Qi [7]构建了单一污染物模型，模型提示不同滞后天数观察到的 PM2.5 浓度和 COPD 死亡率有明显关联，其中当日 PM2.5 浓度的相关性最强，每增加 10 μg/m^3，COPD 死亡率增加 0.16% (95% CI: 0.08%, 0.25%)。Liang, Cai [8]应用广义加性泊松时间序列模型进行统计，得到北京的 PM2.5 浓度升高与 COPD 急性加重住院显著相关。Yang, Chu [9]在东北七座城市招募了 5 万余名儿童，发现 PM1 和 PM2.5 的暴露水平与儿童哮喘发生和哮喘相关症状(喘息、持续性咳嗽等)存在正相关。在湖北，一项研究调查了 4 千余名死于哮喘的个体，结果提示短期暴露于 PM2.5 可能增加哮喘的死亡风险[10]。Zhang, Chai [11]用回归模型分析得出，随着宁波鄞州地区 PM2.5 和 PM2.5~10 的每日平均浓度增加，急性上呼吸道感染、肺炎等疾病的就诊次数相应增加。颗粒物暴露与肺癌发生也存在联系，Han, Liu [12]认为 PM2.5

浓度与肺癌发病率之间存在很强的空间关联，例如京津冀等地既是 PM2.5 的严重污染区，也是癌症的高发病率区。Song, He [13]用归因分数衡量颗粒物对疾病死亡率的贡献，结果表明 2015 年中国环境 PM2.5 对肺癌死亡的贡献高达 23.9%。

在中国，大量人群因吸入颗粒物而面临呼吸系统健康受损的风险，扩大到世界范围，颗粒物暴露与 COPD、哮喘、肺炎、肺癌等疾病的关联也是显著的，因此吸入颗粒物暴露应当成为全球社会关注的严重问题。

3. 颗粒物损伤呼吸系统的防御功能

呼吸系统通过多层次的防御机制保护机体免受外界侵害。颗粒物暴露可系统性破坏这些防御功能，本部分将从物理屏障防御和免疫防御两个维度阐述其损伤机制。

3.1. 物理屏障防御功能缺陷

物理屏障防御机体抵御病原体入侵呼吸系统的第一道防线，其功能主要包括黏液纤毛清除机制、上皮屏障、气道表面液及防御性呼吸反射等[14] [15]。

黏液和纤毛可以阻挡和排出呼吸道异物，使病原体不易在呼吸道沉积，而颗粒物能够削弱黏液纤毛的清除机制。Goto, Lanca [16]观察到工人暴露于生物质燃料烟雾后，其鼻黏膜的纤毛转运能力减弱，颗粒物对线粒体功能的损伤可能引起纤毛拨动异常[17]。PM2.5 有机提取物(OE)对气道上皮的慢性刺激能使 MUC5AC + 黏液分泌细胞扩增，导致黏蛋白分泌增多[18]。表皮生长因子受体(EGFR)的下游途径激活[19] [20]、细胞的自噬过程[21]可促进 MUC5AC 黏液分泌。

上皮屏障的形成有赖于多种连接蛋白对细胞间隙的封闭。在颗粒物暴露条件下，ZO-1、occludin 和 claudin-1 等连接蛋白的表达量减少，导致气道上皮屏障被削弱[22] [23]。消除细胞内的活性氧有助于恢复连接蛋白数量，提前激活细胞内的 Nrf2 [24]，或者阻断 PI3K 信号通路[25]，也可以减少颗粒物对上皮屏障的破坏。

气道表面液覆盖在气道上皮细胞表面，含有抗菌肽、抗氧化剂、抗氧化酶、补体、免疫球蛋白等多种物质，具有抗菌和抗氧化作用。颗粒物表面常带有负电荷，能够吸附抗菌肽形成复合物，干扰抗菌肽发挥作用[26]。此外，颗粒物还能减少由细菌诱导的抗菌肽表达[27]，进一步降低了气道表面液的抗菌活性。

防御性呼吸反射包括咳嗽和喷嚏，两者都能够清除气道的刺激物。有研究发现，柴油机尾气颗粒(DEP)可以激活豚鼠化学敏感性 C 纤维和人迷走神经，从而导致机体出现过度咳嗽[28]。Lv, Yue [29]则证明辣椒素受体(TRPV1)参与了咳嗽过敏的调节过程，阻断该受体可以缓解颗粒物引起的咳嗽过敏和神经源性炎症。

颗粒物还能促进病原体粘附于气道上皮。Mushtaq, Ezzati [30]发现城市颗粒物(UPM)增强了肺炎链球菌对人气道上皮细胞的粘附，运用抗氧化剂可以逆转细菌粘附力增强。Liu, Lee [31]证明颗粒物上调鼻病毒和呼吸道合胞病毒的受体 ICAM-1，促进病毒粘附于气道上皮，ICAM-1 的表达增加由 IL-6/AKT/STAT3/NF-κB 信号通路参与调节。

3.2. 免疫防御功能紊乱

呼吸道中分布着多种免疫细胞，他们是发挥气道免疫防御功能的主力军，它们的数量和功能对于抑制和杀灭病原体至关重要。颗粒物可以引起各类呼吸道免疫细胞的功能失调和数量异常[32]-[35]，从而扰乱呼吸系统免疫稳态，这也是颗粒物诱发气道和肺部疾病的重要原因。

肺巨噬细胞在呼吸道免疫防御中扮演着关键角色，其功能状态直接影响颗粒物诱导的肺部病理进程。

根据目前研究进展表明，颗粒物暴露可以影响肺巨噬细胞数量并损害其吞噬能力。Su, Jin [36]研究证实，PM2.5 暴露通过激活氧化应激依赖的 PI3K/AKT/mTOR 信号通路，以浓度依赖方式诱导肺巨噬细胞自噬，从而导致肺泡巨噬细胞数量显著减少。并有研究进一步证实，PM2.5 暴露可显著削弱小鼠巨噬细胞的吞噬功能。如 PM2.5 不仅直接抑制巨噬细胞对肺炎链球菌的吞噬活性，同时通过下调诱导型一氧化氮合酶(iNOS)的表达，减少一氧化氮(NO)的生成，从而双重削弱巨噬细胞对肺部病原体的清除能力[37]。巨噬细胞具有 M1 和 M2 两种亚型，M1 细胞有很强的抗原呈递能力，也可产生促炎细胞因子介导炎症反应。M2 细胞促进适应性免疫，调节血管生成、组织重塑及伤口愈合，表现出抗炎功能。Zhao, Chen [38]发现 PM2.5 有助于巨噬细胞向促进炎症的 M1 极化，但阻碍其向抑制炎症的 M2 分化。综合上述研究结果，从分子机制角度阐明了 PM2.5 损害肺部固有免疫防御的多重途径：1) 通过诱导巨噬细胞自噬性死亡导致其数量减少；2) 抑制吞噬功能及 iNOS/NO 抗菌通路；3) 干扰 M1/M2 极化平衡。这些发现系统揭示了 PM2.5 通过多靶点作用削弱呼吸道免疫防御功能的分子基础。

T 淋巴细胞在免疫应答中表现出显著的功能异质性，其不同亚群通过特异性免疫调节机制参与宿主防御。研究表明，环境颗粒物暴露可显著干扰辅助性 T 细胞(Th 细胞)亚群的分化稳态，导致 Th 细胞亚群的比例失衡，如在小鼠及大鼠模型中，颗粒物可以上调 Th2 细胞和 Th17 细胞比例，却减少了 T 细胞向 Th1 方向的分化[39]-[41]。而 Th2 与常见的嗜酸性粒细胞性哮喘相关[42]，Th17 则与较难控制的中性粒细胞性哮喘有关，颗粒物暴露后 Th 亚群的失衡或许可以解释颗粒物相关的哮喘发生。我们团队研究发现孕期小鼠暴露于颗粒物可影响子代 Th1 和 Th17 细胞的发育和成熟，增加子代哮喘发生风险[43]。而成年期哮喘小鼠暴露于含持续氧自由基的颗粒物后可增加气道氧化应激反应，增加肺 Th17 细胞和气道中性粒细胞浸润水平[44]，降低对激素治疗的敏感性。

中性粒细胞作为先天免疫系统的关键效应细胞，在宿主防御和组织修复过程中发挥着重要作用。研究表明，颗粒物暴露可通过显著上调促炎细胞因子(IL-1β、IL-6、TNF-α)及趋化因子(CXCL1、CXCL2 等)的表达，促进中性粒细胞–内皮细胞相互作用，最终导致中性粒细胞在肺组织异常募集，形成特征性的中性粒细胞性炎症微环境。值得注意的是，这种颗粒物诱导的中性粒细胞性炎症不仅参与经典的免疫防御反应，更通过破坏血–气屏障完整性、促进基质重塑和建立免疫抑制性微环境等多重机制，为肿瘤细胞肺转移创造了有利条件，显著提高了肿瘤细胞在肺部的定植和转移效率，为理解颗粒物暴露与肿瘤转移的关系提供了新的理论依据[45] [46]。

4. 颗粒物致病的生物学机制

4.1. 氧化应激

氧化应激是指机体在受到各种有害刺激时，细胞内的活性氧(ROS)和活性氮(RNS)生成增加，远超出细胞对其的清除能力[47]。各类细胞和动物模型在暴露于颗粒物后出现了 ROS 生成增多[48] [49]。ROS 的过度生成源于颗粒物和细胞本身。颗粒物中存在着大量 ROS [50] [51]，同时颗粒物中含有的其他物质也可促进 ROS 生成，如过渡金属通过类芬顿反应诱导 ROS 产生[52]，多环芳烃和醌类物质则通过生物转化和氧化还原循环诱导 ROS 生成[53]。正常生理状态下，细胞内的线粒体、过氧化物酶体以及各种细胞溶质酶系统可产生一部分 ROS。颗粒物能引起线粒体超微结构改变和功能紊乱[54] [55]，并能提高 NADPH 氧化酶的活性[56]，由此增加了细胞内的 ROS 生成。

颗粒物诱导的氧化应激可以影响细胞功能。研究者们通常用抗氧化剂或抗氧化酶减轻颗粒物引起的细胞内氧化应激，并观察去除 ROS 后细胞的某项功能变化，以此判断氧化应激是否参与调节该项功能。Tripathi, Deng [57]由此证明氧化应激影响 ADAM33、DPP10、ORMDL3 和炎症因子(IL-6、TNF、CSF2、TSLP、PTGS2 和 IL4R)相关基因的表达，先前的研究提示这些基因与哮喘和 COPD 等呼吸系统疾病有关。

除了影响疾病相关基因的表达，氧化应激还能调节凋亡、炎症、生长和增殖等其他细胞功能。例如 PM2.5 诱导的 ROS 可增强 caspase-9 活性[58]，也可激活细胞凋亡信号通路(促进 ASK1、p38 MAPK 和 JUK 的磷酸化)，通过这两种途径 ROS 使得人肺泡上皮细胞中的 DNA 片段化增加，最终促使细胞凋亡[59]。氧化应激对炎症具有触发作用，Wang, Huang [60]证明颗粒物上调的 ROS 刺激人支气管上皮细胞释放 IL-1β、IL-6、IL-8、MMP-9 和 COX-2 等促炎因子，而使用抗氧化剂拮抗 ROS 生成后发现，MAPK/NF-Kb 和 PI3K/Akt 通路激活诱导的 IL-8 和 IL-1β 表达也明显降低[61]，证明 ROSMAPK/NF-Kb 和 PI3K/Akt 通路共同调控炎症的发生。值得注意的是 MAPK/ERK 和 PI3K/AKT 通路还能够调节细胞的生长和增殖[62]，与肿瘤的发生发展有着密切联系，颗粒物引起的氧化应激极有可能通过这两条通路诱导细胞癌变。

持续的氧化应激会对细胞的重要结构造成损伤和破坏。8-OH-dG 和 8-oxodGuo 是核 DNA 或线粒体 DNA 被氧化后形成的产物，可以作为氧化性 DNA 损伤的标志物。暴露于 PM2.5 后，人支气管上皮细胞和小鼠的 DNA 中都出现了上述标志物的增加[63] [64]，反应了氧化应激对 DNA 的损害。细胞的 DNA 损伤如果影响到原癌基因或者抑癌基因的表达，将会大大增加细胞癌变的可能性。另外，ROS 可以对其他细胞成分如膜脂、蛋白质、碳水化合物、酶等造成氧化损伤[65]，鲜有研究探索这些物质的改变与疾病的关联。

4.2. 炎症

呼吸系统在暴露于颗粒物后常会发生炎症反应，表现为炎症细胞和细胞因子的浸润[66]-[70]。颗粒物对气道和肺部炎症的诱发是通过多种途径实现的。上文提及的氧化应激是途径之一，细胞内过度生成的 ROS 激活了下游的信号通路，最终引起炎症因子的表达改变。颗粒物的促炎方式还可以是非 ROS 依赖的，Zhao, Usatyuk [71]发现颗粒物能够激活转录调节因子 C/EBPβ，从而促进人支气管上皮细胞中 COX-2 和 IL-6 的表达。内吞摄取机制也是一种非 ROS 依赖方式，Yan, Wang [72]观察到 PM2.5 可以刺激人支气管上皮细胞生成 ROS，诱导氧化应激反应，并联合内吞作用刺激细胞产生和分泌 IL-8。此外，微生物模式识别受体(PRR)和 EGFR 在被激活状态下也能影响细胞的促炎因子分泌，运用两种受体所对应的拮抗剂对受体进行阻断，都能使气道上皮细胞的 IL-8 释放减少[73] [74]，然而颗粒物中的何种成分激动了受体仍是未知的。

适度的炎症是机体清除颗粒物所必需的，但炎症持续存在则会对呼吸系统造成不良影响，许多研究阐明了炎症对于呼吸系统疾病的作用。Ramos, Cisneros [75]将豚鼠暴露于木烟，随后其肺部出现了巨噬细胞的数量增多、基质金属蛋白酶(MMP)的活性增强和表达增加，这会促使细胞外基质的弹性蛋白和胶质蛋白分解，推动肺气肿的发生。在另一方面，多种细胞因子和趋化因子如 TNF-α、IL-1β、IL-6、IL-10、IL-17A、GM-CSF、CXCL8 等，在 COPD 的发展中至关重要[76]，颗粒物引起这类炎症因子分泌增加可能会导致 COPD 的出现和加重。对于哮喘而言，颗粒物诱发的炎症能够加深其严重程度。在过敏小鼠模型中，颗粒物使气道的炎症细胞、IgE、IL-17、IL-21 和中性粒细胞趋化因子浸润增加，炎症的加重加剧了小鼠的气道高反应性并刺激气道分泌更多的黏蛋白[77] [78]。炎症还有可能促进肿瘤进展，有文献指出 IL-6 在肿瘤的增殖、迁移和粘附中发挥重要作用，并且可能改变脂质和蛋白质代谢来诱发肿瘤相关恶病质[79]，颗粒物或许是通过诱导肺内 IL-6 表达，继而参与到肺癌的发生发展过程中。

4.3. 表观遗传

表观遗传具有联系动态环境和遗传基因组的功能，当细胞受到外界环境刺激时，DNA 甲基化、组蛋白修饰和 miRNA 等表观遗传方式发生变化，能够进一步调节细胞的基因表达，影响各类疾病的发生、发展以及预后[80]-[83]。

颗粒物可使与呼吸系统疾病有关的基因出现 DNA 甲基化改变。特定基因甲基化的增加或减少对疾

病有着截然不同的影响，然而在颗粒物的作用下，甲基化改变的方向对疾病的影响往往是负性的。HDAC9和CCR6基因的甲基化水平降低分别与Treg抑制能力下降和Th17募集增加有关，可能会引起哮喘的恶化。受试者在暴露于DEP后被检测出了这两种基因的甲基化减少[84]。与HDAC9和CCR6基因不同，Foxp3基因的甲基化水平升高会导致哮喘的加剧，而另一项实验恰恰证明了颗粒物暴露能使该基因的甲基化程度增加而非减少[85]。由上述结论可以推测，颗粒物具有多种调节DNA甲基化的方式，但具体的调节机制有待进一步研究。除了与炎症和免疫相关的基因，抑癌基因和DNA损伤修复基因也受到颗粒物的调节，颗粒物能够引起这类基因的甲基化水平升高、表达水平降低，这可能会导致肺癌的发生和进展。例如，p16是一种抑癌基因，其编码的p16蛋白能够抑制CDK4和CDK6，阻止细胞进行恶性增殖。PARP1基因则编码了碱基切除修复所需的酶，参与DNA损伤的修复过程。有研究表明，颗粒物可以增加p16和PARP1基因的甲基化，不利于其发挥原有的抗癌作用[86]-[88]。实际上，调控呼吸系统疾病的基因数量众多，而颗粒物对这些基因甲基化及表达的影响并未被彻底研究，因此该领域可成为未来研究的方向。

颗粒物也能引起多种miRNA的表达水平改变，这种表观遗传改变同样具有致病意义。受颗粒物调节的miRNA能够影响各类生理机制，如细胞的增殖和凋亡、自噬、异生物质代谢、DNA修复以及炎症调节等，而生理机制的紊乱则可诱发呼吸系统疾病。以调控异生物质代谢的miRNA为例，它的失调会降低细胞对多环芳烃的解毒能力，使细胞内DNA损伤积累，易于发生癌变[89]。此外，一些miRNA与疾病的联系已被证实，对照miRNA疾病数据库可以发现，被颗粒物上调或下调的miRNA与肺癌、哮喘、间质性肺疾病和肺栓塞等疾病有关[90]。

目前已有研究证明，颗粒物对特定的酶如DNA甲基转移酶(DNMT)，组蛋白去乙酰化酶(HDAC) [91]等具有调节作用，从而影响到DNA甲基化、miRNA表达和组蛋白修饰，但更为具体的调节机制亟需进一步探索。

5. 总结与展望

如上所述，大气颗粒物暴露可引发和加剧各类呼吸系统疾病，是一个严重的公共卫生问题。本文总结了颗粒物引起呼吸系统疾病的可能机制，比如气道上皮防御功能的破坏，使呼吸道更易受到病原体的侵袭。免疫细胞的失调与持续性气道炎症有关，也是哮喘发生的重要因素。氧化应激既能使多项细胞功能紊乱，又能对细胞内生物大分子造成损伤。颗粒物对气道及肺部炎症的启动方式有很多，这类炎症往往会导致呼吸道疾病。表观遗传连接了环境变化和基因表达，使颗粒物从基因水平上对细胞功能进行调节。基于上述致病机制，针对大气颗粒物诱发的呼吸系统疾病可采取多靶点干预策略。抗氧化治疗、细胞因子抑制和表观遗传调控等针对性干预手段，有望从分子层面缓解颗粒物诱导的炎症反应和基因表达异常，从而改善相关肺部疾病。然而，临床应用时需审慎评估潜在风险，例如抗炎治疗可能导致的免疫抑制等不良反应。为提高治疗效果并降低副作用，可考虑采用靶向递药系统或基于个体化炎症标志物的精准用药方案。值得注意的是，虽然表观遗传调控疗法在动物实验中展现出良好的应用前景，但其临床转化仍需通过更系统的研究来验证疗效并优化治疗方案。综上所述，这些基于致病机制开发的干预策略，将为颗粒物相关呼吸系统疾病的防治提供新的治疗思路。

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所有作者声明无利益冲突。

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