

空气污染促进动脉粥样硬化形成

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【摘要】 空气污染是全球性健康问题。研究证明,空气污染促进动脉粥样硬化形成的机制涉及炎症反应、脂质代谢紊乱、内皮功能损伤、平滑肌细胞增殖、肠道菌群失调、氧化应激等。该文介绍空气污染促进动脉粥样硬化形成的作用和可能机制。

【关键词】 空气污染;心血管疾病;动脉粥样硬化

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大气污染物包括一氧化碳、氮氧化物、臭氧、二氧化硫等气态污染物和颗粒物(PM),全球每年有超过 370 万人过早死亡是由暴露于 PM 导致,在中国约有 20% 的心血管疾病死亡与空气污染有关。大气污染物可显著促进动脉粥样硬化(AS)形成,其机制与促进炎症反应、诱导氧化应激损伤和自身免疫反应等密切相关^[1]。

1 空气污染促进AS形成的机制

1.1 炎症反应

CD36 和 NOD 样受体热蛋白 3(NLRP3)炎症小体激活的协同作用,可能是空气污染与 AS 之间联系的潜在机制^[2]。直径<2.5 μm 的细颗粒物(PM_{2.5})可激活内皮细胞中 NLRP3 炎症小体^[3],并且调控 Wnt5a/Ror2 信号通路,诱导血管周围脂肪组织炎症反应而加速 AS 进展^[4]。瑞典马尔默的 1 项包括 6 103 名参与者的研究表明,暴露于 PM 导致的 AS 风险与炎症标志物,包括 C 反应蛋白(CRP)、补体 C3、铜蓝蛋白、口腔黏蛋白、触珠蛋白等呈正相关^[5]。巨噬细胞移动抑制因子(MIF)为促炎性细胞因子,MIF 基因敲除小鼠通过促进有丝分裂和自噬溶酶体的形成,对侧流烟雾暴露诱导的 AS 有抑制作用^[6]。柴油废气颗粒物中的亲脂性有机化合物可穿过肺泡上皮,引发远端内皮细胞的炎症反应;煤燃烧排放物暴露会诱导炎症细

胞因子 CRP 及肿瘤坏死因子-α(TNF-α)升高,促进 AS 发展^[7]。网络药理学分析表明,参连提取物可抑制 NLRP3 炎症小体活性,减少白细胞介素(IL)家族因子 IL-1、IL-18 和 IL-33 的释放,抑制由 PM_{2.5} 诱导的 AS 形成^[8]。

1.2 脂质代谢紊乱

PM_{2.5} 诱导的 AS 过程中还有脂质沉积的参与,与 Wnt5a/Ror2 信号通路的激活密切相关^[4]。PM_{2.5} 暴露增加了斑块的不稳定性,PM_{2.5} 通过 Toll 受体 4(TLR4)/髓样分化因子 88(Myd88)/核因子 κB(NF-κB)途径促进泡沫细胞的形成^[9]。遗传性高胆固醇血症患者的动脉内皮细胞受到内源性和外源性微粒的多重攻击,诱导内皮功能障碍,导致 AS 过早发生^[10]。Petri 网理论分析结果显示,烟草烟雾诱导的机体 AS 形成与氧化型低密度脂蛋白(ox-LDL)过度氧化关系密切^[11]。2013—2015 年北京的一项研究对 110 名参与者血浆中的 24 种鞘脂进行靶向脂质分析,鞘脂在 AS 发展过程中充当生物中间体,PM_{2.5} 暴露可通过促进含有致 AS 的载脂蛋白 B 产生,加速 AS 发展^[12]。抗氧化剂 N-乙酰半胱氨酸对心血管系统有保护作用,通过抑制血浆活性氧(ROS)诱导的 ox-LDL 升高,预防 PM 诱导的 AS^[13]。生脉饮可通过改善脂质代谢,抑制 AS 易损斑块的形成^[14]。吸烟组和从不吸烟组均暴露于过滤空气和柴油废气中 2 h,蛋白质组学分析结果显示暴露于柴油废气显著增加了 2 组与 AS 相关的蛋白质水平。交通相关的空气污染通过增加载脂蛋白 B、IL-6 水平,诱导 AS 形成^[15]。燃煤 PM_{2.5} 可诱导小鼠主动脉泡沫细胞累积,促进 AS 斑块形成,其机制与调控丝裂原活化蛋白激酶(MAPK)

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信号通路相关^[16]。

1.3 内皮功能损伤

内皮细胞可以维持心血管稳态,血管舒张因子和血管收缩因子的稳态因暴露于空气污染而出现失衡,诱发内皮功能障碍,促进 AS 病变的进展^[17]。PM_{2.5} 暴露使小鼠血管内皮细胞产生过量的黏附因子、趋化因子和炎性因子,促使血管内膜中巨噬细胞更多地转化为 M1 型。此外,PM_{2.5} 还可通过氧化应激影响内皮细胞的功能导致 AS 形成^[18]。PM_{2.5} 暴露增加了缺氧诱导因子-1 α (HIF-1 α) 的表达,触发内皮细胞损伤^[19]。PM_{2.5} 渗入人脐静脉内皮细胞,可导致线粒体和溶酶体损伤,刺激单核细胞与内皮细胞的黏附,是 AS 发病机制中的关键环节^[20]。自噬通量受阻对内皮细胞的存活不利,PM_{2.5} 可通过内质网应激诱导内皮细胞自噬和凋亡而导致 AS 形成^[21]。

1.4 平滑肌细胞增殖

血管平滑肌细胞 (VSMCs) 从血管中膜向内膜的浸润和增殖是 AS 病理生理过程中的重要步骤^[22]。PM_{2.5} 引发的炎症反应分泌炎性细胞黏附于血管内皮,释放细胞活性物质,导致 VSMCs 增殖;暴露于可溶性烟草烟雾可促使主动脉微剥离,促进 VSMCs 增殖;HIF-1 α 通过诱导人血小板反应蛋白的形成,导致 VSMCs 迁移和增殖,促进 AS 斑块的形成^[23]。PM_{2.5} 还可以通过激活 p38 MAPK 信号通路诱导 VSMCs 增殖,而非环化蛋白 A 可通过减少 p38 MAPK 信号通路,减少 PM_{2.5} 诱导的 VSMCs 增殖^[22]。

1.5 肠道菌群失调

肠道菌群可调节胆固醇代谢和炎症反应。吸入机动车尾气或木烟可通过诱导肠道菌群分布和多样性发生改变,促进小鼠 AS 斑块形成^[24]。通过气管内滴注接触柴油,可显著提高小鼠大肠埃希氏菌、副细菌、阿克曼菌的菌群多样性和群落数量,继而导致免疫和新陈代谢的异常^[25]。连翘苷通过过氧化物酶体增殖物激活受体信号通路可以改善肠道菌群失调,影响胆固醇代谢和炎症反应,缓解 AS 的进展。

1.6 氧化应激损伤

氧化应激是空气污染导致 AS 形成的关键机制,短期暴露于 PM_{2.5} 和黑炭颗粒与血浆髓过氧化物酶 (MPO) 呈正相关,其中 AS 患者血浆可以检测出高水平的 MPO^[26]。PM_{2.5} 通过诱导肺氧化应激

导致独特的脂质变化,生成的高水平循环脂肪酸可引发 AS 病变^[27]。直径 <10 μ m 的细颗粒物 (PM₁₀) 加剧了心脏血流动力学异常,进一步降低了心脏收缩力,西红花苷等抗氧化剂可通过提高过氧化氢酶 (CAT)、超氧化物歧化酶 (SOD)、谷胱甘肽过氧化物酶 (GPx) 活性,减轻氧化应激损伤,抑制空气污染诱导的 AS 形成^[28]。

1.7 免疫功能失调

PM_{2.5} 可导致 CD4⁺T 辅助细胞向 Th1 或 Th2 细胞类型极化,对呼吸和心血管系统造成损害。Wang 等^[29] 随机选择 120 名 PM_{2.5} 暴露者,分别接受 ω -3 脂肪酸和安慰剂治疗 8 周,结果表明 ω -3 脂肪酸可以降低细胞极化并调节人体免疫功能,减少空气污染对血管 AS 的损害。褪黑素能有效缓解 PM_{2.5} 暴露诱导的小鼠巨噬细胞 M1 极化和 AS 形成^[30]。二甲双胍可激活腺苷酸,活化蛋白激酶后抑制信号转导及转录激活因子 3 活性,介导巨噬细胞 M1 表型分化减少,促进 M2 表型分化增加,从而抑制小鼠 AS 形成。CD4⁺CD25⁺Foxp3⁺ 调节性 T 细胞在 AS 发生发展中起重要作用,而 PM_{2.5} 通过下调 CD4⁺CD25⁺Foxp3⁺ 调节性 T 细胞加速小鼠 AS 的发展^[31]。

1.8 铁稳态失衡

铁死亡为细胞程序性死亡,PM_{2.5} 通过介导微小 RNA (mRNA) -132 的表达调控引起线粒体功能异常,诱导细胞铁死亡,促进 AS 的进展。前列腺素内过氧化物合酶 2 (PTGS2) 是铁死亡相关蛋白的表达受体,AS 的严重程度与 PTGS2 的表达呈正相关^[32]。铁过载也会增加 AS 的风险,诱导 AS 小鼠的内皮功能障碍,使受损内皮合成的舒张因子和收缩因子比例失衡^[33]。吸入 PM_{2.5} 可加重小鼠 AS 的形成和发展,其机制与 PM_{2.5} 诱导铁过载引发的全身炎症反应和高脂血症有关^[34]。

2 小结

空气污染促进 AS 的形成和发展,应采取有效措施改善室内外空气质量,控制内外部环境中的风险因素,降低 AS 风险。空气污染引发 AS 的具体机制尚待进一步研究阐明。

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(上接第 84 页)

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