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空气细颗粒物造血毒性与生物学机制研究进展*

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摘 要 近年来，空气细颗粒物（fine particulate matters，$PM_{2.5}$）毒理与健康效应一直是环境化学领域的热点问题. 流行病学和毒理学研究表明，除呼吸和心脑血管系统损伤外，$PM_{2.5}$ 还可对血细胞和造血器官产生不良影响. 为此，本文简要回顾了机体造血过程，基于流行病学数据和毒理学实验结果综述了 $PM_{2.5}$ 造血毒性，从氧化应激、炎症损伤和表观遗传修饰等方面归纳了生物学机制.

关键词 细颗粒物 $PM_{2.5}$，血细胞，造血毒性，生物学机制.

Research progress on hematopoietic toxicity and biological mechanism of ambient fine particulate matters

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Abstract In recent years, the toxicological and health effects of ambient fine particulate matters ($PM_{2.5}$) have been a hot topic in the field of environmental chemistry. In addition to respiratory and cardiovascular system damages, $PM_{2.5}$ posed the adverse impacts on blood cell and hematopoietic organs. For this purpose, this paper briefly reviewed the hematopoietic process of organisms, introduced $PM_{2.5}$-induced hematopoietic toxicity based on epidemiological studies and toxicological experiments, and clarified biological mechanisms, mainly focusing on oxidative stress, inflammatory damage and epigenetic modification.

Keywords fine particulate matters ($PM_{2.5}$), blood cell, hematopoietic toxicity, biological mechanisms.

世界卫生组织（WHO）数据表明，空气污染每年可导致数百万人过早死亡，已成为危害人类健康的最大环境风险之一[1]. 污染物主要包括颗粒物（particulate matters, PMs）、气态污染物（如氮氧化物（NO_x）、硫氧化物（SO_x）和臭氧（O_3）等）、持久性有毒污染物（persistent toxic substances, PTSs）和重金属（heavy metals, HMs），其中 PMs 来源广、毒性强、组分复杂、形态多变，可对大气环境和人类健康带来长期的负面影响和危害. 值得注意的是，国际癌症研究机构（International Agency for Research on Cancer）基于已有研究成果将 PMs 列为第一类致癌化学物[2].

PMs 可细分为初级颗粒物和次级颗粒物，其中由自然因素（如风沙扬尘、森林火灾等）和人类活动（如汽车尾气、煤炭燃烧等）等方式直接排放到大气环境中的颗粒物为初级颗粒物，而次级颗粒物主要

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是由大气环境中已存在的气态污染物经化学反应所形成. 依据空气动力学直径(aerodynamic equivalent diameter, AED)将 PMs 分为可吸入颗粒物 PM_{10}(AED≤10 μm)、细颗粒物 $PM_{2.5}$(AED≤2.5 μm)和超细颗粒物 $PM_{0.1}$(AED≤0.1 μm). 相较于 PM_{10}, $PM_{2.5}$ 粒径小、比表面积大, 且可负载重金属、苯系物、多环芳烃等污染物, 入肺后可穿透气血屏障进入血液循环, 进而对人体健康产生不良影响[3－4]. 除传统呼吸和心脑血管系统损伤外, PMs 还可对机体血细胞和造血器官产生毒性效应, 即造血毒性[5－6], 且毒性效应与其粒径大小、化学组分相关[7]. 人群数据揭示 $PM_{2.5}$ 及其化学组分可诱发贫血(anemia)、血栓(hemophilia)和白血病(leukemia)等血液系统疾病发生发展[8－10]. 体外细胞实验和动物实验结果表明, $PM_{2.5}$ 可促进白血病细胞生长, 并加剧小鼠造血毒性的进展[11－13].

本综述简要阐述机体造血过程, 结合流行病学数据与毒理学实验研究重点探讨 $PM_{2.5}$ 对人群和实验动物血液系统的毒性效应及生物学机制, 以期从造血毒性与健康效应的角度为 $PM_{2.5}$ 健康风险评估提供科学思路.

1 机体造血过程(Hematopoietic development)

人类和小鼠的造血发育过程具有高度保守性[14－15], 其造血发育过程是指各类血细胞产生、增殖、分化、成熟和释放的过程, 主要分为胚胎期造血和出生后造血.

胚胎期造血分为原始造血和定向造血两个时空相互重叠的阶段[16], 不同阶段血细胞的产生、分化和成熟受到机体多种信号的调控, 调控失衡将导致严重的发育缺陷或血液疾病[17]. 小鼠原始造血始于胚胎期 7.5 d(embryonic day 7.5, E7.5), 在卵黄囊血岛区产生原始红细胞、原始巨核细胞、原始巨噬细胞、红系-髓系祖细胞(erythro-mmyeloid progenitors, EMPs)和淋巴-髓系祖细胞(lympho-myeloid progenitors, LMPs)[18－20]. 但原始造血持续时间短暂且产生的血细胞无自我更新能力, 自 E9.5 被定向造血代替. E9.5—E11.5 在背主动脉-性腺-中肾区(aorta gonad mesonephros region, AGM 区)、胎盘和胚胎头部血管内皮细胞产生的造血干细胞(hematopoietic stem cells, HSCs)随血液循环定植于胎儿肝脏并进一步分化[21－23]. 胚胎发育至 E12.5, HSCs 于肝脏进一步发育成熟并分化成前体血细胞(如巨核细胞、淋巴细胞前体)和终末血细胞(如红细胞、各类粒细胞、淋巴细胞等), 随后进入胸腺、脾脏和骨髓, 以维持终身造血活性[24]. 因此, 定向造血阶段对机体血细胞的分化和成熟起着重要的作用.

出生后, 骨髓成为主要造血器官. HSCs 在骨髓中先分化成具有有限自我更新能力和全谱系分化潜能的造血祖细胞(hematopoietic progenitor stem cells, HPSCs)[25], 之后在基因和细胞因子的调控下, HPSCs 定向分化为机体所需的特定血细胞[26]. 终末血细胞伴随着强烈的细胞流动穿越骨髓-血屏障进入外周血循环, 一方面为机体提供物质需求和发挥特定功能, 另一方面以维持机体造血活动的动态平衡[27]. 值得关注的是, 骨髓造血微环境改变将会影响 HSCs 静默、激活和死亡之间的动态平衡, 进而诱发血液疾病[28]. 当骨髓造血功能受损或机体血细胞需求量增加, 作为代偿性造血器官的脾脏可替代骨髓开启髓外造血, 常见于儿童[29].

2 细颗粒物造血毒性的流行病学研究(Epidemiological studies on $PM_{2.5}$-induced hematopoietic toxicity)

随着 PMs 造血毒性研究的不断深入, 已有流行病学证据提示 PMs 可对不同生命阶段人群血细胞和造血器官产生损伤, 且与血液疾病的发生发展相关[8,30](表 1).

2.1 发育阶段

产前暴露于 PMs 可通过改变脐带血细胞表型分布、抑制血细胞发育进程与前体血细胞分化等方式增加儿童血液疾病患病风险[43－44], 其中白血病和贫血关注度较高[45－46].

目前 $PM_{2.5}$ 与儿童白血病之间是否存在关联性尚无具体定论. 部分队列研究未发现 $PM_{2.5}$ 与儿童白血病具有显著的相关性[9,47]. 但 Lee 等[31] 和 Ou 等[10] 研究发现, $PM_{2.5}$ 可增加儿童白血病患病率和白血病患儿死亡率. 研究对象的暴露窗口期、暴露源、暴露水平和暴露评估方法等因素的差异性可能是造成上述结果不同的原因.

表 1　$PM_{2.5}$ 造血毒性的流行病学研究结果

Table 1　Epidemiological studies on $PM_{2.5}$-induced hematopoietic toxicity

人群 Population	样本量 Sample size	年龄 Age groupe	地区 Region	暴露物质 Exposure method	暴露周期 Exposure duration	主要结果 Main findings	文献 Reference
儿童 Children	1261855	—	韩国 Korea	$PM_{2.5}$	2002—2012	致儿童患白血病	[31]
儿童、青少年和年轻成人 Pediatric, adolescent, and young adult	2444+13459	0—39月	美国, 犹他州 Utah, American	$PM_{2.5}$	1986—2015	与儿童白血病相关	[10]
儿童 Children	139368	6—59月	秘鲁, 利马 Lima, Peru	$PM_{2.5}$	2012—2019	增加儿童贫血患病率	[32]
儿童 Children	98557	<5岁	印度 India	$PM_{2.5}$	2015—2016	导致儿童贫血	[33]
儿童 Children	117511	<5岁	撒哈拉以南非洲 Sub-Saharan Africa	$PM_{2.5}$	2006—2020	增加儿童贫血患病率	[34]
成人 Adults	25355	≥18岁	中国东北地区 Northeast China	$PM_{2.5}$	2019—2021	增加血小板数量	[35]
学生 Students	8	24—28岁	青岛—石家庄 Qingdao—Shijiazhuang	PMs、SO_2、CO、NO_2	2—3周	可增加血栓形成的风险	[36]
居民 Residents	82431	(42.83 ± 15.09)岁	中国南京 Nanjing China	$PM_{2.5}$	2017—2018	影响红细胞、单核细胞的数量	[37]
成人 Adults	362396	>50岁	中国台湾 Taiwan China	$PM_{2.5}$	2001—2014	与血小板增加相关	[38]
成人 Adults	118	>40岁	中国焦作 Jiaozuo China	CB	≥1年	增加粒细胞计数量	[39]
农村队列 Rural Cohort	31282	>50岁	中国河南 Henan China	PMs、NO_2	—	增加血小板数量	[40]
成人 Adults	110	50—75岁	中国北京 Beijing China	$PM_{2.5}$、CB、NO_2、噪声	2018—2019	导致血小板低甲基化	[41]
老年人群 Older Population	4121	75—84岁	美国 American	$PM_{2.5}$、NO_2	1年	增加老年人贫血患病率	[42]

$PM_{2.5}$ 还可致儿童贫血发病率增高. Morales-Ancajima 等[32] 和 Mehta 等[33] 研究发现 $PM_{2.5}$ 与儿童贫血相关, 且高浓度 $PM_{2.5}$ 可加重儿童贫血程度. 另一项研究运用多级混合效应模型首次证明了妊娠期、出生时和儿童期 3 个阶段 $PM_{2.5}$ 与婴幼儿贫血之间的关系, 结果显示不同阶段暴露 $PM_{2.5}$ 均可增加儿童贫血患病率[34].

2.2　成年阶段

多项研究表明, PMs 可影响成人红细胞、血小板和白细胞等血细胞数量、形态和功能[37,48－50]. 如研究对比分析有无炭黑暴露的工人血液样本差异性, 结果发现炭黑与嗜酸性粒细胞增加有关[39]. Hou 等[40] 选取河南农村队列研究空气污染物与血小板之间的关联性, 发现 PMs 对农村成年人的血小板功能和性状有影响, 但可通过体力劳动减缓. 国内研究基于外出出差的学生, 收集并分析出差前、返回后 1 d 和返回后 1 周等 3 个时间段的血液样本, 结果显示短期暴露于 $PM_{2.5}$ 可加剧血栓形成[36]. 另有研究发现, 长期暴露 $PM_{2.5}$ 可增加血小板数量, 且对血液凝固性有潜在的不良影响[35,38].

少数队列研究调查了空气污染物与成人白血病患病率之间的相关性, 其数据量不足以明确得出 PMs 与成年白血病具有关联[51－52]. 一项来自丹麦的病例对照研究发现, $PM_{2.5}$ 可通过 DNA 损伤、相关染色体畸变与易位等途径来增加成年人白血病患病率[5].

2.3　老年阶段

PMs 对老年人红细胞和血红蛋白的影响亦受到相关学者的关注[53]. Elbarbary 等[54] 开展了 PMs 与中国老年人贫血患病率和血红蛋白水平之间关系的研究, 结果显示 PMs 可增加老年人群贫血患病率. 另一项研究基于美国 4121 名老年人群队列探讨 $PM_{2.5}$ 与血红蛋白水平或(和)贫血之间的关系, 发现 $PM_{2.5}$ 对血红蛋白和贫血均呈很强的剂量反应关系, 其中 $PM_{2.5}$ 与血红蛋白之间的关联性是由 C 反应蛋白(C-reactive protein, CRP)介导的[42]. Liu 等[41] 开展了 $PM_{2.5}$ 对血小板影响的研究, 结果发现 $PM_{2.5}$ 可导致老年人血小板线粒体 DNA 低甲基化. 此外, Puett 等[55] 探讨了成年人白血病与空气污染物暴露的相关性, 发现 $PM_{2.5}$ 可增加老年人白血病患病风险.

3 细颗粒物造血毒性的实验研究(Experimental studies on $PM_{2.5}$-induced hematopoietic toxicity)

PMs 穿过气-血屏障迁移至血液,与红细胞、血小板和白细胞及其细胞亚群发生相互作用[56]. 另有研究发现,$PM_{2.5}$ 和 $PM_{0.1}$ 诱导肺脏分泌的炎症因子随血液流动至骨髓,通过干扰骨髓造血微环境影响血细胞的增殖、分化与成熟以及 HSCs 的功能趋向[57],进而引发血液肿瘤发生发展[27,58].

3.1 对红细胞的影响

红细胞主要承担输送氧气的功能,其数量、形态或功能异常可导致机体不良反应[59－60]. PMs 通过激活炎症细胞因子(如肿瘤坏死因子-α(TNF-α)和 γ 干扰素(IFN-γ)等)以抑制红系前体细胞的增殖-分化和促红细胞生成素(erythropoietin, EPO)反应性,其结果是红细胞数量降低[61]. 另一项研究将小鼠暴露于汽车尾气源 $PM_{2.5}$ 和 $PM_{0.1}$,发现其浓度与小鼠体内异常红细胞的数量呈线性相关[62]. 也有研究发现,PMs 与小鼠红细胞畸形有关[63]. 此外,小鼠孕期暴露 PMs 可导致红细胞功能下降[64].

$PM_{2.5}$ 还可影响血液中血红蛋白含量,从而引发机体贫血[65－66]. 值得关注的是,白细胞介素-6(IL-6)等炎症因子通过改变血液中铁调素(hepcidin)水平影响红细胞数量和血红蛋白浓度[67]. IL-6 增加血清中循环铁调素浓度,进而减弱十二指肠、脾脏与肝脏对铁的吸收以及铁向骨髓的循环,最终导致缺铁性红细胞生成;其次,$PM_{2.5}$ 诱发炎症导致红系前体细胞因缺铁而生成缺铁性红细胞. 但是,$PM_{2.5}$ 通过铁调素影响红细胞的生物过程和分子机制仍有待阐明.

3.2 对血小板的影响

PMs 及其重金属组分经呼吸道沉积于肺脏,刺激其产生并释放促氧化介质(如活性氧(reactive oxygen species, ROS))和促炎性介质(如炎症因子)至血液,导致血小板活化或形态与功能改变[68－69]. PMs 与血小板生成、激活存在正相关[70]. 此结果在人群样本中得到了证实,Delfino 等于冠状动脉疾病患者血液中发现 $PM_{2.5}$ 与血小板活化标志物 p-选择素(p-selectin)存在关联性[71];而 Yin 等[72] 研究报告发现,PMs 可抑制血小板活化标志物分泌而发挥抗血小板作用. 另一项人群模拟试验研究表明暴露于柴油机尾气的男性志愿者血液中血小板-单核细胞聚集体增加[73].

肺脏为血小板髓外分化、成熟的重要位点,且巨核细胞可独立于血小板发挥促炎作用[74]. 基于此,Jin 等[56] 探讨了 $PM_{2.5}$ 与巨核细胞分化之间的关系,结果显示 $PM_{2.5}$ 促进巨核细胞发育成熟并分化为血小板,从而导致血栓形成.

3.3 对白细胞的影响

$PM_{2.5}$ 入肺后可激活巨噬细胞发挥吞噬清除作用,而高积累则会导致巨噬细胞损伤与凋亡[75]. $PM_{2.5}$ 亦可促进巨噬细胞发生极化改变,具体表现为 M1 亚型相关的白细胞介素-12(IL-12)、IFN-γ 等细胞因子富集和 M2 亚型相关的白细胞介素-4(IL-4)、白细胞介素-10(IL-10)和白细胞介素-13(IL-13)水平发生下降[76]. 而巨噬细胞极化可促进肺脏白细胞与血小板的结合和活化,其结果是具有止血活性的微粒释放至体循环,进而激活全身的凝血状态[77]. 此外,$PM_{2.5}$ 削弱肺脏巨噬细胞内化作用,同时募集自然杀伤细胞和中性粒细胞等白细胞至肺脏以减少组织损伤[78－79].

PMs 刺激肺泡产生炎症因子介导骨髓释放单核细胞和中性粒细胞进入体循环[80－81]. 动物实验证实,PMs 亦可诱导单核细胞和各类粒细胞的累积和功能改变[82－83]. 如 Xu 等[84] 研究发现 $PM_{2.5}$ 可诱导单核细胞和中性粒细胞聚集而产生炎症反应. 另一项研究发现,$PM_{2.5}$ 可诱发小鼠血液毒性,当与甲醛联合暴露后可加剧影响,主要原因是 $PM_{2.5}$ 和甲醛破坏了免疫平衡[30],提示 $PM_{2.5}$ 通过激活免疫系统介导血液毒性效应及作用机制需进一步关注.

3.4 对骨髓的影响

骨髓是各种血细胞储存库. 研究显示,$PM_{2.5}$ 及其负载的有害物质可致骨髓的累积损伤和内皮祖细胞(endothelial progenitor cells, EPCs)释放的受损,进而诱发 EPCs 数量及功能发生改变[85－86]. PMs 与骨髓造血干细胞(BM-HSCs)之间的关联性也得到证实,即 PMs 通过 ROS 引发 BM-HSCs 增殖显著减少[6],$PM_{2.5}$ 可诱导 BM-HSCs 耗竭[57]. 体外细胞培养和动物实验结果表明,$PM_{2.5}$ 可促机体炎症反应和白血病细胞因子表达,且 $PM_{2.5}$ 剂量与白血病细胞增殖呈低促高抑趋势[12].

维持骨髓造血微环境稳态对血液系统的正常运行至关重要. 最近一项研究发现,孕期暴露 $PM_{2.5}$ 与子代血液肿瘤发生有关,可表现为胎儿 BM-HSCs 衰老表型、DNA 的双链断裂和骨髓微环境

产生了高水平的蛋白水解酶, 从而增加骨髓增殖性疾病风险[87]. 骨髓微环境受损可致使子代 BM-HSCs 通过非细胞自主机制逐渐衰老, 增加骨髓增殖性疾病风险[87]. 国内一项研究发现, $PM_{2.5}$ 通过破坏儿童骨髓造血微环境影响 HSCs 功能趋向[88].

4　细颗粒物造血毒性的生物学机制(Biological mechanisms underlying hematopoietic toxicity of $PM_{2.5}$)

$PM_{2.5}$ 造血毒性与氧化应激[11,87]、炎症损伤[89－90] 和表观遗传修饰[91－93] 等有关, 且主要集中于氧化应激假说和炎症假说[27](图 1).

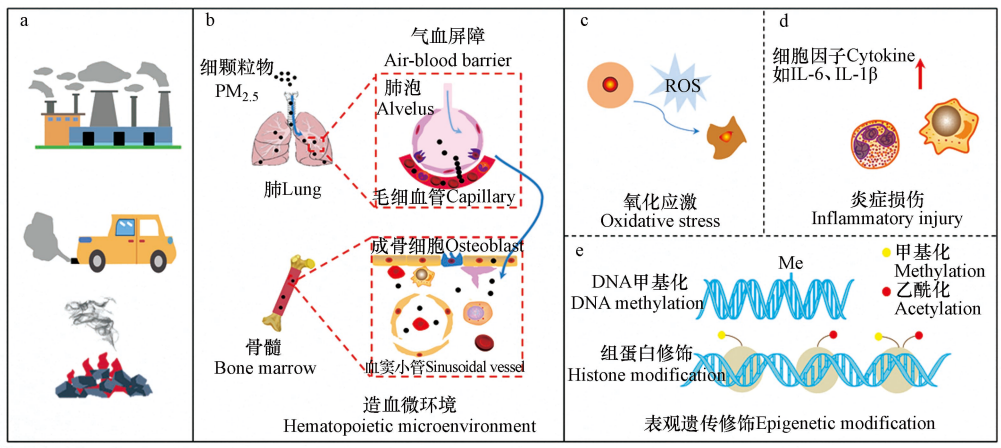

图 1　$PM_{2.5}$ 造血毒性的生物学机制

a. $PM_{2.5}$ 来源; b. $PM_{2.5}$ 内暴露; c—e: 生物学机制

Fig.1　Biological mechanisms of $PM_{2.5}$-induced hematopoietic toxicity

a. Source of fine particulate matter; b. Internal exposure of fine particulate matter; c—e: Biological mechanisms

4.1　氧化应激

造血稳态的维持依赖于 HSCs 和 HPSCs, 而 HSCs 功能选择取决于 ROS 水平高低[88]. Cui 等证实, $PM_{2.5}$ 暴露可抑制小鼠骨髓基质细胞增殖, 该过程依赖于机体氧化应激反应[6]. 最近一项动物研究发现, $PM_{2.5}$ 通过诱导孕鼠子代 ROS 高水平表达导致 BM-HSCs 衰老[88]. $PM_{2.5}$ 亦可诱导 ROS 相关酶(如 NAPDH 氧化酶)生成以刺激 ROS 的生成, 进而加剧白血病发展进程[11]. 值得注意的是, 亚氮应激也被发现是血液系统产生毒性效应的一种机制. 如血小板活化与一氧化氮含量的下降有关, 这是因为一氧化氮作为血小板活化抑制剂, 其水平的降低和过氧亚硝酸盐水平的增加可能激活血小板并发生聚集效应[94]. 但是, $PM_{2.5}$ 诱导亚氮应激引发造血毒性的生物学过程还有待进一步阐明.

4.2　炎症损伤

动物研究发现, $PM_{2.5}$ 诱发炎症反应以损害骨髓微环境稳态, 进而导致血液疾病发生[89]. $PM_{2.5}$ 所激活的炎症反应可影响红系前体细胞的增殖与分化、内源性 EPO 耐药性和血红蛋白浓度水平[90]. 其具体生物学过程可从 3 个方面解释[95], 即其一炎症可能调控 EPO 表达量降低, 进而引发红细胞的生物反应下调, 最终红细胞生成不足; 其二炎症诱发低氧或缺氧致使红细胞生成减少; 其三炎性因子上调铁调素合成而导致贫血发生.

此外, 炎症可刺激血小板活化、聚集. 动物模型发现, $PM_{2.5}$ 暴露后 IL-6、IL-1β 和 CRP 等血浆炎症细胞因子表达增加, 进而促进血管细胞粘附分子-1(VCAM-1)和细胞间黏附分子-1(ICAM-1)等细胞黏附分子的表达. 另一方面, 炎症释放的细胞因子刺激巨核细胞生成而增加血小板生成量. 例如, IL-6 刺激肝脏释放促血小板生成素(thrombopoietin, TPO), 随后 TPO 受体刺激 Janus 激酶 2(JAK2)/信号转导剂和转录激活剂 3(STAT3)等信号途径, 进而诱导巨核细胞的增殖与分化[96].

4.3　表观遗传修饰

$PM_{2.5}$ 影响全生命周期的表观遗传修饰, 特别是 DNA 甲基化(DNA methylation, DNAm)和组蛋白

修饰[97－99]. $PM_{2.5}$ 所引起的机体 DNAm 标志物主要集中在血液[91]. 如, Chi 等[92] 在长期暴露 $PM_{2.5}$ 的人群外周血单核细胞中观察到 5 处胞嘧啶-鸟嘌呤二核苷酸(CpG)位点甲基化, 提示与单核细胞 DNAm 显著相关. 也有报道 $PM_{2.5}$ 暴露与人群外周血白细胞 DNAm 水平增高相关[93]. Li 等[100] 研究发现, $PM_{2.5}$ 导致 RAP1GAP2(RAP1 GTPase activating protein 2)基因位点发生甲基化, 进而调节血小板活性. 此外, Zheng 等[101] 研究发现, 交通源 PM_{10} 与卡车司机血液中白细胞的 H3 赖氨酸 27 三甲基化(H3K27me3)和 H3 赖氨酸 36 三甲基化(H3K36me3)水平呈现显著负相关, 且 $PM_{2.5}$ 及其不同组分亦可影响组蛋白 H3 修饰[99].

5 结语与展望(Conclusions and prospects)

$PM_{2.5}$ 仍是危害人类健康的主要环境风险之一. 人群队列研究和毒理学实验显示 $PM_{2.5}$ 与血液系统疾病之间存在着显著相关性, 其造血毒性研究已取得了一些进展. 考虑到 $PM_{2.5}$ 引起的血细胞或(和)造血器官受损可能受到暴露剂量、暴露频次、暴露途径、暴露评估模型等因素影响, 现有研究工作仍有待加强.

(1)目前研究多集中于贫血和血栓, 较少关注 $PM_{2.5}$ 促血液肿瘤(如白血病)发生过程和机制. 另外, 肺脏是新发现的造血位点, 且作为 $PM_{2.5}$ 直接作用靶器官, 亟需关注 $PM_{2.5}$ 及其化学组分对肺脏造血的影响.

(2)$PM_{2.5}$ 具有高度异质性, 即不同地区、不同季节及不同气象条件下 $PM_{2.5}$ 化学成分具有差异性, 导致 $PM_{2.5}$ 造血毒性的关键组分尚不够明确. 因此, 基于生物过程和毒理机制识别关键毒性组分及其分子作用, 阐明从暴露到机体特定损伤乃至健康危害的过程, 有助于预防和干预 $PM_{2.5}$ 对人群产生的不良健康影响.

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