

重金属暴露对肠道菌群的影响及 益生菌干预的研究进展

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摘要: 重金属污染是全球重大公共卫生问题, 长期低剂量重金属暴露可引发多系统损伤, 并增加慢性疾病发生风险。传统螯合剂疗法存在脏器损伤等不良反应, 故仍需探索安全有效的新型干预手段。研究表明, 重金属暴露可显著扰乱肠道菌群组成与功能, 进而加剧毒性损伤, 益生菌则可通过多种途径影响重金属的体内代谢并降低其毒性。然而, 既往综述多局限于传统益生菌的解毒作用, 较少涉及下一代益生菌 (Next-generation probiotics, NGPs) 的相关研究进展。鉴于此, 本文以铅、汞、镉、砷四种常见重金属为例, 综述重金属暴露对肠道菌群组成及代谢产物的影响, 传统益生菌缓解重金属毒性的机制, 并探讨 NGPs 在重金属解毒中的应用潜力, 旨在为开发基于益生菌干预的重金属暴露防治策略提供理论依据。

关键词: 重金属; 肠道菌群; 益生菌; 下一代益生菌

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Research progress on the effects of heavy metal exposure on gut microbiota and probiotic intervention

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Abstract: Heavy metal pollution is a major global public health issue. Long-term low-dose exposure to heavy metals can induce multisystem damage and increase the risk of chronic diseases. Conventional chelation therapy is associated with adverse effects such as organ injury; therefore, safer and more effective intervention strategies are still needed. Increasing evidence has shown that heavy metal exposure can markedly disrupt the composition and function of the gut microbiota, thereby aggravating toxic effects. Probiotics may reduce heavy metal toxicity through multiple mechanisms by influencing the metabolism of heavy metals in vivo. However, previous reviews have mainly focused on the detoxification effects of traditional probiotics, while relatively few have discussed the recent advances in next-generation probiotics (NGPs). Accordingly, this review summarizes the effects of lead, mercury, cadmium, and arsenic exposure on gut microbiota composition and microbial metabolites, discusses the mechanisms by which traditional probiotics alleviate heavy metal toxicity, and further explores the potential applications of NGPs in heavy metal detoxification, with the aim of providing a theoretical basis for developing probiotic-based intervention strategies against heavy metal exposure.

Keywords: Heavy metals; Gut microbiota; Probiotics; Next-generation probiotics

随着全球工业化快速发展, 各类重金属污染物排放量大幅上升, 严重危害全球环境与公共健康^[1]。重金属是指高原子量、密度大于 4.5 g/cm^3 的金属元素^[2]。此类污染物具有生物蓄积性, 在自然环境中难以降解, 可通过受污染的空气、水源和食物链进入人

体。即使长期低剂量重金属暴露也可能引发神经系统疾病、肝肾损伤, 甚至增加慢性疾病与癌症的发病风险^[3]。根据暴露时间以及暴露剂量的差异, 重金属中毒通常分为急性和慢性两类。目前, 临床对于急性重金属中毒主要依赖螯合剂疗法, 但该疗法对于广泛存在的慢性低水平暴露不仅效果有限, 还可能导致重金属再分布至大脑等脏器以及肝肾功能损害等副作用^[4]。因此, 有必要寻找更为安全有效的防治策略。

肠道菌群是人体内一个庞大而复杂的微生物生态系统, 其基因组总和被称为“人类第二基因

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组”^[5]。肠道菌群主要由细菌和其他微生物构成,其中厚壁菌门、拟杆菌门、放线菌门和变形菌门是主要菌门^[6]。肠道菌群在调控新陈代谢、促进营养吸收、介导免疫反应和维持肠道屏障功能等方面发挥着重要作用^[7-8]。近年来,肠道菌群被认为是重金属毒性的作用靶点,两者之间的互作关系逐渐受到关注^[9]。以乳杆菌和双歧杆菌为代表的益生菌已被证实可在一定程度上缓解重金属的毒作用^[10]。此外,部分下一代益生菌(Next-generation probiotics, NGPs)也显示出重金属解毒潜力^[5]。与既往主要聚焦传统益生菌的综述不同,本文以铅、汞、镉、砷为例,综述重金属暴露对肠道菌群的影响,阐述传统益生菌缓解重金属毒性的机制,并进一步讨论 NGPs 在重金属暴露干预中的应用潜力。

1 重金属暴露对肠道菌群的影响

重金属暴露可导致人类和动物出现一系列严重的健康问题,扰乱肠道菌群结构与功能是其重要毒性机制之一^[11]。当重金属的刺激强度超出肠道菌群的耐受上限时,肠道菌群组成、代谢功能发生改变,短链脂肪酸、胆汁酸、氨基酸等代谢产物也随之异常,进而破坏肠道屏障并增强重金属毒性^[10]。

1.1 铅 铅作为一种常见的有毒重金属,主要通过消化道被人体吸收,其所致健康损害已成为全球公共卫生领域关注的重要问题^[12]。一项动物实验结果表明,以 0.5 mg/ml 醋酸铅溶液经饮水染毒大鼠 28 周后,其肠道菌群的组成与多样性均出现显著下降,在门水平上,拟杆菌门丰度升高、厚壁菌门丰度下降;在属水平上,粪球菌属和颤螺菌属丰度显著下降^[13]。Du 等人的研究也证实,铅暴露可显著降低肠道微生物的多样性,表现为乳杆菌科和瘤胃球菌科等菌群丰度降低,拟杆菌科和肠杆菌科等菌群丰度升高^[14]。

铅暴露对肠道菌群的影响可能存在剂量依赖性。随着铅暴露剂量的升高,粪球菌属与颤螺菌属的相对丰度呈线性下降趋势,乳杆菌属的相对丰度则呈线性上升趋势,相关代谢分析进一步提示,铅暴露可导致小鼠体内氨基酸代谢、核苷酸代谢、外源性物质代谢等通路发生变化,其中乳杆菌属关联氨基酸代谢,双歧杆菌属关联多环芳烃降解以及细胞色素 P450 介导的外源物代谢^[15]。此外,铅暴露可导致肠道紧密连接蛋白(ZO-1 和 occludin)表达显著降低,增加肠道通透性,进一步加剧菌群稳态失衡^[16-17]。

1.2 汞 汞是天然存在的有害重金属元素,主要以单质汞、无机汞以及有机汞三种形态存在^[18]。有机汞的毒性远高于无机汞,其中甲基汞的毒性最为显著^[19]。大量实验研究证实,无机汞暴露可改变肠道

菌群组成:在科水平上,导致蛭弧菌科、理氏菌科、丹毒丝菌科等相对丰度上调,乳杆菌科、链球菌科等相对丰度下调^[20];在属水平上,使粪球菌属、颤螺菌属和螺杆菌属等丰度显著增加,而伊格纳茨菌属、盐球菌属和芽孢杆菌属等丰度显著减少^[21]。

与无机汞相比,甲基汞暴露对肠道菌群的影响更为显著。甲基汞暴露可使厚壁菌门相对丰度上调,拟杆菌门和变形菌门相对丰度下调;在科水平上,使乳杆菌科等有益菌减少,脱硫弧菌科等潜在有害菌增加^[20]。同时,甲基汞暴露可显著改变肠道菌群相关代谢谱,其中脱硫弧菌目与甘氨酸呈负相关,螺杆菌科与谷氨酸和尿酸呈正相关^[22]。此外,汞暴露可上调肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)、白细胞介素-6(interleukin-6, IL-6)等促炎因子表达,损害肠道屏障完整性,促进汞的吸收并进一步加重菌群紊乱^[23]。

1.3 镉 镉作为一种非必需的有毒重金属元素,在自然环境中通常以 Cd^{2+} 形态存在,是当前农业土壤及饮用水源中分布广泛、危害突出的重金属污染物^[24]。镉主要通过受污染的食物和饮用水进入体内,肠道是其毒性作用的关键靶器官之一^[25]。多项研究表明,镉暴露可显著干扰肠道菌群的组成与代谢功能。在慢性低剂量镉暴露实验中,处理组小鼠肠道中普雷沃氏菌属和别样普雷沃氏菌属丰度升高,而图里西杆菌属、克里斯滕森菌科等丰度降低,进而导致小鼠体内脂质代谢与胆汁酸代谢紊乱^[26]。

亚急性镉暴露实验发现,镉处理组大鼠肠道中假黄单胞菌属和厌氧弧菌属丰度上升,阿克曼菌属、短螺旋体属和聚集杆菌属丰度下降,同时出现甘油磷脂代谢产物异常^[27]。此外,Tao 等的研究指出,与对照组相比,镉暴露组中超过半数与肠道菌群相关的代谢功能出现显著下调,主要涉及氨基酸代谢、脂肪酸代谢及糖胺聚糖代谢等通路^[28]。另有研究发现,镉暴露可下调肠道紧密连接蛋白(ZO-1、JAM-A、occludin)的表达,破坏细胞间粘附结构,从而影响肠道屏障完整性及菌群稳态^[29]。

1.4 砷 砷是在环境中普遍存在的有毒类金属,已被国际癌症研究机构列为 1 类致癌物^[30]。地壳中的天然砷在特定条件下可污染地下水,并主要以无机砷形态存在。经口摄入后,约 80% 的无机砷可通过胃肠道被人体吸收^[31]。Yang 等人研究发现,砷暴露组小鼠肠道菌群 α 多样性下降,拟杆菌门相对丰度上升,厚壁菌门相对丰度下降;同时,小鼠的胆汁酸代谢也受到显著影响,表现为次级胆汁酸合成能力下降,初级胆汁酸合成能力上升^[32]。

砷暴露对肠道菌群的影响还可能与暴露窗口期

有关。发育阶段小鼠经砷暴露后,在门水平上,疣微菌门相对丰度显著增加,拟杆菌门和厚壁菌门相对丰度下降;在属水平上,阿克曼菌属和拟杆菌属相对丰度显著增加^[33]。这与成年小鼠模型的观察结果存在差异,在后者中并未观察到疣微菌门的这一显著变化^[32],提示发育期可能是砷影响肠道菌群的敏感窗口。此外,亚慢性砷暴露可增加肠道上皮细胞旁转运,导致肠道上皮通透性异常升高,削弱屏障功能并破坏肠道微生物群稳态^[34]。

2 传统益生菌缓解重金属毒性的机制

联合国粮食及农业组织与世界卫生组织将益生菌定义为:足量摄入时可对宿主产生健康益处的活微生物^[35]。1980 年, Beveridge 等人发现枯草芽孢杆菌因其细胞壁表面的电荷差异而能够与重金属离子结合,提示细菌具有清除重金属离子的特性^[36]。随后, Halttunen 报道乳酸菌具有去除 Cd^{2+} 的能力^[37]。随着研究深入,益生菌缓解重金属毒性的机制已从结合重金属离子扩展到生物转化与代谢排泄调控、肠道菌群调节、肠道屏障修复以及宿主抗氧化和免疫防御调控等多个方面。

2.1 吸附与螯合机制 肠道内的益生菌以革兰氏阳性菌为主,这类菌株的细胞壁富含肽聚糖与磷壁酸,两者均具有带负电的官能团,可螯合带正电的重金属离子,降低重金属在体内的蓄积量^[38]。相关研究已证实该机制的有效性:乳酸乳球菌可通过细胞表面的羟基(- OH)和氨基(- NH_2)富集镉离子,显著降低了镉在鲤鱼组织中的蓄积量^[39]。另有研究表明,凝结芽孢杆菌和植物乳杆菌可直接与汞离子结合,进而抑制其在肠道内的吸收,并促进其随粪便排出体外^[40]。类似地,乳杆菌和双歧杆菌联合补充也可减少砷吸收,促进其随粪便排出,进而显著降低砷在各器官和血液中的蓄积量^[41]。

2.2 生物转化与代谢排泄调控 重金属的化学形态不仅影响其固有毒性,还直接调控其在生物体内的吸收、分布、代谢与排泄过程^[42]。早在 20 世纪,研究已发现细菌可将高毒性的甲基汞转化为低毒性且不易被吸收的无机汞,从而降低甲基汞的神经毒性^[43]。此外,部分益生菌还可通过调控宿主代谢发挥类似作用。例如,植物乳杆菌 CCFM8661 可上调胆固醇 7 α -羟化酶和甾醇 12 α -羟化酶的表达,增加肝脏胆汁酸合成,促进铅与胆汁中谷胱甘肽(glutathione, GSH)结合并排入肠道,同时减少肠道对胆汁酸及伴随的铅的再吸收,增加粪便铅排泄^[44]。一项随机双盲对照试验结果显示,连续口服植物乳杆菌 CCFM8610 可降低志愿者血镉水平;进一步动物实验表明,该菌株可

通过调节胆汁酸肠肝循环,增加胆汁 GSH 输出、胆汁镉排泄及粪镉排泄,从而降低组织中镉蓄积^[45]。

2.3 调节宿主抗氧化与免疫防御 研究发现,短乳杆菌 AC10 与鼠李糖乳杆菌 AC11 联用可下调诱导型一氧化氮合酶基因表达、上调超氧化物歧化酶(superoxide dismutase, SOD)基因表达,从而增强机体抗氧化能力,减轻镉暴露引发的氧化损伤与炎症反应;同时,该联合补充方案还可提高免疫球蛋白 A、免疫球蛋白 G 和免疫球蛋白 M 的水平,通过免疫调节调控炎症反应进程^[46]。乳杆菌和双歧杆菌联合补充可抑制活性氧产生,同时阻断核因子 κB (nuclear factor kappa - B, NF - κB) 信号通路的激活,从而缓解砷诱导的氧化应激及炎症反应^[41]。此外,短乳杆菌 23017 可抑制因汞暴露而激活的 p38 丝裂原活化蛋白激酶和 NF - κB 信号通路,降低 TNF - α 和 IL - 6 及脂质过氧化产物丙二醛水平,并提高 SOD、GSH、过氧化氢酶等抗氧化酶活性^[23]。

2.4 调节肠道菌群,增强肠道屏障功能 重金属暴露可诱导肠道菌群失调,破坏肠道微生态屏障,而益生菌干预的核心效应之一正是恢复被破坏的肠道微生态平衡^[47]。凝结芽孢杆菌 SCC - 19 可显著上调紧密连接蛋白(occludin, claudin - 2 和 ZO - 1)表达,降低血浆和肠道中二胺氧化酶和 D - 乳酸水平,进而降低肠道通透性;同时,该菌株还能逆转镉暴露所致的菌群失调,增加芽孢杆菌属和乳杆菌属等菌群的丰度^[48]。短乳杆菌 23017 可上调因汞暴露而降低的紧密连接蛋白(ZO - 1, occludin)表达,维持肠道屏障功能,减轻汞引起的毒性损伤^[23]。这些研究提示,益生菌通过菌群重塑一屏障修复一毒性降低的连续过程参与重金属暴露干预。

3 下一代益生菌在干预重金属毒性中的应用潜力

NGPs 是指一类具有潜在健康益处、但目前尚未被广泛用于临床健康促进的肠道微生物^[49]。传统益生菌多为食品来源的兼性厌氧菌,易受肠道微环境影响,作用持续性较差^[50]。与之相比,NGPs 多为肠道原生苛养厌氧菌,具有更强的肠道定植能力与功能稳定性^[51]。基于此,NGPs 在重金属暴露防治中可能具有一定应用潜力。

普拉梭菌基因组中含有砷甲基转移酶基因(*arsM*),该基因编码的甲基转移酶是微生物解毒途径中的关键组分,能够参与砷的甲基化代谢^[52]。Coryell 等人研究发现,给暴露于砷的无菌 As3mt - KO 小鼠口服普拉梭菌,可显著降低砷暴露所致的死亡风险^[53]。这一观察结果表明,普拉梭菌对砷毒性具有保护作用,但其保护效应究竟来源于 *arsM* 介导的砷

解毒、其他代谢物的间接保护,还是两者的协同效应,仍需进一步验证。

嗜黏蛋白阿克曼氏菌是一种定植于结肠且具有生物治疗潜力的有益菌株,能通过促进黏蛋白生成等方式增强肠道屏障功能^[54]。Xie 等人研究发现,嗜黏蛋白阿克曼氏菌可通过促进肠道褪黑素合成,发挥恢复杯状细胞数量、清除活性氧的作用,进而有效减轻镉暴露诱导的肠道黏膜屏障损伤^[55]。

大肠杆菌 1917 - pSK18a - MT 是基于大肠杆菌 Nissle 1917 构建的工程化 NGPs,可通过表面展示技术高效表达金属硫蛋白 (metallothionein, MT)^[56]。Zhang 等人研究发现,在亚慢性镉暴露小鼠模型中,大肠杆菌 1917 - pSK18a - MT 可通过表面展示的 MT 螯合肠道游离镉离子促进镉排泄,降低肝脏镉蓄积;同时,该菌株还可激活抗氧化通路、抑制炎症反应,减轻镉诱导的肝损伤,修复肠道黏膜屏障并恢复阿克曼氏菌丰度,从多种途径协同缓解镉诱导的肝损伤^[56]。这一发现为工程化 NGPs 在重金属解毒中的应用提供了重要的概念验证。综上所述,NGPs 可凭借天然的解毒能力与工程化改造缓解重金属毒性,为重金属暴露的微生物生态干预提供新方向,但仍需临床验证。

4 总结与展望

肠道菌群在重金属的毒性效应中扮演着关键角色,重金属暴露可改变肠道菌群组成、多样性和代谢产物,其影响程度受到重金属暴露剂量、化学形态以及暴露时期的影响。传统益生菌可通过吸附螯合、生物转化与代谢排泄调控、抗氧化与免疫调节以及肠道屏障修复等途径缓解重金属毒性。近年来,一些具有特定功能的 NGPs 也展现出良好的应用前景,可在一定程度上弥补传统益生菌干预的不足。

然而,当前的研究仍面临诸多挑战,一方面,现有相关研究证据多源于动物模型,尚缺乏大规模、高质量的随机对照试验,益生菌对人体重金属暴露干预的临床获益仍缺乏充分证据。另一方面,目前益生菌缓解重金属毒性的分子机制尚未完全阐明。值得关注的是,近期一项超过 3.4 万人的宏基因组研究提示,单一菌株的有益作用在人体肠道环境中难以复制,应避免将动物实验结论直接外推至人类,也不应夸大单一菌株功效,研究还指出微生物生态研究需从单菌株思维转向整体微生物生态视角^[57]。未来应优先在人群中开展前瞻性队列研究和随机对照试验,尤其是针对职业暴露人群、污染地区居民等特定人群;同时需结合基因组学、转录组学及代谢组学等技术,进一步阐明益生菌影响重金属毒性的分子机制,为筛选安全有效的益生菌菌株,并制定基于益生菌干预的重金属暴露

防治策略提供科学依据。

利益冲突声明 本研究不存在任何利益冲突

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(上接第 2913 页)

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