

肠道微生物对砷生物转化及多器官毒性影响的研究进展

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摘要

砷作为一种广泛存在的环境类金属污染物, 其慢性暴露可引发心血管疾病、肝癌、糖尿病及神经退行性疾病等多系统病变, 已成为全球重大公共卫生挑战。肠道菌群作为连接砷暴露与宿主健康的关键中介, 通过“砷-菌群-宿主”轴参与砷的生物转化与毒性调控, 其作用机制涉及双向互作: 一方面, 肠道菌群通过还原、甲基化等代谢过程改变砷的化学形态与毒性; 另一方面, 砷暴露可诱导肠道菌群多样性降低、结构失衡及屏障功能损伤, 进而通过炎症反应、氧化应激、代谢产物紊乱及肠-脑轴等途径, 加剧砷诱导的多器官损伤。本文系统综述了砷的代谢特征与多器官毒效应, 重点解析了砷暴露对肠道菌群的影响以及肠道菌群在砷生物转化过程中的作用, 并阐述了菌群失调与砷相关疾病的关联。本文旨在为理解“砷-菌群-宿主”的作用机制提供全景视角, 为开发靶向肠道菌群的砷毒性干预策略及相关疾病防治提供理论依据与潜在靶点。

关键词

砷, 肠道微生物, 砷的生物转化, 多器官毒效应

Research Progress on the Impact of Gut Microbiota on Arsenic Biotransformation and Multiorgan Toxicity

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Abstract

As a widely existing environmental metalloid pollutant, arsenic can induce multisystem disorders such as cardiovascular diseases, liver cancer, diabetes mellitus, and neurodegenerative diseases upon chronic exposure. This has become a major global public health challenge. The gut microbiota serves as a critical intermediary linking arsenic exposure and host health through the “arsenic-microbiota-host” axis, participating in both the biotransformation and toxicity modulation of arsenic. On one hand, gut microbiota metabolize arsenic through reduction, methylation, and other processes, altering its chemical speciation and toxicity; on the other hand, arsenic exposure disrupts the gut microbial community by reducing diversity, altering composition, and impairing barrier function. These changes exacerbate arsenic-induced multi-organ damage via mechanisms such as inflammatory responses, oxidative stress, metabolic disturbances, and gut-brain axis signaling. This review systematically outlines the metabolic characteristics of arsenic and its multi-organ toxicity, with a focus on how arsenic reshapes the gut microbiota and how microbial metabolism influences arsenic biotransformation. Furthermore, it discusses the correlation between dysbiosis and arsenic-related diseases. The objective of this study is to comprehensively understand the underlying mechanisms among arsenic, the microbiota, and the host, thereby offering a theoretical basis and potential strategies for mitigating arsenic toxicity through microbiota-targeted interventions.

Keywords

Arsenic, Gut Microbes, Biotransformation of Arsenic, Multi-Organ Toxic Effects

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1. 引言

砷(As)作为自然界广泛存在的类金属元素,广泛存在于岩石、土壤、水和空气中。虽然砷是地壳中发现的一种自然存在的元素,但近百年来工业化进程导致其在水、土壤和大气中的浓度显著升高,长期接触砷已成为世界范围内的一个主要公共卫生问题[1]-[3]。最近的统计模型估算结果显示,全球有 9400 万至 2.2 亿人口面临接触地下水中高浓度砷的风险[4]。这种慢性砷暴露易引发多系统病变,包括心血管疾病、神经退行性疾病及多种癌症等,其致病机制涉及氧化应激、遗传毒性和表观遗传调控等多个层面[5][6]。因此,明确砷的毒性效应及作用机制,对制定针对性防控策略具有重要意义。

肠道微生物群被认为是人体的“第二基因组”。肠道菌群不仅参与营养物质代谢和免疫调节,还在环境污染物的生物转化中扮演重要角色[7]-[9]。值得注意的是,砷的生物毒性与其化学形态密切相关,而肠道微生物通过还原、甲基化等代谢过程可显著改变砷的生物利用度和毒性特征。流行病学调查与动物实验均显示,砷暴露引发的肠道菌群失调与多种砷相关疾病的病理进程呈现显著关联[10],提示肠道微生

态可能成为砷毒性作用的关键中介环节。现有研究虽然已初步揭示了砷与肠道微生物组之间的相互作用，但关于其具体机制的研究仍不够充分。因此，深入解析肠道菌群在砷毒性中的作用，可为揭示砷致病机制提供新视角。

综上所述，砷暴露与肠道微生物组的相互作用可能是理解砷对人类健康影响的重要切入点。通过对砷暴露后肠道微生物组的深入研究，可以为制定更有效的干预措施提供理论基础，从而减轻砷对人类健康的危害。本文系统综述砷的代谢途径及其多器官毒性效应，重点探讨砷暴露对肠道菌群组成与功能的影响，并解析菌群紊乱在砷相关疾病中的潜在作用。通过整合近年来的实验与流行病学证据，旨在串联砷暴露、肠道菌群紊乱与疾病发生的关联，为砷毒性的防治提供新视角和潜在干预靶点。

2. 砷的代谢与毒性特征

2.1. 砷的化学形态

自然界中，砷主要以无机砷(iAs)和有机砷两种形态存在。无机砷是环境中最为常见的形式，主要包括砷酸盐(iAs^{5+})和毒性更强的亚砷酸盐(iAs^{3+}) [11]。 iAs^{3+} 能够通过其巯基(-SH)结合，干扰细胞氧化还原平衡，加剧氧化应激，从而引发细胞损伤[12]；而 iAs^{5+} 毒性相对较低，通常需在体内还原为 iAs^{3+} 才表现出显著毒性。不同形态无机砷在环境中可通过化学和生物过程相互转化，使其环境行为更为复杂[13]。有机砷普遍被认为毒性较低，主要存在于海洋生物如海鱼、贝类和藻类中，常见形态包括砷甜菜碱、砷胆碱和砷糖等，它们因在人体内几乎不代谢并能快速排出而被视作低毒或无毒[14]。然而，无机砷在生物代谢过程中产生的中间产物——单甲基砷酸(MMA)和二甲基砷酸(DMA)，其毒性高于砷甜菜碱，且可在环境介质中被微生物转化为毒性更高的无机砷，增加了有机砷环境风险评估的复杂性[15]。

2.2. 砷的生物转化与代谢机制

砷在体内的代谢过程复杂，传统上认为无机砷经砷甲基转移酶(AS3MT)催化转化为单甲基砷酸(MMA)和二甲基砷酸(DMA)是一个重要的解毒过程，可促进砷的排泄并降低毒性，因此尿中 MMA 与 DMA 水平常被用作评估砷解毒能力的指标[16]-[18]。然而近年研究发现，甲基化过程中产生的中间代谢物(如三价单甲基砷酸 MMAIII)可能具有更高毒性，其不仅与细胞内氧化应激、细胞功能障碍、凋亡及基因突变相关[19][20]，还与尿路癌和心血管疾病等健康风险的增加有关[21]。这些证据促使我们重新审视砷甲基化过程的毒理学意义与健康影响。

2.3. 砷的多器官毒性效应

2.3.1. 砷的肠道毒性

砷暴露引发的肠道毒性主要表现为肠道屏障功能障碍、免疫及氧化应激反应激活，以及肠道菌群稳态破坏[22]。在 C57BL/6 雄性小鼠模型中，砷处理导致小鼠小肠中紧密连接关键蛋白 ZO-1 和 Occludin 的 mRNA 及蛋白水平显著下降，透射电镜进一步证实小肠上皮紧密连接结构受损[23]。同时，砷暴露会促使肠道炎症因子(TNF- α , IL-6, IL-1 β)水平升高，并通过激活 TLR4/Myd88/NF- κ B 信号通路加剧炎症反应，进一步破坏肠道屏障[23][24]。屏障功能下降使内毒素(如 LPS)更易易位入血，诱发全身性炎症[25]。此外，砷暴露还引起肠道菌群结构改变，病原菌相对丰度增加而益生菌减少，从而加剧肠道炎症状态[23]。这些变化提示，肠道菌群在砷毒性调控中可能具有重要介导作用。

2.3.2. 砷的肝脏毒性

肝脏作为砷生物转化与甲基化的主要器官，长期砷暴露会干扰其脂质代谢和代谢物组成，影响胆汁

酸分泌、脂肪酸合成等通路,导致胆汁酸积累并引发肝功能障碍与组织结构损伤[26][27]。同时,砷暴露诱发氧化应激,引起肝细胞死亡和炎症反应,并通过影响细胞增殖、分化、凋亡和自噬等过程促进肝损伤发展,甚至可导致肝纤维化与肝癌[28]。研究表明,砷的长期暴露会导致肝脏内铁离子积累,进而促进氧化应激,激活 JNK 和 p38MAPK 通路诱导肝细胞凋亡[29][30],而 IKK α 虽通过 p53 依赖性自噬减轻亚砷酸盐诱导的凋亡,自噬对 IKK α 的选择性降解反而加剧肝脏毒性[31]。此外,砷还通过降低 SOD、GPx 等抗氧化酶活性,并抑制 Nrf2 信号通路,削弱抗氧化防御能力,进一步加剧氧化损伤和炎症反应[29][32]。综上所述,砷通过影响肝脏的脂质和胆汁酸代谢以及氧化应激反应,损害抗氧化系统,最终导致肝脏的代谢紊乱和损伤。

2.3.3. 砷的肾脏毒性

砷在肾脏蓄积后主要通过产生过量 ROS 来诱导氧化应激,导致脂质过氧化和 DNA 损伤,并通过激活 NF- κ B 通路促进促炎因子释放,从而造成肾脏损伤[33]。无机砷进入人体后大部分被甲基化代谢,但在排尿过程中在肾脏中浓缩,影响近端小管的功能[34][35]。砷代谢产物也会影响组蛋白 H3K9 甲基化修饰,通过消耗 S-腺苷甲硫氨酸(SAM),干扰脂质代谢基因表达,进一步加剧了肾小管脂质蓄积与纤维化进程[36]。此外,砷可通过外泌体传递长链非编码 RNA,调控肾细胞凋亡相关蛋白 BAX 表达,诱发细胞程序性死亡[37]。最新的研究显示,砷通过 m6A 甲基化修饰抑制 PGC-1 α ,降低谷胱甘肽过氧化物酶活性,诱发铁依赖性细胞死亡[38]。因此,氧化应激、炎症反应及细胞凋亡是砷肾脏毒性的潜在靶点。

2.3.4. 砷的神经毒性

砷暴露与多种神经功能障碍相关,包括记忆减退、注意力缺陷、帕金森病及周围神经病变等[39]-[43]。其神经毒性机制主要涉及氧化应激,表现为活性氧增加、脂质过氧化以及超氧化物歧化酶和谷胱甘肽水平降低[44]。砷还会干扰神经递质代谢,长期暴露可导致大脑中肾上腺素、多巴胺和 5-羟色胺等单胺类递质显著减少[43][45][46]。此外,砷会引起硫胺素缺乏并抑制丙酮酸脱氢酶活性,从而诱发脑病[47]。急性砷中毒可降低乙酰胆碱酯酶活性,这可能与周围神经病变及神经精神症状有关[41]。暴露于砷及其代谢物还会抑制海马区 NMDA 受体活性,导致神经行为与认知功能异常[48]。在分子层面,砷通过激活 p38MAPK 和 JNK3 信号通路诱导神经元凋亡[49]。综上,氧化应激、硫胺素缺乏、单胺类神经递质减少以及关键酶活性抑制共同构成了砷诱导神经毒性的核心机制。

2.3.5. 砷的心脏毒性

砷的心脏毒性机制包括氧化应激、DNA 断裂、细胞凋亡和离子通道的功能变化[50]。砷的代谢中会产生各种类型的活性氧(ROS),如超氧阴离子自由基、单线氧、过氧基团和过氧化氢,这在心脏损伤中起着核心作用[51]。谷胱甘肽(GSH)是一种有效和强大的细胞抗氧化剂,经常被用作氧化应激的标志。有研究报告称,砷暴露会降低心脏 GSH 水平,并且增加氧化谷胱甘肽和蛋白质羧基的数量,促进 DNA 损伤和脂质过氧化[52][53]。在心脏中,砷还可以通过改变离子通道的功能来触发毒性效应,包括钾离子通道和 L 型钙离子通道[5]。

3. 砷暴露对肠道菌群结构的影响

3.1. 砷暴露引起肠道菌群失调

成年人肠道中细菌数量约为 10^{13} 至 10^{14} 个,涵盖 500~1000 个不同物种,其中拟杆菌门和厚壁菌门占主导地位,占肠道微生物总量的 80%以上[54]。研究表明,砷暴露会显著影响肠道微生物组成,特别是在动物模型中可导致微生物多样性和丰度明显下降。孕期砷暴露会使 Balb/C 小鼠子代鼠仔肠道微生物多样

性降低,其中有益菌群如 *Muribaculaceae* 丰度减少,而潜在有害菌群的相对丰度增加[55]。另一项研究显示,C57BL/6 雄性小鼠经 30 天砷暴露后,肠道微生物的 α 和 β 多样性均显著降低,且这种变化与砷暴露呈明显相关性[56]。此外,研究还发现砷暴露会引起小鼠肠道微生物组成显著改变,不同菌群的变化可能与其在代谢和免疫功能中的特定作用有关[57]。这些研究表明砷能够引起微生物群落失衡,并可能导致健康问题的增加。

3.2. 砷暴露对肠道微生物影响的剂量 - 反应关系

动物模型与组织学研究表明,砷暴露对肠道菌群的影响呈现明显的剂量 - 反应关系。多项研究显示,高浓度砷暴露会显著抑制多种微生物的生长与生理功能。例如,C57BL/6 小鼠在高剂量(250 ppb)砷暴露两周后,肠道内拟杆菌门丰度随时间显著上升,黏膜表面微生物膜结构发生降解;而低剂量(10 ppb)暴露组在短期(至第 10 周)未出现显著变化[58]。另一项相似研究显示,当暴露于 100 ppb 砷剂量长达 13 周时,C57BL/6 小鼠模型中肠道菌群的 α 多样性与 β 多样性均发生显著改变,菌群组成结构呈现特征性重构[59]。有趣的是,在慢性砷污染的环境中,某些微生物如 *Desulfomicrobium* 和 *Clostridium* 等,会逐渐适应并在高浓度砷环境中生存,而短期的高浓度砷暴露则可能导致微生物群落的迅速崩溃和功能丧失[60]。这种剂量 - 反应关系也体现了砷暴露对某些肠道微生物的影响具有阈值效应和慢性累积性。尽管美国环境保护署将饮用水砷标准定为 0.01 mg/L (10 ppb) [61],但流行病学调查发现,人类长期(15 年)暴露于中等浓度砷(井水 78.2 μ g/L)后,肠道细菌丰度和群落一致性虽呈负相关趋势,但该差异在统计学上并不显著[62]。这表明单纯依靠群落组成变化可能难以充分解释砷对人类健康的影响,而砷对肠道细菌代谢机制的调控作用值得进一步探讨。

3.3. 砷暴露下肠道微生物的响应差异

除了暴露浓度和时间外,个体特征也显著影响砷暴露对肠道菌群的作用。在不同生命阶段,砷暴露引起的肠道微生物种群变化、细菌抗砷基因表达水平及肠黏膜因子分泌均存在差异[63]。宿主性别同样关键,砷暴露会以性别特异性方式扰乱肠道微生物组的组成轨迹和功能,宏基因组学数据显示不同性别婴儿的功能宏基因组受到不同扰动[64]。从物种类型来看,砷对肠道菌群的影响存在显著种间差异:土壤动物微生物多样性及功能因砷暴露而改变,进而影响宿主生理状态[65];鱼类如虹鳟可通过调节肠道菌群增强免疫应答,且益生菌能提升微生物稳定性以抵抗砷胁迫[66];哺乳动物(尤其小鼠)模型中,砷暴露诱导肠道菌群组成变化并进一步影响宿主代谢与免疫[67]。这些物种特异性的响应为我们理解砷及其他环境毒素对生物体健康的影响提供了重要的生物学基础。

4. 肠道微生物在砷暴露中的作用

4.1. 肠道微生物影响宿主砷吸收与排泄

肠道微生物群是调节宿主砷代谢与毒性的关键中介。研究表明,清除苹果螺的肠道微生物后,其体内砷含量及代谢产物比例显著降低,无菌条件下的实验也证实该生物对砷的转化能力减弱,说明肠道菌群直接影响砷的生物积累与转化过程[65]。斑马鱼模型中亦观察到类似现象:抗生素处理不仅减少了体内总砷及砷代谢产物的积累,还导致肠道内容物丧失砷转化功能[7]。这些结果提示肠道微生物不仅参与砷的生物转化,还可能调控肠道对砷的吸收与排泄。

肠道微生物还通过影响肠道屏障功能调节砷的毒性。它们通过代谢产物(如短链脂肪酸,SCFAs)调控紧密连接蛋白表达,增强上皮屏障完整性,从而减少砷等有害物质的吸收[68]。SCFAs 通过激活 G 蛋白偶联受体(GPR41, GPR43)进一步调节肠道吸收特性[69]。此外,肠道菌群参与胆汁酸代谢,将初级胆汁酸

转化为次级胆汁酸；菌群失调可能改变此过程，提高砷的吸收率[70]。肠道微生物的组成还影响砷的排泄途径，具体体现在尿砷与粪砷比例的变化上[71]。通过肠肝循环，肠道菌群产生的 SCFAs 对肝脏脂质代谢和毒素处理产生积极影响，进而提升宿主对砷的排泄能力[72]。因此，肠道微生物及其代谢产物通过影响紧密连接蛋白、胆汁酸代谢以及肝脏代谢等途径，在调控宿主对砷的吸收和排泄过程中扮演着重要角色。

4.2. 肠道微生物砷生物转化基因的表达与功能

砷生物转化基因(ABGs)是微生物中编码砷代谢酶的功能基因群，包括砷氧化基因(*aoxR*, *arxA*, *aioAB*, *arsJ*)、还原基因(*arsC*, *gstB*, *arrAB*)、甲基化/去甲基化基因(*arsI*, *arsM*)及外排基因(*arsP*, *arsK*, *arsB*) [73]。研究表明，土壤动物肠道中 ABGs 丰度与体内砷累积量呈显著负相关：ABGs 低丰度的蚯蚓体内砷累积量可达高丰度跳虫的十余倍。砷暴露会显著降低蚯蚓 ABGs 丰度，其他土壤动物的 ABGs 丰度则随砷浓度呈先升后降趋势。ABGs 表达与肠道菌群结构密切相关，菌群变化直接影响其表达水平[74]。此外，ABGs 与微生物抗药性基因(ARGs)之间存在交互作用，共同调节微生物对砷的适应性[75]。

在分子机制层面，Ars 操纵子作为微生物砷抗性系统的核心调控单元，最早发现于大肠杆菌和金黄色葡萄球菌的质粒中[76]-[78]。该操纵子通常由多个 ABGs 串联组成，其核心包括亚砷酸盐响应调节蛋白编码基因(*arsR*)、三价砷外排泵基因(*arsB*)及五价砷还原酶基因(*arsC*) [79]。细菌 Ars 操纵子已在多种临床重要病原体中被鉴定和表征，同样也存在于人类肠道共生体中，如 *Bacillus subtilis* 和专性厌氧菌 *Bacteroides vulgatus* [80]。全基因组序列分析表明，人类肠道菌群的主要成员之一的拟杆菌属包含 *arsR*、*arsD*、*arsA*、*arsC* 和 *arsB* 等砷抗性基因，并且 As (III) 的添加使所有 *ars* 基因表达显著上调[57]。因此，ABGs 及其核心调控单元 *ars* 操纵子共同构成了微生物应对砷暴露的核心分子机制(图 1)。

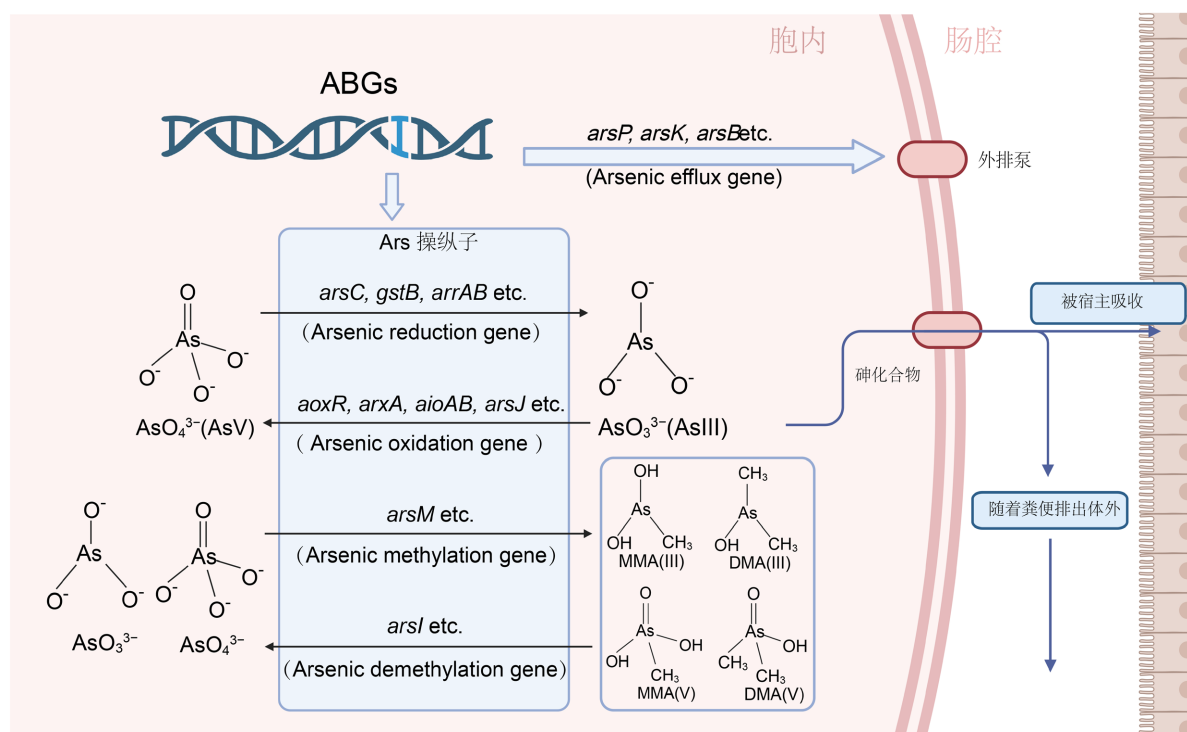


Figure 1. Gut microbiota express ABGs to participate in the biotransformation process of arsenic.

图 1. 肠道微生物群通过 ABGs 的表达参与砷的生物转化过程

4.3. 肠道微生物介导砷的生物转化

4.3.1. 砷的氧化和还原

砷还原是微生物解毒的关键途径,人类肠道微生物组携带的 *arrA* 和 *arsC* 基因,与胃肠道中的 As(V) 还原机制相关。其中 *arsC* 基因编码砷酸盐还原酶,将高水溶性的 As(V) 转化为易被外排的 As(III),再由 *arsB* 基因编码的外排泵将 As(III) 主动泵出细胞外[81]。而 *arsC* 基因可能存在于肠道细菌中,如肠杆菌科[82]。另一项研究指出,来自人类肠道的硫酸盐还原细菌沃氏嗜胆菌可能携带 *arrA* 基因,其载体可导致吸附的 As(V) 的直接还原[83]。

微生物介导的砷氧化,是指微生物通过酶促反应将高毒性的 As(III) 氧化为毒性较低的 As(V) 的过程[84]。这些微生物的砷氧化能力与其基因组中携带的砷氧化相关基因密切相关,例如催化 As(III) 厌氧氧化的 *ArxAB* 基因以及见于好氧或微氧微生物中的 *AioAB* 基因[85]。As(III) 的氧化过程主要存在于环境微生物中,而在肠道中该过程已在多种细菌中进行了研究,其中包括肺炎克雷伯菌、芽孢杆菌属等[86]。某些肠道细菌,如大肠杆菌和芽孢杆菌属的成员,可以通过各种酶系统有效地将 As(III) 氧化为 As(V) 或其他有机砷化合物,从而调节其毒性和生物积累潜力[87]。然而,肠道微生物的砷生物转化以砷还原过程为主,对于砷的氧化过程仍然较少,肠道环境中的砷氧化机制尚不明确。

4.3.2. 砷的甲基化和去甲基化

传统上,砷在肝脏中的甲基化被认为是主要的解毒途径,其产物单甲基砷(MMA)和二甲基砷(DMA)可随尿液排出体外[88]。然而,近年研究发现肠道微生物群在砷的甲基化与去甲基化过程中扮演着核心角色。在砷诱导的肝癌模型中,与传统 C57 小鼠相比,无菌小鼠尿液中砷及其代谢物的排泄量更高,MMA 与 DMA 比例上升,而粪便中砷浓度较低;进一步研究显示,无菌小鼠体内与砷甲基化相关的酶表达下调,表明肠道菌群参与了砷的吸收与转化[89]。微生物介导的砷甲基化由 *arsM* 编码的 S-腺苷甲硫氨酸(SAM)甲基转移酶催化,该基因是哺乳动物 *As3mt* 基因的细菌同源物[90]。研究还发现,将健康人肠道菌群移植给 *As3mt* 基因敲除的无菌小鼠模型后,小鼠能完全抵抗急性无机砷暴露的致死效应,这一保护作用被归因于常见肠道微生物(如普拉梭菌)中 *arsM* 基因簇的活性[91],表明肠道微生物表达的 *arsM* 甚至能弥补宿主肝脏甲基化能力的缺失,构成关键的解毒机制。

砷甲基化通常被视为解毒过程,但当生成毒性更强的甲基化中间体(如 MMAIII 和 DMAIII)时,去甲基化反而可能成为解毒的一部分[92]。在微生物中,由 C-As 裂解酶(*ArsI*)催化的 MMAIII 去甲基化是其有效解毒途径之一[92]。例如,在大肠杆菌中表达源自芽孢杆菌的 *arsI* 基因后,菌株获得了对甲基化三价砷的抗性[78]。然而,*arsI* 基因目前仅发现于需氧细菌中,在人类肠道占主导的厌氧菌中可能较为少见[80],因此肠道微生物介导的砷去甲基化机制及其生理意义仍有待深入探索。

5. 肠道微生物与砷相关疾病的关联

由于砷的代谢机制及其毒性,其暴露可在人体内引起多种疾病。这些疾病包括癌症、心血管疾病(高血压和动脉粥样硬化)、神经疾病、胃肠道疾病、肝脏和肾脏疾病以及对生殖健康的负面影响[93]。在砷相关疾病的发生发展过程中,肠道菌群可能起到一定作用。

5.1. 心血管疾病

环境暴露是心血管疾病(CVD)的重要危险因素。研究表明,砷可能参与 CVD 的发生与发展,但其具体机制尚未明确[94]。早期研究发现,砷暴露会加速动脉粥样硬化斑块形成,并伴随硝基酪氨酸和白三烯合成的显著增加,提示该过程可能与砷诱导的炎症反应有关[95]。

近年来,研究进一步揭示,肠道微生物群在长期砷暴露人群的 CVD 风险中扮演着重要角色[96]。一方面,肠道细菌群引发的宿主炎症反应,能够导致血管内皮功能异常,进而对血压产生影响,增加动脉粥样硬化的发生风险。另一方面,肠道细菌组成和代谢的改变同样会提升 CVD 的患病风险,且这种风险可能贯穿个体的整个生命周期[97]。肠道细菌通过多种途径影响宿主血压变化。例如,双歧杆菌、埃希菌、乳酸菌和链球菌等参与自主神经系统内神经递质的合成过程,进而影响血管张力,推动高血压的发展[98][99]。在肠道微生物代谢物中,三甲胺 N-氧化物(TMAO)被认为是一种潜在的新型促动脉粥样硬化分子,而砷可以通过一系列代谢过程调节 TMAO 的产生[100]。此外,马尿酸盐[101]和 LPS [102]等代谢产物,同样在动脉粥样硬化的发生发展过程中起到促进作用。值得注意的是,肠道菌群的影响是双向的,部分菌株如嗜粘蛋白阿克曼菌通过增强肠道屏障起到保护作用[103],短链脂肪酸和部分次级胆汁酸等代谢物则有助于抑制炎症、减缓动脉粥样硬化。

5.2. 癌症

肠道微生物与 AS 暴露所致的癌症发生发展密切相关。作为公认的一类致癌物,长期砷暴露可引发皮肤癌、肺癌、肾癌、膀胱癌等多种癌症[104],而肠道菌群在砷的代谢、毒性调控及致癌过程中扮演关键角色。砷暴露会引起肠道微生物生物膜降解,这不仅扰乱肠道正常生理功能、增加病原感染风险,还可能提升肠道渗透性,导致异常吸收并增高癌症风险[105][106]。同时,肠道上皮屏障与免疫和神经内分泌网络紧密关联,其受损会打破免疫耐受平衡,诱发肠道乃至全身的炎症性疾病与肿瘤[107]。此外,砷所致菌群结构改变可激活炎症通路,且菌群代谢产生的次级胆汁酸能诱导肝细胞病理性改变与炎症因子分泌,阻碍肝功能,进而增加肝硬化和肝细胞癌的发生风险[108]。

5.3. 糖尿病

2 型糖尿病(T2D)是一种以胰岛素信号通路紊乱为特征的代谢病。砷作为一种内分泌干扰物,其暴露与糖尿病风险增加有关。研究显示,砷可能通过抑制胰岛素激活的信号通路来影响胰岛素分泌[109]。长期砷暴露会引发多种与 T2D 相关的病理机制,包括抑制胰岛素依赖的葡萄糖摄取、诱导胰岛 β 细胞损伤与功能障碍,以及刺激糖异生过程[93]。通过这些机制,砷暴露直接参与了 T2D 的发生与发展。

砷暴露还会改变肠道微生物的群落结构和代谢功能[110],进而间接促进 T2D 发展。肠道菌群紊乱可引起碳水化合物水解异常和营养代谢失衡,并通过诱发炎症、降低胰岛素敏感性等途径,导致高血糖和胰岛素抵抗[111]。此外,菌群能调节结肠大麻素样配体 1 (CB1)表达,影响紧密连接蛋白 ZO-1 和 occludin,增加肠道通透性,从而促进肥胖与胰岛素抵抗,最终引发糖尿病[112]。同时,菌群失调还会影响短链脂肪酸(SCFAs)的生成,而 SCFAs 是脂质合成与糖代谢的关键调节因子[113],其产量异常会间接影响糖代谢,成为砷致糖尿病发生发展的重要助推因素。

5.4. 神经性疾病

慢性砷暴露会损害暴露动物的神经和脑组织,从而影响神经系统。临床研究表明,接触砷会对中枢和周围神经系统造成损害,导致抑郁、记忆力丧失,并影响身体协调性[114]。这些损害与砷诱导的氧化应激、线粒体功能障碍及神经炎症密切相关,而肠道菌群通过“脑-肠轴”信号通路发挥关键介导作用。研究发现,多种神经性疾病中存在有益菌群数量减少的现象,自闭症儿童肠道菌群组成的显著变化就是典型例证[115][116]。此外,长期摄入含有益生菌的发酵乳制品可以调节健康受试者大脑网络的反应性[117]。砷暴露引发的菌群失调可扰乱神经肽 Y (NPY)、 γ -氨基丁酸(GABA)、多巴胺(DA)及 5-羟色胺(5-HT)等神经递质的分泌[12]。研究表明,肠道菌群紊乱还会协同增强砷的神经损伤作用。正常情况下,肠

道菌群产生的 SCFAs 丁酸盐、色氨酸代谢产物以及次级胆汁酸,能直接或间接拮抗砷诱导的神经炎症、氧化应激和神经元损伤[118][119]。然而,慢性砷暴露导致的菌群失调致使这些有益代谢物减少,并可能增加神经毒性物质喹啉酸的产生,同时损害肠道屏障功能[120][121]。这种菌群失调和屏障破坏会促进系统性炎症,并使砷及其代谢物、细菌脂多糖等毒性物质进入血液循环。最终,这些因素通过肠-脑轴作用于中枢神经系统,加剧砷的神经毒性效应,共同促进认知障碍和神经退行性疾病的发生与发展。

6. 结论

砷作为一种普遍存在的环境污染物,由于长期低剂量暴露对多系统生理功能的有害影响,已成为全球性公共卫生问题。本文系统综述了肠道微生物组在砷毒性效应及相关疾病发生发展中的核心介导作用。通过其代谢功能及砷生物转化基因(ABGs)的表达,肠道菌群积极参与砷形态转化、生物利用度及体内分布过程,甚至能在一定程度上补偿宿主砷甲基化能力的缺陷。反之,砷暴露可诱导肠道微生物群落结构和功能紊乱,表现为微生物多样性降低、组成结构改变及生物膜完整性受损,从而破坏肠道屏障功能。这种微生物-屏障联合损伤不仅促进内毒素易位进入体循环,更通过加剧全身炎症反应、氧化应激、代谢稳态失衡及异常的肠-脑轴信号传导,协同放大砷对多靶器官的毒性效应。值得注意的是,肠道菌群失调与砷相关心血管疾病、癌症、糖尿病及神经退行性疾病的发生发展密切相关。砷的毒性不仅源于其对组织器官的直接损伤,也通过对肠道微生物组组成与功能的调控间接介导。因此,以肠道菌群为靶点开发干预策略,有望成为缓解砷毒性的新途径。未来研究需进一步阐明“砷-微生物-宿主”轴的具体分子机制,明确不同微生物类群在砷代谢与毒性中的功能作用,并开发基于微生物组的精准防治策略,从而为砷相关疾病的临床和公共卫生管理提供科学依据。

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