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微囊藻毒素与疾病

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【摘要】微囊藻毒素（MCs）是由蓝藻等藻类产生的环状七肽毒素，因全球水体富营养化加剧而对生态环境和人类健康构成严重威胁。MCs可通过饮用水、食物链、皮肤接触，及气溶胶吸入等途径进入人体，其毒性机制主要依赖于抑制蛋白磷酸酶PP1/PP2A活性，进而干扰细胞信号转导、诱导氧化应激和表观遗传紊乱。大量研究证实，MCs具有多器官毒性：在肝脏中可引发肝纤维化甚至肝癌；在神经系统中可能导致阿尔茨海默病和帕金森病样损伤；在胰腺中干扰胰岛素分泌，增加糖尿病风险；在肾脏中诱发炎症和纤维化；在生殖系统中损害精子质量及卵巢功能。此外，MCs与其他环境污染物的协同效应可能进一步放大其毒性。本文通过对MCs毒性机制的综述，希望进一步聚焦MCs的毒代动力学、复合暴露效应及在慢性疾病中的作用，为制定更严格的环境限值和公共卫生策略提供依据。

【关键词】微囊藻毒素；水体富营养化；环境暴露途径；多器官毒性

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Microcystins and diseases

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【Abstract】Microcystins (MCs) are cyclic heptapeptide toxins produced by cyanobacteria and other algae; they pose severe threats to ecosystems and human health due to increasing global eutrophication. MCs can enter the human body through drinking water, the food chain, dermal contact, and aerosol inhalation. Their toxicity primarily arises from the inhibition of protein phosphatase PP1 / PP2A activity, leading to disrupted cellular signaling, oxidative stress, and epigenetic dysregulation. Extensive studies demonstrate that MCs exhibit multi-organ toxicity: in the liver, they can induce fibrosis and even hepatocellular carcinoma; in the nervous system, they may cause Alzheimer's - and Parkinsonian-like damage; in the pancreas, they disrupt insulin secretion, increasing diabetes risk; in the kidneys, they trigger inflammation and fibrosis; and in the reproductive system, they impair sperm quality and ovarian function. Furthermore, synergistic effects between MCs and other

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environmental pollutants may amplify their toxicity. This article reviews the toxic mechanisms of MCs and highlights the need to focus on their toxicokinetics, co-exposure effects, and role in chronic diseases to inform stricter environmental regulations and public health strategies.

【Keywords】 Microcystins(MCs); Water eutrophication; Environmental exposure pathways; Multi-organ toxicity

藻毒素是由藻类在自然生长或水华过程中产生的有毒次生代谢产物，具有特异性毒性机制，在自然条件下发挥防御、竞争等生态功能，可通过直接接触、饮用水、食物链或气溶胶等途径威胁人类健康和生态系统安全[1-2]。其中，微囊藻毒素（Microcystins，MCs）因其分布广泛、环境稳定性强及毒性显著，成为研究最深入的藻毒素之一。MCs可通过抑制蛋白磷酸酶活性、诱导氧化应激、干扰表观遗传调控等方式，导致肝损伤、神经退行性变、肾功能障碍，及生殖系统毒性等多器官危害。随着全球气候变化和水体富营养化加剧，藻华事件频发，MCs的暴露风险日益突出。本文综述了MCs的环境来源、人体暴露途径及其对不同系统的毒性机制，以期为藻毒素的生态风险防控和公共卫生策略制定提供科学依据。

1 藻毒素的分类与环境来源

1.1 产毒藻类与主要藻毒素类型

藻毒素可以根据其生物来源和毒性效应分为多种类型。按产毒藻种类分类，藻毒素主要来源于蓝藻门、甲藻门、硅藻门和金藻门藻类[3]。按毒性效应分类，则可分为肝、肾、神经、细胞、皮肤、生殖毒素等[4-5]。需要注意的是，同一种藻毒素可以由不同藻类产生，而同一藻类也能产生不止一种藻毒素[2]。

1.2 藻毒素污染产生的环境因素

化肥使用造成的水体富营养化和全球气候变暖背景下的水体温度增高导致藻类爆发增长已成为共识。以太湖为例，自20世纪90年代开始，湖水中总氮、总磷浓度波动上升，引发多起藻华事件，尤以夏季为甚。2005—2006年检测期间发现湖水中溶解态MCs峰浓度为6.69 μg/L[6]，2007年太湖爆发大规模藻华引发饮用水危机。随着政府对工农业污染管控加强，太湖水中总氮浓度下降明显，水质获得明显提升[7]。有研究提出除水温和水氮、磷含量这两个传统因素外，水中营养盐比例、存在形式及其动态代谢过程通过食物网级联效应调控藻华发生与毒性的作用更为显著[8]。Lürling等[9]的实验结果表明，虽然水温升高使得单个蓝藻细胞产毒减少，但环境条件（如富营养化和升温）导致蓝藻暴发性增殖，整体毒素风险仍会显著上升。简而言之，藻毒素的大量产生与人类活动密不可分。

2 MCs的人体暴露途径

MCs进入人体途径按风险等级排序主要包括：口服暴露、皮肤接触、气溶胶吸入。

2.1 口服暴露

水源水库藻华的发生使得饮用水中存在MCs，虽然世界卫生组织推荐将自来水中MCs的含量限制在1 μg/L，但长期低剂量暴露可能会增加结直肠癌和肝癌的患病风险[10-12]。自来水中还包括节球藻毒素、石房蛤毒素、鱼腥藻毒素、柱孢藻毒素等，其毒性效应从肝毒性到神经毒性不等[13]。人体另一摄入藻毒素的重要途径是食用海产品，包括动、植物类。根据Backovic等[14]的统计，在来自全球23个国家的47项研究中，水生生物可食用组织中检出多种藻毒素，包括最常见的MCs、节球藻毒素、β-甲氨基-L-丙氨酸及其衍生物、鱼腥藻毒素、石房蛤毒素、柱孢藻毒素。这些毒素主要富集于鱼类，其次为甲壳类和软体动物。世界卫生组织相关报告也指出口服暴露是MCs进入人体最常见途径[15]。

2.2 皮肤接触

目前，研究更多关注藻毒素的经口暴露途径，但也有研究表明藻毒素可以对皮肤产生毒性作用[16]。MCs可通过皮肤角质层缓慢渗透，10 μmol/L浓度长期暴露会导致角质细胞数量减少并产生细胞毒性，表现为乳酸脱氢酶释放增加；50 ~ 100 μmol/L浓度的微囊藻毒素-LR（MC-LR）能显著抑制细胞迁移，并诱导F-肌动蛋白细胞骨架解聚[17]。1 μg/mL自然环境浓度的柱孢藻毒素及其分解产物能显著抑制人角质细胞增殖，24 h抑制率达到70%，细胞数量减少35%，并阻碍细胞迁移[18]。

2.3 气溶胶吸入

近藻华海域的风浪能够将水中的藻毒素气溶胶化，释放进入大气[1]。海喷雾气溶胶是蓝藻毒素进入大气的主要来源，其形成机制涉及浅层海水中气泡破裂产生的薄膜滴（直径0.2 ~ 10.0 μm）

和射流滴（直径1～250 μm）两类颗粒[19]。这些气溶胶颗粒携带海盐、生物质等组分，可被输送至1 000 km外的内陆地区[20]。有研究报道内陆淡水湖也能产生含有藻毒素的气溶胶[21]。但也有小鼠实验显示MCs吸入主要导致鼻腔上皮损伤，与吸入剂量呈正相关关系，对全身影响有限[22]。

3 MCs的代谢转化与毒代动力学特征

MCs为环状七肽，结构多样，自20世纪80年代第一个MCs的结构被解析，目前已知的同系物高达279种[23]。最常见的MCs同系物是MC-LR、MC-RR和MC-YR，其命名源于第2位和第4位氨基酸的差异（L代表亮氨酸，R代表精氨酸，Y代表酪氨酸）[4]。其中MC-LR具有极强的环境稳定性，在自然条件下降解困难[24]。合成MC-LR的藻类品种多样，多为淡水藻类，故此MC-LR在自然界广泛存在，对人类影响深远。

3.1 吸收与分布

MCs经口摄入人体后，主要通过小肠绒毛上皮吸收[25]。Henri等[26]利用Caco-2细胞模型研究发现，MC-LR能快速从肠腔侧进入小肠绒毛上皮细胞，但在30~45 min后，大部分毒素会再次分泌进入肠腔，仅有0.30%～1.35%的MC-LR能在24 h内转运至基底侧。这一主动外排机制可以解释为何小鼠灌胃实验中仅有0.7%剂量的MC-LR最终进入肝细胞[27]，相比之下，静脉注射实验中1 h后高达67%剂量的MC-LR会富集于肝脏[28]。值得注意的是，除了经口摄入，MCs也可经肺部吸收进入血液循环[29]。

MC-LR在体内的分布会因摄取方式（经口或注射）不同而产生极大改变。Robinson等[28, 30]利用[H^3]放射性标记的MC-LR证实，若MC-LR通过注射进入循环，将主要蓄积于肝脏，少部分进入肾脏、消化道等器官。而由于肠道的主动外排机制，通过口服摄取的MC-LR主要蓄积于消化道（38%），仅少部分毒素蓄积于肝脏、肾脏、脑等器官[27]。

有机阴离子转运多肽（Organic Anion Transporting Polypeptides，OATPs）家族在各器官对MC-LR的摄取中起重要作用。Fischer等[31]通过非洲爪蟾卵母细胞实验证实，MCs的跨膜转运主要依赖OATPs家族介导的主动摄取过程。在受测试的转运体中，大鼠Oatp1b2和人OATP1B1/1B3介导MC-LR的肝细胞摄取，而OATP1A2促进血脑屏障穿透，该转运过程可被牛磺胆酸和溴磺酞竞争性抑制，由此实验发现了MC-LR进入肝细胞的转运载体。后续由Fischer等[31-32]开展的研究证实，OATP1A2在血脑屏障、肾脏等中均有表达，提示OAPTs也是其他器官摄取MC-LR的关键分子。

然而，OATP1B1与OATP1B3存在若干单核苷酸多态性，这种基因变异常导致药物及外源性物质的转运效率改变[33]。*SLCO1B1*（编码OATP1B1的基因）的c.521T>C（p.Val174Ala）单核苷酸多态性在体外实验中显示出转运活性显著降低，该变异在欧洲和亚洲人群中分别具有14%和10%～15%的等位基因频率[34-35]。*OATP1B3*基因则存在两个完全连锁的非同义单核苷酸多态性（T334G和G699A）[36]；功能研究表明，由此形成的334G-699A单倍型对霉酚酸葡糖苷酸的转运功能受损，表现为底物亲和力不变但转运能力显著降低[37]。这些遗传因素与年龄相关的生理变化，如随年龄增长的肝脏代谢功能减退，可能产生协同效应，共同影响MCs的毒代动力学特征。因此，在评估MCs的人群健康风险时，需综合考虑年龄和*OATPs*基因多态性等关键因素，以准确识别易感亚群并制定个体化的风险管理策略。

3.2 代谢与排泄

肝脏是MCs的主要代谢场所。人体主要通过MCs与谷胱甘肽和半胱氨酸结合以清除体内的MCs[38]。研究表明，MCs分子中Mdha7/Dha7位点的α,β-不饱和羰基结构是该结合反应的关键位点[39]。这种共价结合可显著降低MCs的毒性，并减弱MCs对蛋白磷酸酶活性的抑制[40]。不同结构MCs同系物的代谢特征存在显著差异，亲水性较强的MC-RR表现出最高的谷胱甘肽结合效率，而疏水性较强的MC-LF几乎不发生结合反应[41]。值得注意的是，这种结合具有可逆性[42]。Li等[43-44]的研究证实，在大鼠体内MC-RR-半胱氨酸复合物可发生解离，重新释放出具有生物活性的MC-RR，表明MCs的解毒过程可能是一个动态平衡体系。此外，MCs的代谢转化存在明显的种属差异。实验数据显示，大鼠和小鼠对MCs的谷胱甘肽结合效率显著高于人类[45]，说明MCs对人类健康威胁可能被严重低估。

人体内的MCs主要通过尿液与粪便排泄。小鼠静脉注射实验证实，小鼠血浆中MC-LR呈现快速双相清除（α相 $t_{1/2}$=0.8 min，β相 $t_{1/2}$=6.9 min），约24%的MC-LR可在6 d内被排出体外，其中尿液排出9%，粪便排出15%，粪便中超过60%的MCs以原型形式存在[28]。Wang等[46]通过对小鼠MCs暴露后的尿液进行检测，发现MCs能够通过肾脏直接排出。Rankin等[47]发现，喂养MCs 8 d后的犬粪便中可直接检测到未代谢的MCs，证实未吸收或由

肠道再分泌的MCs可直接通过粪便排出。同时，肝脏作为MCs主要代谢场所，可将MCs及MCs代谢物分泌到胆汁，并通过粪便清除。由于肠肝循环的存在，排入粪便的MCs可能会重新吸收入血[48]。

4 MCs及其毒性机制

进入细胞后，MCs通过共价结合丝氨酸和苏氨酸蛋白磷酸酶PP1/PP2A的催化亚基对其发挥强效抑制作用[49]。PP1和PP2A是调控真核细胞蛋白质磷酸化和去磷酸化平衡的关键酶，参与胚胎早期发育、细胞周期进程、程序性死亡，以及肿瘤发生发展等关键生理病理过程[50]。对蛋白磷酸酶的抑制作用还会间接导致细胞过氧化应激、细胞凋亡和细胞骨架破坏[51]。

然而，MC-LR通过共价结合蛋白磷酸酶PP2A抑制其活性，导致下游信号通路异常的传统观点并不能解释其所有的毒理学性质，例如Zhang等[52]发现MC-LR可以直接通过作用于DNA产生毒性；Sun等[53]发现PP2A激动剂并不能逆转MC-LR导致的肝细胞骨架破坏，均说明MC-LR有潜在的PP2A非依赖毒性靶点。有研究采用热蛋白质组分析结合SWATH-DIA质谱技术，发现MC-LR作用于生物体后有129个潜在靶蛋白。在此基础上，生物信息学分析显示这些蛋白显著富集于多巴胺信号、蛋白酶体功能和NF-κB通路，首次证实了MC-LR可直接结合蛋白酶体亚基PSMD4/PSMB9等新靶点，并进一步证明其通过抑制蛋白酶体活性发挥毒性作用[54]。这些研究提示MC-LR进入机体后存在多靶点作用的现象，为MC-LR的新毒性机制研究提供了重要参考。

4.1 MCs的肝毒性

MCs的毒性作用主要体现在肝毒性。1996年，巴西某血液透析中心发生一起群体性MC-LR急性中毒事件，126例患者因使用含高浓度MCs的透析用水后，相继出现以亚急性肝毒性和急性神经毒性为主要特征的临床表现，最终导致60例死亡[55]。MC-LR导致亚急性肝损伤的表现主要为肝区疼痛、黄疸、转氨酶急剧升高，伴随恶心呕吐、出血倾向，重症者可发展为肝衰竭，神经系统症状从耳鸣、眩晕、头痛、耳聋到失明及抽搐不等[55]。

生活中，MCs能够通过饮用水进入人体，微量毒素慢性积蓄产生的毒性作用更常见。研究表明，MCs的暴露与慢性肝病的发生发展相关。Gu等[56]发现15 μg/kg剂量的MC-LR能激活肝星状细胞并影响Hedgehog信号通路，诱导小鼠肝纤维化。非酒精性脂肪性肝炎模型小鼠在MC-LR暴露后，肝脏恢复功能受损并持续促进致癌性改变，提示MC-LR可以与其他风险因素共同推动慢性肝病的发生发展[57]。MC-LR在低浓度下即可通过激活未折叠蛋白反应和脂质生成基因，同时抑制AKT/mTOR通路及自噬过程，诱导肝细胞脂肪变性和纤维化，RNA测序显示MC-LR调控非酒精性脂肪肝相关基因表达，证实其可通过多重分子机制促进代谢性肝病进展[58]。

有临床病例对照研究证明，MC-LR是肝细胞癌（Hepatocellular Carcinoma，HCC）的独立风险因素，且血清MC-LR水平与肿瘤分化程度呈负相关关系，提示其可能影响HCC恶性程度[59]，有小鼠实验性别差异分析表明雌性小鼠肝脏对MC-LR的敏感性显著高于雄性，更易发生肝毒性损伤[60]。MC-LR可抑制PP1/PP2A活性，磷酸化蛋白质组学显示，0.1 μmol/L的MC-LR作用24 h后可导致567个磷酸化位点异常增加，生物信息学分析结果显示异常磷酸化蛋白主要富集于核糖体蛋白S6激酶信号通路、血管内皮生长因子受体介导的血管通透性调控通路等与肝癌发生发展密切相关的信号网络中[61]。Liu等[62]在HL7702人肝细胞模型体外实验中，发现MC-LR暴露可显著干扰Akt/S6K1通路的正常功能，具体表现为AKT、ERK1/2等关键信号分子异常磷酸化水平升高，进而导致细胞内信号传导失常，引发肝细胞糖代谢、脂代谢紊乱，导致HCC。体内实验进一步证明，MC-LR抑制PP2A活性，诱导小鼠肝细胞增殖，并激活Akt/mTORC1/S6K1和MAPK信号通路，导致c-Jun、c-Myc等关键蛋白异常磷酸化[63]。MC-LR还能通过抑制PP2A活性，打破细胞内蛋白磷酸化–去磷酸化平衡，进而诱发氧化应激反应，使肝细胞内氧自由基升高，激活NADPH氧化酶系统，造成DNA氧化损伤，并且通过激活NF-κB等炎症通路导致慢性炎症，这也是MC-LR促进肝癌发生发展的重要级联反应[64]。除对PP2A的直接抑制作用外，MC-LR还可通过改变肝细胞中非编码RNA的表达谱参与HCC的发生。分析MC-LR暴露后HepG2细胞的miRNA表达谱发现，多种miRNAs的表达水平发生显著改变，在此基础上通过KEGG通路分析表明，MC-LR通过miRNAs调控MAPK信号通路、次级代谢物生物合成以及嘧啶和嘌呤代谢等关键通路介导HCC进展[65]。将人正常肝细胞HL7702暴露于不同浓度的MC-LR中，使用高通量测序技术检测发现MC-LR可能通过调控miR-451a、miR-4521和miR-15b-3p

等关键miRNA的表达，进而影响致癌信号通路，最终导致肝毒性[66]。MC-LR也通过调控环状RNA和长链非编码RNA激活致癌信号通路[67-68]，新型lncGCLC在MC-LR诱导的肝细胞恶性转化中持续下调，通过调节GCLC表达促进细胞增殖和肿瘤生长[69]。MC-LR还能够对细胞基因组产生直接作用，MC-LR暴露可导致肝细胞中DNA位点发生异常甲基化，并且显著上调DNA甲基转移酶的表达[70]。MC-LR可通过促进*ALX4*基因甲基化，下调L02细胞和大鼠模型中ALX4的表达，从而驱动HCC的发生[71]。

MC-LR能与多种环境污染物共同作用产生联合毒性。一项中国西南地区5 493名成人的社区横断面调查显示，MC-LR作为潜在协同因子，可显著增强乙型肝炎病毒和黄曲霉毒素的联合肝毒性效应，MC-LR、乙肝病毒和黄曲霉毒素三联暴露时，乙肝病毒DNA阳性者肝损伤风险呈现数量级升高，谷草转氨酶异常风险达11.38倍，丙氨酸氨基转移酶异常风险达17.09倍，显著高于单独乙肝病毒暴露或双因素暴露组（P<0.05）[72]。Gao等[73]的研究通过Luminex技术发现，低剂量、亚慢性联合暴露于MC-LR和黄曲霉毒素可导致C57BL/6小鼠肝脏中IL-18、GM-CSF等促炎因子显著升高，提示此类联合暴露可能通过特定细胞因子网络增加不可逆肝损伤风险。

4.2 MCs的神经毒性

MCs的神经毒性表现复杂。长期低剂量MC-LR暴露可导致多方面的神经系统损伤。在为期180 d的小鼠饮水暴露实验中，浓度为30 μg/L的MC-LR可突破血脑屏障进入大脑皮质、海马和黑质等区域，造成类似阿尔茨海默病的学习记忆功能障碍[74]。有研究发现，MC-LR可在黑质区蓄积，选择性损伤黑质多巴胺能神经元，诱发神经元凋亡，并伴随α-突触核蛋白异常聚集、多巴胺合成关键酶酪氨酸羟化酶和多巴脱羧酶等关键蛋白表达下降[75]；该过程与MC-LR和ERK2激酶结合有关，MC-LR可增强ERK2稳定性，促进分子伴侣介导的自噬，加速酪氨酸羟化酶和多巴脱羧酶降解，导致多巴胺水平下降[76]，最终导致多巴胺含量降低，这些特征与帕金森病的病理改变高度一致。同时，MC-LR还通过激活小胶质细胞、促进TNF-α、MCP-1和IL-6等炎症因子释放，破坏大脑屏障，进入大脑皮质、海马、下丘脑[77]。小鼠饮水暴露实验进一步证实，MC-LR可通过氧化应激和线粒体损伤等途径诱导SH-SY5Y细胞凋亡，且海马区对MC-LR的敏感性显著高于大脑皮质[78]。生物信息学荟萃分析证据支持过氧化应激理论，MC-LR暴露显著升高氧自由基的水平达294%，升高DNA损伤水平达174%，且暴露浓度与神经毒性显著相关，进一步验证了氧化应激的核心作用[79]。MCs对发育期神经系统也有影响，斑马鱼胚胎暴露实验显示，3.2 mg/L的MC-LR可导致孵化延迟、体长减少及运动速度下降，分子层面显示神经递质紊乱，基因表达失调，且幼体体内出现MC-LR蓄积[80]。有来自另一斑马鱼实验的证据显示MC-LR的神经毒性效应具有跨代效应，可通过父系暴露跨代传递，通过表观遗传影响子代神经系统发育，致子代神经发育相关基因表达下调，运动速度显著降低[81]。除MC-LR外，Klima等[82]使用中枢和外周神经元细胞模型实验发现MC-LF也具有神经毒性，但环境暴露浓度不能达到毒性风险水平，提示MCs众多同系物对神经系统的毒性不同。另外，斑马鱼实验证明MC-LR与亚硝酸盐等污染物可产生协同神经毒性，二者能够通过下调*mbp*、*bdnf*等髓鞘形成相关基因表达，破坏神经元结构与功能；同时降低多巴胺含量和乙酰胆碱酯酶活性，损害多巴胺能及胆碱能神经系统；联合暴露导致的丙二醛升高及锰超氧化物歧化酶活性降低也证实氧化应激是其协同神经毒性的关键机制[83]。

4.3 MCs的胰岛毒性

Zhao等[84]的研究通过对太湖渔民群体进行调查和小鼠模型实验，首次揭示了环境浓度的MCs暴露与胰岛功能损伤相关。通过调查发现梅梁湾地区渔民空腹血糖异常且胰岛素水平显著降低，进一步动物实验显示，5 μg/kg和20 μg/kg MC-LR暴露分别使小鼠血糖升高27.9%和降低41.5%，胰岛素水平下降21.9%和56.2%，在此基础上首次鉴定出糖尿病基因*pdx1*及Ppp3ca等7个与胰岛素分泌相关的蛋白标志物，提示MCs亚慢性暴露可能增加人类糖尿病风险。Zhao等[85]使用大鼠胰岛素瘤INS-1细胞模型进一步研究发现，不同浓度的MC-LR暴露可致细胞周期紊乱和凋亡增加、细胞活力降低、葡萄糖刺激的胰岛素分泌紊乱，并下调胰岛素蛋白表达，转录组分析也鉴定出*pdx1*等关键基因差异表达，并发现与1/2型糖尿病相关的信号通路。后续有研究证实，1 μg/L的MC-LR暴露即可改变小鼠血糖血脂谱，上调*FASn*等5个2型糖尿病相关基因[86]，且MCs可显著影响β细胞内质网蛋白加工、应激反应及糖尿病相关通路，并激活PERK/eIF2α/ATF4信号轴[87]。研究显示，MC-LR能够借助

Oatp1b2转运体进入小鼠胰腺细胞，并在慢性低浓度暴露下导致胰岛素分泌功能障碍，还通过透射电镜观察和免疫印迹试验检测到凋亡相关蛋白，提出线粒体途径凋亡是MC-LR胰腺毒性的核心机制[88]。这些研究发现微量MC-LR暴露也能够通过多种机制增加糖尿病风险，建议重新评估地表水中1 μg/L MC-LR的参考剂量限值。

4.4 MCs的肾脏毒性

MCs的肾脏毒性已得到流行病学调查和实验研究证实。流行病学调查显示，MCs暴露与人类肾功能损伤密切相关，中国巢湖渔民血清MCs水平与血尿素氮、肌酐等肾功能指标异常呈正相关关系[84]；在中国中部开展的一项基于人群的病例对照研究发现，MC-LR最高暴露组的慢性肾脏病风险显著增加6.56倍，是慢性肾脏病的独立风险因素[89]。由于肾脏血流量占心脏输出量的25%，静脉注射MC-LR后，肾脏中毒素浓度显著高于其他器官[90]。有研究证明肾脏也能够表达OATPs，表达OATP1B3的人胚胎肾细胞系HEK293细胞对MC-LR敏感性显著提高[91]。动物实验证明，MCs在肾脏快速蓄积并诱发剂量依赖性损伤，急性暴露可导致肾小球充血、近端小管空泡化及肾功能相关指标迅速升高[92]，慢性暴露则引起肾间质纤维化和胶原沉积[93-94]。在分子机制层面，MCs不仅通过特异性抑制蛋白磷酸酶PP1/PP2A破坏细胞骨架和紧密连接，激活PI3K/AKT信号通路诱发肾脏炎症反应，导致肾功能损伤和组织病理学改变[95]，还能诱导线粒体功能障碍，表现为线粒体嵴断裂、膜电位下降，并通过MKK6/p38信号通路抑制parkin介导的线粒体自噬，体外实验进一步证实MCs可致人胚胎肾细胞HEK293出现DNA损伤、内质网应激和凋亡[96]。研究发现，MC-LR与亚硝酸盐联合暴露可通过协同激活TLR4/NLRP3/GSDMD信号通路，显著加剧肾脏炎症反应和细胞焦亡，导致更严重的肾功能损伤[97]，提示MC-LR与环境污染物存在协同作用加剧毒性效应。

4.5 MCs的生殖毒性

MCs具有生殖系统毒性。MC-LR对生殖系统的毒性机制主要涉及以下三点：特异性抑制PP1/PP2A磷酸酶活性，干扰细胞内蛋白质磷酸化平衡；通过表观遗传修饰，如DNMT3A/B介导的DNA甲基化，影响关键基因表达；调控非编码RNA网络[98]。MC-LR对男性生殖系统具有显著毒性作用。一项来自江苏和安徽的横断面研究显示，精液中MCs水平升高与男性精子总数减少（P=0.033）、活力下降（P=0.010）及畸形率增加（P=0.016）显著相关，提示MCs暴露可能通过损害精子质量导致男性不育，该结果与既往动物实验结论一致[99]。MC-LR能够破坏血睾屏障的完整性，导致支持细胞紧密连接蛋白表达下调[100]。在睾丸支持细胞和生精细胞中，MC-LR通过结合PP2A催化亚基抑制其活性，进而激活PI3K/AKT/NF-κB通路，促进促炎因子释放，而在间质细胞中，则通过TLR2受体触发先天免疫反应，动物实验证实，长期暴露导致小鼠的精子数量减少和形态异常[101]。另一方面，环境浓度MC-LR长期暴露可通过靶向小鼠卵巢颗粒细胞，引发氧化损伤，使发育卵泡数量减少30%～50%，进而导致雌性生育力下降[102]。MCs对于女性生殖系统的特殊毒性机制主要体现在对下丘脑–垂体–性腺轴（HPG轴）的影响。MC-LR急性暴露可显著干扰雌性大鼠HPG轴功能，表现为下丘脑促性腺激素释放激素表达下降、血清E2降低而黄体生成素和卵泡刺激素异常升高，同时伴随卵巢组织损伤和性激素合成基因表达紊乱[103]。MCs对雌性哺乳动物生殖系统的毒性作用如诱导细胞凋亡、引发炎症反应、干扰卵泡发育、造成卵巢萎缩等最终都会破坏卵巢类固醇合成功能，引起性激素分泌紊乱。还有研究证明，聚苯乙烯微塑料能够作为载体，显著提升MC-LR在斑马鱼性腺中的生物蓄积量，延长毒素作用时间，通过破坏性腺组织结构、干扰HPG轴相关基因表达，最终引起性激素调控紊乱，协同加剧了生殖毒性[104]。

5 总结与展望

本文综述了藻毒素的类型、造成环境污染的因素、MCs的暴露途径，及其相关毒性效应。人类暴露于MCs的案例全球可见，可导致各系统毒素蓄积和多器官毒性。目前对MCs毒代动力学参数仍缺乏明确认知，亟须深入研究MCs的人体吸收比例和组织特异性分布规律。另一个潜在研究方向是阐明MCs与其他环境污染物的复合暴露效应，及其在慢性疾病发生中的作用机制。另外，当不良生活方式等致病因素与外源性毒素共同作用时能否协同增加疾病风险？解决这些科学问题将为制定MCs暴露限值和风险评估策略提供关键依据，从而更好地保障公众健康。

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