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Hans汉斯

微塑料促进结直肠癌的发生发展

康逸群[1]，曾涵仪[2]，詹　瑾[1]，黄海涛[3]，崔　超[3*]

[1]赣南医科大学第一临床医学院，江西　赣州
[2]赣南医科大学第一附属医院生殖医学科，江西　赣州
[3]赣南医科大学第一附属医院胃肠外科，江西　赣州

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摘　要

自20世纪初高分子合成技术突破以来，塑料制品因其卓越的物理化学特性在全球范围内获得广泛应用。然而，伴随全球塑料年产量攀升至3.59亿吨，由其衍生的环境污染已成为21世纪最严峻的生态挑战之一。值得注意的是，中国作为全球最大的塑料生产国，其环境微塑料污染负荷与人群健康风险呈现显著的地域相关性。近年流行病学研究揭示，自塑料工业化普及后，结直肠癌(Colorectal Cancer, CRC)发病率呈现与塑料制品使用率同步增长的趋势，提示环境微塑料暴露与肠道肿瘤发生可能存在潜在关联机制。我们探讨了微塑料作为这一变化的驱动因素可能发挥的作用，揭示微塑料的致癌效应：微塑料破坏肠道保护功能；微塑料通过干扰菌群、破坏免疫屏障导致肿瘤免疫逃逸；微塑料诱发持续性氧化损伤，进而驱动促癌通路的异常活化；微塑料作为“特洛伊木马”成为毒物载体，与微生物、有机污染物、重金属产生协同致癌效应；最后是微塑料影响结直肠癌患者的预后转归。本综述将为建立基于微塑料暴露的CRC风险预警模型提供方向，并为制定环境健康综合防控策略开辟新路径。

关键词

微塑料，结直肠癌，肠道屏障，氧化应激，生物膜

Microplastics Promote the Occurrence and Development of Colorectal Cancer

Yiqun Kang[1], Hanyi Zeng[2], Jin Zhan[1], Haitao Huang[3], Chao Cui[3*]

[1]The First Clinical Medical College of Gannan Medical University, Ganzhou Jiangxi
[2]The Department of Reproductive Medicine, The First Affiliated Hospital of Gannan Medical University, Ganzhou Jiangxi
[3]The Department of Gastrointestinal Surgery, The First Affiliated Hospital of Gannan Medical University, Ganzhou Jiangxi

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*通讯作者。

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Abstract

Since the breakthrough in polymer synthesis technology in the early 20th century, plastic products have been widely adopted globally due to their exceptional physicochemical properties. However, with annual plastic production soaring to 359 million tons worldwide, plastic-derived environmental pollution has become one of the most severe ecological challenges of the 21st century. Notably, as the largest plastic producer globally, China exhibits significant regional correlations between environmental microplastic pollution levels and human health risks. Recent epidemiological studies have revealed a synchronous increase in colorectal cancer (CRC) incidence and plastic product usage since the industrialization and popularization of plastics, suggesting a potential mechanistic link between environmental microplastic exposure and intestinal carcinogenesis. We explore the role of microplastics as a driving factor behind this trend and elucidate their carcinogenic effects: microplastics compromise intestinal protective functions; disrupt microbiota and impair immune barriers, leading to tumor immune escape; induce persistent oxidative damage, thereby activating pro-carcinogenic pathways; act as a "Trojan horse" by carrying toxicants such as microorganisms, organic pollutants, and heavy metals, resulting in synergistic carcinogenic effects; and ultimately influence the prognosis and outcomes of CRC patients. This review aims to provide direction for establishing a microplastic exposure-based early warning model for CRC risk and to pioneer new approaches for developing comprehensive environmental health prevention and control strategies.

Keywords

Microplastics, Colorectal Cancer, Intestinal Barrier, Oxidative Stress, Biofilm

1. 引言

结直肠癌作为消化系统恶性肿瘤的典型代表，其疾病负担正以惊人的速度全球蔓延。最新统计数据显示，CRC 年新发病例已突破 190 万例，预计至 2040 年将形成 320 万例/年的流行病学态势，伴随约 160 万例的年死亡病例[1]。这种发病率的时空分布特征与全球塑料污染版图存在显著重叠，促使我们重新审视环境污染物在肿瘤发生中的驱动作用。微塑料(<5 μm)已通过大气沉降、食物链富集等途径实现生物圈全域渗透，研究显示，人类通过饮食、呼吸等途径每日摄入数百至数千颗微塑料颗粒，其中胃肠道是其主要的蓄积场所[2]。自 2018 年首次在人粪便样本中检出 9 种聚合物类型，标志着微塑料已完成从环境污染物到人体内源性暴露因子的身份转变[3]。尽管现有研究已证实微塑料暴露可导致肠道通透性增加、菌群失调等病理改变[4]，但其促癌机制仍存在较大空白亟待解决，本文描述的几种可能存在的致癌机制：首先，微塑料通过其物理化学特性破坏肠道粘液层、降低肠道保护功能；其次微塑料通过干扰不同菌群的定植和代谢，削弱了免疫调节功能，为肿瘤的发生和进展创造了免疫抑制微环境；在分子层面，微塑料诱导的氧化应激通过驱动癌相关基因的异常表达；作为复合污染体系的核心组分，微塑料联合有机污染物、重金属产生致癌协同效应；最后探讨了微塑料提高结直肠癌患者对化疗药物的耐药性并影响患者的预后转归。本文希望通过系统阐明微塑料暴露如何促进 CRC 发生发展，为环境致癌物的早期筛查和精准干预提供科学依据。

2. 微塑料

2.1. 微塑料的基本结构及特性

塑料制品在紫外线辐射、机械力和生物活动的共同作用下，逐渐被分解成粒径范围从微米级(<5 mm)到纳米级(1~100 nm)不等的微塑料[5]。微塑料的高比表面积和多孔结构使其对有机污染物和重金属有强吸附性[6]，且由于化学性质稳定，难以自然降解，导致微塑料在环境中长期存留，其表面会因紫外线、氧化或微生物作用发生老化而改变吸附能力和毒性[7]。此外低密度微塑料易通过大气传输[8]，而高密度颗粒更易在土壤或水体中沉降[9]。这意味其传播范围更广，影响程度更深。微塑料的结构和特性使其在环境中表现出复杂的生态效应，这些效应不仅取决于其自身理化性质，还与环境介质和共存污染物的相互作用密切相关。

2.2. 微塑料的来源及接触途径

微塑料的来源可分为两种主要类型：一级来源和二级来源。初级微塑料是为特定用途而制造的，例如化妆品和个人护理产品中的微珠[10]，而次级微塑料是较大塑料制品通过物理、化学和生物过程降解而产生的，包括由于紫外线辐射、环境因素、机械力[11] [12]。越来越多的证据表明，微塑料存在于人体组织中。有研究以美国人的饮食为例，估计人类每年的微塑料消费量范围为 39,000~52,000 个颗粒，具体的数值因年龄和性别而有差异。如果考虑到呼吸吸入的量，这些值将增加到 74,000 和 121,000。此外，通过饮用瓶装水达到建议饮水量的人每年可能会多摄入 90,000 个微塑料，而仅饮用自来水的人每年可多摄入 4000 个微塑料。然而，鉴于方法学和数据的局限性，这些数值有被低估的可能[13]。研究显示人类肺部检测到了 12 种微塑料，主要聚合物是聚氯乙烯(PVC) [14]。此外，所有动脉样本中均检测到微塑料，平均浓度较高，为 118.66 ± 53.87 μg/g 组织重量，浓度分布显示微塑料在动脉粥样硬化斑块中可能积累更多，且以 PET 是最常见类型[15]。人类胎盘组织检出的微塑料，主要为粒径介于 5 至 10 μm 的球形或不规则碎片[16]，值得注意的是，不仅人体粪便样本中同样存在微塑料，在胎粪(新生儿第一次粪便)样本中检测到八种目标微塑料，反映了母体和胎儿暴露的可能性[17]-[19]。这些研究结果表明，微塑料已经暴露于人体并可能长期在体内积累。Du 等人[20]指出，当微塑料污染物与生物体直接接触时；通常会导致短期急性毒性。当微塑料和污染物融入食物网时，就会发生间接接触，导致慢性器官毒性，这将极易诱发消化系毒性。人类接触微塑料的途径包括摄入、吸入和皮肤接触。

2.2.1. 经消化道摄入途径

摄入是最主要途径[21]，基于食物消费模型估算，人类年均摄入量可达 39,000 至 52,000 颗粒[22]。现有研究在多种食品中检出微塑料，包括贻贝[23]、商品鱼类[24]、食盐[25]、食糖[26]和瓶装水[27]。欧洲居民因食用双壳贝类年均暴露量约 11,000 颗粒[28]；而食盐摄入导致的年暴露量在欧洲和中国分别为 37 与 100 颗粒[25] [29]。食品中微塑料的存在引起了人们对食物网内潜在生物累积和生物放大的担忧，这最终可能影响人类健康[12] [30]。

2.2.2. 经呼吸道吸入途径

早期研究显示，室外空气中微塑料浓度为 0.3~1.5 个/立方米，室内浓度可达 0.4~56.5 个/立方米(其中 33%为聚合物)，包含可吸入尺寸颗粒[31]。据估算，个体每日吸入量约为 26~130 个[32]；而基于人体模型采样，轻度活动的男性日吸入量可达 272 个[33]。职业暴露研究揭示，合成纺织、植绒及氯乙烯/聚氯乙烯行业工人因长期吸入微塑料，出现气道病变和间质性肺病相关症状，其损伤已在动物模型中成功复现[34] [35]。人类肺癌组织活检中亦检出 250 μm 塑料纤维[36]，虽未确立因果关系，但提示高浓度暴露或高易感人群可能面临呼吸系统损伤风险。

2.2.3. 经皮肤接触途径

皮肤接触虽然研究较少，但也是一种潜在途径，研究推测纳米塑料(<100 nm)可能穿透皮肤屏障[37]，聚酯与聚丙烯的手术缝合线在植入 21 天后更容易引发炎症，且伴随纤维包裹形成[38]；目前关于该途径的研究虽少，但由于皮肤广泛暴露于粉尘、合成纤维和化妆品微珠等塑料颗粒及外科手术中常用可吸收缝合线的现状，探究微塑料对于皮肤接触毒性仍具有重要意义。

3. 微塑料破坏肠道功能

3.1. 微塑料破坏黏液层

微塑料可通过物理摩擦或化学作用破坏肠道黏液层的完整性。实验表明，聚乙烯对苯二甲酸酯(PET)微塑料在小鼠模型中导致结肠黏液层变薄，杯状细胞数量显著减少，从而削弱黏液屏障的物理保护功能[39]。另有研究发现 3 μm 和 10 μm 的聚苯乙烯颗粒可显著减少 HT29 细胞(肠上皮细胞模型)中杯状细胞的比例，并下调黏蛋白基因(如 MUC2、MUC5AC)的表达，导致黏液分泌不足[40]。微塑料长期诱导的肠道慢性炎症反应也加剧粘液层的破坏，导致黏液层持续变薄和功能退化，在连续 4 周暴露于聚苯乙烯微塑料的小鼠出现结肠隐窝结构异常，黏液分泌细胞再生能力下降，最终导致慢性肠炎和屏障功能衰竭[41]；炎症导致的氧化应激也会损伤黏液层中的黏蛋白结构，降低其黏弹性和保护功能[42]。纳米级微塑料(50 nm PS-NPs)还可跨黏液层转运，可穿透黏液层直接接触肠上皮细胞，甚至通过胞吞作用进入血液循环，导致黏液屏障的局部缺陷[43]从而进一步影响黏液层的修复能力[44]。

3.2. 微塑料影响肠道免疫功能

MPs 还可引起肠道免疫功能失调。微塑料通过激活 TLR-Myd88 信号通路，上调溶菌酶(Lys)、集落刺激因子受体(CSF1R)等免疫相关基因引发肠道局部免疫过度反应，这种失调可能会损害免疫系统有效应对肿瘤的能力，从而可能促进癌症的发生和进展[45] [46]。通过连续灌胃小鼠模型研究发现，聚苯乙烯微纳塑料(PS-MNP)暴露显著抑制了肠系膜淋巴结中 CD8+ T 细胞的分化，并降低肠道分泌型免疫球蛋白 A (sIgA)通过干扰肠道免疫微环境间接影响 T 细胞功能，提示免疫调节失衡可能与肿瘤免疫逃逸相关[4]。Yang 等人通过细胞和动物实验验证纳米塑料(NPs)通过巨噬细胞溶酶体损伤激活 IL-1β 信号通路，驱动 Th17 细胞分化与 Treg 细胞扩增，并诱导 T 细胞耗竭，从而重塑结肠免疫抑制微环境并促进结直肠癌进展[47]。

值得注意的是微塑料影响肠道免疫功能的更主要方式之一是改变肠道微生物群。摄入聚苯乙烯微塑料会导致有益细菌，例如厚壁菌门的细菌的减少，同时增加潜在有害的病原体，例如肠杆菌科和脱硫弧菌科[42] [48]。肠道菌群通过分解宿主无法代谢的膳食成分，包括膳食纤维和蛋白质残基，生成具有重要生理功能的生物活性物质：短链脂肪酸(SCFAs) [49]、芳香烃受体(AhR)配体[50]。其中，SCFAs (以乙酸、丙酸及丁酸为主)由厚壁菌门和拟杆菌门等特定菌群通过膳食纤维发酵产生，而 AhR 配体(吲哚类物质作为 AhR 内源性配体)则源于双歧杆菌等菌属对色氨酸的代谢转化。这两类代谢物共同维护肠上皮细胞间连接结构的完整性，揭示了肠道菌群代谢活性与屏障功能间的分子互作机制[51]-[53]。微塑料通过抑制产丁酸菌的丰度导致菌群代谢产物中的短链脂肪酸(SCFAs)水平显著降低[54]，加剧肠道屏障完整性的破坏[55]。而 PE MPs 暴露条件下，AhR 信号传导途径的活化程度呈现显著抑制特征，提示肠道微生物生成 AhR 内源性配体的功能可能被削弱[48]，这种生物学效应可能与坦纳氏菌科(Tannerellaceae 菌科)中有 AhR 配体合成特性的模式菌，狄氏副拟杆菌(*Parabacteroides distasonis*)的丰度降低存在潜在关联[56]。而研究证实，色氨酸代谢衍生的内源性 AhR 配体，如吲哚类化合物，不仅对肠黏膜屏障的结构完整性具有关键支撑作用，更在调控固有免疫细胞亚群分化、调节免疫应答阈值以及维持黏膜免疫网络动态平衡等方面

发挥中枢调节功能[52] [57]-[59]，AhR 配体的下降也削弱了免疫调节功能，为肿瘤的发生和进展创造了免疫抑制微环境。

4. 微塑料诱导的氧化应激与信号级联通路激活

4.1. 微塑料诱导的氧化应激

有毒理学研究证实，氧化应激机制在微塑料(MPs)介导的生物毒性中具有核心地位[60] [61]。塑料颗粒被细胞吸收时，可改变细胞膜脂质排列，增加膜张力，同时表面自由基与磷脂分子发生氧化反应，导致膜孔隙率升高及通透性异常并显著增加细胞内 ROS 的产生[62]-[64]。如聚苯乙烯纳米塑料(PS-NPs)在人类肠道 Caco-2 细胞模型中通过阳离子表面特性诱导了 ROS 的大量积累，进而引发 DNA 氧化损伤[65]；在结肠炎相关癌症(CAC)模型中，PS-NPs 暴露导致肠道组织 ROS 升高，并伴随超氧化物歧化酶(SOD)、过氧化氢酶(CAT)等抗氧化酶活性异常[66]，导致活性氧的大量积累不能被有效清除。

4.2. 微塑料诱导氧化应激激活信号级联反应

首先由微塑料诱导的大量累积的 ROS 可通过氧化应激致 DNA 损伤，尤其在结直肠癌的早期阶段，未修复的 DNA 损伤可能导致致癌性转化[67]。因此通过阐明微塑料(MPs)对肠道致癌的作用机制需系统解析 ROS 激活的信号级联通路(图 1)。ROS 触发的氧化应激可启动多维度信号传导系统，包括：① MAPKs 超家族(含 JNK、p38、ERK1/2 亚型)；② Nrf2/Keap1 抗氧化通路；③ PI3K/Akt 信号轴；④ TGF-β 细胞分化调控通路。这些通路通过协同作用精确调控细胞周期进展、能量代谢稳态及程序性死亡等生物学事件[68]。ROS 不仅作为 MAPK 通路的上游激活因子，还可通过调控下游激酶磷酸化水平放大其生物学效应[69]。根据上文所提及的微塑料可诱导肠道细胞 ROS 大量产生，而 ROS 异常激活调控 MAPK 信号通路，这不难推测出微塑料通过激活 MAPK 信号通路诱发肠道癌变[70]。实验证据显示，MPs 的粒径参数显著影响 MAPK 通路激活强度——以轮虫(*Brachionus plicatilis*)为模型的研究发现，暴露于 0.5 μm 聚苯乙烯微球(浓度 10 μg/mL，24 小时)较 6 μm 颗粒能更显著上调 MAPK 相关效应蛋白表达，提示小粒径 MPs 具有更强的毒性介导能力[71]。而 Balb/c 小鼠接受 1 mg/d 剂量的 5 μm MPs 给药时[72]，拟镖水蚤(*Paracyclopina nana*)暴露于 0.5 或 6 μm 粒径、20 μg/mL 浓度的 MPs 环境时[73]，上述受试对象也均呈现 MAPK 信号通路的显著激活现象。作为调控基因表达、蛋白合成、细胞增殖与凋亡的关键酶体系，MAPK 家族通过三级磷酸化级联反应参与细胞内信号转导，微塑料暴露显著激活该通路为解释 MPs 毒性效应提供了新视角。

核因子 E2 相关因子 2 (Nrf2)作为调控抗氧化反应元件(ARE)的核心转录因子，通过激活超氧化物歧化酶(SOD)、谷胱甘肽过氧化物酶(GPx)等抗氧化酶编码基因，发挥细胞氧化应激防御功能[74]。当微塑料(MPs)诱导的氧化应激激活 MAPK 信号通路时，会触发 Nrf2/Keap1 通路介导的 ARE 基因表达级联反应[75]。值得注意的是，尽管 Nrf2/Keap1 通路可上调相关的具有细胞保护效应的蛋白表达，但临床研究发现该通路的持续性激活与恶性肿瘤及不良预后存在显著相关性[76]，这也提供了 MPs 暴露导致的氧化应激促进肿瘤转化进程的又一视角。

活性氧(ROS)的过量积累还可显著促进 PI3K/AKT/mTOR 信号通路的活化[77]。实验发现相较于对照组，微塑料处理组中 PI3K、AKT 和 mTOR 的磷酸化修饰程度呈现显著增强，提示该通路在纳米塑料暴露条件下呈现异常激活状态[66]。这一信号级联反应不仅参与氧化应激调控，还与脂肪酸代谢及 DNA 损伤修复密切相关[78]-[80]，现已证实 PI3K/Akt/mTOR 通路的过度激活通过促进细胞增殖、抑制凋亡以及增强代谢适应能力驱动结直肠癌发展[81]。因此可推测出微塑料通过氧化应激过度激活 PI3K/AKT/mTOR 信号轴从而促进结直肠癌的发生发展。

在肿瘤发生起始阶段，TGF-β 蛋白通过双重调控机制发挥抗肿瘤效应：一方面阻滞细胞周期进程，另一方面激活细胞程序性死亡[82]。Smad 蛋白在 TGF-β 信号通路中属于中心介质，ROS 深度参与 TGF-β 信号转导，通过调控 Smad 磷酸化状态，使肿瘤细胞逃脱 TGF-β 在癌变早期施加的增殖抑制效应，这一机制在上皮－间质转化(EMT)中尤为显著[83] [84]。EMT 在癌症转移中起关键作用，在 EMT 进程中，上皮细胞表型发生显著转变，E-钙黏蛋白(E-cadherin)表达水平显著降低，同时伴随细胞连接复合体的动态重构——Zonula occludens (ZO)蛋白、密蛋白(claudins)及闭合素(occludin)发生空间分布改变[85]。这种细胞极性紊乱与细胞骨架重组共同驱动间充质相关转录程序的激活，促使基质金属蛋白酶(MMPs)等水解酶类表达上调[86]。上述分子事件协同打破细胞－基质间稳态，最终赋予癌细胞突破基底膜屏障的迁移侵袭能力，而 CRC 的发展也可能发生此类进程[87]。目前研究进展只在斑马鱼模型上通过微塑料暴露显著激活 TGF-β 信号通路[88]，然而微塑料通过氧化应激激活 TGF-β 信号通路驱动 CRC 发生发展仍需得到进一步验证。

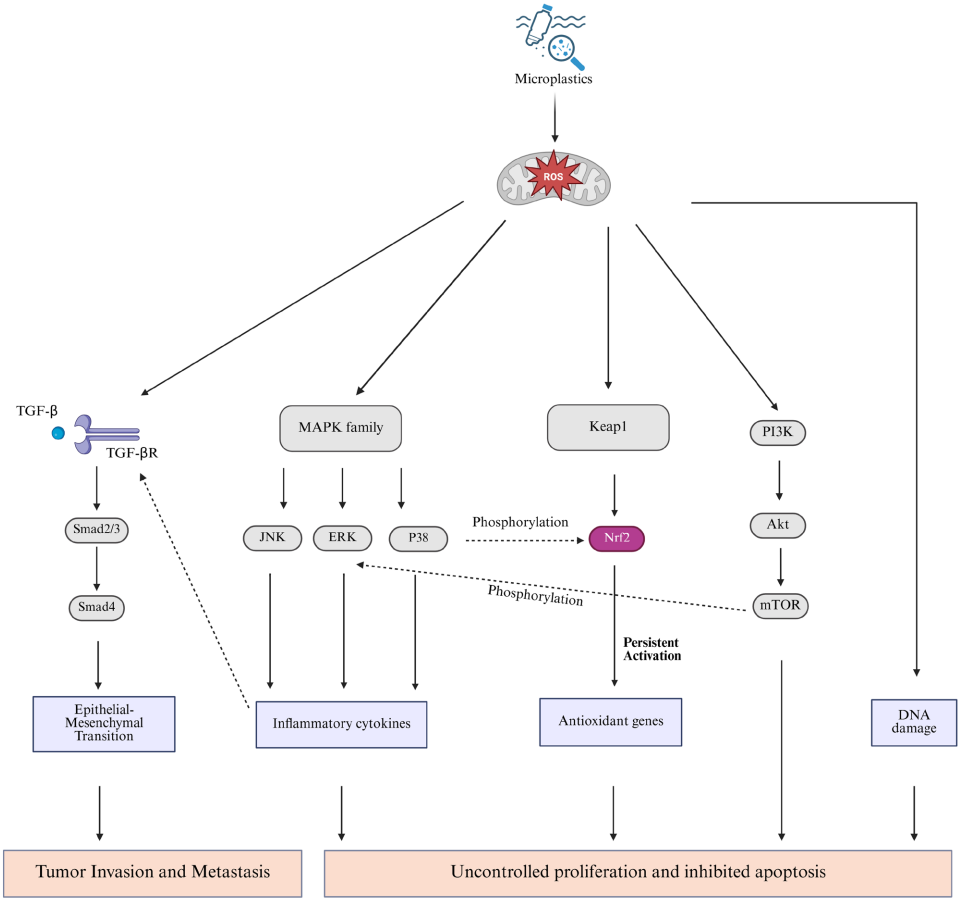

Figure 1. MPs trigger oxidative stress and activate associated signaling cascade networks
图 1. 微塑料(MPs)诱导氧化应激并激活相关信号级联反应

5. 微塑料的“特洛伊木马”效应

微塑料作为“特洛伊木马”可携带多种微生物和化学、金属“乘客”，显著增强其致癌潜力。其高度疏水的表面特性能够促进微生物黏附与定植，形成异质性生物膜结构，从而成为病原体和有害物质的传播载体[89]。生物膜为志贺菌属、副溶血性弧菌等致病菌提供附着位点，并通过水平基因转移(HGT)和

垂直基因转移(VGT)加速抗生素抗性基因(ARGs)的扩散，诱导抗生素抗性细菌(ARB)的产生，延长致癌菌群在肠道的滞留时间，间接推动癌变进程[90]-[92]。例如，携带 pks 基因的大肠杆菌(pks + *E. coli*)可借助微塑料作为载体，在肠道粘液层受损后直接黏附于上皮细胞，持续释放基因毒性物质 colibactin，引起 DNA 双链断裂和基因组不稳定，最终促进结直肠癌发生[93]-[95]。生物膜也可包裹微塑料并改变其表面性质，增强其在肠道内的滞留能力和与上皮细胞的接触机会，进一步增加局部致癌潜力[96]-[98]。除了生物性“乘客”，微塑料还可吸附重金属、多环芳烃(PAHs)等有机毒物，形成复合污染体系，在肠道中协同放大毒性效应。例如，吸附 PAHs 的微塑料可诱导 DNA 损伤和细胞突变，提高结直肠癌发病率[99] [100]；纳米塑料与铜联合暴露可显著增加人结肠癌细胞(HCT-116)基因组不稳定性[101]。微塑料作为载体不仅提升这些有害物质的生物可利用性，还促进其进入组织深处[102]。流行病学研究表明，重金属暴露与结直肠癌发病率呈正相关[103]，进一步证实了微塑料在结直肠癌中协同致癌作用。

6. 微塑料对结直肠癌治疗的阻碍

研究发现结直肠癌患者的肿瘤组织中的微塑料种类和分布比癌旁组织更复杂，由于结直肠癌组织中的 Clathrin 蛋白(一种参与内吞作用的关键蛋白)的高表达促进了 MPs 的主动摄取，且发现 MPs 的积累又与 CEA、CA19-9 和 PDS 水平呈正相关，进一步证实了 MPs 影响结直肠癌患者的生存及预后转归[104]-[106]。体外和体内实验还表明，MPs 会增加 CRC 细胞的自噬水平，特别是通过激活 mTOR/ULK1 轴，导致保护性自噬增强，使得癌细胞对奥沙利铂等化疗药物产生耐药性[107]，从而影响结直肠癌患者的治疗。

7. 结论

在本综述中，我们探讨了 MPs 削弱肠道保护屏障功能，为致癌因子渗透和慢性炎症提供微环境基础，诱导的菌群失调从而降低保护性代谢物水平引发免疫稳态失衡，促进肿瘤免疫逃逸。MPs 通过诱导 ROS 过量累积，驱动 MAPK、PI3K/AKT/mTOR、TGF-β 促癌通路的异常激活，同时干扰 Nrf2/Keap1 抗氧化防御系统，导致 DNA 损伤修复失败与基因组不稳定性，指出了微塑料通过氧化应激诱导结直肠癌发生发展的研究空白；最后还描述了微塑料还与微生物、有机复合物、重金属形成协同致癌复合体放大致癌风险；结直肠癌组织中 Clathrin 蛋白的高表达促进了 MPs 的主动摄取，且微塑料通过上调保护性自噬降低结直肠癌患者化疗敏感性最终导致不良临床结局等几种潜在机制促进结直肠癌的发生发展。塑料制品已全面融入日常生活，其健康风险日益凸显，针对微塑料在结直肠癌中的具体作用，现有研究仍存在诸多空白，目前亟需推进系统性研究，明确其致病路径，并制定针对性防控策略以降低癌症风险及相关健康损害。

8. 挑战与空白

本文阐明的相关机制大部分集中于水生生物或啮齿类动物的短期实验，无法完全模拟人体复杂的生理环境及长期低剂量暴露效应[108]；微塑料的毒性效应与其类型、尺寸、形状及浓度高度相关，但当前缺乏统一的毒性阈值标准，导致实验结果难以直接比较或外推至人体风险[109]。尽管在人体组织中发现微塑料，但直接关联健康结局的流行病学证据“仅是冰山一角”，缺乏大样本队列研究量化暴露与疾病关系[110]。未来需结合体外类器官模型进行长期追踪研究，明确微塑料在结直肠癌发生中的生理病理关系及相关分子机制。

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