科学通报 2024 年 第 69 卷 第 35 期: 5142 ~ 5154
评 述
《中国科学》杂志社
SCIENCE CHINA PRESS

结直肠癌肠道微生物群的性二态性

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2024-05-29 收稿, 2024-09-25 修回, 2024-10-12 接受, 2024-11-13 网络版发表
四川省自然科学基金(2023NSFSC1830)和成都中医药大学附属医院科技发展基金(23YY36)资助

摘要 结直肠癌的风险和预后存在性别差异现象, 这可能归因于性激素水平和肠道微生物群的变化. 结直肠癌肠道微生物群的组成和功能亦存在性二态性, 性激素被认为在性二态性中起着关键作用. 性激素可通过改变肠道微生物群的组成和多样性调节肠道炎症、免疫微环境, 影响结直肠癌的发生进展和治疗反应. 另一方面, 肠道微生物群也参与调节性激素的水平. 性激素与肠道微生物群之间的双向相互交流在结直肠癌的性别差异性发展中发挥了重要作用. 本综述揭示了结直肠癌肠道微生物群的性二态性现象, 深入分析了性激素和肠道微生物群之间的双向相互作用及其调控肠道炎症、免疫微环境的分子机制, 旨在为基于肠道微生物群和性激素的治疗策略提供科学参考.

关键词 结直肠癌, 肠道微生物群, 性激素, 性二态性, 肿瘤微环境

结直肠癌(colorectal cancer, CRC)是常见的消化系统恶性肿瘤, 其在中国全部恶性肿瘤中发病率位居第2位、死亡率位居第4位, 且逐渐趋于年轻化[1,2]. 最新的癌症统计数据(2015~2019年)显示, 男性CRC的年平均发病率及总死亡率均比女性高约30%~40%[3,4], 说明CRC的风险和预后具有较明显的性二态性. 性二态性也称两性异型性, 指同一物种不同性别之间的差异化特征, 通常源于性别偏倚基因的差异表达[5]. CRC的发病涉及遗传、环境、饮食等多种因素, 在环境因素中, 肠道微生物群在CRC生物学中的作用日益被认识[6,7]. 肠道微生物群位于结直肠上皮附近, 是肿瘤微环境的重要组成部分, 肠道微生态失调是CRC的危险因素之一. 与健康人群相比, CRC患者肠道菌群的物种多样性更高, 致癌类群的丰度增加, 而潜在保护类群的丰度较低[8]. 动物模型研究已经确定了几种细菌在CRC发生中的作用, 包括*Fusobacterium nucleatum*、*Escherichia coli*的某些菌株和*Bacteroides fragilis*等[8,9]. 来自机制研究的数据表明, 肠道微生物群可通过释放多种代谢产物(如次级胆汁酸、乙醛、葡萄糖醛酸)和毒力因子(如肠毒素、活性氧)等来与宿主的肠上皮细胞和免疫细胞相互作用, 从而调节CRC的发展[10].

越来越多的证据表明, CRC肠道微生物群也存在性二态性, 其与性激素(主要是雌激素和雄激素)的相互作用可能导致了CRC的性别差异[11,12]. 一方面, 两性之间肠道微生物群的组成存在明显差异, 这可能影响肠道黏膜的免疫功能和代谢过程, 引起CRC的差异性发展[13]. 另一方面, 肠道微生物群还会影响宿主对化学治疗和免疫治疗的敏感性, 使男女患者的临床获益率和生存期出现差异[14]. 近年来, 大量证据证实了“性激素-肠道菌群轴”“微性别组”的存在, 性激素和肠道微生物群之间的双向相互作用被称为“性激素-肠道菌群轴”[15], 而“微性别组”指微生物群、性激素和免疫系统之间的相互作用[16,17]. 这些新兴名词的出现为研究肠道微生物群、性激素和CRC之间的复杂关联作用奠定

引用格式: 吴紫红, 王子明, 王佳梅, 等. 结直肠癌肠道微生物群的性二态性. 科学通报, 2024, 69: 5142–5154
Wu Z H, Wang Z M, Wang J M, et al. Sexual dimorphism of gut microbiota in colorectal cancer (in Chinese). Chin Sci Bull, 2024, 69: 5142–5154, doi: 10.1360/TB-2024-0571

了基础. 最近的研究提示肠道微生物群与CRC性别差异之间可能存在因果关联[14,18,19]. 然而, 有关性激素和肠道微生物群之间的相互作用可能导致CRC性别差异的研究有限. 肠道微生物群是一个庞大而复杂的生态系统, 而性激素在CRC中的作用仍存在争议[20], 且两者均易受时间、空间等环境因素的影响, 个体差异大[21]. 这说明探索肠道微生物群和性激素可能导致CRC性别差异的机制具有一定的挑战性, 需要更有力的证据支持现有的结论. 因此, 本文旨在综述和讨论CRC肠道微生物群的性二态性, 包括揭示CRC肠道微生物群的性二态性现象, 深入分析性激素和肠道微生物群对CRC炎症、免疫微环境的调控机制, 以及探讨性激素信号与肠道微生物群之间的双向相互作用, 以期为在不久的将来将肠道微生物群用于结直肠癌的临床应用提供科学参考.

1 CRC肠道微生物群的性二态性现象

1.1 CRC肠道微生物群的组成存在性别差异

1.1.1 CRC患者

在肠道微生物群的主要门类中, *Firmicutes* (F)和*Bacteroidetes* (B)尤为重要, F/B比率是肠道微生物群整体平衡的关键指标[22]. 例如, F/B比率升高通常与肥胖和饮食习惯有关, 而F/B比率降低通常见于炎症性肠病[22,23]. 肠道微生态失调是诱发CRC的危险因素[14]. 在属水平上, CRC中的优势菌属主要包括*Bacteroidetes*、*Faecalibacterium*、*E. coli*、*F. nucleatum*、*Streptococcus gallolyticus* 和*Peptostreptococcus*[9,24,25]. 最近的研究表明, 男性和女性CRC患者的肠道微生物群组成存在差异[26~29], 这可能是临床上观察到的CRC风险和预后存在性别特异性差异的原因之一. 为了探索肠道菌群与性别之间的相关性, Lin等人[26]根据CRC患者的性别绘制了一张热图, 研究结果显示, 女性患者肠道中*Prevotella* sp. *Marseille-P2931*、*Clostridium colinum*和*Bifidobacterium pseudocatenulatum*等5种细菌水平升高, 而男性患者肠道中*Fusobacterium mortiferum*、*Bifidobacterium adolescentis*和*Succinatimonas hippei*等11种细菌明显增多. 另一项临床研究证实, *Bacteroides*是与CRC相关的重要细菌, 而*Blautia*、*Barnesiella*和*Anaerostipes*被确定为男性和女性患者之间差异最大的3种细菌[19]. 随着CRC病程的延长, 男性患者的肠道微生物β-多样性逐渐增加, 而α-多样性没有明显变化, 表现为微生物群落更加随机, 共生关系更加复杂; 相反, 女性患者的肠道微生物α-多样性和β-多样性都显著下降, 表现为微生物群落更加确定, 但关键物种缺失[27]. 最近的一项研究发现, 与健康女性相比, 健康男性肠道的产短链脂肪酸(short-chain fatty acids, SCFAs)菌水平较低. 然而, 在结肠腺瘤和CRC患者中却没有观察到这种性别特异性差异. 这表明, 某些益生菌的缺乏可能是男性CRC发病率较高的原因之一[30].

1.1.2 CRC模型动物

CRC肠道微生物群的性别差异在动物模型中也很普遍. 先前的研究表明, 与CRC发展相关的基因(如*Wt1*和*Mmp25*)在青春期前小鼠结肠组织中存在显著的两性异型性[31]. 尽管在结肠菌群组成方面没有发现显著的性别效应, 但可以确定的是性别对特定分类菌群的优势度有影响[31]. $Apc^{Min/+}$是一种广泛用于研究家族性腺瘤性息肉病相关CRC发生发展过程的基因工程小鼠模型[32]. 而偶氮甲烷/葡聚糖硫酸钠(azoxymethane/dextran sulfate sodium, AOM/DSS)诱导的CRC小鼠模型则更广泛地用于研究结肠炎相关结肠癌(colitis-associated cancer, CAC)[33]. AOM/DSS处理可明显降低睾丸切除小鼠的肠道微生物群多样性和F/B值[34]. 最近的研究发现, 与雌性小鼠相比, $Apc^{Min/+}$和AOM/DSS雄性小鼠的结肠肿瘤更大、更多, 肠道炎症也更严重[35]. 类似地, 接受雄性小鼠或男性患者粪便样本的伪无菌小鼠肠道微生物群多样性显著降低, 同时显著富集*Akkermansia muciniophila*和促炎细胞因子, 而*Parabacteroides goldsteinii*则明显减少[35]. *A. muciniophila*是一种可以降解肠道内黏蛋白的重要的革兰氏阴性厌氧菌[36], 其可能促进肠道炎症和肿瘤的发生[37]. *P. goldsteinii*可通过抑制脂多糖显著减轻肠道炎症, 维持肠上皮屏障功能[38]. 这些发现表明, 肠道屏障功能的改变取决于粪便供体的性别, 而不是伪无菌小鼠本身的性别. 此外, 在雄性小鼠肠道中观察到磷脂酰胆碱(phosphatidylcholine, PC)及其下游代谢物LPC的上调, LPC可促进细胞增殖和细胞连接损伤, 而*A. muciniophila*的富集或*P. goldsteinii*的耗竭与LPC的水平呈正相关[35]. 这些发现共同提示雄性偏向性肠道微生物群可能在CRC的发生发展中起重要作用.

1.2 CRC干预期间肠道微生物群的性别偏倚现象

CRC肠道微生物群的组成在人类和动物模型中均存在性别差异, 一些特殊的干预措施也会影响肠道微

生物群, 并表现出性别偏倚现象. 一些研究认为, 血清维生素D(VitD)水平与CRC风险和预后呈负相关, 但其他研究似乎并未证实这一观点[29,39,40]. CRC患者的血清维生素D水平和肠道菌群也存在性别差异, 与男性患者相比, 女性患者在补充VitD后更容易感染*F. nucleatum*[29]. 携带脱氧胆酸(deoxycholic acid, DCA)生物合成基因的肠道微生物可抑制$CD8^+$ T细胞效应功能, 促进CRC模型小鼠肿瘤生长[41]. 熊去氧胆酸(ursodeoxycholic acid, UDCA)可通过减轻DCA的影响来抑制结肠癌细胞的活性[42]. 在接受UDCA治疗的患者中, *Faecalibacterium prausnitzii*丰度的增加和*Ruminococcus gnavus*的缺乏与男性结肠腺瘤风险的增加显著相关; 然而, 在女性中却没有观察到这种关联[43]. 这些结果表明, 性别可能会改变UDCA在结肠中的活性并影响特定类别的肠道菌群. 最近的研究发现, 抗PD-L1治疗可显著降低雌性MC38荷瘤小鼠肠道中*Lachnospiraceae*(反应ICIs的反响率)[44]的丰度, 但不会影响雄性小鼠的肠道菌群[45]. 这一发现与临床数据显示的抗PD-L1治疗在男性患者中的疗效优于女性患者的结论相一致[45]. 螺旋杆菌属*Helicobacter* spp.可创造一种慢性肠道炎症环境加剧CRC的进展[46]. 将Th17-增强型共生候选菌*Candidatus savagella*(也称为*Segmented filamentous bacteria*, SFB)接种于*Helicobacter* spp.诱导的CRC遗传易感模型小鼠体内, 可引起小鼠肠道微生物群发生复杂的动态变化[47]. 具体来说, SFB^+雄性小鼠结肠癌的发生率和严重程度明显低于SFB^+雌性小鼠. 此外, 在接种第4天时, *E. coli*的丰度在SFB^-小鼠中明显增加保持稳定; 然而, 在SFB^+小鼠中, 仅在最终发展为CRC的小鼠肠道中检测到*E. coli*丰度显著增加. 这些结果表明, 接种共生菌SFB对雄性CRC小鼠具有性别依赖性保护作用; SFB能稳定肠道微生物群, 防止接种后由*Helicobacter* spp.引起的变化(疾病关联从螺旋杆菌转为大肠杆菌)[47].

总之, CRC肠道微生物群在组成、功能和基于微生物的特殊干预措施方面都存在性别二态性. 由于肠道微生物群受时间和空间等环境因素的影响较大, 且实验室小鼠与人类的肠道菌群也有很大不同. 因此, 归纳出CRC中肠道微生物群的性别差异具有挑战性. 但总的来说, 男性患者/雄性小鼠肠道微生物群中致病菌比例更高, 而女性患者/雌性小鼠倾向于形成更稳定的肠道微生态(图1). 雌激素和雄激素被认为在性二态性中起着重要作用, 性激素与肠道微生物群之间亦存在双向相互作用. 在下一章节中我们将进一步探讨性激素对CRC肠道微生物群的影响及关键机制.

2 性激素对CRC肠道微生物群和炎症微环境的影响

雌二醇(E_2)是女性体内最主要的雌激素, 在CRC的发生发展中具有双重作用. 通常, 雌二醇主要与核受体ERβ结合, 通过增强DNA错配修复[48,49]、调节特定miRNAs和时钟基因[50,51]、诱导细胞周期阻滞[52,53]等直接抑制CRC细胞增殖. 随着CRC的进展, ERβ逐渐丢失, 在缺氧等条件下, 雌二醇可通过膜受体GPER激活非基因组信号, 促进癌基因表达[54~56]. 与雌激素相反, 雄激素主要通过激活核受体引起表观遗传失调和影响CRC进展[57,58], 而其与膜受体的结合则可能诱导细胞凋亡[59,60]. 除了直接影响CRC细胞增殖和凋亡, 雌激素和雄激素还可通过调节肠道微生物群调控结肠炎症微环境, 间接影响CRC的进展.

2.1 雌激素维持肠道微生态平衡, 减轻炎症反应

雌激素是肠道微生物群的关键调节因子, 抑制炎症信号及促炎因子的表达是雌激素降低CAC风险的关键机制之一. 先前的研究表明, 卵巢切除会加剧AOM/DSS模型小鼠结肠炎症和肿瘤形成, 补充雌二醇可显著减轻炎症反应, 抑制恶性进展[61,62]. 在结肠炎的初期阶段, 雌二醇可阻断NF-κB信号转导, 抑制炎症介质的释放, 同时促进Nrf2相关抗氧化酶的表达, 减轻氧化应激损伤和炎症反应[61~64]. 此外, 雌二醇还能通过促进NLRP3炎性小体的表达来减轻肠道炎症[62]. 慢性炎症可引起肠道微生态失衡, 最终诱发肠道肿瘤, 而肿瘤微环境又会导致肠道菌群多样性进一步减少[65,66]. 在AOM/DSS模型中, 使用抗生素可改善肠道微生态, 降低促炎细胞因子水平和结肠肿瘤发生率, 补充雌二醇也能达到类似的效果[66,67]. 具体而言, 雌二醇可增加肠道菌群的多样性和共生菌的丰度, 减少机会性致病菌的感染和F/B的值[66]. 益生菌可促进抗炎因子分泌, 而致病菌则刺激炎症因子、促炎毒素和活性氧(reactive oxygen species, ROS)的释放, 驱动CRC进展[13,18]. *Carnobacterium maltaromaticum*可显著抑制雌性小鼠肠道肿瘤形成的益生菌, 但其对雄性小鼠却无明显影响[68]. 进一步研究发现, 雌激素通过上调结肠SLC3A2的表达来增强*C. maltaromaticum*在肠道的附着和定殖. *C. maltaromaticum*定植改变了肠道菌群的组成, 促进产

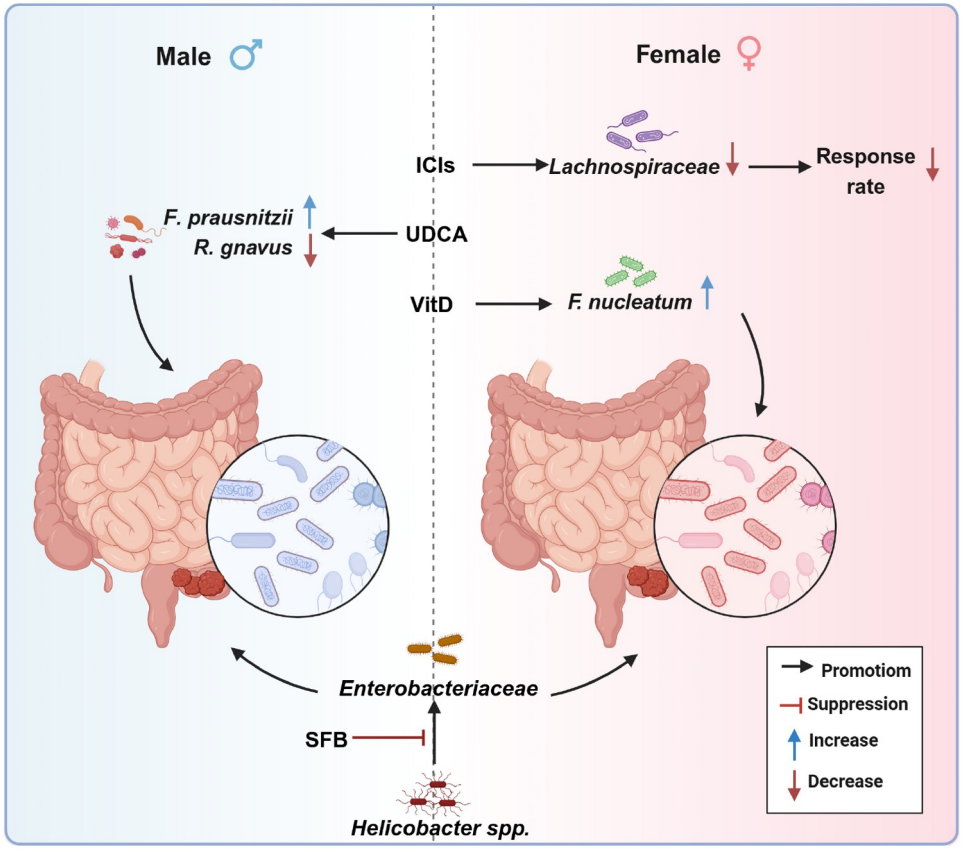

图 1 结直肠癌肠道微生物群的性二态性现象. 肠道微生物群的组成在结直肠癌患者和模型动物中均存在性别差异, 通常, 男性患者/雄性小鼠肠道微生物群中致病菌比例更高, 而女性患者/雌性小鼠倾向于形成更稳定的肠道微生态

Figure 1 Sexual dimorphism of the gut microbiota in colorectal cancer. The composition of the intestinal microbiota demonstrates sex-based differences in both colorectal cancer patients and animal models. Typically, male patients and male mice exhibit a higher proportion of pathogenic bacteria in their intestinal microbiota, while female patients and female mice tend to develop a more stable intestinal microecology. Created with BioRender.com

SCFAs细菌(*F. prausnitzii*和*L. bacterium*)的富集; 同时降低了机会性致病菌(*B. vulgatus*和*Muribaculum intestinale*)的相对丰度. 这些益生菌可激活VitD受体信号, 减少黏膜炎症, 维持肠道屏障功能[68]. 雌激素可促进产SCFAs细菌的生长, SCFAs(如丁酸)是肠道微生物发酵产生的重要代谢产物, 对维持肠道生态平衡至关重要[69]. 一旦在结肠中产生, SCFAs很快就会被结肠细胞吸收, 并进入线粒体中的柠檬酸循环产生ATP, 为细胞提供能量[70]. 肠道碱性磷酸酶(intestinal alkaline phosphatase, IAP)是一种由肠道微生物调控的抗菌肽. 在雌激素的刺激下IAP上调, 减少*Proteobacteria*的丰度和脂多糖的生物合成, 从而预防慢性肠炎[71]. 这些发现表明, 雌激素可增加益生菌的富集、减少致病菌的感染, 维持肠道微生态平衡, 在减轻肠道炎症反应和氧化应激损伤、预防CRC发生发展方面至关重要(图2).

肠道雌激素受体β(estrogen receptor-beta, ERβ)是结肠炎相关结肠癌的保护因子, 雌激素主要通过ERβ影响结肠细胞. 敲除雌性小鼠的ERβ基因会导致肠道微生物群多样性降低和免疫损伤菌群增加[65,72]. 在CRC发展过程中, ERβ的逐渐丧失加剧了肠道菌群多样性的减少和致病菌的富集, 如*Bacteroidetes genus Prevotellaceae*[65]. 这种由ERβ的丧失诱导的致病菌富集在雄性小鼠中更为常见, 其富集的大量菌群参与了细胞运动、膜运输和碳水化合物代谢等过程, 有利于癌细胞的增殖和迁移活动[65]. 先前的研究表明, Nrf2可通过直接调节ERβ的表达来增强雌激素的抗炎作用[73]. 最近的研究发现, *Nrf2*基因型也可改变肠道微生物群的组成[74]. 在*Nrf2*基因型敲除的AOM/DSS小鼠肠道中观察到, *A. muciniophila*、*L. murinus*和*B. vulgatus*的丰度发生了性别特异性变化[74]. 具体来说, 雄性和雌性AOM/DSS小

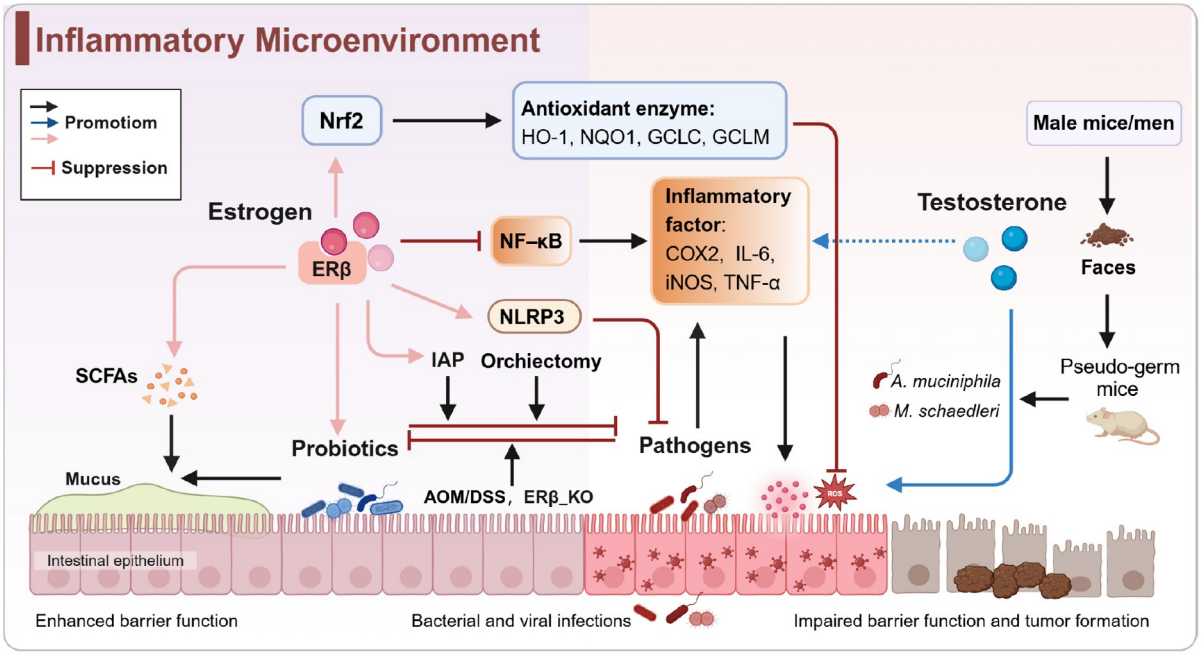

图 2 性激素调节结直肠癌肠道微生态和炎症微环境. 雌激素可通过增加肠道微生物群的多样性和共生菌的相对丰度、降低致病菌的相对丰度来维持肠道微生态平衡, 从而减轻肠道炎症反应和氧化应激损伤, 延缓结肠炎相关癌症进展. 相反, 雄激素可能会诱导肠道微生态失调, 导致肠道炎症恶性进展、肿瘤风险增加

Figure 2 Sex hormones regulate intestinal microecology and inflammatory microenvironment in colorectal cancer. Estrogen can help maintain the balance of intestinal microecology by increasing the diversity of intestinal microbiota and enhancing the relative abundance of commensal bacteria, while simultaneously reducing the relative abundance of pathogenic bacteria. This process contributes to a decrease in intestinal inflammatory responses and oxidative stress damage, ultimately delaying the progression of colitis-associated cancer. In contrast, androgens may induce intestinal microbial dysbiosis, which can lead to the malignant progression of intestinal inflammation and an increased risk of tumor development. Created with BioRender.com

鼠肠道内*B. genus Prevotellaceae*的丰度都有所增加, 而*L. murinus*仅在Nrf2敲除的雄性小鼠中有所降低. 此外, 无论Nrf2基因敲除与否, 雄性小鼠体内的*A. muciniphila*丰度均有所增加[74]. *L. murinus*的丰度与结肠肿瘤的数量呈负相关, 而*B. vulgatus*的丰度与炎症状态、肿瘤数量和腺瘤等级呈正相关[74]. 这些结果表明, 雌激素、ERβ和Nrf2倾向于创造更有利的肠道微生态环境来减轻炎症反应, 抑制CAC的发生发展(图2).

2.2 雄激素诱发肠道微生态失调, 加剧慢性炎症

雄激素, 主要是睾酮, 是一种与CRC密切相关的性类固醇激素. 大多数研究表明, 血液循环中游离睾酮水平与CRC的风险呈正相关[75~77]. 在CRC动物模型中, 包括$Apc^{Pirc/+}$大鼠、$Apc^{Min/+}$小鼠和AOM-小鼠, 与雌性相比, 雄性对结肠腺瘤的易感性增加[78,79]. 最近的研究表明, 睾酮诱导的肠道微生态失调可能在CRC的性别差异中起关键作用[34]. 与雌激素相比, 雄激素似乎更易诱发肠道微生态失调、结肠炎症和肿瘤进展[12,34,35,79]. 研究发现, AOM/DSS处理可显著升高小鼠的血清睾酮水平, 而切除睾丸则明显减轻小鼠结肠炎症和远端结肠腺瘤的严重程度[12,34]. 此外, 睾丸切除的小鼠肠道微生物群多样性和F/B的值也更高. 补充睾酮会促进COX-2、iNOS等炎症介质的释放, 增加*M. schaedleri*、*A. muciniphila*机会性致病菌的丰度, 诱发结肠炎症和黏膜下浸润癌[12,34]. 先前的研究提到, 接受雄性小鼠或男性患者粪便样本的伪无菌小鼠肠道中致病菌富集, 而益生菌则明显减少[35]. 机制上, 这些致病菌的代谢产物会激活甘油磷脂代谢途径, 最终诱导肠道炎症的恶性转化[35]. 这些研究结果表明, 雄激素, 尤其是睾酮, 可能会诱发肠道微生态失调和慢性炎症, 导致男性患CRC的风险高于女性. 这也暗示CRC发病率的性别差异可能是睾酮的间接肿瘤促进效应, 而非雌激素的保护效应.

总之, 雌激素可通过增加肠道微生物群的多样性和共生菌的相对丰度、降低致病菌的相对丰度来维持肠道微生态平衡, 从而减轻肠道炎症反应和氧化应激

损伤, 延缓CAC进展. 相反, 雄激素可能会诱导肠道微生态失调, 导致肠道炎症恶性进展、肿瘤风险增加(图2). 然而, 现有的证据大多数侧重于研究基于性激素或性别特异性的菌株差异, 而有关性激素与肠道微生物群之间的相互作用如何影响炎症信号的具体机制尚待进一步探究.

3 性激素与肠道微生物群共同调节CRC免疫微环境

众所周知, 肿瘤细胞或免疫细胞表达的程序性死亡配体 1(programmed death-ligand 1, PD-L1)可抑制T细胞的细胞毒性[80]. 在AOM/DSS和MC38结肠肿瘤模型组织中检测到大量的PD-L1阳性肿瘤细胞、M_2样肿瘤相关巨噬细胞(tumor-associated macrophages, TAMs)、髓源性抑制细胞(myeloid-derived suppressor cells, MDSCs)、Treg细胞和癌症相关成纤维细胞(cancer-associated fibroblasts, CAFs), 而细胞毒性$CD8^+$ T细胞较少[81~83]. 研究发现, 补充雌二醇可逆转这种免疫抑制性微环境, 增强机体的抗肿瘤免疫[81~83]. 此外, 雌二醇还能降低细胞外囊泡(extracellular vesicles, EVs)中免疫抑制因子TGFβ1的水平, 最终抑制MC38肿瘤的生长[83]. 值得注意的是, 在接种MC38细胞前进行雌二醇预处理可显著减轻肿瘤重量, 而在接种细胞后补充雌二醇则对肿瘤的生长没有明显影响[82]. 此外, 雌激素还可减轻高脂饮食诱导的M_2样巨噬细胞浸润[84](图3). 肠道微生物群可影响宿主免疫系统的发育, 共生菌可促进肠道黏膜免疫系统的成熟, 而致病菌则会导致免疫功能失调[85,86]. 基于雌二醇可降低CRC组织中PD-L1表达的发现, 研究人员还观察到, 在进行抗PD-L1治疗前补充雌二醇会引起雄性小鼠肠道微生物群组成和多样性的改变[66,82,87]. 在 MC38 雄性小鼠中, 雌二醇和抗PD-L1联合治疗促进益生菌*P. goldsteinii*和*L. murinus*的富集, 同时降低了机会性致病菌*Enterobacteriaceae*的相对丰度[87]. 然而, F/B值的变化在不同模型中存在差异, 在MC38模型中, 雌二醇单独或与抗PD-L1联合治疗可上调F/B的值, 但在AOM/DSS模型中该比值显著降低[66,87]. 总之, 这些结果表明, 雌二醇可下调PD-L1的表达, 调节浸润性免疫细胞和肿瘤相关细胞的数量, 并促进有利于免疫恢复的肠道微生态环境的形成. 通过与肠道微生物群的相互作用, 雌二醇可扭转抑制性免疫微环境, 增强机体的抗肿瘤免疫力, 最终阻碍CRC的进展(图3).

雌二醇能提高抗PD-L1治疗的疗效, 但临床数据显示, 抗PD-L1治疗在男性患者中的反响率似乎优于女性患者[45]. 在MC38结肠肿瘤模型中观察到, 抗PD-L1治疗能降低雄性小鼠的睾酮水平, 而不影响雌性小鼠的性激素水平; 抗PD-L1治疗不会影响雄性小鼠的肠道微生物群, 但会降低雌性小鼠中*Lachnospiraceae*的丰度[44]. 使用特定的窄谱抗生素, 如新霉素和甲硝唑, 有助于恢复雄性小鼠的微生态失调, 并减轻免疫检查点抑制剂(immune checkpoint inhibitors, ICIs)相关性结肠炎, 提高雄性小鼠免疫治疗疗效, 而对雌性小鼠则产生负面影响[45]. 这些差异与肠道微生物群的性二态性有关, 尤其是*Lachnospiraceae*和*Muribaculaceae*丰度的差异[88]. *Lachnospiraceae*与ICIs的阳性反应有关[44], 而*Muribaculaceae*在AOM/DS诱导的CRC中起关键作用[88]. 此外, 在抗PD-L1治疗期间使用黏菌素治疗ICIs相关性肠炎会进一步降低睾酮水平、增加雌二醇水平, 引起肠道微生物群的组成和功能发生改变[44]. 这些结果表明, 降低睾酮水平可能有助于提高免疫疗法的临床获益率(图3). 这些发现强调了在使用抗生素治疗ICIs相关性结肠炎时需要考虑肠道微生物群的性别特异性差异.

综上所述, 雌二醇可通过下调PD-L1的表达、调节浸润性免疫细胞的数量以及维持肠道微生态平衡来逆转免疫抑制性微环境, 增强机体抗肿瘤免疫. 相反, 睾酮可能会对抗PD-L1疗法产生负面影响, 降低睾酮水平可能会改变CRC肠道微生物群的组成, 提高免疫疗法效率(图3). 这些结果表明, 性激素和肠道微生物群可能是CRC免疫疗法的关键调节因子, 雌二醇和某些特定的益生菌可能是提高抗PD-L1疗效的重要靶点. 此外, 在使用抗生素治疗ICI相关性结肠炎时, 应考虑到肠道微生物群的性别差异.

4 肠道微生物群调节性激素水平的潜在机制

性激素可改变肠道微生物群的组成和多样性, 肠道微生物群也参与调节性激素的水平[89,90]. 肠道微生物群对宿主性激素水平的调节涉及多种机制(图4). 某些细菌, 尤其是绝经前妇女肠道中的细菌, 拥有参与性激素生物合成和降解的基因, 可代谢性激素及其前体[91]. 在UDP-葡萄糖醛酸转移酶(UDP-glucuronosyltransferases, UGTs)的催化作用下, 游离性激素葡萄糖醛酸化形成共轭性激素, 一部分排泄入尿道或肠道中[92]. 在肠道微生物β-葡糖醛酸酶(β-glucuronidase)的

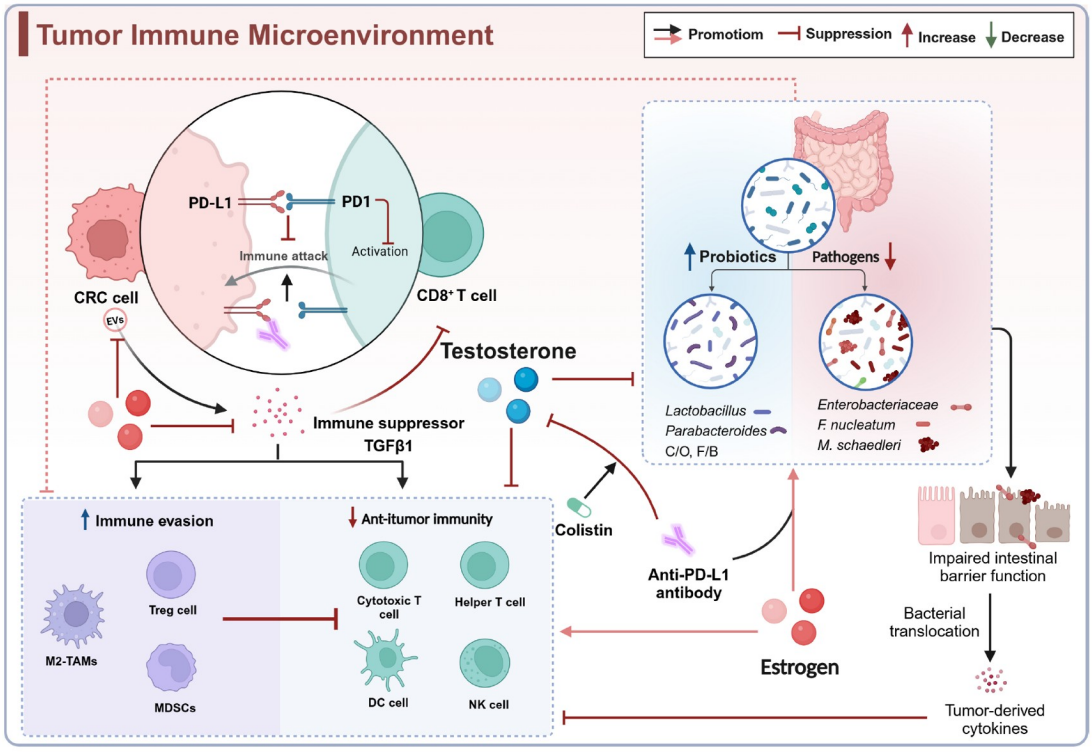

图 3 性激素与肠道微生物群共同调节结直肠癌免疫微环境. 雌二醇可通过下调PD-L1的表达、调节浸润性免疫细胞的数量以及维持肠道微生态平衡来逆转免疫抑制性微环境, 增强机体抗肿瘤免疫. 相反, 睾酮可能会对抗PD-L1疗法产生负面影响, 降低睾酮水平可能会改变结直肠癌肠道微生物群的组成, 提高免疫疗法效率

Figure 3 Sex hormones and gut microbiota co-regulate the colorectal cancer immune microenvironment. Estradiol has the capacity to reverse the immunosuppressive microenvironment and enhance the body's anti-tumor immunity by downregulating PD-L1 expression, modulating the number of infiltrating immune cells, and preserving the intestinal microecological balance. In contrast, testosterone may adversely affect anti-PD-L1 therapy; thus, reducing testosterone levels could potentially alter the composition of the gut microbiota in colorectal cancer, thereby improving the efficacy of immunotherapy. Created with BioRender.com

分解作用下, 共轭性激素又可被分解成具有生物活性的游离性激素, 并通过肝肠循环重新吸收, 维持体内性激素水平[93,94]. 肠道菌群失调会扰乱β-glucuronidase的活性, 导致分解作用减弱、游离性激素水平下降[93,95~97]. 肠道微生物群是雄激素代谢的重要调节因子. 一项探讨肠道菌群对雄激素代谢的影响的研究显示, 与无菌小鼠相比, 成年雄性小鼠远端肠道和粪便中的游离双氢睾酮水平明显升高[96]. 这些发现表明, 血液或肠道中的游离性激素水平与能够代谢性激素的肠道微生物群之间存在联系, 这意味着对粪便中特定细菌丰度的临床检测可能能够反映血清性激素水平.

除了β-glucuronidase外, 最近的证据表明, 一些特定的细菌酶, 如类固醇硫酸酯酶(steroid sulfatase, STS)、类固醇-17, 20-脱甲醇酶(steroid-17, 20-desmolase)和羟基类固醇脱氢酶(hydroxysteroid dehydrogenase, HSD)等, 在性激素的生物合成中也发挥重要作用[98,99]. STS可促进硫酸雌酮(E_1S)和硫酸雌二醇(E_2S)向游离雌酮和雌二醇的转化; 17β-HSD影响雌酮与雌二醇之间的相互转化[100]. 这些发现表明, 肠道微生物群可能会影响雌激素的生物利用度. 睾酮缺乏与抑郁样行为有关[15]. 研究表明, 从睾酮缺乏的抑郁症患者粪便中分离出的*Mycobacterium neoaurum*可在体外降解睾酮[101]. 体内实验证实, *M. neoaurum*可降低大脑和血清中的睾酮水平, 从而导致抑郁行为, 而3β-HSD被确定为降解睾酮的关键酶[101]. 此外, 人类粪便中的某些细菌也被发现可代谢雌激素和雄激素[102]. 虽然这些研究支持细菌酶在性激素代谢中的作用, 但还需要更深入地研究, 以充分了解这一过程所涉及的完整细菌途径及其对人体生理的影响. 除了酶的表达, 肠道微生物还能通过直接影响性腺功能来影响性激素水平[15,103]. 一些肠道微生物可通过脑肠轴调节下丘脑-垂体-性腺轴, 从而干扰内源性性激素的生物合成[104,105]. 此外, 黏

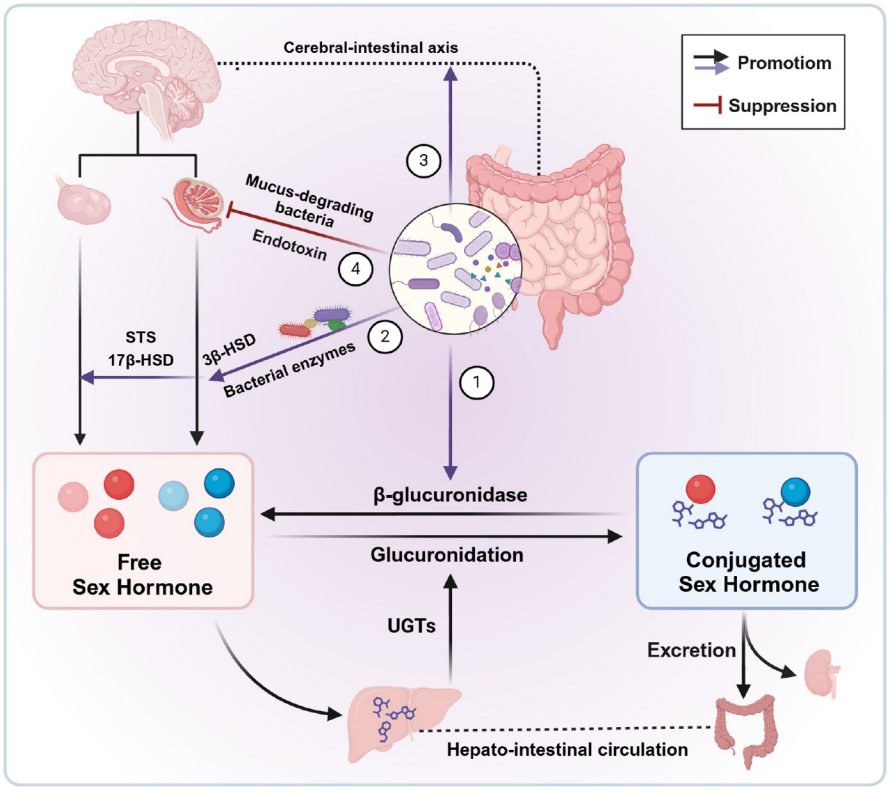

图 4 肠道微生物群调节性激素水平的潜在机制. 肠道微生物群可通过调节β-glucuronidase的活性、表达特定的细菌酶、直接影响性腺功能、破坏肠黏膜屏障诱发全身炎症等来影响内源性性激素水平

Figure 4 Potential mechanisms by which the gut microbiota regulates sex hormone levels. The gut microbiota can influence endogenous sex hormone levels by regulating the activity of β-glucuronidase, expressing specific bacterial enzymes, directly impacting gonadal function, disrupting the intestinal mucosal barrier, and inducing systemic inflammation. Created with BioRender.com

液降解菌可通过破坏肠黏膜屏障促进细菌进入血液循环, 诱发全身性炎症, 抑制睾丸功能[106].

总之, 肠道微生物群可通过调节β-glucuronidase的活性、表达特定的细菌酶、直接影响性腺功能以及破坏肠黏膜屏障诱发全身炎症等来影响内源性性激素水平(图4), 这可能部分解释了CRC风险和预后的性别差异现象.

5 结论与未来展望

CRC肠道微生物群存在性二态性现象源于两性之间性激素水平的差异. 性激素可通过改变肠道微生物群的组成和多样性调节肠道炎症、免疫微环境, 间接影响CRC的发生、进展和治疗反应. 具体而言, 雌激素主要通过增加肠道微生物群多样性和共生菌的丰度、减少致病菌的富集来维持肠道微生态平衡, 从而减轻肠道炎症、逆转免疫抑制性微环境. 相反, 雄激素可能会增加致病菌的富集, 破坏肠道微生态平衡, 降低免疫治疗的效率, 加剧结肠炎症和肿瘤生长. 另一方面, 肠道微生物群也参与调节性激素的循环和代谢, 显著影响性激素水平. 性激素与肠道微生物群之间的双向相互作用在CRC的性别差异性发展中发挥了重要作用. 这些发现提示, 肠道微生物群、性激素及其受体可能是预防和治疗CRC的一种有前途的靶向策略.

然而, 性激素信号与肠道微生物群之间的相互作用对CRC性别差异的直接影响还缺乏足够的证据. 现有的研究多侧重于挖掘肠道微生物群中存在性别偏倚的菌株, 而有关性激素、肠道微生物群影响结直肠肿瘤微环境的分子机制的研究仍较为基础. 未来的研究应着重关注二者之间的相互作用如何影响CRC的遗传和表观遗传, 并深入探索其影响肠道炎症、免疫微环境的分子机制. 关于肠道微生物群与两性发病、预后差异的流行病学证据主要来自对已确诊CRC患者的回顾性研究. 目前仍不清楚所观察到的肠道微生物变化是导致CRC发生的原因还是结果. 值得注意的是, 男性

和女性在饮食和生活方式的选择上存在差异, 而饮食、生活方式可能会影响肠道微生物群的组成, 从而掩盖生物学上的性别差异(性激素状态差异). 为了更好地了解环境因素对肠道微生物群的长期影响及其对预防CRC的意义, 在个体患CRC之前收集详细的肠道微生物群数据的前瞻性研究至关重要. 此外, 肠道微生物群对实验室小鼠的影响可能与人类有很大不同, 拥有天然野生微生物群的小鼠对环境挑战的适应能力更强, 对免疫疗法的反应更接近人类. 总之, 本综述强调了性激素和肠道微生物群在CRC性别差异中的重要作用, 通过调节性激素或肠道微生物群来干预CRC的发展具有潜在的临床应用价值. 未来的研究应进一步探索性激素、肠道微生物群和CRC性二态性之间错综复杂的相互作用, 为CRC的预防和治疗提供新的策略.

参考文献

1 Wu Z, Yan S, Liu Z, et al. Postoperative abdominal complications of gastric and colorectal cancer surgeries in China: A multicentered prospective registry-based cohort study. Sci Bull, 2022, 67: 2517–2521
2 Guan X, Hu X, Jiang Z, et al. Short-term and oncological outcomes of natural orifice specimen extraction surgery (NOSES) for colorectal cancer in China: A national database study of 5055 patients. Sci Bull, 2022, 67: 1331–1334
3 Siegel R L, Giaquinto A N, Jemal A. Cancer statistics, 2024. CA Cancer J Clin, 2024, 74: 12–49
4 Siegel R L, Wagle N S, Cercek A, et al. Colorectal cancer statistics, 2023. CA Cancer J Clin, 2023, 73: 233–254
5 Li C H, Prokopec S D, Sun R X, et al. Sex differences in oncogenic mutational processes. Nat Commun, 2020, 11: 4330
6 Patel S G, Karlitz J J, Yen T, et al. The rising tide of early-onset colorectal cancer: A comprehensive review of epidemiology, clinical features, biology, risk factors, prevention, and early detection. Lancet Gastroenterol Hepatol, 2022, 7: 262–274
7 Tan J Y, Zhang Y, Chen J, et al. Associations between the diet-related inflammation indices and digestive system cancer: A narrative review of epidemiological studies (in Chinese). Fudan Univ J Med Sci, 2024, 51: 404–414 [谭靖宇, 张妍, 陈俊, 等. 饮食相关炎症指数与消化系统恶性肿瘤发病关系的流行病学研究进展. 复旦学报(医学版), 2024, 51: 404–414]
8 Wong S H, Yu J. Gut microbiota in colorectal cancer: Mechanisms of action and clinical applications. Nat Rev Gastroenterol Hepatol, 2019, 16: 690–704
9 Quaglio A E V, Grillo T G, Oliveira E C S D, et al. Gut microbiota, inflammatory bowel disease and colorectal cancer. World J Gastroenterol, 2022, 28: 4053–4060
10 Wong C C, Yu J. Gut microbiota in colorectal cancer development and therapy. Nat Rev Clin Oncol, 2023, 20: 429–452
11 Haziman A A, Ravinderan S, Thangavelu T, et al. A novel role for estrogen-induced signaling in the colorectal cancer gender bias. Ir J Med Sci, 2019, 188: 389–395
12 Song C-H, Kim N, Nam R H, et al. Testosterone strongly enhances azoxymethane/dextran sulfate sodium-induced colorectal cancer development in C57BL/6 mice. Am J Cancer Res, 2021, 11: 3145–3162
13 Fan X, Jin Y, Chen G, et al. Gut microbiota dysbiosis drives the development of colorectal cancer. Digestion, 2021, 102: 508–515
14 Qu R, Zhang Y, Ma Y, et al. Role of the gut microbiota and its metabolites in tumorigenesis or development of colorectal cancer. Adv Sci, 2023, 10: e2205563
15 Wang L, Tang L, Zhai D, et al. The role of the sex hormone-gut microbiome axis in tumor immunotherapy. Gut Microbes, 2023, 15: 2185035
16 Wallis A, Butt H, Ball M, et al. Support for the microgenderome invites enquiry into sex differences. Gut Microbes, 2017, 8: 46–52
17 Calcaterra V, Rossi V, Massini G, et al. Precocious puberty and microbiota: The role of the sex hormone–gut microbiome axis. Front Endocrinol, 2022, 13: 1000919
18 Koyande N, Gangopadhyay M, Thatikonda S, et al. The role of gut microbiota in the development of colorectal cancer: A review. Int J Colorectal Dis, 2022, 37: 1509–1523
19 Yang X, Li P, Qu Z, et al. Gut bacteria and sex differences in colorectal cancer. J Med Microbiol, 2023, doi: 10.1099/jmm.0.001706
20 Das P K, Saha J, Pillai S, et al. Implications of estrogen and its receptors in colorectal carcinoma. Cancer Med, 2023, 12: 4367–4379
21 Zhang J, Yin W, Li P, et al. Interaction between diet- and exercise-lifestyle and phthalates exposure on sex hormone levels. J Hazard Mater, 2019, 369: 290–298
22 Magne F, Gotteland M, Gauthier L, et al. The firmicutes/bacteroidetes ratio: A relevant marker of gut dysbiosis in obese patients? Nutrients, 2020, 12: 1474
23 Stojanov S, Berlec A, Štrukelj B. The influence of probiotics on the firmicutes/bacteroidetes ratio in the treatment of obesity and inflammatory bowel disease. Microorganisms, 2020, 8: 1715
24 Rebersek M. Gut microbiome and its role in colorectal cancer. BMC Cancer, 2021, 21: 1325

25 Fong W, Li Q, Yu J. Gut microbiota modulation: A novel strategy for prevention and treatment of colorectal cancer. Oncogene, 2020, 39: 4925–4943

26 Lin C, Li B, Tu C, et al. Correlations between intestinal microbiota and clinical characteristics in colorectal adenoma/carcinoma. Biomed Res Int, 2022, 2022: 1–11

27 Liao H, Li C, Ai Y, et al. Gut microbiome is more stable in males than in females during the development of colorectal cancer. J Appl Microbiol, 2021, 131: 435–448

28 Watanabe D, Murakami H, Ohno H, et al. Association between dietary intake and the prevalence of tumourigenic bacteria in the gut microbiota of middle-aged Japanese adults. Sci Rep, 2020, 10: 15221

29 Bellerba F, Serrano D, Johansson H, et al. Colorectal cancer, vitamin D and microbiota: A double-blind Phase II randomized trial (ColoViD) in colorectal cancer patients. Neoplasia, 2022, 34: 100842

30 Song C H, Kim N, Nam R H, et al. The possible preventative role of lactate- and butyrate-producing bacteria in colorectal carcinogenesis. Gut Liver, 2024, 18: 654–666

31 Steegenga W T, Mischke M, Lute C, et al. Sexually dimorphic characteristics of the small intestine and colon of prepubescent C57BL/6 mice. Biol Sex Differ, 2014, 5: 11

32 Yu S, Yin Y, Wang Q, et al. Dual gene deficient models of ApcMin/+ mouse in assessing molecular mechanisms of intestinal carcinogenesis. Biomed Pharmacother, 2018, 108: 600–609

33 Dzhalilova D, Zolotova N, Fokichev N, et al. Murine models of colorectal cancer: The azoxymethane (AOM)/dextran sulfate sodium (DSS) model of colitis-associated cancer. PeerJ, 2023, 11: e16159

34 Song C H, Kim N, Nam R H, et al. Changes in gut microbiome upon orchiectomy and testosterone administration in AOM/DSS-induced colon cancer mouse model. Cancer Res Treat, 2023, 55: 196–218

35 Wang L, Tu Y, Chen L, et al. Male - biased gut microbiome and metabolites aggravate colorectal cancer development. Adv Sci, 2023, 10: e2206238

36 Davey L E, Malkus P N, Villa M, et al. A genetic system for *Akkermansia muciniphila* reveals a role for mucin foraging in gut colonization and host sterol biosynthesis gene expression. Nat Microbiol, 2023, 8: 1450–1467

37 Faghfuri E, Gholizadeh P. The role of *Akkermansia muciniphila* in colorectal cancer: A double-edged sword of treatment or disease progression? Biomed Pharmacother, 2024, 173: 116416

38 Li Z, Li C, Chen B, et al. *Parabacteroides goldsteinii* enriched by Pericarpium Citri Reticulatae ‘Chachiensis’ polysaccharides improves colitis via the inhibition of lipopolysaccharide-involved PI3K-Akt signaling pathway. Int J Biol Macromol, 2024, 277: 133726

39 Gwenzi T, Schrotz-King P, Schöttker B, et al. Vitamin D status, Cdx2 genotype, and colorectal cancer survival: Population-based patient cohort. Nutrients, 2023, 15: 2717

40 Emmanouilidou G, Kalopitas G, Bakaloudi D R, et al. Vitamin D as a chemopreventive agent in colorectal neoplasms. A systematic review and meta-analysis of randomized controlled trials. Pharmacol Ther, 2022, 237: 108252

41 Cong J, Liu P, Han Z, et al. Bile acids modified by the intestinal microbiota promote colorectal cancer growth by suppressing $CD8^+$ T cell effector functions. Immunity, 2024, 57: 876–889.e11

42 Režen T, Rozman D, Kovács T, et al. The role of bile acids in carcinogenesis. Cell Mol Life Sci, 2022, 79: 243

43 Pearson T, Caporaso J G, Yellowhair M, et al. Effects of ursodeoxycholic acid on the gut microbiome and colorectal adenoma development. Cancer Med, 2019, 8: 617–628

44 Robinson I, Hochmair M J, Schmidinger M, et al. Assessing the performance of a novel stool-based microbiome test that predicts response to first line immune checkpoint inhibitors in multiple cancer types. Cancers, 2023, 15: 3268

45 Wang L, Jiang G, Jing N, et al. Downregulating testosterone levels enhance immunotherapy efficiency. OncoImmunology, 2021, 10: 1981570

46 Varon C, Azzi-Martin L, Khalid S, et al. Helicobacters and cancer, not only gastric cancer? Semin Cancer Biol, 2022, 86: 1138–1154

47 Wolfe A E, Moskowitz J E, Franklin C L, et al. Interactions o segmented filamentous bacteria (*Candidatus Savagella*) and bacterial drivers in colitis-associated colorectal cancer development. PLoS One, 2020, 15: e0236595

48 Honma N, Arai T, Matsuda Y, et al. Estrogen concentration and estrogen receptor-β expression in postmenopausal colon cancer considering patient/tumor background. J Cancer Res Clin Oncol, 2022, 148: 1063–1071

49 Honma N, Arai T, Matsuda Y, et al. Estrogen receptor-β gene cytosine-adenine (ESR2-CA) repeat polymorphism in postmenopausal colon cancer. Int J Mol Sci, 2023, 24: 4502

50 Moravčík R, Olejárová S, Zlacká J, et al. Effect of miR-34a on the expression of clock and clock-controlled genes in DLD1 and Lovo human cancer cells with different backgrounds with respect to p53 functionality and 17β-estradiol-mediated regulation. PLoS One, 2023, 18: e0292880

51 Hases L, Archer A, Indukuri R, et al. High-fat diet and estrogen impacts the colon and its transcriptome in a sex-dependent manner. Sci Rep, 2020, 10: 16160

52 Mahbub A A. 17β-estradiol enhances 5-fluorouracil anti-cancer activities in colon cancer cell lines. Med Sci, 2022, 10: 62
53 Refaat B, Aslam A, Idris S, et al. Profiling estrogen, progesterone, and androgen receptors in colorectal cancer in relation to gender, menopausal status, clinical stage, and tumour sidedness. Front Endocrinol, 2023, 14: 1187259
54 Bustos V, Nolan Á M, Nijhuis A, et al. GPER mediates differential effects of estrogen on colon cancer cell proliferation and migration under normoxic and hypoxic conditions. Oncotarget, 2017, 8: 84258–84275
55 Bühler M, Fahrländer J, Sauter A, et al. GPER1 links estrogens to centrosome amplification and chromosomal instability in human colon cells. Life Sci Alliance, 2023, 6: e202201499
56 Gilligan L C, Rahman H P, Hewitt A M, et al. Estrogen activation by steroid sulfatase increases colorectal cancer proliferation via GPER. J Clin Endocrinol Metab, 2017, 102: 4435–4447
57 Roshan M H K, Tambo A, Pace N P. The role of testosterone in colorectal carcinoma: Pathomechanisms and open questions. EPMA J, 2016, 7: 22
58 Chen Q, Peng K, Mo P, et al. Histone demethylase JMJD2D: A novel player in colorectal and hepatocellular cancers. Cancers, 2022, 14: 2841
59 Gu S, Papadopoulou N, Nasir O, et al. Activation of membrane androgen receptors in colon cancer inhibits the prosurvival signals Akt/Bad *in vitro* and *in vivo* and blocks migration via vinculin/actin signaling. Mol Med, 2010, 17: 48–58
60 Gu S, Kounenidakis M, Schmidt E M, et al. Rapid activation of FAK/mTOR/p70S6K/PAK1-signaling controls the early testosterone-induced actin reorganization in colon cancer cells. Cell Signal, 2013, 25: 66–73
61 Song C H, Kim N, Lee S M, et al. Effects of 17β-estradiol on colorectal cancer development after azoxymethane/dextran sulfate sodium treatment of ovariectomized mice. Biochem Pharmacol, 2019, 164: 139–151
62 Son H J, Sohn S H, Kim N, et al. Effect of estradiol in an azoxymethane/dextran sulfate sodium-treated mouse model of colorectal cancer: Implication for sex difference in colorectal cancer development. Cancer Res Treat, 2019, 51: 632–648
63 Son H J, Kim N, Song C H, et al. 17β-Estradiol reduces inflammation and modulates antioxidant enzymes in colonic epithelial cells. Korean J Intern Med, 2020, 35: 310–319
64 Armstrong C M, Allred K F, Weeks B R, et al. Estradiol has differential effects on acute colonic inflammation in the presence and absence of estrogen receptor β expression. Dig Dis Sci, 2017, 62: 1977–1984
65 Ibrahim A, Hugerth L W, Hases L, et al. Colitis-induced colorectal cancer and intestinal epithelial estrogen receptor beta impact gut microbiota diversity. Intl J Cancer, 2019, 144: 3086–3098
66 Song C H, Kim N, Nam R H, et al. 17β-Estradiol supplementation changes gut microbiota diversity in intact and colorectal cancer-induced ICR male mice. Sci Rep, 2020, 10: 12283
67 Lee J G, Eun C S, Jo S V, et al. The impact of gut microbiota manipulation with antibiotics on colon tumorigenesis in a murine model. PLoS One, 2019, 14: e0226907
68 Li Q, Chan H, Liu W X, et al. *Carnobacterium maltaromaticum* boosts intestinal vitamin D production to suppress colorectal cancer in female mice. Cancer Cell, 2023, 41: 1450–1465.e8
69 Sun M, Wu W, Chen L, et al. Microbiota-derived short-chain fatty acids promote Th1 cell IL-10 production to maintain intestinal homeostasis. Nat Commun, 2018, 9: 3555
70 Dalile B, Van Oudenhove L, Vervliet B, et al. The role of short-chain fatty acids in microbiota–gut–brain communication. Nat Rev Gastroenterol Hepatol, 2019, 16: 461–478
71 Kaliannan K, Robertson R C, Murphy K, et al. Estrogen-mediated gut microbiome alterations influence sexual dimorphism in metabolic syndrome in mice. Microbiome, 2018, 6: 205
72 Ma Y, Liu T, Li X, et al. Estrogen receptor β deficiency impairs gut microbiota: A possible mechanism of IBD-induced anxiety-like behavior. Microbiome, 2022, 10: 160
73 Song C H, Kim N, Kim D H, et al. 17-β estradiol exerts anti-inflammatory effects through activation of Nrf2 in mouse embryonic fibroblasts. PLoS One, 2019, 14: e0221650
74 Song C H, Kim N, Nam R H, et al. Changes in microbial community composition related to sex and colon cancer by Nrf2 knockout. Front Cell Infect Microbiol, 2021, 11: 636808
75 Mori N, Sawada N, Iwasaki M, et al. Circulating sex hormone levels and colorectal cancer risk in Japanese postmenopausal women: The JPHC nested case–control study. Intl J Cancer, 2019, 145: 1238–1244
76 Liu Z, Zhang Y, Lagergren J, et al. Circulating sex hormone levels and risk of gastrointestinal cancer: Systematic review and meta-analysis of prospective studies. Cancer Epidemiol Biomarkers Prevention, 2023, 32: 936–946
77 Harbs J, Rinaldi S, Gicquiau A, et al. Circulating sex hormone levels and colon cancer risk in men: A nested case–control study and meta-analysis. Cancer Epidemiol Biomarkers Prevention, 2022, 31: 793–803
78 Mahbub A A, Aslam A, Elzubier M E, et al. Enhanced anti-cancer effects of oestrogen and progesterone co-therapy against colorectal cancer in males. Front Endocrinol, 2022, 13: 941834

79 Amos-Landgraf J M, Heijmans J, Wielenga M C B, et al. Sex disparity in colonic adenomagenesis involves promotion by male hormones, not protection by female hormones. Proc Natl Acad Sci USA, 2014, 111: 16514–16519

80 Dammeijer F, van Gulijk M, Mulder E E, et al. The PD-1/PD-L1-checkpoint restrains T cell immunity in tumor-draining lymph nodes. Cancer Cell, 2020, 38: 685–700.e8

81 Kang C, Song C H, Kim N, et al. The enhanced inhibitory effect of estrogen on PD-L1 expression following Nrf2 deficiency in the AOM/DSS model of colitis-associated cancer. Front Oncol, 2021, 11: 679324

82 Song C H, Kim N, Nam R H, et al. Combination treatment with 17β-estradiol and anti-PD-L1 suppresses MC38 tumor growth by reducing PD-L1 expression and enhancing M1 macrophage population in MC38 colon tumor model. Cancer Lett, 2022, 543: 215780

83 Jiang L, Fei H, Yang A, et al. Estrogen inhibits the growth of colon cancer in mice through reversing extracellular vesicle-mediated immunosuppressive tumor microenvironment. Cancer Lett, 2021, 520: 332–343

84 Bader J, Carson M, Enos R, et al. High-fat diet-fed ovariectomized mice are susceptible to accelerated subcutaneous tumor growth potentially through adipose tissue inflammation, local insulin-like growth factor release, and tumor associated macrophages. Oncotarget, 2020, 11: 4554–4569

85 Shi N, Li N, Duan X, et al. Interaction between the gut microbiome and mucosal immune system. Military Med Res, 2017, 4: 14

86 Zheng D, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. Cell Res, 2020, 30: 492–506

87 Song C H, Kim N, Nam R H, et al. Anti–PD-L1 antibody and/or 17β-estradiol treatment induces changes in the gut microbiome in MC38 colon tumor model. Cancer Res Treat, 2023, 55: 894–909

88 Jing N, Wang L, Zhuang H, et al. Sex-biased immune responses to antibiotics during anti-PD-L1 treatment in mice with colon cancer. J Immunol Res, 2022, 2022: 1–26

89 Yoon K, Kim N. Roles of sex hormones and gender in the gut microbiota. J Neurogastroenterol Motil, 2021, 27: 314–325

90 Santos-Marcos J A, Mora-Ortiz M, Tena-Sempere M, et al. Interaction between gut microbiota and sex hormones and their relation to sexual dimorphism in metabolic diseases. Biol Sex Differ, 2023, 14: 4

91 del Castillo-Izquierdo Á, Mayneris-Perxachs J, Fernández-Real J M. Bidirectional relationships between the gut microbiome and sexual traits. Am J Physiol Cell Physiol, 2022, 322: C1223–C1229

92 Milani N, Qiu N H, Fowler S. Contribution of UGT enzymes to human drug metabolism stereoselectivity: A case study of medetomidine, RO5263397, propranolol, and testosterone. Drug Metab Dispos, 2023, 51: 306–317

93 Ervin S M, Li H, Lim L, et al. Gut microbial β-glucuronidases reactivate estrogens as components of the estrobolome that reactivate estrogens. J Biol Chem, 2019, 294: 18586–18599

94 Hu S, Ding Q, Zhang W, et al. Gut microbial beta-glucuronidase: A vital regulator in female estrogen metabolism. Gut Microbes, 2023, 15: 2236749

95 Baker J M, Al-Nakkash L, Herbst-Kralovetz M M. Estrogen–gut microbiome axis: Physiological and clinical implications. Maturitas, 2017, 103: 45–53

96 Colldén H, Landin A, Wallenius V, et al. The gut microbiota is a major regulator of androgen metabolism in intestinal contents. Am J Physiol-Endocrinol Metab, 2019, 317: E1182–E1192

97 Sui Y, Wu J, Chen J. The role of gut microbial β-glucuronidase in estrogen reactivation and breast cancer. Front Cell Dev Biol, 2021, 9: 631552

98 Kwa M, Plottel C S, Blaser M J, et al. The intestinal microbiome and estrogen receptor-positive female breast cancer. J Natl Cancer Inst, 2016, 108: Djw029

99 Anbar H S, Isa Z, Elounais J J, et al. Steroid sulfatase inhibitors: The current landscape. Expert Opin Ther Patents, 2021, 31: 453–472

100 Thomas M P, Potter B V L. The structural biology of oestrogen metabolism. J Steroid Biochem Mol Biol, 2013, 137: 27–49

101 Li D, Liu R, Wang M, et al. 3β-Hydroxysteroid dehydrogenase expressed by gut microbes degrades testosterone and is linked to depression in males. Cell Host Microbe, 2022, 30: 329–339.e5

102 Rizzetto L, Fava F, Tuohy K M, et al. Connecting the immune system, systemic chronic inflammation and the gut microbiome: The role of sex. J Autoimmunity, 2018, 92: 12–34

103 Snigdha S, Ha K, Tsai P, et al. Probiotics: Potential novel therapeutics for microbiota-gut-brain axis dysfunction across gender and lifespan. Pharmacol Ther, 2022, 231: 107978

104 Hokanson K C, Hernández C, Deitzler G E, et al. Sex shapes gut–microbiota–brain communication and disease. Trends Microbiol, 2024, 32: 151–161

105 So S Y, Savidge T C. Sex-bias in irritable bowel syndrome: Linking steroids to the gut-brain axis. Front Endocrinol, 2021, 12: 684096

106 Tremellen K. Gut endotoxin leading to a decline in gonadal function (GELDING) – A novel theory for the development of late onset hypogonadism in obese men. Basic Clin Androl, 2016, 26: 7

Summary for “结直肠癌肠道微生物群的性二态性”

Sexual dimorphism of gut microbiota in colorectal cancer

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Colorectal cancer (CRC) represents a significant public health challenge globally, ranking as the third most commonly diagnosed cancer and the second leading cause of cancer-related mortality worldwide. Recent cancer statistics indicate that the average annual incidence and overall mortality rates of CRC are higher in men than in women, highlighting pronounced sex differences in both the risk and prognosis of the disease. These differences may be attributed to variations in sex hormone levels. Emerging evidence suggests that the gut microbiota associated with CRC exhibits sexual dimorphism, and its interaction with sex hormones —primarily estrogen and androgen—may contribute to these sex differences. The gut microbiota plays a crucial role in the tumor microenvironment, with intestinal microbial dysbiosis identified as a risk factor for CRC. Recent findings have established the concepts of the ‘microgenderome’ and the ‘sex hormone-gut microbiome axis’, which elucidate the bidirectional interactions among gut microbiota, sex hormones, and the immune system. These novel terms provide a foundation for exploring the intricate relationships between gut microbiota, sex hormones, and CRC. However, research on the interactions between sex hormones and gut microbiota that may influence sex differences in CRC remains limited. The gut microbiota constitutes a vast and complex ecosystem, and the role of sex hormones in CRC is still debated. Both factors are influenced by environmental conditions and exhibit significant individual variability. This complexity underscores the challenges in investigating the mechanisms by which intestinal microbiota and sex hormones may contribute to gender differences in CRC, necessitating more robust evidence to substantiate existing conclusions. In this manuscript, we primarily present indirect evidence from two perspectives: inflammation and the immune microenvironment, which supports the notion that interactions between sex hormones and intestinal microbes contribute to sex differences in CRC. Specifically, regarding the inflammatory microenvironment, estrogen can sustain the balance of intestinal microecology by enhancing the diversity of intestinal microbiota and increasing the relative abundance of commensal bacteria while reducing the relative abundance of pathogenic bacteria, thereby alleviating intestinal inflammation. Inflammation and oxidative stress can hinder the progression of colitis-related cancers. Conversely, androgens may induce intestinal microbial dysbiosis, facilitating the malignant progression of intestinal inflammation and increasing the risk of tumors. Concerning the immune microenvironment, estrogen can counteract the immunosuppressive microenvironment and bolster the body’s anti-tumor immunity by downregulating the expression of PD-L1, modulating the number of infiltrating immune cells, and preserving the balance of intestinal microecology. In contrast, androgens may adversely affect anti-PD-L1 therapy, and reducing testosterone levels may alter the composition of the CRC gut microbiota, thereby enhancing the efficacy of immunotherapy. These findings suggest that sex hormones and gut microbiota may serve as key regulators of CRC immunotherapy, with estradiol and certain specific probiotics emerging as potential targets for improving anti-PD-L1 efficacy. Furthermore, sex hormones can influence the composition and diversity of the intestinal microbiota, which in turn plays a role in regulating the circulation and metabolism of sex hormones. This bidirectional interaction is crucial in understanding the development of sex differences in CRC. However, the effects of estrogen and androgens are closely linked to their receptor status and exhibit dual roles in the pathogenesis of CRC. This paper aims to review the sexual dimorphism of gut microbiota in CRC. It will elucidate the phenomenon of sexual dimorphism in gut microbiota associated with CRC and provide an in-depth analysis of the regulatory mechanisms through which sex hormones and intestinal microbiota influence colon inflammation and the immune microenvironment. Additionally, the study will explore the bidirectional interactions between sex hormone signaling and intestinal microbiota, thereby offering a scientific reference for therapeutic strategies that leverage both intestinal microbiota and sex hormones.

colorectal cancer, **gut microbiota**, **sex hormones**, **sexual dimorphism**, **tumor microenvironment**

doi: 10.1360/TB-2024-0571