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肠道不同解剖部位的菌群组成及其在结直肠癌中的作用

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摘要

结直肠癌是由遗传突变、表观遗传改变、慢性炎症、饮食和生活方式等多因素引起的多阶段疾病。最新研究表明，肠道菌群是结直肠癌发展过程中的重要参与者。肠道菌群稳态的失调，可通过诱发炎症、调控宿主防御、氧化应激和改变细菌代谢产物等机制促进结直肠癌的发生发展。值得注意的是，肠道横、纵截面上不同解剖部位的驻留菌群有所不同。根据细菌在肠道中定植部位的不同，可将其划分为 4 种类型：肠腔共生菌、肠黏膜驻留菌、上皮驻留菌和淋巴组织驻留菌。由于结肠共生细菌的易位与结直肠癌的发展密切相关，结直肠癌相关细菌可有望成为用于结直肠癌诊断的非侵入且准确性高的新型生物标志物。本文旨在总结和概述肠道不同解剖部位中的肠道菌群在结直肠癌发生发展中的作用。

1. 引言

结直肠癌是世界范围内癌症致死的主要原因之一[1]，可由基因突变、表观遗传改变、慢性炎症、饮食和生活方式等多种因素引起[2,3]。然而，结直肠癌发生发展过程中涉及的分子机制尚未完全清楚。但越来越多的证据表明，肠道菌群在结直肠癌的发展中扮演着重要角色[4–7]。

肠道微生态系统是既能维持宿主健康，又能诱导宿主病变的多角色系统[8–10]。此系统的平衡能够帮助宿主快速而有效地吸收充足的营养素，促进宿主生长发育、增强免疫力并阻止病原菌入侵[11–17]。相反，肠道微生态系统的失调，则会引起肠道炎症、破坏肠道屏障系统并导致黏膜或组织损伤，甚至成为促进结肠癌发生发展的因素[8,18]。最新研究证据表明，不良的肠道微生态环境，可通过损伤DNA、促进癌基因表达及沉默正常基因等方式促进结直肠癌的发生[4,10,19,20]。

新一代测序技术(如16S DNA测序和宏基因组学测序)的快速发展，在很大程度上提高了人们对肠道菌群的认识[21,22]。同时，也因此对肠道菌群起源和进化及与宿主关系的认识正在逐渐深入。消化道，特别是末端回肠和大肠，是人体菌群的主要来源。对这部分菌群的测序结果发现，人体包含约10^{14}个细菌[23,24]。由于不同个体之间及同一个体的不同消化道解剖部位之间的pH值[25]、氧气含量[26]、抗菌肽[27]和短链脂肪酸水平[28]及肠蠕动强度[29]有所不同，消化道菌群组成的

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差别亦较大。具体表现在，细菌的数量随着消化道的走向自上而下逐渐增加，其中胃、十二指肠和空肠的每毫升肠道内容物中含有10^3~10^4个细菌，回肠每毫升肠道内容物中含有10^8个细菌，而结肠每毫升肠道内容物中含有高达10^{11}个细菌[30,31]。除了细菌数量的变化外，根据肠道横、纵截面解剖部位的不同，细菌的种类也不同[26, 30]。据此，我们将肠道菌群人为地划分为4种类型：肠腔共生菌、肠黏膜驻留菌、上皮驻留菌和淋巴组织驻留菌(图1)。此外，既往研究结果发现，结肠共生细菌的易位与结直肠癌的发展密切相关[32]。本文旨在总结和概述这4类肠道菌群的组成及其在结直肠癌发生发展中的作用。

2. 肠道菌群的组成

2.1. 肠腔共生菌

成人[33,34] 和小鼠[35]的肠腔菌群通常以细菌为主。肠腔共生菌含有多达10^{12}个、1000多种细菌[23,24]，从而构成庞大而复杂的微生态系统。Eckburg等[33]发现，超过90 %的肠腔共生菌属于厚壁菌门和拟杆菌门，而属于放线菌门、变形杆菌门和疣微菌门的细菌较少。Arumugam等[36]分析来自6个国家的39名健康成人粪便时发现，厚壁菌门细菌占39 %、拟杆菌门细菌占25 %、放线菌门细菌占9 %、变形菌门细菌占4 %，这4种细菌属于末端消化道的优势菌，见表1 [22–25,28,37–49]。然而，目前对优势菌作用的了解，尤其是其对整个肠道微生态的影响[50]，仍不十分清楚。

厚壁菌门属于革兰氏阳性、有孢子形成、专性厌氧的球状或杆状菌种，包括肠球菌科、乳酸杆菌科和链球菌属。我们和其他团队的研究均发现，链球菌属中的牛链球菌(*Streptococcus bovis*)在结直肠癌患者中高度富集[51–56]。对于牛链球菌在结直肠癌中的作用，目前尚不清楚。Klein等[57]发现，大多数牛链球菌可以诱导心内膜炎的患者出现结肠腺瘤或无症状肿瘤，这表明牛链球菌参与结直肠癌发生的早期阶段。此外，另有研究发现，血清中牛链球菌诱导RpL7/L12表达的抗原水平在结肠息肉和I/II期结直肠癌患者中明显增加，而在淋巴结或远处转移的晚期患者中并未增加[58]。这些发现表明牛链球菌可能于早期促进结直肠癌的发生。同时，牛链球菌也会获得结直肠肿瘤病灶提供的特定寄宿隐窝，

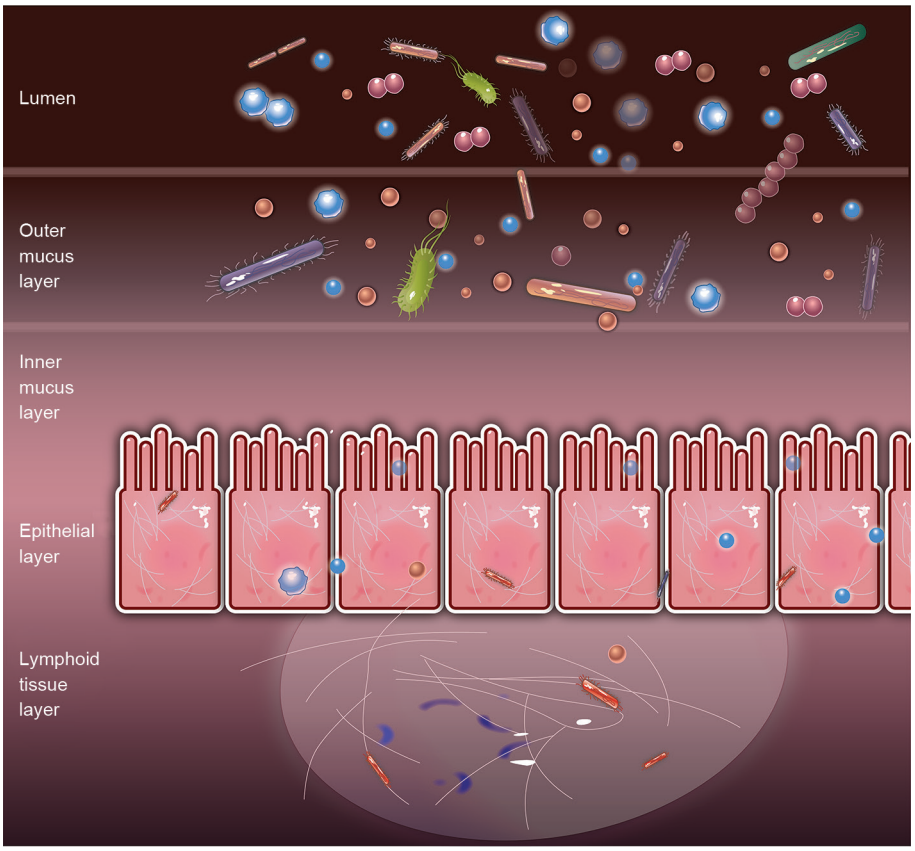

图1. 根据细菌在肠道中定植部位的不同，可将其划分为4种类型：肠腔共生菌、肠黏膜驻留菌、上皮驻留菌和淋巴组织驻留菌。多数细菌定位在肠腔和外黏膜层中，而内黏膜层几乎是无菌的。仅少数种类的细菌可以从肠腔和外黏膜层移动到肠上皮细胞和淋巴组织。

表1 根据不同肠道解剖学定位划分的肠道菌群的组成

Populations		Major bacteria	Refs.
Luminal commensal bacteria	Phylum	Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Verrucomicrobia	[22–25,28,37–42]
	Order	Bacteroidales	
	Family	Rikenellaceae, Lactobacillaceae, Lachnospiraceae, Ruminococcaceae, Paraprevotellaceae	
	Genus	*Bacteroides*, *Prevotella*, *Mucispirillum*, *Lactobacillus*, *Ruminococcus*, *Oscillospira*, *Sutterella*, *Desulfovibrio, Fusobacterium*	
	Species	*Fusobacterium nucleatum*	
Mucus-resident bacteria	Phylum	Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Verrucomicrobia	[40–42]
	Order	Bacteroidales	
	Family	Rikenellaceae, Lactobacillaceae, Lachnospiraceae, Ruminococcaceae, Paraprevotellaceae	
	Genus	*Bacteroides*, *Prevotella*, *Mucispirillum*, *Lactobacillus*, *Ruminococcus*, *Oscillospira*, *Sutterella*, *Desulfovibrio*	
Epithelium-resident bacteria	Species	AIEC, SFB, *Enterococcus faecalis*, *Bacteroides fragilis*, *Clostridium* spp.	[43–47]
Lymphoid tissue-resident commensal bacteria	Species	*Achromobacter* spp., *Bordetella* spp., *Ochrobactrum* spp., *Serratia* spp. PP-DC: *Serratia* spp., SFB, *Ochrobactrum* spp., *Alcaligenes* spp. MLN-DC: *Pseudomonas* spp., *Alcaligenes* spp.	[48,49]

AIEC: adherent-invasive *Escherichia coli*; SFB: segmented filamentous bacteria; PP: Peyer's patch; DC: dendritic cell; MLN: mesenteric lymph node.

通过直接接触或抗原刺激细胞引起白介素-8(IL-8)等炎性细胞因子的释放，反过来进一步促进异常结肠隐窝的过度增殖[59,60]。此外，牛链球菌还会产生IL-8和前列腺素E2(PGE2)等炎性细胞因子，引起结肠的慢性炎症，这种长期存在的不良刺激会逐渐促进正常结肠上皮细胞出现癌变[61]。

梭杆菌属是革兰氏阴性、无孢子形成的厌氧菌属。通过比较结直肠癌患者和健康人群粪便的宏基因组测序结果，我们发现梭杆菌属的典型代表是具核梭菌(*Fusobacterium nucleatum*)，其可作为非侵入性新型生物标志物用于结直肠癌的诊断，这一生物标志物的有效性也已在几个不同种族的人群中均得到验证[62]。此外，越来越多的证据表明，具核梭菌和结直肠癌之间存在着密切关系。一项基于结肠炎、$APC^{min/+}$和转基因小鼠3种模型的研究也发现，具核梭菌可以加速结直肠肿瘤的发生[63]。目前，科研人员对于具核梭菌促癌机制的研究兴趣越来越浓厚，并发现具核梭菌相关的结直肠癌具有高微卫星不稳定性(MSI-H)和更高的CpG岛甲基化表型(CIMP)[64]。此外，有证据表明，先天免疫和适应性免疫也参与肿瘤的发展过程[37]。具核梭菌在接触或侵袭结肠细胞的过程中，可诱导黏蛋白的分泌和炎性细胞因子(如肿瘤坏死因子α，TNF-α)的表达[65]。上述这些因素均使宿主获得腺瘤样变或癌变倾向。同时，具核梭菌也能抑制对抗肿瘤的免疫过程，抑制自然杀伤细胞的活性，从而促进结直肠癌的发展。另有一项新晋研究发现，纺锤菌凝集素Fap2可以结合肿瘤表达的半乳糖和半乳糖胺(Gal-GalNAc)，并可诱发结直肠腺癌[38]。

拟杆菌门，曾称作噬纤维菌–黄杆菌–拟杆菌(CFB)，属于革兰氏阴性、无孢子形成的厌氧棒状菌种。拟杆菌属是其中的主要类群之一[36]。拟杆菌属的代表菌为脆弱拟杆菌(*Bacteroides fragilis*)，在成人和儿童的检出率高达80 %，并且占粪便菌群的0.5 %~1 %[39,66]。近期，我们的研究发现，脆弱拟杆菌在结直肠癌中的丰度显著升高[62]。此外，我们通过对不同阶段结直肠癌患者肠黏膜菌群的16S rRNA测序结果发现，与癌旁正常黏膜相比，脆弱拟杆菌在肿瘤和腺瘤中的丰度显著升高[67]。这些研究结果表明，肠腔中拟杆菌门细菌可能参与结直肠癌的发生发展。研究发现脆弱拟杆菌的促癌机制主要依赖其荚膜多糖A结构和分泌的脆弱拟杆菌毒素。该毒素是锌依赖性的金属蛋白酶毒素，可以刺激调控上皮细胞单层结构的变化，溶解紧密连接、中间连接和电子致密连接结构，并改变单层上皮细胞的渗透性[68]。另外，脆弱拟杆菌毒素可诱导肿瘤抑制蛋白(E-钙黏蛋白)的水解，引起β-连环蛋白定位于细胞核，从而上调原癌基因*c-myc*的转录和翻译水平，促进结肠上皮癌细胞的增殖[69]。值得注意的是，紧密连接、中间连接和E-钙黏蛋白的减少可提高结肠单层上皮细胞的渗透性，这些都属于结直肠癌发展前的早期病理生理变化[70]。根据是否产生毒素，脆弱拟杆菌通常分为不产毒素的脆弱拟杆菌(NTBF)和产毒素的脆弱拟杆菌(ETBF)两大类。越来越多的证据表明，消化道中ETBF的丰度与结直肠癌的发生率之间存在正相关关系[71–76]。Toprak等[71]报道称，与健康人群的粪便相比，结直

肠癌患者的粪便中肠毒素(如脆弱拟杆菌毒素)基因的检出率更高(38 %比12 %，P = 0.009)。由脆弱拟杆菌纯化出来的脆弱拟杆菌毒素可以上调结肠上皮细胞精胺氧化酶(SMO)的表达，导致精胺氧化酶依赖性的活性氧(ROS)增加，从而促进上皮细胞分泌促炎细胞因子及造成DNA损伤[75]。

值得一提的是，位于肠腔中的细菌可以合作形成多细胞群落并且彼此竞争有限的环境资源。万古霉素可选择性地靶向杀死革兰氏阳性菌，也可以杀死盲肠腔中包括革兰氏阴性拟杆菌门细菌在内的多数细菌。由此可见，革兰氏阳性和革兰氏阴性细菌之间存在着相互联系[77]。肠腔中厚壁菌门与拟杆菌门细菌之间的这种联系在有关小鼠肠道的研究中也有报道[78]。这种联系也表现在，当放线菌门的长双歧杆菌(*Bifidobacterium longum*)存在时，拟杆菌门的多形拟杆菌(*Bacteroides thetaiotaomicron*)释放的糖苷水解酶增加[78]。此外，细菌也具有通过改变pH值、控制运动、养分耗竭及产生抗微生物物质（如细菌素）等方式抑制其竞争者生长的潜力[79]。属于厚壁菌门的唾液乳杆菌菌株 UCC118，可以产生双组分细菌素Abp118，并具有抗拟杆菌门和厚壁菌门细菌(包括食源性病原体李斯特菌(*Listeria monocytogenes*)[80]和耐甲氧西林金黄色葡萄球菌(*Staphylococcus aureus*)[81])的广谱活性。

2.2. 肠黏膜驻留菌

肠黏膜是将肠腔共生菌与其下面的肠上皮和全身组织分开的第一道防线。人结肠黏膜的厚度约为400 μm[82]，而小鼠结肠黏膜的厚度约为150 μm[83]。两层结肠黏膜均主要由杯状细胞和潘氏细胞分泌的多种聚糖和大量胶状黏蛋白2(MUC2)构成[84]。无菌小鼠受到细菌刺激后，结肠黏膜的可渗透性需要6周时间才可以逆转[85]。然而，在成年无特定病原体(SPF)小鼠中，由于杯状细胞和潘氏细胞持续分泌MUC2，50 μm厚的结肠内黏膜层每小时即可更新一次，同时内黏膜层逐渐向上移动变为外黏膜层[86,87]。黏液是如何从内黏膜层向上迁移到外黏膜层的机制目前仍然不清楚。除了内黏膜层的屏障功能外，疏松的外黏膜层具有大量分解代谢糖苷酶，从而成为分解黏膜聚糖的特殊共生菌的营养直接来源[40]。因此，只有像*Mucispirillum*属细菌和嗜黏蛋白阿克曼氏菌(*Akkermansia muciniphila*)这样的特殊菌才可以驻留在特殊共生菌提供的特殊场所，从而成为黏膜驻留菌[41,88]。这也可能是细菌在宿主肠道内的解剖学分布不同的原因之一，因为不同细菌对疏松黏膜层的结合能力不同，因此存在分布差异，从而维持消化道微环境的稳态。

最近，Li等[42] 通过16S测序发现，与C57BL/6小鼠肠腔共生菌相比，外结肠黏膜层驻留菌主要来自厚壁菌门和脱铁杆菌门，而较少来自拟杆菌门。然而，通过对菌群多样性的进一步分析发现，黏膜驻留菌和肠腔共生菌之间的多样性无明显差异。值得注意的是，与肠腔的多形拟杆菌和大肠杆菌(*Escherichia coli*)相比，驻留在外黏膜层的多形拟杆菌和大肠杆菌具有更强的潜在增殖能力，并能更好地利用资源(例如，通过回收生物可利用的铁和消耗黏膜作为碳源)[42]。此外，固有的黏膜驻留菌可以通过抑制病原体与宿主黏膜的接触，从而保护宿主[78,81]。

2.3. 上皮驻留菌

肠上皮细胞构成了位于两层黏膜屏障底部的另外一层机械屏障，在维持宿主和菌群之间的平衡中发挥着关键作用[89]。肠上皮细胞包括吸收型肠上皮细胞和分泌型肠上皮细胞。其中，吸收型肠上皮细胞具有代谢和消化功能；分泌型肠上皮细胞包括肠内分泌细胞、杯状细胞和潘氏细胞[90]，其分泌的黏蛋白和各种抗菌肽构成了机械和生物屏障，参与菌群与上皮细胞表面和下面免疫细胞间相互接触的调节[27]。虽然通常认为肠上皮细胞层是无菌区域，但越来越多的研究表明，各种细菌可以黏附甚至侵入肠上皮细胞[43,44,91]。这一过程主要涉及两种机制，即拉链和触发机制，这依赖于细胞骨架的重排，膜扩展的修饰，以及质膜肌动蛋白细胞骨架重组的激活[45]。这是细菌黏附和侵入肠上皮细胞的多步骤过程。目前已发现存在大量毗邻和侵入型细菌；在此，我们主要关注引起先天免疫反应的黏附侵入型大肠杆菌(AIEC)，见表1。

AIEC能够侵入肠上皮细胞并在细胞内进行复制。研究人员已经证明，AIEC与炎症性肠疾病(IBD)密切相关，并且其在炎症因子聚集区域的丰度也与疾病的严重程度密切相关[92,93]。此外，AIEC在结直肠癌的发病机理中发挥着重要作用[46,94]。AIEC和牛链球菌之间的明显区别在于，致病原环状调节蛋白阳性的AIEC在III/IV期结直肠癌患者黏膜上检出率较I期患者更高。这一发现表明，AIEC很可能参与结直肠癌的进展，特别是疾病晚期，并且可能成为有助于预后判断的因素[47]。与非致病菌株不同，AIEC菌株含有鞭毛，通常包括多

种FimH黏附素变种，从而能够更有效地黏附和侵入肠上皮细胞[95]。受到侵袭的肠上皮细胞能分泌促炎细胞因子IL-8和趋化因子CCL20，从而募集巨噬细胞和树突状细胞向感染区域迁移，并进一步分泌干扰素γ(IFN-γ)和TNF-α[96,97] 。此外，细菌鞭毛与肠上皮细胞 Toll 样受体5(TLR5)的结合能够激活经典的NF-κB信号通路[98]。相应地，这些分子可以协同控制IL-8和促血管生成因子的转录，进而促进炎症和血管生成及结直肠癌的发生[99]。

2.4. 淋巴组织驻留菌

肠相关淋巴组织(GALT)包括派伊尔结(PPs)、孤立淋巴滤泡(ILFs)、肠系膜淋巴结(MLNs)和肠道固有层淋巴细胞(ILPs)[100]。既往认为，肠上皮下组织在健康哺乳动物中是绝对无菌的。虽然病原菌可以穿透内黏膜层，逃避抗菌肽和免疫球蛋白A(IgA)的监视，并穿过肠上皮细胞层，但是它们仍旧会很快被GALT的巨噬细胞或其他淋巴细胞清除。然而，最近的研究表明，肠道菌群中存在特殊群体，不仅可以定植在GALT，而且还通过利用来自淋巴组织的营养物质在健康哺乳动物的GALT中自我复制[48,49,101,102]。此外，淋巴组织驻留菌的组成与肠腔驻留菌和肠上皮驻留菌的组成有着较大不同[102]。Obata等[48]发现，PPs是菌群定植的主要肠淋巴组织。聚集在PPs表面的细菌(主要是分节丝状菌和乳杆菌属)与PPs内部的细菌(主要是产碱杆菌属和苍白杆菌属)完全不同，见表1。此外，有研究发现，产碱杆菌属在PPs和肠系膜淋巴结的树突状细胞中的细菌构成中均占主导地位[48]。还有研究发现，GALT通过调节特殊的淋巴组织驻留菌(主要是产碱杆菌属)，控制与克罗恩病和渐进性丙型肝炎病毒感染相关的全身性炎症[48,49,102]。反之，淋巴组织驻留菌可以刺激树突状细胞产生细胞因子，促进组织特异性Th17细胞和第3组先天淋巴细胞的应答反应[102]。

3. 肠道菌群促进结直肠癌进展的机制

3.1. 肠道菌群通过诱发黏膜炎症而促进结直肠癌的进展

一些炎症因子可以帮助调控或形成致瘤微环境，进而导致结肠上皮细胞异常增殖，最终发展成结直肠癌。研究表明，结肠异型增生和结直肠癌的发展深受结肠炎症状态的影响。在IBD患者中，持续的结肠炎症会显著增加结直肠癌的发病风险[103,104]。同时，这些炎症状态也与肠道菌群的失调有关。在肿瘤的发生发展过程中，由上皮细胞形成的物理屏障被打破，上皮细胞间的渗透性增加，从而导致细菌不再与肠道固有层完全隔离[89,105]。这种屏障的破坏引起菌群易位，导致细菌接触抗原提呈细胞和上皮细胞，并激活免疫信号传导途径，诱发机体内免疫稳态的失调，进而形成促炎促瘤的微环境。因此，机体识别细菌和细菌源性分子在结直肠癌的发生发展中起到了关键作用。与结直肠癌发展相关的细菌促炎机制主要包括炎性体的激活[106]和NF-κB途径的激活[107]，两者在受到细菌刺激后激活，并促进细胞的存活和增殖活化。此外，T细胞亚群，如Th17细胞和调节性T细胞，均可以调控肠道炎症反应，从而在与炎症相关的结直肠癌发生发展过程中发挥重要作用[108,109]。值得注意的是，这些细胞的比例和功能亦受肠道菌群的影响，这也进一步证实菌群介导的炎症反应在结直肠癌的发展过程中的重要作用。

3.2. 肠道菌群失调诱导结肠直肠癌的进展

肠道菌群和结直肠癌的进展之间的因果关系一直是科学界的争论点。目前，我们还不能够明确地断定是否存在因果关联，因为大部分证据仅仅提示两者有关，而没有清楚地证明菌群失调是结直肠癌发病的原因还是结果。然而，一些研究表明，与传统饲养条件相比，清除肠道菌群的小鼠和大鼠的肿瘤负荷明显降低[76,110,111]。最近也有研究证明，肠道菌群中的特定细菌可以促进结直肠癌的发展[5,7]。值得注意的是，在肿瘤环境中，免疫细胞仍有定植，并在促瘤和抗瘤免疫中起重要作用。同时，这些免疫细胞也受肠道菌群的影响，即使在结直肠癌发生之后亦是如此。因此，肠道菌群、免疫系统和结直肠癌之间的相互作用并不是一种简单的因果关系，而是一个多方面相互作用、错综复杂的网络关系，所以值得进一步研究。

3.3. 肠道菌群通过细菌代谢产物促进结直肠癌的进展

越来越多的证据表明，不仅是肠道菌群，而且其代谢产物同样可以诱发结直肠癌的发生。短链脂肪酸乙酸、丙酸和丁酸均有抑癌作用；而其他代谢产物，如次级胆汁酸，反而会促进肿瘤发生。所有这些代谢产物已经在其他综述文献中得到详述[12,112]。在本文中，我们旨在简要讨论细菌代谢、饮食和结直肠癌之间的关系。

高蛋白摄取会导致食物蛋白在结肠中发酵产物的增

加，如氨基酸衍生产物支链脂肪酸和苯乙酸[113,114]。部分肠道细菌，包括部分拟杆菌门和厚壁菌门细菌，能代谢芳香族氨基酸以产生生物活性化合物，包括吲哚、酚、对甲酚和苯乙酸。这些含氮的产物，尤其是亚硝基化合物，可以通过DNA烷基化导致的基因突变促进癌变。已有研究证明摄食亚硝基化合物与结直肠癌的发生存在正相关关系[115]。在高蛋白质饮食人群中已发现粪便中亚硝基含量有明显上升。

蛋白质发酵的产物之一，氨，也是一种致癌剂，但在人体中的浓度较低。在大鼠实验中，其已被证明能增加黏膜损伤的程度和结肠腺瘤的数量[116]。硫化氢是通过食源性硫酸盐的还原和其他化合物的代谢在远端肠中产生的产物。在健康个体中以低丰度存在的硫酸盐还原菌，如脱硫弧菌属细菌，能够以乳酸作为底物发酵产出硫化物[117]。而硫化物对结肠上皮细胞具有毒性，同时可以抑制丁酸氧化，导致结肠上皮细胞屏障的破坏[118]。硫化物对正常的人源细胞系具有基因毒性，产生的ROS参与了DNA的损伤过程[75]。作为细菌或饮食的代谢产物，多胺也具有细胞毒性并且与癌症密切相关。一般认为，多胺分解代谢过程中的氧化应激反应是诱发癌症的重要机制[119]。此外，一些肠道细菌，如脆弱拟杆菌，可以促进宿主细胞产生多胺[120]。目前，过度饮酒是致癌的重要危险因素也得到了广泛认同[121]，而菌群的代谢可能会进一步增加其毒性。因为，许多厌氧菌的代谢能够生成乙醇。虽然乙醇本身并非为一种具有明显致癌作用的物质，但其氧化产物乙醛则被公认为是较强的致癌物，可以对机体产生一系列影响，包括维生素叶酸的降解和DNA的损伤[122]。

4. 菌群易位与结直肠癌

除了生态失调，菌群的易位在结直肠癌的发展中也起着至关重要的作用。细菌易位的一般路径是自肠腔到肠系膜淋巴结[104]。一项为期五年纳入158例结直肠癌患者的前瞻性队列研究发现，与没有MLNs细菌易位的结直肠癌患者相比，MLNs细菌易位者的疾病相关生存率和无病生存率均较低[32]。此外，细菌易位是结直肠癌患者的一个预后参考指标[32]。Lescut等[123]发现，癌旁淋巴结中的失调细菌是结直肠癌患者的主要细菌易位源。此外，结直肠癌患者的细菌易位与疾病进展相关[124]。综上所述，靶向易位的菌群可以为预防和治疗结直肠癌提供线索。

5. 粪便细菌与结直肠癌的诊断

我们团队的研究发现，结直肠癌患者粪便中的细菌可以作为一种用于结直肠癌诊断的非侵入性的生物标志物[125,126]。基于探针的双重定量聚合酶链反应(定量PCR)检测方法，我们对203例结直肠癌患者和236名健康人群粪便标本的对照研究找到了与结直肠癌相关性较强的细菌，包括*F. nucleatum*, *Bacteroides clarus*(*B. clarus*), *Roseburia intestinalis*(*R. intestinalis*), *Clostridium hathewayi*(*C. hathewayi*)和m7，并发现*F. nucleatum* + *C. hathewayi* + m7 + *B. clarus*表现出较高的诊断能力，受试者工作特征曲线下面积(AUC)高达0.886[125]。通过比较104例结直肠癌、103例腺瘤患者和102名健康人群的定量PCR结果，我们发现，具核梭菌与粪便免疫化学试验(FIT)组合分析对诊断结直肠癌具有很高的灵敏度(92.3 %)和AUC(0.95)[126]。高丰度的具核梭菌和脆弱拟杆菌已被确定为结直肠癌患者预后不良的独立影响因素[127]。有研究认为，具核梭菌特有的FadA黏附素是结直肠癌的一个潜在的有效诊断靶标，因为*fadA*基因在腺瘤和腺癌患者结肠组织中的表达水平显著高于健康人群结肠组织的表达水平[128]。上述研究表明，探测肠道菌群可能为结直肠癌的诊断提供非侵入性、准确且经济的新途径。

6. 结论与观点

根据不同定植部位划分的4类肠道共生细菌的组成和功能各有不同，对宿主和微生物之间的相互作用也有所不同。整个消化道是一个巨大的互惠互利生态系统。其中一类细菌的变化有可能引起其他细菌群体的级联反应。通过将肠道共生菌群分为更多亚组，我们可以更明确地了解不同菌群的分子作用机制。菌群失调和易位与结直肠癌密切相关，粪便细菌有望成为用于结直肠癌诊断非常有价值的非侵入性生物标志物。此外，肠道菌群是抑制结直肠癌增殖和转移的潜在治疗靶标。

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