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专论与综述

病理共生菌的研究进展

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摘　要：宿主是微生物栖息地，在宿主的皮肤、口腔、呼吸系统等处生存着多种微生物群体。在共生生物中，发现了一类“通常无害，但在特定的遗传或环境条件下可能会致病的共生体”，国际上引入新术语称为“pathobiont”。然而，目前该类微生物的中文名词尚未统一确定。本文对该词构成和相关研究分析后将 pathobiont 定义为“病理共生菌”，并总结其在宿主菌群失调、病原体感染及营养失调等多种条件下的致病性及诱发的多重病理效应，为宿主微生物生态失衡机制的研究提供了新思路。

关键词：病理共生菌；宿主；病理；共生

Definition and progress of pathobiont

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Abstract: The host serves as a habitat for a variety of microorganisms residing in the skin, oral cavity, respiratory system, etc. Some of these microorganisms that are usually harmless but may become pathogens under certain genetic or environmental conditions have been observed. A new term “pathobiont” has been coined, which, however, lacks a formal Chinese term. Through analyzing the word formation and related studies, we propose the definition of pathobionts as pathological symbiotic bacteria. This review briefly summarizes the pathogenicity of pathobionts under various conditions such as host flora imbalance, exogenous pathogen infections, and nutritional imbalance and the multiple pathological effects induced by

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pathobionts, shedding light on understanding the mechanism of microbial imbalance in the host.
Keywords: pathobiont; host; pathology; symbiosis

宿主平均携带有 10^{14} 个微生物，超过 770 种细菌分布到机体各处，包括皮肤、口腔和胃肠道等；与宿主共生长的微生物集合涵盖着细菌、真菌、真核生物、古菌和病毒，这些微生物构成复杂的生物栖息地，影响着动物的健康与疾病[1]。由于细菌的数量远远超过其他微生物，研究人员有时将共生微生物组统称为共生细菌[2]。共生细菌在新生儿出生即开始定殖，由最初小群落逐步转变为一个多样化的生态系统，并与宿主形成互惠互利的关系[3]。

在健康饮食的宿主肠道中，微生物主要由拟杆菌属(*Bacteroides*)、厚壁菌门(*Firmicutes*)、变形菌属(*Proteus*)、疣状微生物群构成[4]，这些肠道共生菌为动物提供定殖抗性，从而抵御病原体的入侵，是宿主维持健康状态的必需因素[5]。在共生菌群中，科学家们发现了一类“通常无害，但在特定遗传或环境条件下可能会致病的共生体”，国际上引入新术语将该类菌群称为“pathobiont”，但目前对该术语的中文定义尚未确定统一。研究这些微生物及其与宿主间相互作用可能有助于深入了解多种疾病的发生发展，对炎症性肠病、营养不良、糖尿病、多发性硬化症及癌症等疾病的成因和潜在治疗方法均具有指导性意义[6-8]，因此本文探讨了宿主病理共生菌的研究进展，重点介绍了其概念、致病条件及宿主效应，以期为研究宿主-共生菌间互作机制提供参考。

1 定义

首先使用构词法解析该词汇，“pathobiont”在词根词缀构成上可分为“patho-”和“-biont”，前者等同于“disease”，译为“与疾病相关的”；后者译为“生物或有机体”，二者综合将该词直译为“疾病相关的生物”。与“pathogen”不同的是，“pathobiont”强调在正常生理环境中无害，但具有致病潜力的生物。当各种遗传、外显子、微生物、宿主等因素扰乱健康微生物群落时，这些共生生物可能成为致病菌，在体内加重炎症表现，诱发自身免疫疾病，严重时可危及生命(图 1)。通常无害的“pathobiont”在不利条件下可能表现出致病表型，而共生区域稳态的失衡往往决定着它的增殖。在生态失调下，“pathobiont”成为具有“新生致病力”的病原体，而失衡通常包括遗传因素、宿主饮食改变，以及过度使用抗生素或其他药物等，遗传和环境因素促成了“pathobiont”致病的随机性。基于上述分析，本文将“pathobiont”的中文术语定义为“病理共生菌”，意在指可能诱发病理效应的共生微生物。

2 病理共生菌研究进展

2.1 宿主病理共生菌致病机制

同机体共生长的密集常驻微生物群落称为共生微生物。这些微生物同宿主共进化，对宿主免疫系统的塑造及肠道稳态至关重要。在发育初期，它们可促进体内营养的消化吸收，在定殖部位保护宿主免受病原体的入侵并抑制邻近微生物的异常增殖[9]，同时还可干预动脉粥样硬化等疾病的发生发展[10]。肠道微生物有 1 000 余种，肠道的细菌细胞和动物细胞的比例近乎 1:1，其与宿主间的共生关系在宿主的环境适应性及机体健康中发挥关键作用[11]。肠道微生物还可通过分解复合碳水化合物为机体提供高达 10%的能量[12]。当宿主处于健康状态时，共生微生物会抑制促炎性 T 细胞介导的炎性反应，维持机体稳态；当处于亚健康状态时，由病理共生菌转变的致病菌可能会激活促炎细胞的应答，造成内环境紊乱。

成年动物的肠道菌群中厚壁菌门(*Firmicutes*)和拟杆菌门(*Bacteroidota*)占主要比例，其中约 40 种菌群处于相对恒定状态[13]。当

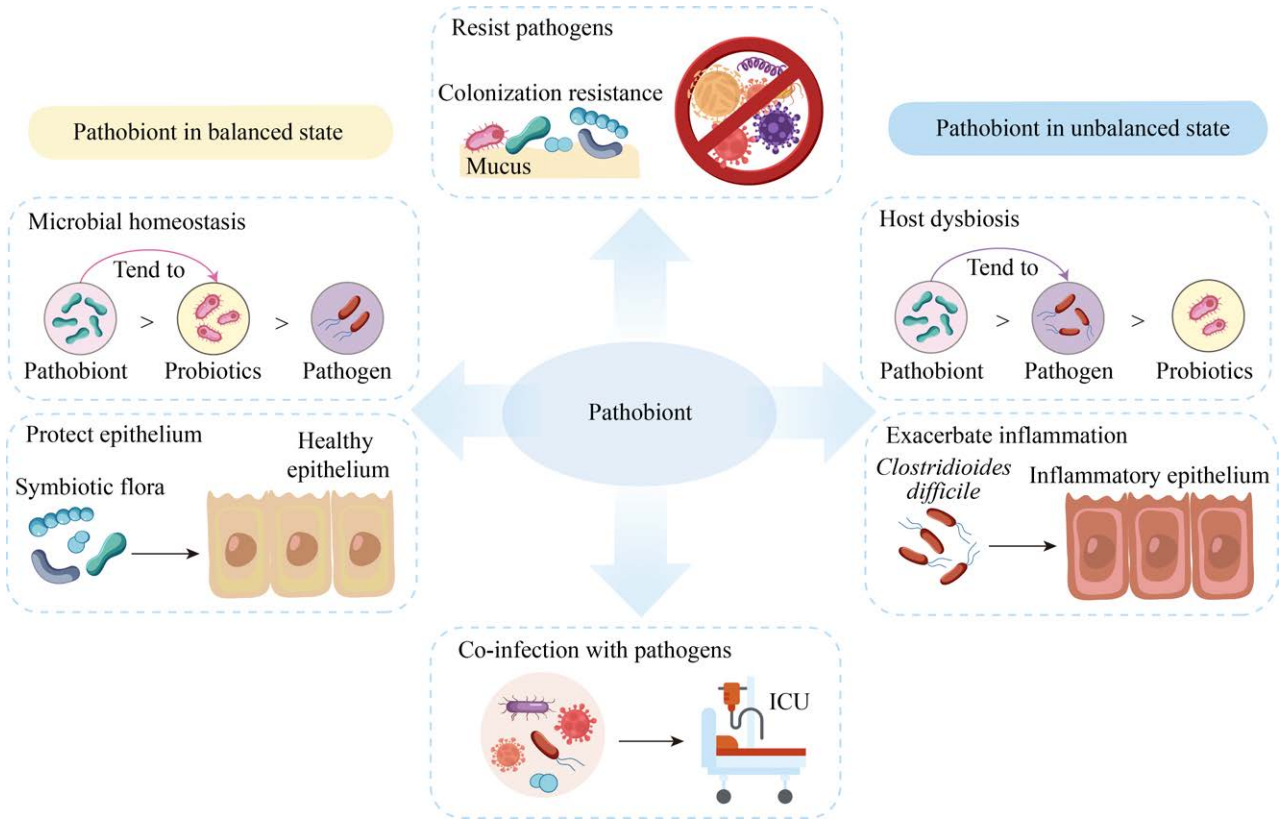

图 1　病理共生菌在肠道微环境中的角色

Figure 1　The role of pathobiont in the intestinal microenvironment.

受到外界严重干扰如过度使用抗生素，可破坏肠道菌群的多样性并导致某些菌种的丰度降低至无法检测的水平[14]。尽管经过一段时间后菌株的种类和相对丰度会恢复至原先相似水平，但当微生物群反复暴露时，某些病理共生菌的致病潜力可能被激活，成为对机体有害的致病菌。肠道共生大肠杆菌是肠道微生物的主要成员，其益生菌菌株可预防膀胱感染的复发[15]，但在失衡状态下却能造成危及生命的感染。共生大肠杆菌携带有基因毒素大肠杆菌素，该毒素可诱导双链 DNA 的断裂。当机体因外源病原体感染等原因处于炎症环境时，炎症以共生菌群为目标促进具有遗传毒性潜力的大肠杆菌扩增，并进一步减少保护性黏蛋白和抗菌肽的产生，为细菌的黏附创造条件。在持续异常增殖下，大肠杆菌成为机体结肠癌的主要诱导者[16]。类似地，产肠毒素脆弱拟杆菌(*Bacteroides fragilis*)产生的锌依赖性金属蛋白酶毒素[17]可通过上皮白细胞介素-17 (interleukin-17, IL-17)及信号转导子和转录激活子 3 (signal transducer and activator of transcription 3, STAT3)信号传导引起宿主肿瘤的发生[18-19]。有研究发现，动物体主要的炎症性肠病(inflammatory bowel disease, IBD)之一溃疡性结肠炎的患者中黏附性侵袭性大肠杆菌(adherent-invasive *Escherichia coli*, AIEC)的患病率也在增加[20-21]。IBD 所引起的环境和营养变化为 AIEC 的不断扩张提供优势，AIEC 的异常增殖并非 IBD 的诱因而是其结果。尽管 AIEC 可能将作为肠道并发症的主要发起者，但不可否认的是，在最初由 IBD 诱导的失衡环境中，AIEC 仅作为菌群失衡的参与者之一，参与诱导机体的炎症反应。在炎性环境下 AIEC 不断获取优势生态位，逐步完成从疾病参与者到疾病发起者的角色转换[22-23]。由此可见，

共生微生物-外源病原体-内源致病菌三者间的联系及相互影响对感染或疾病的控制具有重要意义。当宿主状态发生改变时，原本不致病的良性微生物可能会成为新的侵略者，对机体健康造成损害。表 1 总结了由病理共生菌诱发的相关感染及致病机制。

2.1.1 宿主菌群失调

宿主微生物群落的平衡状态直接关系到动物的健康与疾病。当微生物群落处于失衡状态时，一些原本良性的共生成员可能会进化出逃逸机制并异常增殖，成为致病菌引发感染。宿主对体内共生菌的调控途径是多样的，在某些疾病状态下导致微生物平衡状态发生改变的状况称为菌群失调，如特应性皮炎(atopic dermatitis, AD)可检测到皮肤上的金黄色葡萄球菌(*Staphylococcus aureus*)定殖增强，其丰度异常可能会导致机体免疫稳态的破坏[38]。在宿主肠道中，机体可控制微生物数量，以避免其对单糖和氨基酸的过度竞争，影响内环境稳态。一个健康的肠道主要由专性厌氧菌的多样化群落构成[39-40]，当肠道中病理共生菌的丰度增加或生物膜表型发生异常时，其失控的增殖会促使微生物突破肠上皮黏液屏障，直接与上皮表面相连并释放大量致病生物。

肠道微生物致病的重要原因是功能性和结构性菌群生物膜的大量失调，导致病理共生菌由友转敌。病理共生菌往往不是低丰度的物种，其致病性的表达通常需要在宿主特定遗传或环境的改变导致的炎症性病理环境。牙周细菌齿垢密螺旋体(*Treponema denticola*)是牙周健康中牙龈生物膜下非常微小的组成部分，但在患病的牙周袋中以高丰度茁壮成长，当其从共生状态转为致病表型时，可迅速增进邻近物种的生长，破坏宿主菌群稳态[41]。

2.1.2 宿主内进化

健康宿主携带大量病理共生菌，即使是患病动物这些细菌也早已定殖。已知宿主遗传因素和环境因素会影响疾病的发生和发展，病理共生菌本身性状的改变是否也是影响疾病的重要因素。越来越多的证据表明，共生生物在宿主内并非一成不变，它们会随着宿主内外环境的改变而进化出更稳定的定殖机制。宿主内进化可能导致某些共生生物失去原本的良性特征，增强病理行为，加剧炎症疾病的发展。

肠球菌(*Enterococcus* sp.)是动物健康肠道菌群的一部分，先前研究认为肠球菌是无害共栖菌，但近年来已证实肠球菌的潜在致病性。实际上，只有当肠球菌离开正常寄居部位进入到其他组织器官开始定殖时，该群体耐受机体非特异性免疫清除以诱发感染。抗生素的过量使用或免疫力损伤会打破宿主与肠球菌之间的共生平衡，促使肠球菌在组织局部聚集到达阈值密度，并在黏附素的参与下黏附于胞外蛋白[42]。肠球菌在发挥致病性时可富集于小肠黏膜并移行至肝脏，表现出对酶类、抗菌肽及巨噬细胞等免疫清除机制的顽强抵抗力，这表明肝脏中发现的肠球菌可能是肠道共生菌群中通过适应性或选择性机制获得免疫抗性的亚群[37]。关于病理共生菌的宿主内进化机制，在基因水平中发现，肠球菌在进化过程中细菌细胞壁结构的相关基因表达增加，如编码肽聚糖 N-乙酰葡糖胺脱乙酰酶的 *pgdA* 基因的高表达减弱了肠球菌及粪肠球菌(*Enterococcus faecalis*)对溶菌酶的敏感性[43]。此外，在透射电子显微镜下观察到肠球菌的肝脏分离株表现出祖先菌株不具有的厚荚膜多糖层，这也充当了肠球菌属的毒力因子，即重构的细胞壁部分诱导肠球菌成为具有新生致病力的共生体[44]。

2.1.3 外源病原体感染

当外源病原体侵袭宿主微环境时，可激活体内病理共生菌的潜在毒力并与病原共感染，导致疾病的加重。通常情况下，外源病原体为了获得生态位会上调糖原相关基因表达以提升自身获取营养的能力，如企图入侵肠道的伤寒沙门氏菌(*Salmonella typhi*)在拟杆菌存在时，其编码唾液酸、岩藻糖因子的操纵子水平均上调，

表 1 病理共生菌相关感染及致病机制

Table 1 Pathobiont-related infections and pathogenic mechanisms

Species	Features	Colonization	Pathogenesis	Infections
Porphyromonas gingivalis	Gram-negative rod-shaped anaerobic bacteria	Oral cavity	It causes an imbalance of microorganisms in dental plaque and produces toxic products, promotes cell invasion and induces chronic inflammation	Periodontitis, gingival squamous cell carcinoma[24-25]
Parvimonas micra	Gram-positive anaerobic cocci	Oral cavity	Extracellular polysaccharides mediate host interactions and can adhere to epithelial cells and evade host immune clearance	Periodontitis, odontogenic abscess, apical periodontitis[26]
Fusobacterium nucleatum	Gram-negative anaerobic bacilli	Oral cavity, gastrointestinal tract	Encoding adhesins for interspecies interactions, including Fap2, RadD, and aid1, FadA is a common virulence factor	Periodontal disease, Inflammatory bowel disease[27-28]
Bacteroides fragilis	Gram-negative anaerobic bacilli	Oral cavity and colon, female reproductive tract	Secrete BTF toxin, increase the expression of spermine oxidase. Induces the abnormal accumulation of Treg cells in the intestine, accelerating cell damage and canceration	Diarrhea, inflammatory bowel disease, colon cancer[29-30]
Helicobacter pylori	Gram-negative microaerophilic Helicobacter	Gastric mucus layer and gastric epithelium	It can adapt to gastric acid and secrete CagA and VacA. Enhance the inflammatory response, damage mitochondria and endosomes and change plasma membrane permeability	Atrophic gastritis, gastric cancer, gastric diabetic nephritis, gastric malt lymphoma[31]
Streptococcus gallolyticus	Gram-positive lactic acid bacteria	Gastrointestinal tract	Produces three virulence factors, which bind to type I and type IV collagen and attach to the heart valve. The virulence factors can be expressed randomly to complete the stable colonization	Endocarditis, urinary tract infection, sepsis[32]
Escherichia coli	Gram-negative facultative anaerobic brevibacteria	Intestine	This strain can regulate various toxins such as proteins, cytotoxic necrosis factors, and colicins, disrupt the cell cycle, promote DNA damage, and affect cell differentiation and apoptosis	Gastroenteritis, acute diarrhea, colon cancer[33]
Clostridioides difficile	Gram-positive anaerobic bacilli	Colon	The bacterium has evolved two toxins: tcdA and tcdB, which increase the permeability of the intestinal wall and damage the cytoskeleton	Pseudomembranous colitis, toxic megacolon[34-35]
Enterococci	Gram-positive facultative anaerobic cocci	Gastrointestinal tract	It adheres to host tissues through cell surface adhesins AS, cytolysin, etc. and can survive in macrophages and complete translocation in intestinal epithelial cells	Urinary tract infection, Bacteremia, intra-abdominal infection, endocarditis[36]
Lactobacillus iners	Gram-positive facultative anaerobes	Vaginal	Under dysbiosis, this strain releases hemolysin, which forms a cholesterol-dependent pore in the vaginal epithelium and promotes invasion of pathogens	Bacterial vaginosis[37]

显著增强自身竞争生态位的能力[45]。但病理共生菌也可通过自身方式获得生长优势，在小鼠肠道模型中发现，某些病理共生菌可利用表面黏附素和富含丝氨酸的重复蛋白作为底物形成自身生物膜[46]，其表面黏附素可以 pH 依赖的方式与宿主选择性结合，促使不同生物膜共生体占据肠道不同生态位[47]。外源病原体铜绿假单胞菌(*Pseudomonas aeruginosa*)在入侵肠道后，其毒力基因的表达与生物膜的形成受到定殖区域内不同病理共生菌间的生化信息调节，即群体感应效应[48]。环二鸟苷酸(cyclic di-guanosine monophosphate, c-di-GMP)是一种多效性第二信使，该分子可控制包括大肠杆菌、沙门氏菌等多种共生菌在浮游模式与生物膜固着生长模式间的转变，调控生物膜菌群的社会行为[49-50]。在肠道黏液中，病理共生菌通常以复合生物膜的形式嵌入到细胞外聚合物的基质中[51]。当外界病原体攻击肠道导致生理紊乱时，共生菌可能会从生物膜上脱落并发挥致病力。有研究发现，空肠弯曲杆菌(*Campylobacter jejuni*)的介入可激活健康肠道中非侵袭性大肠杆菌的菌毛、鞭毛及溶血素 E，促使其黏附并易位通过上皮屏障[52]。在葡聚糖硫酸钠(dextran sodium sulfate, DSS)的作用下，病理共生菌会分散并向肝脏或脾脏移行，去极化上皮核酸敏感型 Toll 样受体 9 (Toll-like receptor 9, TLR9)，加重小鼠 DSS 结肠炎的感染程度[53]。这种现象的发生可能与 DSS 引起的肠道黏膜损伤和炎症反应有关。这一发现提示病理共生菌的失调与肠道疾病的发生发展密切相关。

常驻微生物群在根除病原体定殖和重建微生物防御系统以维持体内平衡方面发挥着至关重要的作用。然而，某些共生细菌与感染期间病原体的生长呈正相关。我们前期研究发现宿主体内的几种病理共生菌可促进副鸡禽杆菌(*Avibacterium paragallinarum*)的生长，包括葡萄球菌(*Staphylococcus*)、肠球菌(*Enterococcus*)和芽孢杆菌(*Bacillus*)；这些共生菌主要由革兰氏阳性菌组成，该类菌群在资源有限的条件下为革兰氏阴性病原体创造了合适的生态位。因此，病理共生菌对于副鸡放线菌的入侵与生存极为重要[54]。外源病原体与病理共生菌群之间的共生关系可能会损害抗生素的治疗效果并加剧持续感染。

2.1.4 营养因素

病理共生菌在致病潜力被激活后，可充分利用共生区域其他健康生物未耗竭的营养资源。乙醇胺是实验室条件下肠球菌碳、氮及能量的唯一来源，其可通过 *eut* 操纵子产生短链脂肪酸及乙酸等，发挥肠道抗炎作用[55-57]。但在某些情况下，病原微生物也可以利用这些营养资源获得定殖优势，加剧肠道疾病。例如出血性大肠杆菌(enterohemorrhagic *Escherichia coli*, EHEC)基因组中的 *eut* 操纵子可利用共生区域内的乙醇胺作为碳源，帮助 EHEC 在肠道固定生长时期持续占据肠道生态位，并通过其他毒力因子导致肠道炎症和病变[58]。沙门氏菌也可以利用肠道共生菌群的代谢产物，获得生长和繁殖的优势，从而诱发肠道疾病[59]。

在肠道微环境中，铁对共生菌的生长繁殖及肠道炎症的形成至关重要，与病理共生菌生态位的选择和毒力基因的表达密切相关，当铁供应不当时，一些微生物将无法保持最佳生长状态而影响肠道健康[60]，但过多补铁可能会导致机体出现不良反应并诱发感染。研究发现，IBD 患者的肠外并发症除常见的贫血外，通常也会由于患病期间过度食源性补铁或大剂量口服补铁制剂出现恶心、呕吐、腹泻或黑便等不良反应，引起疾病的恶化[61]。过量的铁及与铁相关的嘌呤或嘧啶代谢物会加速某些潜在阴性菌属如埃希氏菌属(*Escherichia*)、梭菌属(*Clostridium*)的异常增殖，激活病理共生菌的潜在毒性，导致有益菌群的减少及致病菌的扩张[62]。机制上可能是由于肠腔内的铁可诱导活性氧(reactive oxygen species, ROS)的产生，触发氧化应激及肠上皮损伤；或是高铁环境促进铁

依赖性共生体的大量繁殖，改变共生菌间的比例与丰度，增加特定代谢物，导致生态失调[63]。

氧气也是影响共生微生物健康状态的重要因素。哺乳动物的胃肠道是缺氧的，氧气通过结肠黏膜表面到达肠管中心形成低氧梯度，进而建立以专性厌氧菌为主的共生群落结构[64]。然而，在肠道感染的背景下，氧水平是病理共生菌失衡的生态驱动因素之一[40,65]。在非感染性免疫介导的胃肠道疾病中，致病 T 细胞在肠道上皮中干扰氧化磷酸化，导致线粒体功能受损和细胞能量代谢障碍，打破肠腔独特的“生理性缺氧”状态，从而抑制专性厌氧型共生菌的生长，并促进耐氧型和兼性厌氧型成员不断增殖并失去原有的良性状态，最终破坏肠道稳态[66-67]。

与肠道中存在丰富的营养物质相反，健康个体呼吸道中的常驻细菌通常缺乏能量来源，尤其是嗜血杆菌(*Haemophilus* sp.)等微生物需要丰富的营养。烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide, NAD)是生物代谢过程中的关键辅酶，存在于所有细胞中，其分为氧化形式 NAD^+与还原形式 NADH[68]。健康宿主呼吸道中的 NAD^+丰度通常不足以维持嗜血杆菌的生存与生长，我们却在鸟类动物模型中观察到数量可忽略不计的产色葡萄球菌(*Staphylococcus chromogenes*)直接促进了鸡上呼吸道副鸡嗜血杆菌(*Haemophilus gallinarum*)的存活；病理共生菌产色葡萄球菌可直接加速NAD^+的生物合成并从宿主细胞中释放，副鸡嗜血杆菌将其劫持成为自身的 NAD^+来源并不断繁殖，引发呼吸道感染[69]。

2.1.5 共生代谢物介导

胃肠道内的共生代谢物是外源病原体、病理共生菌和致病菌三者间相互作用的关键调控因子，对菌群生态位的选择和机体疾病的控制起着重要作用[70-73]。短链脂肪酸(short-chain fatty acid, SCFA)等多种共生代谢物对肠上皮细胞(intestinal epithelial cell, IEC)的健康状态尤为关键，SCFA 是 IEC 氧化磷酸化的主要能量来源，可调节体内平衡和肠道屏障功能[74]。丁酸盐(butyrate)是一种毛螺菌科(*Lachnospiraceae*)和瘤胃菌科(*Ruminococcaceae*)细菌的发酵代谢物，主要参与上皮紧密连接，保护上皮屏障及宿主免疫健康。艰难梭菌(*Clostridium difficile*)是一种严格革兰氏阳性厌氧菌，最初于 1935 年被定义为新生儿肠道菌群的一部分，可无症状定殖高达 15%的健康人群[36,75]，并且艰难梭菌感染(*Clostridioides difficile* infection, CDI)是抗生素相关性腹泻的主要原因。在 CDI 小鼠模型中，醋酸酯代谢物有助于艰难梭菌的致病性扩张[35]。当遇到抗生素、质子泵抑制剂及化疗药物治疗时，宿主体内的艰难梭菌可分泌基于脯氨酸的环状二肽如 cyclo (Phe-pro)、cyclo (Leu-pro)，该物质可抑制耐甲氧西林金黄色葡萄球菌(methicillin-resistant *Staphylococcus aureus*, MRSA)的肠道生长并调节细菌间的群体感应，使艰难梭菌进化出抑制肠道其他成员生长的能力，增加艰难梭菌成为致病菌的可能性[17,76]。有研究发现，动物远端结肠是机体内微生物群含量最多的部位，在结肠中富含唾液酸和硫酸基团的黏蛋白可作为病理共生菌的定殖因子和营养来源，为共生菌提供保护屏障[36]。肠道微生物群已进化出碳水化合物硫酸酯酶[77-78]，该酶对病理共生拟杆菌属降解并利用硫酸盐远端结肠黏蛋白 O-聚糖至关重要[79-80]，促使该菌属以硫酸盐酶依赖的方式跨过外膜囊泡进入宿主免疫细胞，诱发机体结肠炎[81]。病理共生菌转化为病理状态后的致病机制是多种多样的，主要的 5 种机制总结见图 2。

2.2 病理共生菌的宿主效应

2.2.1 宿主屏障的破坏

健康状态下，病理共生菌可帮助宿主抵御病原体的入侵。有研究表明中华按蚊的肠道粘质沙雷氏菌(*Serratia marcescens*)可通过调节先天免疫途径的 Toll 信号实现对疟原虫的抑制[82]。而病理状态下肠道异常生物膜的形成通常与炎症有关[83]。在啮齿动物结肠炎模型中，病理共

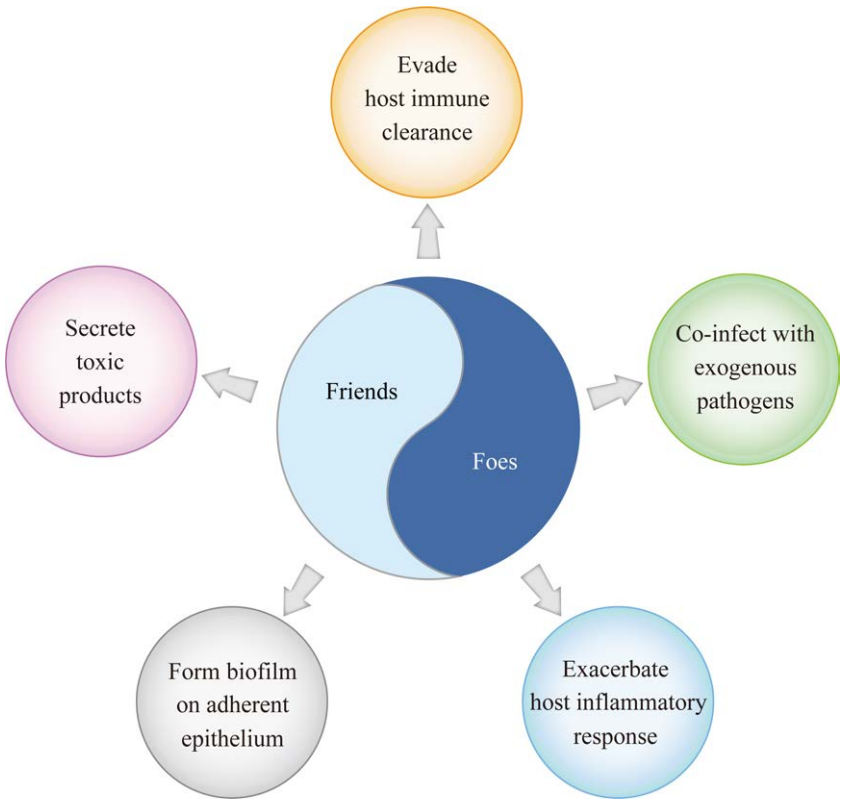

图 2　病理共生菌常见的致病机制
Figure 2　Common pathogenic mechanisms of pathobiont.

生菌群的生物膜发生分散，导致潜在致病菌释放并直接接触肠道上皮细胞，黏附和侵入，进而破坏肠道屏障[84]。在 IBD 人体中同样发现，病理共生菌的生物膜簇可躲避机体黏液屏障，与上皮表面紧密黏附[85]。在结肠炎小鼠中发现了病理共生体转变成致癌性细菌的现象，如分泌大肠杆菌素的致病性大肠杆菌等；造成宿主出现 IBD 感染的肠道“原住民”在获得新生致病力后成为黏膜脆弱拟杆菌、黏附侵袭性大肠杆菌等[86-87]，这些细菌可产生胞外蛋白酶，对肠道健康菌群生物膜进行蛋白质水解，从而破坏组织屏障并加重菌群失衡。

2.2.2　诱导宿主炎症

病理共生菌与病原体具有相似的微生物相关分子模式如脂多糖、脂蛋白和肽聚糖等，良性环境下的微生物与宿主间是共生平衡关系，在病理环境中共生菌具有激活模式识别受体诱导或加重炎症的潜在致病力。有研究在小鼠口腔中发现一种病理共生菌(命名为 NI1060)，其表面上可在受损的牙周组织中选择性地自炎症组织分解产物中获取营养，但实际上不同于同种属 NI440 和 NI968 的完全良性，NI1060 可通过激活细胞内的模式识别受体 Nod1 (pattern recognition receptor Nod1, PRR Nod1)主动引发破坏性牙周炎症[88]。

炎症小体是免疫系统的传感器，是宿主炎症性疾病的重要参与者。诱导炎症小体的关键是 caspase-1 的激活及 IL-1β、IL-18 的成熟与释放。大量病理共生菌在成为致病菌后可进化出靶向肠上皮细胞小 GTP 酶 Rho 家族的毒力因子，该家族是介导肌动蛋白细胞骨架重排的分子开关，并且是神经元生存和死亡的重要参与者[89]。宿主 pyrin 炎性小体的先天免疫复合物可感应体内病理共生菌发出的致病信号即 Rho

GTP 酶活性损伤[90]，该酶损伤可抑制宿主细胞的迁移、破坏上皮屏障完整性，最终导致细胞死亡。蜡样芽孢杆菌(*Bacillus cereus*)在健康宿主中可快速降低消化道内环境中的氧水平，有助于维持肠道厌氧环境，并产生乳酸等物质降低肠道 pH 值，抑制潜在致病成员的生长[91]。但当蜡样芽孢杆菌失去良性后，其进化出的 C3cer 毒素可引起 Rho GTP 酶发生特异性 ADP-核糖基化，诱发肌动蛋白丝破损，造成免疫、血管及神经系统等病理性疾病[92]。当抗生素扰乱机体健康微生物稳态时，肠道中的艰难梭菌将发生 Rho 家族葡萄糖基化，产生毒素 TcdA 和 TcdB，二者结构中的半胱氨酸结构域自动处理葡萄糖基转移酶的结构域，将葡萄糖基部分不可逆地释放到细胞质中以修饰 Rho GTP 酶家族，破坏该酶正常功能，以相似的中毒机制触发炎症，同时 2 种毒力因子可促进 IL-1β 的产生；pyrin 炎性小体通过响应 Rho GTP 酶的修饰和 IL-1β 的增多，激活 caspase-1 诱导细胞焦亡(图 3)，加重艰难梭菌引起的假膜性结肠炎症状[93]。

2.2.3 免疫细胞的保护性应答

健康肠道菌群在应对病理共生菌异常增殖时具有多种方式保持平衡，如产生细菌素或蛋白质毒素，通过代谢相互作用和空间位阻竞争性排斥生态位[94]、控制致病菌复制、调节黏膜屏障以及诱导或控制宿主特定免疫应答等[95-96]。其

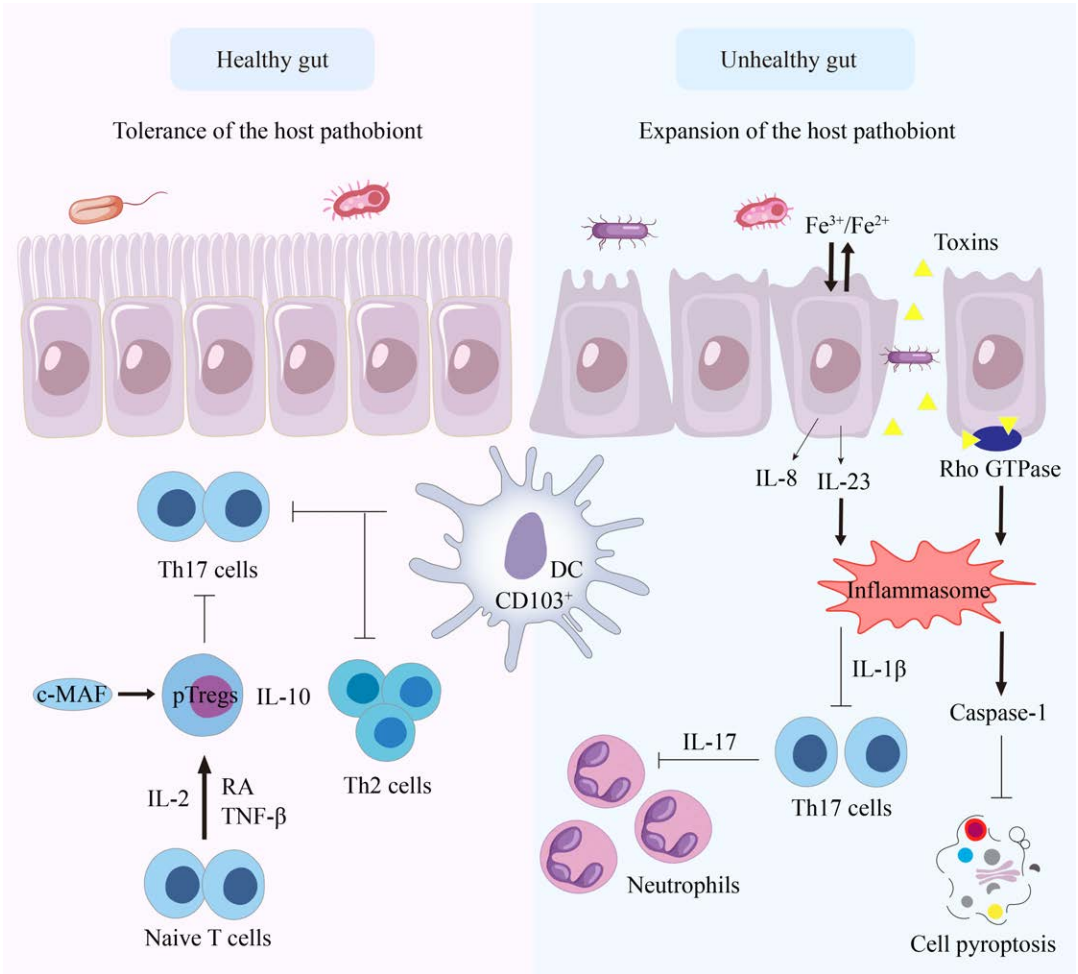

图 3 病理共生菌引发的免疫反应

Figure 3 Immune responses triggered by pathobiont.

他良性微生物分泌的细菌素和蛋白质毒素可显著抑制同菌种或相似菌种的异常繁殖，如大肠杆菌产生的细菌素直接限制肠出血性大肠杆菌的生长[97]。当致病微生物攻击肠道淋巴组织时，初始 $CD4^+$ T 细胞在转化生长因子 β (transforming growth factor beta, TGF-β)、白细胞介素-2 (interleukin-2, IL-2)及维甲酸(retinoic acid, RA)的催化下分化成外周调节性 T 细胞(peripheral Tregs, pTregs)，该细胞群可以抑制效应性 T 细胞的增殖，建立免疫耐受并在调节因子 c-Maf 的控制下分泌 IL-10，从而维持肠道平衡；通常情况下，病理共生菌的快速增殖会诱导肠系膜淋巴结中 $CD103^+$树突状细胞分泌 RA，并在 TGF-β 协助下产生调节性 T 细胞(regulatory T cells, Tregs)[98]，但某些特定条件如 IBD 感染，获取致病力的共生菌与 $CD103^+$树突状细胞的相遇并不以 pTregs 为效应，而是驱动细胞辅助 T 细胞 1 型(T-helper 1 cells, Th1)、辅助 T 细胞 2 型细胞(T-helper 2 cells, Th2)及辅助 T 细胞 17 型(T-helper 17 cells, Th17)的积累，在 IL-17 的刺激下诱导中性粒细胞对捕获的病原菌发挥免疫效应[99]。此外，宿主病理共生菌群落的异常变化会促进先天淋巴细胞(innate lymphoid cell, ILC)的分化与激活，ILC 按细胞因子表达谱分为 ILC1、ILC2 和 ILC3 三类，其中 ILC1s 分泌 IFN-γ、TNF-α，ILC2 分泌 IL-5、IL-9 及 IL-13，ILC3s 与 Th17 细胞、Tc17 细胞共同参与诱导III型免疫反应并刺激前者产生标志性细胞因子 IL-22 与 IL-17[100]。

3 病理共生菌应用及研究意义

宿主异常微生物群诱发的生态失调与过敏、炎症性肠病、癌症、动脉粥样硬化和自身免疫性疾病息息相关[101-102]。除生态失调，病理共生菌也是直接参与疾病的重要成员之一[103-104]，因此控制和改善病理共生菌将有助于疾病的治疗与预防。在某特定部位定殖的正常健康菌群通常会抑制其他细菌的再定殖，即共生微生物具有防止病原体定殖和本土病原菌过度生长的定殖抗性[105]。利用共生微生物治疗疾病这一方法最早在 20 世纪 50 年代应用，目前已有粪便微生物群移植法用于治疗由艰难梭菌引起的复发性结肠炎，健康供体的共生菌菌株在受体中的成功重建了肠道微生物组，使得该疾病的治愈率达 90%[106-108]。Furuichi 等[109]同样巧妙地使用共生菌群的生态控制作用减轻小鼠肺炎克雷伯氏菌(*Klebsiella pneumoniae*)和大肠杆菌引起的肠道炎症；该团队从健康人类粪便样本分离出 18 株能够抑制克雷伯氏菌定殖的菌落联合体命名为 F18-mix，该混合物限制肠道葡萄糖酸的可用性，迫使克雷伯氏菌发生代谢转化从而重塑肠道生态位，降低肠道中克雷伯氏菌的感染水平，并且不会显著影响共生菌群。即病理共生菌的合理应用可使相关常驻细菌获得优势生态位，增强在体内的定殖并改善微生物群比例，以有效治疗肠道感染。在塑造免疫方面，病理共生真菌的定殖表现出影响肠黏膜中各种苔藓亚群网络，有利于预防异常炎症和维持屏障完整性[110]。多样化的病理微生物群可通过多种机制帮助宿主抵抗病原体，包括微生物间的营养代谢竞争[111]、强化黏膜屏障[112-113]及参与局部免疫防御等[114]，共生定殖诱导的稳定生理屏障与全身免疫对维持体内平衡至关重要[115]。

4 总结与展望

病原体诱发疾病的机制除经典地破坏机体某组织器官微生物的丰度和多样性外，还涉及微生物群生物膜表型和功能的紊乱以及共生群落浮游细菌的分散。病理共生菌经黏附扩散可能会成为致病菌并参与疾病的发生发展，包括入侵黏膜屏障、黏附上皮细胞以及激活各种促炎反应等多种途径。在由病理共生菌诱发的 IBD 和结直肠癌中，最典型的共生细菌是黏附侵入性大肠杆菌、脆弱拟杆菌、粪肠球菌等，它们从肠道紊乱的微生物生物膜中逃逸成为致

病菌[116]。此外，研究人员的研究也证明了机会性病原体可以劫持病理共生菌来引发感染，其在感染期间与病原体的生长呈正相关；金黄色葡萄球菌、链球菌(*Streptococcus*)等病理共生菌对红细胞的裂解能力可以破坏宿主屏障，加速病原体在宿主体内的复制[54]。肠球菌也可增加鼠伤寒沙门氏菌(*Salmonella enterica* subsp. *enterica serovar Typhimurium*)的生长与致病性，并且抗生素的使用进一步加剧肠球菌的扩张[42]。因此，在靶向微生物的治疗策略中应当平衡病理共生菌的益生特性和潜在病理特性。当病理共生菌无持续异常增殖或针对免疫低下人群如 ICU 病人时，应当在治疗时主动靶向病理共生菌的病理特性，提前调控共生菌丰度以预防致病菌感染。而针对共感染致病菌可被抗菌药物有效清除时应更关注病理共生菌如何进一步发挥益生特性。实际上，肠球菌在多种微生物感染中的驱动作用为我们提供了一个全新的治疗视角，即将宿主病理共生菌视为潜在的治疗靶点，即以活细菌疗法的形式对抗耐药细菌的感染威胁。例如肠球菌衍生的 β-葡萄糖苷酶可以将香豆素糖苷水解成抗菌苷元，该抗菌苷元可通过竞争铁来抑制鼠伤寒沙门氏菌的生长，即口服香豆素糖苷可以逆转肠球菌对鼠伤寒沙门氏菌的促进感染作用[117]。这意味着可以通过对益生菌等产品进行改造或优化，以植物或饮食疗法抑制宿主的肠道感染。益生菌芽孢杆菌便可通过直接与致病菌相互作用，以及产生抗菌酶、抗菌肽等结构多样的代谢物介导发挥益生作用，维持肠道菌群的稳定和稳态[118-119]。

研究病理共生菌群生物膜的形成及致病菌的分散机制，将有助于寻找由生物膜失调介导各种疾病的新治疗靶点。此外，失调微生物膜中分散致病菌的宏基因组学、元转录组学和代谢组学(包括代谢物的摄取与释放)研究也可为疾病治疗提供思路，在众多由微生物群失调导致的临床疾病中，病理共生菌的研究调查将具有重要意义。

作者贡献声明

蔡亚玮：构思综述主题，撰写文章正文部分，绘制文章图表；徐文娇：撰写总结与展望部分，修改正文部分；沈建忠：提供专业意见，审阅稿件并提出修改意见；朱奎：构思综述主题，设计文章结构，审阅稿件并提出修改意见。

作者利益冲突公开声明

作者声明绝无任何可能会影响本文所报告工作的已知经济利益或个人关系。

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