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专论与综述

胰腺癌相关微生物标志物研究进展

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摘　要：在所有消化系统肿瘤中，胰腺癌的恶性程度很高，患者生存率极低，而胰腺癌发病的具体机制尚不明确。随着近年来包括肠道菌群在内的人体微生物研究的迅速发展，微生物在胰腺癌的潜在发病机制也成为研究热点。本文介绍了与胰腺癌相关的微生物标志物，并分析各种微生物标志物对胰腺癌的作用机制以及微生物形成的肿瘤微环境对胰腺癌的影响，为微生物与胰腺癌关系的进一步研究提供参考，有利于学界未来利用微生物相关技术开展胰腺癌的早期检查、早期预防和临床治疗。

关键词：微生物；胰腺癌；肿瘤微环境

Research progress in microbial markers associated with pancreatic cancer

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Abstract: Among all digestive system tumors, pancreatic cancer is characterized by a high degree of malignancy and a low survival rate of patients. However, the specific mechanism of pancreatic cancer remains unclear. As the research on human microorganisms including intestinal microflora is flourishing in recent years, the potential pathogenesis of microorganisms about pancreatic cancer has become a hot topic of research. In this paper, we introduced the

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microbial markers associated with pancreatic cancer, analyzed their roles in pancreatic cancer, and expounded the effects of the tumor microenvironment formed by microorganisms on pancreatic cancer. This article provides a reference for the further study of the relationship between microorganisms and pancreatic cancer and facilitates the early examination, early prevention, and clinical treatment of pancreatic cancer by using microbiological technology in the future.

Keywords: microbiota; pancreatic cancer; tumor microenvironment

目前研究发现消化道微生态在人体的代谢、免疫和神经调节中发挥重要作用。通过菌群 DNA 测序技术,有研究证明菌群紊乱与疾病的发病机制相关，如糖尿病肾病、肥胖和抑郁症等[1-3]。胰腺通过导管与消化道连通，肠道菌群会进入胰腺形成独特的胰周组织菌群。越来越多的研究显示，微生物与胰腺癌的发生发展存在着密切的关系。与正常人相比，胰腺癌患者的口腔、肠道和胰周组织 3 处的微生态环境中均有更高的异常微生物丰度。本文通过总结口腔菌群、肠道菌群和胰周组织菌群中丰度较高的异常微生物，并分析该菌种与胰腺癌发生发展的相关机制，从微生物角度补充胰腺癌的发病机制。同时，通过对比正常人和胰腺癌患者的消化道菌群种类丰度，总结胰腺癌患者的一些特异性高、丰度高的微生物。如果这些微生物标志物能够加以利用，有望制作用于胰腺癌早期诊断筛查的微生物谱，提高早诊率并及早干预，提高胰腺癌生存率(表 1)。

1 胰腺癌概要

在所有的消化系统常见肿瘤中，胰腺癌的恶性程度较高，是癌症死亡的第三大原因[14]。有统计数据显示，2020 年在全球范围内检出胰腺癌 495 773 例，占所有癌症的 2.6%，位列所有癌症的第 14 位，但胰腺癌的死亡人数却占所有癌症死亡人数的 4.7%，位列第 6 位[15]。在我国，据蔡洁等[16]的统计，2005–2015 这 10 年间胰腺癌的发病率在 6.59/10 万人–8.55/10 万人之间浮动，整体趋势稳中有升；而死亡率在 6.09/10 万人–7.56/10 万人之间浮动，趋势近似发病率；其中，发病率和死亡率男性均高于女性、城市均高于农村。胰腺癌患者的 5 年生存率为 12%，在所有癌症中最低[14]。胰腺癌恶性程度高的原因包括早期诊断困难以及手术、放疗和化疗等传统的治疗效果有限。近年来，免疫治疗应用于多种肿瘤的治疗，但是对于胰腺癌而言效果仍与预期有所差距，主要原因之一是胰腺癌的肿瘤微环境中肿瘤微生物所介导的免疫抑制性[17]。此外，胰腺外的肠道微生物也能够对胰腺癌的发生和发展起到一定作用。因此，寻找人体微生物与胰腺癌的互作关系及其影响机制具有深远的临床意义。

作为消化系统的一个器官，胰腺通过消化道与口腔、肠道都有所联络。随着胰腺癌的进展，肿瘤势必会通过影响肠道微生态与肿瘤微生态造成人体常见微生物的丰度出现异常。有研究发现,生存期较长的胰腺癌患者其肿瘤内微生物中有更高的 α 多样性[12]。而且胰腺癌患者的口腔、肠道和肿瘤内的微生物种群均有重叠，但是各区域的种群丰度有所差异[18]。因此，从微生物角度研究胰腺癌就有了理论依据，也有可能通过微生物开发胰腺癌的新型诊断技术。

表 1 胰腺癌患者的口腔、肠道、肿瘤微生物标志物

Table 1 The microbiota marker in the oral cavity, gut and tumor of pancreatic cancer

部位 Position	种类 Types	作用 Function	参考文献 References
口腔 Oral cavity	牙龈卟啉单胞菌、放线菌聚集杆菌 *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*	牙龈卟啉单胞菌和放线菌聚集杆菌与胰腺癌的高风险相关 *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* were associated with higher risk of pancreatic cancer	[4]
	长型奈瑟菌、轻型链球菌和毗邻颗粒链菌 *Neisseria elongata*, *Streptococcus mitis*, and *Granulicatella adiacens*	在胰腺癌患者的唾液中，长型奈瑟菌和轻型链球菌丰度会降低，毗邻颗粒链菌的丰度会升高，且轻型链球菌和毗邻颗粒链菌的联合应用在鉴别胰腺癌中有 85.7%的敏感度和 52.7%的特异性 The level of *Neisseria elongata* and *Streptococcus mitis* decreased in the saliva of pancreatic cancer patients, while *Granulicatella adiacens* increased, and the combination of *Streptococcus mitis* and *Granulicatella* adiacens had 85.7% sensitivity and 52.7% specificity in the discrimination of pancreatic cancer versus non-cancer	[5]
	细毛菌 *Leptotrichia*	胰腺癌患者唾液中的细毛菌比例明显高于健康人或有其他疾病的患者 A significantly higher ratio of *Leptotrichia* in the saliva of patients with pancreatic cancer than in the saliva of healthy people or those with other disease	[6]
肠道 Gut	幽门螺杆菌 *Helicobacter pylori*	感染幽门螺杆菌的人患胰腺癌的风险更高 People with *Helicobacter pylori* infection are at higher risk of pancreatic cancer	[7]
	变形菌门、厚壁菌门 *Proteobacteria*, *Firmicutes*	在早期胰腺癌阶段，患者肠道微生物以变形菌门和厚壁菌门为主，同时它们会激活多胺和核苷酸的生物合成途径，从而提高胰腺癌患者的血液多胺浓度 *Proteobacterial* and *Firmicutes* dominated in gut microbiota in early stages of pancreatic cancer, and they elevated the polyamine and nucleotide biosynthetic pathways, which elevated the serum polyamine concentrations in pancreatic cancer patients	[8]
	普拉梭菌 *Faecalibacterium prausnitzi*	普拉梭菌的丰度在胰腺癌患者肠道中降低 Level of *Faecalibacterium prausnitzi* decreased in the gut of pancreatic cancer	[9]
	双歧杆菌 *Bifidobacteria*	肠道微生物中双歧杆菌的丰度下降，导致不能抑制转化致癌物的酶活性 The level of *Bifidobacteria* decreased in the gut microbiota, which cannot inhibit the activity of enzymes that transform carcinogens	[10]
胰腺癌肿瘤 Tumor of pancreatic cancer	梭杆菌 *Fusobacterium*	梭杆菌和胰腺癌的发展有关 *Fusobacterium* is associated with the development of pancreatic cencer	[11]
	假黄单胞菌、糖多胞菌、链霉菌和克劳斯芽孢杆菌 *Pseudoxanthomonas*, *Saccharopolyspora*, *Streptomyces*, and *Bacillus clausii*	长生存期的胰腺癌患者的肿瘤有高水平的假黄单胞菌、糖多胞菌、链霉菌和克劳斯芽孢杆菌，因此它们的联合应用可用于长生存期和短生存期的预测 The tumor of pancreatic cancer patients with long-term survival has higher level of *Pseudoxanthomonas*, *Saccharopolyspora*, *Streptomyces* and *Bacillus clausii*, consequently, the combination of them can be used in the discrimination of short and long-term survival and the prediction of prognosis	[12]
	γ-变形杆菌 Gamma-*Proteobacteria*	在胰腺癌肿瘤中，γ-变形杆菌的丰度提高，且 γ-变形杆菌对吉西他滨的耐药性有促进作用 Level of Gamma-*proteobacteria* was increased in the tumor of pancreatic cancer, and Gamma-*proteobacteria* contributed to drug resistance to gemcitabine	[13]

2 胰腺癌微生物标志物及其作用机制

2.1 口腔微生物

众多研究显示，口腔微生物可能直接或间接参与了胰腺癌的发生与发展。牙周病是胰腺癌的危险因素之一，与之相关的是牙龈卟啉单胞菌(*Porphyromonas gingivalis*, Pg)。Michaud 等[19]发现在排除吸烟、肥胖和糖尿病等影响因素后，患牙周病的男性发生胰腺癌的风险比未患牙周病者高 64%。而且对牙龈卟啉单胞菌有高水平抗体的人或牙龈卟啉单胞菌的携带者患胰腺癌的风险明显升高[4,20]。口腔微生物影响胰腺癌发展的机制尚未完全清楚，猜测与口腔微生物通过消化道迁移到胰腺肿瘤内相关[21]。也有研究推测牙龈卟啉单胞菌诱导并促进胰腺癌的机制有：(1) 该菌为革兰氏阴性菌，其组成物质之一的细菌脂多糖(lipopolysaccharide, LPS)能刺激炎症介质的释放，并通过上调 IL-8 的表达诱导基质金属蛋白酶(matrix metalloproteinase, MMP)的合成[22-24]。以上过程都会介导炎症反应的发生，通过激活多种信号通路来促进胰腺癌发展，所引起的炎症也会为肿瘤细胞的定殖与生长提供炎性微环境[25-26]。此外，牙龈卟啉单胞菌还能增强 MMPs 的作用，例如活化的 MMP-9 能降解多种细胞质基质，从而增强肿瘤细胞的侵袭和转移能力[27-28]。(2) 牙龈卟啉单胞菌分泌的核苷二磷酸激酶作用于细胞外 ATP 后，阻断 ATP 与嘌呤受体 P2X7 的结合过程，从而降低 ATP 浓度，进而抑制 ATP 依赖的细胞凋亡，促进细胞增殖[29]。(3) 牙龈卟啉单胞菌通过激活上皮 Toll 样受体(Toll-like receptor, TLR)刺激肿瘤的发生并抑制细胞凋亡，Fan 等[4]表明 TLR 激活是动物模型胰腺癌发生的关键驱动因素。TLR-2 的激活会增强 IL-6-STAT3 轴的信号表达，诱导原癌基因细胞周期蛋白 D1 (cyclin D1)合成，促进肿瘤细胞的增殖[25,30]。除 TLR-2 外，牙龈卟啉单胞菌的感染会通过 LPS 激活 TLR-4，引起 IL-1β 和 IL-6 的表达增加，而且 TLR-4 和缺氧诱导转录因子(HIF-α)的高表达往往预示患者预后较差[31-34]。(4) 牙龈卟啉单胞菌是目前已知的唯一能够产生肽酰基精氨酸脱亚氨酶 4 (peptidylarginine deiminase 4, PAD4)的病原体，该酶通过对蛋白质或多肽的精氨酸残基瓜氨酸化进而促进炎症，或对组蛋白 H3 上的甲基化位点 arginine 2、arginine 18 和 arginine 17 瓜氨酸化，影响细胞的正常增殖和凋亡[35-37]。此外，经 PAD4 修饰的细胞角质蛋白能抵抗半胱氨酸蛋白酶的降解，因此有抑制细胞凋亡的作用[38]。总而言之，牙龈卟啉单胞菌自身产生的各类物质能够激活炎症通路并上调原癌基因的表达，促进胰腺癌的发生和发展(图 1)。

2.2 肠道微生物

幽门螺杆菌感染不仅是引起消化道溃疡、胃癌的重要因素，也是胰腺癌的高危因素。根据相关病例-对照研究的 META 分析，幽门螺杆菌感染和胰腺癌的比数比 OR=1.45 (95% CI= 1.09–1.92)，表明幽门螺杆菌感染可以显著增加胰腺癌的发生风险[7]。同时幽门螺杆菌血清抗体阳性是胰腺癌的一个危险因素[39-40]。与之相对应的是胰腺癌患者幽门螺杆菌感染率显著高于健康对照组[41]。Nilsson 等[42]通过对胰腺癌组织进行石蜡包埋提取 DNA 并进行测序，发现 75%的胰腺癌病例中均有幽门螺杆菌的 DNA 检出。可见幽门螺杆菌与胰腺癌有一定的相关性。

然而，Jesnowski 等[43]通过对胰腺癌患者的胰液和胰腺活检组织进行 DNA 测序，并未检测到幽门螺杆菌的 DNA，这说明幽门螺杆菌并不是以直接作用于胰腺组织来诱发或促进胰腺癌[44]。

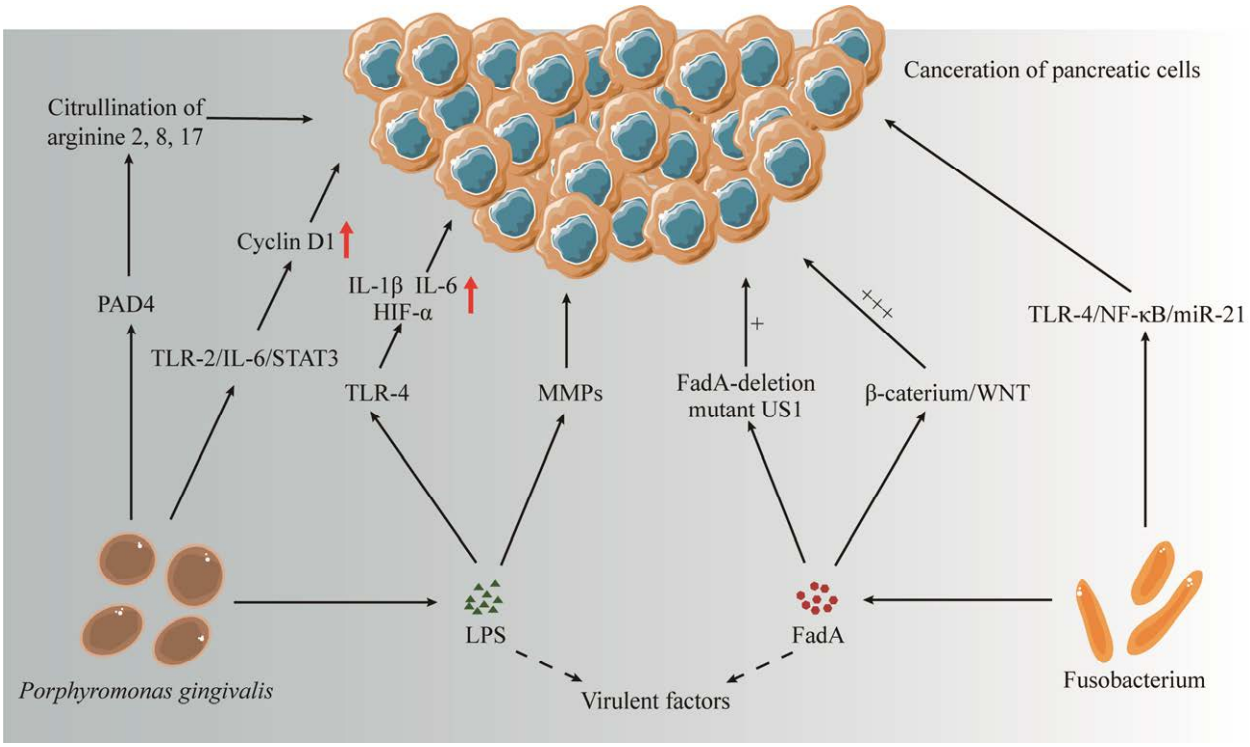

图 1　牙龈卟啉单胞菌和梭杆菌对胰腺癌发生发展的作用

Figure 1　Function of *Porphyromonas gingivalis* and *Fusobacterium* in the development of pancreatic cancer.

有研究显示，幽门螺杆菌对胰腺癌的作用与其特殊的致病物质以及感染部位有关:(1) 在幽门螺杆菌感染还未发展到慢性萎缩性胃炎时，幽门螺杆菌会攻击分泌生长抑素的胃窦 δ 细胞，导致生长抑素的分泌被抑制，生长抑素减少和胃窦 G 细胞合成增加共同刺激胃泌素的分泌增加，从而刺激胰腺细胞的增殖和生长并增加对致癌因素的敏感性[45-46]。胃泌素分泌增加会引起胃酸相应分泌增多，高胃泌素血症、高酸血症以及胃窦 G 细胞功能被抑制三者引起促胰液素分泌增加、刺激基础胰液以及胰腺碳酸氢盐分泌，促进胰腺导管上皮增生。而且人体通过呼吸道和消化道摄入的N-亚硝基化合物会通过血液循环进入胰腺，最后通过胰液经由胰腺导管排出，这是胰腺癌中占比较高的胰腺导管腺癌(pancreatic ductal adenocarcinoma, PDAC)发病机制之一[47]。此外，促胰液素本身也可以加速亚硝胺诱发仓鼠胰腺肿瘤的进程[48]。(2) 幽门螺杆菌感染如未经治疗任其发展，会逐渐演变成严重胃炎和胃溃疡，最后恶化成慢性萎缩性胃炎，胃酸分泌显著减少，导致胃内细菌过度生长，细菌催化硝酸盐转化成 N-亚硝基化合物,此外幽门螺杆菌的定殖和生长均会引起 NO 合成酶升高，促进 NO 合成并转化成 N-亚硝基化合物，并通过血液循环进入胰腺[49-50]。N-亚硝基化合物形成的致癌环境会诱导暴露在其中的胰腺细胞癌变[45]，而且幽门螺杆菌感染会降低体内抑制亚硝基化合物转化的抗坏血酸血清浓度，减缓体内 N-亚硝基化合物的清除，使胰腺细胞暴露的时间更长[51]。(3) 幽门螺杆菌所分泌的细菌毒素相关蛋白(cytotoxin-associated gene A, CagA)具有细胞毒性和免疫调节活性，

尽管在幽门螺杆菌中含量甚微，仍然会引起强烈的免疫应答反应，刺激 IL-8 的分泌[52]。幽门螺杆菌本身会损伤细胞 DNA，加大癌变风险，还可以改变上皮细胞的肿瘤抑制机制[53-54]。此外，在胰腺癌细胞中检出胰腺癌细胞存在 CagA，说明 CagA 诱发胰腺癌的机制和诱发胃癌相似[44]。但有研究表明，感染 CagA 阴性的幽门螺杆菌非毒力菌株患胰腺癌的风险会显著增加，究其原因，可能是 CagA 阴性的菌种相较阳性菌种会引起胃泌素分泌增多，导致促胰液素分泌增多，对胰腺的刺激更为严重[55-57]。(4) 与正常健康人群相比，胰腺癌患者被幽门螺杆菌感染的风险更高[58]。测出的 C 反应蛋白与促炎细胞因子 IL-6 的水平明显高于健康对照组，而且幽门螺杆菌感染者血清中的 IL-8 和血管内皮生长因子(vascular endothelial growth factor, VEGF)水平升高，促进血管生成和恶性肿瘤转移[59]。此外，通过幽门螺杆菌感染者的胃部活检，得出了幽门螺杆菌感染加速了人胃上皮细胞中 TLR-4 表达的结论，前文已提到 TLR-4 的激活在胰腺癌发展过程中发挥重要作用[60]。总而言之，幽门螺杆菌主要通过影响胃内酸性环境以及氮类物质的代谢来间接诱导胰腺细胞的增生和癌变，再结合幽门螺杆菌自身的细胞毒素和促进炎症的特性，使其具有促进胰腺癌发生发展的能力(图 2)。

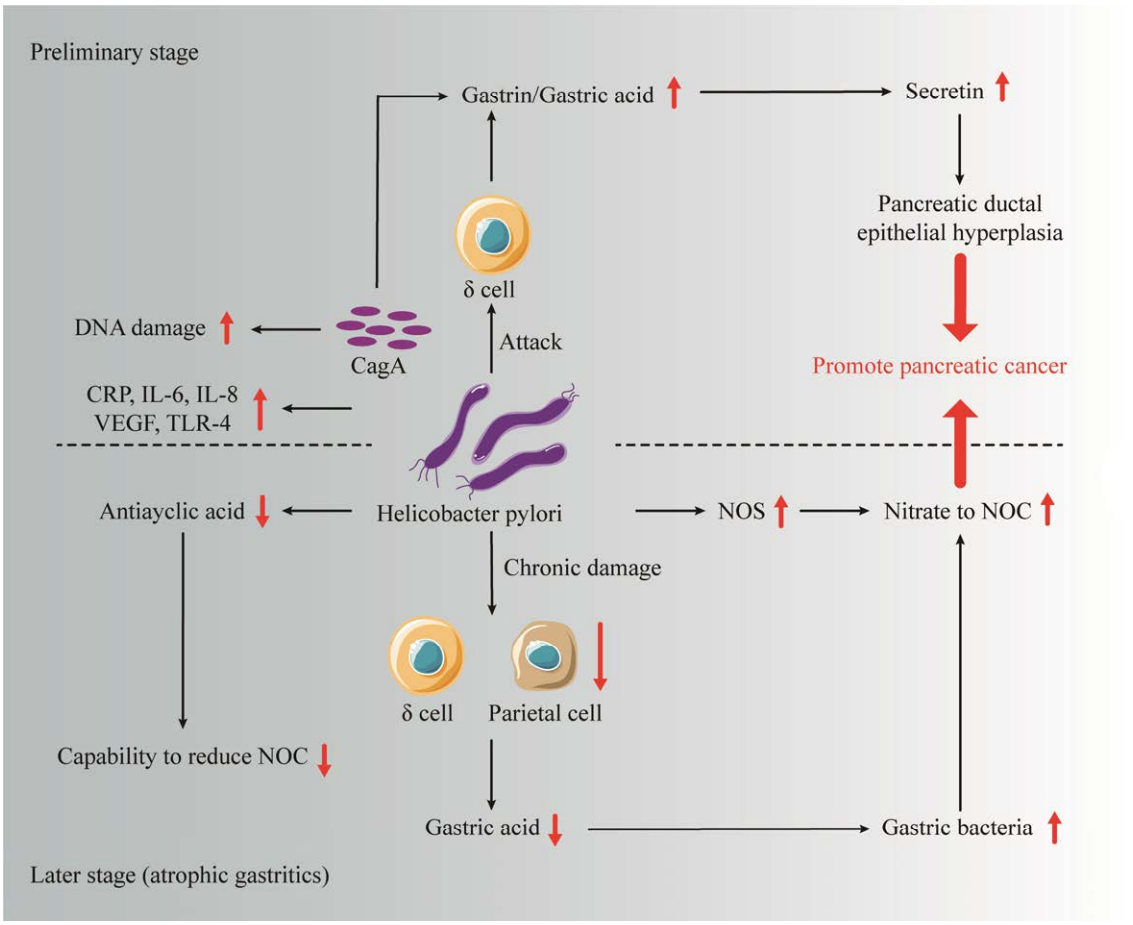

图 2　幽门螺杆菌对胰腺癌发生发展的作用

Figure 2　Function of *Helicobacter pylori* in the development of pancreatic cacner.

此外，普拉梭菌(*Faecalibacterium prausnitzi*)作为健康人群肠道中最常见最丰富的肠道微生物之一，约占健康人粪便细菌总数的5%左右[61]。普拉梭菌在肠道中通过多种途径来发挥重要的抗炎效应，对结直肠癌和炎症性肠病等有显著的保护作用[62-63]。以普拉梭菌水平降低为主要表现的微生态失衡会明显影响消化系统内的炎症反应，特别是慢性炎症等[64]。有研究得出了在胰腺癌患者肠道中普拉梭菌水平下降的结论[9,65]。因此，开发利用普拉梭菌作为辅助诊断胰腺癌或胰腺癌高危因素筛查的生物标志物便有了理论依据。

2.3 肿瘤内微生物及其代谢物

胰腺癌组织内及周围特定的微生物与肿瘤的发生发展相关。众所周知，梭杆菌(*Fusobacterium*)本是一种定殖于正常人口腔和肠道的机会致病菌[66]。但有研究表明，通过对胰腺癌组织标本进行福尔马林固定、石蜡包埋和 TaqMan 基因表达分析，在胰腺癌患者组织标本中梭杆菌的检出率是8.8%[11]。因此可以猜测口腔菌群能够通过各种传播途径转移至消化道和胰腺组织中[20,67]，且胰腺肿瘤的微环境被认为具有缺氧和免疫抑制特性，支持梭杆菌一类的厌氧菌生长，这也从侧面佐证了上述观点。通过对高度不典型增生的导管内乳头状黏液肿瘤——最常见的一种胰腺囊性肿瘤中进行囊内细菌 DNA 检测，发现梭杆菌高度富集[68]。由此可见，在肿瘤细胞与微生物共同形成的肿瘤微环境中，二者势必会相互影响。在检出梭杆菌的胰腺癌患者的组织标本中，尚未被癌细胞侵袭的正常胰腺组织中也能检测到梭杆菌，提示梭杆菌可能在胰腺癌的发病机制中起一定作用[11]。(1) 梭杆菌黏附素 A (fusobacterium nucleatum adhesin A, FadA)是其主要毒力因子，FadA 通过和上皮细胞表面的钙黏蛋白结合激活 β-链蛋白信号通路，引起致癌基因 WNT 基因表达增加[69]。而且 FadA 基因缺失体 US1 的黏附和侵袭能力被大幅削弱，对癌细胞的生长仅有弱刺激[70]。(2) 梭杆菌通过诱导 TLR-4 提高 NF-κB 转录水平，引起 NF-κB 的调节错误，成为诱发胰腺癌的原因之一；与结肠癌细胞株共同培养的梭杆菌通过激活 TLR-4，经一系列信号通路，最后引起 miR-21 的上调，增强了癌细胞的增殖和侵袭能力[71]。(3) 梭杆菌在肿瘤易发模型中有促进炎症、加速肿瘤增殖的作用，其分泌物可以加速 APCmin/+模型小鼠的肿瘤恶化[72-73]。因此，迁移到胰腺组织的梭杆菌能够利用自身特殊物质及诱发炎症的特性诱导胰腺癌的发生和恶化(图 1)。

除了肿瘤微环境中特定的菌群会对肿瘤产生影响以外，肿瘤微环境内的杂菌及其分泌物对胰腺癌的发展、治疗和预后的影响也不容忽视。关于肿瘤微环境具体如何影响肿瘤生长的机制，目前已有胆汁酸机制、免疫机制和毒蕈碱受体机制等。有体外实验发现，胆汁酸能够降低胰腺癌细胞的存活率，其中结合胆汁酸比未结合胆汁酸更有效，无菌胆汁酸比受细菌污染胆汁酸更有效，这表明活细菌可以修饰并降低胆汁中存在的抗肿瘤作用；该机制在行胆道支架植入术后的患者中更为显著，因为术后肠道的细菌非常容易进入胆道系统[74]。除了修饰胆汁，肠道微生物还可以转移到胰腺肿瘤中，与肿瘤内微生物共同诱导免疫抑制性肿瘤微环境，有利于肿瘤生长和扩散，并限制免疫检查点抑制剂的效力。Toll 样受体表达于免疫细胞、上皮细胞和纤维化细胞上，可能是免疫机制的关键介质[75]。此外，肿瘤内微生物也能够通过免疫机制影响肿瘤生长。以小鼠模型和测序技术为工具，研究发现微生物不仅能够破坏免疫系统对肿瘤细胞的监测，间接促进肿瘤的发生，还

能诱导免疫激活，对肿瘤的发生起促进作用[76]。

除了胆汁酸机制和免疫机制，毒蕈碱受体机制也是肿瘤内微生物影响胰腺癌发展的重要途径。毒蕈碱受体(muscarinic receptor)有 M1R–M5R 这 5 个亚型[77]。其中，M1R 的激活可以抑制肿瘤的形成，而 M3R 的过度表达则与胰腺导管腺癌的发生有相关性[78-79]。长期以来，由神经元产生释放的乙酰胆碱被认为是毒蕈碱受体的唯一配体，但是新的研究发现肿瘤内微生物能合成并释放与毒蕈碱受体结合的乙酰胆碱，因而微环境里的各种细胞与物质可以通过激活毒蕈碱受体影响肿瘤的生长[80]。

肿瘤微环境中的真菌也与胰腺肿瘤发生相关，在人类与小鼠模型中，胰腺导管腺癌的真菌丰度比正常胰腺组织高约 3 000 倍，且肿瘤组织中的真菌群落也异于正常组织；另外，该研究还发现了在人类的胰腺癌组织中有马拉色菌富集，其可以激活甘露糖结合凝集素来驱动补体级联反应促进胰腺癌[81]。

肿瘤微环境的情况能够提示肿瘤的预后以及药物的治疗效果。总体而言，胰腺癌患者的生存时间与肿瘤微环境中细菌的多样性呈正相关关系。有学者利用 16S rRNA 基因测序发现并验证了可以用来高度预测胰腺癌患者长期存活率的肿瘤内微生物组，该微生物组具有的特征菌群包括假黄单胞菌、糖多胞菌、链霉菌和克劳斯芽孢杆菌；该研究还将上述联合应用 4 种菌群从而预测胰腺癌患者长期生存期的概率[12]。就具体菌种而言，变形菌门(*Proteobacteria*)是使胰腺癌预后效果变差的主要细菌；另外，属于 β-杆菌属的嗜酸杆菌、弗氏柠檬酸杆菌、宋内志贺氏菌和属于 γ-杆菌属的假单胞菌均与不良预后呈正相关关系[82]。胰腺癌之所以是最致命的恶性肿瘤之一，是因为其高耐药性和低治疗反应。胰腺癌对药物反应的异质性可能源于患者接受治疗时体内的微生物群对免疫反应的调节，从而影响癌症治疗效果。

3 总结与展望

胰腺癌是危险性相当高的一类癌症，其治疗方法及相关研究一直是研究的热点。人体消化道微生态由于对人体具有广泛的作用，近年来成为许多研究者重视的领域。本文对人体消化道微生态与胰腺癌之间的关系进行综述，整理了位于消化道和肿瘤微环境的微生物与胰腺癌的相关关系，提示通过检测口腔、肠道菌群可以协助预测及随访胰腺癌患者。例如，牙周病相关菌群牙龈卟啉单胞菌、胃肠疾病相关的幽门螺杆菌、胰周组织的梭杆菌水平增高，以及胃肠道的普拉梭菌水平下降等，均可以作为胰腺癌的微生物标志物(表 1)。同时也为实现早期预测患病高危人群、发现尚处于早期的患者、及时进行治疗与处理以改变晚期治疗的被动局面提供了研究方向。

菌群移植，如粪菌移植、人工组合菌群移植目前能够应用于一些疾病的治疗，并取得了良好的成果。自身免疫介导的 1 型糖尿病被证实是由遗传易感性和肠道微生态失调共同驱动的，而且还能通过粪菌移植改善肠道微生态的方式治疗 1 型糖尿病[83]。有研究证明粪菌移植能够增加微生物群衍生物吲哚-3-乙酸的富集，并对正在接受化疗的胰腺癌模型小鼠有积极作用[84]。这些证据都说明菌群移植有望能用于胰腺癌的治疗，与化疗、放疗和免疫治疗产生协同作用，而且调节人体内部菌群以提高胰腺癌患者的生活质量与寿命也是未来的一个方向。

目前，实现胰腺癌早期诊断和筛查的微生物谱的建立还有许多障碍。其中一个原因是消化道微生态的组成复杂，而且需要大量的临床数据收集与数据统计去定义和区分健康微生物

组和胰腺癌风险微生物组，并确立有意义的筛选标准。菌群移植用于胰腺癌治疗的研究也凤毛麟角，未能达到形成有效方案的标准。究其原因，主要是胰腺癌患者总生存率低，化疗、放疗和免疫治疗联合菌群移植的试验样本稀缺，难以形成有统计学意义的结果。因此，如果想要将微生物标志物规范化、精准地应用到胰腺癌早期诊断筛查，将菌群移植联合化疗、放疗和免疫治疗应用到胰腺癌治疗中，需要借助宏基因组学和免疫组学等方案，从而能准确把握消化道微生态与胰腺癌的相互作用，促进消化道微生物与胰腺癌的诊断治疗紧密结合。

REFERENCES

[1] CHEN RP, ZHU D, YANG R, WU ZZ, XU NN, CHEN FW, ZHANG S, CHEN H, LI M, HOU KJ. Gut microbiota diversity in middle-aged and elderly patients with end-stage diabetic kidney disease[J]. Annals of Translational Medicine, 2022, 10(13): 750.

[2] 张娴, 陈容平, 陈宏. 基于高通量测序技术分析肠道菌群与肥胖的研究进展[J]. 医学综述, 2017, 23(23): 4577-4583.
ZHANG X, CHEN RP, CHEN H. Research advances in the relationship between gut microbiota and obesity by the application of high-throughput sequencing technologies[J]. Medical Recapitulate, 2017, 23(23): 4577-4583 (in Chinese).

[3] 张艺, 许宁宁, 彭子翀, 陈容平. 粪菌移植通过微生物-肠-脑轴改善抑郁症的研究进展[J]. 微生物学通报, 2022, 49(2): 756-768.
ZHANG Y, XU NN, PENG ZC, CHEN RP. Fecal microbiota transplantation to improve depression by modulating microbiota-gut-brain axis: a review[J]. Microbiology China, 2022, 49(2): 756-768 (in Chinese).

[4] FAN XZ, ALEKSEYENKO AV, WU J, PETERS BA, JACOBS EJ, GAPSTUR SM, PURDUE MP, ABNET CC, STOLZENBERG-SOLOMON R, MILLER G, RAVEL J, HAYES RB, AHN J. Human oral microbiome and prospective risk for pancreatic cancer: a population-based nested case-control study[J]. Gut, 2018, 67(1): 120-127.

[5] FARRELL JJ, ZHANG L, ZHOU H, CHIA D, ELASHOFF D, AKIN D, PASTER BJ, JOSHIPURA K, WONG DTW. Variations of oral microbiota are associated with pancreatic diseases including pancreatic cancer[J]. Gut, 2012, 61(4): 582-588.

[6] TORRES PJ, FLETCHER EM, GIBBONS SM, BOUVET M, DORAN KS, KELLEY ST. Characterization of the salivary microbiome in patients with pancreatic cancer[J]. PeerJ, 2015, 3: e1373.

[7] GUO Y, LIU W, WU J. *Helicobacter pylori* infection and pancreatic cancer risk: a meta-analysis[J]. Journal of Cancer Research and Therapeutics, 2016, 12(Supplement): C229-C232.

[8] MENDEZ R, KESH K, ARORA N, Di MARTINO L, McALLISTER F, MERCHANT N, BANERJEE S, BANERJEE S. Microbial dysbiosis and polyamine metabolism as predictive markers for early detection of pancreatic cancer[J]. Carcinogenesis, 2020, 41(5): 561-570.

[9] HALF E, KEREN N, RESHEF L, DORFMAN T, LACHTER I, KLUGER Y, RESHEF N, KNOBLER H, MAOR Y, STEIN A, KONIKOFF FM, GOPHNA U. Fecal microbiome signatures of pancreatic cancer patients[J]. Scientific Reports, 2019, 9: 16801.

[10] SIVAN A, CORRALES L, HUBERT N, WILLIAMS JB, AQUINO-MICHAELS K, EARLEY ZM, BENYAMIN FW, LEI YM, JABRI B, ALEGRE ML, CHANG EB, GAJEWSKI TF. Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy[J]. Science, 2015, 350(6264): 1084-1089.

[11] MITSUHASHI K, NOSHO K, SUKAWA Y, MATSUNAGA Y, ITO M, KURIHARA H, KANNO S, IGARASHI H, NAITO T, ADACHI Y, TACHIBANA M, TANUMA T, MAGUCHI H, SHINOHARA T, HASEGAWA T, IMAMURA M, KIMURA Y, HIRATA K, MARUYAMA R, SUZUKI H, et al. Association of *Fusobacterium* species in pancreatic cancer tissues with molecular features and prognosis[J]. Oncotarget, 2015, 6(9): 7209-7220.

[12] RIQUELME E, ZHANG Y, ZHANG LL, MONTIEL M, ZOLTAN M, DONG WL, QUESADA P, SAHIN I, CHANDRA V, LUCAS AS, SCHEET P, XU HW, HANASH SM, FENG L, BURKS JK, DO KA, PETERSON CB, NEJMAN D, TZENG CW D, KIM MP, et al. Tumor microbiome diversity and composition influence pancreatic cancer outcomes[J]. Cell, 2019, 178(4): 795-806.e12.

[13] GELLER LT, BARZILY-ROKNI M, DANINO T,

JONAS OH, SHENTAL N, NEJMAN D, GAVERT N, ZWANG Y, COOPER ZA, SHEE K, THAISS CA, REUBEN A, LIVNY J, AVRAHAM R, FREDERICK DT, LIGORIO M, CHATMAN K, JOHNSTON SE, MOSHER CM, BRANDIS A, et al. Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine[J]. Science, 2017, 357(6356): 1156-1160.

[14] SIEGEL RL, MILLER KD, WAGLE NS, JEMAL A. Cancer statistics, 2023[J]. CA: A Cancer Journal for Clinicians, 2023, 73(1): 17-48.

[15] SUNG H, FERLAY J, SIEGEL RL, LAVERSANNE M, SOERJOMATARAM I, JEMAL A, BRAY F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA: A Cancer Journal for Clinicians, 2021, 71(3): 209-249.

[16] 蔡洁, 陈宏达, 卢明, 张愉涵, 陆斌, 由磊, 代敏, 赵玉沛. 2005–2015 年中国胰腺癌发病与死亡趋势分析[J]. 中华流行病学杂志, 2021, 42(5): 794-800.
CAI J, CHEN HD, LU M, ZHANG YH, LU B, YOU L, DAI M, ZHAO YP. Trend analysis on morbidity and mortality of pancreatic cancer in China, 2005–2015[J]. Chinese Journal of Epidemiology, 2021, 42(5): 794-800 (in Chinese).

[17] 李静威, 王俐文, 蒋玲曦, 詹茜, 陈皓, 沈柏用. 胰腺癌免疫抑制性肿瘤微环境研究综述[J]. 上海交通大学学报(医学版), 2021, 41(8): 1103-1108.
LI JW, WANG LW, JIANG LX, ZHAN Q, CHEN H, SHEN BY. Review of immunosuppressive tumor microenvironment of pancreatic cancer[J]. Journal of Shanghai Jiao Tong University (Medical Edition), 2021, 41(8): 1103-1108 (in Chinese).

[18] CHUNG M, ZHAO NS, MEIER R, KOESTLER DC, WU GJ, de CASTILLO E, PASTER BJ, CHARPENTIER K, IZARD J, KELSEY KT, MICHAUD DS. Comparisons of oral, intestinal, and pancreatic bacterial microbiomes in patients with pancreatic cancer and other gastrointestinal diseases[J]. Journal of Oral Microbiology, 2021, 13(1): 1887680.

[19] MICHAUD DS, JOSHIPURA K, GIOVANNUCCI E, FUCHS CS. A prospective study of periodontal disease and pancreatic cancer in US male health professionals[J]. JNCI: Journal of the National Cancer Institute, 2007, 99(2): 171-175.

[20] MICHAUD DS, IZARD J, WILHELM-BENARTZI C, RIBOLI E, BUENO-DE-MESQUITA B, TEAM FOR T TE. Abstract LB-328: plasma antibodies to oral pathogen and commensals and risk of pancreatic cancer in a large European prospective cohort study[J]. Cancer Research, 2012, 72(8_Supplement): LB-328.

[21] AMMER-HERRMENAU C, PFISTERER N, WEINGARTEN MF, NEESSE A. The microbiome in pancreatic diseases: recent advances and future perspectives[J]. UEG Journal, 2020, 8(8): 878-885.

[22] SHA WW, MITOMA H, HANABUCHI S, BAO MS, WENG LY, SUGIMOTO N, LIU Y, ZHANG ZQ, ZHONG J, SUN B, LIU YJ. Human NLRP3 inflammasome senses multiple types of bacterial RNAs[J]. Proceedings of the National Academy of Sciences of the United States of America, 2014, 111(45): 16059-16064.

[23] 王晴萱, 刘俊超, 潘亚萍. 具核梭杆菌调控牙龈卟啉单胞菌感染对口腔鳞状细胞癌 KB 细胞周期和细胞因子分泌的研究[J]. 口腔医学研究, 2016, 32(3): 211-215.
WANG QX, LIU JC, PAN YP. Impact of *Fusobacterium nucleatum* and *Porphyromonas gingivalis* modulation on the cell cycle and cytokines production of KB cells[J]. Journal of Oral Science Research, 2016, 32(3): 211-215 (in Chinese).

[24] HA NH, PARK DG, WOO BH, KIM DJ, CHOI JI, PARK BS, KIM YD, LEE JH, PARK HR. *Porphyromonas gingivalis* increases the invasiveness of oral cancer cells by upregulating IL-8 and MMPs[J]. Cytokine, 2016, 86: 64-72.

[25] BINDER GALLIMIDI A, FISCHMAN S, REVACH B, BULVIK R, MALIUTINA A, RUBINSTEIN AM, NUSSBAUM G, ELKIN M. Periodontal pathogens *Porphyromonas gingivalis* and *Fusobacterium nucleatum* promote tumor progression in an oral-specific chemical carcinogenesis model[J]. Oncotarget, 2015, 6(26): 22613-22623.

[26] CARMI Y, DOTAN S, RIDER P, KAPLANOV I, WHITE MR, BARON R, ABUTBUL S, HUSZAR M, DINARELLO CA, APTE RN, VORONOV E. The role of IL-1β in the early tumor cell-induced angiogenic response[J]. The Journal of Immunology, 2013, 190(7): 3500-3509.

[27] GU ZD, LI JY, LI M, GU J, SHI XT, KE Y, CHEN KN. Matrix metalloproteinases expression correlates with survival in patients with esophageal squamous cell carcinoma[J]. The American Journal of Gastroenterology, 2005, 100(8): 1835-1843.

[28] INABA H, SUGITA H, KUBONIWA M, IWAI S, HAMADA M, NODA T, MORISAKI I, LAMONT RJ,

AMANO A. *Porphyromonas gingivalis* promotes invasion of oral squamous cell carcinoma through induction of proMMP9 and its activation[J]. Cellular Microbiology, 2014, 16(1): 131-145.

[29] RAMOS-JUNIOR ES, MORANDINI AC, ALMEIDA-DA-SILVA CC, FRANCO EJ, POTEMPA J, NGUYEN KA, OLIVEIRA AC, ZAMBONI DS, OJCIUS DM, SCHARFSTEIN J, COUTINHO-SILVA R. A dual role for P2X7 receptor during *Porphyromonas gingivalis* infection[J]. Journal of Dental Research, 2015, 94(9): 1233-1242.

[30] 卢梦玲, 闫超, 赖多, 徐汉虹. Cyclin D1 与细胞周期调控[J]. 生物技术通报, 2011(10): 55-59.
LU ML, YAN C, LAI D, XU HH. Cyclin D1 and cell cycle regulation[J]. Biotechnology Bulletin, 2011(10): 55-59 (in Chinese).

[31] BABALOO AR, SHIRMOHAMMADI A, SANDOGHCHIAN SHOTORBANI S, KAMALZADEH A, GHASEMI S. Evaluation of the effect of IL-36γ expression on chronic periodontitis by enhancing the MAPK and TLR4 signaling pathways: a basic research[J]. Journal of Dental Research, Dental Clinics, Dental Prospects, 2018, 12(3): 159-165.

[32] 李娜, 袁景, 李海霞, 郭建康, 张玉娟. 慢性牙周炎合并牙龈卟啉单胞菌感染 HSP60 及 TLR4 信号通路的表达及意义[J]. 中华医院感染学杂志, 2022, 32(1): 99-103.
LI N, YUAN J, LI HX, GUO JK, ZHANG YJ. Expression of HSP60 and TLR4 signaling pathway-related cytokines in chronic periodontitis patients complicated with *Porphyromonas gingivalis* infection[J]. Chinese Journal of Nosocomiology, 2022, 32(1): 99-103 (in Chinese).

[33] MAI CW, KANG YB, PICHIKA MR. Should a Toll-like receptor 4 (TLR-4) agonist or antagonist be designed to treat cancer? TLR-4: its expression and effects in the ten most common cancers[J]. OncoTargets and Therapy, 2013, 6: 1573-1587.

[34] MOLTENI M, MARABELLA D, ORLANDI C, ROSSETTI C. Melanoma cell lines are responsive *in vitro* to lipopolysaccharide and express TLR-4[J]. Cancer Letters, 2006, 235(1): 75-83.

[35] 刘书培, 张秀森, 李婉莹, 赵迪, 杨泽, 张旭东, 原翔. 牙龈卟啉单胞菌与 ESCC 研究进展[J]. 食管疾病, 2021(4): 302-306.
LIU SP, ZHANG XS, LI WY, ZHAO D, YANG Z, ZHANG XD, YUAN X. Research progress of *Porphyromonas gingivalis* and esophageal squamous cell carcinoma[J]. Journal of Esophageal Diseases, 2021(4): 302-306 (in Chinese).

[36] POTEMPA J, MYDEL P, KOZIEL J. The case for periodontitis in the pathogenesis of rheumatoid arthritis[J]. Nature Reviews Rheumatology, 2017, 13(10): 606-620.

[37] YAO HJ, LI PX, VENTERS BJ, ZHENG ST, THOMPSON PR, PUGH BF, WANG YM. Histone Arg modifications and p53 regulate the expression of OKL38, a mediator of apoptosis[J]. The Journal of Biological Chemistry, 2008, 283(29): 20060-20068.

[38] CHANG XT, HAN JX. Expression of peptidylarginine deiminase type 4 (PAD4) in various tumors[J]. Molecular Carcinogenesis, 2006, 45(3): 183-196.

[39] STOLZENBERG-SOLOMON RZ, BLASER MJ, LIMBURG PJ, PEREZ-PEREZ G, TAYLOR PR, VIRTAMO J, ALBANES D. *Helicobacter pylori* seropositivity as a risk factor for pancreatic cancer[J]. JNCI: Journal of the National Cancer Institute, 2001, 93(12): 937-941.

[40] LINDKVIST B, JOHANSEN D, BORGSTRÖM A, MANJER J. A prospective study of *Helicobacter pylori* in relation to the risk for pancreatic cancer[J]. BMC Cancer, 2008, 8(1): 1-9.

[41] 乔竹风. 胰腺癌与幽门螺杆菌感染相关性初步分析[J]. 贵阳医学院学报, 2012, 37(4): 411-413.
QIAO ZF. Preliminary analysis of the correlation between pancreatic cancer and Helicobacter pylori infection[J]. Journal of Guiyang Medical College, 2012, 37(4): 411-413 (in Chinese).

[42] NILSSON HO, STENRAM U, IHSE I, WADSTROM T. *Helicobacter* species ribosomal DNA in the pancreas, stomach and duodenum of pancreatic cancer patients[J]. World Journal of Gastroenterology, 2006, 12(19): 3038-3043.

[43] JESNOWSKI R, ISAKSSON B, MÖHRCKEA C, BERTSCH C, BULAJIC M, SCHNEIDER-BRACHERT W, KLÖPPEL G, LOWENFELS AB, MAISONNEUVE P, LÖHR JM. *Helicobacter pylori* in autoimmune pancreatitis and pancreatic carcinoma[J]. Pancreatology, 2010, 10(4): 462-466.

[44] 王瑞涛, 刘军, 庞青, 宋燕州, 牟怡平, 刘昌. 幽门螺杆菌感染与胰腺癌发病相关性的 Meta 分析[J]. 现代肿瘤医学, 2015, 23(12): 1691-1694.
WANG RT, LIU J, PANG Q, SONG YZ, YIPING (, LIU C. Helicobacter pylori infection as a risk factor for pancreatic cancer: a Meta analysis[J]. Journal of Modern Oncology, 2015, 23(12): 1691-1694 (in

Chinese).

[45] RISCH HA. Etiology of pancreatic cancer, with a hypothesis concerning the role of N-nitroso compounds and excess gastric acidity[J]. JNCI: Journal of the National Cancer Institute, 2003, 95(13): 948-960.

[46] KUNOVSKY L, DITE P, JABANDZIEV P, DOLINA J, VACULOVA J, BLAHO M, BOJKOVA M, DVORACKOVA J, UVIROVA M, KALA Z, TRNA J. *Helicobacter pylori* infection and other bacteria in pancreatic cancer and autoimmune pancreatitis[J]. World Journal of Gastrointestinal Oncology, 2021, 13(8): 835-844.

[47] HOFFMANN D, ADAMS JD, BRUNNEMANN KD, HECHT SS. Assessment of tobacco-specific N-nitrosamines in tobacco products[J]. Cancer Research, 1979, 39(7 Pt 1): 2505-2509.

[48] HOWATSON AG, CARTER DC. Pancreatic carcinogenesis: effect of secretin in the *Hamster*-nitrosamine model[J]. JNCI: Journal of the National Cancer Institute, 1987, 78(1): 101-105.

[49] VENERITO M, VASAPOLLI R, MALFERTHEINER P. *Helicobacter pylori* and gastric cancer: timing and impact of preventive measures[M]//Advances in Experimental Medicine and Biology. Cham: Springer International Publishing, 2016: 409-418.

[50] PANG YJ, HOLMES MV, CHEN ZM, KARTSONAKI C. A review of lifestyle, metabolic risk factors, and blood-based biomarkers for early diagnosis of pancreatic ductal adenocarcinoma[J]. Journal of Gastroenterology and Hepatology, 2019, 34(2): 330-345.

[51] TOH JWT, WILSON RB. Pathways of gastric carcinogenesis, helicobacter pylori virulence and interactions with antioxidant systems, vitamin C and phytochemicals[J]. International Journal of Molecular Sciences, 2020, 21(17): 6451

[52] ANSARI S, YAMAOKA Y. Helicobacter pylori Virulence Factors Exploiting Gastric Colonization and its Pathogenicity[J]. Toxins (Basel) 2019, 11(11): 677.

[53] KNORR J, RICCI V, HATAKEYAMA M, BACKERT S. Classification of *Helicobacter pylori* virulence factors: is CagA a toxin or not?[J]. Trends in Microbiology, 2019, 27(9): 731-738.

[54] PALRASU M, ZAIKA E, EL-RIFAI W, GARCIA-BUITRAGO M, PIAZUELO MB, WILSON KT, PEEK RM Jr, ZAIKA AI. Bacterial CagA protein compromises tumor suppressor mechanisms in gastric epithelial cells[J]. The Journal of Clinical Investigation, 2020, 130(5): 2422-2434.

[55] CHEN XZ, WANG R, CHEN HN, HU JK. Cytotoxin-associated gene A-negative strains of *Helicobacter pylori* as a potential risk factor of pancreatic cancer[J]. Pancreas, 2015, 44(8): 1340-1344.

[56] RISCH HA, YU H, LU LG, KIDD MS. ABO blood group, *Helicobacter pylori* seropositivity, and risk of pancreatic cancer: a case-control study[J]. JNCI: Journal of the National Cancer Institute, 2010, 102(7): 502-505.

[57] 张迦维, 乔劲鹏, 孙清, 陈暑波. 幽门螺杆菌与胰腺癌患病风险的关系[J]. 中国肿瘤临床与康复, 2019, 26(4): 457-459.
ZHANG JW, QIAO JP, SUN Q, CHEN SB. Relationship between Helicobacter pylori and pancreatic cancer risk[J]. Chinese Journal of Clinical Oncology and Rehabilitation, 2019, 26(4): 457-459 (in Chinese).

[58] MEI QX, HUANG CL, LUO SZ, ZHANG XM, ZENG Y, LU YY. Characterization of the duodenal bacterial microbiota in patients with pancreatic head cancer *vs*. healthy controls[J]. Pancreatology, 2018, 18(4): 438-445.

[59] TAKAYAMA S, TAKAHASHI H, MATSUO Y, OKADA Y, TAKEYAMA H. Effect of *Helicobacter bilis* infection on human bile duct cancer cells[J]. Digestive Diseases and Sciences, 2010, 55(7): 1905-1910.

[60] KAWAHARA T, KUWANO Y, TESHIMA-KONDO S, KAWAI T, NIKAWA T, KISHI K, ROKUTAN K. Toll-like receptor 4 regulates gastric pit cell responses to *Helicobacter pylori* infection[J]. The Journal of Medical Investigation, 2001, 48(3/4): 190-197.

[61] ARUMUGAM M, RAES J, PELLETIER E, le PASLIER D, YAMADA T, MENDE DR, FERNANDES GR, TAP J, BRULS T, BATTO JM, BERTALAN M, BORRUEL N, CASELLAS F, FERNANDEZ L, GAUTIER L, HANSEN T, HATTORI M, HAYASHI T, KLEEREBEZEM M, KUROKAWA K, et al. Enterotypes of the human gut microbiome[J]. Nature, 2011, 473(7346): 174-180.

[62] SOKOL H, PIGNEUR B, WATTERLOT L, LAKHDARI O, BERMÚDEZ-HUMARÁN LG, GRATADOUX JJ, BLUGEON S, BRIDONNEAU C, FURET JP, CORTHIER G, GRANGETTE C, VASQUEZ N, POCHART P, TRUGNAN G, THOMAS G, BLOTTIÈRE HM, DORÉ J, MARTEAU P, SEKSIK P, LANGELLA P. *Faecalibacterium prausnitzii* is an anti-inflammatory commensal bacterium identified by

gut microbiota analysis of Crohn disease patients[J]. Proceedings of the National Academy of Sciences of the United States of America, 2008, 105(43): 16731-16736.

[63] MACHIELS K, JOOSSENS M, SABINO J, de PRETER V, ARIJS I, EECKHAUT V, BALLET V, CLAES K, van IMMERSEEL F, VERBEKE K, FERRANTE M, VERHAEGEN J, RUTGEERTS P, VERMEIRE S. A decrease of the butyrate-producing species *Roseburia hominis* and *Faecalibacterium prausnitzii* defines dysbiosis in patients with ulcerative colitis[J]. Gut, 2014, 63(8): 1275-1283.

[64] LOPEZ-SILES M, MARTINEZ-MEDINA M, SURÍS-VALLS R, ALDEGUER X, SABAT-MIR M, DUNCAN SH, FLINT HJ, GARCIA-GIL LJ. Changes in the abundance of *Faecalibacterium prausnitzii* phylogroups I and II in the intestinal mucosa of inflammatory bowel disease and patients with colorectal cancer[J]. Inflammatory Bowel Diseases, 2016, 22(1): 28-41.

[65] 张德, 周文丽, 王雷, 张娜娜, 王巍峰. 女性胰腺癌患者肠道菌群变化分析[J]. 解放军医学院学报, 2019, 40(11): 1087-1092, 1109
ZHANG D, ZHOU WL, WANG L, ZHANG NN, WANG WF. Changes in intestinal microbiota in female patients with pancreatic cancer[J]. Academic Journal of Chinese Pla Medical School, 2019, 40(11): 1087-1092, 1109 (in Chinese).

[66] HAN YW, SHI W, HUANG GT, KINDER HAAKE S, PARK NH, KURAMITSU H, GENCO RJ. Interactions between periodontal bacteria and human oral epithelial cells: *Fusobacterium nucleatum* adheres to and invades epithelial cells[J]. Infection and Immunity, 2000, 68(6): 3140-3146.

[67] HAYASHI C, GUDINO CV, GIBSON FCI, GENCO CA. REVIEW: pathogen-induced inflammation at sites distant from oral infection: bacterial persistence and induction of cell-specific innate immune inflammatory pathways[J]. Molecular Oral Microbiology, 2010, 25(5): 305-316.

[68] GAISER RA, HALIMI A, ALKHARAAN H, LU LY, DAVANIAN H, HEALY K, HUGERTH LW, ATEEB Z, VALENTE R, FERNÁNDEZ MORO C, del CHIARO M, SÄLLBERG CHEN M. Enrichment of oral microbiota in early cystic precursors to invasive pancreatic cancer[J]. Gut, 2019, 68(12): 2186-2194.

[69] RUBINSTEIN MR, WANG XW, LIU W, HAO YJ, CAI GF, HAN YPW. *Fusobacterium nucleatum* promotes colorectal carcinogenesis by modulating E-cadherin/β-catenin signaling via its FadA adhesin[J]. Cell Host & Microbe, 2013, 14(2): 195-206.

[70] 佟明, 龚昆梅, 包维民. 梭杆菌与结直肠癌关系的研究进展[J]. 实用医学杂志, 2015, 31(23): 3968-3969.
TONG M, GONG KM, BAO WM. Research progress on the relationship between *Fusobacterium* and colorectal cancer[J]. The Journal of Practical Medicine, 2015, 31(23): 3968-3969 (in Chinese).

[71] YANG YZ, WENG WH, PENG JJ, HONG LM, YANG L, TOIYAMA YJ, GAO RY, LIU MF, YIN MM, PAN C, LI H, GUO BM, ZHU QC, WEI Q, MOYER MP, WANG P, CAI SJ, GOEL AJAY, QIN HL, MA YL. *Fusobacterium nucleatum* increases proliferation of colorectal cancer cells and tumor development in mice by activating toll-like receptor 4 signaling to nuclear Factor−κB, and up-regulating expression of microRNA-21[J]. Gastroenterology, 2017, 152(4): 851-866.e24.

[72] 李超, 金莉萍. 肠道细菌与癌症关系的研究进展[J]. 微生物与感染, 2018, 13(6): 379-386.
LI C, JIN LP. Research progress on association between gut bacteria and cancer[J]. Journal of Microbes and Infections, 2018, 13(6): 379-386 (in Chinese).

[73] BULLMAN S, PEDAMALLU CS, SICINSKA E, CLANCY TE, ZHANG XY, CAI DA, NEUBERG D, HUANG K, GUEVARA F, NELSON T, CHIPASHVILI O, HAGAN T, WALKER M, RAMACHANDRAN A, DIOSDADO B, SERNA G, MULET N, LANDOLFI S, CAJAL SRY, FASANI R, et al. Analysis of *Fusobacterium* persistence and antibiotic response in colorectal cancer[J]. Science, 2017, 358(6369): 1443-1448.

[74] SHRADER HR, MILLER AM, TOMANEK-CHALKLEY A, McCARTHY A, COLEMAN KL, EAR PH, MANGALAM AK, SALEM AK, CHAN CHF. Effect of bacterial contamination in bile on pancreatic cancer cell survival[J]. Surgery, 2021, 169(3): 617-622.

[75] PUSHALKAR S, HUNDEYIN M, DALEY D, ZAMBIRINIS CP, KURZ E, MISHRA A, MOHAN N, AYKUT B, USYK M, TORRES LE, WERBA G, ZHANG K, GUO YQ, LI QH, AKKAD N, LALL S, WADOWSKI B, GUTIERREZ J, ROSSI JAK, HERZOG JW, et al. The pancreatic cancer microbiome promotes oncogenesis by induction of innate and adaptive immune suppression[J]. Cancer Discovery, 2018, 8(4): 403-416.

[76] SETHI V, VITIELLO GA, SAXENA D, MILLER G, DUDEJA V. The role of the microbiome in

immunologic development and its implication for pancreatic cancer immunotherapy[J]. Gastroenterology, 2019, 156(7): 2097-2115.e2.

[77] 何花, 张淑香. 毒蕈碱胆碱受体与肿瘤关系的研究进展[J]. 国际呼吸杂志, 2015(12): 934-938.
HE H, ZHANG SX. Research progress of muscarinic cholinergic receptors in tumors[J]. International Journal of Respiration, 2015(12): 934-938 (in Chinese).

[78] ZHANG LF, XIU DR, ZHAN J, HE XK, GUO LM, WANG JL, TAO M, FU W, ZHANG HQ. High expression of muscarinic acetylcholine receptor 3 predicts poor prognosis in patients with pancreatic ductal adenocarcinoma[J]. OncoTargets and Therapy, 2016, 9: 6719-6726.

[79] RENZ BW, TANAKA T, SUNAGAWA M, TAKAHASHI R, JIANG ZY, MACCHINI M, DANTES Z, VALENTI G, WHITE RA, MIDDELHOFF MA, ILMER M, OBERSTEIN PE, ANGELE MK, DENG H, HAYAKAWA Y, WERNER J, REMOTTI H, REICHERT M, TAILOR YH, NAGAR K, et al. Cholinergic signaling via muscarinic receptors directly and indirectly suppresses pancreatic tumorigenesis and cancer stemness[J]. Cancer Discovery, 2018, 8(11): 1458-1473.

[80] SCHLEDWITZ A, SUNDEL MH, ALIZADEH M, HU SE, XIE GF, RAUFMAN JP. Differential actions of muscarinic receptor subtypes in gastric, pancreatic, and colon cancer[J]. International Journal of Molecular Sciences, 2021, 22(23): 13153.

[81] AYKUT B, PUSHALKAR S, CHEN RN, LI QH, ABENGOZAR R, KIM JI, SHADALOEY SA, WU DL, PREISS P, VERMA N, GUO YQ, SAXENA A, VARDHAN M, DISKIN B, WANG W, LEINWAND J, KURZ E, KOCHEN ROSSI JA, HUNDEYIN M, ZAMBRINIS C, et al. The fungal mycobiome promotes pancreatic oncogenesis via activation of MBL[J]. Nature, 2019, 574(7777): 264-267.

[82] CHAKLADAR J, KUO SZ, CASTANEDA G, LI WT, GNANASEKAR A, YU MA, CHANG EY, WANG xiao qi, ONGKEKO WM. The pancreatic microbiome is associated with carcinogenesis and worse prognosis in males and smokers[J]. Cancers, 2020, 12(9): 2672.

[83] HE LN, CHEN RP, ZHANG BZ, ZHANG S, KHAN BA, ZHU D, WU ZZ, XIAO CX, CHEN BL, CHEN FW, HOU KJ. Fecal microbiota transplantation treatment of autoimmune-mediated type 1 diabetes mellitus[J]. Frontiers in Immunology, 2022, 13: 930872.

[84] TINTELNOT J, XU Y, LESKER TR, SCHÖNLEIN M, KONCZALLA L, GIANNOU AD, PELCZAR P, KYLIES D, PUELLES VG, BIELECKA AA, PESCHKA M, CORTESI F, RIECKEN K, JUNG M, AMEND L, BRÖRING TS, TRAJKOVIC-ARSIC M, SIVEKE JT, RENNÉ T, ZHANG DM, et al. Microbiota-derived 3-IAA influences chemotherapy efficacy in pancreatic cancer[J]. Nature, 2023, 615(7950): 168-174.