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肠道微生物与胰腺癌的相关研究进展

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Progress in understanding of relationship between intestinal microecology and pancreatic cancer

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Abstract

In recent years, the association between the gut microbiota

(GM) and pancreatic cancer (PC) has attracted extensive attention. Studies have shown that the oral, intestinal, and pancreatic microbiota of PC patients is different from that of healthy people, showing different characteristics. On this basis, the application of characteristic GM and its metabolites as biomarkers for early diagnosis and prognosis evaluation of PC holds great potential. Intestinal microecological therapy targeting the GM, such as probiotics and fecal microbiota transplantation, may affect the response to chemotherapy and immunotherapy by remodeling the tumor microenvironment, to improve the prognosis. In this paper, we review the role of the GM in PC development, early diagnosis, prognosis assessment, and treatment.

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Key Words: Gut microbiota; Pancreatic cancer; Metabolism; Tumor microenvironment

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摘要

近年来, 肠道微生物(gut microbiota, GM)与胰腺癌(pancreatic cancer, PC)的相关性引发了广泛的关注. 研究表明, PC患者的口腔、肠道及胰腺内微生物群区别于健康人群, 呈现出不同特征. 在此基础上, 应用特征性的GM及代谢产物作为PC早期诊断、预后评估的生物标志物, 具有很大的研究潜力. 以GM为靶点的肠道微生态疗法, 如益生菌、粪菌移植等, 可能通过重塑肿瘤微环境影响对化疗、免疫治疗的应答效果, 从而改善预后. 本文对GM参与PC发生发展、早期诊断、预后评估、治疗等方面的最新研究进行简要综述.

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关键词: 肠道菌群; 胰腺癌; 代谢产物; 肿瘤微环境

核心提要: 胰腺癌(pancreatic cancer, PC)作为预后最差的恶性肿瘤之一, 因其起病隐匿、早筛早诊困难、治疗应答欠佳, 严重危害人类健康. 传统的治疗方式包括手术治疗、化疗和免疫治疗等. 近来, 多种消化系肿瘤微环境内微生物失调的发现拓宽了研究范围, 肠道微生态(gut microbiota, GM)也愈发受到重视. GM在PC起病、早期诊断、预后评估、治疗干预等多个环节能发挥作用.

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0 引言

人体微生态包含了机体不同部位的生物群落, 比如皮肤、口腔、呼吸道、消化道、生殖道等. 其中, 肠道微生态(intestinal microecology, IM)数量最大、功能最复杂. 人体肠道微生物(gut microbiota, GM)已知有细菌、古菌、真菌和病毒组成, 正常成年人的肠道细菌由厚壁菌门和拟杆菌门主导, 此外还存在放线菌门、变形菌门、梭杆菌门和疣微菌门等^[1]. 健康情况下, GM与宿主处于相互依赖又制约的稳定状态, 当这种稳态被抗生素、疾病、创伤等因素破坏, 肠道菌落的构成种类、数量、比例、共生部位和代谢特征会发生改变, 称为肠道微生态失调(microbiota dysbiosis, MD), MD与多种疾病的发生发展密切相关. 16S rRNA基因测序是当前研究微生物群落组成和分布的重要手段^[2]. 此外, 肠道微生态治疗, 如益生菌、益生元、粪菌移植(fecal microbiota transplantation, FMT)等, 作为新兴的治疗方法, 能协助重构患者IM, 促进GM恢复平衡, 以达到缓解病情、改善预后的目的.

胰腺癌(pancreatic cancer, PC)作为预后最差的恶性实体肿瘤之一, 因其起病隐匿、致病机制不清、早期筛查及诊断困难, 常在明确诊断时就已属晚期. 胰腺导管腺癌(pancreatic ductal adenocarcinoma, PDAC)是PC最常见的病理类型, 占PC的80%-90%. PC的治疗方法目前较有限, 外科根治性手术是可能治愈PC的重要手段, 但能够接受手术者仅占少数, 且术后五年生存率仍低于30%. 放化疗、免疫治疗等手段也未取得满意的效果^[3,4].

胰腺不直接与消化道的菌群接触, 且胰腺能分泌大量强碱性的胰液, 被认为不适宜微生物生存, 过去很长一段时间, 胰腺被认为是一个无菌器官. 直到2020年前后在PC肿瘤组织和囊性液中检测到了丰富的微生物菌

群^[5-7], 揭示了IM可能与PC的致病过程相关, “肠—胰腺轴”的概念被提出. 近几年来, 人们对IM参与PC致病机制、诊疗干预、评估预后等方面进行了大量的研究, 本文就该领域所取得的主要研究进展进行述评, 以便同行参阅学习.

1 肠道微生态参与胰腺癌发生发展

GM一般可通过激活致癌信号、增强致癌代谢途径、改变癌细胞增殖、触发抑制肿瘤免疫的慢性炎症等方式促进癌症的发生和发展^[8,9]. 吸烟、肥胖、糖尿病、饮酒、慢性胰腺炎、遗传易感基因等是PC发生的危险因素^[10,11], PC的发生发展涉及一个多因素参与的多步骤复杂变化的过程, 其中持续引起机体内组织结构、代谢和基因表达的异常, 现有的研究成果尚难完全阐明具体病因和病机^[12].

1.1 口腔、消化道中的潜在致病菌群 Li等^[13]发现, 牙周病是PC的危险因素, 诱发牙周病的口腔微生物能迁移、定植到胰腺、肾脏等其他远处组织. 一项荟萃分析提示, 暴露于牙龈卟啉单胞菌(引起牙周病的重要致病微生物之一)可能会导致PC患病风险增加, 在PC患者的唾液、舌苔中发现了高水平的牙龈假单胞菌及其相关放线菌的存在^[14]. Herremans等^[15]研究发现, 长链奈瑟菌、链球菌等细菌在PC与健康人群口腔中丰度明显不同. 关于感染幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)是否增加PC致病风险, 当前相关研究尚未有定论, 未来需要更大样本量、高质量的前瞻性队列研究, 兼顾到不同种族人群、不同*H. pylori*菌株和混杂因素等来进一步探索^[16,17].

尽管真菌在GM中的数量要远少于细菌, 但多项研究表明肠道真菌与PC发病相关. Ost和Round检测发现^[18], 在PC患者粪便和PDAC小鼠胰腺组织中均检测到丰富的真菌, 马拉色菌属(*Malassezia globosa*)是其中数量最多的真菌. 该研究进一步对PDAC小鼠进行抗真菌治疗, 发现抗真菌治疗减小了肿瘤大小并增强了化疗的效果. 当用马拉色菌和另外三种真菌分别重新接种给去除真菌的PDAC小鼠时, 只有马拉色菌定植的小鼠的肿瘤体积比真菌缺失的小鼠大, 表明在PC环境下马拉色菌可能驱动MBL信号传导, 促进肿瘤生长^[19]. Alam等^[20]发现, 在PDAC组织中高表达的IL-33能在真菌(主要是交链孢霉属)的驱动下招募并激活辅助型T细胞II和固有淋巴细胞II, 进而分泌促肿瘤细胞因子来加快病情进展. 由此可见, 肠道真菌有望成为PC干预的靶点.

1.2 胰腺癌患者的肠道菌群特征 PC患者的GM与健康人不同. Mendez等^[21]评估了PDAC小鼠和患者的肠道组织及其代谢产物, 其发现, 在PDAC发生发展的早期, GM中致病和产生脂多糖的变形菌门增加, 厚壁菌门减少^[22].

Del Castillo等^[23]发现PC的GM中乳酸杆菌丰度下降, 也有研究显示假长双歧杆菌在PC肠道中富集^[24]. 整体趋势表现为潜在致病菌的丰度增加和有益菌的减少^[25]. 在PDAC进展的不同阶段, 可切除和不可切除的PDAC患者GM及代谢组份也表现出明显差异, 具体为不可切除的患者组肠道另枝菌属、厌氧棒状杆菌、粪杆菌属和微单胞菌的相对丰度降低, 而假诺卡菌、鲁巴胡管道杆菌和人结肠厌氧棍状菌的相对丰度升高^[26]. 有研究显示, 肠道中富集动物双歧杆菌、肺炎克雷伯菌、嗜热链球菌、产气柯林斯菌等的PC患者死亡风险相应增加^[27].

据此推测, GM是一种潜在的无创早期检测、判断预后的工具, 及时分析GM可能成为PC早期诊断、评估预后的依据, 以解决PC缺乏有效筛查工具和特异生物标志物的难题^[28,29].

尽管很多研究证实了GM与PC的相关性, 但是对于GM与PC的因果关系尚无确凿证据, 许多PC的危险因素如饮食、肥胖^[30]等都能诱发GM的改变. 这类混杂因素使得研究IM与PC关系时需要精心设计严格的对照试验.

1.3 肠道菌群代谢产物对胰腺癌的影响

除了GM的组成比例、相对丰度改变与PC息息相关, 其代谢产物(microbial metabolism, MM)也被证实与PC高度关联^[26]. MM不仅介导GM与宿主之间的相互作用, 而且能介导不同肠道微生物之间的相关作用. 目前关于MM的研究主要集中为三大类, 分别是短链脂肪酸^[31] (short-chain fatty acids, SCFAs)、胆汁酸和色氨酸.

肠道中最多的SCFAs是乙酸、丙酸、丁酸. 戊酸和丁酸在体外试验中通过代谢和表观遗传重编程增强细胞毒性T淋巴细胞和嵌合抗原受体T细胞的抗肿瘤活性, 并显著增强了同系PDAC小鼠模型中抗原特异性ctl和靶向ror1的CAR T细胞的抗肿瘤活性^[32]. Panebianco等^[33]通过动物实验发现, 丁酸在PDAC细胞系中具有促分化、抗增殖、促凋亡和抗侵袭作用, 发挥组蛋白去乙酰化酶抑制剂的功能, 达到抗炎抗癌、抗胰腺纤维化的作用. 通过肠内营养增加肠道SCFAs丰富度, 能直接影响到肿瘤微环境并改善胰腺炎症反应^[31]. 总体来说, SCFAs对PC的发生发展有抑制作用, SCFAs能否作为新的肿瘤检测标志物或治疗靶点有待进一步探索.

胆汁酸对PC的影响则存在争议. 人胰腺癌PANC-1细胞与不同浓度胆汁酸混合培养, 通过检测PANC-1的活力、迁移和侵袭能力, 研究者发现高胆汁酸环境可以通过ROS诱导和EMT通路显著抑制PANC-1细胞的增殖和迁移, 从而促进癌细胞的凋亡^[34]. 不过有其他研究提出了一种相反的观点胆汁酸可引起胰腺细胞损伤, 促进癌细胞增殖, 并可改变PDAC对化疗的应答, 从而影响患者结局^[35].

色氨酸作为一种免疫调节因子, 能通过引起吲哚胺2,3-双加氧酶1的表达上调以抑制CD11c和树突状细胞的成熟以及T细胞增殖, 甚至上调Kyn的表达来诱导和激活芳香烃受体, 导致程序性细胞死亡蛋白1表达上调, 增强抗肿瘤提呈T细胞疗法的疗效^[36].

Irajizad等^[37]近期开发了一个基于MM组合的PC五年风险预测模型, 检测血液中MM的增加是否与PC风险相关, 发现MM组合能与CA19-9互补, MM联合CA19-9评分位于前2.5百分位数的个体的5年绝对风险估计值为>13%, 提示MM能为识别PC高危人群提供了一个潜在的工具, 从而有利于研究相应的预防策略.

1.4 胰腺肿瘤内微生物群

在胰腺肿瘤组织中, Pushalkar等^[38]发现变形菌门、拟杆菌门和厚壁菌门的含量较高. 根据临床前模型, 在胰腺肿瘤组织中检测到的微生物丰度比健康胰腺组织高1000倍^[38]. 胰腺肿瘤组织中发现的细菌序列大部分属于厚壁菌门和变形菌门, 与健康GM的组成相似^[39].

已有研究表明, GM在肿瘤形成过程中触发了许多先天性和适应性免疫反应, 这是当前的研究热点也是关键环节. 而先天免疫系统又能通过识别鞭毛蛋白、脂多糖(LPS)、肽聚糖、toll样受体(TLR)和Nodlike受体(NLR)来调节微生物^[12]. GM与肿瘤内微生物群通过诱导先天免疫抑制和适应性免疫抑制, 局部调节肿瘤微环境(tumor microenvironment, TME), 从而影响癌症的发生、发展和治疗^[40]. 最近发表的研究描述了许多恶性肿瘤组织中拥有自己独特的微生物组, 且验证了这些微生物对癌症生长的驱动作用^[41], 也是影响免疫治疗效果的关键之处.

PDAC的肿瘤细胞因其高度异质性, 具有免疫逃避的固有特性, 可通过遗传改变及下游途径与其它细胞发生交互, 在免疫抑制性微环境的塑造中发挥着巨大的作用. 肠道和胰腺微生物群作为构成TME的一员, 更揭示了其肿瘤免疫微环境塑造的复杂性^[42], 微生物或可通过对TME的调控来阻碍或促进肿瘤发展. 因此有一些研究聚焦于通过激活固有淋巴细胞或在TME中产生炎症反应, 进而引入细胞毒性T细胞, 从而使肿瘤具有免疫活性^[42]. 最近, Simnica和Kobold^[43]将携带破伤风毒素编码基因的非致病李斯特菌注射到PDAC小鼠模型中, 当联合使用低剂量吉西他滨时, 李斯特菌可以刺激记忆T细胞产生细胞毒性T细胞, 致使肿瘤体积缩小80%. Hayashi等^[44]发现, PDAC瘤内具核梭菌通过CXCL1-CXCR2轴的自分泌和旁分泌机制, 抑制肿瘤浸润的CD8+T细胞, 从而导致肿瘤进展.

肠道、胰腺微生物群在TME塑造中的驱动机制, 可能是改善PC预后的突破口, 需要更多的研究来阐明其机

制^[45], 并通过临床转化来改善目前PDAC令人失望的治疗效果。

2 肠道微生态对胰腺癌不同治疗方式及预后的影响

PC的治疗方法包括手术、化疗、HIFU治疗、放疗、靶向及免疫治疗等。多学科综合诊治是任何分期PC的治疗基础, 根据患者身体状况、肿瘤部位、侵及范围、临床症状, 有计划、合理地应用现有的诊疗手段, 以确保最大程度根治、控制肿瘤、减少并发症、改善生活治疗^[3]。研究表明^[46,47], GM与这些治疗方式相互作用, 并影响其疗效。

2.1 关于化疗 胆胰恶性肿瘤化疗后, 随着免疫功能紊乱和肠上皮屏障的破坏, GM的类型和组成常会发生变化, 通常表现为益生菌减少和机会病原菌增加。然而, 这些细菌的增减又反向改变着常用化疗药物的敏感性。GM可通过多种方式影响胆胰恶性肿瘤的化疗耐药性, 包括调节肿瘤周围的局部免疫反应和炎症、通过信号通路调节癌症自噬、影响药物代谢、增加药物转运蛋白的表达以及抗凋亡等^[48,49]。

国外一项研究, 纳入了20例PDAC患者, 在新辅助化疗前后两个时间点收集粪便样本, 发现化疗后的放线菌门相对丰度显著降低, 且其中双歧杆菌属的丰度与肿瘤组织破坏程度呈正相关, 提示双歧杆菌可能对新辅助化疗治疗效果起到了增强作用^[50]。对于接受胰腺十二指肠切除术的PC患者, 通过定向补液维持GM的多样性有利于改善术后恢复^[51]。

2.2 关于免疫治疗 前文提及, PDAC因其复杂的TME被认为是“冷”肿瘤。以免疫检查点抑制剂(immune checkpoint inhibitors, ICI)为代表药物的免疫治疗手段在很多实体肿瘤中都显示出明显的疗效, 但对PDAC的治疗令人失望。

调节GM可以改善肿瘤免疫治疗反应, 减少并发症。研究显示, GM来源的代谢产物氧化三甲胺(trimethylamine N-oxide, TMAO)可增强PDAC对ICI的免疫应答。将TMAO注射至PDAC小鼠腹腔及肿瘤组织中, 可抑制与免疫刺激肿瘤相关巨噬细胞(TAM)表型相关的肿瘤生长, 并激活TME中的效应T细胞, 提高ICI治疗的生存率^[52]。

目前较为成熟的菌群调节方法是FMT, 即将供者的菌群以胶囊或粪菌悬液的形式转移到受者体内, 以恢复受者GM的丰富度。对一些ICI应答欠佳的肿瘤进行FMT也许能有改善^[53,54]。FMT的这一作用已在黑色素瘤等肿瘤疾病中得到证实^[55], 而对PC则缺少证据。近期M.D.安德森癌症中心(MD Anderson Cancer Center)为FMT与PC的临床研究(NCT04975217)招募患者, 这项正在进行中

的研究将在PC患者接受FMT治疗后再手术切除胰腺肿瘤, 随后分别评估FMT对患者口腔、胰腺和肠道微生物群的变化, 以及移植后对PC免疫环境或分子结构变化的影响, 这也是目前唯一一项关于FMT与PC的随机对照试验, 我们关注并期待结果^[56]。

3 结论

综上, 很多研究分析对比PC患者与健康人群的口腔、肠道、胰腺微生物特征, 试图找到PC的潜在致病菌群, 从而对这些致病菌早期干预来降低发病风险。PC发病隐匿、早期发现和诊断困难, 需要高灵敏度、高特异度的生物标志物, GM及其代谢组分在这方面表现出巨大的潜力。PC的治疗难点在于其免疫特性, 研究者们已关注到肠道、肿瘤内微生物与PC预后、免疫应答之间的相关性, 未来研究以GM及其代谢产物为靶点的干预疗法将有助于改善PC的生存预测以及个体化诊疗方案的制定。

4 参考文献

- Heintz-Buschart A, Wilmes P. Human Gut Microbiome: Function Matters. *Trends Microbiol* 2018; 26: 563-574 [PMID: 29173869 DOI: 10.1016/j.tim.2017.11.002]
- Zhao J, Yang Y, Xu H, Zheng J, Shen C, Chen T, Wang T, Wang B, Yi J, Zhao D, Wu E, Qin Q, Xia L, Qiao L. Data-independent acquisition boosts quantitative metaproteomics for deep characterization of gut microbiota. *NPJ Biofilms Microbiomes* 2023; 9: 4 [PMID: 36693863 DOI: 10.1038/s41522-023-00373-9]
- Kolbeinson HM, Chandana S, Wright GP, Chung M. Pancreatic Cancer: A Review of Current Treatment and Novel Therapies. *J Invest Surg* 2023; 36: 2129884 [PMID: 36191926 DOI: 10.1080/08941939.2022.2129884]
- McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. *World J Gastroenterol* 2018; 24: 4846-4861 [PMID: 30487695 DOI: 10.3748/wjg.v24.i43.4846]
- McAllister F, Khan MAW, Helmink B, Wargo JA. The Tumor Microbiome in Pancreatic Cancer: Bacteria and Beyond. *Cancer Cell* 2019; 36: 577-579 [PMID: 31951558 DOI: 10.1016/j.ccell.2019.11.004]
- Riquelme E, Zhang Y, Zhang L, Montiel M, Zoltan M, Dong W, Quesada P, Sahin I, Chandra V, San Lucas A, Scheet P, Xu H, Hanash SM, Feng L, Burks JK, Do KA, Peterson CB, Nejman D, Tzeng CD, Kim MP, Sears CL, Ajami N, Petrosino J, Wood LD, Maitra A, Straussman R, Katz M, White JR, Jenq R, Wargo J, McAllister F. Tumor Microbiome Diversity and Composition Influence Pancreatic Cancer Outcomes. *Cell* 2019; 178: 795-806.e12 [PMID: 31398337 DOI: 10.1016/j.cell.2019.07.008]
- Tijeras-Raballand A, Hilmi M, Astorgues-Xerri L, Nicolle R, Bièche I, Neuzillet C. Microbiome and pancreatic ductal adenocarcinoma. *Clin Res Hepatol Gastroenterol* 2021; 45: 101589 [PMID: 33607375 DOI: 10.1016/j.clinre.2020.101589]
- Lu Y, Yuan X, Wang M, He Z, Li H, Wang J, Li Q. Gut microbiota influence immunotherapy responses: mechanisms and therapeutic strategies. *J Hematol Oncol* 2022; 15: 47 [PMID: 35488243 DOI: 10.1186/s13045-022-01273-9]
- Fan JQ, Wang MF, Chen HL, Shang D, Das JK, Song J. Current advances and outlooks in immunotherapy for pancreatic ductal adenocarcinoma. *Mol Cancer* 2020; 19: 32 [PMID: 32061257 DOI: 10.1186/s12943-020-01151-3]

- 10 Ruze R, Song J, Yin X, Chen Y, Xu R, Wang C, Zhao Y. Mechanisms of obesity- and diabetes mellitus-related pancreatic carcinogenesis: a comprehensive and systematic review. *Signal Transduct Target Ther* 2023; 8: 139 [PMID: 36964133 DOI: 10.1038/s41392-023-01376-w]
- 11 Klein AP. Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors. *Nat Rev Gastroenterol Hepatol* 2021; 18: 493-502 [PMID: 34002083 DOI: 10.1038/s41575-021-00457-x]
- 12 Zhao Z, Liu W. Pancreatic Cancer: A Review of Risk Factors, Diagnosis, and Treatment. *Technol Cancer Res Treat* 2020; 19: 1533033820962117 [PMID: 33357065 DOI: 10.1177/1533033820962117]
- 13 Li L, Zhang YL, Liu XY, Meng X, Zhao RQ, Ou LL, Li BZ, Xing T. Periodontitis Exacerbates and Promotes the Progression of Chronic Kidney Disease Through Oral Flora, Cytokines, and Oxidative Stress. *Front Microbiol* 2021; 12: 656372 [PMID: 34211440 DOI: 10.3389/fmicb.2021.656372]
- 14 Reitano E, de'Angelis N, Gavrilidis P, Gaiani F, Memeo R, Inchingolo R, Bianchi G, de'Angelis GL, Carra MC. Oral Bacterial Microbiota in Digestive Cancer Patients: A Systematic Review. *Microorganisms* 2021; 9 [PMID: 34946186 DOI: 10.3390/microorganisms9122585]
- 15 Herremans KM, Riner AN, Cameron ME, McKinley KL, Triplett EW, Hughes SJ, Trevino JG. The oral microbiome, pancreatic cancer and human diversity in the age of precision medicine. *Microbiome* 2022; 10: 93 [PMID: 35701831 DOI: 10.1186/s40168-022-01262-7]
- 16 Lee AA, Wang QL, Kim J, Babic A, Zhang X, Perez K, Ng K, Nowak J, Rifai N, Sesso HD, Buring JE, Anderson GL, Wactawski-Wende J, Wallace R, Manson JE, Giovannucci EL, Stampfer MJ, Kraft P, Fuchs CS, Yuan C, Wolpin BM. Helicobacter pylori Seropositivity, ABO Blood Type, and Pancreatic Cancer Risk From 5 Prospective Cohorts. *Clin Transl Gastroenterol* 2023; 14: e00573 [PMID: 36854058 DOI: 10.14309/ctg.0000000000000573]
- 17 Zhou BG, Mei YZ, Wang JS, Xia JL, Jiang X, Ju SY, Ding YB. Is Helicobacter pylori infection associated with pancreatic cancer? A systematic review and meta-analysis of observational studies. *Ther Adv Chronic Dis* 2023; 14: 20406223231155119 [PMID: 36890981 DOI: 10.1177/20406223231155119]
- 18 Ost KS, Round JL. Commensal fungi in intestinal health and disease. *Nat Rev Gastroenterol Hepatol* 2023; 20: 723-734 [PMID: 37479823 DOI: 10.1038/s41575-023-00816-w]
- 19 Aykut B, Pushalkar S, Chen R, Li Q, Abengozar R, Kim JL, Shadaloey SA, Wu D, Preiss P, Verma N, Guo Y, Saxena A, Vardhan M, Diskin B, Wang W, Leinwand J, Kurz E, Kochen Rossi JA, Hundeyin M, Zambrinis C, Li X, Saxena D, Miller G. The fungal mycobiome promotes pancreatic oncogenesis via activation of MBL. *Nature* 2019; 574: 264-267 [PMID: 31578522 DOI: 10.1038/s41586-019-1608-2]
- 20 Alam A, Levanduski E, Denz P, Villavicencio HS, Bhatta M, Alhorebi L, Zhang Y, Gomez EC, Morreale B, Senchanthisai S, Li J, Turowski SG, Sexton S, Sait SJ, Singh PK, Wang J, Maitra A, Kalinski P, DePinho RA, Wang H, Liao W, Abrams SI, Segal BH, Dey P. Fungal mycobiome drives IL-33 secretion and type 2 immunity in pancreatic cancer. *Cancer Cell* 2022; 40: 153-167.e11 [PMID: 35120601 DOI: 10.1016/j.ccell.2022.01.003]
- 21 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. *Carcinogenesis* 2020; 41: 561-570 [PMID: 31369062 DOI: 10.1093/carcin/bgz116]
- 22 Han Z, Zhang H, Lu L, Li X, Zhang C, Zhu J, Li C, Wang Q, Chen K. Research Progress in Intestinal Microecology in Pancreatic Cancer Diagnosis and Treatment. *J Oncol* 2022; 2022: 6069403 [PMID: 36510609 DOI: 10.1155/2022/6069403]
- 23 Del Castillo E, Meier R, Chung M, Koestler DC, Chen T, Paster BJ, Charpentier KP, Kelsey KT, Izard J, Michaud DS. The Microbiomes of Pancreatic and Duodenum Tissue Overlap and Are Highly Subject Specific but Differ between Pancreatic Cancer and Noncancer Subjects. *Cancer Epidemiol Biomarkers Prev* 2019; 28: 370-383 [PMID: 30373903 DOI: 10.1158/1055-9965.EPI-18-0542]
- 24 Wei MY, Shi S, Liang C, Meng QC, Hua J, Zhang YY, Liu J, Zhang B, Xu J, Yu XJ. The microbiota and microbiome in pancreatic cancer: more influential than expected. *Mol Cancer* 2019; 18: 97 [PMID: 31109338 DOI: 10.1186/s12943-019-1008-0]
- 25 Chai Y, Huang Z, Shen X, Lin T, Zhang Y, Feng X, Mao Q, Liang Y. Microbiota Regulates Pancreatic Cancer Carcinogenesis through Altered Immune Response. *Microorganisms* 2023; 11 [PMID: 37317214 DOI: 10.3390/microorganisms11051240]
- 26 Guo X, Hu Z, Rong S, Xie G, Nie G, Liu X, Jin G. Integrative analysis of metabolome and gut microbiota in Patients with pancreatic ductal adenocarcinoma. *J Cancer* 2022; 13: 1555-1564 [PMID: 35371330 DOI: 10.7150/jca.52943]
- 27 Matsukawa H, Iida N, Kitamura K, Terashima T, Seishima J, Makino I, Kannon T, Hosomichi K, Yamashita T, Sakai Y, Honda M, Yamashita T, Mizukoshi E, Kaneko S. Dysbiotic gut microbiota in pancreatic cancer patients form correlation networks with the oral microbiota and prognostic factors. *Am J Cancer Res* 2021; 11: 3163-3175 [PMID: 34249452]
- 28 Chen Z, Zhang S, Dong S, Xu H, Zhou W. Association of the Microbiota and Pancreatic Cancer: Opportunities and Limitations. *Front Immunol* 2022; 13: 844401 [PMID: 35309293 DOI: 10.3389/fimmu.2022.844401]
- 29 Nagata N, Nishijima S, Kojima Y, Hisada Y, Imbe K, Miyoshi-Akiyama T, Suda W, Kimura M, Aoki R, Sekine K, Ohsugi M, Miki K, Osawa T, Ueki K, Oka S, Mizokami M, Kartal E, Schmidt TSB, Molina-Montes E, Estudillo L, Malats N, Trebicka J, Kersting S, Langheinrich M, Bork P, Uemura N, Itoi T, Kawai T. Metagenomic Identification of Microbial Signatures Predicting Pancreatic Cancer From a Multinational Study. *Gastroenterology* 2022; 163: 222-238 [PMID: 35398347 DOI: 10.1053/j.gastro.2022.03.054]
- 30 Almanza-Aguilera E, Cano A, Gil-Lespinard M, Burguera N, Zamora-Ros R, Agudo A, Farrás M. Mediterranean diet and olive oil, microbiota, and obesity-related cancers. From mechanisms to prevention. *Semin Cancer Biol* 2023; 95: 103-119 [PMID: 37543179 DOI: 10.1016/j.semcancer.2023.08.001]
- 31 Temel HY, Kaymak Ö, Kaplan S, Bahcivanci B, Gkoutos GV, Acharjee A. Role of microbiota and microbiota-derived short-chain fatty acids in PDAC. *Cancer Med* 2023; 12: 5661-5675 [PMID: 36205023 DOI: 10.1002/cam4.5323]
- 32 Luu M, Riester Z, Baldrich A, Reichardt N, Yuille S, Buseti A, Klein M, Wempe A, Leister H, Raifer H, Picard F, Muhammad K, Ohl K, Romero R, Fischer F, Bauer CA, Huber M, Gress TM, Lauth M, Danhof S, Bopp T, Nerretter T, Mulder IE, Steinhoff U, Hudecek M, Visekruna A. Microbial short-chain fatty acids modulate CD8(+) T cell responses and improve adoptive immunotherapy for cancer. *Nat Commun* 2021; 12: 4077 [PMID: 34210970 DOI: 10.1038/s41467-021-24331-1]
- 33 Panebianco C, Villani A, Pisati F, Orsenigo F, Ulaszewska M, Latiano TP, Potenza A, Andolfo A, Terracciano F, Tripodo C, Perri F, Paziienza V. Butyrate, a postbiotic of intestinal bacteria, affects pancreatic cancer and gemcitabine response in in vitro and in vivo models. *Biomed Pharmacother* 2022; 151: 113163 [PMID: 35617803 DOI: 10.1016/j.biopha.2022.113163]
- 34 Zhu S, Yang K, Yang S, Zhang L, Xiong M, Zhang J, Chen B. A high bile acid environment promotes apoptosis and inhibits migration in pancreatic cancer. *Bioengineered* 2022; 13: 6719-6728 [PMID: 35245979 DOI: 10.1080/21655979.2022.2045823]
- 35 Malhotra P, Palanisamy R, Caparros-Martin JA, Falasca M. Bile

- Acids and Microbiota Interplay in Pancreatic Cancer. *Cancers (Basel)* 2023; 15 [PMID: 37509236 DOI: 10.3390/cancers15143573]
- 36 Hezaveh K, Shinde RS, Klötgen A, Halaby MJ, Lamorte S, Ciudad MT, Quevedo R, Neufeld L, Liu ZQ, Jin R, Grünwald BT, Foerster EG, Chaharlangi D, Guo M, Makhijani P, Zhang X, Pugh TJ, Pinto DM, Co IL, McGuigan AP, Jang GH, Khokha R, Ohashi PS, O'Kane GM, Gallinger S, Navarre WW, Maughan H, Philpott DJ, Brooks DG, McGaha TL. Tryptophan-derived microbial metabolites activate the aryl hydrocarbon receptor in tumor-associated macrophages to suppress anti-tumor immunity. *Immunity* 2022; 55: 324-340.e8 [PMID: 35139353 DOI: 10.1016/j.immuni.2022.01.006]
 - 37 Irajizad E, Kenney A, Tang T, Vykoukal J, Wu R, Murage E, Dennison JB, Sans M, Long JP, Loftus M, Chabot JA, Kluger MD, Kastrinos F, Brais L, Babic A, Jajoo K, Lee LS, Clancy TE, Ng K, Bullock A, Genkinger JM, Maitra A, Do KA, Yu B, Wolpin BM, Hanash S, Fahrman JF. A blood-based metabolomic signature predictive of risk for pancreatic cancer. *Cell Rep Med* 2023; 4: 101194 [PMID: 37729870 DOI: 10.1016/j.xcrm.2023.101194]
 - 38 Correction: The Pancreatic Cancer Microbiome Promotes Oncogenesis by Induction of Innate and Adaptive Immune Suppression. *Cancer Discov* 2020; 10: 1988 [PMID: 33262184 DOI: 10.1158/2159-8290.CD-20-1573]
 - 39 Nejman D, Livyatan I, Fuks G, Gavert N, Zwang Y, Geller LT, Rotter-Maskowitz A, Weiser R, Mallel G, Gigi E, Meltzer A, Douglas GM, Kamer I, Gopalakrishnan V, Dadosh T, Levin-Zaidman S, Avnet S, Atlan T, Cooper ZA, Arora R, Cogdill AP, Khan MAW, Ologun G, Bussi Y, Weinberger A, Lotan-Pompan M, Golani O, Perry G, Rokah M, Bahar-Shany K, Rozeman EA, Blank CU, Ronai A, Shaoul R, Amit A, Dorfman T, Kremer R, Cohen ZR, Harnof S, Siegal T, Yehuda-Shnaidman E, Gal-Yam EN, Shapira H, Baldini N, Langille MGI, Ben-Nun A, Kaufman B, Nissan A, Golan T, Dadiani M, Levanon K, Bar J, Yust-Katz S, Barshack I, Peeper DS, Raz DJ, Segal E, Wargo JA, Sandbank J, Shental N, Straussman R. The human tumor microbiome is composed of tumor type-specific intracellular bacteria. *Science* 2020; 368: 973-980 [PMID: 32467386 DOI: 10.1126/science.aay9189]
 - 40 Yang X, Guo Y, Chen C, Shao B, Zhao L, Zhou Q, Liu J, Wang G, Yuan W, Sun Z. Interaction between intestinal microbiota and tumour immunity in the tumour microenvironment. *Immunology* 2021; 164: 476-493 [PMID: 34322877 DOI: 10.1111/imm.13397]
 - 41 Hanahan D. Hallmarks of Cancer: New Dimensions. *Cancer Discov* 2022; 12: 31-46 [PMID: 35022204 DOI: 10.1158/2159-8290.CD-21-1059]
 - 42 Liu X, Tang R, Xu J, Tan Z, Liang C, Meng Q, Lei Y, Hua J, Zhang Y, Liu J, Zhang B, Wang W, Yu X, Shi S. CRIP1 fosters MDSC trafficking and resets tumour microenvironment via facilitating NF- κ B/p65 nuclear translocation in pancreatic ductal adenocarcinoma. *Gut* 2023; 72: 2329-2343 [PMID: 37541772 DOI: 10.1136/gutjnl-2022-329349]
 - 43 Simnica D, Kobold S. Neoantigen T-Cell Receptor Gene Therapy in Pancreatic Cancer. *N Engl J Med* 2022; 387: 573 [PMID: 35947720 DOI: 10.1056/NEJMc2208623]
 - 44 Hayashi M, Ikenaga N, Nakata K, Luo H, Zhong P, Date S, Oyama K, Higashijima N, Kubo A, Iwamoto C, Torata N, Abe T, Yamada Y, Ohuchida K, Oda Y, Nakamura M. Intratumor *Fusobacterium nucleatum* promotes the progression of pancreatic cancer via the CXCL1-CXCR2 axis. *Cancer Sci* 2023; 114: 3666-3678 [PMID: 37438965 DOI: 10.1111/cas.15901]
 - 45 Halbrook CJ, Lyssiotis CA, Pasca di Magliano M, Maitra A. Pancreatic cancer: Advances and challenges. *Cell* 2023; 186: 1729-1754 [PMID: 37059070 DOI: 10.1016/j.cell.2023.02.014]
 - 46 Bangolo AI, Trivedi C, Jani I, Pender S, Khalid H, Alqinai B, Intisar A, Randhawa K, Moore J, De Deugd N, Faisal S, Suresh SB, Gopani P, Nagesh VK, Proverbs-Singh T, Weissman S. Impact of gut microbiome in the development and treatment of pancreatic cancer: Newer insights. *World J Gastroenterol* 2023; 29: 3984-3998 [PMID: 37476590 DOI: 10.3748/wjg.v29.i25.3984]
 - 47 Pandya G, Kirtonia A, Singh A, Goel A, Mohan CD, Rangappa KS, Pandey AK, Kapoor S, Tandon S, Sethi G, Garg M. A comprehensive review of the multifaceted role of the microbiota in human pancreatic carcinoma. *Semin Cancer Biol* 2022; 86: 682-692 [PMID: 34051351 DOI: 10.1016/j.semcancer.2021.05.027]
 - 48 Bai L, Yan X, Lv J, Qi P, Song X, Zhang L. Intestinal Flora in Chemotherapy Resistance of Biliary Pancreatic Cancer. *Biology (Basel)* 2023; 12 [PMID: 37627035 DOI: 10.3390/biology12081151]
 - 49 Tintelnot J, Xu Y, Lesker TR, Schönlein M, Konczalla L, Giannou AD, Pelczar P, Kyllies 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 D, Boeck S, Strowig T, Uzunoglu FG, Güngör C, Stein A, Izbicki JR, Bokemeyer C, Sinn M, Kimmelman AC, Huber S, Gagliani N. Microbiota-derived 3-IAA influences chemotherapy efficacy in pancreatic cancer. *Nature* 2023; 615: 168-174 [PMID: 36813961 DOI: 10.1038/s41586-023-05728-y]
 - 50 Takaori A, Hashimoto D, Ikeura T, Ito T, Nakamaru K, Masuda M, Nakayama S, Yamaki S, Yamamoto T, Fujimoto K, Matsuo Y, Akagawa S, Ishida M, Yamaguchi K, Imoto S, Hirota K, Uematsu S, Sato S, Sekimoto M, Naganuma M. Impact of neoadjuvant therapy on gut microbiome in patients with resectable/borderline resectable pancreatic ductal adenocarcinoma. *Pancreatology* 2023; 23: 367-376 [PMID: 37088586 DOI: 10.1016/j.pan.2023.04.001]
 - 51 Lu X, Wang Y, Luo Y, Yu B. Influence of different regimens of volumetric therapy on perioperative intestinal flora in the surgical patients with pancreas tumor, a randomized controlled trial study. *BMC Anesthesiol* 2022; 22: 162 [PMID: 35614395 DOI: 10.1186/s12871-022-01693-7]
 - 52 Mirji G, Worth A, Bhat SA, El Sayed M, Kannan T, Goldman AR, Tang HY, Liu Q, Auslander N, Dang CV, Abdel-Mohsen M, Kossenkova A, Stanger BZ, Shinde RS. The microbiome-derived metabolite TMAO drives immune activation and boosts responses to immune checkpoint blockade in pancreatic cancer. *Sci Immunol* 2022; 7: eabn0704 [PMID: 36083892 DOI: 10.1126/sciimmunol.abn0704]
 - 53 Zhang J, Wu K, Shi C, Li G. Cancer Immunotherapy: Fecal Microbiota Transplantation Brings Light. *Curr Treat Options Oncol* 2022; 23: 1777-1792 [PMID: 36279081 DOI: 10.1007/s11864-022-01027-2]
 - 54 Xu H, Cao C, Ren Y, Weng S, Liu L, Guo C, Wang L, Han X, Ren J, Liu Z. Antitumor effects of fecal microbiota transplantation: Implications for microbiome modulation in cancer treatment. *Front Immunol* 2022; 13: 949490 [PMID: 36177041 DOI: 10.3389/fimmu.2022.949490]
 - 55 Baruch EN, Youngster I, Ben-Betzale G, Ortenberg R, Lahat A, Katz L, Adler K, Dick-Necula D, Raskin S, Bloch N, Rotin D, Anafi L, Avivi C, Melnichenko J, Steinberg-Silman Y, Mamtani R, Harati H, Asher N, Shapira-Frommer R, Brosh-Nissimov T, Eshet Y, Ben-Simon S, Ziv O, Khan MAW, Amit M, Ajami NJ, Barshack I, Schachter J, Wargo JA, Koren O, Markel G, Boursi B. Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. *Science* 2021; 371: 602-609 [PMID: 33303685 DOI: 10.1126/science.abb5920]
 - 56 Attebury H, Daley D. The Gut Microbiome and Pancreatic Cancer Development and Treatment. *Cancer J* 2023; 29: 49-56 [PMID: 36957973 DOI: 10.1097/PPO.0000000000000647]

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