



细菌对肿瘤转移的影响

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摘要 肿瘤转移作为肿瘤发展进程中的重要阶段,是导致肿瘤患者死亡的主要原因之一。细菌与肿瘤的发生发展密切相关,且在肿瘤转移中扮演着重要的角色。探究细菌对肿瘤转移的作用,对于肿瘤研究至关重要,有助于进一步揭示肿瘤转移的机制,对于研发新的治疗靶点、制定个性化的治疗策略以及判断肿瘤预后具有至关重要的意义。本文回顾了近年来细菌对肿瘤转移影响的研究最新进展,从胞内菌和胞外菌两个方面展开了深入分析,阐明了细菌与肿瘤转移的关系,重点探究了细菌通过直接影响肿瘤细胞以及通过肿瘤微环境的方式对肿瘤转移产生影响的机制。同时,本文也讨论了过往研究中存在的问题,如对细菌来源和定植部位的了解不足,以及研究深度和广度的缺乏。针对这些问题,本文提出了未来研究应该关注的方向,包括选择合适的细菌标志物、扩大细菌种类的研究范围,以及根据细菌特性设计药物靶点和药物载体,探讨了可能的临床转化方案,期望能为肿瘤转移的诊治提供新的思路和方法。

关键词 细菌, 肿瘤, 转移, 肿瘤细胞, 肿瘤微环境

肿瘤转移是肿瘤患者死亡的主要原因之一^[1]。转移是指肿瘤细胞脱离原发生长部位,通过多种途径,到达远处组织或器官继续生长的多步骤过程,包括侵袭、播散和定植^[2-4]。转移涉及肿瘤细胞内在特性以及肿瘤细胞与肿瘤微环境(tumor microenvironment, TME)之间的相互作用^[4]。从1889年Stephen Paget提出“种子与土壤”假说^[5],再到近年来针对肿瘤微环境各方面的多样化研究^[6,7],肿瘤转移的理论逐渐完善。

100多年前,人类肿瘤中首次发现有细菌存在^[8]。随着研究的深入,一些传统上认为是“无菌”的肿瘤也被发现具有低生物量的细菌群落特征^[9]。酸性、缺氧且拥有丰富的血液供应的TME有利于细菌的特异性定植^[10,11]。此外,在不同类型的肿瘤中,细菌的组成和丰度具有高度异质性,可能与肿瘤发生发展有关^[12]。根据细菌寄生

的部位,可以将细菌分为胞内菌和胞外菌两大类。胞内菌寄居在宿主细胞内,例如具核梭杆菌^[13]、结核分枝杆菌、志贺氏菌、布鲁氏菌和李斯特菌等;胞外菌是寄居在宿主细胞外,如炭疽芽孢杆菌、金黄色葡萄球菌、铜绿假单胞菌、幽门螺杆菌和大肠杆菌等^[14](图1)。

细菌在肿瘤转移中扮演着重要的角色(图2)。2017年,发表在*Science*上的一项研究显示:在原发性结直肠癌与肝转移灶中存在同源的具核梭杆菌,推测细菌可能伴随原发肿瘤细胞迁移至转移部位;不仅如此,在结直肠癌肿瘤内富集的部分细菌,如梭杆菌属、拟杆菌属、硬单胞菌属和普氏菌属等,可能与肿瘤转移有关;并且,使用抗生素治疗结肠癌小鼠可以减少细菌负荷和肿瘤转移^[15]。一项单中心研究发现,与免疫检查点抑制剂单独治疗相比,双歧杆菌制剂联合免疫检查点抑制剂治疗转

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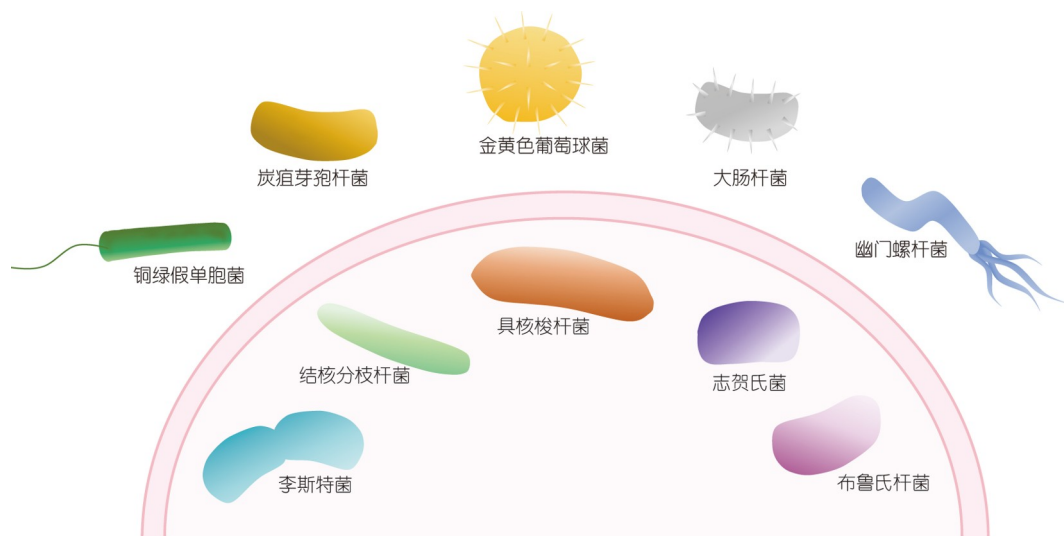


图 1 胞内菌与胞外菌的种类

Figure 1 The species of intracellular bacteria and extracellular bacteria

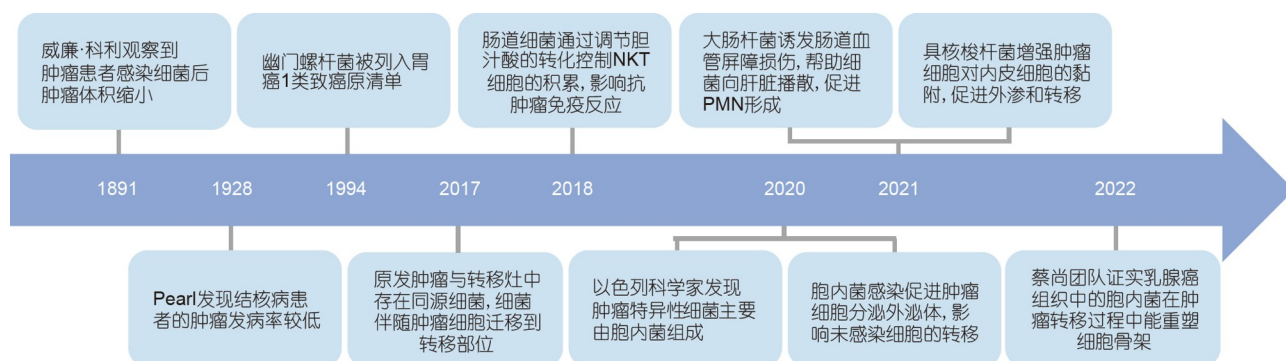


图 2 细菌与肿瘤转移研究的重要事件

Figure 2 Important events in the study of bacteria and tumor metastasis

移性肾细胞癌可显著延长患者的无进展生存期^[16]。

细菌对肿瘤转移的作用在肿瘤研究中具有重要意义,有助于为研发治疗靶点制定治疗策略和判断肿瘤预后提供新的依据。本文阐明了细菌与肿瘤转移的关系,区分了胞内菌和胞外菌在肿瘤转移中的作用,探索细菌通过直接影响肿瘤细胞和通过肿瘤微环境的方式影响肿瘤转移的作用机制,讨论了目前研究中存在的不足与解决方法,以期为肿瘤的诊断和治疗提供全新的策略和视角。

1 胞内菌在肿瘤转移中的作用

1.1 胞内菌与肿瘤转移的关系

1882年,德国医生罗伯特·科赫成功分离并证实了

结核分枝杆菌是肺结核的病原菌^[17],这是人类历史上第一个被证实的胞内致病菌。1928年, Pearl在尸检研究中发现结核患者的肿瘤发病率较低^[18]。1976年, Morales等人^[19]首次将减毒牛型结核杆菌制成的卡介苗用于治疗浅表性膀胱癌患者,并取得良好的疗效。2020年,以色列魏茨曼研究所的研究人员通过对乳腺癌、肺癌、卵巢癌、胰腺癌、黑色素瘤、骨癌和脑肿瘤这七种肿瘤类型的上千个肿瘤组织以及邻近的非肿瘤组织样本进行分析,发现大部分肿瘤组织样本里都含有细菌,且这些细菌主要为胞内菌^[8]。

有研究表明,在肺癌患者中,发生转移的患者肺内拥有丰度更高的嗜血军团菌,可能对肿瘤转移过程产生影响^[20]。2022年,西湖大学蔡尚团队在Cell发表论文,证实乳腺癌组织中存在多种独特的胞内菌能够促进肿

瘤转移^[21]。经过循环系统到达肿瘤组织后^[21]，细菌通过表面的侵袭素和黏附素与细胞膜上受体相互结合，或通过将效应蛋白注入宿主细胞内^[22]的“拉链”与“触发”机制，能够侵入肿瘤细胞内^[23]。在细胞内生长繁殖的特性赋予了胞内菌诸多优势，例如逃避免疫系统的识别和清除，拥有有利的营养环境以及适宜的增殖平台等^[9]。

在肿瘤转移过程中，胞内菌具备一些共同的特性：(1) 参与肿瘤转移的胞内菌存在于肿瘤细胞和免疫细胞中，主要位于细胞质中，且许多胞内菌处于类似于L型细菌^[24]的细胞壁缺陷状态^[8]；(2) 不同类型肿瘤细胞中的胞内菌的组成与比例不同，肿瘤细胞中的胞内菌的组成与比例和正常细胞的不同^[9]；(3) 胞内菌能够激活胞内信号通路，主要通过直接作用于肿瘤细胞参与肿瘤转移^[25]。

1.2 胞内菌直接作用于肿瘤细胞影响肿瘤转移

胞内菌能够调节肿瘤转移中的上皮-间质转化(epithelial-mesenchymal transition, EMT)过程。EMT是指上皮细胞失去极性与细胞间连接，获得间质表型且运动能力增强的动态过程^[26]。在肿瘤转移中，EMT通过上调转录抑制因子，如Slug^[27]、Twist^[28]、Snail和ZEB^[29]与波形蛋白的表达等^[30]，抑制E-钙黏蛋白的表达，诱导上皮细胞向间质细胞表型的转化，导致肿瘤细胞间黏附力减弱，促使肿瘤细胞获得侵袭的能力^[31]。研究表明，具核梭杆菌能够上调长链非编码RNA (long non-coding RNA, lncRNA)的表达，激活Y-box结合蛋白1(YBX1)依赖性的Snail、Slug和Zeb1转录因子翻译，从而促进结直肠癌的转移^[32](图3, 表1)。此外，具核梭杆菌感染能够促进波形蛋白的表达，抑制E-钙黏蛋白的表达，从而增强结直肠癌细胞的迁移能力，促肿瘤转移^[33]。

胞内菌能够通过炎症反应影响肿瘤转移。具核梭杆菌能够诱导肿瘤细胞中促炎细胞因子IL-8和趋化因子CXCL1的分泌，促进结直肠癌的迁移^[34]。此外，具核梭杆菌感染能够促使肿瘤细胞释放富含miR-1246/92b-3p/27a-3p和CXCL16/RhoA/IL-8的外泌体，传递给未被感染的细胞，促进肿瘤转移^[35]。胞内菌还能激活炎症相关的信号通路。具核梭杆菌可以通过激活TLR4/MYD88/NF-κB信号通路，上调结直肠癌细胞中的miRNA-21(miR-21)的表达，抑制RASA1的表达，促进肿瘤生长和转移^[36]。具核梭杆菌还能够通过激活TLR4/Keap1/NRF2信号通路，促进细胞色素氧化酶CYP2J2的

转录，催化亚油酸生成12,13-EpOME代谢物，从而促进肿瘤转移^[37]。

胞内菌能够通过改变细胞骨架影响肿瘤转移。肿瘤细胞的侵袭过程需要肌动蛋白细胞骨架的参与^[38]。细胞角蛋白KRT7是细胞骨架和上皮中间丝的组成部分^[39,40]，且与肿瘤侵袭有关^[41]。在结肠癌组织中，具核梭杆菌能够通过激活NF-κB通路增强KRT7-AS的转录活性，上调KRT7的表达，促进肿瘤转移^[42]。蔡尚团队则发现乳腺癌细胞中的胞内菌能够通过抑制RhoA-ROCK信号通路，重塑细胞骨架，帮助肿瘤细胞抵抗血管中的机械应力，避免肿瘤在转移过程中受到损伤，从而促进肿瘤转移^[21]。

1.3 胞内菌通过肿瘤微环境影响肿瘤转移

胞内菌能够影响肿瘤转移中的黏附过程。在肿瘤转移过程中，经过循环后的肿瘤细胞会黏附于血管内层细胞上，随后外渗，从而进一步扩散和侵袭其他组织^[43]。细胞间黏附分子-1 (intercellular cell adhesion molecule-1, ICAM-1)是一种跨膜糖蛋白，能够增强肿瘤细胞对血管内皮细胞的黏附^[44]，促进如肺癌^[45]、胰腺癌^[46]和黑色素瘤^[47]等多种肿瘤的转移。具核梭杆菌通过ALPK1/NF-κB通路上调ICAM-1表达，能够增强结直肠癌细胞与内皮细胞之间的黏附，促进肿瘤细胞的外渗和转移^[49]。

胞内菌能够影响肿瘤转移中免疫细胞的活化。转移的肿瘤细胞必须躲避免疫系统中非特异性免疫反细胞和特异性免疫细胞的攻击，才能成功地在远器官定植^[1]。胞内菌能够影响非特异性免疫反应细胞的活化。在趋化因子和细胞因子的作用下，单核细胞被募集到肿瘤细胞周围，成为肿瘤相关巨噬细胞(tumor-associated macrophage, TAM)^[48]。TAM可以极化为M1或M2表型^[50]，其中M1巨噬细胞能促进对入侵病原体和肿瘤细胞的炎症反应^[51]，而M2巨噬细胞倾向于发挥免疫抑制表型，有利于肿瘤转移^[52]。具核梭杆菌能够激活NF-κB信号通路，降低miR-1322的表达，从而上调趋化因子CCL20的表达，促进巨噬细胞浸润，同时诱导M2巨噬细胞极化，促进结直肠癌的转移^[53]。

胞内菌也能够通过调节特异性免疫反应细胞的活化，影响肿瘤转移。作为病原体，肿瘤细胞内的细菌可被免疫细胞识别并激活免疫反应，刺激肿瘤特异性T细胞的应答^[8]，杀伤肿瘤细胞从而抑制肿瘤转移。在乳腺癌组织中，具核梭杆菌感染能够明显减少CD4⁺ T细胞

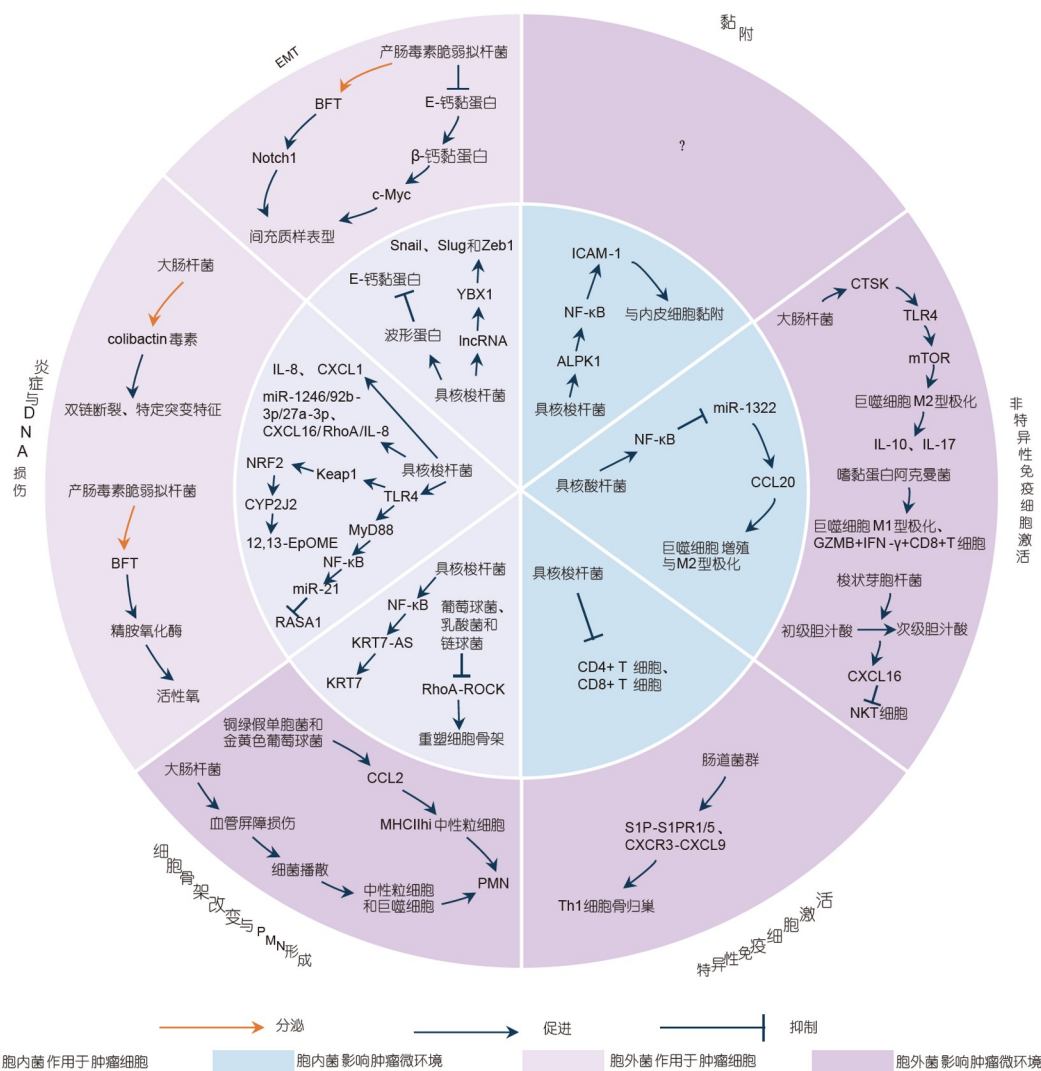


图 3 细菌对肿瘤转移的作用机制

Figure 3 Mechanism of bacterial action on tumor metastasis

和 $CD8^+$ T细胞的积累, 促进乳腺癌的生长和转移^[54].

2 胞外菌在肿瘤转移中的作用

2.1 胞外菌与肿瘤转移的关系

1876年, 罗伯特·科赫成功分离培养并证实了炭疽芽孢杆菌是炭疽的病原菌, 这是人类历史上第一个被证实的胞外致病菌^[55]. 关于胞外菌对肿瘤影响的研究始于1891年^[56], 威廉·科利回顾既往病例时, 观察到一名肉瘤患者感染化脓性链球菌后出现肿瘤体积缩小的情况^[57]. 受此启发, 科利试图使用含灭活链球菌和黏质沙雷菌的疫苗治疗肿瘤患者^[58], 现在这种细菌混合疫苗被称为“科利毒素”. 虽然这种疫苗成功治疗了上百

名患者, 但是由于具体作用机制不明确, 在当时并未受到广泛认可^[59]. 1983年, 马歇尔和沃伦首次从人胃黏膜组织中分离培养出幽门螺杆菌^[60], 并证实了幽门螺杆菌感染可以引起急性胃炎. 随后的研究证明幽门螺杆菌可以引起胃癌^[61], 从而引发了细菌对肿瘤影响的研究热潮. 1994年, 世界卫生组织属下的国际癌症研究机构将幽门螺杆菌正式列入胃癌的1类致癌原清单^[62].

研究发现, 肠道菌群失调与激素受体阳性乳腺癌的转移有关^[63]. 不仅如此, 胞外菌还能够经消化道管腔迁移^[64]或攻击机体屏障^[65]等途径抵达肿瘤组织后, 选择性增殖并影响肿瘤的转移.

在肿瘤转移过程中, 胞外菌具备一些共同的特性:

(1) 参与肿瘤转移的胞外菌多为肠道细菌. 肠道拥有体

表 1 细菌对肿瘤转移的作用机制^{a)}

Table 1 Mechanism of bacterial action on tumor metastasis

肿瘤类型	胞内		胞外	
	细菌	机制	细菌	机制
结直肠癌	具核梭杆菌	上调IncRNA的表达, 激活YBX1依赖的Snail、Slug和Zeb1翻译 ^[32] ; 促进波形蛋白的表达, 抑制E-钙黏蛋白的表达 ^[33] ; 诱导IL-8和CXCL1的分泌 ^[34] ; 促进外泌体的释放与传递 ^[35] ; 上调miR-21的表达, 抑制RASA1的表达 ^[36] ; 促进CYP2J2的转录, 催化亚油酸生成12,13-EpOME ^[37] ; 上调KRT7的表达 ^[38] ; 降低miR-1322的表达, 上调CCL20的表达, 促进巨噬细胞浸润与M2巨噬细胞极化 ^[39] ; 上调ICAM-1表达, 增强细胞间的黏附, 促进外渗和转移 ^[40]	大肠杆菌	产生colibactin毒素, 诱导双链断裂和结直肠癌的特定突变特征 ^[41] ; 诱发血管屏障损伤, 促进肠道细菌向肝脏播散并募集中性粒细胞和巨噬细胞, 促进PMN的形成 ^[42] ; 诱导M2巨噬细胞极化, 促进IL-10和IL-17等分泌 ^[43]
乳腺癌	铜绿假单胞菌、金黄色葡萄球菌和链球菌	抑制RhoA-ROCK信号通路, 重塑细胞骨架, 抵抗血管机械应力 ^[47]	产肠毒素脆弱拟杆菌	分泌BFT, 上调精胺氧化酶的表达, 诱导活性氧的产生 ^[44] ; 分泌BFT, 刺激E-钙黏蛋白裂解 ^[45] ; 上调β-钙黏蛋白的表达, 诱导c-Myc的转录和翻译 ^[46]
	具核梭杆菌	减少CD4 ⁺ T细胞和CD8 ⁺ T细胞的积累 ^[49]	铜绿假单胞菌和金黄色葡萄球菌	上调趋化因子CCL2的表达, 募集MHCIIhi中性粒细胞, 加速PMN的形成 ^[48]
前列腺癌	—	—	产肠毒素脆弱拟杆菌	诱导上皮增生, 使乳腺癌细胞获得间充质样表型 ^[50]
肝癌	—	—	嗜黏蛋白阿克曼菌	招募肿瘤杀伤性M1巨噬细胞, 提高GZMB+IFN-γ+CD8 ⁺ T细胞的比例 ^[51]
黑色素瘤	—	—	梭状芽孢杆菌	介导初级胆汁酸向次级胆汁酸转化, 抑制CXCL16表达, 抑制NKT细胞的积累 ^[52]
	—	—	肠道菌群	通过S1P-S1PR1/5和CXCR3-CXCL9途径, 介导Th1细胞归巢 ^[53]

a) “—”表示没有数据

内最丰富的微生物群, 是胞外菌的主要栖息地, 肠道和微生物群共同形成了独特的共生微生态系统^[66]。(2) 不同肿瘤组织中胞外菌的组成与比例不同, 肿瘤组织中胞外菌的组成与比例和正常组织中不同^[67]。(3) 胞外菌凭借自身代谢产物或调节肿瘤细胞代谢物的表达, 主要通过影响肿瘤微环境参与肿瘤转移^[25]。

2.2 胞外菌直接作用于肿瘤细胞影响肿瘤转移

胞外菌可能通过DNA损伤反应参与肿瘤转移。染色体不稳定性是细胞在有丝分裂过程中染色体分离出现错误所引起的^[68], 与肿瘤转移密切相关^[69]。这种染色体的分离缺陷会导致DNA损伤, 促使肿瘤细胞脱离原发肿瘤, 从而发生转移^[70]。近期研究表明, 胞外菌可以通过分泌毒素对DNA造成损伤。例如, 大肠杆菌可以通过产生colibactin毒素诱导双链断裂和结直肠癌的特定突变特征^[71]; 在乳腺和肠内定植的产肠毒素脆弱拟杆菌可分泌脆弱拟杆菌毒素(bacteroides fragilis toxin, BFT), 通过上调上皮细胞中精胺氧化酶的表达诱导活性氧产生, 从而影响肿瘤的发展^[72]。因此, 尽管目前没有确凿的证据, 但是我们可以通过胞外菌损伤肿瘤细胞DNA的现象, 推测胞外菌能够影响肿瘤转移。

胞外菌能够影响肿瘤转移的EMT过程。E-钙黏蛋白的丢失^[73]、Wnt^[74]和Notch1^[75]等信号通路的失调是EMT的典型机制, 在肿瘤的发展和转移过程中起着促进作用^[76]。产肠毒素脆弱拟杆菌分泌的BFT, 能够刺激E-钙黏蛋白裂解^[77], 上调β-钙黏蛋白的表达, 诱导原癌基因c-Myc的转录和翻译^[78], 同时通过Notch1途径诱导上皮增生, 使乳腺癌细胞获得间充质样表型, 促进乳腺癌细胞的生长和转移^[79]。

2.3 胞外菌通过肿瘤微环境影响肿瘤转移

胞外菌能够促进转移前生态位(pre-metastatic niche, PMN)的形成。在肿瘤转移前, 肿瘤会诱导远处器官中形成PMN, 免疫细胞的积累和炎症环境的形成使这种微环境有利于肿瘤转移^[80]。肝脏是多种肿瘤转移的主要靶器官, 在正常情况下, 结构屏障如肠道血管屏障可以阻止肠道细菌从消化系统扩散入循环系统^[81]。而大肠杆菌能够诱发肠道血管屏障损伤, 从而帮助肠道细菌穿过屏障向肝脏播散, 到达肝脏的细菌能够促进中性粒细胞和巨噬细胞的募集, 从而促进PMN的形成, 有利于结直肠癌细胞向肝脏的转移^[65]。乳腺癌小鼠模型中, 铜绿假单胞菌和金黄色葡萄球菌慢性感染能

够上调趋化因子CCL2的表达,将具有促肿瘤增殖作用的肿瘤浸润性MHCIIhi中性粒细胞募集到肺部,加速PMN的形成,促进乳腺癌的肺转移^[82]。

胞外菌能够调节肿瘤转移过程中非特异性免疫细胞的活性。胞外菌能够影响TAM的极化^[83]。大肠杆菌促进肿瘤细胞分泌的组织蛋白酶K(cathepsin K, CTSK)可以与TLR4结合,通过mTOR依赖性途径刺激肿瘤相关巨噬细胞的M2极化,促进IL-10和IL-17等细胞因子的分泌,进而通过NF- κ B途径促进结直肠肿瘤细胞的侵袭^[84]。与M2巨噬细胞不同,M1巨噬细胞可以产生炎症因子杀伤肿瘤细胞,同时可以通过提高T细胞、NK细胞的数量参与抗肿瘤免疫反应,具有抗肿瘤作用^[85]。被认为是潜在的下一代益生菌的肠道细菌^[86]嗜黏蛋白阿克曼菌能够招募M1巨噬细胞,并且提高GZMB⁺IFN- γ ⁺CD8⁺T细胞的比例,从而抑制前列腺癌的侵袭^[87]。此外,NKT细胞是一类特殊的T细胞,细胞表面同时存在T细胞受体 and NK细胞受体,具有先天免疫的快速反应特征和适应性免疫的抗原特异性,促进肿瘤免疫监视^[88]。胞外菌能够调控NKT细胞的积累。梭状芽孢杆菌等肠道细菌能够介导初级胆汁酸向次级胆汁酸转化^[89],通过下调肝窦内皮细胞表达CXCL16,进而减少NKT细胞的积累,从而抑制肿瘤转移^[90]。

肿瘤转移中,胞外菌同样能够影响特异性免疫细胞的活性。与T细胞杀伤肿瘤细胞不同,调节性T细胞能够通过免疫逃避促进多种肿瘤的转移^[91]。在抗生素雾化的小鼠肺中,调节性T细胞数目减少且T细胞的活性增强,同时黑色素瘤B16的肺转移发生了显著减少^[92]。在口服抗生素破坏肠道菌群后,研究人员发现TME中产生IFN- γ 的效应T细胞数目显著增加,产生IL-17A和IL-10的T细胞数目减少,抑制了胰腺癌、结肠癌和黑色素瘤的增殖和转移^[93]。Th1细胞可以杀伤肿瘤细胞,抑制肿瘤转移^[94]。肠道菌群可以通过S1P-S1PR1/5和CXCR3-CXCL9途径,介导黑色素瘤诱导的Th1细胞发生骨归巢,从而抑制黑色素瘤在骨内的转移和骨溶解^[95]。

3 展望

在过去的几十年里,我们对细菌影响肿瘤转移的认识取得了显著进展。细菌在肿瘤转移过程中发挥着复杂多样的作用机制,包括通过调控肿瘤的生长或死亡^[33]直接影响肿瘤细胞,以及改变肿瘤微环境。然而,该领域仍然存在许多未明确的问题需要进一步地探索

和研究。在临床上,除了少数病例外,肿瘤转移患者绝大部分仍然无法治愈^[1]。细菌在肿瘤转移中的作用是一个复杂且具有挑战性的研究领域,但同时也为探索潜在的治疗方案提供了新的思路。研究细菌通过肿瘤细胞和肿瘤微环境影响肿瘤转移的机制,可以为肿瘤个性化治疗方案的制定提供有价值的见解。但是,目前专门针对细菌与肿瘤转移关系的研究处于起步阶段,检测技术尚有不足,对细菌来源和定植部位的了解不够^[9],并且研究的深度和广度有限,有待于更深入的研究。

相对于肿瘤细胞,细菌在数量上占比较低,因此目前的研究仍然高度依赖深度测序技术。在细菌丰度极低的组织样本中,如何有效消除污染并实现精准分类仍是一个具有挑战性的问题。此前研究多采用16S rRNA基因扩增子测序方式以检测细菌的基因表征。这种技术在提供物种水平检测结果的同时,对低生物量的细菌群落也具有敏感性,通过将测得的数据进行仔细对照,可以过滤掉部分干扰信号^[8]。但是这种技术无法提供细菌基因表达在空间和时间上的变化信息,无法直接观察肿瘤细胞的形态结构,因此难以准确定位细菌与肿瘤细胞的关系。成像技术可以弥补这一缺陷。目前,研究人员开发了基于成像的空间转录组学技术,通过空间条形码寡核苷酸阵列捕获组织RNA,将RNA序列及其空间位置进行关联,生成基因表达矩阵^[96]。这种技术能够显示细菌基因表达与肿瘤细胞的定位关系和分布情况,并且与其他组学如蛋白质组学、代谢组学等结合时,能够实现空间多组学数据的整合分析,有助于进一步揭示细菌对肿瘤转移的作用机制。

由于细菌对肿瘤转移的影响涉及多种作用机制的特性,在临床上检测与肿瘤相关的细菌标志物(例如,大肠杆菌的colibactin毒素)可能比检测细菌种类本身更有价值,这些数据可能为肿瘤预后和进一步治疗方案提供新的参考。在药物研发领域,细菌可以作为潜在的药物研发靶点,或与现有的一线治疗方案进行联合应用,以优化治疗效果。当前,关于胞内菌与肿瘤转移的研究多聚焦于具核梭杆菌,然而,为了更深入地理解胞内菌在肿瘤转移过程中的作用机制,未来应将更多种类的胞内菌纳入研究范围,以更加全面揭示胞内菌对肿瘤转移的影响机制,从而为研制更有效的抗肿瘤疗法提供重要的理论依据。此外,在肿瘤转移过程中,胞内菌主要通过直接影响肿瘤细胞和胞外菌主要通过影响肿瘤微环境的特点,为不同类型不同阶段的患者提供了

个性化治疗方案的选择。因此,在治疗上,依据患者的病情和治疗需求区分胞外菌和胞内菌,对于选择并改造合适的细菌作为药物载体方面具有重要意义。准确地靶向肿瘤细胞或肿瘤微环境有利于将药物精准输送到预设部位,并发挥相应的作用。

目前,大量临床试验正在测试菌群调节对肿瘤转移的抑制效果,方式包括工程细菌治疗与粪菌移植等^[56]。例如,关于含有人类IL-2基因的减毒鼠伤寒沙门氏菌Saltikva,是否能显著延长转移性胰腺癌患者的总生存期,并延长他们的疾病进展时间的II期临床研究目前正在进行中(NCT04589234)^[97]。此外,关于粪菌移植对免疫治疗影响的临床研究也取得了初步成果。一项I期单中心临床试验(NCT03353402)报道了一份典型案例,一名转移性黑色素瘤患者在进行粪菌移植后重新进行抗PD-1治疗,PET-CT成像显示,在第67天患者的转移病灶增大并出现新的转移病灶,然而在第201天,所有转移病灶均已消失^[98]。而在一项II期单臂临床试验(NCT03341143)中,原发性难治性抗程序性死亡分子-1(programmed cell death-1, PD-1)治疗的转移性

黑色素瘤患者接受粪菌移植后,在抗PD-1治疗中发生了肠道微生物群组成的改变和免疫反应的调节,有助于克服患者对PD-1治疗的耐药性^[99]。未来尚需开展更大规模的临床试验,以验证研究结果的准确性,并探寻合适的生物标志物,识别从菌群调节中获益最多的转移性肿瘤的患者,进而为个性化治疗策略的制定提供科学依据。

未来的研究应进一步深入探究细菌影响肿瘤转移的具体调控机制。在技术层面上,解决探测细菌丰度和分布分辨率较低的问题是关键,同时需要挑选合适的生物标志物作为临床检测依据。此外,尽管细菌在药物研发和药物载体方面具有潜在的应用价值,但其潜在的副作用仍然是亟待解决的关键问题,使用广谱抗生素对肿瘤患者的肠道微生物群和免疫治疗的也有一定的负面影响^[100],如何将不良反应控制在临床应用可接受的范围内是未来研究中必须面对的难题。除了基础研究外,还需要进行更多临床试验,全面评估和验证细菌对肿瘤转移患者的治疗效果,为个性化治疗方案的制定提供充足的数据依据。

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Summary for “细菌对肿瘤转移的影响”

The effect of bacteria on tumor metastasis

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Tumor metastasis stands as a critical juncture in cancer progression, often heralding dire outcomes for patients. Recent research has increasingly spotlighted the intricate interplay between bacteria and tumorigenesis, particularly emphasizing their significant role in fostering tumor metastasis. Unraveling the precise contributions of bacteria to this process holds immense promise for advancing cancer research, offering crucial insights into metastatic mechanisms pivotal for prognostication, innovative therapeutic target development, and the tailoring of personalized treatment strategies.

Our review delves into recent strides in understanding how bacteria influence tumor metastasis, scrutinizing their impact from both intracellular and extracellular vantage points. We meticulously examine key milestones in the intersection of bacteria and tumor metastasis, elucidating the complex interrelationships between them. Central to our analysis is a focus on elucidating the diverse mechanisms through which bacteria shape tumor metastasis. Whether through direct interactions with tumor cells or by reshaping the tumor microenvironment, bacteria wield considerable influence. Intracellular bacteria intricately modulate processes such as epithelial-mesenchymal transition, inflammatory responses, and cellular cytoskeletal rearrangements, thereby directly impacting tumor cells and profoundly altering metastatic potential. Moreover, intracellular bacteria exert influence by steering tumor adhesion and immune cell activation, thus reshaping the tumor microenvironment to further drive metastasis. Extracellular bacteria impact tumor cells by triggering DNA damage responses and modulating epithelial-mesenchymal transition dynamics, further skewing the metastatic landscape. Beyond this, extracellular bacteria play a pivotal role in fostering pre-metastatic niche formation and regulating immune cell activity during metastasis, orchestrating their effects through nuanced modulation of the tumor microenvironment.

Simultaneously, we critically evaluate past studies, highlighting limitations such as gaps in understanding bacterial sources and colonization sites, as well as deficiencies in research depth and breadth. Addressing these challenges, we advocate several avenues for future research, including the judicious selection of bacterial markers, broadening the research spectrum to encompass diverse bacterial species, and tailoring drug targets and delivery systems to accommodate bacterial nuances. Presently, a substantial body of clinical trials is investigating the inhibitory potential of microbiota modulation on tumor metastasis, ranging from engineered bacterial therapies to fecal microbiota transplantation. We spotlight select exemplary clinical trials showcasing promising outcomes, underpinning our discussion with potential clinical translation schemes. Our aim is to furnish novel insights and approaches for diagnosing and treating tumor metastasis, thereby bridging the chasm between preclinical inquiry and clinical practice to enhance patient outcomes and propel the trajectory of metastasis research forward.

Bacteria, tumor, metastasis, tumor cell, tumor microenvironment

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