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· 文献综述 ·

胰腺导管腺癌肿瘤微环境的研究进展

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摘要

胰腺导管腺癌(PDAC)是一种恶性程度极高、早期难以诊断、预后极差的恶性肿瘤。近年来的研究发现肿瘤微环境及免疫调节与PDAC的发生密切相关,生物学微环境的研究可能为这种致死性癌症的治疗提供新的策略。笔者就PDAC肿瘤微环境研究的最新进展进行综述。

关键词

胰腺肿瘤; 肿瘤微环境; 免疫调节; 综述文献
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Research progress of tumor microenvironment in pancreatic ductal adenocarcinoma

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is a malignant tumor with aggressive biological behavior, difficult diagnosis at an early stage and dismal outcome. Recent investigations showed that the tumor microenvironment and immunomodulation are closely related to the occurrence of PDAC, and researches upon the biological environment may provide new strategies for the treatment of this lethal condition. The authors address the research progress in the field of PDAC microenvironment.

Key words

Pancreatic Neoplasms; Tumor Microenvironment; Immunomodulation; Review
CLC number: R735.9

胰腺导管腺癌(pancreatic ductal adenocarcinoma, PDAC)占胰腺恶性肿瘤的95%以上,在所有癌症导致患者死亡人数中排名第三^[1-2]。对PDAC遗传

方面的研究^[3]表明,随着时间的推移,突变慢慢积累,突变基因包括KRAS(约90%)、p16/INK4a/CDKN2A(约75%)、TP53(约65%)和SMAD4(约50%)。此外,KRAS、p16/INK4a/CDKN2A和TP53的突变所致的细胞衰老逃逸,这些都会导致肿瘤的进展^[4]。由于缺乏早期症状、常规筛查和有效的治疗方案^[5],其次是治疗困难和早期转移导致<5%的患者存活超过5年^[6],诊断时只有

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10%~20%的PDAC患者适合手术治疗,5年后只有<20%的患者接受了治愈性切除术^[3]。因此,了解PDAC的生物学行为对于开发和改进有效的治疗方案有重要意义。

相关研究^[7]表明,PDAC恶性上皮细胞仅占肿瘤体积的20%左右,而造血基质占肿瘤块的约80%。因此,PDAC的恶性特征可能与基质、逃避免疫监视、促进肿瘤进展和生长,以及耐药性传递和转移方面存在密切的相关性^[8],本文主要综述PDAC细胞基质相关信号调节通路的研究进展。

1 癌症相关成纤维细胞 (carcinoma-associated fibroblasts, CAF)

PDAC基质由支持肿瘤生长所必需的网络组成。异质组分包括胰岛细胞 (pancreatic stellate cells, PSC), 微血管浸润的免疫细胞和活化状态的CAF, 基质中含有多糖、蛋白质、细胞因子、生长因子和酶^[9-10]。先前的研究^[11]表明,升高的基质水平与预后不良相关,基质隔室的消融改善了化疗疗效,认为基质在PDAC的发生过程中发挥了重要作用^[11]。此外,聚糖结合蛋白galectin-1 (Gal1) 在PDAC中大量表达,并且在肿瘤发生过程中起着重要的刺激作用^[12]。PDA小鼠模型中Gal1通过阻碍肿瘤增殖、血管生成、阻碍发育和免疫监视来延缓肿瘤的进展,20%的PDA小鼠生存期有改善^[12]。此外,癌相关间充质干细胞不仅从CAF中分离出来,而且还分泌粒细胞巨噬细胞集落刺激因子 (GM-CSF), 促进PDAC生长、存活、侵袭和转移^[13-14]。

成纤维细胞激活蛋白 α (fibroblast activation protein, FAP α) 是CAF特异性表达的一种膜蛋白, FAP α 发挥多效的肿瘤促进作用,包括阻断免疫监视,使PDAC适应宿主,增强肿瘤血管密度和适应肿瘤生长微环境^[15-16]。因此,CAF中FAP α 的减少,不仅恢复了移植肿瘤的免疫监视 (即抗肿瘤) 效应,而且降低了PDAC的侵袭性。在CAF中,可通过CXCL12促进免疫抑制, CXCL12是一种趋化因子,其通与受体CXCR4的相互作用排出细胞毒性CD8⁺T细胞^[15]。CXCR4的抑制通过恢复和使得细胞毒性CD8⁺T细胞的肿瘤内积累迅速导致多种肿瘤消除作用^[16]。因此CXCR4的抑制作用

是通过CD8⁺T细胞在肿瘤内迅速聚集导致多种肿瘤消除作用,靶向CXCR4可能导致免疫介导的抗肿瘤效应,并在不久的将来开发潜在的治疗方案。

此外,CAF与癌细胞相互作用,部分原因是通过释放化学信使,将化学信使包装成称为CAF衍生外来体 (CAF-derived exosomes, CDE) 的微型双膜状结构^[17]。CDE的代谢产物包括氨基酸、脂质和柠檬酸循环的中间体。CDE可以重新摄取癌细胞的代谢产物。在CDE摄取后,线粒体氧化磷酸化和正常的氧能释放显著降低,而糖酵解和糖消耗在癌细胞中增强^[17]。因此,CDE影响了癌细胞中的碳代谢,即使肿瘤处于营养剥夺条件下,也能进一步促进肿瘤生长^[17]。

令人失望的是,上述有看似非常有意义的实验结果尚未带来令人满意的临床应用。近来对基质生物学的研究有了不同的见解。例如,Özdemir等^[18]在小鼠模型的研究发现,肌成纤维细胞的消融产生了免疫抑制 (即肿瘤促进)、PDAC更多的侵袭性以及预后不良。这个发现引发了疑问,PDAC中的肿瘤基质是否确实是双刃剑^[19]。肿瘤间质串扰的机制和功能可能比以前预期的要复杂得多。仅单独的分组不能验证上皮细胞周围的生物学特性。然而,需要以不偏不倚的方式对多因素参数之间的串扰进行彻底的评估。正增长信号与负增长信号之间复杂的相互作用可能会使肿瘤侵袭延缓或促进^[20]。

2 免疫调节

肿瘤浸润性免疫细胞显示对肿瘤进展、转移和化疗耐药至关重要^[21]。免疫抑制细胞在PDAC发生过程中的增加,包括骨髓来源的抑制细胞 (myeloid-derived suppressive cells, MDSC)、T调节细胞 (T regulatory cells, Tregs) 和肿瘤相关巨噬细胞 (tumor-associated macrophages, TAM)。它们一起降低了CD8⁺T细胞的抗肿瘤功能,从而导致肿瘤识别和消除能力减弱。最初,肿瘤分泌GM-CSF,作用是将骨髓祖细胞募集到周围基质,并可以进一步分化成MDSC^[22]。在肿瘤基质中,MDSC进一步阻断细胞毒性CD8⁺T细胞自然发挥的免疫监视功能^[20]。最近的研究^[23]表明,配体和受体之间的相互作用对于排除这种免疫检查

过程有重要作用。抑制性受体, 例如程序性细胞死亡1受体 (programmed cell death 1 receptor, PD-1) 可以被其从肿瘤细胞分泌的配体PD-1L掩蔽和钝化。PD-1与PD-1L的结合消除了CD8⁺T细胞或自然杀伤细胞的肿瘤消除功能。逃避免疫监测的结果使得其提供了一个肿瘤微环境, 用于培养PDAC扩增。

另一方面, 归因于与抑制性细胞因子如白细胞介素10 (interleukin 10, IL-10)、细胞毒性T淋巴细胞相关蛋白4 (cytotoxic T lymphocyte-associated protein 4, CTLA-4) 和转化生长因子 β (transforming growth factor, TGF- β) 的分泌有关的免疫抑制模式。CD4⁺T细胞亚群可受TGF- β 刺激的影响, 然后分化为获得额外的免疫抑制 (即肿瘤促进) 的白细胞介素17 (interleukin 17, IL-17) 分泌型CD4⁺T细胞 (称为Th17) 功能^[24]。有趣的是, Th17的浸润显示出有致癌性KRAS G12D的参与^[24]。

Wu等^[25]研究发现引起IL-17细胞因子家族之一IL-17B在调节炎症中发挥重要作用, 递送中和抗体降低肿瘤负荷, 并且增加异种移植模型小鼠的存活率, 其表现为抑制的肿瘤增殖和阻止癌转移, 这一研究揭示了这一现象的根本机制。IL-17与其受体的结合诱导REG3 β 的表达, 其进一步促进细胞生长, 并通过激活gp130-JAK2-STAT3依赖性途径而使细胞死亡^[26]。另一项研究报告表明, IL-17B与其受体IL-17RB结合, 然后诱导CCL20/CXCL1/IL-8/TFF1激活, 随后呈现明显的肿瘤促进作用, 如癌细胞侵袭、募集巨噬细胞和内皮细胞, 降低治疗效果^[25]。总之, IL-17在癌症的病理生理学中起着复杂的作用, 从肿瘤发生、增殖、转移到赋予免疫和化疗耐药^[3]。

关于巨噬细胞, TAM可以根据它们分为两种亚型发育状态和功能: 原始状态M1 (促炎症) 和肿瘤发生的M2 (免疫抑制和肿瘤促进)。据报道^[27], M2-TAM的升高部分与淋巴结转移、神经侵袭、化学耐药性、恶化预后和存活风险增加相关。此外, M2-TAM分泌IL-10, 已知其与免疫抑制和促肿瘤功能相关。M2-TAM增强肿瘤侵袭转移能力不仅通过防止肿瘤细胞被CD8⁺细胞毒性T细胞或天然杀伤细胞消除, 而且通过促进癌细胞增殖, 刺激细胞外基质分解, 并增加上皮间质转化^[3], 这

是一个预示癌症干细胞表型的事件^[28]。在这个概念下, 据报道^[29], TAM分泌一种抗菌肽hCAP-18/LL-37, 其含有CD133⁺的恶性细胞亚群并显示癌症干细胞表型。从原始状态M1到PDAC中的促肿瘤M2的关键转变可能是癌症患者预后差的主要原因之一。证据显示, M2通过STAT3途径在小鼠模型中被Reg3 β 介导^[30], 这意味着STAT3通路可能成为有希望的治疗靶点。

3 癌症疫苗

癌症疫苗通过增加肿瘤相关抗原对免疫系统的暴露来刺激免疫系统产生和肿瘤浸润特异性细胞毒性效应T细胞^[31]。最有希望的疫苗是GVAX, 其由设计用于分泌GM-CSF的同种异体PDAC细胞系组成。在给予切除或转移性PDAC患者后, GVAX能够促进外周淋巴细胞中抗肿瘤CD8⁺T细胞的产生, 结果与改善患者的生存率相关。另一项研究显示, 与ipilimumab单一疗法相比, GVAX和ipilimumab (抗体阻断CTLA-4) 的组合治疗可以提高转移性PDAC患者的总体存活率^[32]。同样, GVAX与PD-1/PD-L1阻断的组合一起促进了小鼠模型中的效应T细胞浸润到胰腺肿瘤中^[23]。

由于肿瘤浸润性效应淋巴细胞不足, PDAC最近被认为是“非免疫原性”恶性肿瘤之一^[3]。Lutz等^[33]通过结合GVAX与低剂量环磷酰胺来消除Tregs治疗PDAC的临床试验。通过诱导T细胞的浸润, 患者存活率有所改善, 增强接种后T细胞的应答, 并增加了肿瘤内T细胞/Treg比率。此外, Le等^[34]开发了一种称为GVAXCRS-207基于的GVAX的嵌合疫苗, 其不仅包含GVAX, 而且还包括减毒活利斯特氏菌的间皮素以刺激先天和适应性免疫。据报道^[34], 间皮素是许多人类癌症中表达的常见抗原, 包括PDAC^[35]。GVAXCRS-207加环磷酰胺治疗的结果显示, 能延长患者存活并具有最小的细胞毒性。总而言之, 未来创新的治疗方案可以适应GVAX与其他靶因子的协同效应。

最近开发了另一种由黏蛋白1加基于DNA的可变数目串联重复序列组成的疫苗, 并转染至未成熟的树突状细胞^[36]。在获得质粒构建体pVAX1-MUC1-VNTR6时, 树突细胞不仅产生增加的免疫原性, 而且它们相邻的一起共同培养的T细胞也获

得了明显的细胞毒性,这表明对PDAC的生长有抑制作用^[37]。

4 结语与展望

总而言之,PDAC的发展可被各种肿瘤微环境因子调节,并且其中一些已被用于开发靶向治疗。未来改进的胰腺癌治疗方案可能包括旨在降低不良反应、抑制致瘤性信号通路、重编程免疫抑制、纠正异常miRNA调节和实施癌症疫苗的组合方案^[38-40]。

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