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肿瘤相关成纤维细胞在甲状腺癌增殖、侵袭与治疗中的作用

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【摘　要】甲状腺癌是最常见的内分泌恶性肿瘤之一。肿瘤相关成纤维细胞（cancer-associated fibroblasts，CAFs）是甲状腺癌肿瘤微环境中重要的细胞成分，其细胞起源、表型和功能均具有异质性。CAFs 和肿瘤细胞之间的相互作用不断促进肿瘤的进展。CAFs 可以通过改变胞外基质（extracellular matrix，ECM）结构功能、促进上皮向间充质转化（epithelial to mesenchymal transition，EMT）和增强细胞因子分泌释放等方式，直接或间接促进甲状腺癌的发生发展。根据甲状腺癌中 CAFs 的特点目前已提出了一些可能的治疗策略。现结合文献对 CAFs 与甲状腺癌进展的研究进展进行综述。

【关键词】肿瘤相关成纤维细胞；甲状腺癌；肿瘤微环境
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Role of cancer-associated fibroblasts in the proliferation, invasion, and treatment of thyroid cancer

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【Abstract】Thyroid cancer is one of the most common endocrine malignancies. Cancer-associated fibroblasts（CAFs）are important cellular components in the tumor microenvironment of thyroid cancer, with heterogeneities in their cell origins, phenotypes, and functions. CAFs promote tumor progression through its interactions with tumor cells. CAFs can directly or indirectly promote the development and progression of thyroid cancer by altering the structure and function of the extracellular matrix, promoting epithelial-to-mesenchymal transition, and enhancing cytokine secretion and release. Based on the characteristics of CAFs in thyroid cancer, some possible treatment strategies have been proposed. This article reviews the research advances in CAFs and thyroid cancer progression based on the relevant literature.

【Key words】cancer-associated fibroblasts; thyroid cancer; tumor microenvironment

恶性肿瘤组织由具有自主增殖和侵袭能力的癌细胞、肿瘤相关基质细胞和细胞外环境在内的肿瘤微环境（tumor microenvironment，TME）组成，其中 TME 在肿瘤的侵袭和转移中发挥重要作用[1]。肿瘤相关成纤维细胞（cancer-associated fibroblasts，CAFs）又被称为肌成纤维细胞或反应性成纤维细胞，是 TME 的重要组成部分，CAFs 通常与多种恶性肿瘤细胞并存，如前列腺癌、乳腺癌和胰腺癌等[2-4]。在甲状腺癌中，这些伴生细胞在甲状腺癌起始、淋巴结转移或远端转移中的作用越来越受到关注[5-7]。诸多证据表明肿瘤的发生发展不仅依赖癌细胞基因的改变，还依赖肿瘤细胞与 TME 之间的相互作用[8-10]。CAFs 是一类在肿瘤微环境中出现的成纤维细胞。CAFs 在肿瘤中的功能比较复杂，不仅能促进肿瘤的生长和转移，某些条件下还可以抑制肿瘤生长，上述特征使 CAFs 在肿瘤发生发展和治疗过程中扮演特殊角色[11-13]。因此，CAFs 与癌细胞的相互作用有望成为癌症治疗的靶点。本文将以 CAFs 及甲状腺癌为主题，着重介绍 CAFs 在甲状腺癌中的作用，以期对甲状腺癌的发病机制和治疗提供新的理解和启示。

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1　CAFs

恶性肿瘤组织由癌细胞和各种基质细胞组成，这些基质细胞包括内皮细胞、免疫细胞、成纤维细胞等，上述成分构成癌细胞周围特殊的微环境，影响癌细胞的增殖、侵袭和转移[1]。CAFs 在肿瘤中的分布非常广泛，与正常成纤维细胞不同，CAFs 表现出一系列特殊的表型和功能，这些特征赋予了 CAFs 影响肿瘤细胞生长和转移的能力。

1.1　CAFs 的来源

CAFs 是一个涵盖性总称，与癌症组织中的常驻成纤维

细胞不同，CAFs是一群具有动态异质性特征的间充质细胞群[14]。CAFs的来源比较复杂，可能来自于机体原有的组织成分，也可能是通过转化而来。目前认为，CAFs的主要来源有以下几种：①肿瘤微环境中的成纤维细胞。这些细胞原本是身体中正常的成纤维细胞，在肿瘤的微环境中受到刺激后逐渐转化为CAFs[15-16]。②骨髓间充质干细胞（bone marrow mesenchymal stem cells，BMMSCs）。BMMSCs被证实具有多向分化的潜能，能产生多种不同类型的子代细胞，其中包括CAFs[17-19]。③脂肪来源间充质干细胞（adipose-derived mesenchymal stem cells，ADMSCs）。在胰腺导管腺癌、卵巢癌和结直肠癌中，ADMSCs均可以经体外共培养分化为CAFs，并获得促进癌细胞的增殖、进展和转移的能力[20-22]。④骨髓来源的巨噬细胞。研究发现，将骨髓来源的多能造血干细胞植入受体胰腺后，可在肿瘤组织中鉴定到骨髓巨噬细胞来源的CAFs，并证实这些骨髓来源的巨噬细胞在体外能诱导肿瘤细胞局部侵袭，进而促进胰腺癌的发展[19]。⑤间皮细胞。间皮细胞主要存在于胸膜、腹膜和心包等组织中，也被认为是CAFs的一种来源。研究显示，随着间皮细胞的上皮标记物如E-钙黏蛋白（E-cadherin）和细胞角蛋白的减少，同时间充质标记物如波形蛋白的增加，使间皮细胞在间皮-间充质转化（mesothelial to mesenchymal transition，MMT）的过程中获得间充质表型[23]。Demuytere J等[24]检查了常规腺癌、黏液癌和印戒细胞癌这3种结直肠癌中CAFs的间皮来源，发现与正常腹膜间皮样本相比，癌症患者腹膜间皮细胞标记物表达消失，而间质标记物表达升高，上述结果增加了CAFs起源于间皮的可信度。

1.2 CAFs的特征与功能

与常规成纤维细胞相比，CAFs具有以下4个特征：①CAFs的形态和表型不同于常规成纤维细胞。CAFs的细胞质成分较多而细胞核成分较少，还具有更多的细胞伸展和分支现象[25]。此外，虽然CAFs的表面标记物有α-平滑肌肌动蛋白（α-smooth muscle actin，α-SMA）、成纤维细胞激活蛋白（fibroblast activating protein，FAP）、波形蛋白、成纤维细胞特异性蛋白-1（fibroblast specific protein-1，FSP-1）、I型胶原蛋白等标记物[26-27]，但是这些常见的生物标志物并不是CAFs独有的。例如，α-SMA不足以识别CAFs的所有亚群，也不能区分其他基质细胞[28]，但可以根据其来源进行多重标记以确定其转化前后的特征。②CAFs的代谢更强，在TME中具有强烈的生长和分化能力[29-30]。③CAFs能够通过多种信号调节途径如MEK/ERK、PI3K/AKT、JAK/STAT、MAPK和NF-κB等，参与调节肿瘤细胞的增殖、凋亡和转移等生物学过程[31-32]。④CAFs可以分泌多种细胞因子，如转化生长因子β（transforming growth factor，TGF-β）、干扰素γ（interferon-γ，IFNγ）等，对免疫系统的反应产生影响[33]。CAFs具体功能和介导的机制见图1。基质重塑和可溶性因子的释放有助于肿瘤细胞的侵袭。可溶性因子也有助于肿瘤生长和免疫微环境的变化，同时这也受到肿瘤代谢状态改变的影响。

2 CAFs与甲状腺癌的关系

2.1 CAFs直接促进甲状腺癌发生发展

CAFs是TME中被肿瘤细胞诱导的一组活化成纤维细胞，在多种癌症中与肿瘤去分化和侵袭密切相关。α-SMA阳性CAFs可以通过分泌骨桥蛋白（osteopontin，OPN）促进肿瘤生长[34]。通过分析数据库中正常甲状腺（normal thyroid，NT）、乳头状甲状腺癌（papillary thyroid carcinoma，PTC）和去分化甲状腺癌（dedifferentiated thyroid cancer，DDTC）相关数据，发现α-SMA阳性CAFs的比例在这3种组织中依次增高，且CAFs评分与甲状腺癌分化状态、预后不良、BRAF-RAS评分、甲状腺分化评分显著相关[6]。通过对比免疫组化结果和数据库中的基因表达数据，发现甲状腺肿瘤中CAFs往往和衰老的甲状腺癌细胞同时出现，且均定位在甲状腺肿瘤的侵袭边缘位置，衰老的甲状腺癌细胞通过分泌赖氨酸氧化酶（lysine oxidase，LOX）促进甲状腺癌侵袭[5]。通过对甲状腺全切除的PTC患者进行回顾性病理评估，发现42例（64.6%）PTC患者的肿瘤组织边缘有CAFs的存在，并且发现

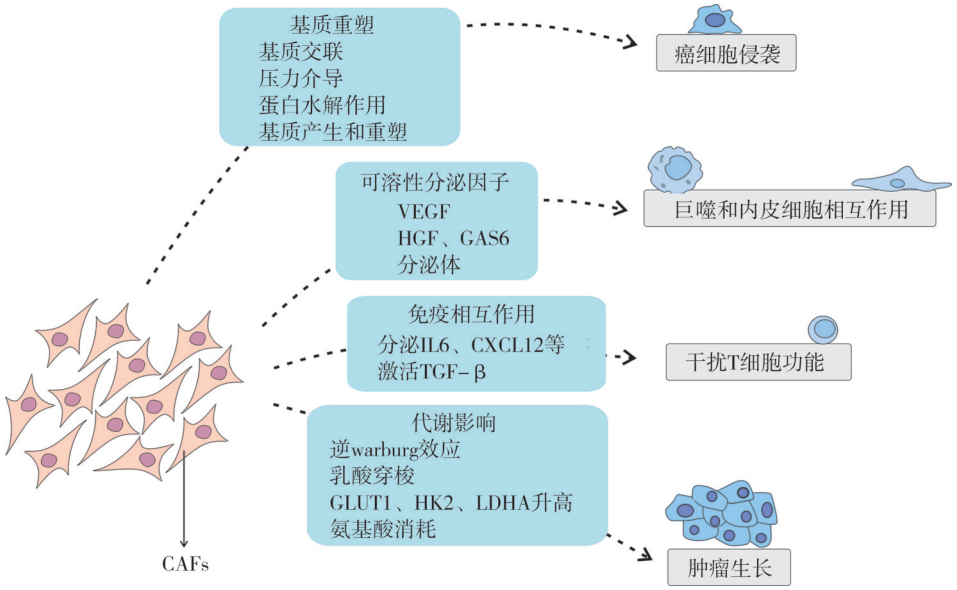

图1 CAFs功能与介导的机制

CAFs是PTC患者淋巴结转移的危险因素之一[35]。Saitoh O等[36]研究证实，大鼠甲状腺肿瘤细胞与皮肤成纤维细胞之间的相互作用可促进肿瘤生长。通过体外共培养，发现经CAFs条件培养基处理的甲状腺癌细胞，其增殖和侵袭能力增强，因为CAFs分泌的可溶性因子能够激活甲状腺癌细胞的上皮向间质转化（epithelial to mesenchymal transition，EMT）[37]。这些研究都说明CAFs与甲状腺癌的进展和侵袭转移密切相关。

2.2 CAFs刺激ECM导致甲状腺癌进展

CAFs通过改变胞外基质（extracellular matrix，ECM）的结构和硬度促进肿瘤进展和转移[38-41]。CAFs可以分泌纤维连接蛋白等胞外基质ECM成分，刺激甲状腺癌细胞的增殖、迁移和侵袭[42-44]。用胰导管腺癌（pancreatic ductal adenocarcinoma，PDAC）原代CAFs的培养上清3D培养PDAC的肿瘤相关实质细胞（cancer parenchymal cells，CPCs）和肿瘤干细胞（cancer stem cells，CSCs）模拟早/晚期PDAC的ECM状态，发现CAFs可以和ECM相互作用，调节PDAC、CPC和CSC细胞之间的行为，导致PDAC进展[41]。LOX是一种负责胶原交联的酶，与ECM直接相关。有研究显示LOX在侵袭性甲状腺癌中高表达。抑制LOX活性能降低间变性甲状腺癌细胞的迁移和侵袭[45]。Jolly LA等[46]发现$BRAF^{V600E}$小鼠甲状腺肿瘤模型中LOX水平高于正常组织，并且BRAF突变诱导的甲状腺癌细胞培养基促进小鼠甲状腺癌模型中CAFs的增殖与迁移。Boufraqech M等[47]也发现高LOX表达的BRAF突变肿瘤促进甲状腺癌进展。但ECM中的LOX和甲状腺癌CAFs之间如何相互作用仍需更多研究来证实。

2.3 CAFs刺激细胞因子分泌导致甲状腺癌进展

CAFs通过分泌生长因子、细胞因子、趋化因子与肿瘤细胞相互作用[48]。甲状腺癌肿瘤微环境中的CAFs分泌大量白细胞介素6（interleukin 6，IL-6），作用于癌细胞并促进肿瘤生长[37]。TGF-β通过激活成纤维细胞，促进其有丝分裂和趋化[49]。PTC患者肿瘤细胞的TGF-β1与成纤维细胞α-SMA的高表达存在显著相关性[50]。通过抑制TGF-β1可减少ATC细胞8505C和SW1736的肿瘤发生、迁移和侵袭[51-52]。因此，在甲状腺癌进展过程中，TGF-β可能是CAFs分化的潜在调节因子。CXC趋化因子配体12（CXC chemokine ligand 12，CXCL12）是甲状腺癌细胞表面受体CXCR4和CXCR7的配体。对PTC的研究发现熊果酸可以通过调节CAFs中CXCL12的分泌来发挥抗癌作用[53]。也有研究发现ATC患者肿瘤基质细胞通过分泌Shh（Sonic Hedgehog），诱导癌细胞迁移[54]。目前以CAFs为直接靶点对甲状腺癌进行治疗的研究不多，但基于CAFs在TME中的重要地位，以及TME中的各种因子与肿瘤之间的关系一直以来受到的重视，探究CAFs通过释放细胞因子的方式影响甲状腺癌的机制显得尤为重要。

3 CAFs在甲状腺癌治疗中的进展与展望

由于增殖阶段的CAFs容易受到DNA损伤因素影响，使DNA/RNA合成遭到破坏，继而导致信号网络失调，所以大多数常规抗癌疗法可能对CAFs产生影响[16]。CAFs通过分泌生长因子刺激肿瘤细胞增殖和血管生成的方式促进肿瘤生长[55-58]。因此，破坏CAFs的分泌功能可减少其对甲状腺癌细胞的刺激作用。甲状腺CAFs可以通过多种方式诱导甲状腺肿瘤细胞离开原发灶并向远端转移，如：上调基质金属蛋白酶9（matrix metalloproteinase-9，MMP-9）和LOXs的表达、激活YAP通路、促进细胞外基质的血管化和降解[5,59-60]。也有研究发现MMP抑制剂BB94可以抑制ATC细胞的迁移和侵袭[52]。PTC患者血清MMP-2、MMP-9含量明显高于对照组，经超声引导下射频消融术（radiofrequency ablation，RFA）治疗后，MMP-2、MMP-9的血清含量明显降低。说明血清MMP-2和MMP-9水平对RFA诊断和治疗PTC具有重要的临床价值[61]。因此，抑制CAFs细胞外基质的降解，可减少其对甲状腺癌细胞的刺激作用，进而缓解甲状腺癌的进展。EMT是指上皮细胞逐渐失去E-cadherin表达，导致细胞间连接崩溃后转变为更具侵略性的间充质样表型的过程[62-63]。CAFs可以通过分泌IL-6、TGF-β、HGF作用于癌细胞，促进癌细胞EMT的发生[37,64-66]。

CAFs作为癌症治疗靶点的研究方向：①靶向生物基质的屏障，有效转运药物；②抑制CAFs分泌活性的分子；③阻断ECM成分，以降低ECM相关信号通路活性；④抑制CAFs活性。通过对TGF-β、MMP、SHH、c-met、CXCL4-CXCL12等靶点用药可影响癌细胞的增殖、存活、迁移和侵袭，进而抑制肿瘤微环境的形成。但目前针对这些靶点的药物研究还停留在临床前研究阶段。

在过去的十几年中，美国FDA批准了多种治疗晚期甲状腺癌的药物，包括用于放射性碘难治性分化甲状腺癌的多靶向激酶抑制剂、MTC多靶点激酶抑制剂、MTC选择性激酶抑制剂等。BRAF和MEK抑制剂主要针对的靶点包括VEGFR、FGFR、PDGFR、RET 、KIT、FLT3、$BRAF^{V600E}$和CRAF等，已被用于多种甲状腺癌的治疗，包括：局部复发ATC、不可切除的局部晚期或转移性MTC、RET突变或RET基因融合阳性的DTC、$BRAF^{V600E}$突变的局部晚期或转移性ATC[40]。目前认为CAFs是导致癌细胞产生耐药性的重要因素[67]，因此解决甲状腺癌中由CAFs导致的耐药问题，对甲状腺癌的药物治疗有重要意义。

4 结 语

CAFs是TME中的重要成分，在调节甲状腺癌的生长和扩散中发挥重要作用。CAFs在甲状腺癌中的数量、分布与甲状腺癌的侵袭、进展呈正相关。本文总结了CAFs在甲状腺癌组织中的分布、CAFs和ECM在甲状腺中的作用以及分泌的因子在甲状腺癌中的作用，同时介绍了CAFs在甲状腺癌代谢中的作用以及CAFs在甲状腺癌治疗中的一些进展和展望。通过对CAFs和甲状腺癌的特征的分析，提出多种方式干预CAFs功能的方案，包括抑制甲状腺癌中CAFs的生长和增殖、调节CAFs的分泌、抑制CAFs的细胞外基质降解作用等。此外，还可以利用CAFs的免疫调节作用和药物传递作用来治疗甲状腺癌。虽然CAFs在甲状腺癌治疗中的应用还处于探索阶段，但是它具有广阔的应用前景，有望成为甲状腺癌治疗新的突破口。

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