癌相关成纤维细胞活化机制的研究进展

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摘　要:癌相关成纤维细胞(cancer associated fibroblasts,CAFs)是肿瘤微环境的重要组成部分,具有活性的 CAFs 已经被证实可促进肿瘤的发生、发展、转移和耐药,成为癌症治疗的重要目标。现已发现细胞因子、炎症、缺氧、活性氧、自噬及放射线等都可以引起 CAFs 的活化。深入了解 CAFs 活化的分子机制和病理机制,有利于为恶性肿瘤治疗提供新的思路和靶点。
主题词:肿瘤发生;肿瘤微环境;癌相关成纤维细胞;活化
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Research Progress in Activation Mechanism of Cancer-associated Fibroblasts

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Abstract:Cancer-associated fibroblasts(CAFs) are an important component of the tumor microenvironment. The activated CAFs have been shown to promote tumorigenesis,development,metastasis and drug resistance,and become an important target for cancer treatment. It has been found that cytokines,inflammation,hypoxia,reactive oxygen species,autophagy,and radiation all contribute to the activation of CAFs. The understanding of the molecular and pathological mechanism of CAFs activation may provide new ideas for cancer treatment using CAF as a therapeutic target.
Subject words:tumor development;tumor microenvironment;cancer-associated fibroblasts;activation

“种子和土壤”假说的提出,肿瘤微环境(tumor microenvironment,TME)在肿瘤发生、发展中的生物学作用受到广泛重视[1,2]。TME 中具有生物活性的成纤维细胞显示出与肌成纤维细胞相似的特征，也称为癌相关成纤维细胞[3]。癌相关成纤维细胞(cancer associated fibroblasts,CAFs) 是 TME 中最丰富的细胞，活化的 CAFs 不仅可通过合成细胞外基质(extracellular matrix,ECM)组分(如胶原蛋白和纤连蛋白等)形成基质结构框架,还可直接与癌细胞和其他基质细胞发生相互作用，在肿瘤疾病的发展和对治疗疗效中发挥重要作用[4]。

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1　CAFs 一般特征

1.1　CAFs 来源

CAFs 作为肿瘤基质中的活化成纤维细胞,具有显著异质性和多源性,其来源主要有:(1)常驻组织成纤维细胞;(2)癌周脂肪细胞;(3)骨髓间充质干细胞;(4)造血干细胞;(5)上皮细胞;(6)内皮细胞[5]。肿瘤基质中处于静息态的成纤维细胞 (normal fibroblasts,NFs)是 CAFs 的主要来源,当受到外来因素刺激时,NFs 会激活成为形态和功能迥异的 CAFs,只有被激活成 CAFs 后才能发挥各种“促恶性”作用[6]。

1.2　CAFs 活化标志

CAFs 特异性表达 α-平滑肌肌动蛋白(α-smooth muscle actin,α-SMA)、成纤维细胞激活蛋白(fibrob-

last activation protein,FAP)、血小板源性生长因子受体 (platelet-derived growth factor receptor,PDGFR)-β、成纤维细胞特异性蛋白 (fibroblast specific protein,FSP)-1 等标志物[7]。也有研究发现 CAFs 中表达的平足蛋白(podoplanin,PDPN)可作为评价肿瘤患者预后的独立影响因子,但 PDPN 是否可作为 CAFs 的标志物尚无统一意见。

2 CAFs 活化机制相关研究

大量研究证实肿瘤发展是肿瘤细胞与基质相互作用、相互影响的结果,其中 CAFs 的活化是关键环节之一[8]。

2.1 生长因子诱导 CAFs 活化

癌细胞和其他基质细胞分泌的许多细胞因子均可诱导 CAFs 的活化, 其中转化生长因子-β(transforming growth factor beta,TGF-β)最为典型[9]。TGF-β 可直接激活 TGF-β/Smad 经典通路,也可通过上调乳糖凝集素-1(galectin-1,Gal1)间接激活此通路,此外还可激活蛋白激酶 B(AKT)和细胞外信号调节激酶(ERK)通路调节 α-SMA 的表达[10~12]。此外,人肝细胞生长因子(hepatocyte growth factor,HGF)、血小板衍生因子 (platelet-derived growth factor,PDGF)、成纤维细胞生长因子 2(fibroblast growth factor 2,FGF-2)、结缔组织生长因子(onnective tissue growth factor,CTGF)、血管内皮生长因子(vascular endothelial growth factor,VEGF)、纤维蛋白原样蛋白 2(fibrinogen.1ikeprotein2,FGL2)、可溶性癌胚抗原(soluble carcinoembryonic antigen,sCEA) 以及血管生长因子(vasohibin-like protein 2,VASH2)等亦可诱导 CAFs 活化[13~16]。Zheng 等[17]发现胰腺癌基质中细胞膜蛋白 CD146 的下调亦可刺激 NF-κB 信号而促进 CAFs 活化,进而诱导胰腺癌的进展。

2.2 炎症因子诱导 CAFs 活化

炎性细胞因子,如趋化因子(chemokine,CXL)、白介素(interleukin,IL)、干扰素(interferon,IFN)以及肿瘤坏死因子(tumor necrosis factor,TNF)等,可由基质细胞和癌细胞产生,不仅调控 CAFs 活化,还可直接或间接促进肿瘤生长[18]。TNF-α 可刺激 CAFs 释放趋化因子配体 2 (chemokine ligand 2,CCL2)、CCL5、CCL7、CXCL8、CXCL12、CXCL14、CXCL16 等,经黏着斑激酶(focal Adhesion Kinase,FAK)传导后激活 ERK 和 AKT 信号通路并增强了下游 β-连环蛋白(β-catenin)和 NF-κB 的转录活性,后者又可以诱导 CAFs 活化,进而促进肿瘤的发生发展[19~21]。IL-1β、IL-6 (LIF)、IL-8 或 IFN, 则可与 CAFs 表面的 IL6-R、CXC 受体 2(CXC receptor 2,CXCR2)等受体结合, 激活 Janus 激酶 1/信号转导与转录激活子 3(janus kinase/signal transducer and activator of tranions,JAK1/STAT3)、Rho GTP 激酶 A(Rho GTPase A,RhoA)/Rho 激酶 (Rho-associated kinases,ROCK) 或 AKT/ERK1/2 信号通路,诱导 CAFs 活化、提高肌球蛋白的收缩性及 ECM 的重塑[22~24]。

2.3 转录因子诱导 CAFs 活化

许多转录因子都可作为 CAFs 活化的介质,如 Notch 信号传导的转录抑制因子(CBF1/RBP-Jκ/suppressor of hairless/LAG-1,CSL)和重组人活化转录因子 3(recombinant human activating transcription factor-3,ATF3)均是 CAFs 活化的负性调控因子[25]。有研究发现,CSL 下调联合 p53 下调或激活胶质瘤相关转录因子(Gli2),均可诱导 NFs 转化为 CAFs[26,27]。程序性细胞死亡因子 4(programmed cell death protein 4,PDCD4)是 CSL 抑制复合物的一部分。Jo 等[28]发现 PDCD4 作为为微小 RNA21(miR-21)的靶基因,参与了 TGF-β1 诱导的癌基质中的肌成纤维细胞的分化。

扭转相关蛋白 (twist-related protein 1,Twist1)和配对相关同源框 1(aired related homeobox 1,Prrx1)是正性调控 CAFs 活化的特异性转录因子, 肌腱蛋白 C (tenascin C,TNC) 是一种糖蛋白, 参与形成 ECM。Yeo 等[29]研究证实 Twist1-Prrx1-TNC 三者可形成“正反馈环”诱导 CAFs 的活化。此外,间充质干细胞(mesenchymal stem cell,MSC)表达的细胞表面分子 CD44 也可通过上调 Twist 转录诱导 CAFs 的活化[30]。近年又发现,豆蔻酰化富含丙氨酸的 C 激酶底物 (myristoylated alanine-rich protein kinase C substrate,MARCKS)、叉头框 F1 基因(forkhead Box F1,FoxF1)以及锌指转录因子(snail 1)等转录因子,通过抑制细胞衰老和激活 AKT/Twist1 信号上调 α-SMA 和 PDGFRα, 促进 FGF-2、HGF 等旁分泌因子的释放,诱导 CAFs 活化并促进肿瘤进展[31~33]。转录因子在 CAFs 活化中扮演者不可忽视的作用, 临床可作为治疗肿瘤的靶点。

2.4 缺氧、活性氧物质、自噬可促进 CAFs 活化

肿瘤发展过程中，由于血供不足往往在肿瘤微环境中出现缺氧区域[34]。缺氧主要通过低氧诱导因子-1α (hypoxia inducible factor 1 subunit alpha，HIF-1α) 激活 G 蛋白介导的丝裂原活化蛋白激酶(mitogen-activated protein kinase，MAPKs) 通路来诱导 CAFs 活化及 ECM 的重塑，反过来促进肿瘤侵袭及血管形成[35,36]。

肿瘤产生的活性氧 (reactive oxygen species，ROS) 可引起 CAFs 细胞内氯通道蛋白 4(chloride intracellular channel 4，CLIC4)及 CCL2 的表达，激发 TGF-β1 及 NF-κB 和 STAT3 的表达，最终诱导 CAFs 活化[37,38]。

自噬作用也被发现参与 CAFs 的活化。Martinez 等[35,39]发现 HIF-1α 和 NF-κB 可驱动 CAFs 中微囊蛋白的自噬降解，进而引起 α-SMA 表达的上调、ECM 组分的沉积和 TGF-β 信号的激活。此外还发现，饥饿可通过自噬诱导成纤维细胞向肌成纤维细胞转化，表现为 α-SMA 合成和应激纤维的表达增加[40]。

2.5 非编码 RNA 及外泌体可诱导 CAFs 活化

微小 RNA(microRNA，miRNA)是一类小的非编码调节 RNA，在各种生理过程中起重要作用，越来越多研究发现 miRNA 与 CAFs 的活化相关。如 Let-7b、miR-6780b、miR-143、miR-133b、miR-155、miR-200s 等 miRNA 可通过激活 NF-κB 级联反应、TGF-β/Smad 等通路，诱导 CAFs 活化、ECM 重塑及基质炎症反应，促进肿瘤的发生发展[16,41,42]。

长非编码 RNA(long non-coding RNA，lncRNA)属于超过 200 个核苷酸的一类非编码 RNA。Ding 等[43]发现 Lnc-CAF/IL-33 可将 NFs 活化为 CAFs，后者促进口腔鳞癌的发展。此外，Zhao L 等[44]发现卵巢癌细胞内的 LINC00092 可与 6-磷酸果糖-2-激酶/果糖-2,6-双磷酸酶 2(6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2，PFKFB2)相互作用，通过糖酵解来维持 CAFs 活化，该研究尚在进一步完善中。

外泌体是细胞分泌的直径为 30~100nm 的囊泡，其中包含有 DNA、RNA、蛋白质、脂质等多种生物分子。Giusti 等[45]证实外泌体可以释放细胞外囊泡(extracellularvesicle，EV)诱导 CAFs 活化。该小组进一步研究发现，EV 内携带的 miR-1247-3p、miR-27a 等可通过 β1-Integrins-GF-κB 信号通路等机制，诱导 CAFs 活化并促进肿瘤细胞的增殖，运动和转移[46,47]。

2.6 ECM 及机械力诱导 CAFs 活化

ECM 主要由纤维蛋白和蛋白多糖组成，还包括赖氨酰氧化酶(lysyloxidase，LOX)、基质金属蛋白酶(matrix metalloproteinase，MMPs)及金属蛋白酶组织抑制因子 (tissue inhibitor of metalloproteinases-1，TIMP)等，其中胶原蛋白是 ECM 蛋白的主要成分。CAFs 是 ECM 的重要来源，ECM 结构的改变可诱导 CAFs 细胞骨架重组和信号传导，进一步调节 ECM 组分和重塑酶的合成[48]。MMPs 和 TIMP 是 ECM 降解和合成中的重要因素，研究发现前列腺癌基质中的 TIMP-1 与 CAFs 上的 TIMF-1 受体(CD63)结合后可激活 ERK1/2 激酶，进而促进 CAFs 的增殖和迁移[49]。

TME 内机械力的改变以及细胞外刺激的信号，可由黏着斑激酶与整合素结合向胞内传递，通过激活磷脂酰肌醇-3 激酶 (phosphatidylinositol 3-kinase，PI3K)和 MAPKs 通路、RhoA/ROCK 通路或 YAP(yes-associated protein) 转录因子等诱导 α-SMA 等的表达，并调控肌球蛋白轻链 9 (myosin light chain 9，MYL9)/ 肌球蛋白调节性轻链 (myosinregulatory light chain，MLC2) 的蛋白表达水平，导致 ECM 重塑和 CAFs 活化[50,51]。

2.7 放射线诱导 CAFs 活化

放射线也能活化 CAFs，促进其增殖、迁移。Hellevik 等[52]使用大剂量 X-ray(18Gy×1f)照射人肺癌 CAFs 后，发现其上清中细胞因子分泌谱发生了明显变化。Wang 等[53]进一步证实 CAFs 可以通过自噬促进放疗后肿瘤的复发。Tommelein 等[54]使用放射线照射结直肠癌后可引起 CAFs 中 DNA 损伤、p53 基因活化、细胞周期停滞和胰岛素样生长因子-1(insulin-like growth factor 1，IGF1)的分泌，并通过旁分泌 IGF1/IGF1R 信号促进癌细胞的生长。然而也有不同的观点，Maria 等发现 CAFs 在辐射暴露后丧失了在体内的致瘤能力。虽然有关放疗和 CAFs 活化之间的关系尚有矛盾之处，然而目前大多数研究仍认为放疗后的 CAFs 可促进肿瘤的发生发展。

3 结 语

TME 改变为 CAFs 的活化提供了有利的条件。TME 中的免疫细胞、炎性细胞、基质细胞、肿瘤细胞

等,可通过细胞因子、炎性因子、缺氧、活性氧、自噬作用、外泌体等影响 CAFs 的表型,诱导其活化,进而导致肿瘤基质结构的变化,这两种改变又互为因果,在肿瘤的发生、发展、转移和治疗疗效中起重要作用,然而有关 TME 对 CAFs 活化的机制研究有待进一步深入[48]。

有关 CAFs 未来的研究,我们提出以下几点展望:(1)TME 中的细胞因子和 CAFs 活化之间的研究除 TGF-β 外,大多数的细胞因子的作用仍停留在现象阶段,内部机制还需深入探究;(2)CAFs 内某些基因的表达与 CAFs 活化之间的关系及机制研究较少,能否通过二、三代测序等技术深入探讨?(3)外泌体囊泡可携带各种非编码 RNA,如 miRNA、lncRNA 及环状 RNA(circular RNAs,circRNA)等,尤其近年较热门的 circRNA 和 lncRNA 与 CAFs 活化的关系研究较少,后续工作有待深入;(4)放疗后肿瘤复发是临床常见的现象,是否与 CAFs 有关?相关性有多大?目前大多数研究集中在 CAFs 经辐射后通过旁分泌或自噬作用,促进肿瘤复发的机制而有关放射线如何调控 CAFs 活化的内部机制研究较少,亦有待进深入探索。

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