

肿瘤相关成纤维细胞在肿瘤中作用的研究进展

Research progress on the role of CAFs in tumors

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[摘要] 肿瘤是由肿瘤细胞及其周围基质细胞和非细胞组分构成的复合体,肿瘤的发生发展是肿瘤细胞与其微环境相互促进、共同演化的一个动态过程,肿瘤微环境在肿瘤的生长转移过程中发挥至关重要的作用。肿瘤相关成纤维细胞(cancer associated fibroblasts, CAFs),作为肿瘤微环境中最主要的组成成分之一,能够分泌多种细胞因子,从而促进肿瘤血管生成,诱导肿瘤细胞发生上皮间质转化,打破组织细胞之间的稳态,使微环境更有利于肿瘤生长。CAFs对乳腺癌、肝癌、胃癌、结直肠癌、卵巢癌、肺癌等多种常见癌有促进作用。本文就近年来CAFs对肿瘤的发生发展、耐药及其他方面的影响及作用机制加以讨论,以期对癌症的治疗提供新的思路。

[关键词] 肿瘤相关成纤维细胞;肿瘤;增殖;侵袭;转移;耐药

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据全国肿瘤登记中心统计,2013年我国新发恶性肿瘤病例约368.2万例,死亡病例222.9万例,全国恶性肿瘤发病率为270.59/10万,死亡率为163.83/10万^[1],占死亡原因的第三位。恶性肿瘤严重威胁人类健康,且其发病率呈逐年上升的趋势。肿瘤的发生发展不仅仅是肿瘤细胞自身癌基因或抑癌基因的改变,肿瘤微环境在肿瘤的发生发展中也发挥着巨大作用。早在1889年就有学者通过对乳腺癌患者尸解数据分析提出“种子与土壤”假说,认为肿瘤转移有器官特异性,只有土壤(微环境)适合种子(肿瘤)才能生长,说明肿瘤与其微环境之间存在相互协同作用^[2]。肿瘤微环境包括细胞及细胞外基质,有形成分主要是细胞组分,包括免疫细胞、内皮细胞、成纤维细胞等,其中肿瘤相关成纤维细胞(cancer associated fibroblasts, CAFs)是肿瘤微环境中最主要的基质细胞,占到肿瘤组织细胞总数的50%左右^[3]。CAFs能够与肿瘤细胞通过直接接触或以旁分泌的方式分泌多种细胞因子和代谢产物而促进肿瘤的发生发展,在肿瘤的生长、转移、耐药及治疗抵抗等方面均发挥重要作用,是近期肿瘤研究的热点之一。

1 CAFs的来源与特征

肿瘤组织中的成纤维细胞统称为CAFs。与普通成纤维细胞(normal fibroblasts, NFs)相比,CAFs具有普通成纤维细胞的一切特性,但比普通成纤维细胞更活跃、增殖速度更快,能分泌更多的细胞因子、基质蛋白及免疫调节因子等。

1.1 CAFs的来源

关于CAFs的来源一直以来都众说纷纭,目前学者们认为CAFs主要有以下几种来源:(1)由肿瘤组织中的成纤维细胞直接转化而来。肿瘤细胞可通过某些方式作用于肿瘤组织中的NFs,使其转化为CAFs,这一说法得到广泛认同并已被大量学者验证。WEN等^[4]发现在前列腺癌中在转化生长因子- β (transforming growth factor- β , TGF- β)的作用下可使NFs转化为CAFs。(2)由骨髓间充质干细胞(BM-MS)和造血干细胞(bone marrow hematopoietic stem cells, BM-HSC)转化而来。有学者^[5]证实在炎症诱导的胃癌动物模型中至少20%的CAFs起源于MSC,HSC是新发现的一种CAFs的来源,HSC起源的循环前体成纤维细胞(CFP),可以优先迁移并分化为CAFs以响应肿瘤,充当骨髓和肿瘤之间的媒介^[6]。(3)上皮性肿瘤细胞通过上皮-间质转化(epithelial-mesenchymal transition, EMT)直接转化为CAFs。但是目前这一说法存在争议,有研究^[7]发现,在适当条件下乳腺癌细胞可通过EMT最终转化为CAFs,但是在喉癌动物模型中并未观察到这一现象^[8]。另外,

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CAFs还可由脂肪干细胞^[9]、内皮细胞^[10]转化而来。

1.2 CAFs的特征

随着人们越来越意识到CAF在肿瘤中的重要作用,全面认识CAF并对其进行深入研究就显得尤为重要。目前关于CAF没有精确的定义,也没有发现其独特的鉴定标记。CAF曾经被定义为 α -平滑肌肌动蛋白(α -smooth muscle actin, α -SMA)阳性的瘤周成纤维细胞,但是 α -SMA并不是CAF特异的标志物,在NFs中也表达 α -SMA^[11]。目前鉴定CAF的主要手段为联合检测几个诸如 α -SMA、FAP、CD10、P53、MMPs等在CAF中表达量较高的分子^[12]。

2 CAFs与肿瘤的发生发展

2.1 CAFs协助肿瘤细胞免疫逃逸

肿瘤是机体正常细胞恶变的产物,在免疫学上的突出特点是具有不同于正常细胞的抗原标志。正常情况下,机体免疫系统中的T细胞、NK细胞、巨噬细胞等对肿瘤均具有杀伤作用,可以有效的监控和排斥癌细胞,但是由于某些因素的影响使一些癌细胞可以逃避免疫监视,继续增殖,最终导致肿瘤的发生^[13]。CAF具有免疫调节作用,可通过分泌多种蛋白质、细胞因子、趋化因子等调控肿瘤微环境(tumor microenvironment, TME)的免疫系统,从而促进肿瘤的生长^[14]。CAF可向TME中分泌大量IL-6,分泌量约为NFs的100倍,IL-6可阻止抗原呈递细胞树突状细胞成熟,诱导单核细胞变为肿瘤相关巨噬细胞,并激活瘤细胞、肥大细胞和肌成纤维细胞促进他们的增殖和迁移,引起炎症反应造成组织重构,炎症反应又可促进肌成纤维细胞的增殖导致更多IL-6的分泌^[15]。CAF产生的诸如TGF- β 、白细胞介素-10(interleukin-10)、血小板源性生长因子(platelet-derived growth factor, PDGF)以及免疫抑制相关因子可诱导抑制性细胞亚群的产生,从而抑制T细胞等免疫细胞的功能^[16]。

2.2 CAFs促进肿瘤增殖

无限增殖是恶性肿瘤的重要标志,CAF可以促进肿瘤细胞的增殖。在肺癌中,用从肺癌组织中分离出的CAF的细胞培养上清刺激肺癌细胞系可明显提高癌细胞生长速度,将CAF与肺癌细胞系(A549)混合后进行裸鼠皮下注射,发现肿瘤生长速度明显快于单种A549组^[17]。CAF可以通过分泌多种生长因子和细胞因子,如肝细胞生长因子(HGF)、表皮生长因子(EGF)、胰岛素样生长因子(IGF)、基质细胞衍生因子(SDF-1)等,激活下游信号通路,进而促进癌细胞增殖^[18]。在卵巢癌中,CAF分泌的HGF可作用于MET受体和下游信号蛋白PI3K/AKT以及葡萄糖调节蛋白78(GRP78)等调节癌细胞的增

殖和耐药^[19]。此外,肿瘤细胞还可通过与CAF相互作用,刺激CAF分泌各种生长因子,形成正向反馈调节。BAE等^[20]在口腔癌中研究发现,癌细胞通过分泌IL-1 α 刺激CAF增殖和分泌生长因子,从而促进癌细胞的生长。

2.3 CAFs促进肿瘤侵袭和转移

肿瘤的转移是一个多步骤、复杂的过程,主要为瘤细胞间黏附性降低肿瘤细胞脱离原发部位,通过降解细胞外基质,基底膜侵入毛细血管或毛细淋巴管,随血流达到其他部位定植的过程。以前普遍认为肿瘤的增殖、侵袭和转移是肿瘤进展的结果。然而,目前研究表明,不仅是癌细胞自身的原因,CAF可通过分泌多种生长因子、趋化因子以及促进细胞外基质(extracellular matrix, ECM)重构等促进癌细胞的增殖、侵袭和转移^[21]。

2.3.1 促进肿瘤细胞发生上皮间质转化 转移的发生首先是细胞间黏附性的改变,瘤细胞间黏附性的缺失使瘤细胞更易脱离原发部位,向其他部位转移。EMT是一种普遍存在于哺乳动物体内的、具有高度保守特性的生物学过程^[22]。其主要变化为细胞间黏附分子如E-钙黏蛋白(E-cadherin)表达降低,而一些间质表型增强,如N-钙黏蛋白(N-cadherin)、波形蛋白(Vimentin)表达增多,从而使细胞由排列紧密的上皮细胞变为结构松散的间质细胞,使细胞间黏附力减弱,运动能力增强^[23-25]。CAF可通过多种途径引起肿瘤细胞发生EMT,在乳腺癌中,CAF可通过分泌TGF- β 诱导乳腺癌细胞发生EMT,并上调转移相关基因MMP2、MMP9的表达,从而促进癌细胞转移,抑制TGF- β 通路可消除CAF对癌细胞侵袭转移的促进作用^[26]。在胃癌、结直肠癌和膀胱癌中也发现CAF分泌的TGF- β 有类似作用^[27-30]。在肺癌中发现,CAF可向上清中分泌IL-6使肺癌细胞发生EMT,并上调转移相关基因MMP2、MMP9、VEGF等的表达,从而发挥促转移作用,在CAF的上清中加入IL-6中和抗体可显著削弱CAF的促转移作用^[17]。

2.3.2 促进肿瘤细胞外基质重塑 细胞外基质(ECM)的结构特征对肿瘤的侵袭转移起着关键作用,ECM刚性增加是大多实体肿瘤的特征^[31],CAF可通过多种方式使ECM重塑,改变其结构和硬度使肿瘤更容易发生侵袭转移^[32-33]。入侵周围组织和降解细胞外基质是肿瘤脱离原发部位的第一步,CAF可通过表达基质金属蛋白酶(matrix metalloproteinase, MMPs)、胶原酶等使ECM降解^[34]。STANISAVLJEVIC等^[35]发现,CAF可通过TGF- β /Snail/RhoA通路提高ECM硬度和促进纤维导向的异质性,从而促进肿瘤细胞的侵袭和转移;CALVO等^[36]研究发现

CAFs中高表达YAP转录因子,YAP可调节ANLN/DIAPH3等多种细胞骨架调节因子和MYL9/MLC2等蛋白的表达水平使ECM硬度增加,而ECM的僵硬增加又可进一步激活YAP,如此形成一个正反馈调节,可极大促进肿瘤细胞转移。

2.3.3 促进肿瘤血管生成 血管生成能力被认为是肿瘤恶性的标志,因为血管是肿瘤转移的通道,丰富的血管能为瘤组织提供充足的氧气和营养成分,促进瘤组织的生长。血管内皮细胞生长因子(vascular endothelial growth factor, VEGF)在促进血管生成方面具有重要作用,许多研究^[37-39]表明VEGF与肿瘤的生长、转移及患者预后相关。在结肠癌中癌细胞分泌VEGF非常微小,CAFs可通过分泌大量IL-6刺激结肠癌细胞分泌VEGF,而且结肠癌细胞可与肿瘤微环境相互作用,促进NFs转化为CAFs从而正向调节IL-6的分泌,进一步使VEGF分泌增多促进肿瘤血管生成。体内实验证实,与靶向癌细胞相比,靶向基质组织的IL-6受体抗体显示更高的抗肿瘤活性^[40]。此外,CAFs还可通过分泌PDGF、HGF、TGF- β 等促进肿瘤血管生成^[41]。

2.4 CAFs促进肿瘤耐药

耐药是药物治疗清除癌细胞的一大障碍,其主要机制包括药物吸收减少和外排增多,药物所针对的靶点基因突变,DNA修复能力增强及抗凋亡信号通路激活等^[42]。近来研究发现,肿瘤细胞耐药很大程度上是由于瘤细胞与其微环境之间的相互作用,CAFs可促进肺癌^[43]、乳腺癌^[44]、结直肠癌^[45]、胰腺癌^[46]等多种癌症耐药。在肿瘤中存在一群可以自我更新和分化的细胞,称为肿瘤干细胞(cancer stem cells, CSCs),CSCs在肿瘤的发生、发展和耐药中起重要作用^[47]。在结直肠癌中,CAFs可分泌IL-17A作用于CSCs上的IL-17A受体,使CSCs维持其干细胞特性并上调NF- κ B的表达,导致癌细胞耐药^[48]。CAFs还可通过分泌TGF- β 使肿瘤细胞发生EMT从而获得CSCs特性,进而发生耐药^[26, 49]。CAFs可通过分泌HGF激活肺癌细胞中Met/PI3K/AKT通路,上调葡萄糖调节蛋白(GRP78)的表达,从而抑制紫杉醇引起的细胞凋亡^[50]。XIA等^[51]构建了针对成纤维细胞活化蛋白(FAP)的DNA疫苗,可将有效杀死CAFs,从而降低肿瘤组织中I型胶原蛋白的表达,成功地抑制了小鼠乳腺癌原发肿瘤细胞的生长和转移。

2.5 其他作用

在结肠癌中,将癌细胞与CAFs共培养可诱导CAFs发生氧化应激和自噬水平的增加,CAFs发生氧化应激可引起结肠癌细胞发生糖酵解酶表达增加,KREB-S循环酶减少等代谢水平改变;CAFs自噬的

增加可提供营养物质如丙酮酸/乳酸来维持癌细胞的生存,促进癌细胞增殖和/或保护癌细胞抵抗氧化损伤^[52]。CAFs与肿瘤细胞间的相互作用对肿瘤放疗也有影响。与CAF条件培养基单独预处理相比,来自CAFs和HeLa细胞混合培养的条件培养基的预处理对于增强经照射的HeLa细胞的增殖和存活具有更强的作用^[53]。CAFs还可通过高表达LOXL2^[54]、CX-CL1^[55]等对癌症患者预后产生影响。

3 CAFs与肿瘤的治疗

与肿瘤细胞相比,CAFs具有遗传稳定性,产生耐药性的可能性较小,靶向其治疗耐药性和肿瘤复发风险较低等特点,因此同时靶向肿瘤细胞和CAFs的组合疗法有望成为提高治疗效果并克服治疗抗性的新策略。目前许多针对CAFs的抗癌药物已经处于临床前期研究或临床试验阶段,这些药物主要通过靶向CAFs特异的表面分子直接损伤CAFs或抑制CAFs分泌促癌因子和参与的信号通路从而抑制癌细胞的增殖、侵袭转移和耐药等。LRRC15在多种实体瘤细胞和实体瘤的CAFs中表达,ABBV-085是单甲基奥瑞他汀E(MMAE)的抗体-药物缀合物,可直接靶向LRRC15,表现出针对LRRC15基质阳性/癌症阴性(或阳性)癌症模型强大的临床前疗效^[56]。小分子二肽基肽酶抑制剂PT-100可通过靶向成纤维细胞活化蛋白(FAP)抑制CAFs。在结肠癌小鼠模型中,联合使用化疗药奥沙利铂和抑制剂PT-100可明显提高瘤组织的化疗敏感性,减少促肿瘤细胞的募集和血管生成^[57]。吡非尼酮(PFD)是一种可靶向CAFs的抗纤维化药物和TGF- β 拮抗剂,研究^[58]发现,在乳腺癌动物模型中联用PFD与多柔比星可有效抑制肿瘤生长和肺部转移。因此,将化疗药与靶向CAFs药物联合使用将是一个很有前景的肿瘤治疗策略。

4 结 语

综上所述,CAFs可分泌多种因子促进肿瘤的发生发展、侵袭和转移,协助肿瘤细胞逃避机体免疫系统的打击,增强肿瘤对放、化疗的抵抗,并且对患者预后也有重要影响,因此靶向CAFs可能成为癌症治疗的一个新思路。但是由于来源不同、表型不同,CAFs在不同肿瘤及同一肿瘤的不同阶段发挥的作用也不尽相同。因此,未来尚需探究在不同类型癌症及癌症各时期CAFs的功能。

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