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基于纳米药物调控肿瘤成纤维样细胞用于肿瘤治疗的研究进展

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摘要 肿瘤成纤维样细胞是肿瘤间质内数量最多的细胞组分. 不同类型实体肿瘤的成纤维样细胞来源有所不同, 但均对肿瘤微环境的塑造起到至关重要的作用. 其可以大量分泌细胞外基质, 促进肿瘤血管新生, 阻碍药物输运, 阻止免疫细胞的肿瘤浸润, 增强肿瘤的化疗及免疫治疗耐受等. 因此, 针对肿瘤成纤维样细胞促进肿瘤发展的功能进行调控, 可重塑肿瘤微环境, 提高肿瘤的治疗效果. 本文简要介绍了肿瘤成纤维样细胞在肿瘤微环境中的重要作用, 并重点介绍基于纳米药物精准调控肿瘤成纤维样细胞的研究进展, 为继续开发基于调控肿瘤成纤维样细胞的肿瘤治疗策略提供思路.

关键词 肿瘤成纤维样细胞, 纳米药物, 肿瘤微环境, 精细调控, 肿瘤治疗

肿瘤组织具有多种细胞成分和非细胞成分组成的复杂微环境. 其中, 肿瘤相关成纤维细胞(cancer-associated fibroblasts, CAFs)为最主要的间质细胞[1], 其通过分泌各种细胞因子、细胞外基质成分、蛋白酶等塑造肿瘤微环境(tumor microenvironment, TME)[2]. CAFs的来源多样, 可由肿瘤生长组织中的固有成纤维细胞或星状细胞(胰腺、肝脏中)在转化生长因子-β(transforming growth factor-β, TGF-β)刺激下分化而成, 也可由肿瘤组织中的上皮细胞、内皮细胞、骨髓间充质干细胞(mesenchymal stem cell, MSC)等细胞分化而成[3], 因此, 我们认为, 将CAFs定义为"肿瘤成纤维样细胞"(tumor fibroblast-like cells, TFLCs)更为准确.

TFLCs在塑造TME的同时, 形成肿瘤组织生理屏障[4,5], 会阻止药物[6]、免疫细胞[7]发挥作用. 因此, 对TFLCs进行调控, 可有效抑制肿瘤发展, 提高治疗效果. 合理设计纳米药物, 然后将药物有效递送至TFLCs, 进而从基因及分子水平调控TFLCs的功能.

本文将简要回顾TFLCs的来源、功能, 着重从三个方面(直接杀伤TFLCs、调控TFLCs功能、调控TFLCs信号通路)介绍利用纳米药物调控TFLCs的策略及其提高肿瘤治疗效力的研究进展(图1), 分析当前策略面临的挑战, 并提出潜在的治疗方案, 为实体肿瘤的治疗提供有效的参考策略.

1 肿瘤成纤维样细胞的来源与功能

尽管大部分TFLCs在形态上比较相似, 也伴有分子水平的α-平滑肌肌动蛋白(α-smooth muscle actin, α-SMA)、成纤维细胞活化蛋白α(fibroblast activation protein, FAP-α)等的高表达, 但其来源有诸多途径. 肿瘤细胞通过释放TGF-β激活肿瘤发生器官或组织中固有的

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Zhang S H, Yang H R, Zhao Y, et al. Research progress on the nanodrug mediated regulation of tumor fibroblast-like cells for tumor therapy (in Chinese). Chin Sci Bull, 2023, 68: 4373–4382, doi: 10.1360/TB-2023-0588

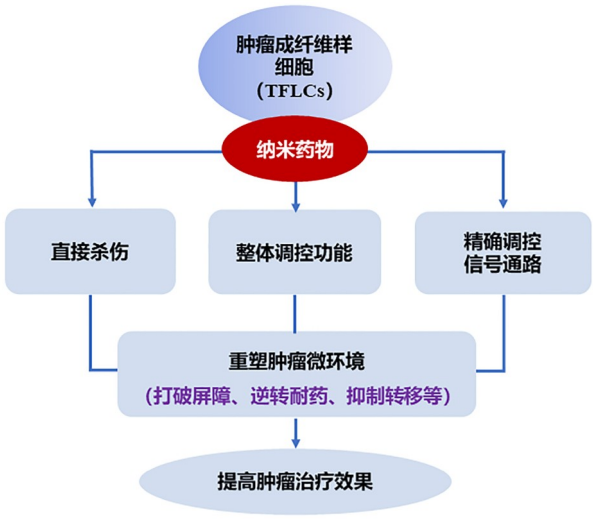

图 1 文章思路图. 利用纳米药物对肿瘤成纤维样细胞进行调控、重塑肿瘤微环境、提高肿瘤治疗效果的策略

Figure 1 Schematic summary of the review. Strategies of using nanodrugs to regulate TFLCs, reshaping the tumor microenvironment and improving the therapeutic efficacy

成纤维细胞, 后者逐渐表现出CAFs的行为和功能; 在肝癌和胰腺导管腺癌中, 肝星状细胞(hepatic stellate cells, HSCs)及胰腺星状细胞(pancreatic stellate cells, PSCs)被激活后, 转变为成纤维样细胞表型, 且可通过旁分泌及自分泌的TGF-β通路持续活化, 进行大量增殖; 此外, 肿瘤组织中的上皮细胞、内皮细胞以及招募过来的成纤维前体细胞等细胞也可分化为TFLCs[3].

TFLCs伴随肿瘤发生发展的各个阶段, 其主要功能为塑造TME, 但不同肿瘤类型、不同亚型TFLCs的功能却存在差异. 例如, 通过对乳腺癌、胰腺癌的单细胞测试结果分析, TFLCs分为三种亚群, 分别为细胞外基质(extracellular matrix, ECM)重塑/肌纤维母细胞性CAFs、促炎和免疫调节CAFs、抗原呈递CAFs[8]. TFLCs还会形成生理屏障, 阻止药物及免疫细胞对肿瘤细胞的攻击, 促进血管新生, 为肿瘤营造转移路径. 还有研究表明, TFLCs在肿瘤免疫耐受方面起到重要作用. 例如, TFLCs能分泌斯钙素1(staniocalcin-1, STC-1)[9], 这种糖蛋白可以通过诱捕钙网蛋白(calreticulin, CRT)损害APC的吞噬作用并抑制T细胞活化[10]; FAP-α阳性的CAFs驱动免疫抑制并对抗程序性死亡受体-配体1(programmed death-ligand 1, PD-L1)免疫治疗产生耐受性[11]. 我们将报道较多的TFLCs功能归结至表1[4,5,7,12~26].

近年来, TFLCs引发的肿瘤耐药性受到越来越多的关注. 一方面, 其物理屏障作用阻止药物渗透; 另一方面, 药物治疗及免疫治疗会引发TFLCs基因表达谱变化. 例如, Kim等人[27]发现化疗诱导胰腺导管腺癌中胎盘生长因子(placental growth factor, PlGF)/血管内皮生长因子(vascular endothelial growth factor, VEGF)上调, 直接激活TFLCs产生ECM, 导致了结缔组织增生, 促进了纤维化. 胰腺癌TFLCs分泌趋化因子CXC配体12(chemokine (C-X-C motif) ligand 12, CXCL12), 使肿瘤细胞抗凋亡蛋白Bcl-2和存活蛋白上调从而产生耐药性[28,29]; 食管鳞癌TFLCs分泌的白介素-6(interleukin, IL-6)也通过相似的机制在耐药中发挥作用[30]. 近期研究发现, TFLCs的外泌体也能够促进耐药的发生, 例如: 晚期头颈癌中, TFLCs产生的外泌体中含有miR-196a, 其通过靶向肿瘤细胞的CDKN1B和ING5, 赋予了肿瘤细胞对顺铂的耐药性[31]. 在基因层面, 晚期PDAC中的TFLCs高表达circ FARP1, 这种特异性的环状RNA可以通过LIF/STAT3轴来促进吉西他滨的耐药[32]. 关于TFLCs耐药的功能归纳在表2[33~45].

关于TFLCs的起源与功能仍不断被挖掘, 为人类更好地认知恶性肿瘤的发生及演化提供了线索.

2 纳米药物对肿瘤成纤维样细胞的调控

TFLCs在肿瘤发展中发挥着诸多重要功能. 因此, 调控其功能, 切断其与肿瘤细胞的交互, 抑制肿瘤生长, 可以为肿瘤的治疗提供辅助策略. 由于大量TFLCs分布于肿瘤血管周围, 纳米药物从肿瘤血管渗出, 可能会先接触到TFLCs, 为利用纳米药物调控TFLCs提供了相对便利的条件. 在此部分内容中, 我们将介绍近些年报道的利用纳米药物调控TFLCs的代表性工作.

2.1 对肿瘤成纤维样细胞的杀伤策略

2013年, Ji等人[46]构建了FAP-α响应的铁蛋白纳米荧光探针, 对CAFs与肿瘤细胞共接种的前列腺癌肿瘤模型实现了快速、特异性成像, 拉开了利用纳米技术对肿瘤间质细胞进行调控的序幕. 同期, Miao等人[6]发现纳米药物进入肿瘤后会被血管周围的间质细胞阻碍, 经鉴定, 这类细胞为CAFs. 因此, Huang与Nie团队[6,47~49]均着力设计纳米药物, 突破CAFs屏障. Ji等人[47]以CAFs上的FAP-α作为靶点, 设计了多个装载化疗药物的多肽载体, 对CAFs进行杀伤, 可实现化疗药物在肿瘤组织中更高效地渗透, 显著提高了化疗药物的效力. Kim等人[48]和Banerjee等人[49]则发现Sigma受体可作为CAFs的特异靶点, 设计纳米药物靶向此受体, 实现对

表 1　TFLCs的功能

Table 1　Functions of TFLCs

功能	肿瘤类型	机制	参考文献
促进血管生成	乳腺癌(MCF-7)	分泌促血管生成物质CXCL12将内皮祖细胞募集到肿瘤中	[12]
	结肠癌(HCT116)	分泌促血管生成物质WNT2驱动病理性血管生成	[13]
	乳腺癌(SUM1315、168FARN、4T1、MDA-MB-468)	表达Twist1诱导CCL2分泌, 募集巨噬细胞促进血管生成	[14,15]
促进肿瘤增殖	卵巢癌(SKOV3ip1)	利用p38调节细胞因子在癌细胞中调动糖原促进肿瘤生长	[16]
	乳腺癌(MDA-MB-231和MCF7)	分泌的外泌体miR-500a-5p通过与泛素特异性肽酶28结合促进增殖	[17]
	食管癌(EC-18和KYSE30)	外泌体的miR-3656下调ACAP2, 通过AKT和β-catenin信号通路促进肿瘤生长	[18]
促进肿瘤转移	上皮性肿瘤(SCC12、A431)	通过蛋白间的物理相互作用促进侵袭	[19,20]
	前列腺癌(LN-CaP)	分泌GDF15直接影响肿瘤上皮细胞	[21]
	肺癌(A549、SK-MES-1、H661)	分泌IL-6通过STAT3信号通路促进肺癌细胞转移	[22]
	乳腺癌(PyMT 20065)	分泌XII型胶原改变I型胶原组织, 从而创造转移性微环境	[23]
塑造肿瘤微环境	黑色素瘤	分泌更多HA进行基质重塑	[4]
	黑色素瘤(B16F10)、胰腺癌(MH6419)	表达Aft4上调I型胶原蛋白的表达和生物合成	[5]
	乳腺癌(MCF-7)	进行有氧糖酵解, 释放出乳酸, 形成酸性微环境	[24]
免疫抑制	乳腺癌	通过CXCL12-CXCR4轴使单核细胞获得促肿瘤的LAM能力, 以支持免疫抑制微环境	[7]
	胰腺导管腺癌(KPC)	分泌HIF2增加免疫抑制性M2巨噬细胞和调节性T细胞在肿瘤中的聚集	[25]
	食管癌(mEC25)、结肠癌(CMT93)	分泌Wnt2通过SOCS3/p-JAK2/p-STAT3信号级联抑制树突状细胞介导的抗肿瘤T细胞作用	[26]

表 2　TFLCs产生肿瘤耐药的机制

Table 2　Mechanisms of treatment resistance by TFLCs

功能	肿瘤类型	机制	参考文献
分泌因子介导的耐药性	前列腺癌(LN-CaP)	分泌外泌体通过TGF-β通路靶向GREM2促进前列腺癌的化疗耐药性	[33]
	乳腺癌(MCF-7)	癌旁分泌的TGF-β1和PDGF引起CAFs分泌IL-6, 引起化疗耐药性	[34,35]
	食管鳞状细胞癌(ESCC)	分泌IL-6促进食管鳞癌对顺铂耐药	[36]
	胃癌(AGS)	细胞外囊泡衍生的膜联蛋白A6通过激活癌细胞表面的β1整合素诱导耐药性	[37]
	非小细胞肺癌(PC-9和HCC827)	通过HGF/IGF-1/ANXA2/EMT信号传导促进EGFR-TKIs耐药性	[38]
促进癌症干性介导耐药性	结直肠癌(HT-29和SW620)	分泌外泌体Wnt可以诱导分化的CRC细胞重编程为CSCs来促进耐药性	[39]
		分泌HIF-1α和TGF-β2可上调CSC中GLI2的表达, 从而增加干性/去分化和耐药性	[40]
免疫调控耐药性	黑色素瘤、膀胱癌	被不同癌细胞的TGF-β激活, 导致PD-1/PD-L1阻断疗法失败, 引起耐药	[41]
调节代谢诱导耐药性	乳腺癌(MCF-7和MDA-MB-468)	肿瘤细胞激活的PI3K/AKT信号通路诱导胞质GPER转运, 引发CAFs中的有氧糖酵解导致耐药	[42]
	胰腺癌(PANC-1和HEK2935)	胰腺癌细胞中的hENT1通过抑制糖酵解和改变HIF-1α介导的葡萄糖转运来逆转化疗耐药性	[43]
异质性和可塑性引起耐药	乳腺癌(MCF-7和MDA-MB-436)	AUF1的异位表达促进IL-6分泌, 引起上皮-间质转化诱导耐药	[44,45]

CAFs的调控. Li等人[50]开发了用于伊立替康(irinotecan, IRI)和NVP-BGJ398(398)共递送的酸响应脂质体, 同时杀死肿瘤细胞和CAFs. 这种联合消除肿瘤"种子"和"土壤"的策略有利于减少肿瘤血管生成、抑制肿瘤的侵袭和转移. Zhao等人[51]将负载多柔比星(doxorubicin, DOX)的羟乙基淀粉-IR780纳米颗粒(NPs)与Cys-Arg-Glu-Lys-Ala(CREKA)肽偶联, 形成CAFs靶向的纳米药物. 该肽与CAFs上过表达的纤连蛋白特异性结合, 通过化疗和光热疗法的组合减少CAFs, 达到调节肿瘤微环境和消除肿瘤干细胞(cancer stem cells, CSCs)的效果.

2.2 肿瘤成纤维样细胞功能调控

TFLCs为肿瘤生长提供"土壤", 如果可以改变"土壤"的功能, 肿瘤的生长自然会受到抑制. 因此, 科学家们在近年的工作中, 开始尝试不直接杀伤TFLCs, 而是对TFLCs的整体功能进行调控, 从而实现对肿瘤的抑制. Ji等人[52]利用MMP-2响应的脂质体装载抗纤维化药物吡非尼酮, 调控胰腺癌星状细胞, 降低了PSCs分泌的多种ECM组分, 提高了化疗药物吉西他滨在胰腺癌组织中的渗透效率, 从而提高了胰腺癌的化疗敏感性. Han等人[53]设计了一个基于酸敏感PEG化阳离子聚合物(聚乙二醇–C=N–聚乙烯亚胺)包覆的金纳米颗粒, 并利用该系统协同递送全反式维甲酸(all-trans retinoid acid, ATRA, PSCs沉默诱导剂)和靶向热休克蛋白47(heat shock proteins 47, HSP47, 胶原特异性分子伴侣)的siRNA, 从而实现对PSCs的调控. 此纳米递送系统可同时诱导PSCs沉默, 抑制ECM增生, 从而促进化疗药物吉西他滨向胰腺肿瘤的渗透, 显著提高化疗药物的抗肿瘤效果. 其机理示意图如图2所示.

近年来, TFLCs塑造免疫抑制微环境的功能也受到关注. Zuo等人[54]合成了三苯基膦-白藜芦醇前药(TPP-RSV), 清除mtROS, 抑制CAFs、透明质酸和胶原蛋白I的表达, 降低TGF-β的表达, 逆转免疫抑制微环境, 增加细胞毒性T淋巴细胞的浸润, 为抑制恶性乳腺肿瘤的生长和转移提供更深入的治疗方案. Geng等人[55]通过熔融共晶混合物、壳聚糖和抗原质粒的自组装合成了一种温控基因表达纳米系统(TNP@CS-A/pDNA), 将CAFs原位工程化为抗原递呈细胞(antigen presenting cells, APC), "化敌为友", 阻断PD-1/PD-L1通路, 协同促进免疫治疗, 同时避免PD-L1抗体临床应用引起的免疫风暴.

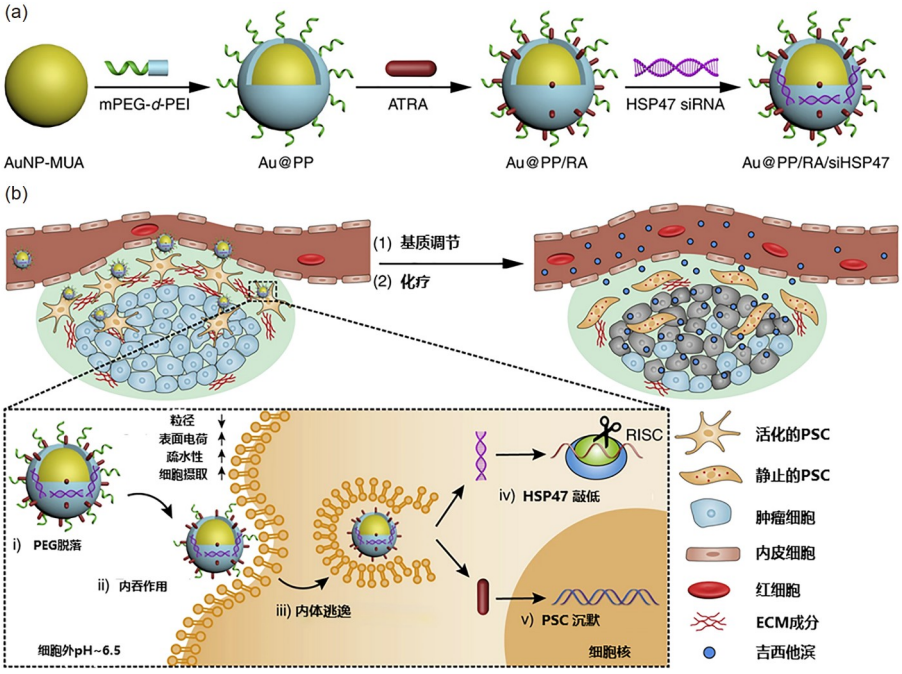

图 2 精准靶向调控TFLCs的协同疗法[53]. (a) 构建了一个基于聚乙二醇化聚乙烯亚胺(PEI)修饰的pH响应型金纳米颗粒体系; (b) 递送全反式维甲酸(ATRA)和靶向热休克蛋白47(HSP47)的siRNA, 抑制PSC活化和ECM增生, 增强抗肿瘤功效

Figure 2 Synergetic therapy for the precise targeting and regulation of TFLCs[53]. (a) Construction of a pH-responsive gold nanoparticle system modified with polyethyleneimine (PEI); (b) delivery of all-trans retinoic acid (ATRA) and small interfering RNA (siRNA) of heat shock protein 47 (HSP47) to inhibit PSC activation and extracellular matrix (ECM) proliferation, enhancing the anti-tumor efficacy

目前, 针对TFLCs进行表型重编程包括基因修饰、表观遗传调节和免疫疗法等方式, 有可能为难治性肿瘤的治疗提供参考方案. TFLCs介导结缔组织增生反应, 松弛素(relaxin, RLN)可以显著改善TGF-β诱导的肿瘤免疫抑制微环境. Zhang等人[56]设计了可以表达RLN的脂质聚γ-谷氨酸/聚合二甲双胍-pRLN纳米颗粒(LPPR), 通过减少促纤维化细胞因子的表达来逆转异常激活的TFLCs, 并消除重塑肿瘤基质微环境的物理屏障, 实现针对结缔组织增生三阴性乳腺癌(triple negative breast cancer, TNBC)模型的免疫检查点阻断治疗的联合方案. Zheng等人[57]基于TNBC患者的剪切波弹性硬度高于非TNBC患者, 设计了TNBC细胞膜修饰的聚交酯酸-乙醇酸(PLGA)纳米颗粒作为肿瘤纳米土壤松动剂, 用特异性递送青蒿琥酯来调节剪切波弹性硬度, 缓解肿瘤缺氧, 放大紫杉醇和PD1抑制剂的抗肿瘤作用, 具有良好的生物安全性和靶向效果.

2.3 基于细胞信号通路靶点的调控

抗体药物、基因药物的发展为肿瘤的精准靶向治疗提供了有力的手段. 针对TFLCs关键信号通路进行阻断, 甚至可以起到“牵一发、动全身”的肿瘤微环境重塑效果. Lang等人[58]将载有CXCL12的siRNA通过多肽自组装载体特异性地递送至CAFs中, 沉默CAFs中CXCL12基因, 从而引发CAFs分泌谱的一系列变化. 这些变化使肿瘤细胞迁移、侵袭和肿瘤血管生成受到明显抑制, 从而抑制了原位前列腺肿瘤的转移. Zhang等人[59]将亲水的RLN模拟肽(B7-33)进行cRGD修饰, 此简单的修饰未影响B7-33的活性, 同时又可保证B7-33有效装载至HUVEC细胞膜制备的纳米颗粒表面(富含整合素蛋白). 以此构建的纳米体系可有效将B7-33递送至肝脏, B7-33通过与肝星状细胞表面RLN受体结合, 阻断TGF-β引起的STAT3通路激活, 阻碍HSCs激活介导的胰腺癌肝转移微环境的塑造, 从而抑制了胰腺癌的肝转移(图3). Zhao等人[60]基于红细胞膜包被的CAFs靶向药物递送系统, 修饰的FnBPA5肽靶向CAFs和ECM的胶原蛋白I和松弛纤连蛋白, 维甲酸会减少CAFs中高尔基体的蛋白质分泌, 可以重编程致密基质并提高Dox在胰腺导管腺癌中的渗透. Feng等人[61]开发了靶向CAFs的可生物降解的聚合物纳米颗粒. 该颗粒负载有肿瘤归巢肽(CREKA肽)和中药α-倒捻子素(α-M), 通过干扰TGF-β/Smad信号传导途径来调节肿瘤微环境, 减少细胞外基质的产生, 提供治疗增生性肿瘤的新选择.

此外, 通过精准靶向调节CAFs对癌细胞的代谢途径也可以改善肿瘤治疗效果. Zang等人[62]通过融合乳腺癌细胞膜(4T1细胞膜)和成纤维细胞膜(CAFs样NIH3T3细胞膜, 称为3T3细胞膜)设计了杂合仿生纳米递送系统. 化疗药物PTX和糖酵解抑制剂PFK15共加载在固体脂质纳米颗粒中, 该体系对癌细胞和CAFs具有同源靶向, PTX和PFK15的协同作用可抑制肿瘤生长并激活免疫应答.

综上所述, 利用纳米药物调控TFLCs的方式可归纳为直接杀伤、整体调控功能及精确调控信号通路. 其适用场景略有不同(归纳至表3), 其三种方式之间也相对独立, 但最终目的均是重塑肿瘤微环境, 抑制恶性肿瘤的进程, 提高肿瘤的治疗效果. 在纳米材料设计方面, 由于TFLCs表面较为特异地表达FAP-α[63]、Sigma受体[64,65]、血小板衍生生长因子受体(platelet derived growth factor receptor, PDGFR)[66]等标志物, 为纳米药物提供了靶标; 纳米制剂可以装载化疗药物对TFLCs直接杀伤, 也可装载抗纤维化的药物或核酸药物, 对

表 3 纳米药物对TFLCs的调控方法及适用场景

Table 3 Regulation methods and application scenes of nanomedicine on TFLCs

对TFLCs的调控方式	方法	适用场景	参考文献
直接杀伤	靶向TFLCs递送纳米药物使其死亡	利用化疗药物同时杀伤肿瘤细胞和TFLCs来增强药物渗透效率	[47,50]
整体功能调控	降低分泌ECM成分的能力	提高化疗药物的渗透效率	[52]
	通过siRNA诱导沉默, 抑制ECM增生		[53]
	抑制细胞因子的表达, 逆转免疫抑制微环境	抑制恶性乳腺癌生长和转移	[54]
	将TFLCs工程化为APC	避免PD-L1抗体临床应用引起的免疫风暴	[55]
调控信号通路靶点	阻断CXCL12及下游多种信号通路	抑制恶性前列腺癌转移	[58]
	阻断TGF-β/STAT3信号通路	逆转肝纤维化, 抑制肿瘤肝转移	[59]
	降低PFKFB3活性阻止TFLCs糖酵解	减少对肿瘤细胞的供能	[62]

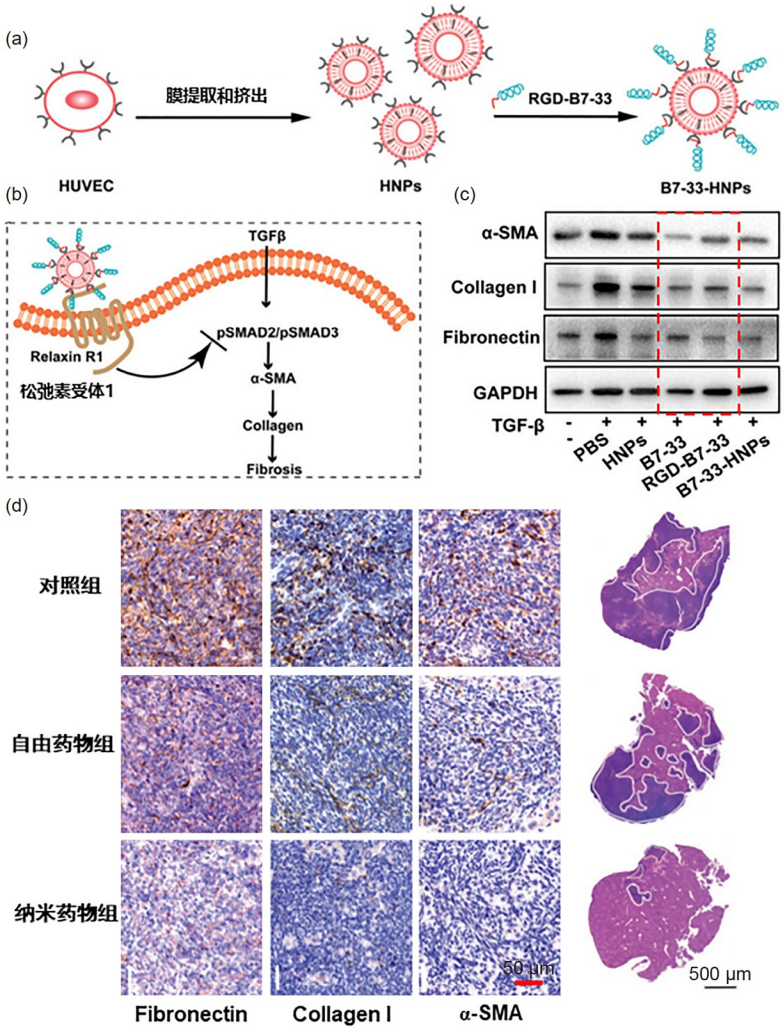

图 3 基于HSCs信号通路靶点重塑肿瘤微环境[59]. (a) 构建了治疗性多肽(B7-33)递送系统(B7-33-HNPs). (b) B7-33-HNPs的抗纤维化机制. (c) 不同配方的体外抗纤维化疗效评估. 红色虚线框显示B7-33的功能在cRGD序列修改后没有降低. (d) B7-33-HNPs对小鼠胰腺癌肝转移的抑制效果

Figure 3 Remodeling of the tumor microenvironment based on HSCs signaling pathway targets[59]. (a) Construction of a therapeutic peptide (B7-33) delivery system (B7-33-HNPs). (b) Anti-fibrotic mechanism of B7-33-HNPs. (c) Evaluation of anti-fibrotic efficacy *in vitro* using different formulations. The red dashed box indicates that the functionality of B7-33 is not reduced after modification with cRGD sequence. (d) Inhibition of B7-33-HNPs on pancreatic cancer liver metastasis

TFLCs的功能进行精细调控[67~72]. 由于TFLCs通常位于肿瘤血管周围, 纳米药物渗透出肿瘤血管后, 更容易与TFLCs相互作用, 因此, 靶向TFLCs的策略对纳米颗粒的类型并不挑剔. 然而, 何种类型、何种尺寸的纳米颗粒更易进入TFLCs, 尚需探索.

3 总结与展望

TFLCs作为大部分实体肿瘤中的主要间质组分, 在塑造肿瘤微环境中发挥着重要作用. 同时, 作为纳米颗粒相对更容易接触到的细胞类型, TFLCs可作为纳米药物重要的靶细胞类型. 然而, 利用纳米药物调控TFLCs仍需进一步发展和完善.

从TFLCs自身说起, 其在肿瘤发展的各个阶段的功能可能有所不同, 在不同肿瘤类型中, 其功能也会有差异. 在与肿瘤长期的交互中, 成纤维细胞初期与肿瘤对抗, 后期却逐渐被肿瘤“驯化”, 成为肿瘤发展的“帮凶”. 然而, 当前对不同的肿瘤类型及肿瘤不同的发展阶段, TFLCs的功能差异研究还尚不充分. 此外, 尽管TFLCs与肿瘤细胞交互的分子机制报道很多, 但它与其他间质细胞类型(如血管内皮、肿瘤相关巨噬细胞)的交互尚缺少具体的分子机制. 或许各种测序技术的发展、生物信息学技术的不断完善, 将对细化研究TFLCs的

亚型、功能及其与肿瘤环境的交互起到推动作用.

TFLCs受到化疗、放疗、免疫治疗等干预后, 可能对药物产生抵抗, 从而导致肿瘤的耐药. 因此, 针对治疗前后TFLCs的对比研究, 可能成为今后的热点. 治疗前后, TFLCs在表型、基因、蛋白等方面的变化, 也将为纳米药物针对TFLCs的调控提供新的靶点.

作为间质细胞组分中数目最多的一类细胞, 如果让TFLCs本身成为对抗肿瘤的群体, 有可能实现对肿瘤细胞的围攻. 事实上, 此方面工作已初见成效. 除前文提到的利用TFLCs呈递抗原的工作外, Miao等人[73]将编码可表达TNF相关因子sTRAIL的质粒加载到脂质包被的鱼精蛋白DNA复合物中, 利用TFLCs分泌sTRAIL, 杀伤肿瘤细胞, 为实体肿瘤的治疗提供了新参考策略. 利用纳米递送技术结合基因编辑等技术, 将TFLCs重编程, 实现肿瘤微环境重塑、逆转免疫抑制或直接对抗肿瘤细胞, 将成为今后TFLCs的重要发展趋势.

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Summary for “基于纳米药物调控肿瘤成纤维样细胞用于肿瘤治疗的研究进展”

Research progress on the nanodrug mediated regulation of tumor fibroblast-like cells for tumor therapy

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Tumor tissues have a complex microenvironment containing various cellular and non-cellular components. Cancer-associated fibroblasts (CAFs) are the largest population in the stroma. CAFs can originate from many cell types, including native fibroblasts, stellate cells, epithelial cells, endothelial cells, and mesenchymal stem cells. We think the more precise description of CAFs is “tumor fibroblast-like cells” (TFLCs). TFLCs play pivotal roles in shaping the tumor microenvironment as the primary stromal cells through secreting various growth factors and extracellular matrix. For example, TFLCs secret vascular endothelial growth factor (VEGF) to regulate tumor angiogenesis, CXCL12 to upregulate anti-apoptotic proteins like Bcl-2 and survivin expression in tumor cells. TFLCs also establish physiological barriers within tumor tissues. For instance, TFLCs promote fabricating tumor extracellular matrix by secreting abundant collagens and fibronectin, which hinders the infiltration of immune cells and the penetration of anti-tumor drugs, and therefore impeding the efficacy of chemotherapy and immunotherapy. Consequently, modulating TFLCs can contribute to effectively suppressing tumor development and improving treatment outcomes.

Due to the abundant distribution of TFLCs around tumor blood vessels, nanomedicines may first come into contact with TFLCs when they permeate from tumor blood vessels. Therefore, this provides relatively convenient conditions for utilizing nanomedicines to regulate TFLCs. The rational design of nanomedicines enables the targeted delivery of therapeutic agents to TFLCs, facilitating the modulation of TFLC functions at the genetic and/or molecular levels. Meanwhile, the phenotype, genes and protein levels of TFLCs could be changed after treatment, which may also provide new targets for nanomedicines.

In this review, we give a concise overview of the origins and functions of TFLCs, and we focus on highlighting recent research progress on using nanomedicines to regulate TFLCs, such as loading chemotherapy drugs to directly deplete TFLCs, loading anti-fibrosis drugs to modulate TFLC function, and employing antibodies or nucleic acid drugs to precisely regulate signaling pathways in TFLCs. All these strategies prove that regulating TFLCs can enhance the efficacy of cancer treatment.

To further develop this field, we need to pay more attention to the subtypes of TFLCs, especially the subtype population and signaling pathway changes of TFLCs before and after the treatments (chemotherapy, radiotherapy and/or immunotherapy). Since TFLCs are the largest stromal cell population in the tumor microenvironment, we may utilize TFLCs as a factory to produce drugs or antigens by using gene editing techniques to enhance the therapeutic efficacy.

Overall, this review can provide feasible references for improving the treatment of solid tumors through regulating the tumor microenvironment.

tumor fibroblast-like cells, nanodrugs, tumor microenvironment, precise regulation, tumor therapy

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