STAT3通路在肿瘤相关成纤维细胞调节肿瘤微环境中的作用

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摘要 目前各种肿瘤的发病率和死亡率仍高居不下, 肿瘤的治疗还是临床医学的一大难题。肿瘤的发展离不开它的“摇篮”, 即肿瘤微环境, 因此探索肿瘤与肿瘤微环境相互作用的调控机制有利于肿瘤治疗。研究显示, STAT3通路在肿瘤微环境的调控中发挥重要作用。因此, 该文针对STAT3通路促进肿瘤相关成纤维细胞(cancer associated fibroblasts, CAFs)激活, 调节CAFs与肿瘤细胞, CAFs与免疫细胞的相互作用等方面进行了综述, 并对靶向STAT3通路的肿瘤治疗药物进行了总结。

关键词 STAT3通路; 肿瘤微环境; 靶向治疗

Role of STAT3 Pathway in Tumor-Associated Fibroblasts Regulating Tumor Microenvironment

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Abstract The incidence and mortality of various tumors are still high, and the treatment of tumors is a major problem in clinical medicine. The development of tumor is inseparable from its “cradle”, that is, tumor microenvironment. Therefore, it is beneficial to explore the regulatory mechanism of the interaction between tumor and tumor microenvironment for tumor therapy. Studies have shown that STAT3 pathway plays an important role in the regulation of tumor microenvironment. This paper reviews the STAT3 pathway that activates CAFs (cancer associated fibroblasts), regulating the interaction between CAFs and tumor cells, CAFs and immune cells, and summarizes the tumor therapy drugs targeting STAT3 pathway.

Keywords STAT3 pathway; tumor microenvironment; targeted therapy

肿瘤微环境(tumor micro-environment, TME)由肿瘤细胞以及存在于肿瘤组织周围的周边血管、免疫细胞、肿瘤相关成纤维细胞、骨髓来源炎性细胞, 以及各种信号分子和细胞外基质共同构成。肿瘤与肿瘤微环境被称作是“种子与土壤”的关系[1]。一方面, 作为“种子”的肿瘤细胞通过旁分泌, 趋化利于自身生长的微环境。另一方面, 肿瘤微环境中的其他细胞通过重塑胞外基质、促进血管生成、调节免疫抑制等, 为肿瘤的生长和转移提供“土壤”。二者相互作用, 相辅相成, 共同促进肿瘤的发生发展。

当前的研究表明, STAT3通路在肿瘤微环境中发挥重要作用。多种肿瘤细胞、肿瘤相关成纤维细胞和肿瘤相关免疫细胞中都存在STAT3通路过度激

收稿日期: 2022-03-13 接受日期: 2022-05-14
国家自然科学基金地区项目(批准号: 81960529)资助的课题
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Received: March 13, 2022 Accepted: May 14, 2022
This work was supported by the National Natural Science Foundation of China (Grant No.81960529)
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活的情况。STAT3通路调节肿瘤与微环境之间的相互作用。

1 STAT3通路的概述

信号转导及转录激活(signal transducer and activator of transcription, STAT)家族蛋白行使信号转导和转录激活的双重功能，其中STAT3备受研究者的关注。最初，STAT3被称为急性期反应因子(acute-phase response factor)，由白细胞介素6(interleukin 6, IL6)激活，调节肝脏的急性期反应。STAT蛋白家族有7个STAT蛋白，包括STAT1、STAT2、STAT3、STAT4、STAT5α、STAT5β、STAT6。STAT蛋白家族成员结构相似，以STAT3蛋白为例，包含6个结构域：N-端结构域(N-terminal domain, NH2)、DNA结合结构域(DNA-binding domain, DBD)、连接结构域(linker domain)、同源结构域(SRC homology 2 domain, SH2)、螺旋结构域(coiled-coil, CDC)、转录激活结构域(transactivation domain, TAD)[3]。

STAT3发挥转录因子的功能主要依赖于TAD结构域，TAD结构域包含多个磷酸化位点，其中Tyr705(Y705)和Ser727(S727)是STAT3的两个最重要的磷酸化位点。STAT3的705和727位点的磷酸化形式为p-STAT3^{Y705}和p-STAT3^{S727}。研究报道，STAT3的Y705位点磷酸化和S727位点磷酸化可以相互促进，存在协同作用[4]。同时，二者存在空间和功能上的差异。Y705位点磷酸化与STAT3的核转位有关，而S727位点的磷酸化则促进STAT3进入线粒体行使功能[5]。目前研究比较多的是p-STAT3^{Y705}，因此通常将p-STAT3^{Y705}作为STAT3通路激活的标志。

随着研究的不断深入，经典的STAT3通路已被阐明(图1)。STAT3通路可以被多种诱导剂激活，包括IL6家族成员IL6、IL11、OSM等[6]。下面以IL6诱导的STAT3通路为例介绍该通路。IL6结合膜受体形成复合物发挥其生物学功能，其受体由2条糖蛋白链(α链IL6Rα和β链GP130)组成。IL6与IL6Rα结合后，识别并结合GP130，每个组分2个分子，形成有生物活性的六聚体复合物。GP130还是其他细胞因子[如IL11，白血病抑制因子(leukemia inhibitory factor, LIF)，肿瘤抑制因子M(oncostatin M, OSM)]的受体，这些细胞因子可与IL6协同活化STAT3通路。IL6与受体结合后启动下游JAK的磷酸化，活化的JAK通过磷酸化STAT3从而激活STAT3通路。进一步的研究显示，骨髓间质细胞通过LIF激活LIFR/p-ERK/p-STAT3^{S727}信号通路，促进转移前生态位的形成，还能通过激活IL6/IL6R/STAT3^{Y705}信号通路促进肿瘤启动，诱导肿瘤细胞的上皮间充质转化(epithelial-mesenchymal transition, EMT)[7]。STAT3磷酸化之后形成同源/异源二聚体进入细胞核通过DNA结合结构域与靶基因启动子结合，启动下游基因的表达，这一系列的级联反应实现了信号从胞外到胞内的转递，称为经典的STAT3通路[8]。

STAT3通路还存在一些负调控剂，包括*PTPN11*基因编码的蛋白酪氨酸磷酸酶-(SH2 domain-containing protein-tyrosine phosphatase-2, SHP2)、细胞信号转导抑制因子(suppressor of cytokine signaling, SOCS)家族的SCOS1和SCOS3和质膜相关的E3泛素连接酶(membrane-associated ring-ch-type finger 3, MARCH3)。SHP2作为磷酸酶，使磷酸化的JAK2和STAT3去磷酸化，避免STAT3通路功能的过度激活引发代谢异常[9-11]。SOCS1和SOCS3则是起负性调节的蛋白质因子，通过抑制STAT的表达从而抑制STAT3的活化，促进细胞的凋亡[12-13]。MARCH3介导IL6受体IL6Rα在K401位点和GP130在K849位点的多泛素化，导致其易位并在溶酶体中降解，从而抑制STAT3通路的激活[14]。

STAT3在哺乳动物发育过程中表达并发挥重要作用。研究显示，STAT3的缺失会导致小鼠的胚胎致死[15]。STAT3可以诱导骨形成，维持骨稳态，在调节骨骼发育中发挥至关重要的作用[16]。此外，STAT3通路调节细胞的增殖、炎症应激和代谢，参与伤口愈合和血管生成等一系列生命活动[17-18]。因此，当STAT3通路被持续激活时，会导致包括肿瘤在内的多种疾病发生。目前发现，异常激活的STAT3通路信号存在于多种原发性肿瘤中，调节CAFs与肿瘤细胞，CAFs与免疫细胞之间的相互作用[19-20]。

2 STAT3通路促进CAFs激活

2.1 CAFs概述

肿瘤相关成纤维细胞(cancer associated fibroblasts, CAFs)是肿瘤微环境中最为重要的成员之一，CAFs主要是由组织中正常的成纤维细胞在生长因子和趋化因子刺激作用下转化而来。此外，肿瘤组织中的上皮细胞、内皮细胞、骨髓间充质干细胞(bone mesenchymal stem cells, BMSCs)等细胞也可

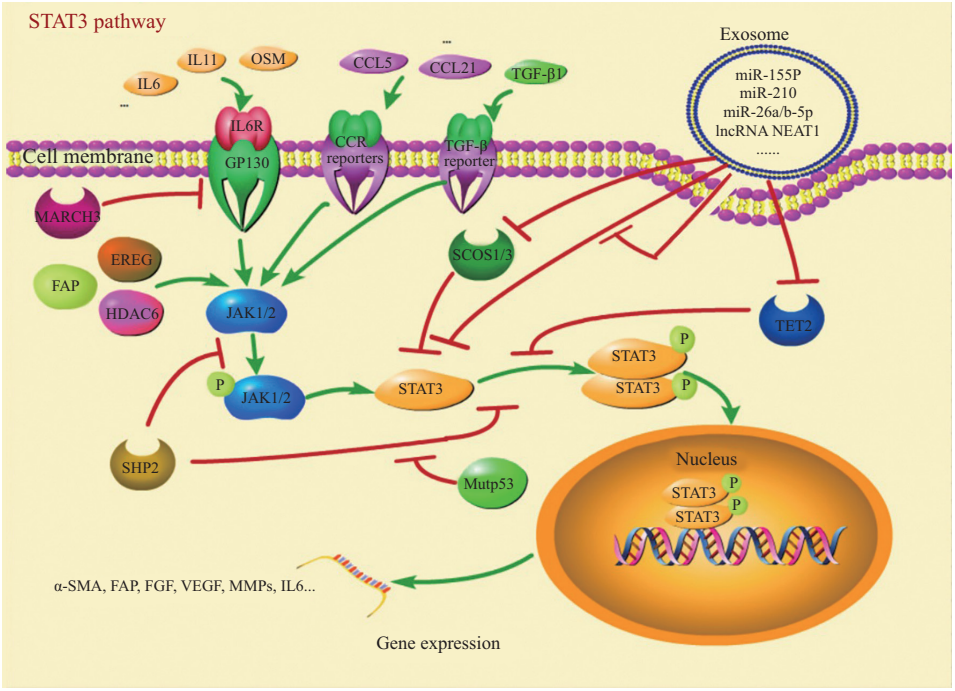

图1 STAT3通路的简介

Fig.1 Introduction to STAT3 pathways

在转化生长因子刺激下通过上皮间质转化(EMT)和内皮间质转化(endothelial mesenchymal transition, EndMT)分化为CAFs。这种由非CAFs向CAFs分化的过程称为CAFs激活或是CAFs转化。

CAFs通过旁分泌方式/非细胞自主性的方式重塑细胞外环境, 分泌调节因子调控肿瘤生长、转移, 耐药、血管生成等多种生物学功能[21]。在多种类型肿瘤分离出的CAFs中, STAT3通路都是异常激活的状态, 这提示了STAT3通路是促进CAFs激活的关键因素, 也是肿瘤持续恶化的原因之一。CAFs主要来源于宿主的正常成纤维细胞。STAT3调节正常的成纤维细胞转化为CAFs主要存在两种方式: 成纤维细胞内在基因的表达改变激活STAT3通路, 促进CAFs转化; 肿瘤细胞来源的诱导因子激活正常成纤维细胞中STAT3通路, 促进其CAFs转化。

2.2 成纤维细胞内在基因的表达改变激活STAT3通路, 促进CAFs转化

成纤维细胞中抑癌基因突变激活STAT3通路, 促进CAFs转化。*p53*是众所周知的抑癌基因, 超过半数的肿瘤中都存在*p53*的缺失或突变。近期的研究发现, *p53N236S*突变可激活STAT3通路, 进而促进小鼠胚胎成纤维细胞(mouse embryo fibroblast, MEF)表达a-SMA等CAFs标志物, 并使其具有促进前列腺癌细胞PC-3生长, 同时促进肺癌细胞H1299迁移和浸润的CAFs特性[22]。此外, 活化的STAT3通路抑制野生型*p53*转录[23]。同时, 也有数据显示, 野生型p53抑制成纤维细胞向CAFs的转化[24-27]。这些数据进一步提示了STAT3通路的活化对CAFs激活至关重要。

成纤维细胞中部分基因的异常表达可激活STAT3通路。上皮调节蛋白(epiregulin, EREG)是一种表皮生长因子, 正常成纤维细胞高表达EREG, 上调IL6激活JAK2/STAT3通路, 从而激活其CAFs表型。CAFs中上调的IL6同时持续激活本身和肿瘤中的STAT3通路, 促进肿瘤的生长、侵袭和浸润[28-29]。乳腺癌分离出的CAFs中, 组蛋白去乙酰化酶6(histone deacetylase 6, HDAC6)高表达, 促进STAT3的磷酸化, 上调环氧化酶-2(cyclooxgenase 2, COX2)的表达, 促进$CD8^+$和$CD4^+$T细胞活化, 诱导形成免疫抑制微环境[28]。在肝癌小鼠模型中, 也发现了CAFs来源的STAT3通路调节肿瘤免疫抑制微环境[30]。研究发现, 在小鼠肝成纤维细胞中, FAP通过依赖于uPAR的FAK-c-Src-JAK2-STAT3通路, 诱导其向CAFs转化, 这一过程中CCL2的分泌增加, 促进髓源性抑制细胞(myeloid-derived suppressor cell, MDSC)的募集。临床上人肝内胆管癌间质的FAP/pSTAT3/CCL2高表达与预后不良正相关, 提示了FAP/pSTAT3/CCL2轴可

作为肿瘤临床治疗的潜在靶点。而在食管鳞状癌中, CAFs中的STAT3通路由其自身分泌的IL6激活, 激活的CAFs促进肿瘤对顺铂的耐药性[21]。

2.3 肿瘤细胞来源的诱导因子激活正常成纤维细胞中STAT3通路, 促进其CAFs转化

在肿瘤发生过程中, 肿瘤细胞趋化其周围正常成纤维细胞激活为CAFs, 形成促肿瘤微环境[31-32]。肿瘤来源的生长因子和趋化因子等分泌蛋白及外泌体激活成纤维细胞的STAT3通路, 促进其CAFs转化[33]。

在肿瘤与CAFs的相互作用研究中, 通常采用制备条件培养基(conditioned medium, CM)或共培养的方式进行实验验证。IL6是已知的STAT3通路激活剂, 也是肿瘤的分泌蛋白之一。制备的骨肉瘤U2OS细胞CM中富含IL6, 并且CM中的IL6激活了成纤维细胞中的STAT3通路, 上调成纤维细胞中CAFs标志物α-SMA、FAP、VEGF和FGF的表达, 同时使激活的成纤维细胞促进U2OS的迁移和浸润[34]。此外, 在结直肠癌中, 肿瘤分泌的TGF-β1活化了成纤维细胞中的JAK1, 激活了STAT3通路, 从而促进其向CAFs转化, 形成促转移的TME, 加速结直肠癌向肝转移[35]。

肿瘤来源的microRNA则通过抑制成纤维细胞STAT3通路的负调节剂, 解除其对STAT3通路的抑制, 释放STAT3通路的活性, 促进血管生成。肺癌细胞A549和H460分离的外泌体中含有miR-210, miR-210可在转录水平抑制成纤维细胞中TET2(methylcytosine dioxygenase 2)从而解除其对STAT3磷酸化的抑制, 升高FGF2、VEGFA等的表达水平, 促进CAFs转化[36]。黑色素瘤细胞B16分泌miR-155p, miR-155p与成纤维细胞中SOCS1的3′UTR结合抑制SOCS1的转录, 减少其对STAT3表达的抑制, 激活STAT3通路, 促进成纤维细胞向CAFs的转化, 促进VEGFα、FGF2、MMP9的表达, 促进血管的生成[37]。

3 STAT3通路调节CAFs与肿瘤细胞之间的相互作用

CAFs分泌的蛋白因子促进肿瘤中的STAT3通路激活, 调节CAFs与肿瘤之间的相互作用。肿瘤的STAT3通路被激活, 一方面激活的STAT3通路可上调肿瘤细胞自身VEGF、FGF、IL6等生长因子促进肿瘤的增殖、耐药, 抑制肿瘤细胞凋亡; 另一方面, 肿瘤细胞分泌蛋白因子促进CAFs的募集, 诱导细胞外基质重塑, 促进肿瘤转移和浸润[38-41]。

研究发现, CAFs分泌的IL6激活肝癌细胞中STAT3通路, STAT3激活后与基质金属蛋白酶抑制剂-1(tissue inhibitor of metalloproteinase 1, TIMP-1)启动子结合, 转录激活TIMP-1, 促进CAFs的募集和激活, 在CAFs与肿瘤之间形成正反馈环[42]。也有研究发现, 肝癌细胞中STAT3通路激活后, 可进一步激活NOTCH通路, 上调NICD和Hes1的表达, 促进肿瘤细胞的增殖能力, 增强肿瘤干细胞特性[43]。在结直肠癌、胃癌和肺癌中, STAT3通路也存在类似的调控方式[44-47]。此外, 在卵巢癌和乳腺癌中, CAFs分泌的IL6可通过激活肿瘤细胞的STAT3通路抑制肿瘤细胞凋亡, 提高肿瘤细胞的存活率, 降低肿瘤细胞对顺铂和紫杉醇等抗肿瘤药物的敏感性, 促进肿瘤细胞的耐药能力[48-49]。

CAFs来源的IL6及其家族成员协同激活肿瘤的STAT3通路。在非小细胞肺癌中, IL6和OSM分别与IL6R/GP130和OSMR/GP130形成转导复合物激活肿瘤中JAK1/STAT3通路, 上调*Snail*、*ZEB1*、*AXL*等基因的表达, 从而诱导EMT发生, 并降低细胞对药物的敏感性, 保护细胞免受靶向药物诱导的凋亡[50]。此外, IL6家族的其他细胞因子可以独立激活肿瘤细胞的STAT3通路。研究发现, CAFs来源的IL11、IL15、IL17α和IL22可活化肿瘤细胞的JAK1/JAK2, 激活STAT3通路, 上调MMP2/9的表达, 促进肿瘤的迁移和浸润[51-54]。

CC类趋化因子配体[chemokine(C-C motif) ligand, CCL]家族的一些成员也是STAT3的激活剂。在口腔鳞状细胞癌(oral squamous cell carcinoma, OSCC)的研究中发现, CCL21识别肿瘤细胞膜上的CCR7, 激活肿瘤细胞中JAK2/STAT3通路, 促进EMT, 同时提高OSCC干细胞特性[55]。在卵巢癌的研究中显示, CAFs分泌CCL5通过激活STAT3和PI3K/Akt信号通路降低卵巢癌对顺铂的敏感性, 从而提高其对顺铂的耐药能力[56]。

lincRNA也可以促进STAT3通路激活。lincRNA是通过抑制靶蛋白的表达, 从而解除靶蛋白对STAT3通路的抑制, 促进STAT3的活化。在子宫内膜癌中, CAFs表达的长链非编码RNA-NEAT1(long noncoding RNA-NEAT1, NEAT1)通过外泌体进入肿瘤细胞, 与miR-26a/b-5-p结合, 释放与miR-26a/b-5-p结合的STAT3, 促进*Stat3*转录表达, 加速体内肿瘤生长[57]。上述研究结果都体现出STAT3通路调节CAFs

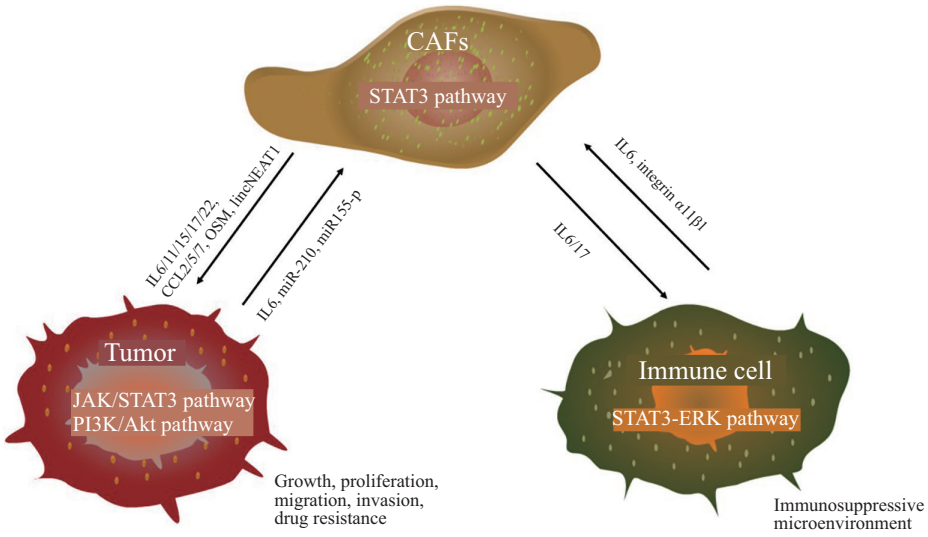

图2 STAT3通路调控CAFs与肿瘤的相互作用

Fig.2 STAT3 pathway regulates the interaction between CAFs and tumors

与肿瘤之间的相互作用(图2)。

4 STAT3通路调节CAFs与免疫细胞的相互作用

肿瘤相关免疫细胞也是肿瘤微环境的重要成员, 它包括T细胞、B细胞、肿瘤相关巨噬细胞(tumor-associated macrophages, TAMs)、髓源抑制细胞(myeloid-derived suppressor cells, MDSCs)、树突状细胞(dendritic cells, DCs)等多种免疫细胞[58]。肿瘤相关免疫细胞可通过分泌炎症因子, 如: IL1、IL6、巨噬细胞集落形成因子、趋化因子、转化趋化因子等促进肿瘤的生长、转移及逃避免疫抑制。

肿瘤相关免疫细胞中p-STAT3(Y705)表达升高, 提示其中STAT3通路活性升高。研究发现, 肿瘤相关免疫细胞的STAT3通路激活主要原因是CAFs来源的IL6的刺激。IL6激活中性粒细胞中STAT3通路, 通过STAT3-ERK1/2轴保护中性粒细胞免于凋亡, 诱导中性粒细胞向促肿瘤的TAM极化[[59-60], 同时, 被趋化的中性粒细胞进一步诱导NF(normal fibroblast)激活成CAFs[61]。在肝癌中, CAFs来源的IL6还可以激活调节性树突状细胞(即抗原呈递细胞)中STAT3通路, 上调吲哚胺2, 3-双加氧酶(IDO)的表达, 促进调节性T细胞(Treg)募集, 形成免疫抑制环境[62]。

5 靶向STAT3通路在肿瘤治疗中的研究进展

鉴于STAT3通路在肿瘤与肿瘤微环境信号转导中的重要作用, 可以把STAT3通路作为临床肿瘤治疗的潜在靶点。以STAT3通路作为靶点进行肿瘤治疗的方式大致可分为两类: 一是直接靶向肿瘤细胞的STAT3通路, 抑制肿瘤细胞的生长、增殖、迁移和侵袭, 促进肿瘤的凋亡; 二是靶向CAFs, 抑制IL6等趋化因子的分泌从而阻断肿瘤细胞STAT3通路激活, 抑制肿瘤的发展。

5.1 直接靶向肿瘤细胞STAT3通路的药物

小分子抑制剂, 如SD-91、LLL12B、SH3GL3、MARCH8、Napabucasin(BBI608)、Stattic、PG-S3-001等是直接靶向STAT3治疗肿瘤的潜在药物。靶向肿瘤细胞的STAT3通路, 通过促进STAT3的降解, 抑制STAT3通路的激活。其中, SD91是STAT3降解剂SD-36的水解产物, 具有更高的STAT3亲和力, 诱导STAT3水解[63]。MARCH8是新的跨膜E3连接酶家族蛋白, 通过泛素–蛋白酶体途径降解STAT3, 抑制肿瘤细胞的增殖和迁移, 促进肿瘤凋亡[64]。

此外, 还有一些小分子抑制剂是通过抑制STAT3的磷酸化, 抑制STAT3通路的激活。比如, LLL12B、Stattic和PG-S3-001作用方式类似, 都具有很高的STAT3亲和力, 与STAT3结合抑制其磷酸化, 降低细胞活力[65-67]。SH3GL3抑制STAT3的磷酸化和入核, 抑制胶质母细胞瘤(GBM)的增殖和迁移, 降低其干细胞特性[68]。Napabucasin(BBI608)通常与其他药物协同进行治疗。在卵巢癌临床前研究中, Napabucasin与蛋白酶体抑制剂MG132和紫杉醇协同, 抑制STAT3的磷酸化, 并上调*p21*等凋亡通路相关的基因, 抑制肿瘤细胞

的增殖, 促进其凋亡, 延长患者生存期[69-70]。部分天然药物通过靶向STAT3通路的上游, 抑制STAT3活化, 阻止STAT3通路的激活。研究发现, 甘松根提取物(nardostachys jatamansi root extract, NJRE)可抑制肝癌细胞中ERK的表达, 抑制STAT3磷酸化, 抑制肿瘤的增殖[71]。此外, 天然的喹奥利嗪类生物碱: Aloperine (ALO)和卵泡二内酯, 通过抑制肿瘤中IL6的表达, 阻断STAT3活化, 从而抑制肿瘤细胞的增殖、迁移和侵袭, 促进细胞凋亡[72-73]。这些小分子抑制剂和天然药物都在体内和体外实验中被验证了具有作为靶向肿瘤细胞的STAT3治疗肿瘤的潜能, 但尚未进行临床试验, 其能否应用于临床还需要进一步的验证。

如前文所述, 肿瘤来源的诱导因子激活成纤维细胞中的STAT3通路, 促进CAF转化。因此, 阻断肿瘤与CAFs之间的相互作用, 也是靶向STAT3通路的策略之一。在口腔鳞状细胞癌研究中, 卵磷脂(ovatodiolide, OV)治疗抑制肿瘤细胞外泌体的合成和miR-21-5p在外泌体中的装载。外泌体中装载的miR-21-5p降低程序性细胞死亡因子4(programmed cell death 4, *PDAC4*)和蛋白酪氨酸磷酸酶基因(phosphatase and tensin homolog, *PTEN*)的转录, 这二者都抑制STAT3表达, 间接抑制了NF的CAFs转化[74]。

5.2 靶向CAFs从而抑制肿瘤细胞STAT3通路激活的药物

CAFs来源的诱导因子可激活肿瘤细胞中STAT3通路, 促进肿瘤进展。靶向肿瘤组织中的CAFs是最近研究比较热门的一种治疗方式。有些天然药物可作为靶向CAFs的药物。靶向CAFs治疗肿瘤的主要方式是通过抑制CAFs的各类趋化因子、细胞因子的分泌, 阻断其对肿瘤细胞的STAT3通路的激活, 进而达到抑制肿瘤发展的目的。在乳腺癌研究中发现, JS-124(葫芦素)抑制CAFs分泌IL6, 阻断CAF/IL6-肿瘤/STAT3的反馈环, 抑制肿瘤的增殖、迁移和侵袭, 诱导其凋亡[75]。而Sp13786抑制CAFs中外泌体的合成, 间接抑制肿瘤中STAT3通路, 抑制肺癌细胞A549的迁移和浸润[76]。Ref-1和STAT3的小分子抑制剂联合处理也有类似的治疗结果, 二者联合治疗抑制CAFs中外泌体的合成和分泌, 通过切断CAFs和肿瘤间的信号交流抑制肿瘤的生长[77]。维甲酸可干扰CAFs的高尔基体合成, 从而抑制CAFs分泌蛋白的合成, 抑制肿瘤的生长[78]。在小鼠实体瘤模型中发现, 纳米颗粒ONP-302通过抑制CAFs促癌功能相关的基因表达、诱导TME中CAFs的凋亡、TAMs基因表达向促炎M1型趋化, 抑制肿瘤的进展[79]。

此外, 最近的研究采用IL6R的单克隆抗体拮抗肿瘤中的IL6R, 阻断CAFs来源IL6信号对肿瘤细胞的串扰, 抑制肿瘤中*AUF1*等基因的表达, 这是一种更精准有效的靶向治疗方式[80]。靶向肿瘤相关免疫细胞也是肿瘤靶向治疗的一种方式。在肺癌研究中发现, 薯蓣皂苷抑制小鼠骨髓来源的巨噬细胞(bone marrow derived macrophage, BMDM) JNK的磷酸化进而抑制STAT3的磷酸化, 诱导M2型巨噬细胞向M1转化, 抑制肿瘤的转移[81]。

6 展望

近年来, 肿瘤的靶向治疗取得了巨大的进步, 国内外都有一些医疗机构将靶向药物应用于临床试验。鉴于STAT3通路在肿瘤与肿瘤微环境相互作用中的调节作用, 靶向STAT3的新药是目前靶向药物的研究热点之一。一些靶向STAT3通路的“药物先锋”已经被用于临床, 但是存在毒副作用较大, 部分患者治疗效果不佳等局限性。更多的靶向药物还是处于临床前开发阶段。

虽然现在还没有合适的靶向STAT3通路的临床药物投入临床应用, 但是许多研究者正以动物模型为手段, 在靶向STAT3治疗肿瘤的道路上披荆斩棘。希望肿瘤的靶向治疗的研究能取得进展, 使得靶向STAT3的药物能够应用于临床。

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