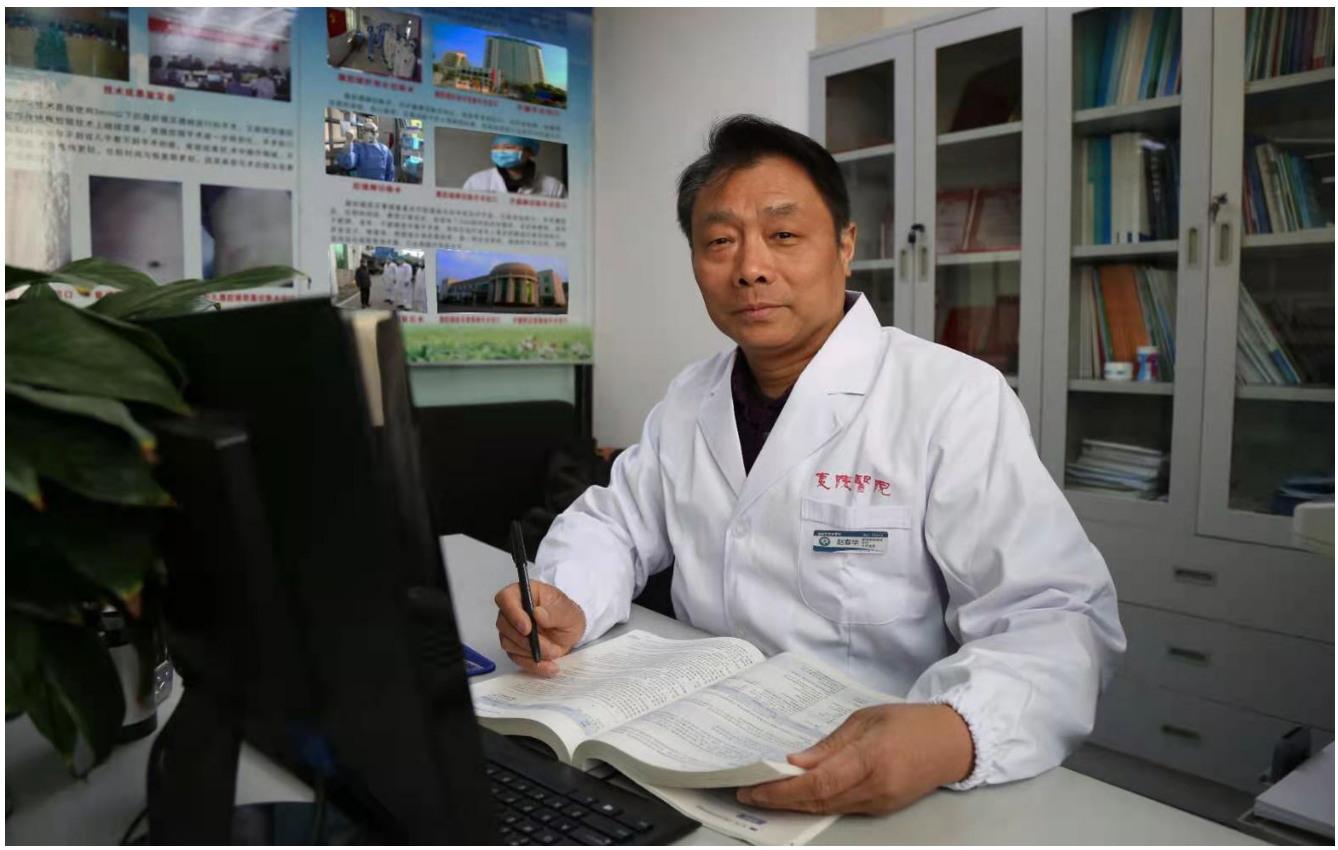
ISSN 1009-3079 (print)
ISSN 2219-2859 (online)

世界华人消化杂志®

WORLD CHINESE JOURNAL OF DIGESTOLOGY

Shijie Huaren Xiaohua Zazhi

2021 年 6 月 28 日　　第 29 卷　　第 12 期　　(Volume 29 Number 12)



12/2021

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ISSN 1009-3079
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编务 张砚梁; 送审编辑 张砚梁; 组版编辑 张砚梁; 英文编辑 王天奇;
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世界华人消化杂志

Shijie Huaren Xiaohua Zazhi

吴阶平　题写封面刊名
陈可冀　题写版权刊名
(半月刊)

创　刊 1993-01-15
改　刊 1998-01-25
出　版 2021-06-28
原刊名 新消化病学杂志

期刊名称
世界华人消化杂志

国际标准连续出版物号
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

编辑部
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《世界华人消化杂志》编辑部
Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: wcjd@wjgnet.com
http://www.wjgnet.com

出版
百世登出版集团有限公司
Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

制作
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《世界华人消化杂志》是一本高质量的同行评议, 开放获取和在线出版的学术刊物. 本刊被国际检索系统《化学文摘(Chemical Abstracts, CA)》、《医学文摘库/医学文摘(EMBASE/Excerpta Medica, EM)》、《文摘杂志(Abstract Journal, AJ)》、Scopus、中国知网《中国期刊全文数据库(CNKI)》、《中文科技期刊数据库(CSTJ)》和《超星期刊域出版平台(Superstar Journals Database)》数据库收录.

《世界华人消化杂志》正式开通了在线办公系统(https://www.baishideng.com), 所有办公流程一律可以在线进行, 包括投稿、审稿、编辑、审读, 以及作者、读者和编者之间的信息反馈交流.

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定价
每期136.00元 全年24期3264.00元

WCJD 世界华人消化杂志®

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Shijie Huaren Xiaohua Zazhi

Founded on January 15, 1993
Renamed on January 25, 1998
Publication date June 28, 2021

NAME OF JOURNAL
World Chinese Journal of Digestology

ISSN
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

EDITORIAL OFFICE
Jin-Lei Wang, Director
World Chinese Journal of Digestology
Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: wcjd@wjgnet.com
https://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

PRODUCTION CENTER
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No. 62 Dongsihuan Zhonglu,
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Telephone: +86-10-85381892

PRINT SUBSCRIPTION
RMB 136 Yuan for each issue
RMB 3264 Yuan for one year

INSTRUCTIONS TO AUTHORS
Full instructions are available online at https://www.wjgnet.com/1009-3079/Nav/36. If you do not have web access, please contact the editorial office.

WCJD 世界华人消化杂志®

在线投稿: https://www.baishideng.com

世界华人消化杂志 2021年6月28日; 29(12): 621-627

DOI: 10.11569/wcjd.v29.i12.621

ISSN 1009-3079 (print) ISSN 2219-2859 (online)

述评 EDITORIAL

靶向SRC治疗胰腺癌的研究新进展

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基金项目: 国家重点研发计划资助项目, No. 2017YFC1308602.

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收稿日期: 2021-02-05
修回日期: 2021-04-06
接受日期: 2021-05-11
在线出版日期: 2021-06-28

Recent progress in SRC targeted therapy for pancreatic cancer

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Supported by: National Key Research and Development Program of China, No. 2017YFC1308602.

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Received: 2021-02-05
Revised: 2021-04-06
Accepted: 2021-05-11
Published online: 2021-06-28

Abstract

Pancreatic cancer (PC) is a highly lethal malignancy with a 5-year survival rate of only 10% and is extremely resistant to chemotherapy. Therefore, developing effective therapeutic drugs is urgently needed. SRC is a proto-oncogenic tyrosine protein kinase and highly expressed in more than 70% of PCs. SRC is involved in regulating the proliferation, infiltration, and metastasis of PC cells as well as tumor angiogenesis, thus representing one of the most promising molecular targets for developing novel drugs. Preclinical studies demonstrate that small-molecule SRC inhibitors display significant anti-cancer activities *in vitro* and *in vivo*, and have a synergistic effect with conventional chemotherapy drugs against PC. Some SRC inhibitors have been evaluated in clinical trials. This article analyzes the regulatory mechanism of SRC and the recent progress and problems in developing drugs targeting SRC for the treatment of PC. Unfortunately, up to date no SRC inhibitor or regiment containing SRC inhibitors has been approved for the clinical treatment of PC. In the authors' opinion, the introduction of precision medicine principles to carry out SRC inhibitor clinical trials, combination of immunotherapy and SRC inhibitors, seeking more selective and effective SRC inhibitors, and further exploration of the SRC regulatory network may be the future directions for developing SRC-targeted therapies against PC.

Key Words: SRC; SRC inhibitor; Pancreatic cancer; Targeted therapy; Chemotherapy; Clinical trial

Citation: Li ZY, Sun XY. Recent progress in SRC targeted therapy for pancreatic cancer. Shijie Huaren Xiaohua Zazhi 2021; 29(12): 621-627
URL: https://www.wjgnet.com/1009-3079/full/v29/i12/621.htm
DOI: https://dx.doi.org/10.11569/wcjd.v29.i12.621

摘要

胰腺癌(pancreatic cancer, PC)致死率极高, 对化疗药物高度耐受, 患者5年生存率仅为10%. 因此, 寻找有效

的PC治疗药物是当今世界性难题. SRC是一种原癌基因酪氨酸蛋白激酶, 在超过70%的PC中呈高表达或高活性状态, 参与调控PC细胞增殖、浸润、转移及肿瘤血管生成, 是研发PC治疗药物最有希望的分子靶点之一. 大量临床前研究证实, 小分子SRC抑制剂在体内和体外实验中表现出强大的抗PC活性, 而且与常规化疗药物协同作用逆转PC耐药. 一些SRC抑制剂已经进入PC治疗的临床试验. 靶向SRC治疗PC具有广阔的应用前景. 本文分析SRC对PC的调控机制以及靶向SRC治疗PC的新进展和存在问题. 作者认为应用精准医学原则指导SRC抑制剂临床试验设计、联合应用免疫治疗、研发更高选择性和更高活性的SRC抑制剂以及对SRC调控网络进一步探讨, 可为靶向SRC治疗PC带来突破.

关键词: SRC; SRC抑制剂; 胰腺癌; 靶向治疗; 化疗; 临床试验

核心提要: SRC在70%胰腺癌中高表达. 小分子SRC抑制剂展示有效的抗胰腺癌活性, 一些SRC抑制剂进入胰腺癌治疗的临床试验. SRC是治疗胰腺癌的潜在分子靶点, 靶向SRC将成为治疗胰腺癌新希望.

文献来源: 李子一, 孙学英. 靶向SRC治疗胰腺癌的研究新进展. 世界华人消化杂志 2021; 29(12): 621-627
URL: https://www.wjgnet.com/1009-3079/full/v29/i12/621.htm
DOI: https://dx.doi.org/10.11569/wcjd.v29.i12.621

0 引言

胰腺癌(pancreatic cancer, PC)是一种致死率极高的恶性肿瘤, 预计在未来二十至三十年内将成为第二大癌症致死原因[1]. 根据我国国家癌症中心发布的最新数据, PC的发病率已高居第10位, 死亡率升高到第6位. 在一些大城市中, PC的发病率和死亡率甚至高达第7位和第5位[2,3]. 大约95%的PC是外分泌细胞肿瘤, 其中最常见的类型是胰腺导管腺癌(pancreatic ductal adenocarcinoma, PDAC)[4]. 其他类型的胰腺肿瘤如神经内分泌肿瘤通常预后较好[5]. PC起病隐匿、进展迅速、早期诊断困难, 约80%-85%的患者就诊时肿瘤已经无法切除或伴有远处转移而失去根治性治疗的机会, PC患者总体5年生存率仅约为10%[1,4]. 在过去的十年中, 由于早期诊断、手术治疗、围手术期管理、放疗技术和系统疗法等方面的进步, PC患者的预后取得一定的改善, 但是药物治疗进展十分缓慢[1].

化疗是晚期PC的主要治疗方法, 但PC对常规化疗药物高度不敏感. 吉西他滨作为临床应用多年的治疗PC一线常用药物, 并未显著延长患者的生存期. FOLFIRINOX(FOL-folinic acid [亚叶酸], F-fluorouracil [氟尿嘧啶], IRIN-irinotecan [伊立替康] 和OX-oxaliplatin [奥沙利铂])方案以及白蛋白结合型紫杉醇联合吉西他滨方案的应用, 使PC患者的生存期得到一定程度的提高[6,7]. 然而, 这些方法仅能为患者提供有限的益处而且有不可避免的毒副作用. 以免疫检查点抑制剂为代表的免疫治疗是当前癌症治疗研究的热点. 靶向细胞毒性T淋巴细胞相关蛋白4 (cytotoxic T-lymphocyte-associated protein 4, CTLA-4)和程序性细胞死亡蛋白1 (programmed cell death protein-1, PD-1)及其配体(PD-L1)的单克隆抗体在一些恶性肿瘤的临床治疗中取得显著疗效[8]. 然而, 针对PC开展的免疫检查点抑制剂治疗的临床试验研究中, 单一免疫检查点抑制剂未能取得显著提高患者生存期的效果; 联合其他药物方案显示初步疗效, 但结果尚需进一步验证[9]. 被批准用于治疗具有微卫星高度不稳定性特征癌症的广谱免疫检查点抑制剂帕博利珠单抗在PC临床试验中仅有5%的反应率[10]. 因此, 寻找有效PC治疗的分子靶点和研发有效药物是当前迫切需要解决的世界性难题.

1 SRC与癌症

SRC最初于1979年由Bishop在劳斯肉瘤病毒(rous sarcoma virus, RSV)中发现, 该基因编码酪氨酸激酶, 可引起鸡发生癌症, 被称为v-Src[11]. 在正常细胞中则被称为c-Src (cellular Src)[12]. 这一发现引起肿瘤发生理论的改变, 即存在于细胞中的基因而非外来基因可以引起癌症. 作为一种原癌基因酪氨酸蛋白激酶, SRC蛋白属于11个激酶成员的SRC家族[13,14]. 该家族成员在肿瘤细胞的增殖、迁移、粘附、侵袭和血管生成等多种信号传导途径中发挥重要作用. 在细胞外信号刺激下, SRC被激活后可诱发核因子及其转录程序的激活; 也可以与具有多种功能的蛋白质相互作用, 如参与细胞骨架重组的蛋白. SRC、YES和FYN是肿瘤细胞普遍表达的三个成员, 它们的激活或失调与多种实体瘤的发生和转移相关[14,15]. 由于在癌症发生发展中起关键作用, SRC成为研发抗癌药物的分子靶点. 当前已有几十种小分子物质被发现具有抑制SRC的活性[16]. 在细胞和动物实验中, 包括达沙替尼(dasatinib)、博舒替尼(bosutinib)和塞卡替尼(saracatinib)在内的多种SRC抑制剂显示出有效的抗肿瘤活性[17-19]. SRC抑制剂已成为癌症研究和药物研发的热点. 根据美国临床试验数据库(ClinicalTrials.gov)的信息, 到目前为止仅达沙替尼就有上百个临床试验已经开展或在进行中.

2 SRC在PC发生发展中的作用和调控机制

SRC在超过70%的临床PC组织中呈高表达或高活性状态, 通过多种机制参与调控PC细胞的增殖、浸润、转移及肿瘤血管生成[20-22]. 例如, SRC上调胰岛素样生长因子1(insulin like growth factor 1, IGF-1)的表达, 促进IGF1-1依赖的PC细胞增殖[23]. 使用siRNA沉默SRC基因通过抑制磷酸化蛋白激酶B、P38丝裂原活化蛋白激酶(mitogen-activated protein kinases, MAPKs)和细胞外信号调节激酶(extracellular signal-regulated kinase1/2, ERK1/2)的活性, 抑制PC细胞的增殖和转移[24,25]. SRC与RAS协同作用导致基因组的不稳定, 促进PC的发生, 敲除SRC可以抑制由RAS驱动的肿瘤生长[22]. KRAS也可以诱导SRC、PEAK1和ERB-B2组成的激酶扩增环路, 驱动PC细胞的增殖和转移; 但抑制ERB2却增加了SRC依赖的PEAK1的表达以及PEAK1依赖的SRC激活[26].

SRC的激活受多种因素的调节. 天冬氨酸β羟化酶与ADAM12/ADAM15结合可激活SRC信号通路, 促进PC的发展和转移[27]. S100A4蛋白可促进SRC和粘着斑激酶(focal adhesion kinase, FAK)的激活, 抑制S100A4蛋白表达可抑制SRC的磷酸化和PC的侵袭、转移以及血管生成[28]. 另外, 肿瘤缺氧微环境及肿瘤微环境中的炎性细胞因子均可激活SRC, 并参与细胞间的通讯[17,29].

SRC被激活后可以调控下游的一系列信号通路和分子. SRC促进信号传导与转录激活子3(signal transducers and activators of transcription 3, STAT3)的磷酸化[30]. 尽管SRC与JAK之间无相互调控作用, 但二者可以联合促进STAT3的磷酸化[31]. STAT3的磷酸化是PC化学耐药性的关键因素[32]. 靶向抑制SRC可以抑制STAT3介导的信号通路, 促进吉西他滨的抗PC效果[33]. SRC在PC细胞核内与STAT3和表皮生长因子受体(epidermal growth factor receptor, EGFR)组成复合体, 与原癌基因c-Myc结合并促进其转录功能; 同时 SRC可直接磷酸化EGFR介导EGFR的反式激活[34]. EGFR激活的失控是导致PC进展和预后不良的主要因素之一[35]. PC细胞中血小板衍生生长因子(platelet-derived growth factor, PDGF)和SRC的共表达可以诱发WNT/β-catenin信号通路关键分子的突变, 从而导致PC的复发[36]. SRC还可以与P300结合, 促进P300酪氨酸磷酸化, 与高迁移率族蛋白A2(high-mobility group protein A2, HMGA2)和组蛋白甲基转移酶SMYD3(SET and MYND domain-containing protein 3)启动子结合, 上调其表达, 进而促进PC细胞的迁移[37]. SRC的持续激活可导致使DNA甲基转移酶1相关蛋白(DNA methyltransferase 1-associated protein, Dmap1)在Tyr 246位点发生磷酸化, 阻止DMAP1和有丝分裂检查点蛋白BUB3的相互结合, 抑制DMAP1/Bub3的促DNA甲基化作用, 进而促进PC细胞的增殖和对化疗药物的耐受[38].

3 抗PC SRC抑制剂的研发进展

基于缺乏有效靶向治疗药物和PC普遍存在SRC高表达或高活性的现实, 加上大量研究发现SRC参与调控PC细胞的多种恶性生物学行为, SRC被认为是研发治疗PC药物最有希望的分子靶点之一, SRC抑制剂也成为抗PC药物的重点筛选对象.

3.1 达沙替尼 达沙替尼是研究最多的抗PC SRC抑制剂, 它通过竞争性与三磷酸腺苷(adenosine triphosphate, ATP)位点结合抑制SRC和Abl激酶的活性. 2017年, 达沙替尼被FDA批准用于费城染色体阳性(Ph+)慢性粒细胞白血病的临床治疗. 大量临床前研究发现, 达沙替尼可通过多种通路抑制PC细胞增殖、粘附、迁移、侵袭和转移[20-22]. 达沙替尼还可以下调上皮间质转化(epithelial-mesenchymal transition, EMT)转录因子SLUG的转录降低, 上调标志蛋白E-钙粘素的转录和翻译, 进而抑制PC细胞的EMT[39]. 然而, 在PC临床试验中, 达沙替尼未能取得如治疗其他类型癌症(如白血病)的效果[40].

3.2 塞卡替尼 与达沙替尼一样, 塞卡替尼具有选择性抑制SRC和Abl激酶的双重活性. 动物实验中, 塞卡替尼可以降低FAK和STAT3信号传导有效抑制PC移植瘤的生长[41]. 然而, 二期临床试验表明, 塞卡替尼并不能改善PC患者的生存期, 并且生物标志物阳性(LRRC19>IGFBP2和PIK3CA突变)患者的频率<3%[42].

3.3 博舒替尼 博舒替尼是一种双重SRC/Abl抑制剂, 已被批准用于费城染色体阳性慢性粒细胞白血病的治疗. 在临床试验中, 博舒替尼显示出比伊马替尼更好的疗效, 尽管服用博舒替尼后患者胃肠道反应更多[43]. 博舒替尼在动物实验中显著抑制PC移植瘤的生长并且抑制STAT3信号传导[44]. 目前, 尚未有博舒替尼治疗PC的临床试验研究报告.

3.4 PP2 PP2是一种ATP竞争性的SRC家族抑制剂. 研究发现PP2具有多方面的抗PC活性. PP2可抑制SRC磷酸化进而下调白介素-8的表达, 抑制PC肿瘤血管生成, 这种抑制作用与ERK1/2和P38 MAPK通路相关[24]. PP2可以抑制PC淋巴管生成, 进而抑制PC的转移[45]. PP2通过抑制转化生长因子β(transforming growth factor-β, TGF-β)受体的功能, 抑制TGF-β介导的信号通路[46]. PP2还可以减少PC干细胞的自我更新以及成瘤性[47]. PP2下调核糖核酸还原酶M2(ribonucleotide reductase M2, RRM2)的表达, 进而降低RRM2调节的转录因子E2F1的活性, 逆转PC的吉西他滨耐药[48]. 然而, 也有研究发现, PP2可抑制PC PK-9和MIA PaCa-2细胞中吉西他滨的抗

肿瘤活性[49], 说明PP2抑制SRC曾敏吉西他滨的效果可能具有细胞依赖性.

3.5 其他SRC抑制剂 CCT3833在KRAS突变的PC中具有显著的抗癌活性, 说明SRC可能是KRAS突变驱动PC的关键治疗靶点[50]. AZM475271通过降低促癌信号TGF-β1的激活, 抑制PC细胞的增殖和转移[51]. KX2-391可以降低PC患者血液中肿瘤标志物CA-199的水平(从38838 U/mL降至267 U/mL)[52]. Oblongifolin C通过泛素-蛋白酶体系统降解SRC, 进而抑制MAPK/ERK信号通路, 提高吉西他滨耐药PC细胞的敏感性, 引起细胞在G0/G1期阻滞, 抑制PC的生长[53].

3.6 多激酶抑制剂 除上述选择性SRC抑制剂外, 一些多激酶抑制剂也具有抑制SRC的活性和抗PC潜力. 例如, 多激酶抑制剂LY-1816可以抑制SRC, 进而抑制PC细胞的增殖、侵袭和迁移; 在动物实验中, LY-1816表现出比达沙替尼和吉西他滨更强的抗癌活性[54]. 新型多激酶抑制剂SKLB261可有效抑制SRC激酶的活性, 抑制PC细胞的增殖、迁移、侵袭并诱导细胞凋亡; 在PC异种移植瘤模型中显示出强大抗血管生成作用, 并且展示出强于达沙替尼、厄洛替尼或吉西他滨的抗肿瘤活性[55].

3.7 SRC抑制剂和其他药物的联合应用 到目前为止, 还没有一种SRC抑制剂在临床试验中被证实具有显著的抗PC活性, 部分原因是由于药物耐受性差, PC基因不稳定对单一药物具有高度适应性迅速产生耐药可能是主要原因[44]. 因此, 联合应用SRC抑制剂与其他药物的治疗策略在科学上更合理, 这样可以增强抗肿瘤功效, 同时最小化固有和获得性耐药性[48,56].

达沙替尼、厄洛替尼和吉西他滨的组合在临床前研究中展示出显著的协同作用, 有效抑制了PC细胞的增殖和移植肿瘤的生长[32]. 达沙替尼可以抑制奥沙利铂诱导的SRC活化, 进而提高奥沙利铂的抗癌活性[57]. MCL-1(myeloid cell leukemia-1)拮抗剂S63845与达沙替尼协同抑制PDAC细胞的增殖和转移[58]. PP2与氟尿嘧啶联合后, 显著降低氟尿嘧啶引起的EGFR/AKT通路的激活, 减少对氟尿嘧啶的化疗抵抗性, 抑制PC细胞的增殖和转移[56]. AZM475271显著提高了吉西他滨的抗肿瘤作用[21]. 然而, 临床试验结果同样让人失望, 达沙替尼和吉西他滨联合治疗晚期PC的临床试验并没有发现达沙替尼可以提高吉西他滨的疗效, 而且因为联合应用毒副作用叠加[59]. 同样, 塞卡替尼与吉西他滨联合使用也未发现可提高吉西他滨的抗癌效果[60].

在对其他实体瘤包括黑素瘤、肉瘤、结肠癌和乳腺癌等的研究发现, 达沙替尼等SRC抑制剂具有很强的免疫调节功能[61], 提示SRC抑制剂可能是免疫疗法的辅助手段. 当前有一项正在进行的II期临床试验正在评估达沙替尼和抗PD-1治疗药物nivolumab组合(NCT02750514)对非小细胞肺癌的治疗作用. 当前, 尚无针对PC的这方面研究报道. PC免疫抑制性微环境是导致免疫治疗效果不理想的重要因素[62], 因此, 有必要开展包括达沙替尼在内的SRC抑制剂和免疫疗法协同作用的研究.

4 结论和展望

PC对药物的耐受是导致治疗效果差的主要原因之一. SRC在超过70%的PC中高表达, 参与调控细胞增殖和转移等信号通路, 是研发靶向药物的重要分子靶点. 尽管在临床前研究中, 多种SRC抑制剂展现出明显的抗PC效果, 但是临床试验并未取得预期结果. 至今尚无一种SRC抑制剂或SRC抑制剂与其他药物联合用药方案被批准用于临床胰腺癌治疗.

针对靶向SRC治疗PC存在的问题, 作者认为可从如下四个方面入手进一步研究. 首先, 尽管临床试验中达沙替尼没有能够提高总体生存期, 但一些PC对达沙替尼表现出持久而稳定的药物反应[40]. 众所周知, PC具有高度异质性[63]. 当前针对SRC抑制剂的PC临床试验未均根据肿瘤分子标志物对患者进行预筛选. 如果能够按照精准医学的原则首先把PC患者细分为不同的亚群, 使治疗药物更有针对性于特定人群, 可提高药物的准确性, 而且避免因选用无效药物而导致的额外费用和毒副作用[64]. 其次, 免疫治疗被认为是当今最有前途的癌症治疗方法, 如果能将SRC抑制剂与免疫治疗结合起来, 无疑是有潜力的治疗策略; 同时可有效解决因免疫抑制性微环境导致的PC免疫治疗效果不理想的问题[62]. 再次, 现有的SRC抑制剂除抑制SRC活性外, 还可以靶向其他激酶, 脱靶(off-target)效应既可导致其疗效欠佳, 也是毒副作用较大的原因. 因此, 需要研发具有更高选择性和更高活性的SRC抑制剂. 最后, 利用单细胞测序、组学技术、生物信息学与大数据分析对复杂的SRC调控网络进一步研究, 可为精准医学和靶向药物的研发提供理论基础. 总之, PC对化疗药物高度耐受, 寻找有效的治疗药物是迫在眉睫的难题. SRC在PC中普遍高表达, 参与多种PC细胞恶性生物学行为的调控; SRC抑制剂在其他恶性肿瘤的临床治疗中取得突破性进展. 因此, SRC无疑是调控PC的重要分子靶点, SRC抑制剂药物的进一步精准研发和临床研究的科学设计可为PC的药物治疗带来突破.

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科学编辑: 刘继红 制作编辑: 张砚梁

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ISSN 1009-3079