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Src 激酶家族与紫杉醇耐药相关性的研究进展

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摘要 Src 激酶家族(SFK)在许多恶性肿瘤中均有高表达,对于肿瘤细胞的恶性行为具有广泛的调节作用。紫杉醇是临床上广泛应用的化疗药物,但由于耐药性的出现使其疗效逐渐下降。本文就 SFK 的结构与调节方式、紫杉醇耐药产生的分子机制以及 SFK 调节紫杉醇耐药的研究进展进行综述,以期为基于紫杉醇的肿瘤治疗方案提供新的治疗参考依据。

关键词 Src 激酶家族;紫杉醇;肿瘤耐药;进展

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Advances of Src kinase family and paclitaxel resistance

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Abstract Src family kinase (SFK) highly expresses in many types of cancers, broadly adjusting their malignant behaviors. Paclitaxel is a widely used chemical agent. However, because of constant resistance, the effect of paclitaxel has been greatly attenuated. The present review summaries the recent research progress of the structure and adjustment of SFK and the molecular mechanism of paclitaxel resistance, as well as the regulation of SFK on paclitaxel resistance, in order to provide new references and evidences upon the paclitaxel-based tumor therapy.

Key words Src kinase family; paclitaxel; cancer resistance; advances

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Src 激酶家族(SFK)是一类膜相关非受体酪氨酸激酶,其成员包括 c-Src、Fyn、c-Yes、Lyn、Lck、c-Fgr、Blk、Hck 以及 Yrk^[1]。Lyn、Lck、c-Fgr、Blk、Hck 仅在造血细胞中表达,而 c-Src、Fyn、c-Yes 则在多种细胞中都有表达^[2]。SFK 可以调节许多生物学过程,如细胞的增殖、分化、自噬、黏附、死亡、侵袭、血管生成等^[3]。

紫杉醇由美国化学家 Monroe E. Wall 和 Man-sukh C. Wani 从太平洋红豆杉的树皮中分离并命

名^[4],广泛用于乳腺癌^[5]、卵巢癌^[6]、头颈癌^[7]等实体瘤的治疗。紫杉醇的主要作用机制为与 β -tubulin 结合,稳定微管,从而干扰细胞的正常周期^[8]。近二十年来,以紫杉醇为中心的化疗治疗方案已经广泛运用于临床^[9-10],然而虽然 70% 以上的病人在治疗开始阶段对紫杉醇的应答良好,但经一段时间的治疗之后,由于耐药的出现,病人对紫杉醇的敏感性逐渐下降^[11],大大制约了疾病的治疗。为提高紫杉醇的治疗效果,国内外学者对引起

紫杉醇耐药的分子机制进行了广泛而深入的研究。探究耐药的分子机制,从分子水平用药物靶向干预,才能更好地提高治疗效果,造福于人类。

研究表明,Src 激酶家族与微管稳定性有紧密联系^[12],截至 2016 年,Src 抑制剂达沙替尼与紫杉醇联用的治疗方案已进入 II 期临床试验^[13]。说明靶向于 Src 激酶家族以提高紫杉醇的疗效具有较好的研究前景。本文主要对 Src 激酶家族与紫杉醇耐药的关系的研究进行总结,以期为提高以紫杉醇为主的治疗方案的疗效提供理论参考和依据。

1 Src 激酶家族

1.1 Src 激酶家族的结构与激活方式

Src 激酶家族(SFK)成员的结构相似,通常由 4 个的 Src 同源结构域(SH1~SH4)、每种激酶特有的特殊结构域(UD)以及含有酪氨酸残基的碳端结构域(CT)组成(图 1)。SH1 结构域是 SFK 的催化结构域,SH2 结构域负责介导酪氨酸磷酸化依赖性的蛋白与蛋白的相互作用,SH3 结构域则介导通过结合在富含脯氨酸的结构域的蛋白与蛋白的相互作用^[14]。

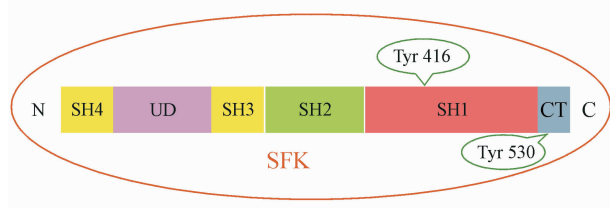


图 1 Src 激酶家族(SFK)的结构

在 SH1 结构域上有一个酪氨酸自磷酸位点(Y416),这个位点的磷酸化可以为底物提供一个与 SFK 结合的区域^[15]。SFk 最重要的酪氨酸调节亚基是位于 CT 结构域的 Y530,这是 SFK 的一个负性调节位点。Y530 可以被 c-Src 以及 c-Src 的同源激酶磷酸化,通过折叠 SH2 和 CT 结构域而使 SFK 上被磷酸化了的酪氨酸位点无法与靶蛋白结合,从而抑制 SFK 的活性^[2,15]。

除了通过酪氨酸残基的磷酸化调节之外,SFK 还可以通过 SH2/SH3 直接调节蛋白相互作用,或者由受体蛋白和自由基调节^[14,16-19]。SFk 可以由 SH2/SH3 的配体,如自磷酸化受体的磷酸化酪氨酸残基,或者 β -arrestin 的脯氨酸区域调节^[20]。受体蛋白 Cbp/PAG 是 E3 泛素连接酶,它可以通过与

SFK 及其下游信号分子作用,对其进行正性或负性的调节^[21-22]。在造血细胞中,受体 LIME、LAT 和 NTAL 可以调节 SFK 的活性^[22]。SFk 的 SH1、SH2 结构域上有高度保守的半胱氨酸残基(Cys245、Cys487),可以被活性氧化和激活^[19],受细胞内自由基的调控。此外,蛋白酪氨酸磷酸酶 SHP-2 可以使 SFK 的 Y530 位点去磷酸化,从而激活 SFK^[23]。

在许多实体瘤(结肠癌、乳腺癌、卵巢癌、肺癌等)中可以检测到 SFK 尤其是 c-Src 的过表达^[24-27]。野生型 SFK 与肿瘤的发生、进展过程联系较为紧密。现阶段对 SFK 调节机制的研究表明,恶性肿瘤中高表达的 SFK 通过调控调节下游转录因子(如 EGFR、HER2、c-Met)和信号通路调节肿瘤细胞的行为^[28]。

2 紫杉醇耐药的分子机制

紫杉醇通过与 β -tubullin 结合稳定微管,从而使细胞停滞于 G₂/M 期,继而细胞的增殖、细胞形态、细胞内的大分子和细胞器均可能受到影响,最终导致细胞的死亡^[29]。

2.1 微管调节蛋白的影响

许多蛋白(如 MAP4、stathmin、TGFB1、Tau 蛋白等)可以直接与微管蛋白作用,调节微管的聚合和稳定性^[30]。由于紫杉醇的作用主要依赖于微管稳定性的维持,因此,影响微管生物学功能的过程都有可能与紫杉醇耐药相关。细胞中高表达或激活 MAP4(磷酸化),可以稳定微管,增强紫杉醇的作用,而促进微管解聚的蛋白 stathmin 则与 MAP4 作用相反^[31]。TGFB1(一种细胞外基质蛋白)的缺失,可以通过 integrin 依赖性的微管蛋白的去稳定而引起卵巢癌细胞对紫杉醇的耐药^[32]。Tau 蛋白可以作用于 β -tubullin,使紫杉醇与 β -tubullin 结合减少,微管的聚合受到影响^[33]。Xie 等^[34]认为,Tau 蛋白的表达水平可以作为判断肿瘤细胞是否对紫杉醇耐药的指标。

2.2 凋亡信号通路的影响

许多重要的凋亡调节因子(如 p53、survivin、Bcl-2 等)均可与微管蛋白相互作用,且影响微管的功能^[35-36]。某些凋亡调节因子的异常会影响微管的装配、稳定以及细胞内信号传递,引起紫杉醇耐药。虽然 Debernardis 等^[37]认为,p53 的突变对紫杉醇耐药的影响极小,但改变 p53 的表达和结构可以

通过影响微管的行为调节紫杉醇的作用^[36]。抗凋亡蛋白 Bcl-2 的过表达则会增强紫杉醇的耐药^[38]。

Survivin 是凋亡蛋白抑制因子家族成员之一,它在细胞分裂与凋亡的调节中都发挥着重要作用^[39-40]。紫杉醇可以上调 survivin 的表达,从而减弱自身诱导细胞凋亡的作用^[41]。Zaffaroni 等^[42]研究发现,70% 以上的晚期乳腺癌组织中可以检测到高水平的 survivin,且与临床出现的紫杉醇耐药呈相关性。除抑制细胞凋亡,survivin 还可以稳定微管,因此,其抑制凋亡的能力因与紫杉醇的相互作用而增强。使用多种方式沉默 survivin,可以增强紫杉醇诱导的凋亡^[40-41,43]。Song 等^[39]发现,抑制 Smac 和激活 caspase,使 survivin 下调,同样可以增强凋亡诱导作用。另外,由于 survivin 可以稳定微管蛋白,所以除了抑制凋亡,增加 survivin 的表达还会引起诱导微管解聚药物(如长春花碱)的耐药^[44]。

2.3 P-糖蛋白的影响

细胞内紫杉醇的药物浓度取决于细胞对于药物的摄取和外排。紫杉醇是一个疏水分子,可以由肿瘤细胞摄取,并由跨膜 ABC 转运体外排。现有研究表明,有 15 种 ABC 转运蛋白与耐药相关,与紫杉醇耐药相关的有 P-糖蛋白、ABCC10(MRP7)和 ABCB11(BSEP/PFIC2/SPGP)^[45]。高表达 P-糖蛋白的乳腺

癌和卵巢癌细胞对紫杉醇的应答较差,而且易引起预后不良^[46-47]。Oguri 等^[48]发现,在 17 种非小细胞肺癌细胞中高表达的 ABCC10 在紫杉醇耐药中发挥的作用比 P-糖蛋白的作用大。除转运体蛋白高表达之外,P-糖蛋白基因有将近 50 种 SNPs(单基因多态性),基因表达的不同会使转运蛋白的功能及其对紫杉醇的外排能力改变,引起耐药^[45]。

2.4 β-tubulin 突变的影响

β-tubulin 是紫杉醇的主要作用靶点,因此,β-tubulin 突变可能会影响微管的装配、运动和稳定性,引起紫杉醇耐药^[30]。Yin 等^[49]利用随机突变的 β-tubulin cDNA 转染 CHO 细胞,从而发现有 28 种 β-tubulin 突变与紫杉醇的耐药相关。而 Ale 等^[50]检测了呈 30 种紫杉醇耐药细胞株的移植瘤,但并未发现其中有 β-tubulin 的突变。而且到目前为止,β-tubulin 突变与紫杉醇耐药产生的分子机制尚未明确。因此,β-tubulin 突变与紫杉醇耐药的关系仍需后续研究进一步完善。

3 SFK 与紫杉醇耐药的研究

SFK 在肿瘤细胞中的过表达可以通过调节转录因子和信号通路对细胞的行为进行调控(图 2),紫杉醇可以通过干扰细胞周期的进程,诱导细胞发生凋亡、自噬等过程,最终导致细胞的死亡。

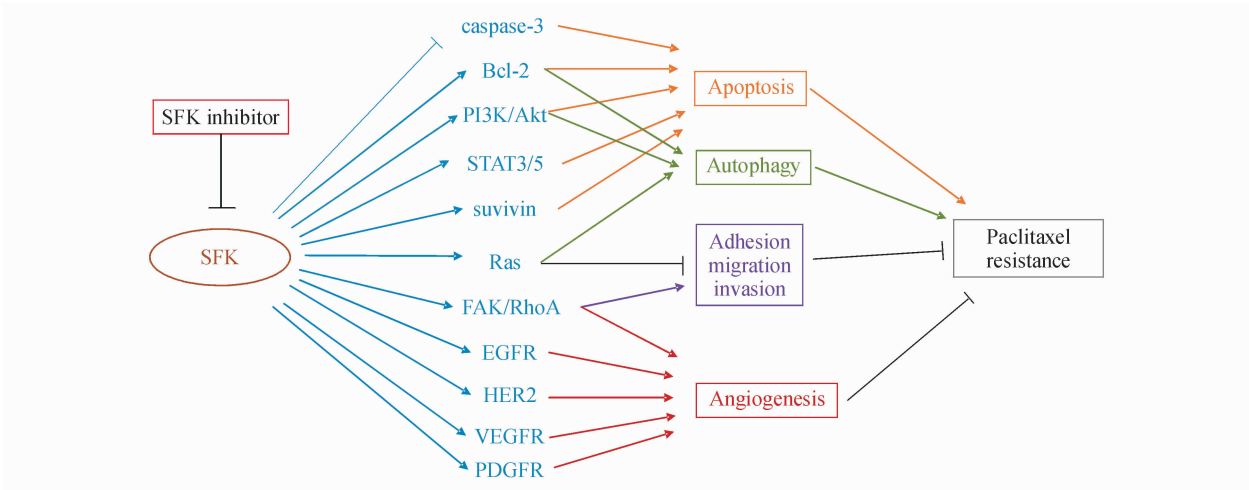


图 2 SFK 调控紫杉醇耐药的分子机制

SFK 抑制剂调节效应蛋白、转录因子、信号通路,通过增强凋亡、自噬、细胞黏附、侵袭和转移以及血管生成,逆转细胞对紫杉醇的耐药现象。

3.1 调节细胞凋亡

诱导凋亡是紫杉醇的一个重要作用机制。

SFK 可以直接调节凋亡相关蛋白的表达。沉默 SFK,可以激活 caspase-3^[51],使 survivin^[52]、Bcl 家族中的 Bcl-2^[53]、Mcl-1^[54]和 Bcl-xl^[55]下调,逆转细胞对紫杉醇的耐药。此外 SFK 抑制剂可以通过抑制 PI3K-Akt^[56]通路、抑制转录因子 STAT3/5^[54]的

激活,达到逆转耐药的效果。此外,SFK可以磷酸化肿瘤抑制因子FHIT的114位酪氨酸残基,从而抑制FHIT的功能。因为FHIT可以同时抑制survivin和AKT,SFK抑制剂可以激活FHIT,增强紫杉醇诱导的凋亡。

3.2 调节细胞自噬

细胞的自噬作用通过细胞器消化、释放氨基酸和脂肪酸过程,为ATP的形成提供了底物,使细胞可以在恶劣的环境下存活^[57]。持续性的自噬,可以引起细胞的2型程序性死亡^[58]。研究表明,抑制SFK可以诱导自噬。在卵巢癌细胞中,SFK抑制剂达沙替尼所诱导的自噬与两个关键的自噬调节基因Beclin-1和Atg12有关^[53]。另外,诱导自噬可以增强紫杉醇的抗肿瘤活性:Ras相关特征基因ARHI,可以抑制卵巢癌和乳腺癌细胞的增殖和转移,并诱导自噬^[59]。随后Zou等^[60]发现,ARHI的表达可以诱导自噬,并增强紫杉醇对细胞增殖的抑制作用。在宫颈癌细胞中,增加抗自噬蛋白Beclin-1的表达,可以增强由紫杉醇诱导的自噬和凋亡^[61]。这些研究都说明,紫杉醇的耐药很可能可以通过SFK的调节作用逆转。虽然抑制SFK调节自噬的确切机制仍未明确,但抑制SFK,使Bcl-2表达和AKT-mTOR-p70S6K通路受到抑制,仍是该调节机制中重要的组成部分^[56]。

3.3 调节微管稳定性

紫杉醇的作用依赖于微管的稳定性。MAP4^[62]、E-MAP-115^[63]、TGFB1^[32]的表达增加,statmin^[64]、survivin^[40-41,43]的表达减少,可以促进微管的装配,增加其稳定性,从而改善细胞对紫杉醇耐药的现象。在裸鼠异种移植瘤模型中,tubulin结合辅助因子C(TBCC)可以增强紫杉醇对乳腺癌细胞的作用^[65]。SFK中的Fyn可以调节微管的多聚化和纺锤体的稳定性^[66-67]。因此,SFK很可能通过调节微管的稳定性调节细胞对紫杉醇的耐药现象。SFK的抑制剂PP2(抑制Lck和Fyn)可以增强人卵巢癌细胞耐药株CaOV3TaxR与小鼠卵巢癌细胞耐药株ID8TaxR中微管的稳定性,逆转耐药细胞株对紫杉醇的抵抗性^[68]。此外,Fyn可以磷酸化MAP2 67位的酪氨酸残基,磷酸化的MAP2可以与受体蛋白Grb2结合^[69],Fyn还可以与tubulin结合^[66-67]。因此,SFK可以通过直接或者间接调控的方式影响微管的装配与稳定性,调控细胞对紫杉醇的耐药。

3.4 调节肿瘤血管生成

肿瘤血管的形成是所有实体瘤的一个重要的也是共同的特点^[70]。由肿瘤细胞与肿瘤微环境的共同作用产生的促血管生成因子,如VEGF、IL-8等,通过促进上皮细胞的增殖和迁移,促进实体瘤中血管的形成^[70]。人类及其他哺乳动物细胞中都有高表达的VEGF受体^[71],血管周围细胞则可以通过激活PDGF-PDGFR细胞通路稳定血管和使血管成熟化^[72]。在乳腺癌治疗中,联用曲妥珠单抗和VEGF-Trap同时靶向肿瘤细胞和内皮细胞,可以显著抵制血管生成^[71]。在卵巢癌治疗中,联用与FDGF具有良好亲和力但无内在活性的适配体AX102和贝伐单抗同时靶向血管周围细胞和内皮细胞,也可以显著抑制血管生成^[73]。

抑制SFK可以抑制肿瘤细胞中的EGFR^[74]、HER2通路^[75]、内皮细胞中的VEGFR通路^[76]以及血管周围细胞中的PDGFR通路^[77],还可以引起下游靶点的抑制,如FAK、RhoA等,从而调控细胞的侵袭转移、增殖及血管生成。而紫杉醇也可以抑制内皮细胞、血管周围细胞和肿瘤细胞的增殖和转移^[35,78-79],若细胞对紫杉醇耐药,紫杉醇抑制血管生成的作用会被大大削弱。因此使用SFK抑制剂,对内皮细胞、血管周围细胞及肿瘤细胞本身的血管生成相关通路进行调节,也可称为逆转紫杉醇耐药的一种途径。Monache等^[80]研究表明,Src抑制剂S13可以通过抑制VEGF2的激活和FAK表达,抑制肿瘤血管生成,增强紫杉醇对肿瘤生长的抑制。此外,在乳腺癌、肺癌、结肠癌和肾癌动物模型中,由于紫杉醇对内皮细胞有强杀伤作用,可以反过来增强贝伐单抗、舒尼替尼的抗肿瘤作用^[81]。

4 总结与展望

当前,在临床应用中,紫杉醇单用或与其他化疗药物联用,已成为包括卵巢癌、乳腺癌、肺癌在内的恶性肿瘤的首选药物。同时,由于紫杉醇的周期阻滞作用,可以使肿瘤细胞阻滞于G₂/M期,因此,紫杉醇也可用于肿瘤化疗或放疗的增敏^[82]。然而由于耐药性的出现,又使紫杉醇为主的治疗方案的应用受到制约。SFK在多种肿瘤细胞中高表达,同时在肿瘤细胞中具有广泛的调节作用。紫杉醇的直接靶点为 β -tubulin,而 β -tubulin又是微管装配的主要原料。从微管稳定性角度而言,SFK抑制剂

可以通过直接结合 tubulin 或者通过调节微管结合蛋白增强微管的稳定性,逆转细胞对紫杉醇的耐药;诱导凋亡是紫杉醇的重要作用之一,SFK 抑制剂可以直接调节凋亡蛋白的表达,或者调节凋亡相关通路,增强紫杉醇对紫杉醇耐药细胞的凋亡诱导作用;紫杉醇可以抑制实体瘤血管生成,SFK 抑制剂可以通过调节内皮细胞、血管周围细胞和肿瘤细胞本身的信号通路,加强紫杉醇的抑瘤作用;紫杉醇还可诱导自噬,SFK 通过调节自噬相关基因或其转录因子,紫杉醇的增殖抑制作用。近来发表的研究表明,SFK 抑制剂使激活的 caspase 8 去磷酸化,从而使紫杉醇抵抗细胞的坏死性凋亡增加^[83]。

虽然 SFK 调控紫杉醇耐药的分子机制仍未完全阐明,但 SFK 抑制剂与紫杉醇联用确已收到较为良好的效果。临床前研究中,Src 抑制剂达沙替尼与紫杉醇联用,通过抑制 Src 的激活,显著提高紫杉醇对卵巢癌细胞增殖的抑制作用^[84]。临床研究方面,I 期临床实验表明,受试者对 Src 抑制剂与紫杉醇联用的治疗方案耐受性较好^[13,85-86];II 期临床实验进一步对两者联用的有效性和安全性进行考察^[13],但对实验结果的分析目前仍未见报道。因此,研究 SFK 对紫杉醇耐药的作用及作用机制可为基于紫杉醇的肿瘤治疗方案提供新的治疗参考和依据。

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