Rac1在肿瘤耐药中的研究进展

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摘要 Ras相关C3肉毒毒素底物1(Ras-related C3 botulinum toxin substrate 1, Rac1)对于包括癌症在内的各种疾病的发展和进展至关重要, 并且已有研究表明Rac1与肿瘤耐药性相关。该综述概述了Rac1在调节耐药性中的作用, 以及相关机制和可用的抑制剂, 这可能为未来靶向癌症耐药性的治疗提供新的方向和选择。

关键词 Rac1; 癌症; 耐药性; 抑制剂

Advances in the Research of Rac1 in Tumor Drug Resistance

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Abstract Rac1 (Ras-related C3 botulinum toxin substrate 1) is critical for the development and progression of various diseases, including cancer, and it has been shown that Rac1 is associated with drug resistance. This review outlines the role of Rac1 in modulating drug resistance, and the associated mechanisms and available inhibitors, which may provide new options for future therapies targeting cancer drug resistance.

Keywords Rac1; cancer; drug resistance; inhibitor

Ras相关C3肉毒毒素底物1(Ras-related C3 botulinum toxin substrate 1, Rac1)是鸟苷三磷酸水解酶(GTPases) Rac家族的成员, 是小GTPases Rho家族的一个亚科, 在多种细胞活动中起分子开关作用[1]。Rac1、Rho和Cdc42是小GTPases Rho家族中最重要的三个特征成员, 其中Rac1的相关研究最多[2]。自被发现以来, Rac1参与了各种细胞功能, 包括细胞迁移和侵袭、细胞黏附、细胞增殖、细胞凋亡、活性氧(reactive oxygen species, ROS)的产生和炎症反应等[3]; 并且Rac1在许多癌症(例如卵巢癌、宫颈癌、乳腺癌、胃癌和肝细胞癌)中高度表达和过度激活[4-8]。越来越多的研究表明, Rac1是肿瘤治疗的潜在靶点, 并且在调节肿瘤耐药性中发挥着重要作用[9]。本文就Rac1在肿瘤耐药性中的作用和相关调控机制, 以及靶向Rac1的抑制剂予以综述。

1 Rac1的分子结构和活性调节

1.1 Rac1的分子结构

人类*Rac1*基因的分子量约为21 kDa, 其位于7p22染色体上, 由7个外显子组成, 基因全长约为29 Kb。*Rac1*基因编码的蛋白质是一种GTP酶, 包含192个氨基酸, 属于小GTP结合蛋白的RAS超家族。Rac1的N-端包含一个由G1~G5共5个序列组成的保守的G结构域, GDP/GTP结合和GTP水解由该结构域介导。Rac1的C-端包含一个高变区(hyper-variable region, HVR)[10-11], C末端序列项为CAAX(C代表半胱氨酸, A代表脂肪族氨基酸, X代表任何氨基酸), 它是一个共识序列, 其在Rac1进行翻译后修饰时来确定蛋白

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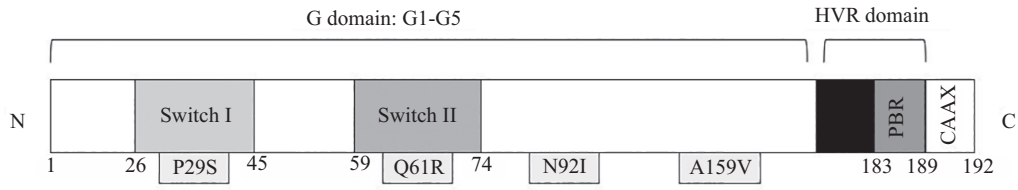


图1 Rac1的分子结构

Fig.1 Molecular structure of Rac1

质的亚细胞定位[12], 以便Rac1发挥其生物学功能。Rac1 P29S或N92I的突变体可以通过促进Rac1固有非活性结合状态(Rac1-GDP)的分解来提高活性结合状态(Rac1-GTP)的水平, 从而形成“自发激活”状态, 促进肿瘤的发生[13-14]。其他形式的Rac1突变体也在肿瘤中被发现, 如头颈部肿瘤中常见的Rac1 A159V突变和原发性前列腺癌中常见的Rac1 Q61R突变[15-16](图1)。

1.2 Rac1的活化

Rac1通常循环于失活状态(GDP结合状态)以及活性状态(GTP结合状态)之间。Rac1的活性主要由鸟嘌呤核苷酸交换因子(guanine nucleotide exchange factors, GEFs)和GTP酶激活蛋白(GTPase-activating proteins, GAPs)调节。其中GEFs通过将Rac1-GDP转换为Rac1-GTP来激活Rac1, 而GAPs通过将Rac1-GTP水解为Rac1-GDP来使Rac1失活[17]。而GDP解离抑制因子(guanine nucleotide dissociation inhibitors, GDIs)可以抑制胞质中GDP从GTPases上解离, 使GTPases远离其调节因子和效应因子, 从而阻断蛋白活性[18]。开关I和II直接参与活性GTP结合状态的形成, 并在核苷酸交换和水解时经历结构重排, 这是启动细胞内信号级联的重要步骤[19]。

1.3 GEFs参与Rac1的活性调节

Rac1信号转导的核心是GEFs, GEFs分为Dbl或DOCK家族, 它们介导GEFs活性的结构域不同。Dbl GEFs具有负责其GEFs活性的特征Dbl同源(Dbl homology, DH)结构域, 而DOCK GEFs缺乏DH结构域, 但具有2个高度保守的区域, 被称为DOCK同源区域1/2(Dock homology region 1/2, DHR1/2), 其中DHR2结构域的失活已被证明可以阻断Rac的激活、细胞迁移和吞噬作用[20], 并且GEFs的失调, 通常与肿瘤进展和患者预后不良有关[21]。

GEFs的异常表达与Rac1的活化有关。GEFs家族由80多个成员组成, 至少有20个直接参与激活Rac1[22], 例如: 磷脂酰肌醇-3,4,5-三磷酸依赖性Rac交换因子1(PIP3-dependent Rac exchanger 1, P-Rex1)、VAV2/3鸟嘌呤核苷酸交换因子(guanine nucleotide exchange factor VAV2/3)和T淋巴瘤侵袭转移诱导因子1(T lymphoma invasion and metastasis induction factor 1, Tiam1)[23]。其中Tiam1是Rac1的特异性GEF, Tiam1-Rac1信号转导在癌症的发生和进展中发挥重要作用[24]。除此之外, Trio(triple functional domain)和Kalirin也是两个独特的GEFs, 两者都具有双GEFs结构域, 并且Trio可以通过激活Rac1来调节肿瘤细胞的迁移和侵袭[25]。例如, Trio的下调会使胃癌细胞中的Rac1活性显著降低, 并且削弱细胞的迁移和侵袭能力[26]。SOS1(Son of sevenless-1)为一种双效GEF, 当SOS1与表皮生长因子受体途径底物8(epidermal growth factor receptor pathway substrate 8, EPS8)和Abi结合因子1(Abi-interactor 1, ABI1)结合形成三重复合物时, 该复合物则具有Rac-GEF的作用[27-28]。复合物中EPS8为酪氨酸激酶受体的作用底物, ABIl为非受体酪氨酸激酶。已证明三重复合物SOS1/ABI1/EPS8能够活化Rac1, 从而激活Rac1的相关生物学功能[29]。

2 Rac1介导肿瘤耐药的相关机制

2.1 Rac1促进肿瘤化疗耐药性

化疗是最常用的癌症治疗方法之一, 既是辅助治疗方式, 也是新辅助手段。尽管其被广泛使用, 但对化疗药物的耐药性仍然是成功治疗癌症的一个主要问题。化疗耐药性主要归因于DNA的修复能力增强、细胞凋亡数减少和上皮–间充质转化(epithelial-mesenchymal transition, EMT)等机制[30]。在GEFs激活Rac1后, 可以引起与化疗耐药相关的一些下游信号通路的激活。在此我们阐述了以下几种相关机制: Rac1通过激活WASp家族Verprolin同源蛋白2(Wiskott-Aldrich syndrome protein family verprolin-

homologous protein 2, Wave2)促进肌动蛋白–细胞骨架重排, 从而增强细胞的刚度和化疗耐药性。此外, Rac1还可激活AKT/FOXO3a信号通路, 从而进一步提高细胞糖酵解水平, 增强化疗耐药性。在DNA修复和抗凋亡机制方面, Rac1上调抗凋亡分子的表达水平以增强患者对化疗的耐药性。Rac1还可以通过调节EMT相关标志物的表达来增强患者对化疗的耐药性(图2)。

2.1.1 肌动蛋白细胞骨架重排 Rac1作为一种细胞骨架调节蛋白, 主要通过促进肌动蛋白细胞骨架重塑来调节细胞黏附和运动[30]。因此, Rac1在调节细胞迁移和侵袭中的研究更为广泛。但近年来的一些研究发现它作为肌动蛋白细胞骨架调节因子还可以增强肿瘤的化疗耐药性。例如, Rac1在顺铂耐药的宫颈癌组织中的表达量显著高于顺铂敏感的组织, 并且在SH3结构域结合蛋白1(SH3-domain binding protein-1, SH3BP1)诱导的Rac1激活下, Wave2进一步激活肌动蛋白相关蛋白复合物2/3, 引起肌动蛋白聚合, 使宫颈癌细胞的化疗耐药性增强[31]。沉默Rac1或抑制剂抑制Rac1的活性可抑制肺癌细胞中肌动蛋白细胞骨架重排以及降低细胞对抗肿瘤药物的耐药性[32]。此外, 卵巢癌细胞的顺铂耐药性也与Rac1介导的肌动蛋白细胞骨架形成有关, 肌动蛋白细胞骨架组织以及细胞硬度的增加可以增强细胞的化疗耐药性[33]。

2.1.2 抗凋亡及DNA修复增强 肿瘤耐药的主要机制之一就是细胞凋亡数减少以及DNA修复能力增强[34], 并且已有研究表明该机制可由Rac1介导。例如, LIU等[35]研究发现, 在三阴性乳腺癌中, 抑制TUFT1(tuftelin 1)可以下调Rac1的表达, 并促进经阿霉素治疗的细胞凋亡, 从而增强细胞的化疗敏感性。在宫颈癌中, 抑制Rac1 GTPase的激活可以促进宫颈癌细胞凋亡, 从而逆转细胞对顺铂的化疗耐药性[36]。靶向Rac1/p21活化激酶1(p21 activated kinase 1, PAK1)/LIM激酶1(LIM domain kinase 1, LIMK1)/丝切蛋白(cofilin, CFL)途径也可以诱导细胞凋亡并影响宫颈癌细胞的化疗敏感性, 其中Rac1的下调也逆转了宫颈癌细胞的紫杉醇耐药性[37]。在胃腺癌中, 抑制Rac1可以显著诱导细胞凋亡, 从而逆转胃腺癌细胞对顺铂的耐药性。此外, PI3K/AKT通路位于Rac1的上游并激活Rac1, 而c-Jun N-端激酶(c-Jun N-terminal kinase, JNK)通路位于Rac1的下游, 抑制PI3K/AKT或JNK也可以逆转细胞对顺铂的化疗耐药性[38]。在白血病细胞中, Rac1失活通过抑制生态位信号和下调细胞周期抑制因子p21、p27和p57的表达水平来提高白血病干细胞的化疗敏感性, 这些抑制因子可以维持细胞静止, 减少药物诱导的淋巴瘤干细胞凋亡[39]。此外, Rac1还参与了DNA的损伤反应[40]。胶原蛋白

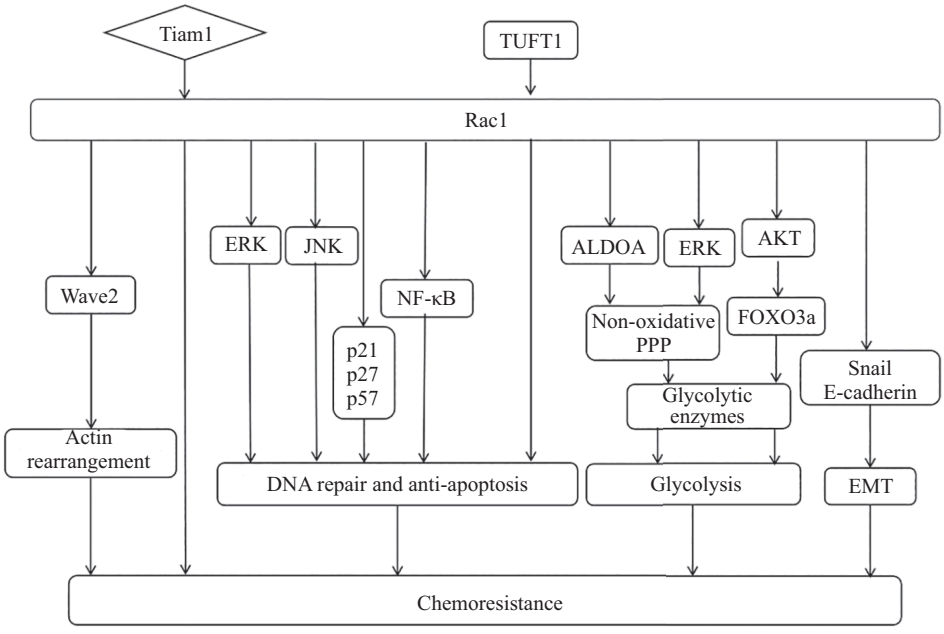


图2 Rac1介导的肿瘤化疗耐药机制

Fig.2 Mechanism of tumor chemoresistance mediated by Rac1

/α2β1整合素信号通过抑制Rac1活化来抑制药物诱导 的DNA损伤和JNK激活, 恢复骨髓细胞白血病蛋白1(myeloid cell leukemia-1, Mcl-1)水平, 从而增强白血病对阿霉素的化疗耐药性[41], 并且抗凋亡分子肿瘤坏死因子α诱导蛋白8(tumor necrosis factor, alpha-induced protein 8, TNFAIP8)通过与Rac1相互作用来激活细胞外调节蛋白激酶(extracellular regulated protein kinases, ERK)途径, 从而抑制细胞凋亡并增强急性髓系白血病对阿霉素的化学耐药性[42]。因此, 进一步阐明Rac1抑制药物诱导的细胞凋亡以及DNA损伤反应这一机制, 对癌症化疗耐药性的治疗具有重要意义。

2.1.3 *靶向肿瘤代谢* 肿瘤代谢不仅促进癌症进展, 还影响治疗耐药性和药物敏感性。靶向关键的糖酵解酶可以调节肿瘤代谢, 从而使耐药的肿瘤细胞对化疗敏感[43]。LI等[6]研究表明, Rac1通过激活醛缩酶A(aldolase A, ALDOA)和ERK信号通路上调糖酵解水平并激活非氧化磷酸戊糖途径(pentose phosphate pathway, PPP), 从而导致核苷酸代谢的增强, 提高乳腺癌细胞对顺铂的化疗耐药性。在宫颈癌中, PPP的关键酶6-磷酸葡萄糖酸脱氢酶(6-phosphogluconate dehydrogenase, 6PGD)的表达下调, 导致Rac1活性降低, 并提高宫颈癌细胞对化疗的敏感性[44]。此外, 抑制Rac1可以阻断食管鳞状细胞癌中的AKT/FOXO3a信号通路, 并且下调对有氧糖酵解至关重要的酶丙酮酸激酶(pyruvate kinase, PKM)、乳酸脱氢酶A(lactate dehydrogenase A, LDHA)、ALDOA和己糖激酶1(hexokinase 1, HK1)的表达来抑制糖酵解, 从而在体内外逆转细胞对顺铂的化疗耐药性[45]。这些研究表明: 以Rac1为靶点, 深入研究肿瘤代谢相关分子机制对改善肿瘤耐药具有重要指导意义。

2.1.4 *促进上皮–间充质转化(EMT)* 越来越多研究表明: 上皮–间充质转化在肿瘤耐药中扮演着重要角色[46]。而有研究发现, 下调Rac1的表达可以增强卵巢癌顺铂耐药细胞株SKOV3/DDP对顺铂的敏感性, 并且与亲本株相比, 耐药株的Vimentin和Snail表达显著下调, E-cadherin表达显著上调[47]。这表明Rac1介导的EMT过程有助于肿瘤耐药。

2.2 Rac1促进放疗和靶向药物耐药性

除了化疗之外, 放射治疗和靶向治疗也是肿瘤治疗的主要方式。放疗使用的电离辐射(ionizing radiation, IR)会使癌细胞的DNA损伤, 从而导致细胞死亡[48]。已有研究表明, Rac1也会影响肿瘤对放疗的耐药性。在肺癌中, Rac1通过靶向PAK1/LIMK1/CFL信号通路来促进EMT, 从而增强肺癌对放疗的耐药性[49]。在宫颈癌中, 降低Rac1 GTP的活性会导致HeLa细胞在紫外线或γ辐射下的DNA修复能力减弱, 细胞增殖和存活数减少, 进而增强宫颈癌细胞对放疗的敏感性[50]。此外, 质谱和生物信息学分析表明, Rac1蛋白还可能是鼻咽癌CNE1细胞放射增敏过程中的主要靶点。RP-4是一种由大黄酸衍生的新型放射增敏剂, 通过靶向Rac1-NADPH通路, 增强鼻咽癌细胞对放疗的敏感性[51]。Rac1还可以增强肿瘤对靶向药物的耐药性。在肝细胞癌中, 敲低Rac1使糖酵解水平下调从而逆转肝细胞癌对索拉非尼的耐药性[52]。抑制Rac1导致前列腺癌细胞中的EMT标志物Snail表达下调, E-cadherin表达上调, 表明Rac1促进前列腺癌细胞侵袭和迁移, 进而导致细胞对恩杂鲁胺耐药[53]。总之, Rac1通过参与各种机制来调节肿瘤细胞对靶向药物以及放、化疗的耐药性。

2.3 Rac1的突变影响肿瘤耐药性

有研究表明Rac1的获得突变与癌症相关, 这些突变有助于形成肿瘤, 并使肿瘤对靶向治疗产生耐药性。此外, 基因组的不稳定性导致Rac1突变率增加, 进而影响癌症的化疗耐药性[23]。Rac1的两个主要致癌突变体为Rac1 P29S和Rac1 A159V, 主要见于黑色素瘤和头颈癌[54]。

以黑色素瘤为例, Rac1 P29S是人类皮肤黑色素瘤中第三个最常见的突变密码子, 它可以破坏Rac1的GDP结合状态, 有利于形成其活跃的GTP结合状态, 从而促进肿瘤发生[55]。从药理学角度来看, Rac1 P29S突变与RAF抑制剂的耐药性和PD-L1的上调有关[23]。Rac1的P29S突变体可以通过维持较高水平的丝裂原活化蛋白激酶(mitogen activated protein kinase, MAPK)活性来赋予黑色素瘤对RAF和MAPK激酶抑制剂的耐药性[56]。最近的一项研究表明, Rac1 P29S可以增强黑色素瘤对BRAF抑制剂的耐药性, 通过抑制血清应答因子(serum response factor, SRF)/心肌素相关转录因子(myocardin-related transcription factor, MRTF)复合物逆转黑色素瘤对BRAF抑制剂的耐药性[57]。与黑色素瘤中的Rac1 P29S突变一样, 在头颈部鳞状细胞癌(head and neck squamous cell carcinoma, HNSCC)中发现的Rac1 A159V突变与患者的不良预后相关。虽然该Rac1突变与临

床结局之间的关系尚未明确, 但基因集富集分析发现, 活性Rac1与免疫相关基因集的功能障碍有关[58]。与其他癌症亚型相比, 黑色素瘤对免疫检查点抑制剂(immune checkpoint inhibition, ICI)具有较高的应答率, ICI显著改善了黑色素瘤患者的预后。与Rac1野生型以及其他突变体相比, Rac1 P29S突变的黑色素瘤患者的PD-L1表达水平显著增加。这表明Rac1 P29S可能对抗PD-1或PD-L1 ICI更为敏感[59]。Rac1介导的治疗耐药性受到CDK9的影响, CDK9抑制与抗PD-1 ICI联合治疗对携带Rac1 P29S突变的黑色素瘤患者具有良好的疗效[60]。由此我们可以看出, 药物靶基因的突变也是肿瘤耐药性的重要机制。

2.4 Rac1b促进肿瘤耐药性

Rac1b是Rac1的新型剪接变体, 也是小GTPases Rho家族的成员[61]。与Rac1相似, Rac1b也与多种癌症(例如肠道肿瘤、甲状腺癌、肺癌、胰腺癌和乳腺癌)的发生和进展有关[62-65]。此外, Rac1b也被证明可以参与调节肿瘤的化疗耐药性。在结直肠癌中, Rac1b可以通过激活NF-κB信号通路来增强细胞的增殖能力, 从而增强化疗耐药性。敲低Rac1b或抑制Rac可以降低与化疗相关的NF-κB的活性, 并增强细胞对奥沙利铂的敏感性[66]。CHEN等[67]使用基因工程小鼠模型发现在HER2/Neu驱动的乳腺肿瘤 中, Rac1b由大量的乳腺癌干细胞(breast cancer stem cell, BCSC)表达, 这些BCSC需要由Rac1b来维持活性, 而Rac1b功能的缺失使其对阿霉素的化疗敏感性增加。

2.5 GEFs异常表达与耐药性相关

Rac鸟嘌呤核苷酸交换因子参与Rac的活化, 如前文所总结的。GEFs的表达或者活性失调与肿瘤耐药性相关[23]。

在人乳腺癌SKBR3细胞中Rac1主要由Rac-GEF Tiam1激活, Rac1激活可以增强由磷酸酶张力蛋白同系物(phosphatase and tensin homolog, PTEN)缺失或胰岛素样生长因子I受体(insulin-like growth factor I receptor, IGF-IR)过表达导致的曲妥珠单抗耐药性[68]。Tiam1还可以激活结直肠癌中的Rac, 抑制Tiam1增强了肿瘤对化疗药物的敏感性并降低了肿瘤侵袭性[69]。此外, 抑制Tiam1/Rac信号转导可以增强白血病细胞对氟达拉滨的敏感性[70]。如前所述, P-Rex1也是Rac1的特异性GEFs之一。在前列腺癌中, 抑制P-Rex1/Rac通路逆转了贝伐珠单抗/舒尼替尼的耐药性, 并削弱了前列腺癌干细胞的特性[71]。最近的一项研究发现, 抑制Rac-GEF VAV3阻碍了Rac活化和信号转导, 并克服了急性淋巴细胞白血病对酪氨酸激酶抑制剂的耐药性[72]。鉴于GEFs在调节Rac1信号通路以及抑制肿瘤中Rac1活性的作用, 阻断Rac1与特定GEFs的相互作用可能是改善肿瘤耐药的途径之一。

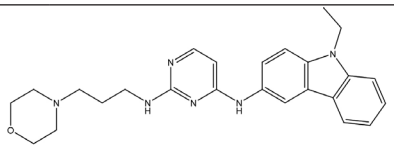
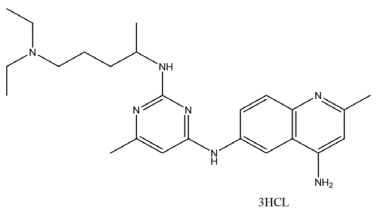
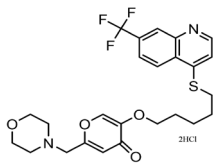
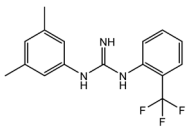
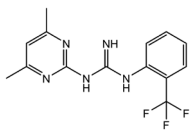
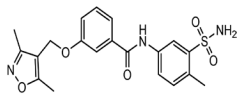
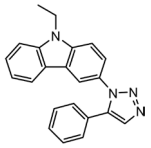
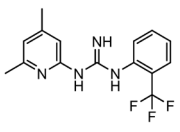
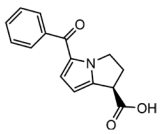
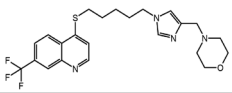
3 Rac1抑制剂逆转肿瘤耐药性

Rac1在许多癌症中都被异常激活或者高表达。因此, 靶向Rac1以及化疗药物或小分子靶向药物与Rac1抑制剂的联合治疗可能是提高肿瘤细胞对化疗的敏感性、克服肿瘤细胞对靶向药物耐药性的可行方案(表1)。

NSC23766是Rac1的第一个特异性抑制剂, 通过Rac特异性的GEFs Trio或Tiam1, 有效地抑制Rac1结合和激活, 并且不干扰紧密相关的Cdc42或RhoA结合或激活[74,82]。已有研究表明, NSC23766在许多疾病(例如心肌异常、椎间盘退变、肺炎、类风湿性关节炎以及肾纤维化)的治疗中都发挥着重要作用, 其还可以抑制Rac1驱动的肿瘤生长和转移[83-88]。除此之外, 研究证明NSC23766还可以改善肿瘤的化疗耐药性。如在人乳腺癌SKBR3细胞中, NSC23766抑制Rac1活性后, 可显著逆转曲妥珠单抗耐药性[68]; 在胃腺癌中, NSC23766通过抑制Rac1逆转细胞对氟尿嘧啶和顺铂的耐药性[38]。但其IC_{50}(50 μmol/L)过高, 因此不能很好地应用于临床。EHop-016是基于NSC23766结构并优化合成的Rac1抑制剂, 它具有更低的IC_{50}[73]。关于EHop-016用于改善肿瘤耐药性的报道也越来越多。在食管鳞状癌中, EHop-016与顺铂联用后通过抑制糖酵解来逆转顺铂耐药性[45]。在甲状腺癌细胞中, EHop-016与达布拉非尼(Dabrafenib)联用可以逆转细胞的Dabrafenib耐药性[89]。ZINC69391是基于对接的虚拟文库筛选确定的新型Rac1抑制剂。该化合物的作用方式与NSC23766相似, 可以阻断Rac1与其GEF Tiam1的相互作用, 阻止GEF诱导的Rac1活化[76]。目前并没有报道证明ZINC69391可以用来改善肿瘤的耐药性。另一种有效的抑制剂是硫代喹啉型化合物, 被命名为EHT1864, 它对Rac亚型具有选择性, 以高亲和力与Rac结合并抑制GEFs结合, 导致与其效应物失去相互作用, 并有效阻断Tiam1和Ras介导的转化[75]。EHT1864与米哚妥林联合使用协同降低了急性髓系白血病细胞MV4-11和MOLM-13 MID-Res的细胞活力, 并诱导了G_1期细胞周期停

表1 Rac1抑制剂

Table 1 The inhibitors of Rac1

抑制剂 Inhibitors	结构 Structure	靶点 Target	半抑制浓度 IC_{50}	参考文献 References
EHop-016		Rac1	1.1 μmol/L	[73]
NSC27366		Rac GTPase	50 μmol/L	[74]
EHT1864 2HCl		Rac1 Rac1b Rac2 Rac3	/	[75]
1A-116		Rac1	4 μmol/L 21 μmol/L	[76]
ZINC69391		Rac1	50-100 μmol/L	[77]
Z62954982 (ZINC08010136)		Rac1	12 μmol/L	[78]
MBQ-167		Rac1 Cdc42	103 nmol/L 78 nmol/L	[79]
1D-142		Rac1	(14.6±0.4) μmol/L	[80]
R-ketorolac		Rac1 Cdc42	0.57 μmol/L 1.07 μmol/L	[81]
GYS32661		Rac1 Rac1b	1.18 μmol/L	[66]

IC_{50}: 对Rac1-GTP活性的抑制率达到50%时所需的化合物的浓度。

IC_{50}: the concentration of each compound that inhibits Rac1-GTP activity by 50%.

滞和促进了细胞凋亡, 从而克服了细胞的米哚妥林耐药性[90]。此外, 在体内EHT1864可以增强白血病细胞对化疗药物阿糖胞苷的敏感性[91]。将EHT1864的中心杂环修饰为咪唑结构得到了一种咪唑衍生物, 并将其命名为GYS32661。它可以抑制结肠癌细胞中的Rac1和Rac1b的活性, 并增强细胞对奥沙利铂的敏感性[66]。

近年来, Rac1抑制剂在临床应用中取得了一些突破。FDA批准的可用于人类的药物外消旋酮咯酸对Cdc42和Rac1 GTP酶有选择性抑制作用, 并且外消旋酮咯酸已被证明可以显著抑制卵巢癌细胞的黏附、迁移和侵袭[92]。此外, 一些临床有效的抑制剂, 如MBQ-167, 是一种临床前候选药物, 用于治疗晚期实体瘤[19]。目前来看, Rac1抑制剂在体内外治疗肿瘤耐药性方面具有较大的潜力。

4 结语和展望

综上表明Rac1参与调节肿瘤细胞对放、化疗以及小分子靶向药物的敏感性。此外, Rac1也参与了妇科癌症的耐药性调节, 但目前针对性研究较少。因此, 靶向Rac1在妇科癌症耐药性方面的治疗具有良好的前景。本课题组目前正在着重研究Rac1在调节卵巢癌顺铂耐药性中的作用以及相关分子机制, 以期为卵巢癌的耐药性治疗提供新的方法。

尽管癌症治疗取得了进展, 但耐药性仍然是恶性肿瘤患者当前治疗的阻碍。靶向Rac1的抑制剂被认为是克服Rac1介导的肿瘤耐药性的首选。目前已经开发出越来越多的具有更强效力和较小毒性的Rac1抑制剂, 而且不同抑制剂的组合也被证明在逆转肿瘤耐药性方面产生协同作用。然而, Rac1抑制剂在临床应用方面仍然受限。这是由于目前可用的抑制剂的疗效和毒性未达到临床使用标准, 因此, 应进一步评估抑制剂的益处和风险。

总之, Rac1与癌症进展和耐药性密切相关, 并且Rac1是克服耐药性的潜在靶标之一。因此阐明Rac1及其抑制剂在肿瘤耐药中的作用, 可以为改善肿瘤耐药提供新的方法和理论基础, 研究人员也可以更好地开发靶向Rac1的药物。

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