

基于ERK1/2翻译后修饰调控及空间性调节的抗癌策略研究进展

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Research Progress of Anti-cancer Strategies Based on ERK1/2 Post-translational Modification and Spatial Regulation

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Abstract: ERK1/2 is a key protein that mediates cell signal transduction, and it is involved in regulating biological processes such as chromatin remodeling, nuclear disintegration, proliferation, survival, metabolism, and cell migration and differentiation. Its overactivation is closely related to the occurrence and progression of cancer, and the mechanism is manifested as the overactivation of ERK1/2 by gene mutations of upstream pathway molecules or regulators and the reactivation of ERK1/2 after inhibition against the above targets. ERK1/2 is a potentially valuable target. In this review, the mechanism of post-translational modification and spatial regulation of ERK1/2 and the application status of corresponding small-molecule inhibitors were discussed. The current antitumor strategy of targeting and regulating ERK1/2 was summarized, and the possibility of exploring potential targets was elucidated, thus providing new insights into the developmental research of ERK1/2 as an ideal anticancer target.

Key words: ERK1/2; Tumor; Targeted therapy; Post-translational modifications; Dimerization; Small molecule inhibitor

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摘要: ERK1/2是一种介导细胞信号转导的关键蛋白,参与调节细胞的染色质重塑、核解体、增殖、存活、代谢、迁移和分化等生物学过程。其过度激活与癌症的发生进展密切相关,机制表现为上游通路分子或调节因子的基因突变使ERK1/2过度激活及针对上述靶点进行抑制后的ERK1/2再激活。因而ERK1/2为一个有潜在价值的靶点。本文对ERK1/2的翻译后修饰调控及空间性调节的机制研究和相应小分子抑制剂的应用现状进行了讨论,总结并展望了目前靶向调控ERK1/2的抗癌策略及针对潜在靶点展开探索的可能性,为ERK1/2作为抗癌理想靶点的开发性研究提供了新思路。

关键词: ERK1/2; 肿瘤; 靶向治疗; 翻译后修饰; 二聚化; 小分子抑制剂
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0 引言

癌症是一种由多因素多步骤介导的、以细胞恶性增殖和异常分化为主要特征的细胞疾病^[1-2]。细胞外信号调节激酶1/2(extracellular regulated protein kinases1/2, ERK1/2)是丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)家族成员之一,

在细胞生命过程中行使重要作用，其异常激活也与肿瘤的发生发展密切相关^[3]。因此针对ERK1/2的翻译后修饰调控（post-translational modifications, PTM）及空间性调节机制展开讨论对抗癌靶点的开发具有重要的现实意义，并可能为临床上癌症的治疗提供新方向。

1 ERK1/2的激活、再定位及功能行使

ERK1/2于1988年第一次被分离鉴定^[4]，其激活始于胞外刺激性分子配体（如有丝分裂原和激素）与细胞质/器膜上受体的结合^[5]。激活状态下，上游信号可经由RAS/RAF/丝裂原活化蛋白激酶激酶1/2（MAP/ERK kinase-1, MEK1/2）级联通路^[6]或者新近发现的非经典内体信号轴（G蛋白偶联受体-β2肾上腺素能受体）^[7]激活ERK1/2。MEK1/2分别对ERK1/2蛋白激活环内丝氨酸-谷氨酸-酪氨酸（TEY）序列的T202与Y204位点（ERK1）或T185与Y187位点（ERK2）进行磷酸化从而激活ERK1/ERK2，使其以同源二聚体^[8]或单体的形式将激活信号传递至细胞质的核糖体S6激酶（ribosomal S6 kinase, RSKs）、MAPK相互作用激酶（MAPK interaction kinases, MNKs）或细胞核的ETS转录因子（ETS-like protein-1, Elk-1）等底物，达到调控下游分子表达的目的^[9-10]。此外，ERK2也可以直接与

DNA序列结合以抑制细胞因子（如干扰素γ）诱导的基因表达，对基因的转录调控具有直接作用，不会受到其激酶失活突变的影响^[11]。目前所报道的ERK1/2底物中大约一半为细胞核蛋白，主要参与诱导细胞的增殖过程^[12]；另一半为细胞质蛋白，广泛参与调节细胞的增殖、存活、生长、代谢、迁移和分化等过程^[10]，见图1。

2 ERK1/2在恶性肿瘤中的再激活

研究表明ERK1/2在人类多种恶性肿瘤中存在异常激活现象^[13]，其机制包括上游级联激酶的异常激活，例如结肠癌中的EGFR突变^[14]、胰腺导管腺癌中的K-RAS点激活突变^[15]、黑色素瘤中的B-RAF激酶激活^[16]及MEK1或MEK2的激活突变^[17]；同时亦存在靶向抑制其上游级联激酶后ERK1/2本身的再激活^[18-19]。由此，近些年来针对靶向ERK1/2信号转导成分或调节因子的小分子抑制剂的开发进展迅速，目前已经批准上市的包括靶向抑制表皮生长因子受体（EGFR）的厄洛替尼（Erlotinib）^[20]，但随即，Ercan等研究发现使用Erlotinib治疗并产生耐药性的患者会伴随ERK2的扩增^[18]。此外，靶向KR-AS^{G12C}的AMG510、靶向BRAF^{V600E}的维莫非尼（Vemurafenib）及达拉非尼（Dabrafenib）、靶向ME-

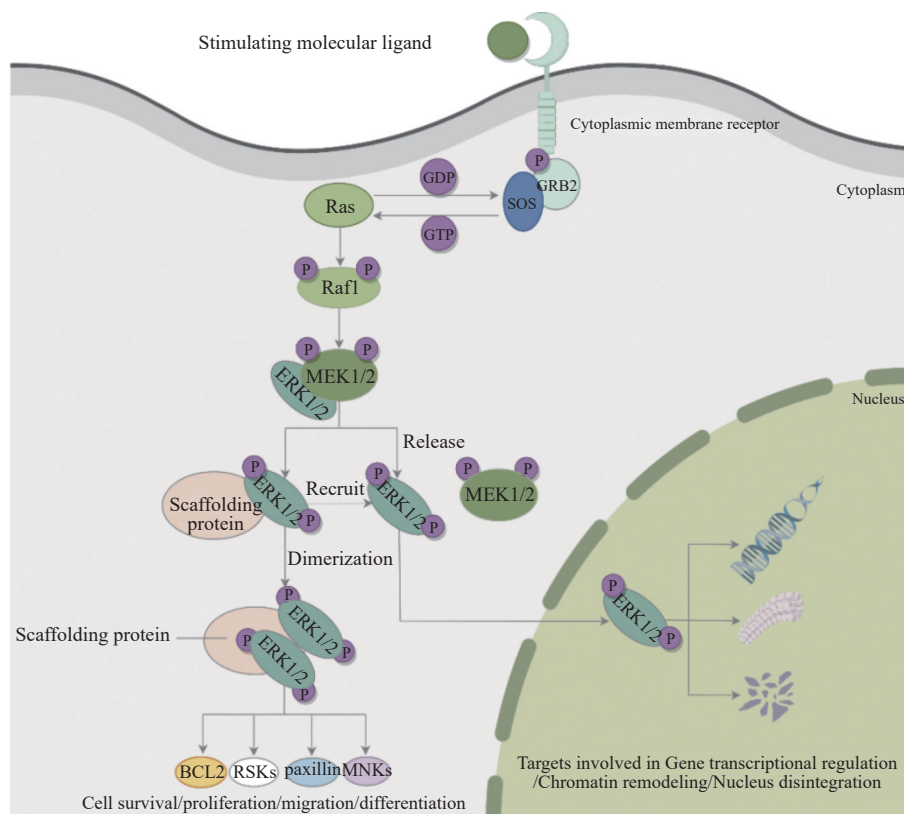


图1 细胞中ERK1/2的激活、再定位及功能行使模式图（Figdraw绘制，ID: STSRUeccaf）

Figure 1 Activation, relocalization, and functional exercise patterns of ERK1/2 in cells (Figure by Figdraw, ID: STSRUeccaf)

K1/2的曲美替尼 (Trametinib) 和比美替尼 (Binimetinib) 虽然临床治愈率可观, 但研究者们很快发现治疗所导致的耐药产生^[21]。亦有研究报道基质细胞分泌的肝细胞生长因子可以通过间质表皮转化因子受体诱导ERK1/2途径的重新激活, 从而介导BRAF黑色素瘤对Vemurafenib诱导的RAF抑制的耐药性^[19]。以上结论提示ERK1/2可能是一个重要的抗肿瘤治疗靶点。

3 ERK1/2的翻译后修饰调控

3.1 磷酸化与去磷酸化

作为影响ERK1/2蛋白质和细胞功能的关键PTMs之一, 磷酸化可以发生在ERK1/2的多个丝/苏氨酸残基上并产生不同的生物学后果。最为经典的, ERK1/2上苏氨酸-谷氨酸-酪氨酸 (TEY) 基序的双磷酸化由MEK1/2介导, 致使前者发生激活, 对细胞的增殖及核内基因转录等产生重要作用^[7]。作为机体内平衡蛋白激酶磷酸化水平的策略实施者, 磷酸酶在ERK1/2去磷酸化过程中发挥主要作用。研究发现, 双特异性磷酸酶6 (dual specificity phosphatase 6, DUSP6) 可以逆转ERK1/2上TEY基序的MEK1/2磷酸化^[22], 密度增强磷酸酶-1可实现对ERK1/2蛋白的募集及去磷酸化^[23], 肾细胞癌中肝/肾碱性磷酸酶^[24]及DUSP10^[25]可对ERK1/2发挥去磷酸化作用, 具体机制有待进一步研究。

针对ERK1/2的磷酸化进行抑制性调控是目前靶向ERK1/2调控的主流策略之一, 许多小分子抑制剂的开发研究进展良好^[26]。三磷酸腺苷 (adenosine triphosphate, ATP) 竞争性ERK1/2抑制剂能够竞争性结合ATP位点, 从而阻断后者催化激活ERK1/2及后续信号传递的过程, 达到抑制肿瘤发生进展的目的。Aronov等于2007年设计出第一个具有ERK1/2选择性的ATP竞争性抑制剂6p (ERK1/2 $K_i=2$ nmol/L), 它能够有效抑制Colo205人结肠癌细胞增殖 ($IC_{50}=0.54$ μ mol/L)^[27]。随后他们发现VX-11e对ERK2具有选择性抑制作用 (ERK1/2 $K_i<2$ nmol/L), 能显著遏制HT-29人结肠癌细胞的增殖 ($IC_{50}=29$ nmol/L)^[28]。单用VX-11e可导致使用BRAF抑制剂治疗进展的黑色素瘤患者源性异种移植 (patient derived xenograft, PDX) 模型的肿瘤生长受到抑制^[29]。Ohori等筛选得到化合物FR1802-04, 其对ERK1和ERK2的 K_i 值分别为0.31 μ mol/L和0.14 μ mol/L^[30]。研究发现FR180204能显著抑制间皮瘤细胞^[31]及宫颈癌HeLa细胞的生长^[32]。ADTL-EI1712/22ac是一种口服有效的ERK1和ERK5的选择性双靶点抑制剂, 其浓度为1 μ mol/L时对ERK1/5

的抑制率分别为93.54%和89.35%, 可诱导MKN-74人胃癌细胞死亡^[33]。SCH772984是一种高选择性和ATP竞争性ERK抑制剂 (ERK1 $IC_{50}=4$ nmol/L, ERK2 $IC_{50}=1$ nmol/L), 其在约88%的BRAF-突变 ($n=25$) 和49%的RAS-突变 ($n=35$) 肿瘤细胞系中显示抗增殖作用 ($IC_{50}<500$ nmol/L), 在人黑色素瘤或胰腺癌细胞系建立的BRAF或KRAS-突变异种移植模型中的剂量依赖性抗肿瘤活性亦得以体现^[34]。此外, Hicks等发现SCH772984与BRAF抑制剂联用可导致间变性甲状腺癌体内模型中肿瘤生长的显著抑制^[35]。GDC-0994/Ravoxertinib是具有口服活性的ERK1/2抑制剂 (ERK1 $IC_{50}=6.1$ nmol/L, ERK2 $IC_{50}=3.1$ nmol/L), 使用剂量大于30 mg/kg时, GDC-0994对人结直肠癌细胞皮下荷瘤裸鼠的肿瘤生长抑制率可达49%^[36]。GDC-0994的体内I期研究 (NCT01875705) 表明, 其对MAPK信号的抑制范围为19%~51%, 具有可接受的安全性, 并在BRAF突变型结直肠癌患者中诱导33%的总体反应和4%的部分反应^[37]。在一项Ib期研究 (NCT02457793) 中, GDC0994与他药联用于晚期实体瘤患者, 但由于无法处理不良事件和累积毒性, 该试验受到限制^[38]。Ulixertinib/BVD-523是一种有效、可口服及高度选择性的ERK1/2抑制剂 (ERK2 $IC_{50}<0.3$ nmol/L), 在BRAV600E突变型黑色素瘤细胞系中显示出抗增殖作用 ($IC_{50}<2$ μ mol/L), 此外, Ulixertinib在黑色素瘤和结直肠癌的PDX模型中表现出显著的剂量依赖性抗肿瘤活性^[39], 其亦能抑制神经母细胞瘤的细胞增殖, 降低相应皮下荷瘤小鼠模型的总生存期^[40]。已经结束的临床试验表明, Ulixertinib在治疗恶性实体瘤过程中具有可接受的安全性和良好的药代动力学特征 (NCT0178-1429)^[41]。此外, 血液系统肿瘤治疗的安全性及临床活性评估 (NCT02296242)、Ulixertinib与他药联用治疗转移性胰腺癌 (NCT02608229)、单药治疗葡萄膜黑色素瘤 (NCT03417739) 及MAPK通路突变的晚期实体瘤、非霍奇金淋巴瘤或组织细胞疾病患者的研究 (NCT03698994) 因为疾病进展、患者较高死亡率或不同程度的不良事件而受到限制。近年来以Ulixertinib为对象的多项临床研究 (NCT04488003、NCT04566393、NCT05804227、NCT03454035、NCT05221320、NCT04145297及NCT05985954) 也正在有条不紊地开展。同样作为ATP竞争性抑制剂, 口服生物利用度良好的ASN007在广泛实体瘤和淋巴瘤细胞系中展现出相对GDC-0994及Ulixertinib更低的 IC_{50} 值, 其对ERK1和ERK2的 IC_{50} 值均为2 nmol/L; ASN007在携带KRAS或

NRAS-突变的肿瘤细胞或PDX模型中均表现出较强的抗肿瘤功效,此外,ASN007在对BRAF和MEK1/2抑制剂耐药的黑色素瘤PDX模型中显示出较好的疗效^[42]。Tolcher等在BRAF、KRAS、HRAS和NRAS-突变的晚期实体瘤患者中进行了一项I期研究,早期结果表明ASN007耐受性良好,临床活性长达12个月(NCT03415126)^[43]。MK-8353/SCH-900353是一种有选择性、可口服的ERK1/2抑制剂($ERK1\ IC_{50}=23.0\text{ nmol/L}$, $ERK2\ IC_{50}=8.8\text{ nmol/L}$),在几种BRAF-突变肿瘤模型中显示出抗增殖作用,在Colo205细胞异种移植瘤模型中建立了MK-8353的抗肿瘤活性^[44]。在一项临床研究(NCT0135-8331)中,MK-8353对BRAFV600突变型黑色素瘤患者具有良好的耐受性,并表现出抗肿瘤活性,但其抗肿瘤活性与药效学参数并无明显相关性^[45]。有报道称MK-8353与他药联用治疗晚期或转移性实体瘤患者过程中在一定浓度范围内具有可接受的安全性和耐受性(NCT03745989)^[46]。另一项MK-8353与他药联用治疗晚期恶性肿瘤患者的安全性和耐受性的临床研究(NCT02972034)正在进行中。Temuterkib/LY3214996是高效的选择性ERK1和ERK2抑制剂(IC_{50} 值均为5 nmol/L),与其他已报道的ERK1/2抑制剂相比,LY3214996在BRAF或RAS突变细胞系和异种移植模型中显示出相似或更好的抗肿瘤活性;LY3214996和他药联用具有良好的耐受性,并在多种体内癌症模型(包括KRAS-突变结直肠癌和非小细胞肺癌)中产生有效的肿瘤生长抑制或消退效应^[47-48]。目前,LY3214996已作为单药治疗应用于健康参与者(NCT04033341)、急性髓系白血病(NCT04081259)、不可切除或转移性结直肠癌(NCT04616183)、晚期/转移性癌症(NCT02857270)和胰腺癌治疗(NCT04386057)的临床研究中。LY3214996与他药联用治疗KRAS-突变型癌症(NCT04916236)及复发性胶质母细胞瘤(NCT04534283、NCT04391595)的研究正在进行中。然而,ERK1/2作用的过程十分复杂,若单纯将治疗靶点聚焦于抑制ERK1/2磷酸化可能导致其信号转导紊乱并产生不良后果,这提示我们可针对ERK1/2的其他翻译后修饰调节展开ERK1/2药物作用靶点的开发研究。

3.2 泛素化与去泛素化

泛素化是由泛素分子通过不同种类的泛素活化酶(E1酶)、泛素结合酶(E2酶)、泛素连接酶(E3酶)以及起平衡作用的去泛素化酶(deubiquitinating enzymes, DUBs)引导蛋白质特异性修饰的过程^[49]。丝裂原活化蛋白激酶激酶1(MAP/

ERK kinase kinase -1, MEKK1)通过其植物同源结构域作为E3泛素连接酶被报道促进ERK1/2的多泛素化降解,从而降低后者活性^[50]。Zhu等研究发现泛素连接酶TRIM15可介导针对ERK1/2的赖氨酸63位点(K63)连接的多泛素化修饰,从而调控药物反应性和耐药性黑色素瘤的生长^[51]。目前已经鉴定的ERK1/2去泛素化酶包括USP15及USP37。USP15能够使ERK2去泛素化,但不调节其蛋白稳定性^[52]。USP37去泛素化并稳定ERK1/2,从而增强癌细胞增殖^[53]。

相较于针对蛋白的泛素化/去泛素化天然调控展开靶点开发策略研究,基于泛素体(uAbs)对人工诱导蛋白质降解的蛋白质组编辑器设计开发似乎更得科学家们的青睐。Stephens等描述了两种由热休克蛋白70(heat shock protein70, HSP70)相互作用蛋白的人羧基端组成的uAbs,它们能够泛特异性捕获所有内源性ERK1/2蛋白形式,通过泛素-蛋白酶体途径去除ERK1/2,起到靶向抗癌作用^[54]。

3.3 其他PTMs

3.3.1 SUMO化 由小泛素样修饰物(small ubiquitin-like modifiers, SUMOs)参与的SUMO化(Sumoylation)是一种重要的PTM, SUMOs在不同的癌症中经常过度表达,为癌细胞自我更新所必需^[55]。现有针对ERK家族开展的SUMO化研究主要集中于ERK5,后者发生SUMO化可对前列腺癌中ERK5的核定位和细胞增殖等过程产生促进作用^[56]。虽然目前未曾见到ERK1/2发生SUMO化的研究性报道,但有研究者通过蛋白组学分析对人类细胞中的SUMO2/3位点进行了鉴定,并提供了ERK1蛋白序列的三个SUMO化位点:EPRTTEGVG-PGVPGEVEMVKGQPF、DLNCIINMKARNYLQSLPSK及DDLPERL^[57]。SUMO E1活化酶抑制剂TAK981目前处于I期临床试验,用于治疗不同类型的癌症,其不仅可以阻断肿瘤细胞周期进程,还可以激活抗癌免疫^[58]。鉴于SUMOs作为临床抗肿瘤治疗靶点的潜力、核定位的特殊性以及可自身磷酸化和泛素化的特性^[59], ERK1/2的SUMO化研究似乎可以成为研究者们发现ERK1/2的翻译后修饰调控新靶点的途径。

3.3.2 甲基化 甲基化是一种重要的表观遗传调控类型,可以广泛发生在DNA、RNA以及蛋白质中。其中蛋白质甲基化影响蛋白质活性并指导蛋白质翻译、定位和信号转导^[60]。Vougiouklakis等证明了蛋白质赖氨酸甲基转移酶SUV420H1在K302和K361处介导ERK1的三甲基化,并且甲基化位点的突变降低了ERK1的磷酸化水平^[61],这为肿瘤中ERK1/2的级联调控提供了新的见解。

4 空间性调节

4.1 核易位

ERK1/2向细胞核的易位被证明是细胞进入细胞周期所必需的^[62]。核ERK1/2在增殖中的重要性促使人们对其核穿梭的分子机制进行了许多研究。静息状态下ERK1/2在细胞质中与锚定蛋白相互作用。受刺激后与锚定物分离，转移到细胞核中^[63]。Plotnikov等^[12]设计了一款ERK1/2核输出序列衍生的肉豆蔻酰化拟磷酸肽，它被证明可以诱导黑色素瘤细胞凋亡，甚至可以抑制PLX4032（RAF抑制剂）和U0126（MEK抑制剂）抗性黑色素瘤细胞的活力。由此可见，抑制ERK1/2核易位可能是一种有效的抗癌策略。

4.2 构象变化

研究可知，ERK1/2发挥作用必然需要经历双重磷酸化，继而触发激活域内的剧烈构象变化，重组底物结合位点，并重新定位参与活性位点残基的催化^[64]。基于此，靶向调控ERK1/2结构变化的小分子抑制剂应运而生，主要包括共价抑制剂与变构抑制剂。

共价抑制剂是一类能通过共价键与特定的靶蛋白氨基酸残基结合，导致蛋白质构象改变，从而抑制靶蛋白发挥生物功能的小分子化合物，具有生化效率高、作用时间长、剂量和给药频率低等优点^[65]。Liu等研究发现包括ERK1/2在内的200多种激酶在ATP结合位点附近具有可产生共价作用的半胱氨酸残基，这些残基位于ATP结合口袋后面，便于共价抑制剂的结合^[66]。Ohori等设计并合成了ERK2共价抑制剂LL-Z1640-2/FR148083（ERK2 IC_{50} =80 nmol/L）^[67]。研究显示LL-Z1640-2能有效抑制成人T细胞淋巴瘤细胞的体内外生长^[68]。CC-90003是一种不可逆的选择性ERK1/2抑制剂（10 nmol/L<ERK1/2 IC_{50} <20 nmol/L），对93%的BRAF-突变肿瘤细胞及76%的KRAS-突变肿瘤细胞具有体外抗增殖效应；在HCT-116人结肠癌异种移植模型的体内研究中，CC-90003在一定剂量范围内展现良好的耐受性及肿瘤生长抑制效应。此外，CC-90003的应用可导致肺癌（LXFA-983）和胰腺导管腺癌（PAXF-2059）模型中的生长停滞^[69]。Mita等在RAS或BRAF-突变肿瘤患者中开展了CC-90003的首次Ia期人体研究（NCT02313012），但因缺乏客观反应、不利的药代动力学特征和意外的神经毒性，研究被迫终止^[70]。Chiang等确定了一种新型的共价ERK1/2抑制剂Laxiflorin B，其为一种中草药化合物，可在非小细胞肺癌细胞中介导凋亡，在非小细胞肺癌皮下荷瘤裸鼠模型中也表现出强烈的肿瘤抑制作用，具有低毒性^[71]。虽然共价抑制剂具有很大的

潜力，但在临床试验中尚未取得较大进展。

除了靶向ERK1/2的催化位点外，研究者们还通过靶向ERK1/2蛋白ATP结合口袋背侧的变构区开发了ERK1/2变构抑制剂^[62]。ERK1/2具有两个不同于活性位点的蛋白质对接位点：D-募集位点（D Recruitment sites, DRS）和F-募集位点（F Recruitment sites, FRS），靶向ERK1/2上的这些位点能够破坏关键的蛋白质-蛋白质相互作用，克服传统ATP竞争性抑制剂应用时产生的许多问题^[72]。DRS存在于ERK1/2的活性构象和非活性构象中，而FRS只存在于ERK1/2的双磷酸化活性构象中。由于激活状态的ERK1/2参与肿瘤细胞增殖，靶向FRS可能是一种更有效的ERK1/2变构抑制剂设计策略。Samadani等筛选获得了一类能与FRS相互作用、抑制BRAF突变或ERK1/2信号活化的黑色素瘤细胞增殖的化合物，其中SF-3-029和SF-3-030是激活蛋白-1启动子最有效的抑制剂（5 mmol/L< IC_{50} <10 mmol/L）^[73]。上述变构抑制剂不与ATP结合袋相互作用，因此可与ATP竞争性抑制剂联合使用，提高药物治疗效果，克服小分子抑制剂选择性低、脱靶及耐药等缺点。

4.3 二聚化

Canagarajah等从磷酸化ERK2的晶体结构推导出二聚化激酶的模型，发现双磷酸化后的ERK2单体与未磷酸化ERK2单体通过彼此的亮氨酸333（L333）、L336和L344残基相互作用而形成二聚体^[74]。随后，有研究发现ERK1也能形成二聚体，且ERK1/2形成的二聚体主要是ERK1及ERK2同源二聚体，ERK1-ERK2异源二聚体是不稳定的^[75]，说明二聚化在ERK1活性增强中的重要性。此外，Wilsbacher等表明，磷酸化的ERK1/2二聚体与未磷酸化的ERK1/2二聚体具有不同的构象，且ERK1/2磷酸化促进其同型二聚体的形成，而H176处产生的突变足以破坏ERK1/2二聚化^[76]。随后的研究发现，肺癌、结直肠癌和膀胱癌细胞系中的ERK1/2二聚化因导入二聚缺陷突变体ERK2^{H176E}被阻遏时，其增殖和恶性进展亦被阻止。表明虽然ERK1/2的主要增殖驱动信号可能在细胞核中产生，但ERK1/2的细胞质成分是肿瘤细胞增殖和转化发生的必要条件，ERK1/2二聚体对于细胞质而非核底物的激活是必不可少的^[77]。这也提示，ERK1/2的二聚化特性足以导致ERK1/2功能发生质核分流，阻断ERK1/2亚定位特异性信号而非总信号可以作为抑制致癌ERK1/2信号转导的策略。

基于前期研究^[77]，Herrero等通过层层筛选验证与ERK2有亲和力的化学结构的衍生物，并于2015年

报道了DEL-23379这一同属于变构抑制剂的ERK2二聚化抑制剂，DEL-23379在携带BRAF-突变的肿瘤细胞系中具有最大的细胞抑制潜能，其还能阻止黑色素瘤和结直肠癌细胞系异种移植模型的肿瘤生长^[78]。DEL-23379其因比肩前述ATP竞争性抑制剂和共价抑制剂的有效性且仅阻断ERK2细胞质特异性信号产生的低毒性，为我们提供了靶向调节蛋白二聚化作用这一全新研究方向，后续研究者在此基础上设计出多种化合物以期了解ERK1/2二聚化抑制的结构基础^[79]。然而，DEL-23379在未分化甲状腺癌细胞系中抑制ERK2二聚化而非磷酸化的特异性遭到质疑^[80]，虽然目前基于ERK1/2二聚化调控展开的抗癌策略研究较少，但此种策略相较于其他疗法展现的优势及为靶向抗肿瘤治疗提供新线索所

体现出的价值是可观的。

5 结语

ERK1/2具有多种调节活性，在肿瘤细胞的染色质重塑、核解体、增殖、存活、代谢、迁移和分化等生命过程中占据重要地位。作为一个抗癌靶点，ERK1/2的临床潜在价值毋庸置疑。本文总结了靶向ERK1/2蛋白层面的多种调控机制，尽管其调控范围广泛，但已建立的复杂调节机制网络并不能完全解释多种细胞外刺激如何激活ERK1/2导致不同的细胞结果，这表明关于ERK1/2蛋白活性和功能的调节仍有很大研究空间。另一方面，本文亦在相应部分归纳了基于上述机制开发的ERK1/2靶向小分子抑制剂（表1），主要包括ATP竞争性抑

表 1 ERK1/2小分子抑制剂的临床前及临床研究现状概览
Table 1 Overview of preclinical and clinical research status of ERK1/2 small-molecule inhibitors

ERK1/2 inhibitor type	ERK1/2 Inhibitor	ERK1/2 inhibitory activity	Basic research on anticancer effects		NCT identifier and clinical phase (I / II)	
			<i>In vivo</i>	<i>In vitro</i>	Completed	Ongoing
ATP competitive inhibitor	6p	ERK1/2 Ki=2 nmol/L	NA	A	NA	NA
	VX-11e	ERK1/2 Ki<2 nmol/L	A	A	NA	NA
	FR180204	ERK1 Ki=0.31 μmol/L ERK2 Ki=0.14 μmol/L	NA	A	NA	NA
	ADTLEI1712/ 22ac	Inhibitory rate on ERK1 of 1 μmol/L ADTLEI1712 is 93.54%	NA	A	NA	NA
	SCH772984	ERK1 IC ₅₀ =4 nmol/L ERK2 IC ₅₀ =1 nmol/L	A	A	NA	NA
	GDC0994/ Ravoxertinib	ERK1 IC ₅₀ =6.1 nmol/L ERK2 IC ₅₀ =3.1 nmol/L	A	A	NCT01875705 I NCT02457793 I	NA
	Ulixertinib/ BVD-523	ERK2 IC ₅₀ <0.3 nmol/L	A	A	NCT01781429 I NCT02296242 I / II NCT02608229 I NCT03417739 II NCT03698994 II	NCT04488003 II NCT04566393 NA NCT05804227 I NCT03454035 I NCT05221320 II NCT04145297 I NCT05985954 I
	ASN007	ERK1/2 IC ₅₀ =2 nmol/L ERK2 IC ₅₀ =5 nmol/L	A	A		NCT03415126 I
	MK8353/ SCH900353	ERK1 IC ₅₀ =23 nmol/L ERK2 IC ₅₀ =8.8 nmol/L	A	A	NCT01358331 I NCT03745989 I	NCT02972034 I
	Temuterkib/ LY3214996	ERK1/2 IC ₅₀ =5 nmol/L	A	A		NCT04033341 I NCT04081259 I NCT04616183 I / II NCT02857270 I NCT04386057 II NCT04916236 I NCT04534283 II NCT04391595 I
Covalent selective inhibitor	LL-Z16402/ FR148083	ERK2 IC ₅₀ = 80 nmol/L	A	A	NA	NA
	CC-90003	10 nmol/L < ERK1/2 IC ₅₀ < 20 nmol/L	A	A	NCT02313012 I	NA
	Laxiflorin B	NA	A	A	NA	NA
Allosteric inhibitor	SF-3-029 and SF-3-030	5 mmol/L < ERK1/2 IC ₅₀ < 10 mmol/L	NA	A	NA	NA
	DEL-23379	ERK2 IC ₅₀ = 0.5 μmol/L	A	A	NA	NA

Notes: NA: not available; A: available.

制剂、共价抑制剂以及变构抑制剂, ATP竞争型抑制剂作为靶向抗癌主流研发产物为ERK1/2抑制剂的临床研究打下坚实基础, 但其亦存在毒性高(完全阻断ERK1/2活性)及低靶标选择性的劣势, 共价抑制剂及变构抑制剂的开发规避了ATP竞争性抑制剂的高脱靶率, 但其不可逆结合特性所带来的毒性和安全性风险亦需要研究者们重点关注。尽管迄今为止均未出现被批准上市的ERK1/2抑制剂, 但其在临床前和临床试验中显示出的良好抗肿瘤疗效及对上游激酶抑制剂诱导的获得性耐药的逆转能力均揭示ERK1/2抑制剂开发应用的临床价值。

利益冲突声明:

所有作者均声明不存在利益冲突。

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