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·综述·

HGF/c-Met信号通路在口腔鳞状细胞癌中的研究进展

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【摘要】 口腔鳞状细胞癌(oral squamous cell carcinoma，OSCC)是严重威胁人类健康的恶性肿瘤,其典型的生物学特征包括局部侵袭性强、淋巴结转移率高以及治疗后易复发等特点。来源于间充质的肝细胞生长因子(hepatocyte growth factor,HGF)、间充质上皮转化因子(cellular-mesenchymal to epithelial transition factor,c-Met)及HGF/c-Met信号通路参与调控OSCC的发生发展。一方面,HGF和c-Met蛋白在OSCC中过表达,且多项研究提示与肿瘤恶性特征和不良预后显著相关;HGF/c-Met信号通路的异常激活(由HGF依赖性自/旁分泌或MET基因突变、扩增、融合及蛋白过表达等非依赖性机制驱动)可通过激活下游信号通路,协同促进肿瘤细胞侵袭转移和血管生成;另一方面,HGF/c-Met还可通过促进乳酸分泌增加、诱导程序性细胞死亡配体(programmed death ligand 1,PD-L1)表达上调、激活和扩增髓源性抑制细胞以及促进调节性T细胞(regulatory T cells,Tregs)细胞增殖的方式介导免疫逃逸;此外,HGF/c-Met信号通路与磷脂酰肌醇3-激酶(phosphatidylinositide 3-kinases,PI3K)/蛋白激酶B(protein kinases B,AKT)、表皮生长因子(epidermal growth factor receptor，EGFR)、Janus激酶(Janus kinase,JAK)/转录激活蛋白(signal transducer and activator of transcription,STAT3)等关键通路和非编码RNA形成的串扰也可促进肿瘤进展。针对这一通路,目前已开发出三类靶向药物:HGF单抗、c-Met单抗和酪氨酸激酶抑制剂,其中部分药物已进入临床试验阶段。然而,治疗过程中出现的耐药现象,特别是EGFR等替代信号通路的双向代偿性激活,成为临床面临的重大挑战。本文通过深入分析HGF/c-Met通路在OSCC中的作用机制及其与其他通路的交互关系,梳理现有治疗药物的研究现状,旨在为开发更有效的联合治疗策略、实现个体化精准治疗提供重要依据,最终改善患者的临床预后和生活质量。

【关键词】 口腔鳞状细胞癌；　肝细胞生长因子；　间充质上皮转化因子；　作用机制；
磷脂酰肌醇3-激酶；　蛋白激酶B；　表皮生长因子；　靶向治疗；　单克隆抗体；
酪氨酸激酶抑制剂

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Research progress of HGF/c-Met signaling pathway in oral squamous cell carcinoma

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【Abstract】 Oral squamous cell carcinoma (OSCC) is a malignant tumor that seriously threatens human health. Its typical biological characteristics include strong local invasiveness, high lymph node metastasis rate, and high recurrence rate after treatment. Hepatocyte growth factor (HGF), cellular-mesenchymal to epithelial transition factor (c-Met), and the HGF/c-Met signaling pathway are involved in the regulation of the occurrence and development of OSCC. HGF

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and c-Met proteins are overexpressed in OSCC, and multiple studies have suggested that they are significantly associated with the malignant characteristics of tumors and poor prognosis. Furthermore, the abnormal activation of the HGF/c-Met signaling pathway (driven by HGF-dependent autocrine/paracrine or non-dependent mechanisms such as MET gene mutations, amplification, fusion, and protein overexpression) can synergistically promote tumor cell invasion, metastasis, and angiogenesis by activating downstream signaling pathways. However, HGF/c-Met can also mediate immune escape by promoting lactate secretion increase, inducing programmed death ligand 1 (PD-L1) expression upregulation, activating and expanding myeloid-derived suppressor cells, and promoting the proliferation of regulatory T cells (Tregs). In addition, the crosstalk between the HGF/c-Met signaling pathway and key pathways such as phosphatidylinositide 3-kinases (PI3K)/protein kinase B (AKT), epidermal growth factor receptor (EGFR), Janus kinase (JAK)/signal transducer and activator of transcription (STAT3), and non-coding RNAs can also promote tumor progression. Currently, three types of targeted drugs have been developed targeting the HGF/c-Met pathway: HGF monoclonal antibody, c-Met monoclonal antibody, and tyrosine kinase inhibitors. Some of these drugs have entered clinical trials. However, the emergence of drug resistance during treatment, especially the bidirectional compensatory activation of alternative signaling pathways such as EGFR, has become a major challenge in clinical practice. This article aims to provide an in-depth analysis of the mechanism of action of the HGF/c-Met pathway in OSCC and its interaction with other pathways, and to review the current research status of existing therapeutic drugs. The aim is to provide an important theoretical basis for developing more effective combined treatment strategies and achieving individualized precise treatment, ultimately improving the clinical prognosis and quality of life of patients.

【Key words】 oral squamous cell carcinoma; hepatocyte growth factor; cellular-mesenchymal to epithelial transition factor; mechanism; phosphatidylinositide 3-kinases; protein kinases B; epidermal growth factor receptor; targeted therapy; monoclonal antibodies; tyrosine kinase inhibitor

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口腔颌面部恶性肿瘤已成为全球最常见的恶性肿瘤之一，2020年约有377 713例新发病例和177 577例死亡病例，是欠发达国家癌症负担的重要组成部分[1]。口腔鳞状细胞癌（oral squamous cell carcinoma，OSCC）占所有口腔颌面部恶性肿瘤约90%，目前早期治疗方法以手术切除为主，但会对患者面部造成不可逆的损伤，降低其术后生活质量，甚至对心理状态产生负面影响[2]。靶向治疗因可精准地攻击肿瘤细胞，降低手术治疗所产生的并发症，备受临床医生和研究人员的关注[3-4]。肝细胞生长因子（hepatocyte growth factor，HGF）/间充质上皮转化因子（cellular-mesenchymal to epithelial transition factor，c-Met）信号通路参与肿瘤细胞进展、转移和预后[5]，该信号通路的异常激活通常与癌症晚期有关，并且与生存率低、放疗抵抗和西妥昔单抗耐药性有关[6]。以上提示可能是OSCC的有效治疗靶点。本文就基于以该信号通路为靶点的OSCC相关抑制剂的最新研究做一综述。

1　HGF/c-Met结构与生物学功能

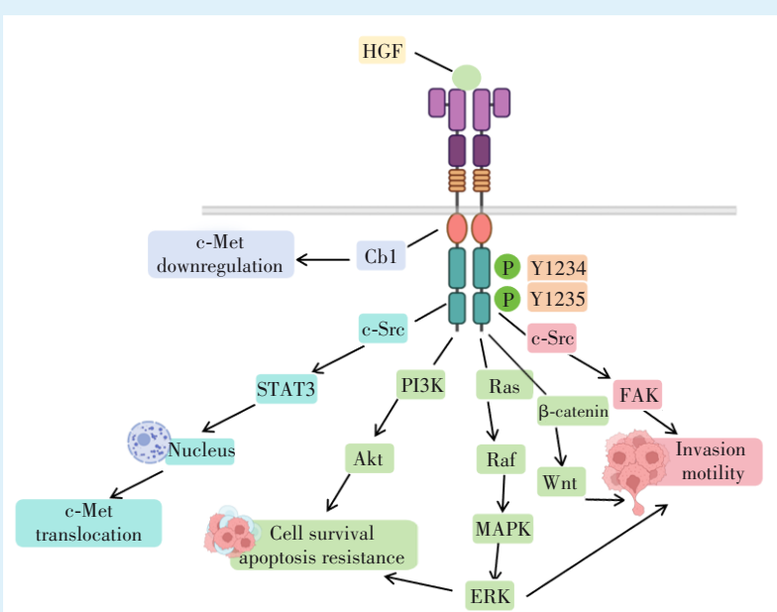
HGF是间充质干细胞产生的旁分泌因子，广泛存在于皮肤、肺和肝脏等多种组织，可根据细胞类型诱导不同的细胞运动、存活、增殖和形态发生[7]。HGF位于人染色体7q21，是由一条55-60 kDa的高亲和力α链和一条32-34 kDa的低亲和力β链组成的异二聚体，α链可促进β链与肝细胞生长因子受体结合。成熟的HGF包含N端结构域、丝氨酸蛋白酶样结构域和四个Kringle结构域[8]。

c-Met蛋白作为一种跨膜受体酪氨酸激酶，由原癌基因MET编码而来，是HGF唯一已知的高亲和力激活受体，主要由上皮细胞产生，在正常组织内多与胚胎发生、伤口愈合、组织修复和免疫调节相关[9]。c-Met蛋白位于人染色体7q21-q31，是由一个45 kDa的高糖基化α亚基和一个145 kDa的

跨膜β亚基组成的异二聚体。成熟c-Met蛋白的细胞外部分包括N末端结构域、富含半胱氨酸的结构域和四个免疫球蛋白样丛蛋白转录因子结构域，细胞内部分包括羧基末端结构域、酪氨酸激酶结构域和近膜结构域[10]。

2　HGF/c-Met致癌机制

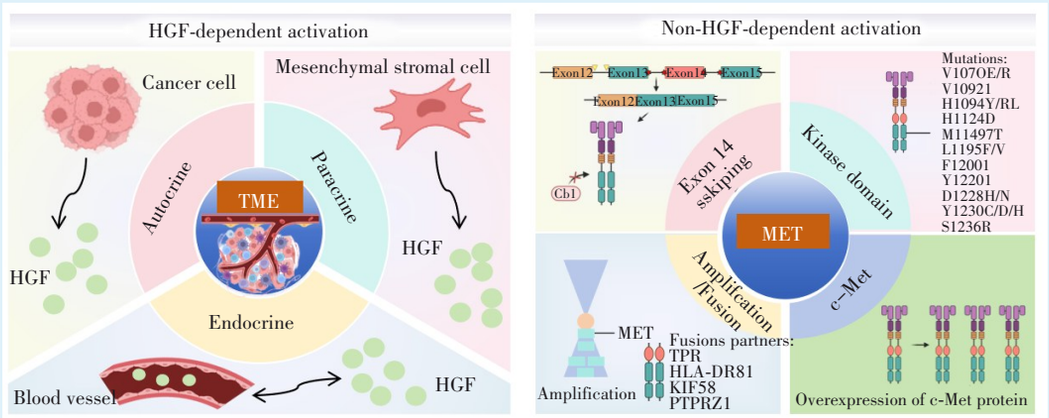
HGF/c-Met信号通路是调控细胞生长、增殖、迁移和血管生成的关键通路之一，其异常激活与多种恶性肿瘤的发生发展密切相关[11]。在正常生理状态下，HGF与c-Met蛋白结合后诱导受体二聚化，触发酪氨酸激酶结构域内Tyr1234/Tyr1235以及羧基末端结构域内Tyr1349/Tyr1356的自磷酸化，进而招募下游效应分子，激活PI3K/AKT、细胞外调节蛋白激酶（extracellular regulated protein kinases，ERK）/丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）和无翅相关整合位点（Wingless-related integration site，Wnt）/β-连环蛋白（β-catenin）等重要信号通路[12-14]（图1）。该通路的负调控主要通过近膜结构域Tyr1003与E3泛素连接酶Casitas B系淋巴瘤原癌基因（Casitas B-lineage lymphoma，Cbl）结合，介导c-Met蛋白泛素化降解来实现，从而维持信号的时空特异性[15]。然而，在肿瘤细胞中，HGF/c-Met信号通路常因多种机制而异常激活，导致细胞恶性转化和侵袭性生长。目前，HGF/c-Met信号通路被发现在肝癌、肺癌、结直肠癌等多种恶性肿瘤中异常激活[16-18]，其激活方式可分为HGF依赖性和非HGF依赖性2类（图2）。HGF依赖性激活主要由肿瘤微环境（tumor micro environment，TME）中的自分泌、旁分泌或内分泌异常引起，如肿瘤细胞自身分泌HGF（自分泌）、间质细胞异常释放HGF（旁分泌）或循环HGF水平升高（内分泌），导致c-Met蛋白持续磷酸化及下游信号通路的过度激活。非HGF依赖性激活包括多种基因组和表观遗传学改变：MET基因外显子14跳跃突变或缺失[19-20]：导致近膜结构域缺失，阻碍Cbl介导的降解，延长HGF/c-Met信号活性；MET基因激酶结构域突变[21]：增强激酶活性，使c-Met蛋白在无配体情况下持续激活；MET基因扩增[22]或融合[23]：增加c-Met蛋白表达或产生融合蛋白，促进信号通路的组成性激活；c-Met蛋白过表达[24-25]：不依赖基因改变，可能由转录或翻译调控异常引起，增强HGF/c-Met信号传导。综上所述，HGF/c-Met对维持细胞的正常生理活动十分重要，但在被异常激活时会导致正常细胞功能失调、组织稳态紊乱，从而导致肿瘤细胞的产生。因此，靶向HGF/c-Met信号通路的抑制剂已成为抗肿瘤药物研发的重要方向，部分药物已进入临床研究阶段，为相关癌症的治疗提供了新的策略。未来，进一步探索该通路的调控机制及与其他致癌信号的交叉作用，将有助于优化靶向治疗并克服耐药性问题。



The HGF/c-Met signaling pathway can activate multiple downstream signaling pathways, thereby leading to the proliferation, invasion and metastasis of tumor cells. HGF: hepatocyte growth factor; c-Met: cellular-mesenchymal to epithelial transition factor; Cbl: casitas B-lineage lymphoma; STAT3: signal transducer and activator of transcription-3; PI3K: phosphatidylinositide 3-kinases; Akt: protein kinases B; MAPK: mitogen-activated protein kinase; ERK: extracellular regulated protein kinases; FAK: focal adhesion kinase; c-Src: cellular-Src; Ras: rat sarcoma; Raf: rapidly accelerated fibrosarcoma

Figure 1　The signal cascade reaction generated by HGF activating the c-Met protein

图1　HGF激活c-Met蛋白的信号级联反应



The activation pathways of the HGF/c-Met signaling pathway include HGF-dependent and HGF-independent ones. HGF: hepatocyte growth factor; TME: tumor micro environment; MET: mesenchymal to epithelial transition factor; c-Met: cellular-mesenchymal to epithelial transition factor; TPR: treponema pallidum repeat; HLA-DR81: human leukocyte antigen-DR81; KIF58: kinesin family member 58; PTPRZ1: protein tyrosine phosphatase receptor type Z1

Figure 2　Activation pathway of the HGF/c-Met signaling pathway

图2　HGF/c-Met信号通路的激活途径

3　HGF/c-Met在OSCC中的作用

3.1　c-Met蛋白与OSCC的关系

在OSCC中，HGF/c-Met信号通路的异常激活主要通过c-Met蛋白过表达、MET基因扩增和蛋白突变三种机制实现[26]。其中，c-Met蛋白过表达最为常见，在OSCC组织中的发生率高达80%，且与患者较差的总生存期和无进展生存期显著相关。虽然c-Met蛋白突变和MET基因扩增的检出率相对较低（约13%），但它们与c-Met蛋白的过表达有关，且已被提议作为局部晚期OSCC患者的独立预后因素[27]。值得注意的是，c-Met蛋白的表达水平与肿瘤恶性特征密切相关，包括肿瘤细胞低分化、血管生成增加以及更晚期的肿瘤范围-淋巴结转移-远处转移情况（tumor node metastasis，TNM）分期等不良预后指标[28-30]。这些发现不仅确立了c-Met蛋白在OSCC进展中的关键作用，也为其作为预后生物标志物和潜在治疗靶点提供了重要依据。

3.2　HGF与OSCC的关系

在OSCC的肿瘤微环境中，癌相关成纤维细胞作为重要组成成分，通过旁分泌方式大量分泌HGF，而非由肿瘤细胞自身产生。研究表明[31]，与肿瘤细胞共培养的成纤维细胞较正常成纤维细胞具有更强的HGF分泌能力，且OSCC基质中可观察到明显的HGF过表达现象。癌相关成纤维细胞是肿瘤微环境的主要成分，可促进癌症的发生、进展和转移。这种微环境来源的HGF通过多重机制促进肿瘤进展：一方面显著增强淋巴内皮细胞的增殖、侵袭能力并促进淋巴管生成；另一方面与基质金属蛋白酶等转移相关因子协同作用，这从OSCC患者组织和唾液中HGF等因子水平显著高于健康对照者得到证实[32]。值得注意的是，HGF的高表达不仅与更晚期的TNM分期密切相关，还与肿瘤微环境中的炎症细胞浸润存在显著关联[33]。这些发现共同揭示了肿瘤微环境来源的HGF通过促进淋巴管生成、增强侵袭转移能力等多种途径参与OSCC的恶性进展，其表达水平可能作为预测OSCC转移潜能的潜在生物标志物，值得开展更深入的机制研究和临床转化探索。

3.3　HGF/c-Met信号通路与OSCC的关系

HGF/c-Met信号通路在OSCC的发生发展中扮演着关键角色。在生理状态下，该通路受到严格调控维持平衡，但其异常激活可显著促进上皮-间充质转化，使肿瘤细胞获得侵袭性表型，表现为侵袭能力增强、转移潜能提高和抗凋亡特性[34-37]。研究表明[38]，HGF/c-Met通路的激活可上调板状足蛋白表达，诱导板状伪足形成，从而促进OSCC细胞迁移。同时，该通路通过激活MAPK/ERK、p38/PI3K、AKT/核因子κB（nuclear factor kappa-B，NF-κB）等多条下游信号级联反应[39]，协同促进肿瘤细胞侵袭周围组织、诱导新生血管形成和转移扩散[40-41]。值得注意的是，该通路还通过多重机制影响肿瘤微环境中免疫抑制性细胞的浸润和活性并减少肿瘤免疫的发生、促进肿瘤细胞生长[42-43]：1）促进糖酵解依赖性乳酸分泌增加，抑制细胞毒性T

淋巴细胞(cytotoxic t lymphocytes,CTLs)功能[44];2)PD-L1表达上调并与程序性细胞死亡受体(programmed cell death protein 1,PD-1)结合导致T细胞耗竭和活化减少[45-46];3)以信号传导及转录激活蛋白(Signal transducer and activator of transcription,STAT3)依赖性方式激活和扩增髓源性抑制细胞,抑制T细胞免疫反应[47];4)促进Tregs细胞的增殖,阻碍CTLs细胞的活化和免疫介导的抗肿瘤作用[48]。鉴于HGF/c-Met通路在促进OSCC恶性进展和免疫逃逸中的核心作用,开发针对该通路的靶向抑制剂(如c-Met激酶抑制剂或HGF中和抗体)展现出重要的治疗前景,为改善OSCC患者预后提供了新的干预策略。

3.4 OSCC中的HGF/c-Met信号通路串扰

HGF/c-Met信号通路在OSCC的发生发展中与其他关键信号通路形成复杂的调控网络。研究表明[31],该通路与PI3K/AKT信号通路存在显著串扰。c-Met蛋白抑制剂JNJ-38877606不仅能抑制c-Met表达,还可阻断PI3K/AKT信号活化,从而有效减弱肿瘤细胞的增殖、侵袭和淋巴管形成能力。同时,HGF/c-Met与EGFR通路在OSCC中常呈现共表达特征,二者通过共享MAPK/ERK和PI3K/AKT等下游信号节点形成交互作用[49-50]。联合使用克唑替尼和EGFR抑制剂可协同阻断两条通路,显著增强促凋亡效果[51]。此外,研究发现非编码RNA通过新颖的分子机制参与HGF/c-Met通路的串扰:miR-365-3p通过抑制角蛋白16表达促进c-Met蛋白的溶酶体降解,进而抑制下游c-Src/STAT3/FAK/ERK信号级联反应,减少OSCC细胞的侵袭转移和对5-氟尿嘧啶的化疗耐药[52];而miR-802则直接靶向MET基因发挥抑癌作用[53]。值得注意的是,HGF/c-Met还能与JAK/STAT3等其他重要通路[54-55]形成交叉调控网络,通过多途径协同促进肿瘤细胞存活、增殖和耐药表型的形成。这些通路间的复杂互作机制为深入理解OSCC的分子发病机制提供了新视角,同时也提示联合靶向多条相关通路可能成为未来OSCC治疗的优化策略。

4 HGF/c-Met抑制剂在OSCC治疗中的研究现状

HGF/c-Met信号通路因其在过去几十年的研究中展现出良好的致癌特性,已被认为是一种很有前景的癌症治疗靶标,并且已经开发了多种靶向药物来抑制该通路的激活包括抗HGF单克隆抗体[56-57]、抗c-Met蛋白单克隆抗体[58]和酪氨酸激酶抑制剂[59]3大类,其中以酪氨酸激酶抑制剂为重点研究内容。

4.1 抗HGF单克隆抗体

在OSCC靶向治疗领域,HGF单克隆抗体非拉妥组单抗(Ficlatuzumab)展现出显著的临床潜力。作为目前OSCC中唯一进入临床开发的HGF抑制剂[60],非拉妥组单抗通过特异性阻断HGF与c-Met蛋白的结合,有效抑制肿瘤相关成纤维细胞诱导的OSCC细胞迁移、侵袭、增殖以及c-Met蛋白磷酸化过程。最新临床研究数据表明,在一项Ⅱ期随机对照试验(NCT03422536)中,该药物显著延长了患者的无进展生存期和总生存期。基于这些积极结果,一项旨在进一步评估其疗效和安全性的Ⅲ期临床试验(NCT06064877)正在积极招募受试者。虽然不同临床试验结果存在一定异质性,但非拉妥组单抗在改善总生存期和无进展生存期等关键预后指标方面表现出明显优势,有望成为未来OSCC治疗的重要选择,为患者提供新的靶向治疗机会。

4.2 抗c-Met单克隆抗体

在c-Met靶向治疗领域,目前主要有奥那妥组单抗(Onartuzumab)和依玛妥珠单抗(Emibetuzumab)两种单克隆抗体处于研发阶段。奥那妥组单抗通过特异性抑制c-Met蛋白的二聚化过程,有效阻断HGF/c-Met信号通路的激活,从而发挥抗肿瘤作用[61]。而依玛妥珠单抗则具有双重作用机制:不仅能竞争性抑制HGF与c-Met蛋白的结合,还能促进c-Met蛋白的降解,这使得其在HGF依赖性和非HGF依赖性的肿瘤模型中均显示出良好的治疗潜力[62]。值得注意的是,虽然这些c-Met蛋白单抗在多种实体瘤中展现出应用前景,但目前在OSCC中的相关研究仍较为有限。未来需要通过系统的临床试验来验证这些药物对OSCC患者的确切疗效,包括评估其在不同分子分型患者中的治疗效果、确定最佳给药方案,以及探索与其他靶向药物的联合治疗策略,从而为OSCC患者提供更多有效的治疗选择。

4.3 小分子酪氨酸激酶抑制剂

小分子酪氨酸激酶抑制剂通过特异性阻断c-Met蛋白激酶的活化,有效抑制HGF/c-Met信号通路下游的转导过程,进而发挥抗肿瘤增殖、侵袭和转移的作用[63-64]。根据作用机制和选择性的不同,c-Met蛋白的酪氨酸激酶抑制剂可分为两大类:

ATP竞争性抑制剂(Ⅰ型)和非ATP竞争性抑制剂(Ⅱ/Ⅲ型)。其中,选择性抑制剂对c-Met蛋白激酶的抑制效力需至少比其他激酶高10倍以上,确保在临床相关暴露剂量下仅特异性靶向c-Met蛋白;而非选择性抑制剂则同时对c-Met蛋白及其他激酶[如血管内皮细胞生长因子受体(vascular endothelial growth factor receptor,VEGFR)、AXL等]具有相近的抑制活性,这种多靶点特性可能通过协同作用进一步增强抗肿瘤效果[65]。这种分类不仅为临床用药选择提供了理论依据,也为开发新型c-Met蛋白抑制剂指明了方向,未来需要根据肿瘤分子特征合理选择选择性或非选择性抑制剂,以实现精准治疗。

4.3.1　克唑替尼(Crizotinib)　克唑替尼作为一种多靶点酪氨酸激酶抑制剂,在OSCC治疗中展现出显著潜力。临床前研究表明[66],该药物不仅能有效抑制OSCC小鼠模型的伤口愈合和肿瘤侵袭能力,还可诱导肿瘤细胞凋亡并显著降低异种移植模型的肿瘤负荷。特别值得注意的是,在针对癌症干细胞样细胞的实验中,克唑替尼成功阻断了肿瘤球体形成,并在与顺铂联合使用时表现出协同增效作用,显著增强了抗肿瘤效果[67]。然而,尽管克唑替尼与顺铂联用取得了令人鼓舞的结果,但OSCC治疗仍面临顺铂耐药这一重大挑战。目前尚缺乏针对铂类耐药患者使用克唑替尼的对比研究数据,这一关键问题亟待后续研究深入探索。未来研究应着重评估克唑替尼在顺铂耐药患者中的疗效,并进一步优化其联合用药方案,以期为临床治疗提供更有效的策略选择。

4.3.2　卡博替尼(Cabozantinib)　卡博替尼是最近开发的一种多靶点酪氨酸激酶抑制剂并且已在各种癌症中观察到有希望的效果[68]。临床前研究证实,该药物不仅能有效抑制小鼠、斑马鱼模型及人OSCC手术标本中肿瘤细胞的转移扩散,还可显著抑制转移灶的生长[69]。此外,其临床研究数据更为亮眼,在一项针对22例OSCC患者的Ⅰ期临床试验(NCT03667482)中,卡博替尼联合西妥昔单抗治疗使75%的患者病情稳定,中位总生存期和无进展生存期分别延长至8.1个月和3.4个月。更令人振奋的是,在另一项Ⅱ期试验(NCT03468218)中,卡博替尼与帕博利珠单抗联用使52%的患者获得部分缓解,39%实现病情稳定,中位总生存期和无进展生存期更是分别达到22.3个月和14.6个月的优异结果[70]。这些突破性数据不仅证实了卡博替尼在OSCC治疗中的卓越潜力,更为重要的是提示其与免疫检查点抑制剂联用可能产生显著的协同效应,为改善OSCC患者预后开辟了新的治疗途径。未来研究应进一步探索卡博替尼的最佳用药方案及其在分子分型指导下的精准应用策略。

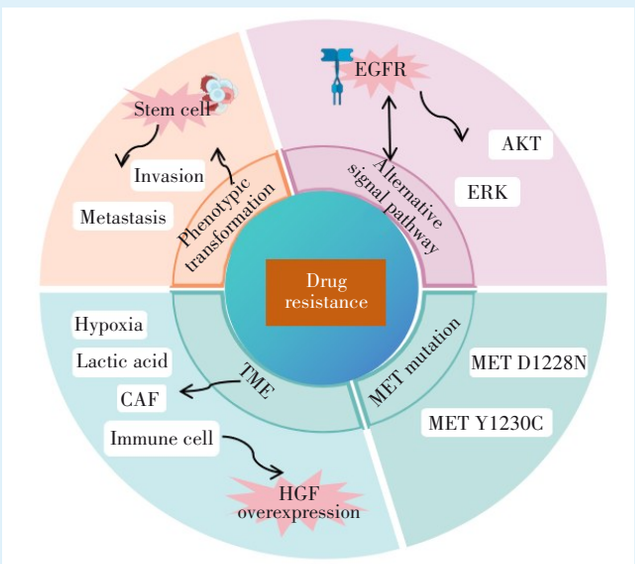
4.3.3　戈伐替尼(Golvatinib)　戈伐替尼[71]作为一款靶向c-Met/血管内皮细胞生长因子受体2(vascular endothelial growth factor receptor 2,VEGFR-2)的双重酪氨酸激酶抑制剂,在头颈鳞癌治疗领域展现出独特的治疗价值。临床前研究证实,该药物能有效抑制异种移植模型的肿瘤生长和血管生成过程。在一项针对95例顺铂耐药HNSCC患者的Ⅰ/Ⅱ期临床试验(NCT01332266)中,戈伐替尼联合西妥昔单抗治疗虽未显著改善无进展生存期,但观察到了总生存期的延长趋势。这一结果提示,戈伐替尼在克服顺铂耐药方面可能具有潜在优势,其双靶点抑制作用可能通过同时阻断肿瘤增殖和血管生成两条通路发挥协同效应。然而,鉴于当前临床数据仍存在局限性,未来需要开展更大规模的Ⅲ期临床试验,进一步验证其确切疗效,并探索最佳用药方案和获益人群特征,以明确该药物在HNSCC临床治疗中的实际应用价值。

除了以上药物以外,SU11274、AMG-208、JNJ-38877606等其他小分子酪氨酸激酶抑制剂已在其他癌症中进行了临床前和临床研究[72-73],其疗效有待在OSCC中进一步评估。

5　靶向HGF/c-Met治疗在OSCC中的耐药机制

在不同类型的肿瘤治疗中可能发生的内在和/或获得性耐药机制是限制临床抗癌疗效提高的主要因素[74],因此,深入了解肿瘤的耐药驱动机制,并通过早期识别耐药及其相关机制来提高临床疗效至关重要。HGF/c-Met抑制剂面临多种耐药机制,包括替代信号通路(如EGFR、VEGF等)的代偿性激活[75-76]、肿瘤组织学表型转化[77]、肿瘤微环境动态重塑[78]以及MET基因获得性突变[79]等(图3)。其中,替代信号通路的激活是目前OSCC研究的重点方向。替代信号通路的代偿性激活是指肿瘤细胞可以通过激活其他信号通路补偿被抑制的信号通路,从而使肿瘤细胞能够继续存活和增殖。研究表明[80],当EGFR信号通路被药物抑制时,肿瘤细胞可通过改变/激活HGF/c-Met信号来维持下游关键效应分子(如ERK和AKT)的活化状态,从而产生治疗耐药性。值得注意的是,EGFR和HGF/

c-Met信号通路间的代偿作用是双向的，体外敲低c-Met蛋白或使用c-Met蛋白抑制剂使EGFR对西妥昔单抗敏感，c-Met蛋白的抑制也显示西妥昔单抗在EGFR过表达的OSCC细胞中显性活性[51, 81]。这种复杂的代偿机制不仅解释了单一靶向治疗易产生耐药的原因，更凸显了肿瘤细胞通过多途径逃逸药物抑制的复杂机制。基于通路间的代偿关系，开发同时靶向HGF/c-Met和EGFR等关键通路的联合治疗策略，可能成为克服OSCC靶向治疗耐药的有效途径。



The mechanisms of resistance to HGF/c-Met inhibitors mainly include compensatory activation of alternative signaling pathways, transformation of tumor histological phenotype, dynamic remodeling of tumor microenvironment, and acquired mutations of MET gene. HGF: hepatocyte growth factor; TME: tumor microenvironment; CAF: cancer-associated fibroblasts; Akt: protein kinases B; ERK: extracellular regulated protein kinases; EGFR: epidermal growth factor receptor; MET: mesenchymal to epithelial transition factor

Figure 3　The drug resistance mechanism of HGF/c-Met inhibitors

图3　HGF/c-Met抑制剂的耐药机制

6　总结与展望

HGF/c-Met信号通路作为肿瘤进展的关键驱动因素[82]，其促癌机制研究已取得重要突破，其异常激活常导致不受控制的侵袭性和转移性表型。虽然针对该通路的靶向药物研发已成为抗肿瘤治疗的重要方向，且临床前研究在多种肿瘤细胞系中展现出显著疗效，但现有HGF/c-Met抑制剂在OSCC临床治疗中仍面临三大挑战：药物不良反应、获得性耐药及通路间串扰效应。值得注意的是，联合靶向治疗策略通过协同作用显著提升了抗肿瘤活性，尽管其安全性和有效性仍需大规模临床验证。未来研究应着重于：①深入解析HGF/c-Met与上下游通路的交互网络和阐明这些通路互作在肿瘤发生发展中的调控机制；②着重解决分别来自预先存在或新发突变的对HGF/c-Met抑制剂的原发性和获得性耐药；③进一步确认现有HGF/c-Met药物的临床益处并评估药物的潜在长期益处和安全性。随着对HGF/c-Met致癌机制的深入认识，有望突破现有治疗瓶颈，为OSCC患者开发出更有效的精准治疗新方案。

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