

原发性肝癌索拉非尼耐药机制的研究进展

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摘要: 多激酶抑制剂索拉非尼是被美国食品药品监督管理局批准的用于治疗晚期肝癌的一线分子靶向药物, 然而, 该药在肝癌治疗中存在原发性或获得性的耐药现象, 影响了肝癌的疗效。目前研究发现, 除肿瘤细胞、肿瘤干细胞本身的耐药机制外, 肿瘤微环境中的免疫细胞、基质细胞等, 可通过分泌特定细胞因子或通过直接接触作用、缺氧、自噬等, 在肝癌对索拉非尼的耐药中起到关键性的作用。全文总结了原发性肝癌对索拉非尼耐药机制的研究进展, 旨在为临床上肝癌的治疗提供新的策略。

关键词: 原发性肝细胞癌; 索拉非尼; 耐药; 肿瘤干细胞; 肿瘤微环境

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Research Progress in Mechanisms of Sorafenib Resistance in Hepatocellular Carcinoma

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Abstract: Sorafenib, a multikinase inhibitor with antiproliferative, antiangiogenic and proapoptotic properties, constitutes the effective first-line drug approved by FDA for the treatment of advanced hepatocellular carcinoma (HCC). However, primary or acquired drug resistance affects the efficacy of sorafenib in the treatment. In addition to the resistance of tumor cells and cancer stem cells, the immune cells, stromal cells and other components of tumor microenvironment (TME) also play a key role in the resistance of HCC to sorafenib through specific cytokines, direct contact, hypoxia, autophagy, or other mechanisms. This article summarizes the research progress in mechanisms of resistance to sorafenib, to provide information for new clinical treatment strategy of hepatocellular carcinoma.

Subject words: hepatocellular carcinoma; sorafenib; drug resistance; cancer stem cell; tumor microenvironment

原发性肝细胞癌 (hepatocellular carcinoma, HCC) 是我国常见的恶性肿瘤, 其死亡率居肿瘤中第三位^[1]。目前肝癌治疗方法包括手术切除、肝移植、射频消融、化疗栓塞、靶向治疗和免疫治疗六大类^[2]。

索拉非尼是美国食品药品监督管理局 (food and drug administration, FDA) 批准的治疗 HCC 的一线小分子靶向药物, 不仅抑制细胞内的丝氨酸/苏氨酸激酶, 还抑制受体酪氨酸激酶包括血管内皮生长因

子受体 (vascular endothelial growth factor receptor, VEGFR), 血小板衍生生长因子受体 (platelet-derived growth factor, PDGFR) 等, 从而抑制肿瘤血管生成和增殖^[3]。然而应该指出, 在一些三期临床试验中仅有 2%~3% 肝癌患者对索拉非尼治疗有部分反应, 大多数患者对索拉非尼表现出原发性耐药^[4]。另外, 索拉非尼延长晚期 HCC 患者的生存时间只有 2~3 个月, 之后完全失效, 表现出获得性耐药^[5]。索拉非尼原发性/获得性耐药性已成为降低 HCC 患者总体生存期的主要因素。全文综述近几年该领域相关文献, 介绍肝癌索拉非尼耐药的分子机制研究进展。

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1 肿瘤细胞介导索拉非尼的耐药

1.1 肿瘤相关细胞因子

陆续有文献证实,肝癌细胞分泌的生长因子如成纤维细胞生长因子3、4、19(fibroblast growth factor 3、4、19,FGF3、4、19)、VEGF、肝细胞生长因子(hepatocyte growth factor,HGF)、表皮生长因子(epidermal growth factor,EGF)等,可通过自分泌途径与肿瘤表面的相应受体结合,激活丝分裂原活化蛋白激酶通路(mitogen-activated protein kinase,MAPK)、PI3K/蛋白激酶B(AKT serine/threonine kinase 1,AKT)、Notch及Hedgehog等信号通路参与索拉非尼耐药^[6-8]。Ungerleider等^[9]发现转化生长因子- β (transforming growth factor beta,TGF β)可上调多种受体酪氨酸激酶(receptor tyrosine kinases,RTKs)的表达,可通过AKT通路参与索拉非尼耐药,而使用TGF β 受体I抑制剂LY2157299能够在体外有效地阻止AKT活化并诱导细胞凋亡。

1.2 肿瘤细胞内的相关转录因子或核蛋白

Shao Z等^[10]研究发现E26转化特异性序列1(ETS proto-oncogene 1,ETS-1)可激活孕烷X受体(pregnenane X receptor,PXR)转录因子的活性,导致PXR下游多药耐药相关基因的表达,引起索拉非尼耐药。Liu J等^[11]证实无远端同源框2(distal-less homeobox 2,DLX2)是参与细胞周期调节的转录因子,通过促进上皮-间质化(epithelial $\rightarrow$ mesenchymal transition,EMT)标志物的表达和激活细胞外信号调节蛋白激酶途径来抵抗索拉非尼。Hua L等^[12]发现核干细胞因子(nucleostemin,NS)/G蛋白核仁3(G protein nucleolar 3,GNL3)是在干细胞和癌细胞中大量表达的核仁蛋白,可调节p53途径和抗凋亡蛋白Bcl-2(B-cell lymphoma-2,Bcl-2),而促进HCC细胞对索拉非尼耐药。

1.3 非编码RNA

越来越多的研究发现长链非编码RNA(long non-coding RNA,lncRNA)失调在肝癌的发生、发展中起着重要作用。Xu等^[13]发现lncRNA-SRLR与核因子Kappa B(nuclear factor kappa b subunit 1,NF- κ B)直接结合,通过白介素6/信号传导与转录激活因子3(signal transducer and activator of transcription 3,STAT3)通路的活化引起索拉非尼耐药,且与HCC患者对索拉非尼治疗的不良反应相关。

微小RNA(microRNA,miRNA)是一类小的非编码调节RNA,如miR-122、miR-128、miR-137、miR-153、miR-21、miR-216a、miR-217、miR-221等,可激活RAS/RAF/ERK、PI3K/AKT/mTOR或HGF/c-Met/Akt信号通路参与HCC细胞对索拉非尼的耐药^[14-15]。

2 肿瘤干细胞对索拉非尼耐药机制

Xin HW等^[16]证实肝癌标签保留细胞(label retaining cancer cells,LRCC)被认为是一群新的肿瘤干细胞(cancer stem cell,CSC或tumor initiating cell,T-IC),对索拉非尼表现出一定耐药性,索拉非尼治疗后LRCC在瘤细胞中的比率明显上升。此外,索拉非尼耐药克隆表现出肿瘤干细胞的特性,通过激活胰岛素样生长因子1(insulin like growth factor 1,IGF)和成纤维细胞生长因子(fibroblast growth factor,FGF)信号传导促进索拉非尼耐药^[17]。Sakurai T等^[18]发现癌性锚蛋白重复序列(Gankyrin)激活IL-6/STAT3信号通路后,可上调CSC的标志物原癌基因(B-cell-specific moloney leukemia virus insert site 1,Bmi1)和上皮细胞黏附分子的表达,最终诱导索拉非尼耐药并促进HCC的发展。

3 肿瘤微环境对索拉非尼的耐药机制

肿瘤微环境(tumor microenvironment,TME)包括癌相关成纤维细胞(cancer associated fibroblast,CAF)、肝星状细胞(hepatic stellate cells,HSC)、血管内皮细胞(vascular endothelial cell,VEC)、平滑肌细胞、周细胞、细胞外基质(extracellular matrix,ECM),以及免疫和炎症细胞如调节性T细胞(regulatory cells,Tregs)、肿瘤相关巨噬细胞(tumour-associated macrophages,TAM)和肿瘤相关中性粒细胞(tumor-associated neutrophils,TAN)等,还包括生理因素,如缺氧、自噬等。各组分共同构成的肿瘤微环境,也可介导HCC对索拉非尼的耐药,从而促进了HCC发生发展。

3.1 血管内皮细胞

索拉非尼可通过靶向VEGF和PDGFR抑制血管生成。血管生成参与索拉非尼耐药的理论依据有两方面:其一,Sennino B等^[19]发现多种促血管生成

生长因子可通过刺激炎症性细胞因子,驱动非依赖 VEGF 的血管生成,引起抗 VEGF 治疗的耐药;其二,Kuczynski 等^[20]陆续发现肿瘤可以不依赖新生血管生成,而选择肿瘤内预先存在的血管,从而对索拉非尼的抗血管生成治疗产生耐药。

3.2 癌相关成纤维细胞

癌相关成纤维细胞是肿瘤基质中最主要细胞,可通过分泌 EGF、FGF、HGF、IL-6、VEGF、PDGF、血管生成素 1(angiotensin 1, ang-1)、ang-2、基质细胞衍生因子-1(stromal cell-derived factor-1, SDF-1/CXCL12)和金属蛋白酶(matrix metalloproteinase, MMP)等,通过 IL-6/STAT3/Notch 信号通路增强 HCC 细胞的干细胞特征,引起 HCC 对索拉非尼耐药^[21]。HSC 构成肝癌微环境中活化 CAFs 的主要来源, Khawar IA 等^[22]发现 Huh-7 细胞与 HSC 共培养时,对索拉非尼的敏感性降低,然而具体机制尚未深入研究。

3.3 肿瘤相关巨噬细胞

肿瘤相关巨噬细胞(tumour-associated macrophages, TAM)是来自循环单核细胞的浸润性巨噬细胞亚群。Wei X 等^[23]发现具有由 II 型 T 辅助细胞(helper T cell 2, Th2)细胞因子激活的替代性活化的巨噬细胞(alternatively activated macrophage, M2)表型,可通过表皮生长因子受体(epidermal growth factor receptor, EGFR)/ β -连环蛋白(β -catenin)信号通路促进细胞增殖、侵袭和索拉非尼耐药。Lovet 等^[24]发现 HCC 细胞中 VEGF-A 过度表达可诱导 TAM 中 HGF 上调,并导致肿瘤增殖并促进血管生成,引起索拉非尼耐药。

3.4 肿瘤相关中性粒细胞

Zhou SL 等^[25]证实肿瘤相关中性粒细胞(tumor-associated neutrophils, TAN)通过分泌 CC 类趋化因子配体 2(C-C motif chemokine ligand 2, CCL2)和 CC 类趋化因子配体 2 (C-C motif chemokine ligand 17, CCL17)将巨噬细胞和 Tregs 细胞募集到 HCC,促进新血管形成、生长、转移以及对索拉非尼的耐药。

3.5 EMT

索拉非尼耐药细胞表型明显变化,细胞形态呈梭形,细胞黏附力下降,发生 EMT,侵袭力也随之增强;体外培养 HCC 耐药株基因表达谱发现,EMT 有关的基因蛋白变化尤为显著^[26]。Zhang 等^[27]发现糖结合蛋白(galectin-1, Gal-1)在 HCC 细胞中过表达,可通过磷脂酰肌醇 PI3K/3-激酶丝氨酸/苏氨酸激酶

AKT 级联诱导 EMT,参与索拉非尼耐药。此外,其他一系列信号通路如丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)、Wnt/ β -Catenin、Notch1、TGF- β /smad、Hedgehog 等,可激活 EMT 蜗牛家族转录抑制因子 1 (snail family transcriptional repressor 1, Snail)表达,引起索拉非尼耐药^[28-29]。

3.6 缺氧

晚期 HCC 瘤体中存在缺氧现象。Zhou TY 等^[30]发现缺氧诱导了 Yes 相关蛋白(YAP)的核转位和靶基因的反式激活,促进 HCC 细胞存活并逃避细胞凋亡,从而导致索拉非尼耐药。此外,Zhao D 等^[31]发现索拉非尼诱导的低氧诱导因子 2 α (hypoxia inducible factor 2 subunit alpha, HIF-2 α)上调可激活转化生长因子 α (transforming growth factor alpha, TGF- α)/表皮生长因子受体途径,引起缺氧环境下 HCC 细胞对其耐药。

3.7 自噬

自噬可参与肿瘤发生发展的多个阶段。Lu 等^[32]研究发现细胞表面糖蛋白 CD24 在肿瘤组织和索拉非尼耐药 HCC 细胞系中过表达,可刺激蛋白磷酸酶 2(protein phosphatase 2A, PP2A)蛋白产生增加并诱导 mTOR/AKT 途径的失活,进而增强自噬参与索拉非尼耐药。晚期糖基化终产物(the receptor of advanced glycation endproducts, RAGE)在 HCC 细胞中高表达,通过 AMPK/mTOR 依赖性方式增加自噬,并引起 HCC 细胞对索拉非尼耐药^[33]。

3.8 细胞外基质

细胞外基质(extracellular matrix, ECM)主要包括胶原蛋白和纤连蛋白等,是形成基质结构框架的主要成分。Azzariti A 等^[34]发现由 HSC 产生的层粘连蛋白 332(laminin-332, Ln-332),作为肝癌细胞表面上 α 3 β 1 和 α 6 β 4 整合素的配体,引起黏着斑激酶(focal adhesion kinase, FAK)泛素化参与索拉非尼耐药。Nguyen 等^[35]发现富含胶原蛋白的微环境通过整合素 β 1 及其下游效应物 c-Jun 氨基末端激酶(c-Jun N-terminal kinase, JNK)参与肿瘤硬化期间对索拉非尼的耐药。此外,Gao 等^[36]使用体外细胞培养系统,调节硬度模仿正常或肝硬化的肝组织,发现机械力激活 Yes 相关蛋白 1 引起 HCC 细胞对索拉非尼耐药。

3.9 衰老细胞

近几年发现衰老细胞可以分泌多种生物活性分

子,如炎症细胞因子、趋化因子和生长因子,这种现象被称为衰老相关的分泌表型(senes-cence-associated secretory phenotype,SASP)。Niu LL 等^[37]发现 SASP 的典型生物标志物,白细胞介素 6 可以激活免疫应答,p16 是细胞衰老的重要诱导因子,分化抑制剂 1(inhibitor of differentiation protein 1,ID1)下调可激活 SASP 相关的 p16/IL6 通路并引起磷酸化 AKT 的活化参与索拉非尼耐药。

4 结 语

索拉非尼作为治疗晚期肝癌的传统一线分子靶向药物,在临床肝癌的治疗中具有一定地位。HCC 可以通过自分泌和旁分泌途径参与索拉非尼耐药,促进 HCC 生长和发展。此外,肿瘤微环境中的基质细胞、免疫细胞及细胞外基质等,也可通过细胞因子、缺氧、自噬等参与 HCC 对索拉非尼的耐药。虽然目前 HCC 对索拉非尼的耐药机制进行了初步探索,但大多数还局限于肿瘤细胞本身,有关肿瘤微环境中其他组分与索拉非尼的关系研究相对较少。

有关 HCC 对索拉非尼的耐药,我们提出以下几点展望:(1)肿瘤微环境中的 CAFs、TAM 等细胞,其介导索拉非尼耐药的具体分子机制还需进一步深入研究;(2)热门非编码 RNA,如 miRNA、长链非编码 RNA 及环状 RNA 等,是否介导 HCC 对索拉非尼的耐药亦可深入研究;(3)目前大多数预测 HCC 对索拉非尼有效性的生物标志物及联合用药方案也仅局限于细胞水平和动物水平,后续需要结合临床深入研究。总之,对这些科学问题的研究将为提高索拉非尼治疗 HCC 有效性,提供新的思路和治疗靶标。

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