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EGFR基因突变与肿瘤靶向治疗

Progress of EGFR Mutation and EGFR-targeted Therapy

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中文关键词： 表皮生长因子受体 酪氨酸激酶抑制剂 突变 靶向治疗 肿瘤

英文关键词:epidermal growth factor receptor tyrosine kinase inhibitors mutations targeted therapy tumor

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作者	单位	E-mail
薛丽[a]，白玉杰[b*]	海南医学院，a.科学实验中心；b.海南省干细胞研究所，海口 571101	yujiebai@163.com

中文摘要:

表皮生长因子受体(epidermal growth factor receptor，EGFR)属于受体酪氨酸激酶超家族，在多种恶性肿瘤中表达。配体与EGFR结合诱导形成二聚体和构象变化，活化酪氨酸激酶及信号转导途径，产生细胞增殖、侵润、转移及抗凋亡等效应。EGFR酪氨酸激酶抑制剂(tyrosine kinase inhibitors，TKIs)类靶向药物，如吉非替尼和厄洛替尼等已应用于临床。临床研究显示仅10%~30%患者对TKIs敏感，部分位于EGFR激酶结构域的活化突变与药物敏感性相关。检测EGFR基因突变有助于预测对药物敏感性和提高疗效。随着治疗绝大多数敏感的患者获得继发耐药性，其中约半数有继发突变T790M，降低药物对靶分子的亲和力，其他许多位于EGFR下游信号途径或旁激活途径的分子也参与耐药形成。因此，未来个体化用药和准确预测敏感性，不仅仅要分析EGFR基因，而且要综合考虑下游和其他信号途径的基因，如PI3K，K-RAS，BRAF，MET和PTEN等。

英文摘要:

The epidermal growth factor receptor(EGFR) belongs to the super-family of receptor tyrosine kinase and is expressed in many malignancies. Upon their ligand-induced dimerization and conformational change, it initiates activation of intracellular tyrosine kinase and a vast array of cell signaling pathways. The cascade of intracellular activation results in cell proliferation, invasion, metastasis and decreased apoptosis. EGFR represents a critical player in many types of malignancies and becomes a natural goal of the targeted therapy. Both monoclonal antibodies and tyrosine kinase inhibitors (TKIs), such as erlotinib and gefitinib, have already entered clinical application. Clinical trials have shown that only 10%-30% of patients responded to the TKIs treatment. Further studies have found that some mutations within the kinase domain activated the kinase and conferred sensitivity to the treatments. The detection of mutations will likely predict the sensitive patients and improve the outcome of current EGFR-targeted therapy. During the treatment, the vast majority of responders developed acquired resistance. Roughly half the mutant EGFR cases with acquired resistance to TKIs have a secondary mutation (T790M) that reduces drug affinity to the kinase target. Many molecules on the downstream of EGFR or by-pass activating pathways also contribute to the drug resistance. In the future, patient-specific treatment approach will have to consider not only the EGFR itself, but also genes on downstream and compensatory pathways, such as PI3K, K-RAS, BRAF, MET and PTEN.

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