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Resistance to biologic drugs

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Background

The extreme interest about targeted therapy of cancer was fueled by the success of imatinib in the treatment of chronic myeloid leukemia. Since then, several targeted treatments have changed the natural history of many cancers but drug resistance is a frequent event that adversely affects the outcome of treatment.

EGF/EGFR are highly expressed in colorectal cancer cells and the two primary signaling pathways activated by EGFR are the RAS-RAF-MAPK and PI3K-PTEN/PTEN/AKT pathways. When activated, the PI3K/AKT pathway leads to protein synthesis, cell growth and anti-apoptosis, while the RAS/RAF/MAPK pathway controls cell cycle progression and proliferation.

KRAS and BRAF

KRAS is a small G-protein that is a pivotal component of the EGFR signal transduction. KRAS activating mutations in codon 12 are detected in up to 40% of mCRC patients (1). Several studies have clearly demonstrated that codon 12 mutations of KRAS confer resistance to cetuximab in patients with mCRC (1). In the CRYSTAL study, patients whose tumors had KRAS mutation (37%), did not have any improvement in progressione-free survival (PFS) or overall survival (OS) when cetuximab was added to fluorouracil-irinotecan combination (2). Given the results of these analyses, the use of cetuximab has been limited to mCRC patients with wild-type KRAS tumors. On the contrary, codon 13 mutations have a less clear role in the development of resistance (1). The serine-threonine kinase BRAF is the principal effector of KRAS. BRAF mutations (mainly V600E) are downstream to KRAS and are found in less than 10% of colorectal cancers. Overall survival differs by somatic mutation status regardless of treatment administered. In the NORDIC VII trial, patients with mutated BRAF had low response rate and markedly shorter PFS and OS compared to wild-type patients (4). In other studies, BRAF-mutated patients did not respond to anti-EGFR treatment and had significantly shorter PFS and OS compared to BRAF wild-type (1).

PIK3CA

Phosphatidylinositol 3-kinase is composed of an 85 kDa regulatory subunit and a 110 kDa catalytic subunit. The protein encoded by PIK3CA gene represents the catalytic subunit, which uses ATP to phosphorylate PtdIns, PtdIns4P and PtdIns(4,5)P2. This gene has been found to be oncogenic and has been implicated in cervical cancers; however the role of PIK3CA mutation in EGFR resistance in mCRC patients remains controversial. PIK3CA mutations have been associated with resistance to the anti-EGFR therapy since they can coexist with KRAS mutations; however it has been difficult to establish a definitive relationship with each of the mutations (5).

PTEN deletion

Enhanced P13K signaling is often due to the activation of genes involved in the P13K pathway such

as PIK3CA and AKT1, or loss of phosphatase and tensin homolog (PTEN). A combined analysis of KRAS, BRAF, and PTEN showed increased RR in up to 45% for chemo-refractory patients receiving cetuximab from 39% with KRAS, PTEN and BRAF wild-type tumors where PTEN mutations were all resistant to cetuximab, unlike KRAS mutation where 12.5% in this study, responded to cetuximab (6).

IGF1R

The type 1 insulin-like growth factor receptor (IGF- 1R) is a member of a family of trans-membrane tyrosine kinases that includes the insulin receptor and the insulin receptor-related receptor. The IGF-1R signaling pathway is important in different types of cancers and includes transduction of the IGF signal by the MAPK and PI3K/Akt. The IGF-1 downstream signaling cascade is thought to induce EGFR independent PIK3CA and AKT activity, which might be another explanation for the lack of efficacy of anti-EGFR monoclonal antibodies in KRAS wild-type colorectal cancer (7).

HER family members and MET

In vitro studies demonstrate that cells developing acquired resistance to cetuximab exhibited increased steady-state EGFR expression secondary to alterations in cellular trafficking and degradation. In addition, cetuximab-resistant cells manifested strong activation of HER2, HER3 and cMET. EGFR upregulation promoted increased dimerization with HER2 and HER3 leading to their transactivation. Blockade of EGFR and HER2 led to loss of HER3 and PI3K/Akt activity. These data suggest that acquired resistance to cetuximab is accompanied by dysregulation of EGFR internalization/degradation and subsequent EGFR-dependent activation of HER3 (8).

Conclusions

Several molecular mechanisms of resistance to anti-EGFR treatments are being unraveled and among them KRAS and BRAF mutations appear to be the most reliable indicators of benefit or failure of anti-EGFR therapeutics in colorectal cancer.

References

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