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Epidermal growth factor receptor-targeted therapy in colorectal cancer

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1. ABSTRACT

The epidermal growth factor receptor (EGFR) family plays an important role in colorectal cancer (CRC). EGFR participates in the key process of tumorigenesis and invasion, and its expression correlates with the prognosis of CRC. EGFR-targeted therapy has been widely utilized in stage III and IV CRC. The EGFR antibodies, cetuximab and panitumumab, are widely used in treatment of CRC. There are clinical trials and *in vivo* studies being carried out on the efficacy and mechanism of their action in CRC treatment. In this review, we will describe the EGFR-targeted therapy used in CRC, focusing on the efficacy and mechanisms of the most commonly used EGFR antibodies, cetuximab and panitumumab.

2. INTRODUCTION

Colorectal cancer (CRC) is a malignant neoplasm of the colon or rectum that develops from abnormal growth of cells with the ability to invade or spread in the body (1,2). CRC poses a great health burden and is the third most commonly diagnosed cancer in men, and the second most commonly diagnosed in women in the U.S., accounting for approximately 20% of all new cancer cases annually (3). Although advances have been made in CRC therapy, there were still 694,000 deaths from the disease globally in 2012 (4), and the 5-year survival rate is only 62% in the U.S., mainly due to complications of metastatic disease (5). In the management of CRC, surgery is a major therapy for patients with localized cancer, but chemotherapy is also required for patients with stage II or later stage CRC. In recent years, advancements in our understanding of genetic factors involved in tumorigenesis have provided novel targets for therapy of CRC patients ineligible for surgery or who fail to respond to chemotherapy.

Expression of the epidermal growth factor receptor (EGFR) family occurs in most epithelial cell cancers, including CRC. A meta-analysis showed that high expression of EGFR predicts poor survival for patients with colon cancer (6), and EGFR has been used as a marker of circulating tumor cells in colon cancer (7).Thus, EGFR is a major therapeutic target in CRC (8). In this review, we will briefly describe the use of EGFR-targeted therapy in CRC, and focus on the efficacy and mechanisms of action of the most commonly used EGFR antibodies, cetuximab and panitumumab.

3. EGFR IN COLORECTAL CANCER

EGFR is the cell-surface receptor for the epidermal growth factor family, and belongs to the ErbB protein family (9). EGFR mutations may lead to tumorigenesis (10). Microarray analysis of tissues from patients with stage II colon cancer showed that EGFR expression was associated with poor survival (11). Galizia and colleagues have confirmed this finding, and have also shown that EGFR expression is an independent prognostic indicator of colon cancer recurrence (12).These clinical studies thus demonstrate a close relationship between EGFR and CRC outcome.

In vivo and *in vitro* studies further elaborate the mechanisms underlying the relationship between

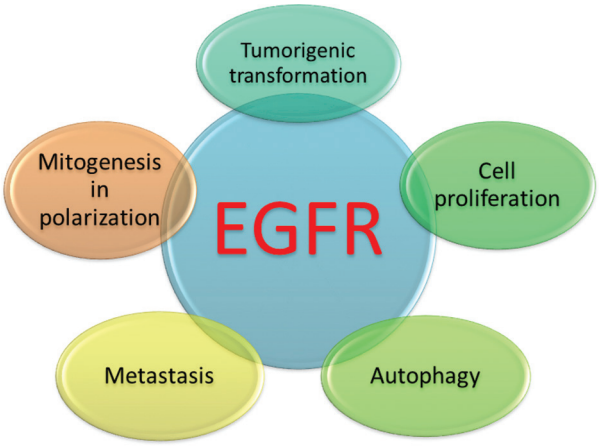

Figure 1. Role of EGFR in malignant colon cancer cell behavior. EGFR contributes to malignant activity in colon cancer cells, including transformation of non tumorigenic cells into cancerous cells, mitogenesis of polarizing colon cancer cells, proliferation of cancer cells, cellular metastasis and autophagy.

EGFR and CRC. EGFR has been found to contribute to malignant behaviors of colon cancer cells, including transformation of non tumorigenic cells into tumorigenic cells, mitogenesis of polarizing colon cancer cells, proliferation of cancer cells, cellular metastasis and autophagy (13-19) (Figure 1). The proliferation of tumorigenic cells can be induced by activation of extracellular signal-regulated protein kinases 1 and 2, which is stimulated by Src-mediated cross talk between EGFR and aryl hydrocarbons (20). Interestingly, EGFR can transform a nontumorigenic cell line into a tumorigenic but not a metastatic line, unless there is also attenuation of transforming growth factor (TGF)-beta signaling (21). Moreover, TGF- alpha can stimulate EGFR to create a beneficial microenvironment for metastasis (22). In addition to its effect on malignant cancer cell behaviors, EGFR is also involved in signaling required for the effect of the colonic microenvironment on claudin-2 expression, leading to tumorigenicity of colon cancer cells (23).

In contrast to EGFR over expression, inhibition of EGFR has been shown to decrease vascularization and tumor cell proliferation, and increase apoptosis in an orthotopic model of human colon cancer in nude mice (24). An *in vitro* study with human colon cancer cells confirmed the finding that suppression of the EGFR gene inhibited human colon cancer cell growth (25). Furthermore, carcinogens such as nicotine can promote colon cancer through EGFR signaling pathways (26). These findings confirm the effect of EGFR in promoting progression of colon cancer and show that EGFR plays a significant role in the occurrence and development of CRC. EGFR-targeted treatment can be considered a breakthrough strategy in CRC therapy.

The antibodies cetuximab and panitumumab were approved by the U.S. Food and Drug Administration in 2009 and 2006, respectively, for use in the treatment of KRAS wild-type colon cancer, but CRC with the KRAS mutation is resistant to these EGFR inhibitors (27,28). The resistance occurs because the activating mutation of KRAS stimulates the RAS/RAF/MAPK pathway in an EGFR-independent manner (29). Because 35%–40% of CRC patients have the KRAS mutation, the absence of the mutation has been seen as the most important predictive biomarker for patients who can benefit from anti-EGFR reagents like cetuximab and panitumumab (30).Both drugs have been shown to increase first-line treatment efficacy in CRC (31-33). Therefore, we will first discuss the efficacy and biochemical mechanisms of cetuximab and panitumumab, the most commonly used drugs in CRC treatment.

4. CETUXIMABIN CRC TREATMENT

4.1. Cetuximab efficacy in CRC treatment

Cetuximab is regarded as a well-tolerated second-line therapy for treating colon cancer patients with liver metastasis, even when complicated by liver dysfunction and icterus (34,35). Case reports have also shown the efficacy of combined treatment with cetuximab and irinotecan on colon cancer patients with liver metastasis (36-38). Furthermore, cetuximab combined with chemotherapy using the 5-fluorouracil (5-FU), leucovorin and oxaliplatin (FOLFOX) regimen was successfully used as first-line treatment for colon cancer with liver metastases (39). Combining cetuximab with chemotherapy also improved the outcome of patients with metastases to lung, periaortic and celiac lymph nodes, and with lymphangitis carcinomatosa (40,41), and several case studies have shown cetuximab to be effective in treating CRC patients with recurrence (42-44). While these findings were from case reports, an *in vivo* study also reported that cetuximab could synergize with metronomic chemotherapy of paclitaxel to suppress human colon cancer xenografts (45). Greater understanding of the efficacy of cetuximab in CRC treatment will be gained from well-designed clinical studies employing larger sample numbers which combine cetuximab with others drugs for metastatic or recurrent CRC treatment.

Randomized trials have now been carried out to test the efficacy of cetuximab combined with chemotherapy in patients with stage III colon cancer. Alberts and colleagues (46) assessed the benefit of adding cetuximab to the modified sixth version of the FOLFOX regimen (mFOLFOX6) in 2686 patients with resected stage III wild-type KRAS colon cancer. The addition of cetuximab did not improve disease-free survival compared with mFOLFOX6 alone. More recently, Huang *et al*. reported on the efficacy of adding cetuximab to the leucovor in, 5-FUandirinotecan (FOLFIRI) regimen in patients with resected stage III colon cancer (47). Although their sample was smaller than Alberts's study, with only about 150 patients, patient follow-up extended to

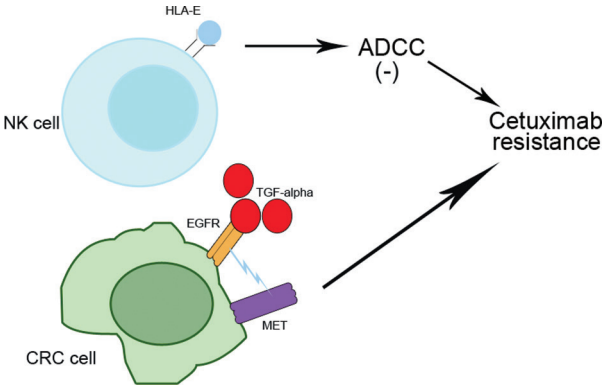

Figure 2. Promotion of cetuximab resistance. HLA-E required for cell recognition by natural killer (NK) cells may inhibit antibody-dependent cellular cytotoxicity (ADCC) of cetuximab, leading to the cetuximab resistance. Over expression of TGF-α, an EGFR ligand, may also promote cetuximab resistance by inducing EGFR-MET interaction in CRC cells.

nearly 6 years. This study also failed to show a significant trend toward improved disease-free survival or overall survival by adding cetuximab to FOLFIRI compared to FOLFIRI alone. Finally, Taieb and colleagues (48) reported an open-label, randomized phase 3 trial on the efficacy of adding cetuximab to standard adjuvant FOLFOX4 in 2559 patients with stage III colon cancer. They too did not find a significant trend toward improved disease-free survival compared with FOLFOX4 alone. It is possible that the failure to find a significant beneficial effect of combined cetuximab therapy in these trials was partially due to the heterogeneity of responses observed in study patients. Notably, these heterogeneous responses suggest that further investigation of the efficacy of chemotherapy plus cetuximab in specific patient subgroups is warranted.

4.2. Cetuximab efficacy and resistance in CRC treatment: Mechanisms

Though cetuximab has shown efficacy in the treatment of CRC, even in5-FU-resistant colon cancer (49), several factors may influence its effectiveness and also affect cetuximab resistance. Since EGFR is the target of cetuximab, EGFR amplification was associated with the response to the cetuximab-based regimen (50). In addition, activation of intracellular Akt and p44/42 MAPK signaling pathways was also associated with sensitivity to cetuximab treatment in a colon cancer cell line (51), suggesting that cetuximab efficacy is not governed by single factor alone but is also influenced by the activation status of several intracellular signaling pathways. However, resistance to cetuximab treatment in CRC has been observed and involves many factors. In colon cancer cells, the antibody-dependent cellular cytotoxicity of cetuximab can be inhibited by expression of human leukocyte antigen E (HLA-E), which is required for cell recognition by natural killer cells and contributes to cetuximab resistance (52,53). In addition to HLA-E, overexpression of TGF-alpha, an EGFR ligand, has been shown to promote cetuximab resistance by inducing EGFR-MET interactions in CRC cell lines (54,55) (Figure 2). In contrast, cetuximab resistance can be decreased by temsirolimus via regulation of cancerous inhibitor of protein phosphatase 2A (CIP2A) expression in colon cancer cells (56).

Additional genetic factors may also control the response to cetuximab. In colon cancer cell lines, HCT116 cells with the phosphatidylinositol 3-kinase, catalytic subunit alpha (PIK3CA) mutation were increasingly resistant to cetuximab compared with PIK3CA wild-type controls, and a similar effect was also found in cell lines with a phosphatase and tensin homolog (PTEN) null gene and dual mutations in PIK3CA and the Ras/B-Raf proto-oncogene, compared to cells without the dual mutations and PTEN loss (57). These mutant genes have been implicated in tumorigenesis as well, suggesting that the cetuximab resistance could be determined by genetic factors without additional inducement. Recently, Cho and colleagues found through whole genome sequencing that cells harboring the G719S and G724S mutations in the EGFR were responsive to cetuximab therapy in a CRC case (58), but this finding requires replication in a larger sample.

Although clinical trials have failed to observe a beneficial effect of cetuximab in adjuvant chemotherapy of CRC cancer, the use of cetuximab combined with single or multiple reagents still garners attention. When combined with the tyrosinekinase inhibitor gefitinib, the anti-tumor effect of cetuximab was augmented in colon cancer cell lines (59). The combination of cetuximab and trastuzumabled to inhibition of cell proliferation in colon cancer cells in a time- and dose-dependent manner and was associated with abnormal copy numbers of the EGFR gene (60). Cetuximab-conjugated gamma-poly (glutamic acid)-docetaxelnanomedicines induced cell death of HT-29 cells by enhancing cell cycle arrest in the G2/M phase compared to therapy without cetuximab conjugation (61). In addition to chemotherapy, adjuvant high-intensity focused ultrasound therapy was also observed to enhance the anti-tumor effect of cetuximab in a colon cancer xenograft model in mice (62). Regarding possible mechanisms underlying the effects of combination therapy, Solmi and colleagues (63) found that cetuximab combined with EGF treatment induced apoptosis inhuman colon cancer cells. Furthermore, the beneficial effect of adjuvant cetuximab treatment in chemotherapy has been associated with functional changes in immune cells. For example, the combination of chemotherapy and cetuximab promoted phagocytosis of colon cancer cells by human dendritic cells, leading to a robust cytotoxic T-lymphocyte anti-tumor response (64). However, drugs utilized in chemotherapy, including 5-FU, gemcitabine and irinotecan, not only up-regulated EGFR expression on the surface of colon cancer

cells, but more importantly, also enhanced sensitivity to antibody-dependent cell cytotoxicity mediated by lymphokine-activated killer cells or cetuximab in a manner that was independent of KRAS status (65).

4.3. Side effects

Although *in vivo* and *in vitro* studies have demonstrated the benefits of cetuximab in CRC treatment, the side effects of cetuximab cannot be ignored. Common side effects include acne-like rash, fevers, chills, rigors, urticaria, pruritis, rash, hypotension, bronchospasm, dyspnea, wheezing, angioedema, dizziness, anaphylaxis, and cardiac arrest. In patients with colon cancer, rare and serious side effects were sometimes reported, including fatal toxic epidermal necrolysis and diffuse alveolar damage (66,67). It is unclear why colon cancer patients developedsuch fatal side effects following cetuximab treatment, or if these side effects were the result of cetuximab treatment alone or involved other factors. Further studies will therefore be required to properly assess the safety of cetuximab in treatment of CRC.

5. PANITUMUMAB

5.1. Panitumumab efficacy in CRC treatment

Similar to cetuximab, panitumumab is an antibody which prevents EGFR activation by binding to the EGFR extracellular domain and inhibiting the cascade of intracellular signals triggered by EGFR (68). Panitumumab administered in conjunction with the single agent regorafenib was reported to slow CRC progression (69). The benefits of panitumumab in adjuvant FOLFIRI chemotherapy have been observed in colon cancer cases with multiple hepatic metastases, and with metastases to urinary bladder and uterus (70-72). Panitumumab combined with FOLFOX was also used to successfully treat stage IV sigmoid colon cancer with liver and ovarian metastases which had acquired resistance to prior chemotherapy regimens (73). Similar efficacy was recently reported in a patient with resected sigmoid colon cancer with urinary bladder invasion (74). In addition to these case studies, Leone and colleagues (75) completed a clinical trial examining 49 patients with colon cancer and advanced liver metastases. They found that the combination of panitumumab with infusional oxaliplatin and oral capecitabine resulted in high response and respectability rates for patients with extensive liver metastases. However, randomized trials with larger samples will still be required to validate the effect of panitumumab combined with adjuvant chemotherapy, which may provide additional information on the use of panitumumab in CRC treatment.

5.2. Panitumumab efficacy in CRC treatment: Mechanisms

In vitro studies exploring the mechanisms of panitumumab action in CRC treatment have found that in addition to targeting EGFR, panitumumab diminished colon cancer cellular proliferation by inducing autophagy regardless of KRAS mutations (76).When panitumumab was combined with gefitinib, colon cancer cellproliferation was inhibited in the early stages of growth, as were migration, invasiveness and matrix macromolecule effectors implicated in cancer progression (77).This finding suggests that panitumumab may have anti-tumorigenic effects through pathways extending beyond EGFR signaling alone. Future studies may thus reveal unexpected roles for panitumumab in cancer treatment.

5.3. Side effects

The side effects of panitumumab are similar to cetuximab and include skin rash, fatigue, nausea, diarrhea and decreased magnesium levels. Moreover, some colon cancer cases reported cardiac arrest or epistaxis after panitumumab treatment (78,79). Serious secondary effects like cardiac arrest will require further examination in larger samples to confirm cause and effect, since this particular side effect has only been rarely observed.

6. CONCLUSIONS

In conclusion, EGFR-targeted therapy can benefit CRC patients, particularly those in stage III or IV. Although *in vitro* studies have reported on the efficacy of cetuximab or panitumumab combined with other treatments in CRC cell lines, clinical evidence is still lacking on improved outcomes gained by combining cetuximab or panitumumab with adjuvant chemotherapy in CRC. Considering the differing results from *in vitro* studies and clinical trials, as well as the heterogeneity of patient responses, the efficacy of combining anti-EGFR reagents and chemotherapy will require further validation.

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Abbreviation: EGFR: epidermal growth factor receptor; CRC: colorectal cancer; TGF: transforming growth factor; 5-FU:5-fluorouracil; FOLFOX:5-fluorouracil, leucovorin, oxaliplatin; mFOLFOX6: modified sixth version of the regimen; FOLFIRI: leucovorin, fluorouracil andirinotecan; NK: natural killer; ADCC: antibody-dependent cellular cytotoxicity

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