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Clinical Cancer Research

CCR Translations

See related article by Gerdes et al., p. 1126

Can the "Right" EGFR-Specific mAb Dramatically Improve EGFR-Targeted Therapy?

Francesco Sabbatino and Soldano Ferrone

EGF receptor (EGFR)–specific monoclonal antibodies (mAb) display limited therapeutic efficacy in EGFR-positive solid tumors. To overcome this limitation, the significant improvement of the antibody-dependent cell-mediated cytotoxicity–mediated antitumor activity of a novel EGFR-specific mAb is described. Its potential impact on the efficacy of immunotherapy for EGFR-positive solid tumors is discussed. *Clin Cancer Res; 19(5); 958–60. ©2013 AACR.*

In this issue of *Clinical Cancer Research*, Gerdes and colleagues (1) describe the development and characterization of the functional properties of the novel EGF receptor (EGFR)–specific monoclonal antibody (mAb) GA201. The latter immunoglobulin G (IgG)1 mAb was generated by humanization of the EGFR-specific rat mAb ICR62 and glycoengineering of its Fc portion to enhance its binding to FcγRIIIA expressed on effector cells.

EGFR has been shown to be expressed and activated in several epithelial malignancies, including colorectal cancer (CRC), squamous cell carcinoma of the head and neck (HNSCC), and carcinoma of the pancreas, lung, cervix, renal cell, prostate, bladder, and breast (2). Like other growth factor receptors, EGFR can mediate oncogenic signals involved in proliferation and survival of tumor cells. This background information has provided the rationale to develop EGFR-targeted therapies, with small-molecule EGFR tyrosine kinase inhibitors (TKI) and with EGFR-specific mAbs (3).

Several lines of evidence have convincingly shown that both TKIs and mAbs can blockade proliferative and/or antiapoptotic pathways in tumor cells and that these mechanisms play a major role in their therapeutic activity. However, the EGFR-TKIs and the EGFR-specific mAbs inhibit EGFR activation through different mechanisms; the latter block the EGF binding to EGFR (4), whereas the former inhibit its autophosphorylation (5).

In addition to inhibiting EGFR-activated signaling, IgG1 EGFR-specific mAbs may display antitumor activity through an antibody-dependent cell-mediated cytotoxicity (ADCC) mechanism, that is, by mediating the lysis of target cells by effector cells such as monocytes, macrophages, and natural killer (NK) cells. This effect is influenced by the binding affinity of the mAb to the Fcγ receptors (FcγR) expressed by effector cells, as indicated by the association between polymorphism of FcγRIIIA and extent of lysis of target cells in ADCC (ref. 6; Fig. 1).

Some EGFR-TKIs (erlotinib and gefitinib) and EGFR-specific mAbs (chimeric IgG1 cetuximab and humanized IgG2 panitumumab) have received U.S. Food and Drug Administration (FDA) approval for treatment of various types of cancer either as single agents or in combination with chemotherapy or radiotherapy. In general, EGFR-TKIs have been poorly effective in the treatment of malignancies with an EGFR pathogenesis, except for those which selectively target EGFR abnormalities responsible for the oncogenic signal. This is exemplified by the significant therapeutic efficacy of erlotinib and gefitinib in patients with lung adenocarcinoma harboring activating mutations in the EGFR tyrosine kinase domain (7). Modest clinical efficacy has also been reported for the FDA-approved EGFR-specific mAbs cetuximab and panitumumab (8).

The antitumor activity mediated by EGFR-TKIs can be bypassed by mutations in molecules, which activate oncogenic signals downstream EGFR blockade. These mutations seem to counteract also the immune-mediated antitumor activity of the available EGFR-specific mAbs. This is exemplified by the poor therapeutic efficacy of the EGFR-specific mAbs, cetuximab and panitumumab, in patients with KRAS-mutated CRC (8). These findings are surprising as no mechanism is readily available to explain why signaling activation downstream EGFR blockade can be associated, if not cause the resistance of CRC cells harboring KRAS mutations to the immune attack mediated by the IgG1 EGFR-specific mAbs used.

In this issue of *Clinical Cancer Research*, Gerdes and colleagues (1) postulate that these surprising findings reflect the poor ADCC activity of the presently FDA-approved EGFR-specific mAbs. This possibility is supported by the results Gerdes and colleagues (1) have obtained with their own newly developed mAb GA201. Comparison of the binding characteristics and of the functional properties of the latter mAb with the mAb cetuximab in *in vitro* assays and

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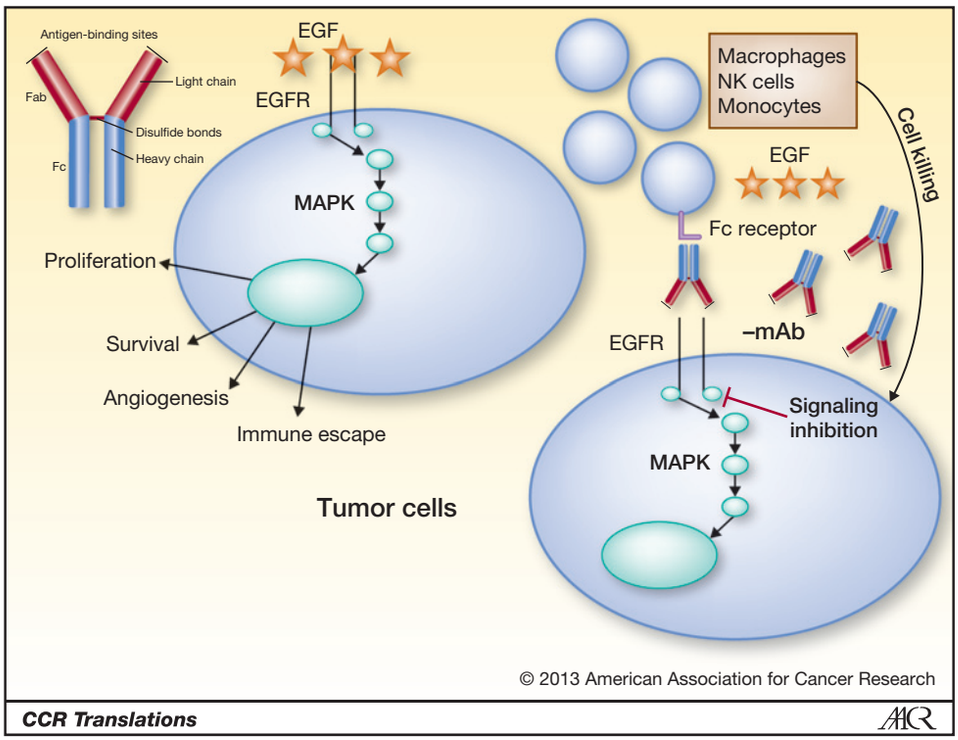

Figure 1. EGFR-specific mAb can mediate antitumor effect by inhibiting EGFR activation and mediating cell-dependent lysis of tumor cells in ADCC.

in animal model systems has shown that these 2 IgG1 mAbs recognize distinct and spatially distant EGFR epitopes. Furthermore, mAb GA201 displays a lower affinity for EGFR than cetuximab. Nevertheless, the 2 mAbs do not differ in their ability to inhibit tumor cell proliferation and to induce apoptosis *in vitro*. Both mAbs exert these effects by inhibiting EGFR/HER2 heterodimerization and downstream signaling. However, mAb GA201 displays a significantly higher activity than cetuximab in ADCC assays conducted with several types of effector cells and with target cells expressing different EGFR levels. Whether this difference reflects at least in part the distinct characteristics of the EGFR epitopes recognized by the 2 mAbs remains to be determined. Furthermore, at variance with cetuximab, the ADCC activity of mAb GA201 is not influenced by its affinity for FcγRIIA and FcγRIIIA as the extent of lysis of target cells mediated by mAb GA201 is similar when FcγRIIIA high- and low-affinity human NK cells are used as effectors. It is noteworthy that differences in affinity of FcγRIIIA, which reflect its polymorphism, seem to have clinical significance, as an association between FcγRIIIA polymorphism and clinical response to cetuximab in patients with CRC has been reported (9). This association is not unique of cetuximab as it has been described also in patients with follicular lymphoma and in patients with breast cancer treated with the CD20-specific mAb rituximab (10) and with the HER2-specific mAb trastuzumab (11), respectively. Finally, at variance with cetuximab, mAb GA201 is not affected in its ADCC activity by the presence of KRAS mutation in target cells. mAb GA201 mediates lysis of target cells even when they express low EGFR level and the human NK cells used as effectors express a low-affinity FcγRIIIA.

The conclusions derived from the described *in vitro* experiments have been corroborated by those derived from *in vivo* experiments. Using various types of human tumor cell lines grafted in immunodeficient mice, Gerdes and colleagues (1) have convincingly shown that mAb GA201 is significantly more effective than cetuximab in controlling tumor growth, both as a single agent and in combination with chemotherapy. More importantly, the *in vivo* antitumor activity of mAb GA201 does not seem to be affected by variables such as level of EGFR expression and/or presence of KRAS mutations, which abrogate the cetuximab antitumor activity.

In view of the potential clinical relevance of Gerdes and colleagues' results (1), it is noteworthy that the mAb GA201 broadens the patient population who may be treated with EGFR-targeted immunotherapy. Specifically, the patients to be treated with mAb GA201 will include also those with low-affinity FcγRIIIA as well as those with KRAS-mutated tumors.

The comparison of the properties of mAb GA201 and cetuximab would have benefited from the identification of the normal tissue(s) with an EGFR expression level sufficient to trigger an ADCC by mAb GA201. Are the likely side effects caused by this mechanism a major obstacle to the clinical use of mAb GA201? Furthermore, does mAb GA201, like other tumor antigen–specific mAbs (12), trigger a tumor antigen–specific T-cell response? Finally, in view of the postulated role of cancer-initiating cells in disease recurrence and metastatic spread, does mAb GA201 either

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as a single agent or in combination with chemotherapeutic agent(s) and/or inhibitor(s) of core stem cell pathways (Notch, Sonic Hedgehog, Wnt) target cancer-initiating cells? Nevertheless, Gerdes and colleagues' compelling results emphasize the urgency to translate to a clinical setting the strategies developed with mAb GA201, once its potential toxicity has been better defined.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: F. Sabbatino, S. Ferrone
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): F. Sabbatino, S. Ferrone
Writing, review, and/or revision of the manuscript: F. Sabbatino, S. Ferrone

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