Correlation between Gene Expression of IGF-1R Pathway Markers and Cetuximab Benefit in Metastatic Colorectal Cancer

Fei Huang, Li-an Xu, and Shirin Khambata-Ford

Abstract

**Purpose:** This study examined potential correlations between markers related to the insulin-like growth factor-1 receptor (IGF-1R) pathway and clinical benefit from the anti–epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab in metastatic colorectal cancer (mCRC).

**Experimental Design:** Gene expression profiles for 70 pretreatment specimens from metastatic lesions of patients with chemorefractory mCRC receiving cetuximab monotherapy were analyzed using 74 predefined Gene-Chip probesets representing 33 unique IGF-1R pathway markers to determine correlations with progression-free survival (PFS) and disease control rate.

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**Conclusions:** These results suggest that markers of the IGF-1R pathway may play a role in predicting benefit from cetuximab therapy in mCRC. Additional clinical studies are warranted to validate these findings. *Clin Cancer Res;* 18(4); 1156–66. ©2012 AACR.

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Introduction

Cetuximab is an anti–epidermal growth factor receptor (EGFR) monoclonal antibody that has antitumor efficacy in metastatic colorectal cancer (mCRC; refs. 1, 2); locoregionally advanced recurrent or metastatic squamous cell carcinoma of the head and neck (3, 4); and advanced non–small cell lung cancer (NSCLC; ref. 5). In unselected patients with mCRC, cetuximab significantly improved survival as a single-agent therapy and in combination with chemotherapy in treatment-naive patients (2, 6–8). Whereas these original studies bundled all known exon-2 mutations as one single “resistance genotype,” more recent studies have indicated that patients with tumors carrying the G13D mutation may not benefit from therapy, suggesting that this mutation may not have the same effect as the rest on exon-2 (9, 10). These findings represent a significant breakthrough in mCRC treatment because they allow cetuximab to be directed to patients who are most likely to benefit. However, not all patients with wild-type K-Ras benefit from cetuximab-based therapy, and further refinement of patient selection is desirable.

In chemotherapy (particularly irinotecan)-refractory patients, there is a growing list of candidate predictive markers under investigation. These include EGFR gene copy number measured by FISH, ligand gene expression (amphiregulin and epiregulin [EREG]) or polymorphisms (EGF), mutations in components of the MAP-Ras-Raf pathway, loss of the PTEN gene, and PIK3CA expression levels or
IGF-1R Pathway Markers and Cetuximab Benefit in CRC

Translational Relevance

Patients with metastatic colorectal cancer (mCRC) whose tumors harbor the wild-type K-Ras gene may derive benefit from treatment with the anti-epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab, whereas those patients with tumors bearing certain K-Ras mutations do not benefit. However, not all patients with wild-type K-Ras tumors benefit from cetuximab, underscoring the need for additional markers to help in patient selection. Preclinical evidence suggests that the EGFR and insulin-like growth factor-1 receptor (IGF-1R) pathways interact to drive tumor growth and survival. This study evaluated whether expression levels of the IGF-1R pathway markers correlate with cetuximab benefit in patients with chemorefractory mCRC, including the subset of patients with wild-type K-Ras. The results provide initial evidence that markers of the IGF-1R pathway may predict benefit from cetuximab therapy in mCRC, but this preliminary finding requires validation in additional clinical studies.

Methods

Patients and study design

The CA225-045 trial was a phase II pharmacogenomic study in which 110 patients with chemorefractory mCRC received single-agent cetuximab after failing at least one chemotherapeutic regimen for advanced disease or refusing prior treatment. Details of the study design and patient cohort have been described previously (13). Patients received cetuximab at its standard dose (400 mg/m² loading dose; then 250 mg/m² weekly) for 3 weeks and then were eligible for dose-escalation every 3 weeks to a maximum of 400 mg/m² weekly, provided they had not experienced greater than grade II skin rashes. Tumor responses were evaluated every 9 weeks according to modified WHO criteria (42). The disease control rate (DCR) was defined as the proportion of patients with a complete response (CR), partial response (PR), or stable disease (SD). Progression-free survival (PFS) was defined as the time from enrollment until disease progression or death. The study protocol was approved by the Institutional Review Board at each participating center and all patients provided written informed consent before study procedures were conducted.

Gene expression profiling and K-Ras mutational status

A biopsy specimen for use in predictive marker discovery was collected before cetuximab therapy by 3 passes with an 18-gauge needle through a single metastatic lesion. Total RNA was isolated from these tumor samples and 1 mg RNA was used for gene profiling on U133Av2.0 GeneChips according to the manufacturer’s instructions (Affymetrix). K-Ras exon-2 and B-Raf V600E mutation analyses were performed at the participating center and all patients provided written informed consent before study procedures were conducted.

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conducted using genomic DNAs isolated from these tumors as described previously (13).

Gene expression data analysis of preselected genes

A total of 74 preselected probesets, representing 33 unique IGF-1R pathway–related genes were evaluated, including those encoding for ligands (IGF-1, IGF-2, and INS), receptors (IGF-1R, INSR, and IGF-2R), binding proteins (IGFBP1, 2, IGF2BP1, and IGF2BP2), insulin–induced genes (INSIG1 and INSIG2), insulin receptor substrates (IRS1–4), adapters and downstream effectors (GRB7, GRB10, GRB14, SHC1–3, and AKT1–3), and related genes INSR and IDE.

The Affymetrix gene expression data were normalized using a Robust Multichip Average (RMA) method (43, 44). Thresholds for high versus low marker expression level were established on the basis of whether the signal intensity was above or below the median value across all subjects if the signal intensities of a given marker displayed a normal distribution. However, for IGF-1R and IGF-1, the distribution of signal intensities appeared to be a mixture of 2 components; therefore, for these 2 markers, mixture models of 2 normal distributions were used to determine the cutoff points for classifying expression as high versus low.

Statistical analysis

Gene expression profiles were compared with clinical benefit parameters by univariate analyses. A log-rank test with a 2-sided α = 0.05 was used to compare differences in PFS between patients having high versus low marker expression in the overall population and wild-type K-Ras subset. A Cox proportional hazards model was also used to assess the effect of marker status on PFS in both populations separately. For these analyses, the HR of the marker effect, its 2-sided 95% confidence interval (CI), and the P value were determined. The DCR and its 95% CI were calculated for the overall population.

Patient characteristics and clinical outcome

Correlations between markers from the IGF-1R pathway and clinical benefit from cetuximab therapy were determined for the overall population of 70 patients with known K-Ras mutational status and the subset of 43 patients with wild-type K-Ras tumors. Demographic and clinical characteristics are shown in Table 1. Of the 70 patients, the objective best response was CR/PR in 5 patients, SD in 17 patients, and progressive disease (PD) in 48 patients. For the subgroup with wild-type K-Ras, the objective best response was CR/PR in 5 patients, SD in 15 patients, and PD in 18 patients. Therefore, the DCR was 31.4% in the overall population and 46.5% in the wild-type K-Ras population. The corresponding median PFS values were 60 days (95% CI, 59–67) and 61 days (95% CI, 58–56), respectively.

Distribution of gene expression signal intensity in study population

For most genes, the median expression value was used as the threshold to classify the tumors as high or low expressing for the study population. Therefore, for each of these candidate predictive markers, 50% of the overall population was classified as having high expression. As exceptions, cutoff values between high and low expression for IGF-1R and IGF-1 expression were determined using mixture models of 2 normal distributions (log2 expression level >7.15 for IGF-1R defining 62.9% of the population as high, and log2 expression level >5.82 for IGF-1 defining 40% of the population as high; Fig. 1).

Correlation of candidate marker expression with DCR and PFS

Overview of the analyses. Analyses were conducted for the 74 probesets (representing 33 unique markers) specified in the Methods section (see Supplementary Table). With an FDR control at the 0.15 level, only INSIG2 expression was found to be significantly correlated with DCR and PFS. However, given the small sample size in this study, a liberal...
FDR control at 0.4 was applied to evaluate the overall results. With this control, significant correlations were found for 6 markers, detailed below. For the remaining 27 unique markers, correlations were not significant. For the 6 candidate markers with significant correlations, an additional analysis was conducted to evaluate their effect in patients with high versus low EREG expression within the population with K-Ras wild-type tumors, in light of the predictive effect that this ligand marker had shown in a data set generated from this same study (13). In addition, mutational analysis for B-Raf V600E was carried out in 44 of 70 samples with available material; given the low sample number, the results of this co-analysis were not informative (not shown).

**IGF-1R.** Higher IGF-1R expression was significantly associated with a DCR benefit during cetuximab therapy in the wild-type K-Ras subgroup (62.5% vs. 26.3%; P = 0.031), but not in the overall population (36.4% vs. 23.1%; P = 0.295) when compared with lower IGF-1R expression (Fig. 2). Higher IGF-1R was also associated with a PFS benefit, particularly in the wild-type K-Ras subgroup where median PFS was 122 days compared with 60 days for low IGF-1R expression (HR = 0.406; 95% CI, 0.202–0.823; P = 0.01; Table 2). This difference in PFS between the high and low IGF-1R expression groups was particularly evident for the patients with longer PFS times. The PFS benefit associated with higher IGF-1R expression in the wild-type K-Ras subpopulation was not evident in patients with K-Ras mutant tumors, whereas lower IGF-1R expression was associated with a lack of clinical benefit with cetuximab regardless of K-Ras mutation status (Fig. 3A).

**GRB7.** Higher GRB7 expression was associated with higher DCR rates in response to cetuximab, but differences compared with lower GRB7 expression did not reach statistical significance in either the overall population (40.0% vs. 22.9%; P = 0.197) or the subpopulation with tumors bearing wild-type K-Ras (58.3% vs. 31.6%; P = 0.125; Fig. 2). Nevertheless, higher GRB7 expression was associated with a PFS benefit in both cohorts (Table 2): median PFS for the high and low GRB7 expression groups were 65 versus 59 days, respectively, in the overall population (HR = 0.484; 95% CI, 0.276–0.849; P = 0.01), and 122 versus 57 days, respectively, in the wild-type K-Ras subgroup (HR = 0.396; 95% CI, 0.19–0.828; P = 0.011). The PFS benefit associated with higher GRB7 expression was not evident in K-Ras mutant tumors, whereas lower GRB7 expression was

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**Figure 1.** Distribution of signal intensities of gene expression in the overall study population for IGF-1R (A), IGF-1 (B), GRB7 (C), INSIG2 (D), IGFBP3 (E), and INSR (F). The vertical line identifies the cutoff for high versus low expression. High expression for IGF-1R and IGF-1 is defined by signal intensity log2 > 7.15 and > 5.82, respectively, whereas for the other markers, high expression is defined by signal intensity above the median value for the study population.
associated with a lack of clinical benefit with cetuximab regardless of K-Ras mutation status (Fig. 3B).

INSIG2. Lower INSIG2 expression was associated with cetuximab benefit, particularly in patients with tumors harboring wild-type K-Ras. Lower expression (compared with higher expression) was associated with significantly better DCR rates in both the overall population (51.4% vs. 11.4%; \( P = 0.001 \)) and the wild-type K-Ras subpopulation (62.6% vs. 18.2%; \( P < 0.0001 \)).

Table 2. Correlation of candidate marker expression with median PFS (days)

<table>
<thead>
<tr>
<th>Marker [Probe ID]</th>
<th>Overall population</th>
<th>K-Ras WT population</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>High Low HR (95% CI), ( P )</td>
<td>High Low HR (95% CI), ( P )</td>
</tr>
<tr>
<td>IGF-1R [203628_at]</td>
<td>(n = 44) 62 (n = 26) 59 0.546 (0.314–0.949); ( P = 0.03 )</td>
<td>(n = 24) 122 (n = 19) 60 0.406 (0.202–0.823); ( P = 0.01 )</td>
</tr>
<tr>
<td>GRB7 [210761_s_at]</td>
<td>(n = 35) 65 (n = 35) 59 0.484 (0.276–0.849); ( P = 0.01 )</td>
<td>(n = 24) 122 (n = 19) 57 0.396 (0.19–0.828); ( P = 0.011 )</td>
</tr>
<tr>
<td>INSIG2 [209566_at]</td>
<td>(n = 35) 58 (n = 35) 115 2.21 (1.297–3.765); ( P &lt; 0.0003 )</td>
<td>(n = 22) 57 (n = 21) 156 4.08 (1.945–8.559); ( P &lt; 0.0001 )</td>
</tr>
<tr>
<td>IGF-1 [211577_s_at]</td>
<td>(n = 28) 58 (n = 42) 62 1.773 (1.032–3.045); ( P = 0.036 )</td>
<td>(n = 19) 57 (n = 24) 121 1.813 (0.906–3.63); ( P = 0.089 )</td>
</tr>
<tr>
<td>IGFBP3 [210095_s_at]</td>
<td>(n = 35) 59 (n = 35) 63 1.605 (0.94–2.741); ( P = 0.081 )</td>
<td>(n = 20) 61 (n = 23) 120 1.535 (0.768–3.067); ( P = 0.222 )</td>
</tr>
<tr>
<td>INSR [207851_s_at]</td>
<td>(n = 35) 59 (n = 35) 62 1.618 (0.96–2.717); ( P = 0.066 )</td>
<td>(n = 20) 61 (n = 23) 121 1.331 (0.683–2.595); ( P = 0.399 )</td>
</tr>
</tbody>
</table>

NOTE: For each marker, the Affymetrix probeset ID is listed; for a complete list of probesets for each gene, see the Supplementary Table. Abbreviation: WT, wild-type.
subpopulation (76.2% vs. 18.2%; \( P < 0.0001 \); Fig. 2). Similarly, lower \( \text{INSIG}_2 \) expression was associated with a PFS benefit in the overall population (median: 115 vs. 58 days; HR = 2.21; 95% CI, 1.297–3.765; \( P = 0.003 \)), and an even greater benefit in the wild-type \( \text{K-Ras} \) subpopulation (median: 156 vs. 57 days; HR = 4.08; 95% CI, 1.945–8.559; \( P < 0.0001 \); Table 2). The PFS benefit associated with lower \( \text{INSIG}_2 \) expression was not evident in patients with \( \text{K-Ras} \) mutant tumors, whereas higher \( \text{INSIG}_2 \) expression was associated with a lack of clinical benefit regardless of \( \text{K-Ras} \) mutation status (Fig. 3C). Interestingly, within the \( \text{K-Ras} \) wild-type, high \( \text{EREG} \)-expressing population (\( n = 31 \)), the patients with low \( \text{INSIG}_2 \)-expressing tumors had significantly better PFS than those with high expression (\( P = 0.001 \)). No \( \text{INSIG}_2 \)-related effect was observed in the low \( \text{EREG} \)-expressing cohort, suggesting that the effect of \( \text{INSIG}_2 \) is independent from the ligand effect (Fig. 4). \( \text{INSIG}_2 \) was the only one of the 6 markers evaluated in conjunction with \( \text{EREG} \) to show such independence; for the 5 additional markers, PFS curves separated between high- and low-expressers in the \( \text{K-Ras} \) wild-type, high \( \text{EREG} \)-expressing population, but the differences did not reach statistical significance (data not shown).

**IGF-1.** Lower IGF–1 expression was associated with a significantly higher DCR with cetuximab in the subpopulation with tumors containing wild-type \( \text{K-Ras} \) (62.5% vs. 26.3%; \( P = 0.031 \)) and showed a trend for a higher DCR in...
the overall population (40.5% vs. 17.9%; \( P = 0.066 \)) compared with higher expression levels (Fig. 2). Lower IGF-1 expression was also associated with a PFS benefit, which reached statistical significance in the overall population (median: 62 vs. 58 days; HR = 1.773; 95% CI, 1.032–3.045; \( P < 0.036 \)), and a similar trend in the subgroup with wild-type K-Ras (median: 121 vs. 57 days; HR = 1.813; 95% CI, 0.0906–3.63; \( P < 0.089 \); Fig. 3D and Table 2).

**IGFBP3 and INSR.** Lower expression levels of IGFBP3 and INSR were associated with numerically higher DCR rates and showed trends for longer PFS compared with higher expression levels of these genes (Fig. 3E and F and Table 2).

**Discussion**

This study indicates that there is a potential correlation between cetuximab benefit in mCRC and expression of certain markers in the IGF-1R pathway. The IGF-1R and its ligand IGF-1 are the main activity drivers of this signaling axis; however, other components, such as the IGF-binding proteins (IGFBP), have a dual function acting as ligand sinks that inhibit signaling and as ligand reservoirs that maintain signaling. Downstream effectors, such as GRBs, connect IGF-1R signaling to the proliferative MAPK pathway. In parallel, the INSR and its output (such as the INSIG proteins) cross-talk with the IGF-1R,
and probably contribute to regulate its overall activity (28).

In this study, higher IGF-1R, higher GRB7, and lower INSR expression were associated on univariate analyses with longer PFS, particularly in patients with wild-type K-Ras tumors. Conversely, lower gene expression levels of IGF-1R and GRB7 and higher expression levels of INSIG2 were associated with a lack of cetuximab benefit regardless of K-Ras mutation status. Lower IGF-1 expression was also associated with a PFS benefit with cetuximab, whereas lower IGFBP3 and INSR expression levels showed trends for a PFS benefit. These observations would point to a potential link between markers suggestive of high IGF-1R signaling and low INSR activity and greater sensitivity to EGFR inhibition. Furthermore, at least for one of these markers, INSIG2, this effect would appear to be independent of the association between EREG expression and cetuximab activity.

These observations are consistent with a study of a cohort of 85 patients with chemorefractory mCRC who received a cetuximab-based regimen, in which higher IGF-1R protein expression detected by immunohistochemistry was associated with significantly longer median overall survival (OS) compared with low IGF-1R (16.1 vs. 6.7 months; \( P = 0.006 \); ref. 45). However, IGF-1R expression was not related to response rate or disease progression. Other studies have reported trends that diverge from our results. In a study of 113 patients with chemorefractory mCRC treated with cetuximab or panitumumab (a fully human monoclonal anti-EGFR IgG2), tumor IGF-1R activation, measured by phosphorylation status, correlated with inferior response to both chemotherapy and anti-EGFR treatment (46). In a cohort of 112 patients with irinotecan-refractory mCRC treated with cetuximab plus irinotecan, negative IGF-1 protein expression (score of 0 or 1 by immunohistochemistry) was associated with longer median PFS compared with positive (score of 2–4) IGF-1 expression (7.5 vs. 3.0 months; \( P = 0.002 \); ref. 31). This PFS benefit with negative IGF-1 expression was even more pronounced in the subset of 69 patients with wild-type K-Ras tumors (10.0 vs. 3.2 months; \( P = 0.002 \); ref. 31). Further indication of the relevance of this pathway for cetuximab clinical benefit has come from the observation that 5 IGF-1/IGF-1R pathway polymorphisms were significantly associated with PFS or OS in a cohort of 130 patients with mCRC who received cetuximab monotherapy, with several appearing independent of K-Ras mutation status in the multivariate analysis (47).

Taken together, these results indicate that markers of the IGF-1R pathway are of interest for predicting cetuximab benefit in mCRC; in our study, the lack of control group and the lax significance threshold used necessitate further validation in well-controlled and appropriately powered studies before these findings could be considered for use in clinical practice. Without having a control arm (that received no cetuximab therapy), it is not possible to discriminate whether these candidate markers are truly predictive for cetuximab benefit or rather prognostic for disease outcome. In fact, several of the markers that were associated with clinical benefit in our study have already been shown to be prognostic in CRC. For example, higher plasma levels of IGF-1 and IGFBP3 were associated with improved OS in all 3 arms of a randomized trial of patients with mCRC treated with different first-line chemotherapy regimens (48). Adjustments for both factors showed that IGFBP3, but not IGF-1, was also independently associated with prolonged time to disease progression. In addition, upregulation of INSIG2 gene expression has been associated with poor prognosis on initial staging of CRC and may act by suppressing chemotherapy-induced, Bax-mediated apoptosis (49, 50). This observation is in line with this study, where low expression of INSIG2 is correlated with prolonged survival and improved disease control, thus reinforcing the caveat of whether our findings are truly predictive or prognostic.
In previous reports from other solid tumors, high GRB7 expression was independently associated with reduced OS in primary breast cancer, particularly in the subset with node-positive disease (51). Although high GRB7 and HER2 expression were strongly correlated, coexpression of HER2 together with GRB7 was associated with a significantly poorer prognosis than expression of HER2 alone. GRB7 upregulation has also been associated with resistance to the dual EGFR/HER2 tyrosine kinase inhibitor lapatinib (52). Notably, these negative prognostic correlations oppose the results reported herein, suggesting that the specific association between high GRB7 expression and cetuximab PFS benefit may indeed be predictive. However, the positive correlation with DCR did not reach significance in our study, further indicating the necessity of validation in adequate and well-controlled trials.

Future development of these observations will have to consider the integration of these or any other candidate predictive marker with the patient selection platforms already existing (i.e., K-Ras mutation–based selection). The CA225-045 study generated the initial results indicating that EREG expression could be predictive of cetuximab benefit (15). This marker was combined with K-Ras mutation, as combimarker, in an exploratory analysis of the randomized controlled data set from the NCIC-C017 trial of cetuximab versus best supportive care in chemorefractory metastatic colorectal cancer (mCRC) (28). Its predictive robustness was validated in the phase III CA225-045 study, with DCR of 26% in patients with high EREG expression vs 15% in those with low expression (P = 0.03) (33). A recent meta-analysis of 14 phase III trials in mCRC found that patients with high EREG expression were more likely to achieve PFS benefit with cetuximab than with chemotherapy or as single-agent therapy (34). It would be of interest to establish how the most relevant candidate markers described here could be used concurrently with those previously characterized in this data set. For instance, our analysis suggests that low INSIG2 expression could act independently from high EREG expression to refine patient selection within the group of patients with K-Ras wild-type tumors, although the limited size of our sample warrants cautious interpretation of these results. Unfortunately, the limited availability of sample material for co-analysis makes a full examination of our IGF-related expression markers and the 4 predictive markers from the Baker score unfeasible; the same is true for the interesting analysis that would result from the combination of mutational testing, as reported by Spindler and colleagues (24), and expression analysis.

An additional question that remains for these and any other candidate predictive markers, particularly those that are gene expression related, is that of stability and status concordance between the different potential sources of sample specimens. Although mutational concordance has been the object of prior investigations (54–56), little is known on the concordance in gene expression levels from primary to metastatic sites, particularly for components of the IGF-1R pathway. Furthermore, the expression levels of members of the IGF-1R pathway can be affected by exposure to chemotherapy or radiotherapy (57–59), so it is pertinent to note that the samples in this study were collected from metastatic sites and immediately prior to cetuximab treatment without any intervening therapy. Any validation process would have to address the predictive robustness of these candidate markers in samples from primary and metastatic sites, samples collected at different points in the course of treatment throughout the disease, and when cetuximab is used in combination with chemotheraphy or as single agent.

Finally, the link between the EGFR and the IGF/IGF-1R pathways provides a rationale for the development of combined therapeutic strategies, a promising approach in preclinical models (36–41). However, clinical data with the combination of cetuximab or panitumumab with the anti-IGF-1R monoclonal antibodies cixutumumab, dalotuzumab, or ganitumumab have been underwhelming (60–62). It is possible that a better insight on mechanisms of tumor dependence specific for these 2 pathways could enhance the chances of success for such strategies; in that regard, studies such as these could help improve patient selection strategies for the development of these regimens.

On the other hand, blocking the IGF-1R pathway with TKIs, whose inhibitory spectrum is different from antibodies (because, for instance, they can potentially inhibit the KRAS (ref. 28), could yield better clinical results, given the extent of transversal cross-talk in this signaling network.

In summary, this study provides preliminary evidence that IGF-1R pathway–related markers may play a role in predicting benefit from cetuximab therapy in mCRC. Additional studies are warranted to validate these findings and to determine which candidate predictive marker(s) can best be integrated into clinical practice for selecting patients most likely to benefit from cetuximab.

Disclosure of Potential Conflicts of Interest

S. Khambata-Ford is a former employee of Bristol-Myers Squibb. F. Huang and L.-a. Xu are current employees of Bristol-Myers Squibb.

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