that in contrast to the correlation of mutations with responses to the *EGFR* kinase inhibitors gefitinib and erlotinib, *EGFR* mutations are not critical for the response of a tumor to cetuximab.

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Lack of Mutations in *EGFR* in Gastroenteropancreatic Neuroendocrine Tumors

TO THE EDITOR: Lynch et al.[1] and Paez et al.[2] correlated the presence of somatic mutations in the tyrosine kinase domain of the gene that encodes the epidermal growth factor receptor (*EGFR*) with responsiveness to gefitinib in non–small-cell lung carcinoma. Neuroendocrine differentiation is present in a substantial number of gastroenteropancreatic neuroendocrine tumors,[3] and EGFR expression occurs in such tumors.[4]

We sought EGFR-activating mutations in a series of rare gastroenteropancreatic neuroendocrine cancers. DNA was isolated from flash-frozen specimens of carcinoid and pancreatic endocrine tumors; *EGFR* exons 18, 19, and 21 were amplified by the polymerase chain reaction with primers described by Lynch et al.[1]; and amplicons were sequenced and assessed for predictive *EGFR* mutations (single-nucleotide substitutions in exons 18 and 21 and in-frame deletions in exon 19). Research authorization was obtained from all the patients, and the study was approved by the institutional review board.

No mutations in the *EGFR* kinase domain that were predictive of a response to gefitinib were detected in DNA from 62 human carcinoid tumors from a variety of sites, including both primary lesions (22 from the lung, 28 from the ileum, and 1 from the colon) and metastatic lesions (30 from the liver and 1 from the ovary). Most carcinoid tumors in this study were indolent; 20 matched sets, which included an ileal primary lesion and a hepatic metastatic lesion from the same patient, were examined.

As a verification of our detection procedure, DNA controls encoding *EGFR* mutations L858R within exon 21, delE746-A750 within exon 19, and delL747-P753insS within exon 19 (gifts from Drs. Daphne Bell and Daniel Haber, Massachusetts General Hospital, Charlestown, Mass.) were correctly identified. We noted in one ileal carcinoid the reported germ-line synonymous coding-region single-nucleotide polymorphism C/T in *EGFR* exon 21 (dbSNP:2229066; nucleotide position 2694 in GenBank accession number X00588); it was also detected in normal surrounding tissue. Similarly, no mutations in *EGFR* exons 18, 19, and 21 were found in DNA from 18 primary pancreatic endocrine carcinomas. In contrast to our results, Lynch et al.[1] found no mutations in *EGFR* exons 19 and 21 in 40 primary pancreatic tumors (we do not know whether this group included rare pancreatic endocrine tumors) and one bronchial-carcinoid tumor-cell line.

Our results indicate that somatic activating mutations of the *EGFR* kinase domain that are predictive of responsiveness to gefitinib are uncommon in gastroenteropancreatic neuroendocrine cancers, pancreatic endocrine carcinomas, and carcinoid tumors (primary as well as metastatic lesions).

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