Letters to the Editor

Therapeutic potential of epidermal growth factor receptor–related protein

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To the Editor:

The importance of the epidermal growth factor receptor (EGFR) family in the etiology and progression of human cancer is underscored by the fact that both EGFR and ERBB2 are molecular targets for the development of new cancer therapies, including monoclonal antibodies (e.g., cetuximab/Erbitux and trastuzumab/Herceptin) and tyrosine kinase inhibitors (e.g., gefitinab/IRESSA and erlotinib/Tarceva). In two recent articles, a soluble EGFR-related protein (ERRP) has been reported to act as a pan-ERBB inhibitor, and the authors suggest that ERRP may be a potential therapeutic agent for cancer patients (1, 2). The ability of soluble EGFR/ERBB proteins to inhibit ligand-induced receptor activation and downstream signaling pathways is well established (3–5). In addition, expression of endogenous soluble EGFR/ERBB isoforms has been shown in human tissues (5–7). However, because of the apparent chimeric nature of ERRP and the lack of evidence showing the existence of a human *ERRP* gene, we have reservations about the potential therapeutic value of this protein for cancer patients.

The *ERRP* cDNA clone (Genbank accession no. AF187818) was derived from rat gastroduodenal mucosa mRNA and contains sequence at the 5′ end that encodes a portion of the ligand-binding domain (i.e., subdomains I–III) of rat Egfr and sequence at the 3′ end that is identical to rat peptidase D (*Pepd*); these two genes are localized to rat chromosomes 14 and 1, respectively. This type of chimeric cDNA structure often is found in cDNA libraries and also is a frequent result of 3′-RACE PCR cloning, two techniques that were used to clone the *ERRP* cDNA (8). This chimeric structure suggested to us that ERRP might be a fusion product between rat *Egfr* and *Pepd* cDNA sequences and not the product of a novel *ERRP* gene. In support of this interpretation, analysis of Genbank sequences shows no evidence that such a chimeric *ERRP* gene exists in rat, human, or any other genome. This finding raises additional questions about the published ERRP expression studies in human tissues and cell lines, which were done using a polyclonal antibody directed against a peptide from the Pepd region of ERRP (9). If, as proposed here, ERRP is not a naturally occurring EGFR-related gene product, then its therapeutic value for cancer patients may be limited, as this chimeric rat protein would be expected to generate an immune response in humans. In conclusion, we believe that more rigorous validation of the proposed human ''*ERRP* gene'' sequence is needed to support the authors' claim that ERRP may be an effective therapeutic agent.

References

1. Marciniak DJ, Rishi AK, Sarkar FH, Majumdar AP. Epidermal growth factor receptor-related peptide inhibits growth of PC-3 prostate cancer cells. Mol Cancer Ther 2004;3:1615–21.

2. Xu H, Yu Y, Marciniak D, et al. Epidermal growth factor receptor (EGFR)-related protein inhibits multiple members of the EGFR family in colon and breast cancer cells. Mol Cancer Ther 2005;4:435–42.

3. Basu A, Raghunath M, Bishayee S, Das M. Inhibition of tyrosine kinase activity of the epidermal growth factor (EGF) receptor by a truncated receptor form that binds to EGF: role for interreceptor interaction in kinase regulation. Mol Cell Biol 1989;9:671–7.

4. Lee H, Akita RW, Sliwkowski MX, Maihle NJ. A naturally occurring secreted human ErbB3 receptor isoform inhibits heregulin-stimulated activation of ErbB2, ErbB3, and ErbB4. Cancer Res 2001;61:4467–73.

5. Doherty JK, Bond C, Jardim A, Adelman JP, Clinton GM. The HER-2/*neu* receptor tyrosine kinase gene encodes a secreted autoinhibitor. Proc Natl Acad Sci U S A 1999;96:10869–74.

6. Lee H, Maihle NJ. Isolation and characterization of four alternate c-erbB3 transcripts expressed in ovarian carcinoma-derived cell lines and normal human tissues. Oncogene 1998;16:3243–52.

7. Reiter JL, Threadgill DW, Eley GD, et al. Comparative genomic sequence analysis and isolation of human and mouse alternative EGFR transcripts encoding truncated receptor isoforms. Genomics 2001;71:1–20.

8. Yu Y, Rishi AK, Turner JR, et al. Cloning of a novel EGFR-related peptide: a putative negative regulator of EGFR. Am J Physiol Cell Physiol 2001;280:C1083–9.

9. Moon WS, Tarnawski AS, Chai J, Yang JT, Majumdar AP. Reduced expression of epidermal growth factor receptor related protein in gastric cancer. Gut 2005;54:201–6.

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