Re: Clinical and Biological Features Associated With Epidermal Growth Factor Receptor Gene Mutations in Lung Cancers

Shigematsu et al. (1) recently described 28 unique epidermal growth factor receptor (EGFR) gene mutations in 617 lung cancer patients and further confirmed the previously described clinical characteristics associated with these somatic mutations. We believe that the authors did not properly annotate two of these mutations (D8 and Δ9). For example, they described D8 as a duplication with a nucleotide substitution; we suggest that this is more likely to be a simple duplication (Fig. 1, A). In general, it is reasonable to assume that a sequence variant results from a single mutation rather than from a concatenation of multiple events. If we apply this assumption to Δ9, this variant can be described as two distinct deletions rather than as one deletion with two substitutions (Fig. 1, B). The two-deletion hypothesis is supported by the identification in two patients (2) of a Δ9-like EGFR gene mutation that has precisely the same deleted sequences as Δ9 except for three bases (i.e., ATC) at the 5′ end (Fig. 1, C). EGFR gene mutations located between CAAGGAA repeats are predominantly in-frame deletions in lung cancers of patients who are nonsmokers. By contrast, base substitutions are the type of mutation most frequently reported in the Human Gene Mutation Database (http://www.hgmd.org) and in a database of somatic mutations in the gene encoding p53 (http://www-p53.iarc.fr). Clearly, deletions play a more important role than base substitutions in mutagenesis of the bases located between the repetitive sequences in the EGFR gene.

Although in some Asian populations, approximately 50% of lung cancer patients harbor somatic EGFR gene mutations (3), it is too early to conclude that EGFR gene mutations are a primary cause of lung cancer. EGFR gene mutations are observed predominantly in lung cancers from nonsmokers; gain-of-function EGFR gene mutations that promote angiogenesis may facilitate cancer development from a few initial tumor cells in this particular subpopulation of patients. On the contrary, EGFR gene mutations are rarely identified in lung cancers in cigarette smokers, which are usually more malignant than lung cancers in nonsmokers (3). It has been observed that cancer patients with EGFR gene mutations have longer survival times than those without EGFR gene mutations (3). Also, the identification of an EGFR gene mutation that results in a truncated protein in a lung cancer patient (http://www.egfr.org) argues for a causal effect in carcinogenesis in this case. Furthermore, the possible causal effects of EGFR gene mutations are not consistently supported by therapeutic data. Early studies indicated that lung cancers’ response to gefitinib was highly dependent on the presence of EGFR mutations. However, recent clinical trials showed that the combination of gefitinib with chemotherapy did not dramatically improve the survival of cancer patients (4). These findings suggest that EGFR gene mutations may not be a primary cause of lung carcinogenesis. When a therapeutic target is the actual cause of cancer, a high rate of clinical remission should be expected (5), but gefitinib treatment for lung cancers with an EGFR gene mutation did not induce clinical remission in a clinical trial with a large sample size (4).

Since the initial suggestion that angiogenesis is important in cancer growth, several drugs that inhibit angiogenesis have been developed. The EGFR inhibitor, gefitinib, was found to inhibit renal cancer growth by decreasing capillary density (6), suggesting the enhancing effect of EGFR-mediated angiogenesis in the development of renal cancer in this animal model. However, no studies of gefitinib have been performed in lung cancer animal models, nor have inherited gain-of-function EGFR gene mutations been identified by genetic linkage analysis except for T790→M, an EGFR gene mutation that confers drug resistance, which has been identified in one family (7). Whereas the exact roles of the EGFR gene mutations and some other angiogenic genes in lung cancer development remain to be elucidated, the exponential accumulation of somatic EGFR gene mutations, including the inherited mutation, T790→M (7), has intensified the red-hot debate over the modifying effects of angiogenesis in cancer development.

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References


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Response

We wish to comment on several points raised by Pardinas et al. concerning our findings regarding EGFR gene mutations in lung cancers (1). First, they suggest that two of the complex mutations we described, D8 and Δ9, may not be due to combinations of deletions or insertions and nucleotide substitutions as we indicated. Instead, they suggest that D8 may have resulted from a single duplication and that Δ9 may have resulted from two distinct deletions. One of the arguments they propose is that “it is reasonable to assume that a sequence variant results from a single mutation rather than from a concatenation of multiple events.” We have no difficulty in accepting this proposal, but we note that they also suggest that the Δ9 mutation arose as a result of two deletions. It is not possible to know precisely how these complex mutations arose, and we can foresee a single genetic event simultaneously resulting in two distinct forms of mutations. Although the hypothesis advanced by Pardinas et al. is plausible, we do not believe it negates our original interpretation of how these mutations arose but offers instead an alternative mechanism.

Second, Pardinas et al. suggest that because treatment of non–small-cell lung cancers (NSCLCs) with tyrosine kinase inhibitors (TKIs) such as gefitinib or erlotinib was not associated with clinical remission in one study (2), EGFR mutations may not be the primary cause of lung carcinogenesis. The study they cite did not perform mutation analysis. Multiple studies have demonstrated high (albeit variable) rates of clinical response for EGFR gene mutation containing NSCLC tumors following therapy with TKIs. However, only some studies have demonstrated improved survival following TKI therapy (3), whereas others have not (4). Activation of EGFR signaling in solid tumors is a highly complex multifactorial process, and increased gene copy number (of EGFR or its family members), autocrine loops, the presence of specific mutations associated with resistance to TKIs, and other factors may play a role in tumorigenesis as well as in responses to targeted therapies. Also, not all activating mutations are created equal (5,6). Although the common activating EGFR mutations have been shown to have oncogenic activity in vitro, not all impart sensitivity to TKIs (6). EGFR gene mutations occur early during lung cancer pathogenesis and they exhibit a limited field effect, and can be detected in histologically normal small airways adjacent to mutant tumors (7). They have also been described in atypical adenomatous hyperplasias, which are putative precursor lesions of peripheral adenocarcinomas. Thus, although many genetic changes contribute to lung carcinogenesis, EGFR gene mutations probably represent mutations that drive the cell toward tumor rather than acting as incidental changes.

The final point raised by Pardinas et al. involves a report that concludes that one of the actions of TKIs is inhibition of angiogenesis. We presume that they raise this point to suggest that the tumor action of TKIs may occur via actions unrelated to inhibition of kinase activity. It is well known that EGFR activation has effects on multiple downstream signaling pathways, including promotion of angiogenesis, and clinical trials targeting both tyrosine kinase activity and angiogenesis have been proposed. Thus, angiogenesis may be a downstream result of tyrosine kinase activation, and it is not surprising that TKIs inhibit angiogenesis.

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References


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