EGFR Gene Mutations: A Call for Global × Global Views of Cancer

William R. Sellers, Matthew Meyerson

Successful medical therapy depends largely on penetrating the molecular underpinnings of pathogenic processes. Gradually, we have begun to link pathogenesis to alterations in the genome. The completed human genome sequence coupled with the development of technology capable of high-resolution genome interrogation holds special promise for cancer therapeutics because, unlike most medical illness, cancer presents with a separate genome that can be readily isolated. Thus, comparative analysis of the diseased and normal genomes may in theory identify the pathogenic genome alterations. Indeed, identification of genetic alterations leading to the inactivation of tumor suppressor genes and/or activation of oncogenes has revealed many of the regulatory pathways deregulated during cancer initiation and progression.

Although the development of novel therapeutics based on the discovery of specific genetic lesions (e.g., the p53 mutation) has been difficult recently, a number of therapeutics targeting specific genetic alterations have gained a foothold in the clinic. Successes have included treatment of acute promyelocytic leukemia bearing retinoic acid receptor translocations with all-trans-retinoic acid (1,2), of chronic myeloid leukemia bearing Bcr-Abl translocations with imatinib (3), and of breast cancers bearing Her2/Neu gene amplifications with trastuzumab (4). These examples argue strongly for a renewed effort to gain a genome-wide or "global" view of somatic alterations in the cancer genome. Efforts in this area have yielded immediate success, including the discovery of prevalent BRAF and PI3KCA gene mutations in melanoma, colorectal carcinoma, and other cancers (5,6).

Multiple groups have reported finding mutations in the gene encoding the epidermal growth factor receptor (EGFR) in non–small-cell lung cancer. Such mutations appear to confer sensitivity to EGFR inhibitors in vitro and are associated with patient response to EGFR inhibition (7–9). EGFR gene mutations are more common in patients with adenocarcinoma, in females, in nonsmokers, and in Japanese patients. Subsequent studies have also reported high frequencies of EGFR gene mutations in lung adenocarcinoma patients from Japan and Taiwan (10,11).

In this issue of the Journal, Shigematsu et al. (12) report results of their sequence analysis of exons 18–21 of the EGFR gene in a large collection of non–small-cell lung cancers (n = 617). They examined the prevalence of specific mutations and looked in detail at associations of mutations with specific clinicopathologic features, including clinical outcome. Their data show that EGFR gene mutations are independently associated with a number of clinical factors and suggest new avenues for exploring the predisposing factors contributing to the genesis of this subgroup of lung cancers.

One notable finding reported by Shigematsu et al. is that the lung cancers from patients of East Asian ancestry have a substantially higher frequency of EGFR gene mutations than lung cancers from patients of other ethnicities. Their analysis included patients from Japan and Taiwan. In addition, four of the five U.S. or Australia patients of East Asian ancestry had EGFR gene mutations. This apparent relationship between the presence of an EGFR gene mutation and ancestry rather than current geographic residence (10,11) argues against environmental exposure as the principal explanation for the ethnic difference (10–12) and suggests that polymorphic variation in a germline modifier gene contributes to the emergence of lung adenocarcinomas bearing EGFR gene mutations. One intriguing notion is that polymorphic variation in the EGFR gene itself might alter the activity or expression of a mutant EGF receptor. For example, a CA-repeat polymorphism in intron 1 of the EGFR gene has been associated with increased EGFR expression (14). Of specific note, a greater proportion of Asians than Caucasians have an EGFR gene with more than 20 CA repeats (13,14). Moreover, repeat length is associated with response to erlotinib in head and neck cancer cell lines and with the occurrence of erlotinib-mediated skin toxicity in colorectal cancer patients (15). However, in these latter two instances, shorter repeats were associated with response (15). Whether this specific variant is associated with a predisposition to developing lung cancers bearing EGFR gene mutations is unknown and bears examination in both Caucasian and Asian patient populations.

Progress in defining the common sequence variation and haplotype structure (16) of the human genome allows one to ask whether specific EGFR haplotypes (i.e., concordant sets of polymorphic alleles in the EGFR gene) might be associated with the presence of somatic EGFR gene mutations. If so, one prediction is that a specific allele that is more common in East Asians might be enriched in Caucasians whose tumors have EGFR gene mutations. However, in a preliminary analysis, we have not observed any association between specific haplotypes of the EGFR gene and somatic mutations in the EGFR gene (Freedman M, Meyerson M, Altshuler D, Sellers WR, unpublished observations).

If EGFR polymorphisms do not account for the ethnic predisposition to somatic EGFR mutations, then possibly a genetic modifier might be found elsewhere in the genome. Presumably,

Affiliations of authors: Department of Medical Oncology, Dana-Farber Cancer Institute, Departments of Medicine and Pathology, Brigham and Women’s Hospital, Departments of Medicine and Pathology, Harvard Medical School, Boston, MA (WRS); Broad Institute of Harvard and the Massachusetts Institute of Technology, Cambridge, MA (MM).

Correspondence to: William R. Sellers, MD, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02115 (e-mail: William_Sellers@dfci.harvard.edu).

DOI: 10.1093/jnci/dji079

Journal of the National Cancer Institute, Vol. 97, No. 5, © Oxford University Press 2005, all rights reserved.
such a modifier might enhance EGFR signaling, but it could also act in synergistic parallel pathways or alter other aspects of tumorigenesis such that EGFR-dependent tumors would contribute disproportionately to disease in patients bearing such a germline modifier allele. Here, the development of methods capable of interrogating more than 100,000 single-nucleotide polymorphisms per sample should enable whole genome scans for common germline genetic variants associated with this well-defined phenotype (i.e., lung adenocarcinomas bearing EGFR gene mutations).

Shigematsu et al. (12) showed that EGFR gene mutations are more prevalent in females than in males and, importantly, that this association is independent of smoking status. Men and women might be differentially exposed to an environmental factor. However, one potentially important difference between females and males is their exposure to estrogenic versus androgenic sex steroids. Could there be a link between EGFR gene mutation status and differences in sex steroids and steroid receptors? Of interest here is that activation of EGFR was first linked to oncogenesis through the discovery that the EGFR gene is a retroviral oncogene of the erythroblastosis virus (i.e., v-ErbB) (17). Notable in this discussion is that the v-ErbB gene, found in the same virus, is derived from the thyroid hormone nuclear receptor (TR) gene. ErbB is the dominant transforming activity, while ErbB is likely to provide a block in differentiation (18). The co-selection of these two genes by the retrovirus raises the possibility that this combination is particularly important for cellular replication and transformation and suggests a functional link between members of the nuclear receptor family and the transforming activity of EGFR. Thus, given its oncogenic role in breast cancer, the estrogen receptor (ER) would be a prime suspect for a nuclear receptor cooperating with EGFR activation and thereby accounting for the female preponderance found in lung adenocarcinomas bearing EGFR gene mutations. Of note, Stabile et al. (19), recently showed that in non–small-cell lung cancer cell lines, the combination of fulvestrant (an ER antagonist) and gefitinib cooperatively inhibit epidermal growth factor–stimulated proliferation and tumor growth in nude mice. These data lend credence to the idea that enhanced ER activity may be required for the maintenance of an EGFR-dependent lung cancer and provide the initial rationale for the clinical testing of estrogen antagonists or aromatase inhibitors in combination with EGFR inhibitors.

Shigematsu et al. (12) also extended the observation that lung adenocarcinomas harboring EGFR gene mutations are more commonly associated with never having smoked (8,9). This association might simply be due to the fact that there are fewer smokers at risk for EGFR mutant lung cancers as a result of competing illness (e.g., cardiovascular disease or other cancers). Probing this association further will require studying the incidence of EGFR gene mutations in a population-based cohort. Such an approach would allow one to ascertain the true number of smokers and nonsmokers at risk for developing lung cancer (nonsmokers typically outnumber smokers) and to determine whether the incidence of EGFR gene mutations in smokers and nonsmokers is truly different. If it is, one could hypothesize that smoking might induce preneoplastic alterations in the lung epithelium that, while compatible with subsequent RAS gene mutations, are incompatible with subsequent EGFR gene mutations.

Finally, Shigematsu et al. (12) looked in detail at the clinical outcomes of patients with EGFR gene mutations. Although there was no overall difference in outcome between patients with and without EGFR gene mutations, there was a trend of poorer survival in patients harboring exon 19 deletions. However, this finding was not statistically significant and will need to be tested in larger cohorts.

The discovery of EGFR gene mutations in lung cancer points out the need for a comprehensive and global view of the genomes of human cancers. The likelihood that germline genetic variation associated with ethnicity predisposes an individual to EGFR gene mutations highlights the need to derive global views of cancer genomes from patients of all ethnicities across the globe. While we work toward such “global × global” views of cancer, it will be important to conduct clinical trials with broad representation across different ethnic groups. It may be necessary to consider the power of clinical trials to detect differences within ethnic subgroups rather than assuming equality across such groups. Although ethnic variation in the incidence of somatic mutations complicates the task of defining the cancer genome, these differences provide unique opportunities to discover the predisposition factors linked to the development of cancer.

REFERENCES


