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EGFR mutation in various tissues

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Abstract Somatic mutations have been demonstrated in various tumors. *EGFR* mutations were first demonstrated in adenocarcinoma of the lung, and a large-scale retrospective study has clearly shown that these mutations are specifically observed in this form of the disease. Recently, possible occurrence of *EGFR* mutations in other tumor types including ovarian and colorectal malignancies has been reported. This raises the possibility of application of EGFR-specific tyrosine kinase inhibitors (EGFR-TKI) to the treatment of these malignancies, although broad success in this venture would depend on the frequency of such mutations. In this article, we discuss somatic mutations in various tumors as well as potential application of TKI to their treatment. Ethnic difference in the frequency of somatic mutations is another area of interest since it is closely related to clinical response to EGFR-TKIs. Preliminary studies have revealed such ethnic variations regarding *EGFR* mutation and gene amplification. Ethnic difference of transcriptional regulation of *EGFR* has also been demonstrated. We recently found a biomarker related to clinical response to EGFR-TKI that might explain the ethnic differences in response to this therapy. Various tyrosine kinases are known targets of TKIs. Thus genomics of individual patients may allow personalized target-based therapeutics.

Keywords EGFR mutation · Tyrosine kinase inhibitor · Ethnicity · HLA

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EGFR mutation in various cancers

Somatic mutations have been demonstrated in various tumors. *EGFR* mutations were first demonstrated in adenocarcinoma of the lung, and a large-scale retrospective study has clearly shown that these mutations are specifically observed in this form of the disease [10]. However, extensive analysis of somatic mutation in various tumors subsequently demonstrated the existence of *EGFR* somatic mutation in many human tumors such as colorectal and head and neck cancer, renal cell carcinoma, prostate cancer, and cholangiocarcinoma [4, 7, 8]. Gwak et al. [5] reported *EGFR* mutation in cholangiocarcinoma and found that it was detectable in 13.6% (3/22) of patients. The type of mutation was deletion of exon 19. This is commonly observed in intrahepatic and poorly differentiated tumors. These and other researchers also reported this *EGFR* mutation in squamous cell head and neck carcinoma [7], and Cohen's group demonstrated a new mutation on *erb2* and gene amplification in this disease [3]. The mutation has also been reported in persistent ovarian and primary peritoneal carcinoma in clinical phase II trials of gefitinib [14]. Similar types of mutation have been reported in lung cancers, although these seem to be of minor occurrence [4]. Thus somatic mutations of *EGFR* exist in various tumors. Because of limited samples, it

remains unknown whether *EGFR* mutation in cancer is correlated with clinical response to EGFR-specific tyrosine kinase inhibitors (EGFR-TKI). *EGFR* mutation in other types of tumors than lung cancer seems correlated with immunohistochemical expression but correlation with gene amplification is unknown [14]. Functional aspects of *EGFR* mutation in other types of tumors are also only partially understood. To clarify the significance of somatic mutations in various tumors, tissue banking is necessary. In addition, validated and standardized analytical methods and cross-validation are important to give consistent results. We should also consider how to conduct clinical trials of target-based drugs for less common tumors based on biological data.

Ethnic difference in *EGFR* mutation

Ethnic difference in *EGFR* mutation is another important topic. It is considered that ethnic differences may determine both the frequency of *EGFR* mutation and response to TKi [2]. However, although it has not been fully discussed whether these differences are due to ethnic or merely geographical divides, ethnicity can explain differences in clinical response because of the data acquired in Asian–US patients. It is also considered that differences among the regions of Asia might be obtained: patterns of *EGFR* mutation may differ between Japanese, Chinese, Korean, South Indian, and Turkish individuals [16]. Expanding genome databases should eventually pinpoint the contribution of ethnicity in this regard. Already there is some evidence related to ethnic differences. A CA repeat exists in exon 1 of *EGFR*, related to transcriptional level of this gene. The length of CA repeat varies and is related to ethnicity [9]. Japanese have longer CA repeat compared with Caucasians. Moreover, intron 1 polymorphism reportedly mediates response to EGFR-TKI [1].

What are the differences among the types of *EGFR* mutation? The deletion mutation in exon 19 and point mutation L858R in exon 21 are the two major mutations. Previously, we speculated that the deletion mutation is more frequently detected in Japanese and Asian lung cancer patients as compared with Caucasians. However, recent data seem to refute ethnic difference in the types of *EGFR* mutations [12].

A predictive biomarker related to ethnic difference of sensitivity to gefitinib

Ethnic difference might also exist in sensitivity to drugs. In most such cases, gene polymorphism including microsatellite polymorphism and single nucleotide polymorphism may explain ethnic difference of response to drugs.

Using microarray technique, we analyzed gene expression profiles of peripheral mononuclear cells in lung cancer patients receiving gefitinib as a first-line monotherapy. Our results revealed that HLA genotype was closely related to response to this agent. On the other hand, large ethnic difference of HLA genotype was recognized. Previous reports have demonstrated that HLA genotype plays a role in the metabolism of certain drugs and may be a prognostic factor in malignancies such as gastric, ovarian, and cervical cancers [6, 11, 13, 15, 17]. We hypothesize that HLA subtype may be related to response to gefitinib and might explain ethnic differences. Cross-validation study of this HLA biomarker is ongoing.

Ethnic difference of gefitinib toxicity profile

Subpopulation analysis of gefitinib's toxicity in the ISEL study revealed that only southwest Asian and Taiwanese patients exhibited high ratios of interstitial lung disease (ILD) while on this therapy [16]. However, ILD might not have been induced by gefitinib. More interestingly, the data indicated that Indian–British patients experienced severe (grade 3) skin toxicity along with higher response to gefitinib. Although these phenomena are based on subpopulation analysis, we can speculate that ethnic difference might guide toxicity as well as clinical response to EGFR-TKI. Genomic and biomarker research is necessary to further elucidate these preliminary findings.

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