JOURNAL CLUB

Genomic landscape of non-small-cell lung cancer in smokers and never-smokers

Whole-genome and transcriptome sequencing studies were performed on 17 tumour and adjacent normal tissue samples from smokers, former light smokers and never-smokers diagnosed with non-small-cell lung cancer.

This sequencing-based study revealed a markedly distinct genomic landscape in smokers and never-smokers. Smokers had an average mutation frequency 10-fold higher than never-smokers and a significantly higher number of point mutations of the cancer genome LUC9, involving DNA repair genes. A positive correlation was found to exist between the amount of smoking exposure and mutational burden.

The mutation spectrum differed significantly with C:G→A:T transversions being the most predominant point mutation in smokers and C:G→T:A transitions in never-smokers. Each group had distinctive sets of mutations: KRAS, TP53, BRAF, JAK2 and JAK3 in smokers and EGFR mutations, ROS1 and ALK fusions in never-smokers—all potential novel therapeutic targets. The EGFR and KRAS mutations were identified in founder clones, suggesting a role in cancer initiation.

Most of the samples had diverse clonality patterns and no correlation was found between smoking status and tumour clonality. Further analysis revealed a total of 3726 point mutations including kinase genes, chromatin-associated genes and significant alterations of DACH1, RELN and ABCB5 genes in both smokers and non-smokers. Mutations in 54 genes were identified that could be targeted with existing drugs.

This study has identified a vast number of potential therapeutic targets that require further exploration. Further studies that confirm dominant genetic alterations in founder clones need to be targeted to develop potentially curative treatment.

► Ramaswamy Govindan, Li Ding, Malachi Griffith, *et al.* Genomic landscape of non-small cell lung cancer in smokers and never-smokers. *Cell* 2012;150:1121–1134.

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