Tracing Oncogene Rearrangements in the Mutational History of Lung Adenocarcinoma

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Abstract

Mutational processes giving rise to lung adenocarcinomas (LADCs) in non-smokers remain elusive. We analyzed 138 LADC whole-genomes, including 83 cases with minimal contribution of smoking-associated mutational signature. Genomic rearrangements were not correlated with smoking-associated mutations and frequently served as driver events of smoking signature-low LADCs. Complex genomic rearrangements, including chromothripsis and chromoplexy, generated 74% of known fusion oncogenes, including EML4−ALK, CD74−ROS1, and KIF5B−RET. These fusion oncogene-associated rearrangements were frequently copy number-balanced unlike other collateral rearrangements, representing a genomic signature of early oncogenesis. Mutation timing analysis revealed that fusions and point mutations of canonical oncogenes were often acquired in the early decades of life. During a long latency, cancer-related genes were disrupted or amplified by complex rearrangements. The genomic landscape was different between subgroups—EGFR-mutant LADCs had frequent whole-genome duplications with p53 mutations, whereas fusion oncogene-driven LADCs had frequent SETD2 mutations. Our study highlights LADC oncogenesis driven by endogenous mutational processes.

Keywords: *Lung Adenocarcinoma, Cancer, Genome, Fusion Gene, Complex Rearrangements, Precision Medicine*

Biography

He graduated from Seoul Nat'l Univ. College of Medicine and conducted post-doctoral research at Wellcome Sanger Institute. Using bioinformatic interpretation of genome sequences, he has made many contributions in basic and clinical settings, such as the detection of KIF5B-RET fusion oncogene (Genome Res 2012), understanding clonal evolution of lung adenocarcinoma into small cell carcinoma (JCO 2017) & the identification of somatic mutations in the earliest stage of human life (Nature 2017).