

Mutation landscape of non-small cell lung cancer with a high risk of metastasis and recurrence

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Motivation and Aim: Previous studies have found that various combinations of premalignant changes in the small bronchi epithelium distant from the tumor are associated with the risk of progression of non-small cell lung cancer (NSCLC): patients with basal cell hyperplasia (BCH) more often have distant metastases, whereas patients with BCH combined with squamous metaplasia (SM) predominantly show locoregional relapses [1, 2]. The molecular mechanisms of this association are still not understood. Here, we aimed to assess somatic genetic alterations in NSCLC patients with different premalignant bronchial lesions.

Methods and Algorithms: The study included 59 patients with NSCLC divided into three groups: 1) cases with isolated BCH and a high risk of distant metastasis; 2) cases with the presence of BCH and SM (BCH+SM) and a high risk of locoregional recurrence; 3) cases without premalignant lesions. Premalignant lesions were identified in hematoxylin and eosin-stained sections of formalin-fixed paraffin-embedded samples of small bronchi distant (3–5 cm) from the tumor. DNA samples were isolated from fresh-frozen tumor and peripheral blood samples and sequenced on a NextSeq 500 (Illumina) instrument using SureSelect XT Human All Exon v7 kit (Agilent). Data were analyzed using the GATK pipeline, and genetic variants were annotated using the ANNOVAR. Copy number alterations (CNAs) were detected by CNVkit.

Results: Patients with BCH and a high risk of metastasis have alterations in genes involved in the regulation of interleukin synthesis, T-helper differentiation, and defense response to Gram-negative bacterium. Patients with BCH+SM and a high risk of locoregional recurrence demonstrate mutations in genes that are related to exocytosis and cell adhesion.

Conclusion: The mutational landscape of NSCLC differs between patients with a high risk of distant metastasis and locoregional recurrence. The detected genetic features confirm the stratification of NSCLC patients according to the type of premalignant changes in the bronchial epithelium and may underlie the NSCLC progression.

References

1. Pankova O.V., Denisov E.V., Ponomaryova A.A., Gerashchenko T.S., Tuzikov S.A., Perelmuter V.M. Recurrence of squamous cell lung carcinoma is associated with the co-presence of reactive lesions in tumor-adjacent bronchial epithelium. *Tumour Biol.* 2016;37(3):3599-3607.
2. Pankova O.V., Tashireva L.A., Rodionov E.O., Miller S.V., Tuzikov S.A., Pismenny D.S., Gerashchenko T.S., Zavyalova M.V., Vtorushin S.V., Denisov E.V., Perelmuter V.M. Premalignant changes in the bronchial epithelium are prognostic factors of distant metastasis in non-small cell lung cancer patients. *Front Oncol.* 2021;11:771802.