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Uncovering innovative molecular targets for lung cancer therapy on the highly recurrent chromosomal gain of 1q21

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Background/Aims Genotype directed/personalized therapies have revolutionized cancer treatment. Nevertheless, resistance development and treatment failure often limit its effectiveness. Somatic copy-number amplifications strongly contribute to carcinogenesis and treatment resistance. One such example located on chromosome 1q21 is the pro-survival gene MCL-1, which is frequently amplified/overexpressed in lung adenocarcinoma (LUAD). Of note, MCL-1 amplifications mostly co-occur with the amplification of a large genomic area on 1q21, resulting in the overexpression of MCL-1 and 315 additional genes, with mostly unknown function in tumorigenesis. Thus, this study aims to identify the role of potential critical cancer drivers affected by the chromosomal gain of 1q21 in LUAD.

Results/Methods Bioinformatic analysis evaluated the impact of increased expression of these amplified genes on lung cancer patient survival. Elevated expression of 1q21 genes, such as BCAN or NUF2, in lung cancer patients is clearly associated with reduced survival, even more significant than previously published MCL-1, suggesting their potential important role in LUAD carcinogenesis. To perform in-depth functional analysis of the role of these potential oncogenic drivers, different lung cancer cell lines and CRISPR/Cas9 genome editing technologies are used to induce overexpression/knockout of the respective genes and to assess the impact on cell proliferation, viability, migration, and sensitivity to commonly used therapies. Also, the most promising candidate genes are studied in a clinically-relevant Kras- and Tp53-loss-driven lung cancer mouse model allowing the rapid CRISPR/Cas9-mediated somatic modification of certain genes.

Conclusion This study will not only answer biological questions on the functional role of genes on the 1q21 amplicon, but also aid the urgently needed identification of molecular targets for the development of new treatment strategies in lung cancer.