2021 ESMO congress

1800O

Multi-omic characterization of lung tumors implicates AKT and MYC signaling in adenocarcinoma to squamous cell transdifferentiation

Á. Quintanal-Villalonga[1], H. Taniguchi[2], Y.A. Zhan[1], M.M. Hasan[2], S.S. Chavan[1], F. Uddin[1], V. Allaj[1], P. Manoj[1], N.S. Shah[2], J.M. Chan[1], M. Ciampricotti[2], A. Chow[1], U. Bhanot[1], J. Egger[1], J. Qiu[3], E. De Stanchina[3], N. Rekhtman[4], H.A. Yu[2], T. Sen[1], C.M. Rudin[2]

[1] Molecular Pharmacology/Medicine Dept., MSKCC - Memorial Sloan Kettering Cancer Center, New York, NY, USA, [2] Department of Medicine, MSKCC - Memorial Sloan Kettering Cancer Center, New York, NY, USA, [3] Antitumor Assessment Core, MSKCC - Memorial Sloan Kettering Cancer Center, New York, NY, USA[4] Pathology, MSKCC - Memorial Sloan Kettering Cancer Center, New York, NY, USA

Background

Lineage plasticity facilitates therapeutic resistance in multiple cancers. In lung adenocarcinomas (LUADs), this phenomenon includes small cell and squamous cell (LUSC) histologic transdifferentiation in the context of acquired resistance to targeted inhibition of driver mutations. The incidence of LUSC transdifferentiation in *EGFR* mutant tumors occurs in up to 9% of cases relapsed on osimertinib and has been associated to poor prognosis. The paucity of well annotated pre- and post-transdifferentiation clinical samples has precluded the performance of informative molecular analyses: little is known about the molecular mechanisms leading to this histological transition.

Methods

We performed multi-parameter profiling of microdissected histological components of mixed histology (LUAD/LUSC) tumors, together with pre-/post-transdifferntiation clinical samples, including detailed genomic, epigenomic, transcriptomic and proteomic characterization. Clinical findings were validated in preclinical models including cell lines and patient-derived xenograft treatments.

Results

Our results suggest that LUSC transdifferentiation is primarily driven by transcriptional reprogramming rather than mutational events, and indicate that the resulting squamous tumors retain transcriptomic and methylation profiles of their previous LUAD state. We observed coordinated upregulation of PI3K/AKT, MYC and PRC2 pathway genes in the LUSC component of mixed histology tumors. Concurrent activation of PI3K/AKT and MYC induced squamous features in *EGFR*-mutant LUAD preclinical models, further augmented under selective pressure of osimertinib. Pharmacologic inhibition of EZH1/2 in combination with osimertinib prevented relapse and squamous transdifferentiation in an EGFR-mutant patient-derived xenograft model, and inhibition of EZH1/2 or PI3K/AKT signaling re-sensitized resistant transdifferentiated LUSC tumors to osimertinib.

Conclusions

Our findings provide the first comprehensive molecular characterization of LUSC transdifferentiation, suggesting putative drivers and promising therapeutic targets to constrain or prevent lineage plasticity in this setting.

Legal entity responsible for the study

The authors.

Funding

Supported by NCI R01 CA197936 and U24 CA213274 (CMR), the SU2C/VAI Epigenetics Dream Team (CMR), the Druckenmiller Center for Lung Cancer Research (CMR, TS, AQV), Parker Institute for Cancer Immunotherapy grant (TS); International Association for the Study of Lung Cancer grant (TS), NIH K08 CA-248723 (AC). We acknowledge the use of the Integrated Genomics Operation Core, funded by the NCI Cancer Center Support Grant (CCSG, P30 CA08748), Cycle for Survival, and the Marie-Josée and Henry R. Kravis Center for Molecular Oncology. We also acknowledge Maria Corazon Mariana and Emily Lin from the PPBC Biobank for their invaluable help. The PPBC Biobank and Pathology Core Facility are supported by the NCI Cancer Center Support Grant P30-CA008748.

Disclosure

H.A. Yu: Financial Interests, Advisory Role: AstraZeneca; Financial Interests, Advisory Role: Daiichi Sankyo; Financial Interests, Advisory Role: Janssen; Financial Interests, Advisory Role: Blueprint Medicine. C.M. Rudin: Financial Interests, Advisory Role: Amgen; Financial Interests, Advisory Role: AstraZeneca; Financial Interests, Advisory Role: Epizyme; Financial Interests,

Advisory Role: Genentech/Roche; Financial Interests, Advisory Role: Ipsen; Financial Interests, Advisory Role: Jazz; Financial Interests, Advisory Role: Lilly; Financial Interests, Advisory Role: Syros; Financial Interests, Advisory Board: Bridge Medicines; Financial Interests, Advisory Board: Earli; Financial Interests, Advisory Board: Harpoon Therapeutics. All other authors have declared no conflicts of interest.