Therapeutic Targeting of KMT2D Mutant Lung Cancer Via RTK-RAS Signaling Inhibition

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Technology

The Wong Lab at NYU Langone Health has identified an oncogenic driver mutation which activates the RTK/Ras pathway, and proposes that targeting the RTK-Ras signaling through SHP2 inhibition could be an effective therapy for lung squamous cell carcinoma (LUSC) patients carrying the identified mutation. Using a novel organoid system, the Wong lab has identified a gene, KMT2D, which is essential for LUSC tumorigenesis. The researchers demonstrated that this gene mutation drives LUSC formation both in organoids and in vivo. Mutations in this gene have already been shown to be present in at least 20% of LUSC patients. Deletion and loss of function of the identified gene activates RTK/Ras signaling, a key pathway that is frequently dysregulated in lung cancers. The Wong lab has also shown that these mutated LUSC tumors, both in organoid model and in vivo, are selectively sensitive to Src homology region 2 (SH2)-containing protein tyrosine phosphatase-2 (SHP2) inhibitors.

Background

Lung cancer remains the one of the most commonly diagnosed malignancies and the leading cause of cancer death worldwide. LUSC represents a major subtype of lung cancer with limited treatment options. Genomic analysis of LUSC patient tumors revealed numerous highly altered genes and pathways, but few driver mutations have been associated with the disease. Several targeted therapies tested in LUSC patients have demonstrated very limited clinical benefits and no targeted therapies have been approved in the clinic. Therefore, identifying driver mutations, as well as effective therapeutics represent an urgent unmet need for LUSC patients.

Preclinical models have been essential in studying lung cancer development and in testing therapeutics. Due to the lack of established driver mutations, the development of LUSC preclinical models that recapitulate human LUSC genetics and pathology remains challenging.

Applications

- Targeting RTK-Ras signaling through SHP2 inhibition could be an effective therapyfor treating LUSC patients carrying the identified oncogene.
- The identified mutation could be used as an important biomarker to stratify patients in the clinic that will be likely to respond to SHP2 inhibition.

Advantages

- SHP2 inhibitors are currently in clinical trials for other tumor types and they can be repurposed for treating LUSC patients carrying the identified oncogene.
- There is already evidence that the identified oncogene is mutated in 20% of LUSC patients. However, this is the first time that it has been shown to drive LUSC. This makes it a strong candidate/biomarker that can be used to stratify LUSC patients in the clinic.

IP Status

Non-provisional patent application pending