Novel Immune Based Therapeutic Strategies to Target Tumors with Alterations in LKB1 Pathway

An efficient approach to treat a large subset of patients with non-small cell lung carcinoma who don't respond to conventional immune therapy.

Technology

The inventors have developed a novel immune-based therapeutic strategy to promote immune responses in patients with LKB1 or LKB1/KEAP1 mutations that are resistant to standard care of therapy by targeting the LIF/LIFR/STAT3-axis. They have developed novel Kras driven genetically engineered mice models with LKB1, KEAP1 and LKB1 mutations using CRISPR/Cas9 system that aids in characterizing of mechanisms promoting immune evasive tumor progression. They have highlighted that tumor genetics can dictate the inflammatory nature of the immune microenvironment of lung tumors and identified an immunosuppressive macrophage signature predictive of survival in LUAD patients. They have discovered that LIF is a master regulator of tumor inflammatory pathways responsible for the immunosuppressive microenvironment of LKB1-mutant tumors. Inhibiting LIF in LKB1-mutant lung tumors resulted in alteration of the myeloid immune infiltration, improved T-cell function, and overall reduced tumor burden, in addition to reduction in inflammatory cytokines and chemokines, including IL6, IL33, G-CSF, CXCL1, CXCL5 and CCL2. These cytokines and chemokines are also shown to be increased in LKB1 mutant tumors. There is an ongoing clinical trial which utilizes neutralizing antibodies against LIF which can be tested in patients with LKB1 mutant LUAD. Targeting these pathways as a monotherapy or as a combination therapy with the current standard therapy using CPI aids in overcoming therapy resistance.

Background

Lung cancer is the leading cause of cancer-related deaths worldwide, with lung adenocarcinoma being the most common subtype. The response rate of lung adenocarcinoma LUAD to the current primary treatment modality of using checkpoint inhibitors (CPIs) to enhance immune response in order to curb tumor progression remains low. Tumors adapt various immune evasion mechanisms, including modulation of tumor microenvironment (TIME), which are mostly unknown. In about 20% of patients with LUAD, mutational inactivation of Liver Kinase B1 (LKB1), which co-occurs with loss of function mutation of Kelch-like ECH associated protein 1 (KEAP1), confers resistance to standard of care chemotherapy combined with CPI. LKB1 mutant tumors display immunosuppressive molecular phenotype in addition to promoting pro-inflammatory signature leading to tumor growth through LIF (leukemia inhibitory factor) signaling. Therefore, targeting the LIF signaling axis presents a novel therapeutic opportunity to target this aggressive subtype of lung cancer.

Applications

Technology ID

PAP02-04

Category

Life Sciences/Therapeutics/Oncology

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- **Therapeutic strategy:** A novel therapeutic strategy targeting the LIF/LIFR/STAT3 or IL33 can be used to elicit immune responses in LKB1 mutant NSCLC patients resistant to standard care of therapy.
- **Novel biomarkers:** LKB1 mutation, gene expression changes in LIF/LIFR/STAT3 and IL33 may serve as novel biomarkers for NSCLC patients that respond to the therapy.

Advantages

This novel approach opens up a new door to treat a large cohort of patients (~20%) with aggressive LUAD who are resistant to immune therapy and/or do not elicit immune responses and are untreatable with the standard care of therapy.

Intellectual Property

Provisional patent application pending.