Methods of Treating Cancers Having a Deregulated Metabolic Pathway

Category

Life Sciences/Diagnostics

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Technology

Researchers at NYU Langone Health have identified the NRF2/KEAP1 pathway, as well as glutamine transporters, as new anti-cancer therapeutic targets, especially lung cancer. Studies using lung cancer mouse models have demonstrated that NRF2 promotes lung tumors, while KEAP1 protects against disease progression. To further study the importance of Keap1, a CRISPR-based screen was performed on samples from KRAS-driven NSCLC cell lines. The loss of either GPD2 or SLC1A5 was synthetic lethal in KEAP1 mutants but not in WT cells. GPD2 is a metabolic enzyme and SLC1A5 encodes a glutamine transporter. Glutamine is the most abundant amino acid, used in multiple biosynthetic, metabolic, and regulatory pathways. In addition, KEAP1-deficient cell lines are highly sensitive to glutamine and serine (amino acids imported by SLC1A5) deprivation.

Background

Lung cancer kills over 150,000 Americans every year, more than any other tumor. The most common type of lung cancer is non-small-cell lung cancer (NSCLC), which is further broken down into three main groups: large cell carcinoma, lung adenocarcinoma, and squamous cell carcinoma. A large subset of NSCLCs develop either gain-of-function mutations in anti-oxidant transcription factor, erythroid 2-like 2 (TFE2L2 or NRF2), or loss-of-function mutations in the negative regulator of TRF, named KEAP1. For example, 20% of KRAS-driven lung adenocarcinomas have KEAP1 mutations.

Reactive oxygen species (ROS) can be the result of metabolic upregulation caused by tumor growth. ROS were initially considered to stimulate cancer. However, recent studies suggest they might block tumorigenesis at high levels.

Applications

- Novel targets against NSCLC
- The glutamine transporter SLC1A5 (and others in its protein family) is a target for developing inhibitors as data shows lung tumors to be dependent on this transporter's activity
- Screening for patients that are likely to respond to glutamine transporter inhibitors based on genetic factors, such as NRF2/KEAP1 expression and KRAS mutation status

Advantages

- Targeting patients that have a deregulated metabolic pathway, such as the NRF2/KEAP1 pathway described, is a step towards precision medicine. This allows treating individual patients via a personalized approach based on their genomic data
- A novel way of treating a highly lethal disease with few targeted treatment options

IP Status

Non-provisional patent pending