Methods for Preventing Cancer Cachexia in Aggressive Lung Cancers

Characterization of novel mechanisms driving cachexia and associated therapeutic targets for lung-cancer patients.

Technology

Researchers in the Papagiannakopoulos lab have identified a novel mechanism driving cancer cachexia in a genetically defined subset of lung cancer, offering new treatment strategies to prevent cachexia in these patients. Specifically, they observed that mutations in the tumor suppressor *Lkb1* promoted reduced food intake and cachexia in mouse models of LUAD. To improve caloric intake and maintain weight, they used high-fat diets (HFDs), which paradoxically exacerbated cachexia in mice with *Lkb1* mutant tumors. Further mechanistic studies revealed that cachexia is driven locally by the production of specific prostaglandins, rather than circulating systemic factors, and the production of these cachexia-promoting prostaglandins is further altered by dietary fat. They demonstrated that inhibiting specific prostaglandin synthesis alleviated sickness behaviors in mice, and pharmacological inhibition of prostaglandins and their synthesis enzymes improved these behaviors in LUAD and other mouse models. Additionally, they characterized a novel role for lung sensory neurons in the sickness behaviors associated with cachexia, showing that abrogating vagal sensory neuron signaling mitigated anorexia, sickness, and overall cachexia symptoms. Together, these findings provide new therapeutically actionable insights into preventing cachexia in a subset of lung cancer patients that often face a poorer prognosis.

Background

Lung cancer is the leading cause of cancer-related death in the U.S., responsible for over 150,000 deaths annually. Non-small-cell lung cancer (NSCLC) is the most common subtype, comprising over 80% of all lung cancer cases and including large cell carcinoma, lung adenocarcinoma (LUAD), and squamous cell carcinoma. Mutations in the tumor suppressor gene *Lkb1* occur in approximately 20% of LUAD patients and are linked to resistance to standard-of-care therapies.

Cachexia is characterized by weight and muscle loss that cannot be rescued or reversed with nutritional support. It is driven by changes in catabolic signaling, systemic inflammation, and loss of appetite, which prevent protein synthesis while accelerating muscle catabolism. Despite affecting approximately 70% of cancer patients and accounting for up to 22% of cancer deaths, no effective medical interventions or therapeutic strategies for cachexia currently exist. Additionally, cachexia reduces quality of life, tolerance to cancer therapy, and overall survival. Cachexia is especially prevalent in lung cancer patients, affecting up to 50% of cases, yet the reasons why certain patients develop it remain unclear. This work sheds new light on the biological drivers of cachexia in lung cancer and points to promising therapeutic strategies for its prevention.

Applications

Technology ID

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Category

Life Sciences/Therapeutics/Oncology
Life Sciences/Therapeutics/Metabolic Diseases
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- Treatment or prevention of cachexia in lung cancer patients using inhibitors of prostaglandin synthesis or their receptors.
- Development of novel, targeted therapies that disrupt vagal nerve function or prostaglandin synthesis to treat or prevent cachexia.
- Use of local lung prostaglandin levels or *Lkb1* mutation status as a biomarker for cachexia in lung-cancer patients.

Advantages

- **Novel drug targets for cachexia:** Prostaglandins or their synthesis enzymes are novel therapeutic targets for preventing or treating cachexia.
- **Novel predictive biomarker:** *Lkb1* mutations can be used to predict patient risk of developing cachexia or sensitivity to high-fat diets.
- **Increased tolerance to therapies:** Preventing and/or management of cachexia can increase patient tolerance to therapies and overall survival.
- **Increased quality of life:** Preventing and/or management of cachexia will increase the quality of life for lung-cancer patients.

Intellectual property

NYU has pending provisional patent applications covering methods of treating cachexia in cancer by targeting prostaglandins, receptors or sensory neurons.