Targeting the Stress-Response Pathway to Promote Anti-tumor Responses

An efficient approach to treat a subset of patients who do not respond to current checkpoint inhibitors.

Technology

The inventors have demonstrated that ATF4, the major integrated stress response (ISR) transcription factor, enables lung adenocarcinoma (LUAD) tumor progression through the modulation of anti-cancer immune response: progression of ATF4-deficient LUAD is severely delayed in immunocompetent mice compared with that in the immunodeficient NSG mice. An ATF4 target gene, which encodes a secreted protein, was identified as a potent immunomodulatory factor and its genetic deletion phenocopied ATF4-loss. The inventors have developed a panel of human synthetic antibodies that are selective for the human protein and inhibit its function in mouse models of LUAD and pancreatic cancer (PDAC), resulting in tumor infiltration of T cells and suppression of tumor growth. Collectively, it was found that disrupting this novel ATF4-target axis in tumors reinvigorates anticancer immunity, revealing a novel therapeutic approach for cancer immunotherapies.

Background

Solid tumors are still difficult to treat in spite of the remarkable progress in immunotherapy and targeted anti-cancer therapy. Many cancers do not respond well to the current immunotherapies, such as PD-(L)1 and CTLA-4 inhibitors, that are commonly used as the primary treatment modality. Tumors develop unique capacities to invade the host normal tissue, hijack scarce resources, including nutrients to survive and proliferate, and evade anti-tumor immune responses. In order to execute such adaptation, cancer cells activate a wide range of stress responses that in turn shape tumor progression. The ISR governs the expression of a plethora of genes crucial for tumors to adjust to stress and promote tumor progression. Elevated levels of ISR are commonly observed across multiple cancer types and develop due to severe conditions of the tumor microenvironment. Here, NYU Inventors have found an important role for this pathway in suppressing anticancer immune response in LUAD and PDAC. They have also shown that targeting this axis provides a novel platform for an antibody-based therapeutic strategy to inhibit cancer that evades current therapies.

Applications

- A novel therapeutic strategy targeting the ATF4 axis can be used to elicit immune responses in multiple solid tumors that evade anti-tumor immunity.
- Small molecules or biologics (antibodies) targeting the ATF4 signaling or its secreted target may be used to promote anti-tumor immune responses in patients and may also be used in combination with standard of care immunotherapy.

Advantages

Technology ID

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Category

Life Sciences/Therapeutics/Oncology

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Learn more

- Targeting the ATF4-axis presents a novel therapeutic strategy to promote anti-tumor immune responses in patients that do not respond to standard-of-care checkpoint blockade inhibitors.
- Therapeutics against ATF4-induced protein as monotherapy or in combination with existing checkpoint blockade inhibitors may overcome therapy resistance in cancer patients.

Intellectual Property

NYU has filed a PCT patent application covering the composition of antibodies targeting the ATF4-induced protein and their method of use (PCT/US2024/019489).