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

A novel therapeutic approach for treating patients who do not respond to front-line immunotherapies.

Background

Despite remarkable progress in the development of immunotherapies and targeted anti-cancer therapies, solid tumors remain difficult to treat. Indeed, many solid tumors do not respond well to current front-line immunotherapies such as PD-(L)1 and CTLA-4 inhibitors. One reason for this challenge is that tumor cells develop unique properties that allow them to invade normal tissue, evade anti-tumor immune responses, and hijack scarce nutrients necessary for survival and proliferation. To execute such adaptations, cancer cells activate a wide range of stress responses that shape tumor progression. Among these, the integrated stress response (ISR) governs the expression of numerous genes crucial for tumors to adjust to stress and promote their progression. Elevated levels of ISR are commonly observed across multiple cancer types, arising from the severe conditions of the tumor microenvironment. NYU Inventors have discovered that this pathway plays an important role in suppressing the anticancer immune response in lung adenocarcinoma (LUAD) and pancreatic cancer (PDAC) and have developed a novel antibody-based therapeutic strategy for targeting cancers that evade traditional immunotherapies.

Technology

The inventors have demonstrated that ATF4, the major ISR transcription factor, enables LUAD tumor progression through modulation of the anti-cancer immune response. Specifically, they discovered that the progression of ATF4-deficient LUAD is severely delayed in immunocompetent mice compared to immunodeficient mice. Further investigation revealed that an ATF4 target gene, LCN2 (Lipocalin 2), acts as a potent immunomodulatory factor, and its genetic deletion phenocopied ATF4-loss. Unlike most current targets explored for immunotherapy that are membrane-anchored receptors, LCN2 is a secreted protein. The inventors have developed a panel of human synthetic antibodies that are selective for human LCN2. The antibodies showed single-agent efficacy in improving tumor infiltration of T cells and suppressing the growth of challenging tumor models. Collectively, it was found that disrupting the ATF4-axis in tumors via targeting LCN2 reinvigorates anticancer immunity, revealing a novel approach for design of anti-cancer immunotherapy.

Cell Lines Available for Licensing (murine):

- KRAS G12D/+; p53-/-; LCN2 -/-; +hLCN2 (PAP02-17)
- KRAS G12D/+; p53-/-; LCN2 -/-; +mLCN2 (PAP02-18)
- KRAS G12D/+; p53-/-; LCN2 -/-; +empty vector (PAP02-19)

Applications

Technology ID

PAP02-05

Category

Life Sciences/Therapeutics/Oncology

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- This innovation is a promising therapeutic candidate for the treatment of:
  - Lung adenocarcinoma (LUAD) and pancreatic cancer (PDAC), as demonstrated by efficacy in mouse models of both cancers
  - Potential therapy for other types of solid tumors that are resistant to front-line immunotherapies such as PD-(L)1 and CTLA-4 inhibitors

Advantages

- Novel immune-oncology target: LCN2 is a previously unexplored target for cancer therapy
- Single-agent efficacy: LCN2-targeting antibodies are effective at suppressing tumor growth as a monotherapy
- Treatment of high-mortality cancers: *In vivo* models validate LCN2 antibodies as novel therapies for high-mortality cancer types like LUAD and PDAC

Intellectual Property

NYU has filed a PCT patent application covering the composition of LCN2 antibodies and their method of use (PCT/US2024/019489).