Non-Genetic Induction of Tumor Neoantigens via Translational Errors

A new avenue for cancer immunotherapies and biologics.

Technology

NYU Langone Health researchers have developed a novel approach to cancer therapy by targeting non-genetic neo-antigens through the induction of Phenylalanine to Tyrosine (FtY) misincorporation. This new technology leverages the nutrient-poor environment characteristic of pancreatic ductal adenocarcinoma (PDAC) tumors, which typically have low levels of immunogenic tumor neo-epitopes (iTNEs) and are resistant to immune checkpoint blockade (ICB) therapies. By altering the nutrient environment to create an imbalance between phenylalanine (Phe) and tyrosine (Tyr), this misincorporation can increase up to 20% for every phenylalanine codon, generating neo-antigens on cell surface proteins or peptides that major histocompatibility complexes can present. These neo-antigens are not restricted by genetic mutations or variants, offering a new avenue for targeting cancer cells. To induce FtY misincorporation in vivo, the FDA-approved drug nitisinone (NTBC) was administered to mice via drinking water. The treatment successfully increased FtY misincorporation in orthotopic pancreatic cancer xenografts and significantly reduced tumor growth in a T-cell dependent manner. This approach generates non-genetic neo-antigens that can be targeted by biologics or the immune system, offering a promising new strategy for treating cancers like PDAC that are typically resistant to conventional therapies.

Background

PDAC is an aggressive disease with poor prognosis and is predicted to become the second leading cause of cancer-related deaths in the United States by 2030. Current standard of care for PDAC patients includes combined surgery, chemo- or radiation-therapy. Unfortunately, due to late detection, recurrence, and unsuccessful therapies, the overall 5-year survival is <12%. This poor outcome highlights an incomplete understanding of PDAC biology, limiting the effectiveness of existing therapies. PDAC tumors are characterized by a complex, nutrient-deprived stroma, commonly harbor oncogenic mutations in KRAS and TP53, and exhibit low levels of immunogenic tumor neo-epitopes (iTNE), including neoantigens. Targeting specific mRNA translational processes may offer a new therapeutic approach. mRNA translation is a highly regulated process involving ribosomes, tRNAs, and accessory proteins to synthesize proteins from mRNA templates. Errors in this process are rare but can be influenced by amino acid (AA) imbalances, leading to AA misincorporation. Understanding the conditions that trigger mRNA translation errors could help generate non-genetic iTNEs and sensitize tumors to immune therapies. Although immune checkpoint blockade (ICB) has been ground-breaking in cancer treatments, it has limited efficacy in many solid tumors, including PDAC, which often lack sufficient immunogenic neoantigens. Neoantigens are crucial for PDAC therapy, as they can stimulate T-cell killing in long-term survivors.

Development Status

Technology ID

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Category

Life Sciences/Therapeutics/Oncology

Life Sciences/Therapeutics/Immunoth

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Research is currently underway to elucidate conditions, mechanisms, and effects of Tyr:Phe imbalance on FtY misincorporation and immunogenic TNEs in PDAC cells, assess effects of Tyr on PDAC tumorigenesis, and efficacy of targeting FtY iTNEs using immune-dependent therapies.

Applications

- **PDAC treatment:** To develop biologics to target non-genetically driven neo-epitopes that stimulate T-cell responses to provide improved treatment outcomes for PDAC patients.
- **Combination therapy:** FtY-inducing conditions could be used in combination with other therapeutics that target FtY misincorporated proteins or peptide therapy
- **Broader cancer treatment:** It offers a new therapeutic strategy for cancers that are resistant to conventional treatments, expanding the scope of effective cancer therapies.

Advantages

- **Non-genetic targeting:** Generation of neoantigens without genetic mutations and enabling the targeting of essential surface proteins, critical for tumor survival.
- **Enhanced immune response:** by increasing presentation of neo-antigens, this approach can stimulate a robust T-cell dependent anti-tumor response.
- **Tumor-specific treatment:** NTBC-induced FtY misincorporation is specific to cancer cells with altered nutrient environment, potentially reducing off-target effects and minimizing harm to healthy cells.

Intellectual Property

NYU has filed for a provisional patent for this technology.