Targeting MHC-1 Antigen Presentation Machinery for Cancer Immunotherapy

Innovative therapeutic strategy to promote antigen presentation in immunologically “cold” tumors.

Technology

Researchers in the laboratories of Dr. Jun Wang and Dr. Iannis Aifantis at NYU Langone Health have identified a novel mechanism by which cancer cells suppress major histocompatibility complex class 1 (MHC-1) antigen presentation (AP), enabling evasion of T-cell-mediated anti-tumor immunity. As described in *Chen et al. Cell 2023*, using proprietary CRISPR-Cas9 screens, they discovered new cancer-associated down-regulators of MHC-1 AP using both antigen-specific and MHC-1-specific screening methods in mouse and human acute myeloid leukemia (AML) cell lines. These efforts uncovered 44 novel MHC-1 AP regulators, which were further validated *in vivo* using a murine AML model. Subsequent studies concentrated on three novel regulators: SUSD6, TMEM127, and WWP2. The researchers demonstrated that these regulators interact with each other and with MHC-1 to facilitate its ubiquitination and subsequent lysosomal degradation, thereby resulting in AP suppression. They showed that SUSD6 deficiency (via CRISPR-inactivation) enhanced T-cell responses (via IL-2 secretion) *in vitro*, delayed leukemia progression, and prolonged survival in a $CD8^+$ T cell-dependent manner *in vivo*. Moreover, they established that SUSD6 enhances anti-tumor immune responses as evidenced by an almost 80% decrease in tumor volume in an AML xenograft model. They also observed similar effects in additional solid and hematological cancer models, suggesting that this mechanism may be universally applicable across cancer types. TMEM127 deficiency also replicated the phenotypes observed with SUSD6 in mouse models. Altogether, inhibition of these novel MHC-1 AP down-regulators presents a promising avenue for single-agent treatment of immunologically “cold” tumors. Notably, such MHC-1 AP promoters could be used in combination with existing immune-checkpoint therapies to potentiate their efficacy against immunologically “cold” tumors.

Background

The discovery and development of immune checkpoint inhibitors (ICIs, i.e., Anti-PD-1/PD-L1) has significantly transformed cancer treatment, offering lasting clinical efficacy with relatively mild side effects across various tumor types. These therapies target immune evasion mechanisms within the tumor microenvironment (TME) to restore tumor-specific T cell immunity. ICIs are particularly effective in "inflamed" or "hot" tumors, which are characterized by substantial $CD8^+$ T cell infiltration that triggers a cytotoxic response capable of killing cancer cells. However, many tumors are "cold," likely because they lack sufficient T cell infiltration, and therefore, do not respond to ICIs or quickly develop resistance. Major histocompatibility complex class 1 (MHC Class 1), also known as human leukocyte antigen (HLA), is essential for determining the specificity of $CD8^+$ T cells and for their activation and proliferation. Myeloid cells act as professional antigen-presenting cells (APCs), and some tumor cells can also present tumor antigens on their surface via MHC-1. $CD8^+$ T cells engage the MHC-1 through antigen-specific T

Technology ID

WAN05-08

Category

Life Sciences/Therapeutics/Oncology

Life Sciences/Therapeutics/Autoimmu

Disease

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cell receptors (TCRs), triggering a cytotoxic response. Tumors are thought to evade $CD8^+$ T cell responses by inhibiting antigen presentation (AP). While this is a known immune evasion strategy seen in the context of viral infections, it has not been extensively studied in the context of cancer. The NYU inventors have now identified a novel mechanism for MHC-1 AP suppression in cancer cells, which presents a novel therapeutic strategy (inhibition of specific MHC-1 AP suppressors) for overcoming ICI resistance and treating immunologically "cold" tumors.

Development Stage

In published work, the inventors have genetically validated these targets *in vivo* using mouse models of AML and other solid tumors (i.e., melanoma, lung). The inventors have also genetically validated additional targets identified in their CRISPR screens, including LRP10. In collaboration with NYU's internal drug development accelerator (Therapeutic Alliances), the inventors have generated anti-SUSD6 antagonistic antibody clones (unpublished), which are now being functionally characterized in different formats. NYU is seeking an industry partner to de-risk these anti-SUSD6 antagonistic antibody clones and/or develop other therapeutics based on this novel immune evasion mechanism and its regulators.

Applications

- **Cancer immunotherapy adjuvant:** Therapeutic strategy for sensitizing immunologically "cold" tumors to immune-checkpoint inhibitors.
- **Anti-cancer prophylactic:** Prevention strategy for patients at risk of developing cancer.
- **Therapy for other immune-regulatory diseases:** Potential therapy or prophylactic for patients who have or are at risk of developing autoimmune diseases.

Advantages

- **Sensitize "cold" tumors to checkpoint blockade:** Restoring antigen presentation re-invigorates anti-tumor T-cell activity in non-responder or resistant tumors.
- **Broadly applicable mechanism:** Targeting SUSD6 and TMEM127 to promote antigen presentation is applicable across both solid and hematological tumor types.
- **Novel immune-oncology targets:** SUSD6 and TMEM127 are novel therapeutic targets for boosting the anti-tumor immune response.
- **Multiple therapeutic indications:** In addition to cancer, this pathway could be targeted for the treatment of auto-immune disorders by increasing MHC-1 AP suppression.
- **Modality agnostic targeting:** SUSD6 or TMEM127 activity could be modulated by antibodies, gene-editing, ASOs, or cell-based therapies (i.e., CAR-myeloid/CAR-M).

Intellectual Property

NYU has a pending U.S. non-provisional patent application covering the mechanism of modulating MHC-1 AP for the prevention and/or treatment of cancer and autoimmune diseases through the targeting of key regulators using different therapeutic modalities (e.g., gene therapy, cell therapy, ASOs, small molecules, and antibodies).

References

1. Chen, Xufeng et al. , https://pubmed.ncbi.nlm.nih.gov/37557169/