Natural Human Antibodies to Treat Cancer

(No. T4-2152)

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Overview

Ovarian cancer is the fifth leading cause of cancer-related death in women. Due to a lack of early detection methods, it is often diagnosed at a late stage, resulting in negligible changes to cure. Like other aggressive epithelial malignancies such as pancreatic cancer, its highly metastatic nature significantly decreases survival rates. Therefore, there is an urgent need to develop effective therapies for ovarian carcinoma and other highly metastatic cancers. Prof. Irit Sagi and Ziv Shulman isolated natural tumor-reactive antibodies from tumors of patients with ovarian carcinomas that mediate cell-mediated tumor cell killing. Notably, several antibodies were found to target MMP14, which is expressed in extremely high levels on the cancer cell surface and has a prominent role in tumor progression and metastasis. These antibodies can be used as novel therapeutic and targeting agents for cancer and prognosis markers for high-grade serous ovarian carcinoma (HGSOC).

Background and Unmet Need

Ovarian carcinoma is the most lethal gynecological malignancy and the fifth leading cause of cancer-related death in women. High-grade serous ovarian carcinoma (HGSOC), the most prevalent subtype of ovarian carcinoma, has a five-year survival rate of only ~29%. Early detection is unavailable due to the lack of specific screening methods, resulting in a late-stage diagnosis of most patients (80-85%) with negligible chances to cure. Treatment typically includes surgery followed by standard of care chemotherapy. However, the absolute majority of women who achieve a state of remission will relapse in a matter of months due to reseeding of microscopic residual disease (MRD) remnants and develop metastasis. As opposed to other cancer types, HGSOC patients do not respond to immune checkpoint blockers and so far, there is no immune-mediated treatment for this disease. Therefore, there is an urgent need to develop effective therapeutic strategies to treat HGSOC, eliminate MRD, and prevent disease recurrence. The highly metastatic and invasive nature of HGSOC is characteristic of multiple aggressive epithelial malignancies in general, including pancreatic cancer. Acquisition of this migratory potential depends on the cancer cellâ€™s capacity to undergo epithelial to mesenchymal transition (EMT) and remodel its adjacent extra-cellular matrix (ECM). MMP14 is a pivotal player implicated in both processes and is highly expressed in multiple subtypes of cancers, including ovarian pancreatic cancers, making it a highly desirable therapeutic target.

The Solution

The teams of Profs. Sagi and Shulman isolated B cells from human carcinomas of HGSOC patients and identified 20 tumor-reactive autoantibodies against tumor-associated antigens (including MMP-14) that induce cell-mediated cytotoxicity.

Technology Essence

The researchers isolated tumor-infiltrating antibody-secreting cells (ASC) obtained from the primary tumors of stage

III HGSOC patients. The tumor specimens from four patients were reduced to a single cell suspension. Following PCR amplification and sequencing, distinct heavy and light chain sequences were obtained, generating a dataset of immunoglobulin transcripts that encode for human antibody genes with potential binding and killing activity against human ovarian carcinoma. The raw data were evaluated for parameters indicative of an evolving antibody-mediated immune response, including clonal expansion of immune cells that carry the same antibody and evaluation of the antibody maturity. Several 30 antibodies were expressed and analyzed, and 17 demonstrated binding to the surface of ovarian carcinoma cells, some of which had effector functions such as antibody-dependent cell-mediated cytotoxicity (ADCC) (Figure 1). Notably, some of these antibodies were found to specifically bind MMP14 expressed on the surface of ovarian carcinoma cells. Importantly, high MMP14 expression (RNA or protein) is indicative of a poor prognosis. Therefore, in addition to their applications for tumor targeting, these antibodies could also be used as prognosis markers.

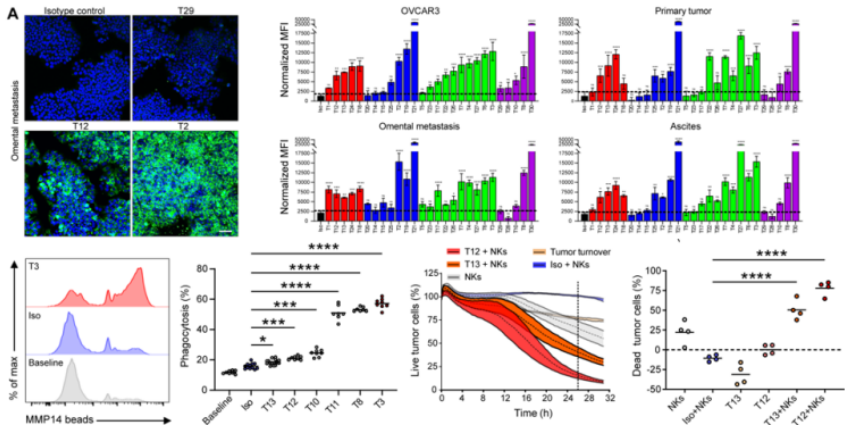

Figure 1 - HGSOC infiltrating Antibody secreting cells (ASC) derived monoclonal antibodies are tumor-reactive: (A) Representative fluorescence images OVCAR3 cells stained with different monoclonal antibodies and quantification of mean fluorescence intensity. (B) Longitudinal quantification of antibody-dependent cell-mediated cytotoxicity (ADCC) targeting OVCAR3 cells, in the presence of NK cells and isotype control.

Applications and Advantages

- Noval therapeutic agent for cancer, specifically HGSOC and possibly additional cancers (pancreatic, breast):
  - As a standalone therapy of monoclonal antibodies
  - As antibody-drug conjugation (ADC) to treat cancer
  - As chimeric antigen receptor (CAR)
  - As bispecific antibodies
- Prognosis markers for HGSOC

Development Status

The antibodies were tested in various effector functions and some of which show promising potential. Furthermore, the antibodies were found to target tumor cells in mouse models of ovarian cancer. 9 antibodies showed binding to MMP14 with various affinities. Additional antibodies show very strong reactivity with human HGSOC cancer and in vivo mouse ovarian cancer without binding the surrounding tissues.

References

Mazor RD, Nathan N, Gilboa A, et al. Tumor-reactive antibodies evolve from non-binding and autoreactive precursors. *Cell*. Published online March 18, 2022. doi:10.1016/j.cell.2022.02.012

Patent Status

USA Published: Publication Number: 2024-0166768-A1