Docket #: S23-114

Methods and proteins for targeting human progenitor exhausted T cells

Immune checkpoint blockade, a class of immunotherapy treatment which works by blocking inhibitory receptors on T cells to improve immune responses, has proven to be a remarkable clinical advance in the treatment of many diseases, particularly in cancer. However, most patients do not benefit from checkpoint blockade, and many of those who do eventually experience progression of disease. While the use of immune checkpoint blockade has revolutionized cancer treatment, there is a need for greater mechanistic understanding of how checkpoint blockade works in patients.

Recent studies have suggested that the success of immune checkpoint blockade may be related to the expansion of a population of T cells known as progenitor exhausted T cells. This population of progenitor exhausted T cells is known to express the inhibitory receptor PD-1 and the transcription factor TCF1. However, TCF1 is not expressed on the cell surface, making it difficult to target. Furthermore, there is no validated way to target these progenitor exhausted T cells in humans, as most studies have been performed in mice. Thus, there is an unmet need for more markers that can specifically identify progenitor exhausted T cells in humans. Doing so could enable the selective targeting and activation of the exhausted T cell population, potentially leading to improved patient responses to immune checkpoint blockade.

Inventors at Stanford have profiled the T cell compartment of patients with lung cancer using single-cell-paired RNA and T cell receptor sequencing methods at high depth and regional resolution. They have identified a population of progenitor exhausted CD8+ T cells in the lymph node of patients that are clonally linked to terminally exhausted T cells in the tumor. Additionally, by performing antigen specificity assays, the inventors found that this progenitor exhausted T cell population comprises a subset of tumor antigen-specific T cells, suggesting they are involved in the tumor response. Computational analysis identified several genes that

preferentially mark these lymph node progenitor exhausted T cells, including CCL5, CMC1, EOMES, IL32, SIRPG, RARRES3, CST7, GZMM, and PDIA3. This invention can enable methods that can specifically target progenitor exhausted T cells in humans to modulate this population for clinical benefit.

Applications

- Immunology research
- Selective targeting and activation of progenitor T cell population during immune checkpoint blockade treatment
- Immunotherapy

Advantages

- There is currently no clinical standard for targeting these progenitor exhausted T cells in humans.

Publications

- Pai, J. A., Hellmann, M. D., Sauter, J. L., Mattar, M., Rizvi, H., Woo, H. J., ... & Satpathy, A. T. (2023). " Lineage tracing reveals clonal progenitors and long-term persistence of tumor-specific T cells during immune checkpoint blockade". Cancer Cell, 41(4), 776-790.

Patents

- Published Application: WO2024206930

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