Targeting neutrophils for T cell-mediated anti-tumor immunotherapy

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Oncology practice has been transformed in recent years by advances in T cell-focused immunotherapy, including immune checkpoint inhibitors (ICIs) and chimeric antigen receptor (CAR) T cells. Unfortunately, progression free survival in patients with solid tumors is observed in only a minority of ICI-treated patients and only in a subset of cancer types. CAR-T cell therapy is largely ineffective and not FDA approved for non-hematopoietic tumors.

Durable cancer eradication by T cells requires antigen presenting cells (APCs) to induce clonal expansion of tumor antigen-specific CD8 T cells capable of acquiring effector functions, infiltrating tumors, and generating memory T cells (Fig. 1). Intratumoral APCs also directly induce T cell influx into tumors. However, several solid tumors have an immunosuppressive tumor microenvironment (TME) that inhibits T cell infiltration into the tumor, thus limiting the impact of current T cell-focused immunotherapies. Therapies that directly target antigen to conventional dendritic cells (cDCs), canonical professional APCs are restricted by their low abundance and dysfunction as the tumor progresses and the need for toxic adjuvants to induce their immunogenicity.

Neutrophils, the most abundant circulating leukocytes in humans, can acquire APC functions in vitro and neutrophils with markers of APCs are detected in cancer patients. We developed an antibody-tumor antigen conjugate (AAC) targeting human FcγRIIIB (expressed almost exclusively on neutrophils), which delivers antigen to neutrophils, and turns a subset of them into highly immunogenic APCs that activate CD8 and CD4 T cells without the need for adjuvants. In a mouse model of melanoma with an immunosuppressive TME, this AAC therapeutically expands and induces the tumor infiltration of T cells and natural killer cells (Fig. 2), thus achieving a major goal in immunotherapy of TME reprogramming. Further, AAC significantly reduces tumor growth, the ICI anti-PD-1 has no effect and AAC combined with anti-PD-1 further decreases tumor growth compared to either agent alone (Fig. 3). The combination therapy also induces the intratumoral accumulation of memory T cells known to have durable anti-tumor properties.

The developed AAC elicited T cell-mediated acquired immunity in melanoma as a representative example has the potential to treat a range of other solid tumors upon conjugation of anti-FcγRIIIB to applicable tumor antigens. This approach has several advantages over existing immunotherapies as it can be used to non-invasively generate a large pool of highly immunogenic tumor antigen-carrying APCs from abundant neutrophils and be achieved in the absence of adjuvants. Further, this approach provides the groundwork for transformative combination treatments with ICIs.

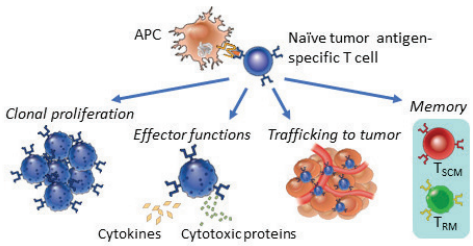

Fig. 1: APC induced T cell functions required for anti-tumor immunity. T_{SCM}, T_{RM} ; memory T cell subsets.

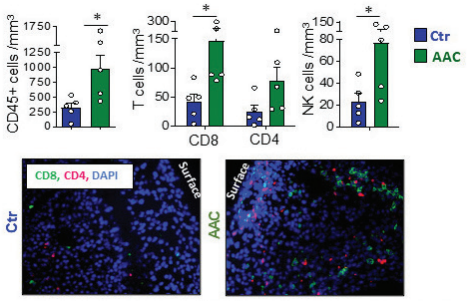

Fig. 2: Targeting neutrophils to induce tumor infiltration of T cells and NK cells. AAC, consisting of an anti-FcγRIIIB (which engages neutrophils of FcγR humanized mice) conjugated to Ovalbumin (Ova), a model T cell dependent antigen, was given to mice with a day 5 established B16F10 melanoma expressing Ova. The tumors were harvested on day 15 and analyzed by flow cytometry (top panels) for total leukocytes (CD45+), CD8 and CD4 T cells, and NK cells per mm3 volume of tumor. Tumors were also harvested for immunohistochemistry (bottom panels) to localize CD8 and CD4 T cells. DAPI; nuclear stain.

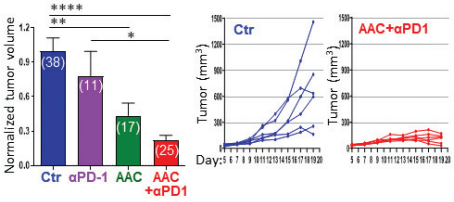

Fig. 3: AAC significantly reduces tumor growth and in combination with anti-PD-1 markedly regresses melanoma. Mice with a 5-day established B16F10-Ova were treated with isotype-control conjugated to Ova (Ctr), anti-PD1, AAC or a combination of AAC plus anti-PD1. The measured volume (mm^3) of tumors harvested at day 19 were normalized to the average of the control (Ctr) group. The number of mice per group are in parentheses. Profiles of tumor growth over time of independent mice in control and AAC+anti-PD-1 from one representative experiment are shown.