T CELL IMMUNOTHERAPIES TRIGGER NEUTROPHILS TO ELIMINATES HETEROGENOUS TUMORS

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Background Immune surveillance can eliminate developing cancers at the early stages of malignant transformation. The selective pressure that the immune system imposes on tumor cells, however, can “edit” tumors, yielding immune escape variants. Many tumors contain clones that cease to express antigenic proteins. Intra-tumoral antigenic heterogeneity is an important mechanism by which progressing tumors become refractory to standard immunotherapeutic interventions. This is particularly problematic for interventions that target a single antigen, such as adoptive T cell therapies and CAR T cells.

Current immunotherapies in the clinic consist of strategies that mobilize the adaptive compartment of the immune system. The most common approaches include immune checkpoint blockade with antibodies, infusion of ex vivo educated or genetically modified tumor-specific T cells, and therapeutic anti-tumor vaccination. Moreover, a wave of agents that target tumor necrosis factor receptor (TNFR) superfamily members expressed by activated T cells, such as glucocorticoid induced TNF receptor (GITR), 4-1BB and OX40 are being further investigated.

The role of neutrophils in tumor promotion versus tumor elimination is not well understood. The pro-tumorigenic role of neutrophils in chronic inflammation has been described. Higher neutrophil-to-lymphocyte ratios are associated with deleterious outcomes in patients receiving immune checkpoint blockade. Moreover, neutrophil effector mechanisms such as the formation of NETs can promote metastases and can shield tumors from effector T cell elimination. In other models, however, neutrophils and NETs can directly kill cancer. The role of neutrophils as potential effectors in the context of immunotherapies that target T cells remains incompletely defined.

Methods We applied a combination therapy consisting of cyclophosphamide (CTX), CD4+ T cells specific for the melanoma antigen Trp1 (Trp1 cells), and an anti-OX40 agonist or anti-CTLA-4 antagonist antibodies to mice bearing advanced antigenically heterogeneous melanomas.

Results Complete eradication of heterogeneous melanomas was observed in mice treated with the combination therapy. Surprisingly, regressing tumors were heavily infiltrated with neutrophils with a distinct anti-tumorigenic phenotype and neutrophil depletion abrogated tumor eradication. Upon closer examination, we observed that inducible nitric oxide synthase expressed by neutrophils was necessary for heterogenous tumor elimination. In support of these findings, extensive neutrophil activation in biopsies of melanoma patients treated with immune checkpoint blockade. Moreover, our findings uncover a novel interplay between T cells mediating the initial anti-tumor immune response, and neutrophils mediating the destruction of tumor antigen loss variants.