The Antigenicity of the Tumor Cell — Context Matters

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Although tumors with a high mutational load have been associated with a dismal prognosis, in this era of immunotherapy, mutations may provide a target for cancer-specific cytotoxic treatment and may become beneficial. Next-generation sequencing of hundreds of tumor types has revealed that many more somatic mutations occur in the DNA of cancer cells than were known previously. Many of these mutations occur in the coding regions of genes and are therefore transcribed into RNA, which is then translated into proteins. Fragments of these proteins may appear ultimately as altered peptides displayed by HLA molecules on the surface of tumor cells, where they can be recognized as “foreign” peptides — so-called neoantigens — by T cells, in much the same way that T cells sense microbial peptides.

The efficacy of immunotherapies, such as immune checkpoint inhibitors, which are designed to boost the patient’s own immune system, has been shown to correlate with mutational burden. Repertoires of T cells that target neoantigens have been identified in patients and have been shown to coevolve with changes in the spectrum of neoantigens over time. In patients who were successfully treated with adoptive T-cell therapy, the T cells responsive to neoantigens disappeared concomitantly with the loss of cognate antigen, whereas newly occurring mutations were paralleled by new T-cell reactivity. These discoveries pave the way for new personalized and truly tumor-specific immunotherapies.

Patient-specific candidate neoantigens may be computationally predicted on the basis of the mutations found in the respective tumor. However, only a very small number of candidate neoantigens seem to evoke an immune response in patients. In fact, of the hundreds of mutations identified in, for example, melanoma that could provide a wealth of T-cell targets, only a few (between two and five) have been found to be successful in producing neoantigen-specific T cells, which can be identified among tumor-infiltrating lymphocytes. A similar scenario has been observed with respect to neoantigen-reactive T cells in the peripheral blood; these are represented almost exclusively by T cells carrying the programmed cell death 1 (PD-1) receptor, which, when activated, represses the cytotoxic functions of T cells. The T-cell receptors (TCRs) expressed by these T cells have been shown to recognize autologous tumors but were found reactive to a very small fraction (approximately 1%) of the predicted candidate neoantigens. Are computational predictions of neoantigens inadequate? Does the tumor suppress reactive T cells or induce their death? And most important, can we improve T-cell responses to neoantigens — that is, both strengthen their response and render them responsive to a greater number of neoantigens?

The realization of this goal could complement the clinical research that has yielded the checkpoint inhibitor drugs, such as nivolumab, which blocks the PD-1 receptor.

A creative and unexpected approach to addressing these questions was recently described by Strønen et al., who tested whether T cells from healthy donors could recognize tumor neoantigens and become activated by them. Would the immune system in a person who does not have cancer respond to neoantigens in the same way as the immune system in a person who has cancer? Among several hundred mutations in expressed genes that were identified by sequencing of the DNA and RNA of tumors from three patients with melanoma, the authors selected 57 on the basis of the affinity with which the mutant peptides were predicted to bind to the major histocompatibility allele HLA-A*02:01. The authors
Figure 1. Outsourcing Cancer Immunity.

Cancer cells harbor many mutations that produce potentially immunogenic mutant proteins that are, however, not recognized by the patient’s immune system. Strønen et al. recently reported a means of identifying donor-derived T-cell responses to such mutations. Using computer-based prediction algorithms, they first selected candidate neoantigens among peptides encoded by mutations from tumors of three patients with melanoma that — in theory — seemed likely to elicit an immune response. These mutant peptides were then synthesized and expressed in antigen-presenting (dendritic) cells obtained from a healthy donor and were coincubated with T cells from that same person. Neoantigen-reactive T cells activated by some of these transduced dendritic cells multiplied, and the “potent” T-cell receptor genes were isolated. T cells from a second healthy donor, when genetically engineered to express the neoantigen-reactive T-cell receptors, were shown to destroy tumor cells derived from the original melanomas. mRNA denotes messenger RNA.
then synthesized messenger RNA fragments corresponding to the putative neoantigens and introduced these fragments into monocyte-derived dendritic cells (“professional” antigen-presenting cells of the immune system) from an HLA-A*02:01–positive healthy donor. They tested in vitro the ability of these transfected antigen-presenting cells to induce the proliferation of naive cytotoxic T cells from the same healthy donor from whom the dendritic cells were obtained. The three patients, in aggregate, had T-cell responses to only 2 of the neoepitopes, whereas the T cells from the healthy donor were activated by 11 of the neoepitopes. Clones of the T cells that were responsive to the neoepitopes responded to low concentrations of the mutant and not the wild-type version of the cognate antigen. TCR sequences were identified and genetically transferred to the T cells of a second healthy donor. The therapeutic potential of such TCR-modified T cells was shown by their ability to kill the melanoma cells from the HLA-A*02:01–positive patient, from which the mutations were originally derived (Fig. 1). These experiments show that T cells from the blood of a healthy donor represent a valuable platform for testing the immunogenicity of neoantigens, including neoantigens neglected by the patient’s own immune cells in vivo. Still, the T cells from healthy donors were not — by a long shot — responsive to all the candidate neoantigens. Strønen et al. went on to show that the “hit” rate of candidate neoantigens (i.e., the success to predict candidate neoantigens capable of inducing an immune response) is improved with estimates of the stability of the binding between peptides and major histocompatibility complex molecules, relative to the use of computational binding affinity predictions alone.

The study by Strønen et al. is a reminder that insights can be gained from nonintuitive and accessible experimental systems — in this case, the peripheral blood from healthy persons matched for at least one HLA allele with the patient. The repertoires of T cells from multiple donors can be used to study the properties that define an immunogenic neoantigen. Donor-derived T cells are activated by mutant epitopes that fly beneath the radar of the impaired immune system of the patient. This finding opens possibilities for a new generation of personalized immunotherapies through the genetic introduction of neoantigen-specific, donor-derived TCRs into a patient’s T cells by means of adoptive transfer.

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