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Putting T cells to work – outsourcing neoantigen detection in head and neck cancer?

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The recent genomic characterization of head and neck squamous cell carcinomas by The Cancer Genome Atlas demonstrated the high frequency of mutations affecting these cancers (Cancer Genome Atlas Network, 2015). This high rate of genomic alterations allows head and neck cancers to be highly immunogenic, thus promoting responses to immune therapies (Allen *et al*, 2015; Ferris, 2015). For instance, inhibitors of immune checkpoints like the anti-PD-1 monoclonal antibodies nivolumab and pembrolizumab have demonstrated promising results in head and neck cancer (Ferris *et al*, 2016; Chow *et al*, 2016), both recently receiving FDA approval in the setting of recurrent or metastatic disease. Additional immunotherapies under investigation include adoptive cell therapy (ACT), which leverages anti-tumor activity against specific tumor antigens to produce a targeted immune response using autologous dendritic cells or lymphocytes (Rosenberg and Restifo, 2015). Recently, targeted T cell therapy achieved durable, complete regression in select cases of metastatic HPV-positive cervical cancer, and similar trials have begun at the NIH to investigate such applications in HPV-positive head and neck cancers (Stevanovi *et al*, 2015). This approach works particularly well when there are easily-identified target antigens, such as viral oncoproteins. However, the applications of these immunotherapies utilizing checkpoint inhibitors or autologous T cells carry limitations, as they inherently depend upon the recognition of tumor cell genomic alterations as foreign “neoantigens” to establish an underlying immune response. When these neoantigens escape detection from the immune system, alternative approaches are necessary.

In a recent paper published in *Science*, Strønen *et al.* investigated the possibility of expanding the T cell response to neoantigens by utilizing donor T cells (Strønen *et al*, 2016). The authors’ goals were to (1) determine whether immune responses could be generated

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against predicted neoantigens using donor-derived T cells and (2) whether this technique could be utilized to identify and target a pool of neoantigens otherwise “neglected” by the host immune system. Strønen and colleagues obtained tumor cells from a stage IV melanoma patient expressing human leukocyte antigen (HLA)-A*02:01. Sequencing of these tumor cells revealed 249 mutations, more than half of which were predicted to bind to HLA-A*02:01; however, only two of these mutations were detected by host T cells.

The authors selected 20 candidate neoantigens based on predicted high binding affinity of the peptide-HLA complex. The authors initially transfected HLA-A*02:01 autologous antigen-presenting dendritic cells with mRNA encoding the candidate mutation epitopes. These dendritic cells were later exposed to donor T cells, and multimer technology was used to detect antigen-specific T cell reactivity to the 20 candidate neoantigens. T cells from four different blood donors recognized between three to five of the selected neoantigens, only one of which was also recognized by autologous T cells from the original melanoma patient. This finding suggests that there are several candidate neoantigens capable of detection by T cells that were neglected by the patient’s autologous T cells. The authors then made clones of several of these reactive T cells and demonstrated that they could recognize third-party melanoma cells only if the mutant epitopes were introduced, suggesting that this response is highly tumor/patient-specific. Repeat experiments utilizing tumor cells from two additional melanoma patients resulted in detection of 6 of 23 predicted epitopes from the first patient and 0 of 10 predicted epitopes from the second patient, emphasizing the variability in diversity of candidate antigens and potential for T cell responses among different patients.

In addition to assessing neoantigen recognition by donor T cells, Strønen et al. next investigated the potential for T cell receptor (TCR) gene transfer. TCRs from neoantigen-reactive donor-derived T cells were sequenced and transfected into new peripheral blood T cells. Transfected T cells reacted to three of four predicted neoantigen epitopes from the original melanoma patient’s tumor cells, as measured by functional T cell assays (degranulation and interferon-gamma production). These experiments are an important proof-of-concept demonstrating that engineered TCRs derived from screened donor T cells can be used effectively to target neoantigens “neglected” by host T cells, whether by immune tolerance or other mechanisms.

The findings from Strønen et al. have significant potential for impact in the context of head and neck cancer, especially given the established high frequency of mutations encoding potential neoantigens (Cancer Genome Atlas Network, 2015). Interestingly, one of the mutant genes recognized by this approach was MLL2, which has been detected as a mutated gene in head and neck cancers (Seiwert *et al*, 2015). As the authors note, the host response to neoantigens can overlook the vast majority of these mutations, necessitating alternative approaches. Other approaches used to broaden the neoantigen-specific T cell response include dendritic cell vaccines loaded with neoantigen peptide (Carreno *et al*, 2015). Strønen et al. have demonstrated a novel approach utilizing donor-derived T cells when the host is unable to detect these neoantigens. The authors showed that it is possible to “outsource” donor T cells to first identify host tumor neoantigens before subsequently engineering TCRs, which could then be transfected into autologous T cells to enhance the host immune response. This focused targeting of neoantigens provides a potential method to overcome some of the

limitations of current immunotherapies such as checkpoint inhibitors, which may otherwise have limited efficacy in the presence of neglected neoantigens.

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