

Evasion of Adoptive T-Cell Therapy through Loss of MHC

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Directed activation of the immune system has become an increasingly feasible and effective option for cancer treatment. Normally, cytotoxic CD8 T-cells are activated to lyse target cells by the T-cell receptor binding small protein fragments (antigens) presented at the cell surface by major histocompatibility (MHC) molecules. For adoptive immunotherapy, T-cells are genetically engineered with receptors that recognize specific antigen-MHC molecules present on cancer cells. These modified T-cells are then expanded *ex vivo* and transferred back into patients to eradicate tumors. Adoptive T-cell therapy against the antigen NY-ESO-1 has shown great promise in preclinical models and in early stage clinical trials. Unfortunately, some tumors persist or relapse after therapy. Dr. Zandra Klippel and colleagues in the Warren laboratory in the Clinical Research Division examined NY-ESO-1-specific T-cell therapy in a mouse model of multiple myeloma. As reported in the journal *Gene Therapy*, the researchers demonstrate loss of heterozygosity at the MHC loci as one mechanism of immune evasion for tumors that fail therapy.

In the current study, Dr. Klippel and colleagues examined adoptive T cell therapy against multiple myeloma. Multiple myeloma is the second most common blood cancer diagnosed in the United States and has thus far been incurable. The researchers reprogrammed CD8 T cells from multiple myeloma patients with a T-cell receptor specific to the antigen NY-ESO-1 and a particular MHC subtype called HLA-A2. NY-ESO-1 belongs to a set of cancer-testis antigens, whose expression is limited to human germ line cells in the testis and in various types of human cancers, making them ideal cancer antigens for tumor immunotherapy. The reprogrammed T-cells effectively recognized and destroyed multiple myeloma cells that expressed NY-ESO-1 in complex with HLA-A2 *in vitro*. The researchers then transferred these reprogrammed T cells in a mouse model of multiple myeloma and observed potent antitumor activity in four of six mice (see figure).

The authors examined the tumors of the two mice that failed adoptive T-cell therapy to understand the mechanism of immune escape. Therapy failure could be due to a number of potential mechanisms, including the lack of T cell persistence, the loss of antigen or MHC expression, the inability of T cells to migrate to the tumor, or the inhibition of T-cell function after infusion. The

researchers found comparable mRNA levels of the antigen NY-ESO-1 in the control and therapy-resistant tumors. However, when the researchers examined the tumor cells by flow cytometry, they saw complete loss of cell surface HLA-A2 in therapy-resistant tumors.

Next, Klippel *et al.* asked if the loss of MHC expression was at the genomic level and performed loss of heterozygosity (LOH) analysis on the tumor cells derived from control and resistant mice. The researchers observed LOH at three MHC loci in myeloma cells from one resistant mouse and at five loci in the other mouse. Although the genomic events were not identical in the two resistant mice, both involved loss of the *HLA-A*02* allele, which is necessary to display the antigen NY-ESO-1 on the cell surface. The researchers confirmed these results by HLA-typing the resistant tumor cells by PCR.

Other preclinical and clinical studies of NY-ESO-1-specific T-cell therapy for sarcoma, melanoma, and multiple myeloma have reported similar results: antitumor activity in some patients but failure in others. The mechanism of resistance was not examined in any of these studies, but the results of Klippel *et al.* suggest loss of MHC may be involved. The authors caution their results are derived from a genetically unstable multiple myeloma cell line; however, cancer cells display genomic instability as well. Overall, the results of this study demonstrate that LOH of MHC should be examined as an immune escape mechanism in patients who fail adoptive NY-ESO-1-specific T-cell therapy in current clinical trials. To overcome this immune evasion mechanism, an alternative approach for adoptive T-cell therapy is to genetically modify T cells to recognize molecules on cancer cells without relying on MHC presentation using chimeric antigen receptors (CARs).

[Klippel ZK, Chou J, Towler AM, Voong LN, Robbins P, Bensinger WI, Warren EH.](#) 2014. Immune escape from NY-ESO-1-specific T-cell therapy via loss of heterozygosity in the MHC. *Gene Ther.* Epub ahead of publication, doi: 10.1038/gt.2013.87.

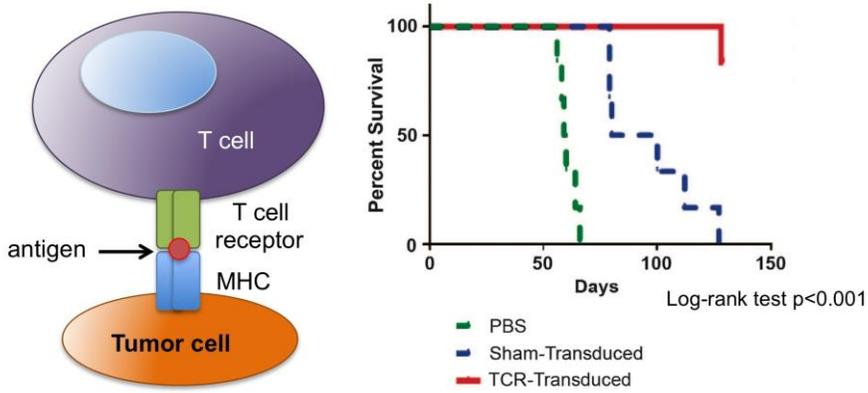


Image modified from Klippel, et al. 2014

T cells can be redirected to selectively kill cancer cells by introducing T-cell receptors that recognize specific cancer cell antigens in complex with MHC. Adoptive transfer of reprogrammed NY-ESO-1-specific T-cells exhibits potent antitumor activity in some but not all xenografts of multiple myeloma in mice, suggesting immune escape mechanisms in the cancer cells.