Targets of Tumor Immunity After Allogeneic Hematopoietic Stem Cell Transplantation

Yishay Ofran and Jerome Ritz

Abstract The effectiveness of allogeneic hematopoietic stem cell transplantation for hematologic malignancies results from the donor immunity to antigens expressed in leukemia cells in the recipient. Similar immune responses have now been identified in patients with renal cell cancer with tumor regression after allogeneic hematopoietic stem cell transplantation. Further studies to identify relevant antigens and mechanisms of resistance may improve the effectiveness of this approach in patients with solid tumors.

Allogeneic hematopoietic stem cell transplantation (HSCT) currently provides effective and potentially curative therapy for a variety of hematologic malignancies. Transplant preparative regimens that include high-dose chemotherapy and total body irradiation contribute substantially to leukemia control, but it is now evident that the clinical effectiveness of this approach is due primarily to immunologic recognition and the elimination of recipient leukemia cells by donor T cells (1). This immunologic effect has been termed graft versus leukemia (GVL). Considering the potent role of GVL, patients who cannot tolerate myeloablative conditioning can nevertheless undergo allogeneic HSCT after receiving reduced intensity conditioning, which is designed to prevent rejection and facilitate the engraftment of donor stem cells rather than directly suppress leukemia cell proliferation. The successful maintenance of remission after reduced intensity conditioning and allogeneic HSCT in patients with advanced leukemia is a clear indication of the ability of the donor immune system to detect and eliminate recipient leukemia cells *in vivo*.

Many studies have been undertaken to identify the precise targets of GVL and to better understand the immunologic mechanisms that lead to complete remissions after allogeneic HSCT. In patients with HLA-identical donors, minor histocompatibility antigens (mHA) in the recipient are recognized by donor T cells and are the primary targets of allo-immunity. Leukemia cells as well as normal cells in the recipient express these antigens, and donor T-cell responses directed against these mHA can result in the eradication of leukemia *in vivo* (2). In addition to mHA, leukemia cells also express tumor-associated antigens, and recognition of these epitopes by donor T cells also contributes to the elimination of leukemia cells *in vivo* (3). Although the immune response to antigens expressed in tumor cells is beneficial, this response also results in graft versus host disease (GVHD) when the target antigens are widely expressed by normal tissues in the recipient. T cells are the primary mediators of both GVL and GVHD, but recent studies have shown that GVL and GVHD are also associated with B cell responses to both tumor-associated antigens and mHA (4, 5).

In all cases, mHA derive from genetic polymorphisms in the recipient that are not present in the donor. Donor T and B cells are not tolerant to proteins and peptides derived from these gene sequences, and these epitopes are therefore recognized as foreign antigens when encountered in recipients after transplantation. Although many types of genetic diversity have been shown to lead to immunogenic mHA, most known mHA occur as a result of nonsynonymous single nucleotide polymorphisms. The number of mHA epitopes that have been identified is relatively small. Thus far, less that 30 have been identified (6), and this likely represents only a small fraction of the total number of human mHA. The HapMap project has already identified over 10^7 single nucleotide polymorphisms in the human genome and $>10^4$ of these single nucleotide polymorphisms result in altered amino acids in coding regions. mHA can also result from other common genetic variations (7) and thus the extent of immunogenic disparity between HLA-identical individuals is very large, even if they are siblings (8).

In this issue of CCR, Tykodi et al. (9) report the identification of a new HLA-A*0201 restricted mHA, encoded by a single nucleotide polymorphism in an alternative splice variant of the *C19orf48* gene. CD8 T cells specific for this novel epitope were identified in two patients with renal cell cancer who showed partial tumor responses after allogeneic HSCT. The function of this gene is unknown, but studies in this report show that this gene is expressed in normal tissues and in many different tumor cell lines. All tumor cell lines that expressed HLA-A*0201 and were at least heterozygous for the immunogenic single nucleotide polymorphisms were susceptible to lysis by donor T cells.

In conjunction with this report, a recent article by Takahashi et al. (10) showed that regression of renal cell cancer after allogeneic HSCT was associated with the development of T-cell responses to epitopes derived from HERV-E, an endogenous human retrovirus. HERV-E is frequently activated and expressed in renal cell cancer, and four patients who underwent

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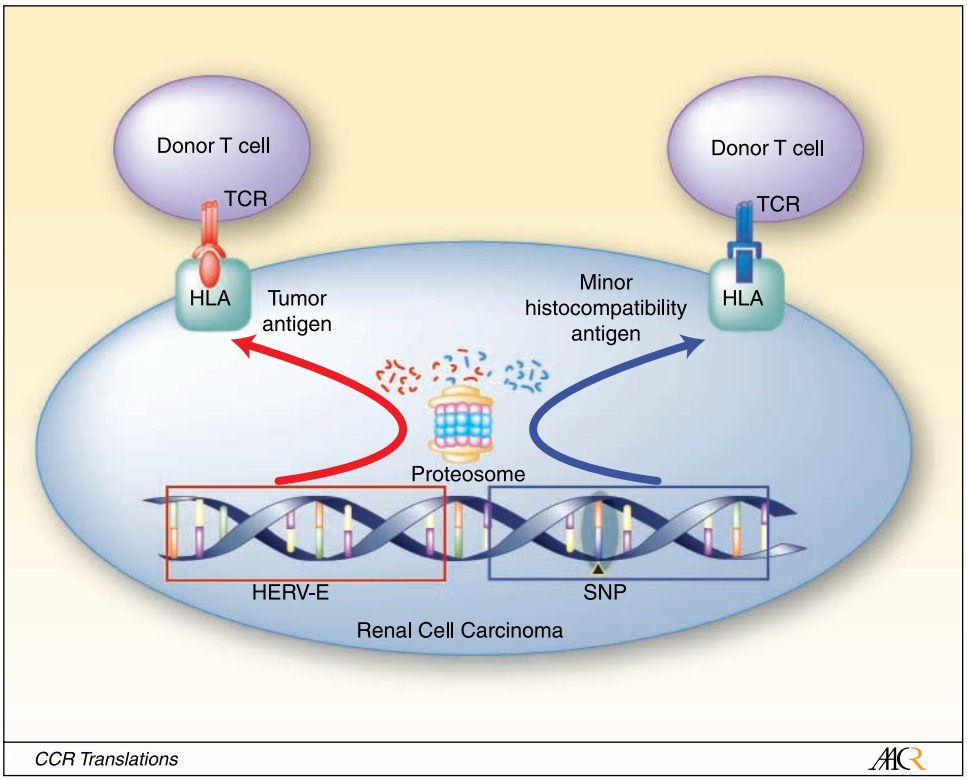

Figure 1. Expression of target antigens recognized by donor T cells. Allogeneic donor T cells are able to recognize both mHa (*blue rectangle, right*) and tumor-specific antigens (*red oval, left*). While mHa result from a specific genetic polymorphism (e.g., single nucleotide polymorphism; *SNP*), the tumor-associated antigen in this example is derived from an endogenous retroviral sequence that is present in all cells but only expressed in tumor cells. Proteins containing these sequences undergo proteosomal processing which results in the generation of distinct peptides. In both examples, peptide epitopes are expressed in HLA class I molecules and recognized by donor CD8 T cells bearing distinct T-cell receptors. These protein sequences are not expressed in the HLA-identical donor, who therefore does not develop T-cell tolerance to these epitopes.

allogeneic HSCT developed specific CD8 T-cell responses to novel epitopes derived from HERV-E sequences. This antigen is only expressed in cancer cells and not in normal tissues despite its presence in all cells at the genomic level. The HERV-E epitope thus functionally serves as a tumor-specific antigen that was recognized by donor T cells after transplant. During follow-up, tolerance developed in two of the four patients. In both, disease progression was associated with the disappearance of antigen-specific T cells.

Taken together, these interesting new reports show that renal cell cancers express both mHA and tumor-associated antigens and that these antigens can be recognized by donor T cells after allogeneic HSCT (Fig. 1). Importantly, T-cell responses to these antigens were associated with documented tumor regression after allogeneic HSCT.

In contrast to hematologic malignancies, where GVL frequently results in complete remission, clinical outcomes after allogeneic HSCT for solid tumors have been disappointing. A recent review of allogeneic HSCT in patients with metastatic breast cancer, melanoma, and renal cell cancer revealed evidence of significant graft versus tumor activity, but few complete responses were documented and patients seldom maintain partial responses for prolonged periods (11, 12). The reasons for the different results in hematologic and solid tumors are not known. It may be that solid tumor epitopes elicit weaker responses or that solid tumors are more inherently resistant to immune-mediated destruction than hematopoietic tumors. The development of progressive disease despite ongoing GVHD in many patients suggests that tumor cells can become resistant to allogeneic tumor immunity. In patients with hematologic malignancies, this occurs most often in patients with chemotherapy-refractory disease before transplant. Patients with solid tumors undergoing allogeneic HSCT often have large tumor burdens and refractory disease and this likely contributes to poor outcomes. Finally, the relative resistance to allogeneic tumor immunity may be a result of multiple mechanisms that solid tumors use to actively suppress both innate and adaptive immune responses (13).

This is an important area of investigation. If the results of allogeneic HSCT for solid tumors can be improved, this may introduce an entirely new therapeutic modality in our armamentarium against these cancers. Nonmyeloablative conditioning regimes are generally well tolerated and reliably support engraftment of donor stem cells. A better understanding of the antigenic targets and mechanisms of effective allogeneic immunity against solid tumors may also facilitate the development of more effective approaches to induce autologous tumor immunity. The report by Tykodi et al. is an important step in this process. Through detailed analysis of patients with solid tumors who respond to allogeneic HSCT, it is possible to identify immunologic targets that are capable of mediating tumor rejection. Unfortunately, the vast majority of such epitopes remain unknown and further work in this area is needed to develop new methods for identifying these immunologic targets. With the identification of additional tumor rejection antigens, it will be possible to better define criteria for tumor response and develop approaches to overcome resistance. Taken together, these types of studies are needed to move this field forward and determine whether allogeneic HSCT might play an important future role in the treatment of solid tumors.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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