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Abstract

Adult T-cell leukemia/lymphoma (ATL) is a distinct hematologic malignancy caused by human T-lymphotropic virus type 1 (HTLV-1). ATL is resistant to conventional chemotherapeutic agents, and currently there are only limited treatment options available. Although early experience of myeloablative chemoradiotherapy together with autologous hematopoietic stem cell rescue for ATL was associated with a high incidence of relapse and fatal toxicities, allogeneic hematopoietic stem cell transplantation (HCT) has been explored as a promising alternative treatment achieving long-term remission in a proportion of patients with ATL. The potential benefit of allogeneic HCT for ATL patients is considered to be due to the high immunogenicity of HTLV-1-infected cells, which was associated with the existence of post-transplant graft-versus-HTLV-1 and/or graft-versus-ATL effects.

HTLV-1 was the first retrovirus to be directly associated with a human malignancy, and approximately 20 million people worldwide are estimated to be infected with this virus. Among the HTLV-1 regulatory and accessory genes, *Tax* transforms rodent cells and immortalizes human primary T cells. In addition, Tax-transgenic mice develop spontaneous tumors. Another HTLV-1 component gene, *HTLV-1 bZIP factor (HBZ)* promotes the proliferation of ATL cells. Transgenic mice expressing HBZ in their CD4 T cells share many symptoms and immunological features with HTLV-1-infected humans.

We document *HBZ*-specific CD4 T cell responses in an ATL patient after HCT, and have identified a novel HLA-DRB1*1501-restricted HBZ-derived naturally-presented minimum epitope sequence, RRRAEKKAADVA (HBZ114-125). This peptide was also presented on HLA-DRB1*1502, recognized by CD4 T cells. Notably, HBZ-specific CD4 T cell responses were only observed in ATL patients after allogeneic HCT (3 of 7 patients), but not in non-transplanted ATL (0 of 5), or in asymptomatic HTLV-1 carriers

(AC) (0 of 5). In addition, in one acute-type patient, HBZ-specific CD4 T cell responses were absent in complete remission before HCT, but became detectable after allogeneic HCT. We surmise that HTLV-1 transmission from mothers to infants through breast milk in early life induces tolerance to HBZ, and results in insufficient HBZ-specific T cell responses in HTLV-1 AC or ATL patients. On the other hand, after allogeneic HCT, the reconstituted immune system from donor-derived cells can recognize virus protein HBZ as foreign, and HBZ-specific immune responses are provoked which contribute to the graft-versus-HTLV-1 effect.