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Allogeneic T cells: maestro in the co-ordination of the immune response after hematopoietic stem cell transplantation

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Allogeneic hematopoietic stem cell transplantation (HSCT) is currently used to treat different bone marrow disorders and hematologic malignancies.[1] In this context, allogeneic donor T cells play key roles in the post-transplant immunity as they can attack the patient's malignant cells in a phenomenon referred to as graft-*versus*-leukemia (GvL), which is the beneficial aspect of tissue disparity. However, donor T cells also react against the tissues of the patient contributing to the development of one of the main complications after allogeneic HSCT, graft-*versus*-host disease (GvHD).

Moreover, the description of the GvL effect in hematologic malignancies led to the development of a cell therapy approach using donor lymphocytes or donor lymphocyte infusion (DLI) in order to treat patients with hematologic relapse following allogeneic HSCT. DLI is currently an effective treatment to restore remission in patients with relapsed chronic myeloid leukemia (CML).[2]

In terms of allogeneic immune response post transplant, it has been demonstrated that allogeneic cytotoxic CD8$^+$ T cells are the main mediators of the GvL effect as well as GvHD, while CD4$^+$ T cells are mainly 'helpers' in the immune response by inducing maturation of dendritic cells (DC) and activation of other immune cells such as CD8$^+$ T cells and B cells. It is currently known that CD4$^+$ T cells can stimulate the production of auto-reactive as well as allo-reactive antibodies in the context of allogeneic HSCT,[3,4] but the importance of the co-operation between CD4$^+$ T cells and B cells in the immunity after HSCT has so far only been reported against DDX3Y, a male specific antigen,[5,6] and needs further investigation.

Different HLA class II restricted polymorphic antigens have previously been characterized as targets for allogeneic CD4$^+$ T cells in a patient suffering from CML who received DLI after allogeneic HSCT.[7,8] One of the identified antigens was derived from PTK2B, a protein belonging to the focal adhesion kinase family. As reported in this edition of the Journal, in their study, Kremer *et al.*[9] chose to focus their attention on the response towards this specific antigen, as it has been documented that PTK2B can be an antibody target in certain transplanted patients treated with DLI for CML relapse.[10] However, it is still unclear whether the antibody response activated in these patients is of an allogeneic or an autologous nature and whether there is a specific T-cell

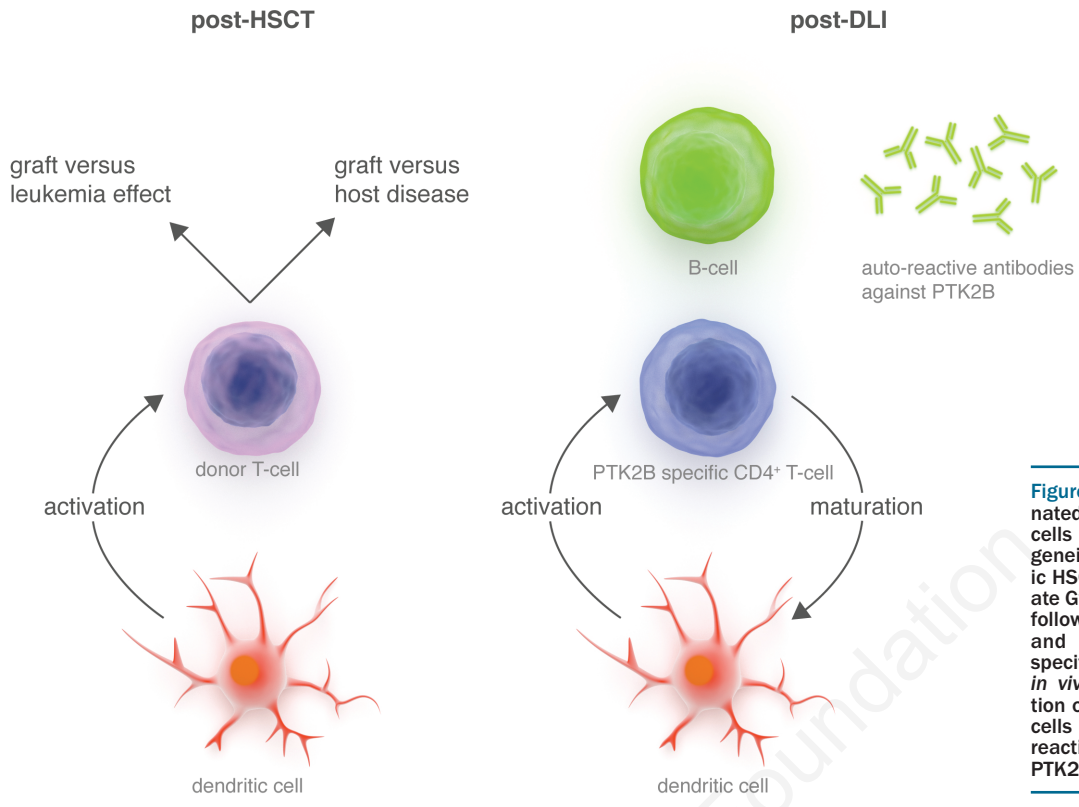

Figure 1. Model of a co-ordinated response between B cells and T cells after allogeneic HSCT. After allogeneic HSCT, donor T cells mediate GvHD and GvL. After DLI following relapse, activation and expansion of PTK2B specific CD4+ T cells occur *in vivo*, followed by activation of dendritic cells and B cells and secretion of autoreactive antibodies against PTK2B.

response against PTK2B in this specific cohort of patients.

The authors first demonstrated the specificity of an LB-PTK2B-1T CD4+ T-cell clone isolated from the bone marrow of a patient with relapsed CML after HSCT by showing that those cells only reacted upon stimulation with the patient, but not the donor, EBV-LCL cells loaded or not with an LB-PTK2B-1T peptide. They then set up a clonotypic PCR that specifically amplifies the DR3 region of this clone, and using this method they were able to show that LB-PTK2B-1T specific CD4+ T cells only expanded in patients after they received DLI treatment.

The authors then assessed the helper function of these LB-PTK2B-1T specific CD4+ T cells *in vitro* by setting up co-cultures using either monocytes differentiated into immature DC or CD19+ B cells. In both types of co-cultures, LB-PTK2B-1T specific CD4+ T cells were able to induce DC maturation as well as B-cell activation in an antigen specific manner *in vitro*, as measured by the upregulation of HLA-DQ, CD86 and CD54 or CD86 only, respectively, illustrating the helper function of this PTK2B CD4+ T-cell clone.

The helper function of these LB-PTK2B-1T specific CD4+ T cells was then investigated *in vivo*. The authors measured the levels of anti-PTK2B IgG antibodies in the serum of patients before HSCT, after HSCT and after DLI to address whether a co-ordinated response between B cells and T cells occurs in patients, and to determine at which stage of the treatment this response develops. Interestingly, it was found that such reactivity against PTK2B was only observed in patients after they received DLI treatment and not before or after HSCT or before DLI.

In the last part of their study, the authors showed that the antibody response observed *in vivo* was directed against the C-terminal part of the PTK2B protein and that the antibody epitope was actually located in a non-polymorphic region of the C-terminal part of the protein, while the T-cell polymorphic epitope is located in a different region of this protein. Finally, using a sequencing method to analyze whether there are any differences in the PTK2B protein between the patient and the donor, the authors confirmed that the B-cell response after DLI was autologous.

The importance of the co-operation between CD4+ T cells and B cells in the immune response after HSCT has previously been demonstrated against the DDX3Y antigen, this response consisted of an allo-reactive antibody response and auto-reactive CD4+ T-cell response.[5,6] Interestingly, in their study, Kremer *et al.* showed the induction of an allo-reactive T-cell response together with an auto-reactive antibody response directed against different parts of the C-terminal region of the PTK2B protein after DLI treatment post HSCT (Figure 1). The authors argued that this could be due to a break in B-cell tolerance following DLI because of the release of cytosolic contents following T-cell mediated tissue damage. However, this needs to be investigated further. In this context, it will be interesting to assess whether this antibody response is only transitory, as is the case during the co-ordinated response between T cells and B cells against foreign pathogens.

As the present report is based on a patient case, it will be key to perform further studies to analyze the nature of the B- and T-cell response against this specific antigen in a higher number of patients after allogeneic HSCT and after DLI to gain a better understanding of the co-operation between

these two cell types in those contexts. It will also be essential to extend that study to other antigens that have been described as potential targets for allo-reactive $CD4^+$ T cells to have a clearer picture of the role of this co-ordinated response post HSCT. Moreover, additional studies will also be needed to understand how this co-ordinated response between T cells and B cells is initiated in transplanted patients.

In summary, Kremer *et al*. reported for the first time a co-ordinated response between allogeneic T cells and autologous B cells against a specific antigen, PTK2B, following DLI after allogeneic HSCT in a patient relapsing from CML. As we gain a better understanding of the key roles of T cells in immunity after allogeneic HSCT, further studies aiming to evaluate the role of reactive antibodies in the immune response in patients post HSCT or post DLI will be key. Such studies will provide a better understanding of the roles of $CD4^+$ helper T cells and how different cell types co-operate in this immune response.

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Financial and other disclosures provided by the author using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are available with the full text of this paper at www.haematologica.org.

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Moving towards patient-centered decision-making in chronic myeloid leukemia: assessment of quality of life and symptom burden

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Chronic myeloid leukemia (CML) was a fatal disease for almost all patients until the introduction of allogeneic stem cell transplantation (SCT) and of interferon-alfa (IFNα). However, these were of benefit only for a minority of patients.[1] The targeted therapies, first imatinib, then the other tyrosine kinase inhibitors (TKIs), have dramatically changed the scenario. The scientific community enjoyed the expected normal life span for most TKI-treated CML patients, considering the extrapolation of the survival curves.[2,3] More recently, the scientific community is focusing on the importance of achieving a deeper and deeper response that can only be measured through molecular methods.[4-7] It is expected and predicted that the deeper the response the better the outcomes, where, today, outcome is considered in terms of overall survival, while tomorrow it is likely to be treatment-free survival.[8,9] Accordingly, the choice of treatment has traditionally been based on efficacy criteria including rate, time and depth of response.[8,9] This policy has sound clinical bases because CML is a cancer, and the ultimate objective is to provide a cure. Consequently, outcome assessment in CML has, till now, been heavily disease oriented. While this policy must be implemented, we should also bear in mind the fact that the disease course and treatment approaches have radically changed over the last decade. Currently, based on at least ten years of experience with imatinib and on the availability of other TKIs, less than 20% of patients are still at risk of dying of leukemia, less than 20% can achieve a treatment-free remission, and more than 60% are facing a situation of chronic, life-long treatment.[9]

For many years, we have dedicated our efforts and resources to the evaluation of the response, achieving remarkable success in the standardization of the methods used to assess minimal residual disease (MRD), and widespread agreement on the evaluation of treatment