Autologous graft versus myeloma: it's not a myth

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Graft-versus-tumor (GVT) effects have been thought to mostly result from allogeneic transplants; however, there is a growing body of research that supports a possible autologous GVT effect. In early clinical studies, a positive correlation between lymphocyte count recovery after autologous transplantation and overall survival has been observed. However, mechanistic studies to identify the mediators of autologous GVT responses have been lacking. In this issue of the *JCI*, Vuckovic et al. observed a T cell–dependent autologous GVT effect in the Vk*MYC myeloma model. Moreover, the authors showed that CD8$^+$ T cells mediate myeloma control through IFN-γ secretion, which could be further augmented with a CD137 agonist, suggesting a therapeutic approach for enhancing autologous GVT.

Current approaches for multiple myeloma

Multiple myeloma (MM), characterized by the accumulation of malignant antibody-producing plasma cells, is the second most common blood cancer after non-Hodgkin lymphoma (NHL) in the United States (1). Thanks to the understanding of disease biology, an increasing number of individualized treatments are available that have largely improved patient outcomes. Despite the large number of experimental therapeutics being tested for myeloma, such as immunotherapies, histone deacetylase (HDAC) inhibitors, chimeric antigen receptor (CAR) T cell therapy, MM remains incurable. For transplant-eligible patients, high-dose therapy (HDT) followed by autologous stem cell transplantation (SCT) is the standard of care (1). While allogeneic transplantation can provide a potential cure due to the graft-versus-tumor (GVT) effect, this approach is prohibitive because of the high risk of treatment-associated mortality, including the development of graft-versus-host disease (GVHD). Especially for patients with MM, allogeneic SCT does not confer superior overall survival (OS) compared with autologous SCT. Therefore, allogeneic SCT is not considered a first-line treatment for MM and is only done in clinical trial settings. On the other hand, post–autologous transplant patients who received maintenance therapy with the immunomodulatory (IMiD) agent lenalidomide had remarkably improved survival rates compared with those who did not, suggesting that the host's immune system can be improved to keep the cancer at bay (2).

There is a significant body of evidence suggesting that the immune system has a critical role in myeloma disease control. IMiDs have been shown to improve the function of NK cells and T cells, both of which contribute to disease regression (3, 4). With the immunomodulatory effects of IMiDs, it remains elusive whether patients are capable of generating spontaneous antitumor immunity. An array of early clinical studies have reported a positive correlation between lymphocyte count recovery after autologous SCT and OS, suggesting an autologous GVT effect. Many of these studies were done retrospectively and involved a wide range of diseases, including MM, B cell/T cell NHL, Hodgkin lymphoma (HL), mantle cell lymphoma, acute myeloid leukemia, metastatic breast cancer, and ovarian cancer (5). These studies found that, among the autograft immune effector cells, CD4$^+$ T cells (in MM), NK cells (in diffuse large B cell lymphoma), and cytotoxic DCs (in classical HL) are associated with better clinical outcomes. For post–autologous SCT MM patients, it was reported that a higher CD4$^+$ T cell count and an increase in the ratio of CD4$^+$ to CD8$^+$ T cells were associated with superior outcomes (6). However, mechanistic studies on the factors that mediate autologous GVT have been lacking.

Mechanisms of autologous GVT in MM

In this issue, Vuckovic et al. used the Vk*-MYC murine myeloma model to examine spontaneous T cell antimyeloma immunity in the autologous transplant setting (7). Bone marrow transplantation (BMT) with myeloma-experienced BM performed in myeloma-bearing mice induced clone-specific, T cell–dependent disease control. This effect was generated by memory T cells within the myeloma-experienced graft as well as by priming of naive T cells. Compared with the mice that received myeloma-free BM, CD8$^+$ T cells from mice that received myeloma-experienced BM had distinct T cell receptor (TCR) repertoires and greater clonotype overlap. These CD8$^+$ T cells induced antimyeloma immunity through IFN-γ secretion, which could be further enhanced by a CD137 (also known as 4-1BB) agonist and PD-1 blockade. Furthermore, Vuckovic and colleagues showed that secretion of IL-17A from donor BM directly stimulated myeloma cells through the IL-17 receptor

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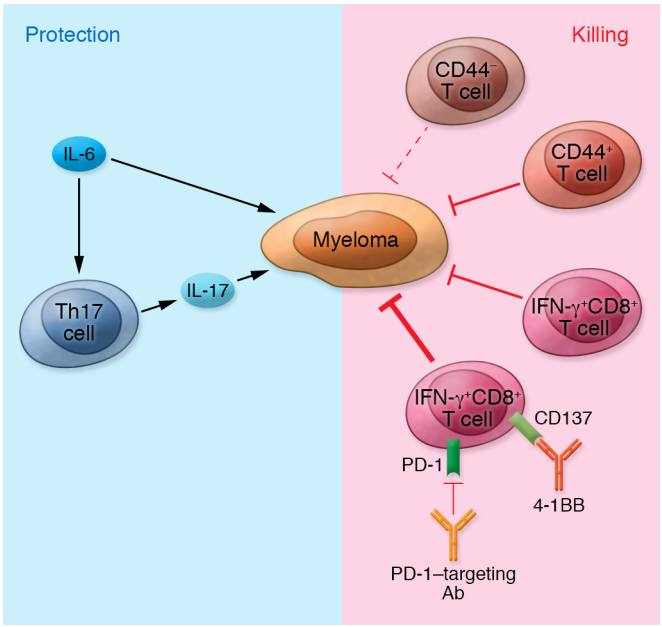

Figure 1. Autologous GVT effects are mediated by IFN-γ–expressing CD8⁺ T cells. Expansion of CD8⁺ T cells from autologous, myeloma-experienced BM promotes antimyeloma effects. Of the transplanted CD8⁺ T cell population, CD44⁺ cells are the most effective at killing myeloma cells, suggesting that antigen experience is critical for antitumor immunity. Th17 cells support myeloma cells via IL-17A secretion, though this effect is not the result of enhanced Th17 cell differentiation. The antimyeloma effects of CD8⁺ T cells are mediated by the secretion of IFN-γ, and this immunity can be enhanced by treatment with a CD137 agonist and PD-1 blockade.

to promote tumor growth and immune evasion, which was independent of Th17 cell differentiation (Figure 1).

In contrast to clinical observations, Vuckovic et al. found that CD8⁺ T cells, rather than CD4⁺ T cells or NK cells, are critical for autologous GVT (7). This observation raises the question as to whether this discrepancy is due to the murine model and/or the tumor clone used. Could this CD8⁺ T cell dependency be a specific phenomenon for the Vk*MYC model? Is it possible that specific antigens with this clone triggered a CD8⁺ T cell response? The authors emphasized that the observed antimyeloma immunity was clone specific. Had the T cells experienced a different myeloma cell clone, would the observed outcome be different? It will be worthwhile to confirm this observation in a different murine myeloma model. In addition, the authors examined the TCRβ chain diversity and clonal types. It is likely that this particular TCRβ chain profile reflects the myeloma cell clone used in the study. Is TCRβ clonality the key for the autologous GVT effect? Given the heterogeneity of human disease, are similar profiles observed in patients? What are the factors influencing the clonality? How can we incorporate this information into predicting disease control or relapse?

Vuckovic and colleagues also reported that the most effective antimyeloma CD8⁺ T cells were within the CD44⁺ subset, suggesting that antigen experience contributes to antitumor immunity (7). Mice that received myeloma-experienced CD44⁺ T cells were found to have an expansion of CD8⁺ T cells but not CD4⁺ T cells. It is not surprising that both activated DNAM-1⁺ PD-1⁺CD8⁺ T cells as well as exhausted DNAM-1⁻PD-1⁺Tim-3⁺CD8⁺ T cells were observed upon engraftment of CD44⁺ T cells. Nonetheless, it is impressive to see that, despite having an exhausted phenotype, these CD44⁺ T cells still exhibited superior antimyeloma immunity. Guillerey et al. recently reported that the exhaustion marker TIGIT was upregulated on CD8⁺ T cells during disease progression (8). This TIGIT expression was also the reason for disease relapse in autologous transplantation in the Vk*MYC mouse (9). However, Vuckovic and colleagues did not mention TIGIT in this study. Is TIGIT also expressed in the myeloma-experienced graft? What could have contributed to the differences in disease control? Paradoxically, it has been reported that human effector CD8⁺ T cells derived from naive cell subsets possess better quality for adoptive immunotherapy compared with those derived from memory cell subsets (10). Perhaps the transgenic expression of antigen receptor and forced expansion "aged" the memory T cells differently in the human setting. Nonetheless, it will be extremely intriguing to see whether the myeloma-experienced T cells from human patients also exhibit superior antimyeloma immunity.

Since Th17 cells have been suggested to induce myeloma progression through IL-17 production (11), Vuckovic and colleagues undertook the task to elucidate the role of IL-17 after autologous transplantation. In this setting, myeloma development was impaired following IL-17 neutralization, confirming the negative impact of IL-17 on disease control (7). The effect of IL-17 is probably not due to its action on the donor graft, as the study by Vuckovic et al. showed that transplantation with IL-17 receptor–deficient donor BM did not notably reduce disease burden. When both donor and recipient BM were lacking the IL-17 receptor, there was a systemic increase in IL-17 levels, which further induced the activation of multiple pathways involved in myeloma survival and immune evasion. However, the study did not rule out the possible effect of IL-17 on the recipient's BM compartment.

IFN-γ is thought to be an integral part of antitumor immunity. However, depending on the context, it can either be immune activating or immune suppressing. IFN-γ can promote antitumor immunity through direct cytotoxic effects on tumor cells, activation of macrophages, and inhibition of FoxP3⁺ Treg function (12, 13). Vuckovic and colleagues showed that IFN-γ is critical for the CD8⁺ T cells to control myeloma. On the other hand, IFN-γ has also been shown to induce PD-L1 expression on ovarian cancer cells, leading to immune eva-

sion (14). Additionally, our group recently observed that myeloma cells can produce IFN-γ, which leads to Treg expansion (15). These data again highlight the dual effects of IFN-γ in myeloma-immune microenvironment crosstalk. Nonetheless, Vuckovic et al. demonstrated that IFN-γ–producing, $CD8^+$ T cell–dependent antimyeloma immunity can be further enhanced by treatment with a CD137 agonist. The agonist produced activation and exhaustion profiles, including PD-1 upregulation, similar to those seen in mice transplanted with myeloma-experienced BM. Moreover, the addition of PD-1 blockade with the CD137 agonist further improved T cell–mediated myeloma control.

Concluding remarks

In summary, these data provide important insight into spontaneous host antimyeloma immunity and the crosstalk between myeloma cells and the T cell compartment. Although it remains to be determined whether this phenomenon can be translated to the human setting, this study suggests a possible new targeting strategy to improve post-transplantation recovery and perhaps clear minimal residual disease. Furthermore, it will be intriguing to examine whether the autologous GVT effect is myeloma specific or can also be found in other hematological malignancies.

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