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Alloreactive Cellular Strategies for Targeted Leukemia Immunotherapy Via Transient Donor Cell Engagement

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ABSTRACT

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective treatment for hematological malignancies, with graft-versus-leukemia (GVL) effects playing a crucial role in disease eradication. This article reviews the principles of cellular immunotherapy, focusing on exploiting alloreactivity to induce anti-leukemic responses while minimizing prolonged donor cell persistence and associated graft-versus-host disease (GVHD). We discuss the mechanisms of alloreactivity, the clinical evidence supporting this approach, and future directions for optimizing cellular immunotherapy strategies.

KEYWORDS

Allogeneic hematopoietic stem cell transplantation (allo-HSCT), graft-versus-host disease (GVHD).

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative therapy for various hematological malignancies. The success of allo-HSCT relies on the graft-versus-leukemia (GVL) effect, where donor-derived immune cells recognize and eliminate recipient leukemic cells (3, 4). This alloreactive response, however, is frequently accompanied by graft-versus-host disease (GVHD), a major cause of morbidity and mortality following allo-HSCT (1, 2).

GVHD occurs when donor T cells recognize recipient tissues as foreign, leading to an inflammatory response that can damage multiple organs. Strategies to enhance GVL while minimizing GVHD have been a central focus of research in this field. One approach involves exploiting the transient nature of donor cell alloreactivity to induce potent anti-leukemic effects without the need for long-term donor cell persistence. This review explores

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the scientific basis and clinical potential of this approach.

METHODS

A comprehensive literature search was conducted using PubMed, Embase, and other relevant databases. The search strategy focused on studies investigating the mechanisms of alloreactivity in the context of allo-HSCT, the role of donor T cells and NK cells, and clinical trials evaluating cellular immunotherapy approaches that aim to enhance GVL while minimizing GVHD. Search terms included "allogeneic hematopoietic stem cell transplantation," "graft-versus-leukemia," "graft-versus-host disease," "alloreactivity," "donor lymphocyte infusion," and "cellular immunotherapy." Studies published in English were included, with a focus on original research articles, clinical trials, and reviews.

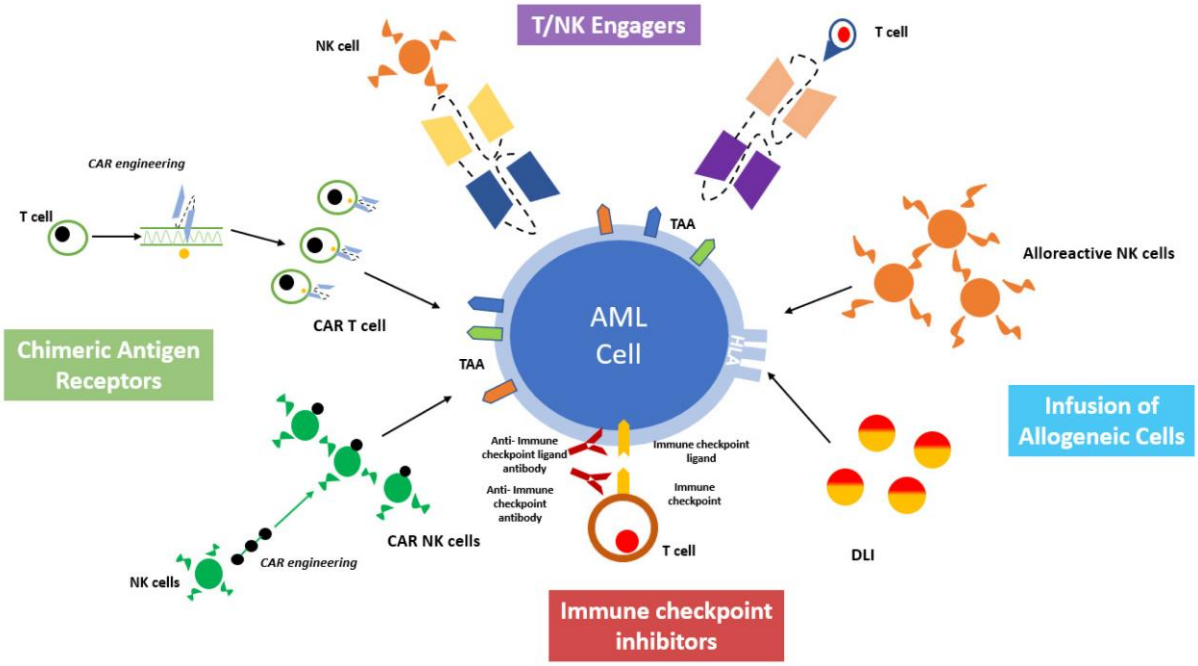

Fig. Harnessing Immune Response in Acute Myeloid Leukemia

RESULTS

Mechanisms of Alloreactivity and GVL

Allorecognition, the process by which donor T cells recognize recipient cells as foreign, is a key driver of GVL. This recognition is primarily mediated by the interaction of donor T cell receptors (TCRs) with recipient human leukocyte antigen (HLA) molecules presenting allogeneic peptides (1). Donor T cells can directly kill leukemic cells through the release of cytotoxic molecules such as perforin and granzymes. The anti-leukemic effect of donor lymphocyte infusions (DLIs) has been demonstrated in numerous studies (5).

In addition to T cells, natural killer (NK) cells also play a role in GVL. Donor NK cells can recognize and eliminate recipient leukemic cells that have lost HLA expression, a common immune evasion mechanism in cancer (26,

27). The balance between activating and inhibitory signals regulates NK cell activity, and donor NK cell alloreactivity can be harnessed to enhance GVL (28, 29, 30, 31).

Transient Alloreactivity and GVL without Donor Cell Persistence

Several lines of evidence suggest that potent GVL effects can be achieved without prolonged persistence of donor cells. Studies have shown that donor cell elimination by recipient immune cells can still result in sustained anti-leukemic responses (6, 7, 8). This phenomenon highlights the importance of the initial alloreactive trigger in inducing long-term disease control.

The mechanisms underlying this transient alloreactivity include:

- Alloantigen-presenting cells: Recipient antigen-presenting cells (APCs) can present donor-derived alloantigens to recipient T cells, leading to the activation of recipient T cells that contribute to the anti-tumor response (7, 8).
- Cytokine-mediated effects: Donor T cells can release cytokines, such as interferon-gamma (IFN-γ), that promote anti-leukemic activity and modulate the recipient immune environment (9, 10).
- Cross-reactive T-cell responses: Alloreactive T cells can cross-react with tumor-associated antigens, leading to the elimination of leukemic cells (18, 19).
- Innate immune activation: Donor immune cells can activate recipient innate immune cells, such as NK cells and macrophages, which can contribute to the anti-leukemic response (30, 31).
- MHC-CD8 engagement: T-cells can kill B cell malignancies in a TCR-independent manner through MHC-CD8 engagement. (21, 22)

Clinical Evidence

Clinical studies have demonstrated the feasibility and efficacy of cellular immunotherapy approaches that exploit transient alloreactivity. For example, some studies have shown that infusion of HLA-mismatched donor cells, which are rapidly eliminated by the recipient, can induce significant anti-leukemic responses in patients with refractory hematological malignancies (12, 13, 14). These responses can occur even in the absence of sustained donor cell engraftment, suggesting that the initial alloreactive trigger is sufficient to induce long-term disease control. Additionally, recipient leukocyte infusions following nonmyeloablative allogeneic hematopoietic cell transplantation have shown clinical relevance as an anti-tumor therapy. (10)

DISCUSSION

Cellular immunotherapy strategies that harness transient alloreactivity offer a promising approach to enhance GVL while minimizing GVHD. By carefully modulating the alloreactive response, it may be possible to achieve durable remissions without the need for prolonged donor cell persistence. Several factors can influence the efficacy of this approach, including the dose and timing of donor cell infusion, the degree of HLA mismatch, and the conditioning regimen used prior to transplantation. Additionally, the presence of regulatory T cells (Tregs) in patients with acute myeloid leukemia has been associated with poor prognosis. (42, 43, 44)

Emerging strategies to further optimize cellular immunotherapy include:

- Targeting specific immune checkpoints: Blocking inhibitory signals, such as PD-1 and CTLA-4, can enhance T cell activation and anti-leukemic activity (34, 35).

- CD40 ligation: CD40 ligation can reverse T cell tolerance in acute myeloid leukemia. (38)
- Adoptive transfer of genetically modified T cells: Engineering T cells to express chimeric antigen receptors (CARs) or modified TCRs can enhance their specificity and anti-leukemic activity (45, 46).
- Combination therapies: Combining cellular immunotherapy with other anti-cancer agents, such as targeted therapies or immune checkpoint inhibitors, may further improve outcomes (50, 51).
- Depleting tumor-specific Tregs: Depleting tumor-specific Tregs at a single site eradicates disseminated tumors. (52)
- HLA-DP-specific CD4+ T cells: Patient HLA-DP-specific CD4+ T cells from HLA-DPB1-mismatched donor lymphocyte infusion can induce graft-versus-leukemia reactivity in the presence or absence of graft-versus-host disease. (53)
- MHC class II upregulation: HLA class II upregulation during viral infection leads to HLA-DP-directed graft-versus-host disease after CD4+ donor lymphocyte infusion. (54)
- CD4+ T cells with cytotoxic potential: Cytokine-Dependent Induction of CD4+ T cells with Cytotoxic Potential during Influenza Virus Infection. (57)

CONCLUSIONS

Cellular immunotherapy holds great promise for the treatment of hematological malignancies. Harnessing the power of alloreactivity while mitigating the risk of GVHD remains a central challenge. Strategies that exploit transient donor cell activity to induce sustained anti-leukemic responses offer a promising avenue for future research and clinical application. Further studies are needed to identify the optimal approaches for different patient populations and disease subtypes.

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