Review Article

Stem Cell INVESTIGATION

Evaluation of TCR repertoire diversity in patients after hematopoietic stem cell transplantation

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Abstract: T-cell receptor (TCR) repertoire analyses have been widely used to identify T cell populations of interest in cancer and autoimmunity and for characterizing immune repertoire reconstitution after hematopoietic stem cell transplantation (HSCT). Several decades of development and progress have led to the use of techniques for evaluating TCR repertoires in a more comprehensive, unbiased and fast manner, and the mechanisms of T cell immune reconstitution after HSCT and the new approaches used for recovering T cell repertoire diversity post HSCT have been more exhaustively documented to some degree. To better understand and characterize this progress, here we review recent studies on TCR repertoire diversity recovery in patients with leukemia and autoimmune disease who have received HSCT, impact factors and improvements in approaches for TCR repertoire recovery after HSCT.

Keywords: Hematopoietic stem cell transplantation (HSCT); T cell receptor (TCR) repertoire diversity; immune reconstitution

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Introduction

Hematopoietic stem cell transplantation (HSCT), including allogeneic HSCT and autologous HSCT, is performed to treat a broad spectrum of illnesses. Favorable outcome for HSCT depends on either complete hematopoietic or immune reconstitution. Moreover, immune reconstitution is one of the primary factors that determines long-term prognosis following transplantation, particularly T cell immune reconstitution, which is important for disease relapse and virus infection. While the recovery of peripheral T cells occurs in transplant recipients via thymus-dependent and thymus-independent pathways, the regeneration of a population of phenotypically naive T cells with a broad T cell antigen receptor (TCR) repertoire relies entirely on the de novo generation of T cells in the thymus (1), however, early T cell reconstitution also depends on the persistence and function of T cells that are adoptively transferred with grafts (2,3). Therefore, dynamic analysis of the TCR repertoires of T cells in patients after HSCT is important for estimating the immune reconstitution in different clinical situations.

The T cell receptor and its diversity

The TCR includes the α, β, γ and δ chains, which form α/β or γ/δ heterodimeric chains that are expressed on mature T cell surfaces. TCRs are specific for antigen recognition in conjunction with major histocompatibility complex (MHC) molecules, leading to T cell activation and proliferation. Each TCR chain, similar to the immunoglobulin (Ig) heavy and light chains, is encoded by multiple gene segments. The variable domains of TCRs are assembled by the somatic recombination of one variable (V), diversity (D, only for β

or δ chain), and joining (J) segment each, and they comprise three hypervariable or complementarity-determining regions (CDR1, CDR2, CDR3) within the TCR. CDR3 is involved in the response to specific interactions with antigenic peptides. For example, in the TCR β chain, nucleotide transferases add or remove nucleotides at various Vβ-Dβ and Dβ-Jβ junctions during the recombination process, and the CDR3 region of the Vβ-Jβ combination may vary in length by as many as 6-8 amino acids (4). The mechanisms of such recombinations are mediated by a recombinase that recognizes recombination signal sequences (RSSs) and brings the exons together. Overall, such a TCR rearrangement makes up 10^{16} to 10^{18} diverse TCR repertoires.

Therefore, analysis of TCR repertoires could provide a global picture of the distribution and clonal expansion of TCR subfamilies in patients and normal individuals. This type of evaluation can help to characterize the features of the host T cell immune status and identify T cell populations of interest in cancer and peripheral immune reconstitution after HSCT (5-7).

Recovery of diversity of TCR repertoire in patients after HSCT

Since the early 1990s when the TCR repertoire analysis technique of using polymerase chain reaction (PCR)-based CDR 3 size spectratyping and DNA sequencing, or PCR-Genescan, was established, TCR repertoire analysis has been used to evaluate the recovery of immune repertoires after HSCT. Until now, TCR repertoire diversity analysis has been a common method for characterizing immune reconstitution after HSCT and analyzing the oligoclonal expansion of T cells during virus infection, graft-versus-leukemia (GVL) effects, and graft-versus-host disease (GVHD). In addition, this effective technique has been used to compare quantifications of TCR repertoire recovery between different types of HSCTs, such as allogeneic or autologous HSCT, cord blood (CB) or peripheral blood (PB) HSCT, unrelated donor (UD) or related donor HSCT, haploidentical HSCT (haplo-HSCT), and T-cell-depleted (TCD) HSCT (8-14).

Significant immune renewal example data have come from comparisons of TCR repertoires in patients with severe combined immunodeficiency (SCID) before and after HSCT. At one month after transplantation, there was progressive improvement in TCR Vβ repertoire diversity in all cases (15). A study by Wu *et al*. used an 8-point scoring system for each Vβ subfamily to quantify TCR repertoire changes over time and showed that, in contrast with 10 normal donors who display highly diverse and polyclonal spectratypes, the mean complexity score for patient samples with chronic myelogenous leukemia (CML) before and early after TCD allogeneic bone marrow transplantation (BMT) (3 months) was significantly lower. These data revealed markedly skewed repertoires consisting of absent, monoclonal, or oligoclonal profiles for the majority of Vβ subfamilies in all patient samples. Normalization of the repertoires began in patients at 6 months after BMT, but the majority of the patients continued to display abnormal repertoires up to 3 years after BMT (16).

Data from a prospective comparison of the immune reconstitutions of pediatric recipients of positively selected $CD34^+$ peripheral blood stem cells from unrelated donors (UD) *vs*. recipients of unmanipulated bone marrow from matched sibling donors (MSD) indicated delayed early memory-type T cell recovery with reduced TCR diversity in the UD-HSCT group, and T cell reconstitution occurred greater than 100 days after for the UD-HSCT compared with MSD-BMT group. After UD-HSCT, the TCR repertoire becomes severely skewed and demonstrates significantly reduced diversity during the first year, but only minor abnormalities are observed after MSD-BMT. TCR diversity simultaneously increases with the number of naive T cells. In both of the groups, transient expansion of γδ T cells was observed (11). During the first year after transplantation, TCR repertoires are highly abnormal. Notably, two years after transplantation onward, TCR diversity was higher in CB recipients than bone marrow transplant recipients. These data indicate an efficient thymic regeneration pathway for CB lymphoid progenitors despite a low number of cells infused compared with that for bone marrow, suggesting complete clinical immune recovery after CB HSCT (14). In pediatric recipients of T cell depleted highly purified, $CD34^+$ haploidentical HSCT during the first post-transplant year, early reconstituting T cells had a predominantly primed, activated phenotype with a severely skewed TCR repertoire complexity. Naive T cells emerged 6 months post transplantation paralleled with an increase in TCR repertoire diversity (10). Overall, broad T cell repertoire diversity in recipients indicates favorable long-term immune reconstitution after HSCT. Delayed T cell recovery and restricted TCR diversity after HSCT are associated with increased risks of infection and leukemia relapse after HSCT (17). In contrast, higher TCR diversity early after transplantation possibly implies lower risk for both

GVHD and relapse following HSCT transplantation (18).

Previously, TCR repertoire diversity evaluations were based on analysis of the TCR Vβ repertoire, which represents the diversity of the TCRαβ$^+$ T cell repertoire and occupies greater than 90% of the T cells in blood (5,7,8,19). Recently, it has been demonstrated that TCRγδ repertoire reconstitution is an important marker post HSCT (20,21), and TCRγδ$^+$ T cells are effective antiviruses and GVLs after HSCT (22,23). In addition, the samples for TCR repertoire analysis are, in order, peripheral blood mononuclear cells, CD3$^+$ cells, CD4$^+$ cells, CD8$^+$ cells, CD45RA$^+$ cells, CD45RO$^+$ cells, CD45RO$^+$HLA-DR$^+$ cells, and Treg cells, thereby providing differences in TCR diversity in different T cell subsets and characterizing their significance and contribution to immune reconstitution after HSCT (9,11,13,24).

TCR repertoire analysis using the traditional PCR-Genescan technique may also provide stable and comparable data for the clinic. In addition, TCR repertoire diversity analysis has increased utilization; however, little is known about the minimum number of sequences necessary for accurately and efficiently describing the composition of the TCR repertoire in patients after HSCT. Data from Packer *et al*. has reported that by analyzing 75 to 100 in-frame sequences, they were able to estimate the TCR diversity within 5.0% to 7.4% of the values obtained in endpoint analysis (213-312 sequences per sample) in patients with multiple sclerosis (MS) who underwent autologous HSCT (12). Moreover, technical challenges have also limited the faithful measurement of TCR diversity after HSCT, and novel approaches, such as TCRβ-based oligonucleotide microarrays, have also been reported and confirmed their specificity, clonal discrimination, sensitivity of detection, and feasibility for monitoring T cell population diversity in patients with HSCT (8). Recently, novel techniques such as 5' rapid amplification of complementary DNA ends PCR combined with deep sequencing and high-throughput TCR sequencing (TCR-seq) using next generation sequencing platforms were used to quantify TCR diversity, enabling quantification of T cell diversity at unprecedented resolution (13,18,25). TCR-seq studies have provided new insight into the healthy human T cell repertoire, such as revised estimates of repertoire size and the understanding that TCR specificities are more frequently shared among individuals than previously anticipated (25). For example, the use of this technique was capable of accurately comparing the frequency of individual TCRs between patients after CB or T cell-depleted PB HSCT. After 6 months, CB-graft recipients had approximately the same TCR diversity as healthy individuals, whereas recipients of T cell-depleted PB stem cell grafts had 28- and 14-fold lower CD4$^+$ and CD8$^+$ T cell diversities, respectively. After 12 months, these deficiencies improved for the CD4$^+$ but not the CD8$^+$ T cell compartment (13). This method improves the global view of T cell repertoire recovery after allo-HSCT and may identify patients at high risk for infection or relapse.

TCR repertoire reconstitution in patients with autoimmune diseases after autologous HSCT

Autologous HSCT is commonly employed for hematologic and non-hematologic malignancies and autoimmune diseases. Clinical trials have indicated that immunoablation followed by autologous HSCT has the potential to induce clinical remission in patients with refractory systemic lupus erythematosus (SLE) (26). There are numerous reports showing that children with systemic juvenile idiopathic arthritis (sJIA) and patients with SLE, severe MS and poor-prognosis MS have been successfully controlled by autologous HSCT (24,26-29). The characteristics of the recovery of TCR diversity is similar to that for leukemia patients, and the T cell repertoire is skewed before and until one year after HSCT in MS patients with shared expansions before and after a transplant in a given individual (27,28). Significantly, TCR repertoire reconstitution could be followed up for long time after HSCT in these patients. For example, at the time of follow up (mean: 11.5 years), four patients with sJIA remained in complete remission, the CD8$^+$ TCR Vβ repertoire was highly oligoclonal early during immune reconstitution, and the re-emergence of pre-transplant TCR Vβ CDR3 dominant peaks was observed after transplantation in certain TCR Vβ families. Furthermore, the re-emergence of pre-ASCT clonal sequences in addition to new sequences was identified after transplantation (29). In a phase II study of HSCT for poor-prognosis MS, high-throughput deep TCRβ chain sequencing was used to assess millions of individual TCRs per patient sample, and it was demonstrated that HSCT has distinctive effects on CD4$^+$ and CD8$^+$ T cell repertoires. In CD4$^+$ T cells, dominant TCR clones present before treatment were undetectable following reconstitution and patients largely developed new repertoires, while dominant CD8$^+$ T cell clones were not effectively removed, and the reconstituted CD8$^+$ T cell repertoire was created by clonal expansion of the cells present before treatment.

Importantly, patients who failed to respond to treatment had less diversity in their T cell repertoires early during the reconstitution process (24). Therefore, accurate TCR characterization in different T cell subsets may enable the monitoring of pathogenic or protective T cell clones following HSCT and cellular therapies.

Factors that impact TCR repertoire reconstitution after HSCT

It is well known that delayed T cell immune reconstitution after HSCT may increase risks for infection and leukemia relapse (17). In allo-HSCT, T cell differentiation of donor progenitors within a recipient thymus is required to generate naive recent T cell emigrants (RTEs). These cells account for durable T cell reconstitution, generate a diverse TCR repertoire and robust response to infections (30). The factors that impact delayed T cell repertoire reconstitution may be associated with the type of HSCT, the transplant regimen, the composition of grafts (e.g., T cell depletion and Treg addition), and the incidence and degree of GVHD (10,11,14,31,32). For example, adoptive transfer of Tregs with HSCT leads an accelerated diversity of TCR Vβ repertoire donor lymphoid reconstitution by preventing GVHD induced damage in the thymic and secondary lymphoid microenvironment (33). Moreover, assessment of the host immune status has become a key issue in allogeneic HSCT. In long-term follow-up of patients, pre-transplant recipient thymic function correlates with clinical outcome in terms of survival and the occurrence of severe infections due to persistent immune defects (30). Data reported by Wu *et al*. also indicated that reconstitution of a normal T cell repertoire from T cell progenitors in adults is influenced by interactions between recipient and donor hematopoietic cells because complete donor hematopoiesis after HSCT strongly correlates with the restoration likelihood of the T cell repertoire complexity (16).

In contrast, the persistence and function of T cells that have been transferred with grafts also greatly contribute to peripheral reconstitution. Recently, T memory stem cells (TSCMs), which have demonstrated superior reconstitution capacity in preclinical models, have been proven *in vivo* and at the antigen-specific and clonal level to directly differentiate from naive precursors infused within grafts and contribute to peripheral reconstitution by differentiating into effectors in the early days following haploidentical transplantation combined with posttransplant cyclophosphamide (PT-Cy) (2,3). Thus, the abundance of naive T cells (TN) or TSCMs in grafts may influence the outcome of patients after HSCT.

Improvement in TCR repertoire recovery after HSCT

The thymus is crucial for reconstituting the T cell compartment following lymphodepletion by HSCT and establishing a normal, diverse TCR repertoire after immune responses to antigens. Thus, enhancing the thymic output function is one approach for improving the recovery of the TCR repertoire after HSCT, and cytokines that have been demonstrated to improve thymic function, such as IL-7 and IL-15, may be used (34-36). In addition, both keratinocyte growth factor (KGF) and sex steroid ablation (SSA) have shown promising effects in the improvement of thymic regeneration (37-41). Moreover, it has been demonstrated that G-CSF administration leads to higher $CD4^+$ TCRβ diversity in donor T cells, and this is associated with lower reactivation of cytomegalovirus and Epstein-Barr virus after HSCT (42).

In contrast, donor lymphocyte infusion (DLI), particularly adoptive T cell transfer, is a direct approach for rapidly improving T cell immune function after HSCT to overcome virus infections and disease relapse (43,44). DLIs have been demonstrated to induce clinical responses in patients with relapsed CML and those with other relapsed hematologic malignancies after allogeneic HSCT, and the response and conversion to complete donor hematopoiesis in patients after DLI has been associated with the normalization of TCR complexity (45). The outcome of patients with high-risk/advanced-stage hematologic malignancies who received TCD haplo-HSCT combined with donor T lymphocytes pretreated with IL-10 has been recently reported (ALT-TEN trial). This study has indicated that IL-10-anergized donor T cells (IL-10-DLI) contain T regulatory type 1 (Tr1) cells specific for host alloantigens, limiting donor *vs*. host reactivity, and memory T cells capable of responding to pathogens. After the infusion of IL-10-DLI in 12 patients after haplo-HSCT, fast immune reconstitution with a progressively normalized TCR Vβ repertoire and T-cell function was detected in patients (46).

Conclusions and future perspectives

Evidence from over 25 years of TCR repertoire characterization indicates that it is a feasible and informative immune biomarker for evaluating the global T cell immune

status and monitoring pathogenic or protective T cell clones following HSCT and cellular therapies; however, little is known about whether it is befitting when patients recover completely normalized TCR repertoires after HSCT or whether it is necessary to confirm that it should contain particular antigen-specific clonally expanded T cells directed against leukemia and viruses in patients after HSCT based on the normalized TCR repertoire background. A number of studies have indicated that lower antigen-specific clonally expanded T cells e.g., WT1+ CTL, are associated with disease relapse in patients after HSCT (47-49). Therefore, evaluation of the TCR diversity may also be combined to characterize and quantitate the leukemia- and virus-specific TCR repertoires to maximize the prediction value of immune reconstitution in patients after HSCT. Moreover, recent years, resident memory $CD8^+$ T cells (T_{RM}) were described to be an important role in immune surveillance (50-52), whether the local T_{RM} display specific TCR repertoire, and whether they have any contribution to evaluation for the immunity in patients after HSCT, it may be interesting for further investigation.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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