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Precision in donor selection: identifying ideal stem-cell donors through their T-cells

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Introduction

HLA-identical siblings have always been considered ideal donors for allogeneic hematopoietic stem-cell transplantation (alloHSCT) in the treatment of hematologic cancers. Recent data suggest that we should rethink this paradigm. In “High Graft CD8+ Cell Dose Predicts Improved Survival and Enables Better Donor Selection in Allogeneic Stem-Cell Transplantation With Reduced-Intensity Conditioning”,[1] we identify a group of stem-cell donors whose grafts contain an optimal composition of T-cells, leading to a dramatic decrease in disease relapse risk and improved overall survival following alloHSCT. To demonstrate this, we analyzed the outcomes of 200 patients with hematologic malignancies who underwent alloHSCT after reduced-intensity conditioning (RIC). The analysis focused on T-cell content of peripheral blood stem-cell grafts. We found that higher graft CD8+ T-cell dose (CD8hi), a trait found only in grafts collected from young donors, was associated with improved survival due to a reduction in the risk for cancer relapse without a significant increase in graft-versus-host disease (GVHD). Though not all young donors mobilized CD8hi grafts, we found that a low CD4:CD8 ratio in the peripheral blood could identify these ideal donors prior to transplant. The likelihood of finding CD8hi donors correlated inversely with age, and elderly RIC transplant recipients had a low chance of receiving an ideal graft from their similarly aged siblings. Here, we examine these findings and their implications on choosing donors according to age and relatedness. We also explore biological mechanisms that determine the CD4:CD8 ratio in healthy donors.

Graft Content and Transplant Outcomes

We found that the graft T-cell dose had a drastic impact on the outcomes of RIC transplants[1]. The importance of an adequate CD8+ T cell dose in alloHSCT has been previously demonstrated in smaller cohorts[2,3]. In our study, grafts had significant heterogeneity in T-

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cell content with greater than a log difference in T-cell numbers between smaller and larger grafts. CD8+ T-cell dose correlated inversely with donor age, while CD4+ dose did not. While only 13% of donors older than age 50 produced CD8hi grafts, approximately 40% of donors younger than age 50 produced such grafts. Importantly, CD8+ T-cell dose was an independent predictor of disease relapse, and a high CD8+ T-cell dose was associated with more rapid T-cell engraftment, but not with higher rates of GVHD or non-relapse mortality. Patients who received CD8hi grafts also saw improved overall and relapse free survival, despite the inclusion of many single-allele mismatched donors in this group.

Donor age alone was not a sufficient predictor of the CD8+ T-cell dose and the outcomes of patients transplanted from young vs. old donors were not different if the CD8+ T cell dose was not taken into account. RIC alloHSCT recipients had improved overall survival when they received CD8hi grafts from younger donors, but not if they received CD8lo grafts from other donors, young or old.

Donor age and relatedness in alloHSCT

Our findings appear to identify donor age as a key contributor to RIC alloHSCT outcomes. The impact of donor age on transplant outcomes has been extensively explored. Kollman et al. studied almost 7,000 unrelated bone marrow transplants and found that donor age inversely correlated with overall and disease-free survival[4]. Different rates of acute and chronic GVHD, but not of disease relapse, drove this association. In contrast, Rezvani et al. found no significant difference in non-relapse mortality between donors aged greater than 60 years and younger donors, though only 8% of donors were older than age 60 in their study[5]. They found that grafts from older siblings produced less acute GVHD than grafts from young, unrelated donors, but relapse rates or survival were not reported.

Alousi et al. conducted the largest contemporary study that compared older siblings with younger unrelated donors. They analyzed a heterogeneous cohort of 2172 transplant procedures registered in CIBMTR in patients over age 50. In a subset of patients with good performance scores, grafts from older sibling donors led to a survival advantage driven by lower rates of relapse and non-relapse mortality[6]. Outcomes were similar for both donor types in patients with lower performance scores.

What appear to be discordant results between these studies most likely stems from differences in disease mix, graft source and conditioning regimens that were used in the studied cohorts, making their conclusions difficult to apply to clinical practice.

In our study, only young donors produced CD8hi grafts, but donor age alone was not associated with improved outcomes. Myelodysplastic syndrome (MDS) is the only disease where we were able to demonstrate an independent effect of donor age and relatedness regardless of CD8+ T-cell dose.[7] The reason is that MDS affects older individuals, where because of a vast age gap between sibling donors and unrelated donors, an advantage for young unrelated donors appeared to be independent of other factors.

Aging impacts stem cell function and T-cell properties

Age-related variables that may affect alloHSCT outcomes include differences in the phenotype and function of hematopoietic stem-cells (HSC) and T-cells.

Human HSC increase in frequency with age, become less quiescent, and exhibit more myeloid-biased differentiation potential[8]. Aged HSC transcriptionally up-regulate genes associated with the cell cycle and myeloid lineage specification. This bias towards myeloid differentiation may lead to slower recovery of the lymphoid compartment, slower immunologic reconstitution and functionally different mature T cells that arise from aged HSC. Although not well characterized, these differences may have an impact on the graft-versus-host and graft-versus-leukemia (GVL) responses that determine alloHSCT outcomes. CD8+ T-cells undergo age-related changes in phenotype, function and compartmentalization that affect the type and number of T-cells in stem-cell grafts that are harvested from peripheral blood. Memory T cells are a minority of circulating CD8+ T cells at any age, but the proportion between effector and naïve T-cells varies significantly with age[9]. Thome et al. examined the spatial regulation of human T cells throughout life[10], and found that Naïve CD8+ T cells localize to blood and lymphoid tissue and the proportion of naïve CD8+ T cells decreases with age, while effector and memory CD8+ T cells increase. These changes are likely the result of increased antigen exposure over time. It is therefore possible that CD8hi grafts from younger donors contain a higher number of naïve CD8+ T cells that are responsible for a potent GVL effect.

Though they did not examine donor age directly, Beatty et al. found that following alloHSCT, leukemia antigen-specific CD8+ T cells can become functionally unresponsive due to replicative senescence and telomere shortening[11]. Older donors therefore create a theoretical disadvantage because of similar age-related senescence that limits their expansion and may impair their ability to mount a GVL response. Donor telomere length has also been examined in alloHSCT for aplastic anemia, a non-malignant disorder, and was found to be associated with outcomes[12].

Role of Donor CD4:CD8 Ratio

Our findings suggest that the donor CD4:CD8 ratio indicates the potency of the GVL response. Therefore it is critical to understand what factors are responsible for the variability in this ratio among normal donors. These factors may play an important role in alloHSCT and also in adoptive cell therapy such as chimeric antigen receptor T-cells and other forms of cancer immunotherapy.

Prior studies have shown a hereditary component to the CD4:CD8 ratio, possibly determined by a major recessive gene with a polygenetic component[13]. However, genome wide association studies (GWAS) did not identify such a gene, but instead suggest that CD4+ and CD8+ populations are regulated through independent quantitative trait loci[14]. These loci explain only 8% of the variability in the CD4:CD8 ratio, limiting our ability to draw much from this evidence.

Environmental contributors to the CD4:CD8 ratio are also not easy to determine, but viral infection is an obvious culprit because CD8+ T cells proliferate rapidly during viral infection. Tripp et al. noted that in mice, CD8+ T cells are normally present in the spleen and lymph nodes in lower numbers than CD4+ T cells, but during viral infections they expand to outnumber CD4+ T cells[15]. This expansion, while likely multifactorial, can at least be partially traced to circulating interleukins, primarily IL-7[16–17]. Cytokine effects can cause CD8+ T cells to proliferate up to 12-fold and can change the CD4:CD8 ratio within days. The length of time the CD4:CD8 ratio would remain altered following a viral infection is largely unknown, and the kinetics of this immune activation are likely virus-specific. In our study, CMV serostatus was not associated with the CD4:CD8 ratio. The CMV serostatus, however, reflects past exposure to the virus, and is not reflective of active viral proliferation, which could be more critical to CD8+ proliferation. To complicate things further, the magnitude of CD8+ proliferation in response to viral infection may also depend on polymorphisms in interleukin receptors and other host factors.

Graft Content and Donor Selection

How should we apply these findings clinically? First, the protective effect of CD8hi grafts against relapse appears to be specific to transplants performed with RIC, where disease relapse rates of 30–50% have been described[18]. In myeloablative transplants, Cao et al. found that the dose of T cells or their major subsets did not affect outcomes[19]. Waller et al. reported similar negative findings for the Blood and Marrow Transplant Clinical Trials Network[20]. This lack of association between T-cell doses and outcome may be because the GVL response plays only a partial role in myeloablative transplants, whereas RIC transplants rely solely on the GVL response to cure malignancy. In addition, studies of myeloablative transplants generally enroll patients up to an upper age limit of 50 or 60 years, and therefore their donors tend to be young. Additional factors such as sample size and disease mix may have concealed the effect of T-cell graft content on myeloablative transplant outcomes.

Second, an easy and feasible way to identify ideal donors should be determined. The changes in hematopoiesis and T-cell phenotype that result in drastic differences in graft content are age-related, but donor age alone is not a sufficient predictor of outcomes. A more direct way to improve donor selection would be to screen donors for their potential to mobilize grafts with high CD8+ T cell content, which could lead to significant improvements in RIC transplant outcomes. We examined 21 alloHSCT donors to evaluate traits in the peripheral blood that could predict high CD8+ graft dose. Donors with a higher proportion of CD8+ cells or low CD4:CD8 ratio in the peripheral blood mobilized grafts with higher CD8+ cell doses[1].

Taken together, our findings suggest that ideal alloHSCT donors can be identified through T-cell characteristics, mainly their CD4:CD8 ratio. There are myriad contributors – from genetic predisposition to environmental factors – to a donor's CD4:CD8 T-cell ratio, and it remains to be determined how this ratio affects the anti-tumor response in the recipient. Methods to identify these ideal donors must be prospectively examined.

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