The optimal donor profile in the era of next generation sequencing?

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Introduction

Major improvements in the results after allogeneic HSCT were driven by deeper insights into the immunology of stem cell transplantation and more sophisticated donor selection. Still, the failure rate after allogeneic HSCT is relatively high due to relapse or non-relapse mortality. Additional immunogenetic donor selection criteria that would increase the success rates are desperately needed. Currently, matching for HLA-A, -B, -C, DRB1 and DQB1 at the allele level is still considered the gold standard for immunogenetic donor selection.

Donor selection is key to transplantation success

Historically, donor selection for HSCT was based on HLA-A, B, DR serology matching. Meanwhile, knowledge and technology have evolved and matching for HLA-A, B, C, DRB1 and DQB1 at high resolution (ARD) is regarded as gold standard2. However, GvHD remains a serious risk for transplantation success and many retrospective studies have indicated beneficial effects of considering additional factors for donor selection: DPB13, KIR4–6, MICA7, HLA-E8.


NGS delivers extended profiles at minimal costs

The application of next generation sequencing (NGS) has considerably decreased costs for high-throughput genotyping. In addition, it opens up completely new opportunities mainly because, in contrast to Sanger, the addition of other genetic loci increases total costs only minimally. On the other hand, the reotyping of large numbers of samples at a later time point would require significant investments.

Results and Conclusion

We propose applying a forward-looking profile for genotyping potential stem cell donors. This profile includes several factors that have been reported to improve donor selection but are currently not considered in clinical practice. In particular, besides the 6 HLA genes [A, B, C, DRB1, DQB1 and DPB1], the complete KIR gene family at allelic level resolution, blood groups ABO and Rh, CCR5, MICA/B and HLA-E. Until now we have already generated genotyping data on KIR for 2.9 million donor samples including 1.4 million at allelic resolution and on MICA/B and HLA-E for 600,000 samples. We anticipate that in the next years independent studies will confirm at least some of the candidate genes as relevant parameters for donor selection. By incorporating these factors into the genotyping profile now, several million donors will be available in a few years and will then facilitate quick implementation of those additional criteria thereby improving the outcomes of patients after matched unrelated donor HSCT.

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