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*Letter*

# The CREG Public Epitope Donor Database May Serve as a Convenient Method for Rapidly Identifying HLA-Matched Platelet Donors

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Dear Editor,

Addressing the issue of platelet transfusion refractoriness (PTR) is a major concern for the global medical community. The incidence of PTR in patients with hematological diseases is 5% to 14% [1,2]. For patients who frequently undergo platelet transfusions, PTR presents a more serious challenge, as 30% to 70% of these patients do not effectively respond to randomized donor platelet (RDP) transfusions [3,4]. PTR is caused by a combination of factors, with 80% attributed to non-immunological reasons and 20% to immunological reasons [5]. Anti-HLA antibodies and anti-HPA antibodies are key contributors to immune-related PTR. The coping strategies mainly include selecting platelet donors with HLA matching for transfusion, whose HLA antigens are negative and match the detected anti HLA antibodies, or selecting platelets with cross-matching negative for transfusion. However, implementing these strategies requires a large pool of HLA-typed donors, and even then, achieving a complete match for all patients, especially those who are highly immunized or have rare haplotypes, remains challenging. Additionally, these methods are both time-consuming and expensive. Consequently, finding an alternative approach for HLA antigen matching has become a significant research focus in recent years.

The application of DNA typing technology has enabled the identification of polymorphic regions in HLA molecules, allowing for the detection of numerous public and private HLA epitopes. A private epitope is unique to a single HLA gene product, whereas a public epitope is shared among multiple HLA gene products. These human leukocyte antigens, which have similar structures and share common HLA epitopes, are called cross-reactive groups (CREG). HLA-A and HLA-B antigens in the 10 major CRRG are A1C, A2, A10C, BW4, B5C, B5C2, BW6, B7C, B8C, and B12C. An evaluation of more than 50 000 serum samples from immunized individuals revealed that 96% of the definable antibodies reacted with 12 CREG [6]. The benefit of CREG matching on graft survival is due to the underlying matching between HLA-A and HLA-B loci [6].

This advancement has led to the development of numerous strategies for evaluating HLA compatibility at the molecular or epitope level. Kallon et al. found that HLA-A and HLA-B epitope matching is equivalent to HLA antigen matching in raising platelet counts. HLA epitope-matched platelet provision may represent a clinically effective transfusion strategy for patients immunologically refractory (IR) to random platelet transfusions [7]. Knowledge of the restricted HLA antibody and epitope specificity could enable a more cost-effective future approach to specific epitope avoidance without the alternative approach of further increasing the size of a platelet donor pool [8]. Marsh et al.'s research addressed an important question and significantly advanced development of this field [8]. Building a donor database that directly provides HLA-A and HLA-B loci public epitopes may provide a simple and fast way to find platelet HLA matching donors more easily.

HLA antigens are viewed as a series of antibody targets or epitopes, with public HLA epitopes being used as key indicators for selecting suitable donors rather than relying solely on HLA antigen matching. This approach aims to

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develop a platelet HLA typing system that is more closely aligned with clinical practice compared to traditional serological response methods or precise amino acid sequence analysis. It helps to avoid immune reactions that may occur after platelet transfusion, thereby improving the overall efficiency of platelet transfusion and significantly reducing the occurrence of ineffective platelet transfusion. At the same time, it is possible to avoid platelets with pre-existing HLA antibody positivity for patients, thereby improving the safety and effectiveness of treatment. For patients with pre-existing antibodies, it is important to select donor platelets that lack the specific antibody recognition eplets [9]. These measures can further expand the range of existing donor selection, overcome the limitations of HLA standard antigen full matching methods, and not continuously expand the storage capacity solely for rare HLA phenotypes, thereby effectively reducing the cost and resource requirements of library creation [10]. However, the absence of a donor database that directly provides HLA-A and HLA-B public epitopes hinders research on the effectiveness of HLA epitope matching.

A research team of Jining used the typing technology of direct detection on HLA CREG public epitopes in DNA samples. Using the nucleotide sequence encoding the HLA antigen public epitope and the closely linked HLA antigen-specific single nucleotide polymorphism site, the polymorphic fragments of these sites were specifically amplified by PCR. The corresponding HLA public epitopes were determined according to whether the PCR amplification products were generated or not. The seven most clinically significant CREG public epitopes (A1C, A2, A10C, B5C, B7C, B8C, B12C) at the HLA-A and HLA-B loci of the donors were directly detected by 13 PCR, which covered all HLA-A and HLA-B antigens. Using these 7 epitopes as markers for selecting compatible donors, a CREG public epitope donor database for platelet HLA-A and HLA-B loci was created, encompassing 565 donors. In this database, 96.87% of the people in the Jining area have about 81.68% probability of finding at least one ABO and HLA epitope perfectly matched donor.

The construction of a platelet public epitope donor database for HLA CREG lays the foundation for further exploring alternative HLA antigen-matching methods and finding a more concise method to provide platelet HLA-matched donors. Additionally, this initiative offers donor resources and data support for assessing the efficacy of HLA epitope-matched platelet transfusions, provides evidence for evidence-based medicine (EBM), and explores which HLA epitope-matched platelet transfusions are most effective in the Chinese population and which HLA-A or HLA-B epitopes are more important for clinical research.

It is hoped that this letter will draw the attention of readers of *Blood and Genomics* in China, encouraging active participation in this research. This could provide more evidence-based medical data for HLA epitope-matched platelet transfusions and facilitate finding suitable platelet donors for patients with ineffective transfusions and HLA antibody positivity.

Yours Sincerely
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