Transfusion Medicine Reviews 31 (2017) 118–125

Contents lists available at ScienceDirect

Transfusion Medicine Reviews

journal homepage: www.tmreviews.com

Platelet Immunology in China: Research and Clinical Applications

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ARTICLE INFO

Available online 6 December 2016

Keywords:
Platelet immunology
Human platelet alloantigens
Immune-mediated thrombocytopenia
Anti-CD36
Chinese population

ABSTRACT

Immunization against human platelet alloantigens (HPAs) is associated with a number of clinical complications. The detection and identification of clinically relevant platelet antibodies are important for the diagnosis and management of patients affected with immune-mediated thrombocytopenias. Human platelet alloantigen frequencies and the characteristics of antiplatelet antibodies vary widely between ethnic groups. Since 2008, the importance of platelet immunology in the field of transfusion medicine has gained greater recognition by clinical laboratories in China. Laboratories in China have established and improved methods for platelet antibody detection and HPA genotyping techniques, which are used for the diagnosis of alloimmune platelet disorders in clinic and research environments. Research has revealed the frequencies of HPA alleles in different Chinese ethnic groups and compared the differences in HPA gene frequencies between the Chinese Han and other ethnic groups of the world. Production of anti-CD36 isoantibodies is an important risk factor for immune-mediated thrombocytopenia in the Chinese population. Advances in research and clinical application of platelet immunology have significantly improved the clinical diagnosis, treatment including transfusion support, and prevention of alloimmune platelet disorders in the Chinese population.

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Platelets are one of the most important cellular products issued by blood centers in China. Platelet products are often prescribed for the prophylactic treatment to reduce the risk of bleeding in hemato-oncology and for the treatment of bleeding in patients with a wide range of conditions. Platelets have important functions in hemostasis, in which they adhere to damaged blood vessels, aggregate en masse, and through cross-links with fibrinogen or other proteins, form a fibrin clot to prevent further blood loss [1-2]; in addition, platelets are also involved in inflammation, innate and adaptive immunity and diseases ranging from heart disease to autoimmunity and even cancer [3-5].

Platelets perform their functions through ligand-receptor interactions involving the glycoproteins (GP) expressed on their cell surface membranes. Platelet membrane GPs can be expressed in polymorphic forms caused by single-nucleotide polymorphisms in the genes that encode them. The amino acid changes resulting from these single-nucleotide polymorphisms induce changes in GP structure to form antigens that can elicit antibody generation through exposure from pregnancy, platelet transfusions, or, rarely, transplantation [6-7]. To date, 36 human platelet alloantigens (HPAs) have been identified (HPA-1–HPA-29bw and Lap[a]) and are known to be expressed on 6 different

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http://dx.doi.org/10.1016/j.tmrv.2016.12.001
0887-7963/

platelet GPs: GPIIb, GPIIIa, GPIbα, GPIbβ, GPIa, and CD109 [8-36]. In addition to HPAs, platelets express other antigens, including CD36 (Nak[a], GPIV), GPVI,blood group antigens (I, P, and ABO(H)), and human leukocyte antigens (HLA I classes A, B, and, to a lesser degree, C). Human platelet antigens show variation in genotype frequency across populations [37].

Immunization against HPAs is associated with a number of clinical conditions, including fetal and neonatal alloimmune thrombocytopenia (NAIT), platelet transfusion refractoriness (PTR), posttransfusion purpura (PTP), passive alloimmne thrombocytopenia, transplantation-associated alloimmune thrombocytopenia, and other platelet immune disorders [38-40]. The detection and identification of clinically relevant platelet antibodies are important for the diagnosis and management of patients affected with immune-mediated thrombocytopenias.

Human platelet alloantigen frequencies and the characteristics of antiplatelet antibodies vary widely between ethnic groups. The most commonly reported alloimmune thrombocytopenia–associated HPA alloantibody in white populations is anti–HPA-1a, followed by anti–HPA-5b. In contrast, anti–HPA-4 antibodies are the most common in Japanese patients with immune thrombocytopenia[41-45]. Understanding the characteristics of clinically relevant platelet antibodies in the Chinese population and developing the ability to detect relevant platelet antibodies in Chinese blood centers and hospitals are important for improving care for patients affected with immune-mediated thrombocytopenia in China. Summarizing results from literature searches using PubMed Database, Chinese Bio-Medical Literature Database, and Chinese Core Journal of Peking University Directory, this review introduces recent research and clinical advances in the field of platelet immunology in China.

Platelet Immunology in China

With the request from the International Society of Blood Transfusion and International Society of Blood Transfusion Working Party of Platelet Immunology, the 14th International Society of Blood Transfusion Platelet Immunology Workshop and co-research projects were organized and designed by Dr Guo-Guang Wu and the Nanning Institute of Transfusion Medicine in China in 2007 to 2008. The aims of the Platelet Immunology Workshop were to evaluate and share the latest knowledge and techniques in platelet immunology for the laboratory diagnosis of platelet immune disorders and to reach a consensus regarding various standards in platelet immunology and molecular testing. Five main techniques were addressed, including serological testing, genotyping, and the detection for the drug-dependent antibodies against platelet. Forty-two laboratories from 23 countries participated in the workshop, including 7 laboratories from China [46]. This successful global collaboration stimulated and accelerated both clinical and research projects relating to platelet immunology in the field of transfusion medicine in China. Several large blood centers, including Beijing, Shanghai, Zhejiang, Guangzhou, Shenzhen, Qingdao, and Nanning Blood Center, established specific platelet immunology laboratories for the diagnosis of platelet immune disorders and for in-house development of platelet serologic and molecular testing techniques. Some blood centers created their own HPA-typed donor registries which helped to improve the outcomes of patients receiving platelet transfusions therapy with compatible platelet products in China. The importance of platelet immunology also continues to gain recognition by hospital clinical departments in China.

Techniques for Platelet Antibody Detection and HPA Genotyping in China

Serologic methods that are used in China's laboratories for the detection and identification of platelet antibodies are divided into “Whole” (Intact) Platelet Methods and Platelet Membrane Glycoprotein Capture techniques, which are platelet immunofluorescence test–flow cytometry, solid-phase red cell adherence assay, mixed passive hemagglutination, monoclonal antibody-specific immobilization of platelet antigens, and modified antigen-capture enzyme-linked immunosorbent assays. Commercial kits used by some of laboratories are MASPAT kits (Sanquin, Amsterdam, the Netherlands), LIFECODES Pak Series kits (Immucor, Norcross, GA), and Capture P kits (Immucor).

The molecular HPA genotyping techniques used by laboratories in China include DNA-base polymerase chain reaction with sequence-specific primers (PCR-SSP), TaqMan Real-Time PCR (TaqMan), sequencing-based typing (SBT), and PCR followed by Luminex bead detection. Some laboratories have developed and published their new techniques for PCR-SSP and SBT [47-48], as well as for real-time PPCR for HPA genotyping [49]. The commercial kits that are used by laboratories are G&T Multi-PCR HPA Genotyping Kit (G&T, Los Angeles, CA). The immortal lymphoblastiod cell lines of rare human platelet–specific alloantigen and CD36 have been established and studied in the Nanning Institute of Transfusion Medicine. These cell lines can be used to provide reference DNA for routine laboratory reagents and perpetual research materials for long-term studies [50].

Frequencies of HPA Alleles in the Chinese Population

The frequencies of several human platelet antigens (HPAs) vary between different populations and are a major determinant for the prevalence of HPA alloimmunization and its clinical associated entities. Study HPA allele frequencies and comparing between different ethnic populations can help to elucidate the potential alloimmunization risk associated with pregnancy and transfusion in each ethnic group in Chinese population.

China is the most populated country in the world and is a multiethnic nation. Of the 56 ethnic groups, the Han group is the largest, accounting for 91.59% of the total population, and the Zhuang group is the second largest, according to the Chinese National census conducted in 2000 [51].

Table 1 shows the frequencies of HPA alleles in Han (Shanghai area), Zhuang (Guangxi area), Miao (Guizhou area), Dong (Guizhou area), Khalkhas (Xinjiang area), Li (Hainan area), Uighurs (Xinjiang area), Zang (Lhasa area), people from Hong Kong, and Taiwanese (Taiwan area) [47,52-60]. All blood samples were collected from unrelated blood donors who confirmed their ethnic group. Genotype frequencies were compared between Han and other ethnic groups using a χ^2 or Fisher exact test; gray boxes in Table 1 indicate a statistically significant difference (where <.05 was considered statistically significant). The genotype distribution in the Han group was similar to that in the Zhuang group, except for *HPA-3* and *HPA-4*. By contrast, significant differences of multiple HPA allele frequencies were found between Han and Miao, Dong, Khalkhas, Li, Uighurs, Zang, and Taiwanese groups. In the Chinese ethnic groups that investigated, an individual with either homozygous for the *HPA-1b*, *HPA-2b*, *HPA-3b*, *HPA-4b*, *HPA-5b,* or *HPA-6bw* allele was rare. The other low-frequency antigens of *HPA-7bw*, *HPA-8bw*, *HPA-9bw*, *HPA-11bw*, *HPA-12bw*, *HPA-13bw*, *HPA-14bw*, and *HPA-16bw* were first detected in whites and exhibited private antigens that were not detected in the studied Chinese ethnic groups. This suggests that the risk of platelet alloimmunzation caused by these HPAs is extremely low in the Chinese population. The gene frequency of *HPA-4b* in Chinese populations is present from 0.0000 to 0.045. The gene frequency of the *HPA-15a* is higher than that of *HPA-15b* in the Han, Zhuang, Miao, Khalkhas, Zang, and Taiwanese groups, whereas *HPA-15b* is more frequent than *HPA-15a* among the Li and Uighurs groups. The prevalence of HPAs in a given population is a major determinant for the prevalence of HPA alloimmunization and its clinically associated entities: fetal alloimmune thrombocytopenia, NAIT, PTR, PTP, transplantation-associated alloimmune thrombocytopenia, posttransfusion passive alloimmune thrombocytopenia, and platelet transfusion in the Chinese population.

A comparison of HPA genotype frequencies between Chinese Han and European whites in Germany [61], American whites in the United States [62], Vietnamese (Kinh) in Vietnam [63], Koreans in Korea [64], Parsis in Indian [65], Argentineans in Rosario of Argentina [66], and African Beninese in sub-Saharan [67] is shown in Table 2. Statistically significant differences were found for the genotype distribution of