An overview of serology and molecular biology of the Rh blood group system

The Rh blood group system is one of the most complex, polymorphic, and clinically significant blood group systems, with numerous alleles that can affect transfusion and maternal-fetal safety (1,2). Understanding the serology and molecular biology of the Rh system is crucial for transfusion compatibility and prevention of hemolytic disease of the fetus and newborn (HDFN). In that context, this special series on "Serology and Molecular Biology of the Rh System" aims to present updates and recent technological advances in serology and molecular testing for accurate determination of the Rh status to improve transfusion practices, to prevent alloimmunization and to avoid HDFN. The specific articles well presented in this series were written by international leaders in the field of blood groups.

In the first chapter, Dr. Nadarajan provides an introductory overview of the Rh system including the history of its discovery and proposed terminologies (3). Dr. Nadarajan also discusses the importance of serological Rh typing in characterizing and solving problems associated with Rh antigens in blood donors, pregnant women, and potential red cell recipients. The availability and the correct use of different Rh typing reagents and techniques are well explained to ensure a safe result and resolve discrepancies. In addition, Dr. Nadarajan points to the limitations of serological techniques, especially in the face of Rh variant antigens.

In chapter two, Dr. Keller makes an excellent narrative review of the RH genetic variation providing to the readers with information that can be used to reduce Rh alloimmunization and increase personalized patient care related to alloimmunization (4). In addition, Dr. Keller shares her findings on *RHD* genotyping of 879 patient samples (5) referred to a large national US reference laboratory and an effective strategy used in US to personalize donor unit selection in RH alloimmunized patients based on *RH* allele information. In this context, Dr. Keller highlights the benefits of molecular methods in developing a personalized approach to patient care and the challenges in the *RH* allele selection due to ambiguous phenotypes.

In chapter three, Dr. Sippert *et al.* (6) present in a very nice narrative review the molecular of altered RhCE phenotypes and the impact of *RHCE* variability and complexity in transfusion therapy, especially for sickle cell disease (SCD) patients. Their review provides an overview of progress in identifying the genetic basis and characterization of *RHCE* variant alleles in patients with SCD and blood donors and highlights the importance of conducting studies that help us better understand the clinical significance of most antibodies formed in patients with variant RhCE phenotypes.

In chapter four, in an excellent narrative review, Dr. Fichou presents the molecular genetics of hybrid genes and their antigen expression and discusses the contribution of hybrid alleles and micro-conversions in *RH* genes to the complexity of the Rh blood group system and their relevance in transfusion therapy, especially for patients with SCD (7). He also discusses the molecular epidemiology of *RH* hybrid genes through several interesting studies that have contributed significantly to the RH genetic polymorphism. Dr. Fichou presents various approaches that have been used in hybrid identification for the past ten years that are currently used in several laboratories and the new promises. Dr. Fichou himself has contributed to the development of the quantitative multiplex polymerase chain reaction (PCR) of short fluorescent fragments (QMPSF) for hybrid identification (8) that has been used to characterize *RH* variant alleles involving hybrid alleles associated with partial antigens or lack of high frequency antigens in SCD patients.

In chapter five, Dr. Khandelwal *et al.* provide a detailed overview on the application of next generation sequencing (NGS) for donor and patient Rh blood group antigen typing (9). In their review, they show how this technology has been successful in correctly describing genetic changes in the Rh system, identifying new alleles, and determining haplotypes. With this scenario, they present the NGS as a new promise for high genetic resolution and throughput required for optimal RH genotyping, patient-donor matching, and transfusion care. Furthermore, they draw attention to the challenges that remain related to data storage, bioinformatic capacity, development of appropriate pipelines and ethical issues to implement NGS as a routine method for RH genotyping.

In chapter six, in his narrative review, Dr. Wagner provides extensive, accurate and relevant information on the importance of Del phenotype, on the molecular mechanisms leading to *DEL* alleles and on their prevalence in different populations (10).

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Dr. Wagner also presents important considerations on the limitations of serological discrimination of DEL from weak D and D negative and the clinical implications of Del phenotype.

Considerable progress has been made in our understanding of serologic features and the molecular basis of Rh antigens. The allelic diversity in Rh system makes it highly complex and the alloimmunization risk associated with a variant remains uncertain. Therefore, updated information in this area is essential for a good understanding of this complex system and for transfusion and maternal-fetal safety. This special series provides an overview of several aspects of the Rh blood group system, including terminology, advances in serology and in molecular understanding and the applications of the current knowledge in the clinical setting.

As a Guest Editor, I am very grateful to the experts for agreeing to contribute to this special series, for their relevant contribution, for the time spent writing these excellent reviews and for sharing their experiences and knowledge. I hope, this special series on "Serology and Molecular Biology of the Rh System" contributes to a better understanding of the Rh system and serves as a reference for the transfusion medicine community.

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