Molecular Pathology in Transfusion Medicine

New Concepts and Applications

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KEYWORDS

• Genotype • Phenotype • Serology • Antigen • Antibody • Blood donors • Transfusion • Red blood cells

KEY POINTS

- Virtually all the red blood cell and platelet antigen systems have been characterized at the molecular level and highly reliable methods for red blood cell and platelet antigen genotyping are now available.
- Genotyping is a useful adjunct to traditional serology and can help resolve complex serologic problems.
- Although red blood cell and platelet phenotypes can be inferred from genotype, knowledge of the molecular basis essential for accurate assignment.
- Genotyping of blood donors is an effective method of identifying antigen-negative and/or particularly rare donors.
- Cell-free DNA analysis provides a promising noninvasive method of assessing fetal genotypes of blood group alloantigens.

OVERVIEW

Testing performed in transfusion medicine focuses on detection of antigens expressed on the cell membrane of red blood cells (RBCs) and/or platelets and the detection of antibodies against RBC or platelet antigens in a patient's plasma. Detection of these antigens and antibodies is critical because RBC or platelet units that are positive for a given antigen and that are transfused into a patient who has antibodies

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against that specific antigen may cause decreased blood product survival, hemolytic transfusion reactions, hyperhemolysis reactions, and even death.

RBCs and platelet antigens and antibodies are traditionally detected using serologic assays. These assays overwhelmingly use hemagglutination principles to indicate the presence of an antibody in the tested serum and the presence of the antigen on the tested RBC or platelet product. For example, forward typing of a patient's RBC antigens is performed by combining the patient's RBCs with known anti-A, anti-B, and anti-D antisera. Any reaction resulting in agglutinated RBCs suggests that the RBCs have that antigen on their surface (eg, agglutination in anti-A reaction suggests the presence of the A antigen on the RBC membrane). To cause agglutination, the assays rely on the agglutination capability of the tested antibodies (eg, ABO testing) for the IgM class and secondary antibodies (eg, antihuman globulin antibodies and anti-C3 antibodies) for the IgG class.

ADVANTAGES OF MOLECULAR TESTING

Molecular testing is complementary to traditional serologic testing used for most transfusion medicine testing.[1] Molecular testing does not replace serologic testing, and serologic testing is still very much the backbone of transfusion medicine testing. Serologic testing is well characterized, sensitive enough to find and identify most clinically significant alloantibodies, and useful for most patient situations. Serologic testing is limited, however, in specific patients and situations, including the following:

- Patients with confounding antibodies (warm or cold autoantibodies or cold agglutinins, and neonates with passive maternal antibodies)
- Patients with antigens or antibodies for which testing antibodies or antisera are not available (partial or variant antigens, rare antigens, and high-incidence antigens)
- Patients with a mixture of circulating RBCs or plasma (recently transfused, after bone marrow transplant, and after plasmapheresis)
- Patients in whom antigen zygosity needs to be determined
- Patients with select diseases (ie, sickle cell) where frequent transfusions increase immunohematological difficulties
- Mass screenings of blood donors

In each of these situations, serologic testing may be of limited sensitivity and specificity or may be prohibitive in time, effort, or cost.

Obscuring autoantibodies or multiple alloantibodies can cause unexpected agglutination in test reactions. This can result in an inability to rule out alloantibody possibilities, making it difficult or impossible to identify any clinically significant alloantibodies in a patient's serum. Antibodies against low-incidence antigens may not be effectively identified because of the limited availability of antisera and antigen-positive test RBCs. Similarly, antibodies to high-incidence antigens may be difficult to identify because of the lack of commercially available antisera or antigen-negative reagent RBCs. In patients who have received multiple RBC transfusions, the transfused RBCs may obscure the presence or absence of antigens of interest on a patient's native RBCs. Likewise, the serum of patients receiving multiple plasma transfusions or automated plasma exchange cannot be evaluated for antibodies from the patient's native immune system because of obscuring or dilution by the transfused plasma. For many RBC or platelet antigens, the phenotypes of homozygous and heterozygous patients are often indistinguishable by serologic means. For example, although there is the concept of "dosing," observing differences in the strength of hemagglutination when reagent

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