Recent Developments and Future Directions of Alloimmunization to Transfused Blood Products

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• Alloimmunization • Transfusion • Rejection • Immunity

Immunization is defined as the generation of an immune response against an antigen. Whereas immunization often is discussed as an adaptive response to foreign antigens encountered as part of a microbial infection, alloimmunization in particular is the response to antigens that differ as a function of coming from a separate member of the same species. In current medical practice, alloimmunization is perhaps most closely managed in the context of solid organ transplantation. With few exceptions, solid organs will undergo rejection by the recipient immune system in the absence of pharmacologic immunosuppression. Such appears not to be the case for transfusion, however. Outside the context of RhD, the rate of alloimmunization to red blood cell (RBC) antigens is quite low (approximately 3%) even in the absence of immunosuppressive drugs.[1,2] Alloimmunization to transfused platelets is substantially higher when focusing on responses to major histocompatability complex (MHC) I molecules (approximately 20% to 40%).[3–6] However, rates of alloimmunization to platelet-specific polymorphisms (eg, human platelet antigens) are at lower levels, similar to RBC antigens.[3–6] Alloimmunization to transfused soluble proteins also has been observed in some settings, but data on exact specificities and rates are unclear.[7] Overall, this low response rate to alloantigens is in contradistinction to antibody responses to microbial infection, which approach 100% in immunocompetent individuals; indeed, it is precisely by such serology that one monitors epidemiology of infectious pathogens.

The exact reasons why immunization to transfused blood is lower than expected is unclear, but several lines of thought have evolved. First, the extent of antigenic difference between most donor and recipient antigens is quite low. Whereas an infectious

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microbe may introduce numerous completely foreign proteins, most blood group antigens consist of a single amino acid difference. Also, transfused RBCs or platelets may be weakly immunogenic because of the conditions under which the antigen is encountered. Research in recent years has shown that in many cases, activation of innate immune pathways is required for acquired immunity to develop. Such activation appears to occur predominantly in response to encountering chemical motifs found on microbes but not on human tissues. Pattern recognition receptors are ligated by such motifs and provide required signals to allow the full development of immunity.[8,9] If processed and stored under sterile conditions, it is not immediately obvious how a bag of blood would deliver the requisite activation of innate immunity. Finally, transfused RBCs can introduce a large quantity of antigen that persists for a substantial amount of time, both of which are variables that often are associated with weak responses or tolerant states. Each of the variables listed has a potential role in regulating the immunogenicity of transfused blood. Understanding the factors that regulate whether an individual becomes alloimmunized is of central importance to improving transfusion management. Identification of the variables that determine alloimmunization would generate both screening tests to identify high-risk patients and also lead to the rational basis of developing therapeutic interventions.

RISK FACTORS FOR HUMORAL IMMUNIZATION TO TRANSFUSED ANTIGENS: PREDICTION AND PREVENTION

Recipient Factors Hypothesized to Regulate Alloimmunization

Although a sterile bag of blood may not have the requisite microbial products to activate innate immunity upon transfusion, it does not necessarily follow that the transfusion recipient will not have ongoing activation of innate immunity from other sources. Blood seldom is transfused into healthy people, and exposure to transfused foreign antigens may occur in the context of various underlying pathophysiologies, many of which may have a component of innate immune activation. Murine models have shown that treating recipients with activators of innate immunity can substantially increase both the frequency and magnitude of alloimmunization to an antigen on transfused RBCs.[10–13] Although this suggests a rather straightforward paradigm, additional work has suggested that not all inflammation is equivalent, and different subtypes of innate immune activation may have alternate effects upon alloimmunization.[14] Early studies in people have shown a correlation between alloimmunization and having a febrile episode in temporal association with the transfusion.[15] Much additional work, however, needs to be done to determine if inflammation really is a risk factor for alloimmunization in people, and if so, the nature of the inflammation involved.

In addition to acquired inflammation, immunogenetics outside the HLA may play a substantial role. It is known that polymorphisms in transcriptional regulators of immunoregulatory cytokines can affect rates of organ transplant rejection, but little is known about their role in alloimmunization. In addition, association of polymorphisms in coding regions of immunoregulatory gene products also has been suggested to play a role in tendency toward alloimmunization.[16]

Donor and Unit Factors Hypothesized to Regulate Alloimmunization

In addition to recipient factors, it is also possible that substances contained within transfused products may lead to innate immune activation. An obvious example would be direct microbial contamination of the blood product. Clearly, this is highly unlikely for the panel of infectious pathogens for which the blood supply is screened routinely. Moreover, the deferral of symptomatically ill donors and donors with certain