The Concept of Compatibility: Towards a Functional Understanding of Immunohematology

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A variety of strategies has been developed to assure safety of hemotherapy. Such strategies aim in particular at avoiding transfusion-transmitted infections. Safety of hemotherapy requires – in addition to safety of transfusion from infections – tolerance of the recipient towards the blood component to be transfused and tolerance of the blood component to be transfused towards the recipient, i.e. compatibility of recipient and blood component. Diagnostic strategies in immunohematology contribute significantly to safety strategies in the field of hemotherapy. However, immunohematology contributes to transfusion safety much more than diagnostic strategies. It contributes a conceptual understanding of compatibility, underlying diagnostic strategies.

Immunohematology defines compatibility at the basis of structure, i.e. compatibility is dependent on structural components of single cells, single antibodies, and their interaction. Currently available techniques derived from the spectrum of biochemistry, biophysics and molecular biology allow structural components of cells, antibodies, cell-cell interactions and cell-antibody interactions to be determined at a much higher degree of resolution than ever before. Typing of alleles underlying the expression of different HLA antigens and typing of alleles underlying the expression of different forms of the Rhesus protein D (Rh(D)) exemplarily demonstrate the potential of high-resolution techniques in immunohematology to determine specificity – and thereby also compatibility, according to the understanding of compatibility in today's immunohematology – at the basis of structure.

In contrast to immunohematology, transfusion medicine provides a different understanding of compatibility. Transfusion medicine defines compatibility not primarily at the basis of structure, but at the basis of function, i.e. at the basis of the outcome of an immune response in the setting of hemotherapy, cell therapy, or organ transplantation. Immune interactions relevant to the outcome of immune responses in transfusion

and transplantation medicine occur in the context of a highly complex and dynamic biological system that is characterized by plasticity under functional aspects. Under these conditions, structure does not necessarily predict function. Thus, albumin attenuates the activation of neutrophil granulocytes induced by antibodies against neutrophil-specific antigens [1]; challenge of healthy individuals negative for the antigen Rh(D) with red blood cells expressing the highly immunogenic protein Rh(D) results in about 20% of individuals that do *not* respond to the allogeneic stimulus [2, 3]; and antibodies passively administered together with their specific antigen may enhance or suppress antibody responses, depending on antibody isotype, antigen size and solubility, and the repertoire of Fcγ receptors expressed by the recipient [4].

The concept of compatibility in today's immunohematology does not sufficiently consider that specificity – and thereby compatibility – may be defined by functional aspects of the immune system in its respective condition as much as by structural components of immune cells and immune receptors. A concept of compatibility in immunohematology that takes into account functional aspects of the immune response requires the understanding of regulatory mechanisms that determine the proper recognition of 'self' and 'non-self' blood cell antigens in the context of complex dynamic interactions at the cellular and humoral level of the immune system. The reviews compiled in the present issue of TRANSFUSION MEDICINE AND HEMOTHERAPY, completing a series of reviews initiated in the preceding issue, focus on the understanding of immune interactions contributing to the outcome of immune responses and may be of relevance to a definition of compatibility that considers both structural and functional aspects of the immune response to blood cells.

In the first review, *Fredrick G. Karnell* and *John G. Monroe*, USA, summarize the role of membrane lipids for the regulation of immune cell activity: Lipid rafts are plasma membrane

compartments enriched in cholesterol and glycolipids that provide specialized microenvironments in which a large number of biological processes take place. Current evidence indicates that lipid rafts are of crucial importance for the initiation and maintenance of signaling events in immune cells. Here, Karnell and Monroe highlight the role of lipid rafts as signaling platforms for immune receptors on B lymphocytes, T lymphocytes, and mast cells [5].

Specific membrane lipids may be recognized as antigen by a subset of natural killer T (NKT) cells: NKT cells express a T cell receptor and mature in the thymus, but they also frequently express a variety of molecular markers and perform functions that are typically associated with NK cells. Unlike most conventional T cells, many NKT cells do not recognize peptide antigens bound to MHC class I or MHC class II molecules. Instead, these cells respond to lipid antigens, which they recognize with their T cell receptors, as ligands bound to MHC-like CD1d molecules. Current evidence suggests that the most important function of NKT cells is to regulate the activation of other immune cells, fine-tuning the immune system based on subtle changes in the lipid pool. *Elliot S. Jerud, Gabriel Bricard and Steven A. Porcelli*, USA, review the role of CD1d-restricted NKT cells for the induction of tolerance in the setting of allo- and autoimmune responses [6].

Glycosylation is the most common and most diverse post-translational modification of proteins. Different glycosylation patterns of proteins may influence T cell responses during diseases, creating neopeptides or blocking existing T cell responses to unmodified peptides by changing epitopes or abolishing binding to MHC molecules. *Jörn Dengjel and Stefan Stevanović*, Germany, summarize the current knowledge of naturally presented MHC ligands carrying glycans and discuss the impact of glycosylated MHC class I and class II peptides on the regulation of cellular immune responses [7].

T lymphocytes are commonly thought to develop independently of B lymphocytes: While it is widely recognized that T cells provide help to B cells in the production of antibodies to protein antigens, the contribution of B cells to T cell development and function is less well understood. *Marilia Cascalho* and colleagues have recently investigated the possibility of B cell-dependent T cell development taking advantage of a transgenic mouse model and have demonstrated that T cell development and thymocyte selection is modified by the presence of B cells [8]. In this issue, *Marilia Cascalho and Jeffrey L. Platt*, USA, explain how B cells contribute to thymocyte selection and T cell development, and discuss how B cells and B cell products may help to restore cellular immunity in a variety of clinically relevant conditions such as acquired immunodeficiency syndrome, chronic immunosuppression and cancer chemotherapy [9].

A different type of cell-cell dialogue with direct relevance for the outcome of immune responses is presented by *Gabrielle Lui, Paolo Carrega and Guido Ferlazzo*, Italy [10]: Functional links between natural killer (NK) cells and dendritic cells

(DCs) have been recognized during the recent years. NK cells and DCs help each other to acquire their complete functions, both in the periphery and in the secondary lymphoid organs. In vitro, IL-12, IL-18, IL-15 and type-I IFN are implicated in the activation, proliferation and cytotoxicity of NK cells by mature DCs, while TNF- α secreted by NK cells is involved in the maturation of DCs. Cell-to-cell contacts, not completely understood yet, are also implicated in the NK cell/DC cross-talk. Thus, current scientific evidence indicates that NK cells can detect the presence of transformed cells, support the maturation process of DCs, direct the polarization of the adaptive immune response toward a Th1 response in the lymph nodes and, in association with DCs, may favor the generation of cytotoxic T cells. Insight into the principles of NK cell/DC cross-talk is of central importance for the design of immunotherapeutic protocols aiming at the control of both innate and adaptive immune responses.

Under certain conditions, endothelial cells (ECs) may have the capacity to act as antigen-presenting cells. *David R. Johnson*, USA, reviews experimental work investigating antigen presentation by resting ECs in vivo by testing immune responses against *E. coli* β -galactosidase (β -gal) in two lines of transgenic mice that express β -gal exclusively in their ECs. The data suggest that ECs effectively present intracellular 'self' proteins to the immune system. However, antigen presentation by ECs does not delete or anergize a large population of specific lymphocytes that respond to the same protein following conventional immunization with protein or expression vector DNA. These observations demonstrate context sensitivity in the immune recognition of ECs. *David Johnson* discusses the implications of these findings for transplantation tolerance and for the control of persistent infections [11].

Robert Brawura-Biskupski-Samaha and Tomasz Grzela, Poland, review an impaired regulation of immune responses by the impaired induction of apoptosis, taking advantage of the clinical condition of the autoimmune lymphoproliferative syndrome (ALPS). The authors present an update on the currently known types of ALPS and characterize their immunological and molecular background. They demonstrate that ALPS may serve as a very attractive in vivo model to understand a variety of lymphocyte-dependent aspects of the induction of autoimmune reactions and the development of alloimmune responses [12].

RNA interference (RNAi) technology has meanwhile become an important technique to study lymphocyte development, activation and effector mechanisms. Functional studies of lymphocytes using the methodological approach of RNAi are in the center of the data summarized by *Yen-Yu Lin, Chien-Fu Hung and Tzzy-Chou Wu*, USA [13]. RNAi technology has been used to modify the properties of lymphocytes in order to influence the outcome of immune responses and to create opportunities for potential therapeutic applications in vivo. While the application of RNAi technology to influence immune responses in vivo is quite promising, significant obsta-

cles still need to be overcome before this technology can be successfully translated into clinical practice.

The series of reviews presented here closes with an update on concepts developed to understand the role of blood transfusion as an active regulator of the immune response, and with a manuscript highlighting the potential of the methodological approach of proteomics in the detection and avoidance of adverse drug reactions – a topic with direct relevance to the field of immune regulation induced by blood transfusions: *Leo M.G. van de Watering*, The Netherlands, discusses different aspects of the immunoregulatory effects of blood transfusions in the light of our current understanding of immune responses [14]. *Marc R. Wilkins*, Australia, explores recent advances in proteomic technology and how this technology has been applied to the understanding of dose-related, non-dose-related, time-related and withdrawal-based adverse drug reactions [15]. Recent research in experimental models has discovered changes in proteins associated with adverse drug reactions. Proteomic technology may contribute significantly to

the discovery of proteins involved in immune regulation induced by blood transfusions, and may serve as a useful tool in hemovigilance.

The reviews presented in the current and in the preceding issue of TRANSFUSION MEDICINE AND HEMOTHERAPY may stimulate a discussion process with respect to the development of new strategies to understand and to influence what we call ‘compatibility’ in immunohematology. The issue has become possible by the strong commitment of the authors who accepted the invitation to contribute to this issue and who were willing to share their experimental data and to let the reader participate in new and original approaches to understand immune responses. For an in-depth comprehension of the context of their work, readers are referred to the detailed up-to-date reference lists accompanying the reviews. I would finally like to take the opportunity to express my sincere gratitude to all of the colleagues who accepted to contribute to this issue of TRANSFUSION MEDICINE AND HEMOTHERAPY. It has been a great pleasure to work together on this occasion.

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