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Intersecting Worlds of Transfusion and Transplantation Medicine: An International Symposium Organized by the Canadian Blood Services Centre for Innovation

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ABSTRACT

The principal theme of the symposium was centered on how the world of regenerative medicine intersects with that of transfusion medicine, with a particular focus on hematopoietic stem cells (HSCs) and stem cell therapies. The symposium highlighted several exciting developments and identified areas where additional research is needed. A revised map of human hematopoietic hierarchy was presented based on the functional and phenotypic analysis of thousands of single stem and progenitor cells from adult bone marrow and fetal liver. These analyses revealed that multipotency is largely restricted to the HSC and multipotent progenitor compartments in adult bone marrow where most progenitors are unipotent, whereas fetal liver contains a large number of distinct oligopotent progenitors. Furthermore, unlike adult bone marrow, multipotency is extended in the downstream progenitors in the hierarchy in the fetal liver stage. Production of platelets ex vivo from HSCs is emerging as a potentially viable option because of advances in culture techniques that combine cytokine mixtures, small molecules, and shear stress. However, limited HSC expansion and low platelet yield from culture-derived megakaryocytes remain problematic. Evidence was presented to support stricter guidelines for transfusion of platelets and red blood cells practices in allogeneic HSC transplant patients, although evidence is often extrapolated from general indications. Basic principles of human leukocyte antigen testing in HSC transplant were described, emphasizing the need for a national (and global) stem cell donor registry. Ongoing research is aimed at improving cellular cryopreservation including the establishment of a new thawing protocol that improves viability of umbilical cord blood CD34+ cells. Umbilical cord blood transplantation practices have also been improved; recent studies suggest noninferior outcomes when patients are transplanted with umbilical cord blood vs a matched adult donor. Finally, mesenchymal stem cell infusion is an example of a cellular therapy useful for immunomodulation. Preclinical trials suggest that mesenchymal stem cells may be effective in managing sepsis. In conclusion, practices and research surrounding HSCs are continuing to evolve rapidly as new information is obtained.

Contents

Abbreviations: CMP, common myeloid progenitor; GVHD, graft-vs-host disease; HLA, human leukocyte antigen; HSC, hematopoietic stem cell; HSCT, hematopoietic stem cell transplantation; IRI, ice recrystallization inhibitor; MEP, megakaryocyte-erythroid progenitor; MHC, major histocompatibility complex; MPP, multipotent progenitor; MRD, minimal residual disease; MSCs, mesenchymal stem cell; RBC, red blood cell; RCT, randomized controlled trial; UCB, umbilical cord blood.

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Canadian Blood Services manages the national supply of blood, blood products, and stem cells, and directs the related services for all provinces and territories excluding Quebec. Canadian Blood Services also operates an integrated, pan-Canadian service delivery model that includes leading an interprovincial system for organ donation and transplantation.

Through its Centre for Innovation, Canadian Blood Services facilitates the creation, translation, and application of new knowledge to support a safe, effective, and responsive system of blood and related biologics for Canada. Every year since 2003, the Centre for Innovation organizes an international symposium [1-9]. The symposium has a different focus every year depending on the most relevant research topics at the time, although it is always centered on transfusion medicine. The most recent symposium took place September 17, 2016, in Toronto and focused on hematopoietic stem cells (HSCs) in the context of transfusion medicine. Hematopoietic stem cell transplantation (HSCT) provides the best treatment option for many patients suffering from life-threatening hematologic malignancies. Research in this area has led to improved and emerging treatments for these potentially deadly diseases. The expert speakers at this year's symposium provided insight on these recent breakthroughs while highlighting commonalities with transfusion practice.

Intersecting Worlds of Transfusion and Transplantation Medicine

Dr Robert Skeate, associate medical director for Canadian Blood Services, opened the symposium by describing how transfusion and transplantation medicines overlap. Transfusion medicine is an area of medicine that involves multiple specialties including hematopathology, anesthesia, critical care, and obstetrics. Within the evolving field of regenerative medicine, and in particular the advances made in HSCT, the overlap of expertise between transfusion practice and cellular therapy is becoming more evident. Within Canada, the Canadian Society for Transfusion Medicine annual conference is now expanding its program to include cellular therapy as it relates to transfusion. AABB and the International Society of Blood Transfusion are similarly making cellular transplantation a priority, with AABB going as far as modifying their motto to "Advancing Transfusion and Cellular Therapies Worldwide." Dr Skeate then discussed how transplantation and transfusion practices can affect each other. As an example, he described his experience while working at the University of Minnesota. While he was investigating an increase in the use of O-negative red blood cell (RBC) products for patients with non–O-negative blood type, he discovered that a large number of products were used by the bone marrow transplant group, which had just expanded its program to include umbilical cord blood (UCB) transplantations. When a patient receives an ABO-mismatched bone marrow transplant, immune-mediated hemolysis can occur due to the development of anti-ABO antibodies, necessitating transfusions of O-negative RBCs [10]. When UCB is used, often 2 UCB units are transplanted—if even one of those UCB units is ABO mismatched, the patient will likely need transfusions of O-negative RBCs. Another example he described occurred during a clinical trial using natural killer cell infusions to treat solid malignancies [11]. Two non–type O patients received natural killer cell products from group O donors but because the products were not B cell depleted, the patients developed severe anemia due to anti-A/B antibodies hemolyzing their entire blood volume. As such, these patients were functionally group O and needed O transfusions until the issue was resolved. Thus, the transfusion medicine investigation resulted in a modification to the cellular therapy protocol.

Session 1: Hematopoietic Stem Cells

Hematopoietic Stem Cells and Differentiation of Blood Cells

Key messages

- HSCs, multipotent progenitors (MPPs), common myeloid progenitors (CMPs), and megakaryocyte-erythroid progenitors (MEPs) are heterogeneous cell populations.
- HSCs, MPPs, and other cellular progenitors are present at distinct stages of human ontogeny: fetal, neonate, and adult.
- The contribution of HSCs and MPPs to steady-state hematopoiesis varies significantly between neonatal and adult ontogeny.

Dr Sasan Zandi, a former postdoctoral fellow in Dr John Dick's laboratory at the University of Toronto and Princess Margaret Cancer Center who is now a hematopathology resident at the University of Toronto, described his research exploring the complex hierarchy within the HSC compartment. Since the discovery of HSCs by Dr James Till and Dr Ernest McCulloch in 1961 [12], HSCT has become routine clinical practice to treat hematologic malignancies.

Hematopoietic stem cells are the most studied human stem cell population with well-defined in vitro and in vivo assays [13]. As such, their complex hierarchy has been intricately characterized for decades, most frequently through fractionation using cell markers followed by functional characterization of their proliferative and differentiation potential through transplants in animal models and in vitro colony-forming analyses. Hematopoietic stem cells that possess long-term multilineage engraftment and that can be propagated in serial transplantation are referred to as long-term HSCs. These cells are exceedingly rare and divide infrequently. In contrast, short-term HSCs and MPPs—which possess the same differentiation potential of long-term HSCs and have significant overlaps in cell surface antigen profiles—have reduced self-renewal activity preventing long-term engraftment and serial transplantation activity. Short-term HSCs and MPPs have more active cell cycles and make up the transient amplifying population which is capable of rapidly filling the hematopoietic compartment with all the terminally differentiated cells of the blood system [4]. However, evolving concepts are adding to the complexity of the HSC system; the classic hematopoietic hierarchy has been challenged in both mouse and human models over the last decade. Advances in the ability to isolate and assess the function of single cells have enabled high-resolution lineage analysis of the HSC and MPP compartments [14]. These analyses uncovered a