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Review

Transfusion-related immunomodulation and cancer

Hadi Goubran[a,*], David Sheridan[a], Julia Radosevic[b], Thierry Burnouf[c,d], Jerard Seghatchian[e,*]

[a] Saskatoon Cancer Centre and College of Medicine, University of Saskatchewan, Saskatchewan, Canada
[b] Human Protein Process Sciences, Aubers, France
[c] Graduate Institute of Biological Materials and Tissue Engineering, College of Biomedical Engineering, Taipei Medical University, Taipei, Taiwan
[d] International PhD Program in Biomedical Engineering, College of Biomedical Engineering, Taipei Medical University, Taipei, Taiwan
[e] International Consultancy in Blood Components Quality/Safety Improvement, Audit/Inspection and DDR Strategies, London, UK

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ABSTRACT

Blood and blood-component therapy triggers immunological reactions in recipients. Transfusion-related immunomodulation [TRIM] is an important complex biological immune reaction to transfusion culminating in immunosuppression. The mechanisms underlying TRIM include the presence of residual leukocytes and apoptotic cells, the transfusion of immunosuppressive cytokines either present in donor components or generated during blood processing, the transfer of metabolically active growth factor-loaded microparticles and extracellular vesicles and the presence of free hemoglobin or extracellular vesicle-bound hemoglobin. TRIM variables include donor-specific factors as well as processing variables. TRIM may explain, at least in part, the controversial negative clinical outcomes observed in cancer patients receiving transfusion in the context of curative-intent surgeries. The use of novel technologies including metabolomics and proteomics on stored blood may pave the way for a deeper understanding of TRIM in general and its impact on cancer progression.

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1. Introduction

Classically, blood or blood-component therapy can trigger immunologic reactions that result from an interaction between inherited or acquired recipient antibodies and foreign antigens associated with cellular or humoral components of the transfused blood products. It is an accepted fact, however, that the administration of blood components can induce profound negative effects on the human immune system, a condition termed "transfusion-related immunomodulation" (TRIM). Evidence is accumulating that TRIM represents a complicated set of physiologic responses that include both immunosuppressive and pro-inflammatory effects mediated by residual leukocytes, apoptotic cells, and numerous

* Corresponding authors at: Saskatoon Cancer Centre, 20 Campus Drive, S7N 4H4 Saskatoon, Canada.
E-mail addresses: hadi.goubranmessiha@saskcancer.ca (H. Goubran), jseghatchian@btopenworld.com (J. Seghatchian).

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biological response modifiers such as cytokines, soluble mediators and soluble HLA peptides, as well as cell-derived microparticles/extracellular micro-vesicles and free hemoglobin [1,2].

Early reports of TRIM in the 1970s stemmed from the observation that red blood cell (RBC) transfusion was associated with fewer episodes of organ rejection in renal transplant recipients, implying an immunosuppressive effect of allogenic transfusions [3]. This phenomenon was therapeutically exploited before effective immunosuppressant drugs became available, to reduce renal allograft rejection [4]. Mechanisms for TRIM include suppression of cytotoxic cell and monocyte activity, release of immunosuppressive prostaglandins, inhibition of interleukin-2 (IL-2) production, and an increase in Tregs and suppressor T-cell activity [5–8].

The TRIM influence on immune competence in recipients is well established, its negative effects on surveillance against malignancy and cancer recurrence after a curative resection is theoretically conceivable but remains controversial. It could therefore account for the association between perioperative transfusion of allogeneic blood products and the risk for recurrence observed in many types of cancer.

2. Pathophysiology of TRIM

2.1. Residual leukocytes and apoptotic cells

Leukocytes present in blood components may play a crucial role in inducing TRIM. Out of the 19 randomized controlled trials of the effect of allogeneic leukocytes in transfusion, 13 looked into the effect of leukocyte-containing red blood cell concentrates (RCCs) transfused in a surgical setting, on the occurrence of postoperative infections and/or mortality. In contrast to conflicting outcomes of the trials in other settings [9], in cardiac surgery there is evidence that leukocyte-containing RCCs increase postoperative complications associated with mortality [10]. No controlled clinical trial was conducted in oncologic surgery but several authors have suggested that filtered whole blood and/or RCCs, or leukocyte- and buffy coat-reduced RCCs in artificial medium or their own plasma, may reduce postoperative immunosuppression. It was also anticipated that the use of autologous blood might minimize the risk of perioperative transfusion, but studies have unexpectedly shown similar postoperative infectious complications and cancer recurrence and/or survival rates in patients receiving autologous blood donated before operation and those receiving allogeneic blood [11,12]. Two mechanisms of the TRIM have been suggested: one is HLA-dependent and directed against adaptive immunity and the second, which is mild, non-specific, and directed against innate immunity [13].

Pre-storage leukoreduction of RCC units is now routine and implemented at national levels in many countries to avoid the accumulation of bioactive substances released from white cells implicated in TRIM. Beneficial effects include a reduction in the risks of febrile transfusion reactions, CMV transfusion transmissions, alloimmune platelet refractoriness, *etc.* although some unresolved issues remain as not all populations of WBC are reduced to a similar extent [14]. In addition there are problems regarding mortality and organ dysfunction in cardiac surgery and possibly other categories of patients [13].

The few viable leukocytes and possibly their EV remaining after leukoreduction may still modulate the immune response in the recipient [15]. Cytokine concentrations remain non-trivial in aged leukoreduced units [16]. Furthermore, exposure of leukoreduced stored RCC supernatant to whole blood triggers release of IL-6, IL-10, and TNF-α [17], reduces lipopolysaccharide-induced release of TNF-α by monocytes [18], and induces regulatory T-cell (Treg) activation [19]. In humans, Treg cells comprise ~1–2% of circulating $CD4^+$ T-helper cells that co-express a very high density of the IL-2 receptor-alpha ($CD25^{hi}$), inhibit IL-2 production and suppress the functions of Th1 responses by $CD4^+$ and $CD8^+$ T cells [19–21]. The activation of Treg cells is antigen non-specific as it can occur due to LPS and through the Toll-like receptor-4 pathway to lead to immune suppression [22].

The RBC storage lesion (RSL) is a complex biological phenomenon that implies deterioration in quality and likely contributes to TRIM. The non-specific effect might, therefore, result from the infusion of apoptotic blood cells as there is solid evidence that apoptotic changes occur during refrigerated storage. Immunosuppression resulting from the infusion of apoptotic cells may be linked to transforming growth factor beta (TGF-β) normally found within the mitochondrial space of white cells and the alpha granules of platelets [23] and is released upon the breakdown of membranes or activation [24]. Perhaps more important than infused TGF-β, is the infusion of the apoptotic cells themselves. Apoptotic cells express phosphatidylserine (PS) on their surface [25]. PS expression by apoptotic cells favors their uptake by phagocytes, such as macrophages or conventional dendritic cells, inducing the secretion of anti-inflammatory cytokines, such as IL-10 or TGF-β, as well as inhibition of the secretion of inflammatory cytokines such as IL-12 or IL-1β, IL-6 and TNF [26–28].

2.2. Inflammatory mediators

Although TGF-β is at center stage as a transfusion-related inflammatory/immunosuppressive cytokine [23], together with secondary cytokines released upon the phagocytosis of apoptotic cells, RBCs also contain non-polar lipids and a mixture of pro-inflammatory lyso-phosphatidylcholines (lyso-PCs) [29]. Lyso-PC modulates the activity of natural killer T (NKT) and T cells [30], acts as an NK cell chemoattractant [31], induces dendritic cell maturation [32], and stimulates the production of pro-inflammatory cytokines [33]. Ecosanoids (prostaglandins, thromboxanes and leukotrienes) can also accumulate in RCCs [34]. The overall effects of these biological substances are immunosuppression and promotion of tumors [35–38].

2.3. Microparticles

Blood cells and tissues generate heterogeneous populations of microparticles [MPs; also called extra-cellular vesicles, EVs)], that are microvesicles ranging from approximately 50 nm to 1 μm in diameter. Under normal physiological conditions, MPs are continuously shed into the circulation from the membranes of all viable cells such as megakaryocytes, platelets, red blood cells, white blood cells and endothelial cells. MP shedding can also be triggered by pathological activation of inflammatory processes and activation of coagulation, fibrinolysis, complement systems, or even by shear stress in the circulation. It is therefore expected that *ex vivo* processing of blood into its components during apheresis, centrifugation, pathogen reduction [39], contact with surfaces and storage adds to the already variable pool of MPs of each donor unit. Structurally, MPs have a bi-phospholipid layer exposing highly negatively charged coagulant-active PS and expressing various membrane receptors [40]. Physiologically, they shuttle bioactive molecules such as lipids, proteins or nucleic acid between cells and therefore can, when transfused, transfer genetic information such as miRNA to immune competent cells playing an immunomodulatory role [41].

RCCs have been shown to contain a mixed population of MPs, not all originating from erythrocytes. The concentration of the different EVs (the RBC EVs and the non-RBC EVs), their composition, as well as their effects on the quality of the blood product vary depending on the manufacturing methods used to produce the RBC