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Review

Extracellular vesicles in transfusion-related immunomodulation and the role of blood component manufacturing

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ABSTRACT

There is an emerging interest in the risks posed by the ability of blood transfusion to modulate the immune system of recipients. Observational trials suggest that RBC transfusions may be associated with increased morbidity and mortality, however studies demonstrating the deleterious consequences of transfusion-related immunomodulation have had conflicting results. Efforts to understand the biological mechanisms responsible for TRIM are under way, and are focusing on the role that the extracellular vesicles (EVs) that accumulate in a red cell concentrate (RCC) during storage may play. EVs are heterogeneous submicron-sized vesicles that vary in size, composition and surface biomarkers. The biophysical and biochemical parameters of EVs reflect their mechanism of formation and cell sources. RCCs have been shown to contain a mixed population of EVs and not all EVs in RCC are solely from the constituent RBCs. 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 RCC units. This article will review current evidence of the role of extracellular vesicles in transfusion-related immunomodulation and will discuss the impact that different methods used to collect, manufacture and store blood have on the composition and characteristics of EVs in RCCs.

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1. The risks associated with life-saving blood transfusions

Transfusion of red blood cell concentrates (RCCs) is a necessary, lifesaving medical intervention. RCCs are given to increase oxygen delivery to tissues in clinical situations where the circulating RBC level is low (anemia). Approximately 1.2 million RCCs are collected and transfused each year in Canada [1,2], and more than 90 million units are transfused globally [3]. RCCs are used to treat patients in a wide variety of medical and surgical interventions. Approximately 30% of critical care patients and more than 50% of cardiac surgery patients will receive blood products during their hospital stay [4,5]. Unfortunately, like any medical therapy, blood transfusion comes with risks.

As a global industry committed to improving the safety of blood products, significant efforts have been made to reduce the infectious risks associated with blood transfusion. For example, the occurrence of transfusion-related infections is now very low (approximately 1 in 8 million for HIV, 1 in 6.7 million for Hepatitis C and 1 in 1.7 million for Hepatitis B) [6]. With the risk of transfusion-transmitted disease significantly reduced, efforts are now focusing on several immune and non-immune transfusion adverse events such as acute and delayed hemolytic reactions, Transfusion Related Acute Lung Injury (TRALI), Transfusion Associated Circulatory Overload (TACO), and hypotensive reactions that have been associated with increased mortality and morbidity in transfusion recipients (summarized in [7,8]).

There is an emerging interest in the risks posed by the ability for blood transfusion to modulate the immune system of recipients. Transfusion Related Immunomodulation (TRIM) has been implicated in adverse clinical outcomes such as increased infection, acceleration of cancer growth, multiple organ dysfunction and short-term mortality after transfusion [9,10]. Purported mechanisms for TRIM include the release of immunosuppressive prostaglandins, activation of T lymphocytes by exosomes, inhibition of cytokine production (IL-2), suppression of monocytes and cytotoxic T-cells and increase in T-cell suppressor activity [9,11,12]. A large number of observational trials have suggested that RBC transfusions may be associated with increased morbidity and mortality [8], with several studies attempting to demonstrate the deleterious consequences of transfusion induced immune suppression with conflicting results [13–17]. While efforts to understand the biological mechanisms responsible for TRIM are under way, and clinical studies to examine the outcomes associated with immunomodulation continue, the role that blood component manufacturing has on the cell and cell-free components within blood components is rarely appreciated. This article will review current evidence of the role of extracellular vesicles (EVs) in transfusion-related immunomodulation and will discuss the impact that different methods used to collect, manufacture and store blood have on the composition and characteristics of EVs in RCCs.

2. Extracellular vesicles – what are they?

2.1. A definition of extracellular vesicles

The first discovery of extracellular vesicles was in 1964 when Chargaff and West [18,19] identified "subcellular factors" in cell-free plasma and showed that these factors played a role in blood clotting. In 1967, Wolf [20] confirmed the presence of these subcellular factors using electron microscopy when he was studying the "platelet dust" that was known to be shed by platelets during storage [19,21]. In most recent reviews, EVs are classified based on the mechanism of formation and the biophysical properties of the vesicles [22]. Accordingly, EVs can be categorized into two major types: exosomes and microvesicles [19].

2.2. Mechanism of microvesiculation

Microvesiculation is a controlled process by which EVs or membranous vesicles are formed and released *in vivo* and *in vitro* by cells in response to a variety of conditions and stimuli including hypoxia, oxidative stress and shear stress [23–26]. Cells can release a mixed population of EVs which are heterogeneous submicron-sized vesicles surrounded by a phospholipid bilayer and contain proteins, lipids, and a variety of genetic molecules [27–31]. Although the term cell-derived vesicle or EV is usually used when referring to exosomes and/or microvesicles [32,33], this is dependent on the formation, function, cell of origin, and characterization.

2.2.1. Exosome formation

Exosomes are released by many types of cells and they existing in most, if not all, of the biological fluids including, but not limited to, saliva, urine, milk, blood, seminal and cerebrospinal fluid [19,33]. There are two general path-