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Review

Big things from small packages: The multifaceted roles of extracellular vesicles in the components quality, therapy and infection

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Contents

Transfusion and Apheresis Science (TRASCI) regularly publishes themes dedicated to latest developments. In 2015, the theme sections of two issues [52 & 53] of TRASCI were dedicated to extracellular vesicles (EV) which include microvesicles (MV) also called microparticles (MP), as well as smaller EVs designated exosomes. The 52 theme section "Highlights of the role of PMP in health/disease & advancements in PRT and quality in transfusion establishments" was followed by the 53 issue "Blood cells–derived microvesicles with potential pathogenic roles in therapeutic blood components and specialized diagnostic tools in disease" [1]. The latter, in a series of 8 papers, discussed various aspects of blood components-derived microvesicles, the methods of investigation, their clinical importance, role in inflammation and transfusion, as well as their involvement in cancer [1].

Transfusion medicine-related studies traditionally focus predominantly on MPs (MVs) rather than exosomes, partly due to the routinely applied methods incapability to detect reliably small vesicles. The editors were aware of a potential need to extend the scope of the EV studies, asking in their editorial: "Aren't we missing the bulk MPs with a smaller size (<500 nm), the most populous, with specific, more hidden, potentially more potent functional activity?

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Should we revisit past studies that used standard flow-cytometry approaches to assess MPs as the sole main assessment technology?" [1].

In the current thematic section, we intended to cover, wherever possible, the smaller EVs not readily detected by routine unmodified flow cytometry methods. The characterisation of EVs, including exosomes in relation to blood and blood products quality is discussed in the first four papers [2–5], followed by two papers analysing ever more important roles of mesenchymal stromal cells (MSC)-derived EVs in cell therapy [6,7]. We also included two papers [8,9] reflecting the growing number of publications pointing at the role of EVs in the infection, hijacking cellular pathways to facilitate pathogen spread and interfere with immune responses.

Finally, as the debate on the age of red cells still continue and a better understanding of red cells storage lesion are becoming more clear using newer technologies including the proteomic, we included an update on red cell storage lesion highlighting the role of EV in the quality of red cell components [1].

In the first paper entitled: "Unresolved clinical efficacy & safety hazards of blood derived-EV/MV in stored blood components: An overview of our past/present experiences on the roles of EV/MV in various biological phenomena", Dr Jerard Seghatchian and Dr Jean Amiral review various assays for clinical assessment and biochemical observations on EV/MV in blood components applied as diagnostic tools [2]. Apart from past and present assays for identifying and quantifying MPs, they present technological developments that can be expected in the expanding field of EV/MV detection to open clear prospects for routine use. The authors also review current state of knowledge on the processing steps in the production of blood components (whole blood holding time, apheresis, leukoreduction, pathogen inactivation treatment, storage, etc.) that can trigger MP formation from red blood cells, white blood cells and platelets. They also highlight the fact that these sub-cellular components are present at high concentrations in each transfused units, but are not actually measured or controlled. There may be a delicate transfusional balance existing between a possibly beneficial haemostatic effect provided by EV/MV to bleeding patients and their likely detrimental side-effects (thromboembolism, inflammation, transfusion-related acute lung injury, etc.) in predisposed patients, due to their highly procoagulant membrane and their content of multiple growth factors, and important effects of EVs on the inflammatory status of patients. This supports the current views that the EV-contained molecules have a potential to act as novel effector elements of inflammation and affect pathogenesis by different types of biological response modifiers that are carried and released by leukocytes, erythrocytes, platelets or endothelial cells present in blood components. Future research, apart from current application of proteomics and capture technologies, is expected to help in defining the roles of MP subpopulations in inflammatory diseases and their cellular origin. This knowledge is likely to stimulate the development of new therapeutic strategies that target either MP release or action.

The following manuscript by the same authors entitled "Measurement of extracellular vesicles as biomarkers of consequences or cause complications of pathological states, and prognosis of both evolution & therapeutic safety/efficacy" focuses on the various levels of involvement of EVs (biomarkers, causative agents or resulting products) in various pathological processes [3]. EVs can also contribute to safety and efficacy evaluation of the blood components therapeutic use. EV immunomodulatory potential has been well documented, and depending on their cargo and target cell, they can act in both pro- and anti-inflammatory way, and activate various coagulation-related pathways. After summing up the generation, classification and factors affection EV production in vivo, the authors address the EV association with malignancy and a significance of particular membrane associated proteins for the EV–target cell interaction outcome. They also discuss EVs as diagnostic markers, extent of their therapeutic efficacy and their value for quality and risk assessment of blood products. The final parts of the review are dedicated to laboratory tools for exploring, characterising and measuring EVs with special emphasis on authors' experiences of capture-based assays, and a major role the EVs are expected to play in cellular therapy, tissue repair and regeneration.

Released MPs (MVs) were initially described in platelets and red blood cells, and an increased production of EVs under stress conditions during blood processing and storage is well documented. Less is known about EV variability in donor blood prior to transfusion and if/how this variability may be reflected in the EV content of blood components to be transfused. This is an important topic of the paper by Dr. E. Maurer-Spurej and co-authors entitled "Microparticle content of platelet concentrates is predicted by donor microparticles and is altered by production methods and stress", addressing this issue using ThromboLUX measurement of EVs between 50 and 550 nm in platelet-rich plasma or platelet concentrates without a need for prior platelet removal. According to their data, EV content variability in the final product is to a large extent determined by the variability in donors, although the processing methods and post-processing treatments, such as irradiation, pathogen inactivation, use of additive solutions and transport can substantially modify the EV content and numbers. Benefits of better donor characterisation using new technologies is being continuously discussed and it could help make decisions on more appropriate use of certain donor products in certain patient groups. While the premise of the elevated number of EVs present in platelets and red cells indicating "lower" quality is generally accepted, it appears that EVs present in platelets may sometime benefit heavily bleeding patients due to the increased pro-coagulation effects of the EVs. Further studies in this area will undoubtedly help identify donors/donations better suited for particular applications, which should in the end improve the transfusion outcomes.

This theme, although using a different approach, is continued in the paper by Dr. Baek and co-authors entitled "Does smoking, age or gender effect the protein phenotype of extracellular vesicles in plasma?" [6]. EV involvement in the development and progression of various diseases, disorders and immune regulation is well established [5,7–10]. However, the precise evaluation and quantitation of this involvement requires establishment the variability within