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BIOLOGICAL FUNCTIONS OF PLASMA MEMBRANE-DERIVED EXTRACELLULAR VESICLES AND THEIR ROLE IN DISEASES

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ABSTRACT

Plasma Membrane-derived Extracellular Vesicles (PMEVs) are membrane-coated vesicles of diameter 0.1 to 1.5μm, carrying various proteins inherent in their parental cells. PMEVs are released when cells undergo activation/apoptosis via blebbing and shedding and have a function in intercellular communication. Exposition of phosphatidylserine (PS) on the outer membrane leaflet that mark them as a biologically distinct entity could also explain a role for PMEVs in phagocytosis and thrombosis. The purpose of this review is to outline and discuss some of the functions of PMEVs in detail to throw more light on its biological effects as more research delve into emerging therapies targeting the microvesicle communication system. The role of PMEVs as a differentiation agent and therefore its possible use in differentiation therapy is discussed. In some experiments, the myeloid differentiating agents all trans retinoic acid (ATRA), phorbol 12-myristate 13-acetate (PMA) and histamine, which inhibit promonocyte proliferation, induced an intracellular Ca^{2+}-mediated PMEV release from HL-60 promonocytes. These PMEVs caused HL-60 cells to enter G0/G1 cell cycle arrest and induce terminal monocyte-to-macrophage differentiation through TGF-β1 mediation. The review also discusses the relationship between PMEVs and diseases where it is known that patients with certain inflammatory diseases show increased PMEV levels in the plasma. The review conclude on the fact that PMEVs have a lot of biological functions that are beneficial to the physiological functions in humans and therefore more work is required to elucidate their composition and the mechanisms involved in exertion of their effects.

Keywords: Plasma membrane, Extracellular, Cytokines, Microvesicles, Inflammatory, Differentiation.

Contribution/ Originality

This study contributes to the existing literature by addressing some aspects of extracellular vesicle release as well as their functions. The topic is of general interest and will be beneficial to potential readers who would want to clarify types of plasma extracellular vesicles, their functions or pathological effects.

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1. INTRODUCTION

Plasma Membrane-derived Extracellular Vesicles (PMEVs) are sub-cellular vesicles released upon shear stress, cell activation, injury or apoptosis [1]. Typically PMEVs range in size from 0.1μm to 1.5μm [2]. They express surface markers from their parental cells that allow identification of PMEVs sub-groups according to their origin: from platelets (P-PMEVs), leukocytes (L-PMEVs), red blood cells (R-PMEVs), endothelial cells and other tissue cells [3]; [4]; [5]. They harbor cell-derived membrane-bound and cytoplasmic proteins (e.g. chaperones) as well as bioactive lipids [6]. However, PMEVs are not replicas of the maternal cells and plasma membrane, suggesting a level of selectivity in their formation and sorting of cellular proteins released in them [7]. According to proteomic data, plasma PMEVs are enriched in Ig μ-chains, J-chains, profilin I and cyclophilin A, suggesting that PMEVs-bound IgM may provide a mechanism for their clearance [5]. PMEVs can be formed through several induction pathways, which determine their different molecular profiles and biological activities.

A major aspect in cell biology is communication, which occurs through a direct contact between cells or by means of soluble substances, which react with cells [8]. PMEVs released by cells influence other cells through the transfer of molecules which is a mechanism to deliver a message in a highly concentrated manner [8]. PMEVs therefore exert their effects either via stimulation of target cells by receptor interaction or by direct transfer of their contents which can include membrane proteins, lipids and cytoplasmic components of the parent cell or RNA [9]. By this, PMEVs may facilitate cell-to-cell interactions and transfer of signals and receptors between different cell types, inducing the signalling and response in distant cells [10].

1.1. PMEVs Formation and Release

Plasma Membrane-derived Extracellular Vesicles are released from the cell surface membrane following cellular activation or death by either chemical stimuli such as cytokines, endotoxins or a physical stimulus such as shear stress [11]. On cellular activation, there is a rise in cytosolic calcium (ca^{2+}) concentration possibly through the entry of extracellular ca^{2+} via ca^{2+} channels in the plasma membrane which are normally closed at physiologic or resting membrane potential, but are activated at depolarized membrane potentials [12]. This consequently leads to the activation of enzymes such as calpain, gelsolin, scramblase as well as protein kinases. Simultaneously, enzymes such as translocase and phosphatases are inhibited, therefore resulting in cytoskeletal reorganisation, loss of membrane asymmetry, membrane blebbing and hence PMEV formation and release (figure 1).

Much still remains to be understood about the mechanisms by which PMEVs are formed and shed. It appears that the release of the PMEVs population initiated by outward budding from the surface of the plasma membrane is followed by a fission event that in many ways resembles the abscission step in cytokinesis [13]. The release of PMEVs also appears to share similarities with the events associated with viral budding [14]. There are also structural similarities between PMEVs and apoptotic blebs, both of which form by outward protrusion of the plasma membrane. Unlike apoptotic bodies, however, shed PMEVs do not contain cytosolic organelles and/or

nuclear fragments [15]. A recurring theme, however, is that the initiating events involve both lateral and vertical redistribution of plasma membrane constituents resulting in alterations in local membrane curvature. In fact, there is research to show that membrane curvature proteins could be integral in inducing plasma membrane bending and consequently, membrane vesicle shedding [16]. Here it was shown that lipid aggregation into microdomains within the plasma membrane can result in, and act to stabilize, membrane-bending forces and interactions between constituent molecules [17]

1.2. PMEVs and Exosomes

Plasma Membrane-derived Extracellular Vesicles and exosomes are distinct vesicle populations [18]. The release of PMEVs and exosomes happens in two mechanisms of unconventional exocytosis that have received much attention over the past few years. Whilst PMEVs are released into the extracellular space by outward budding and fission of the plasma membrane from the cell surface, exosomes are formed intracellularly via endocytic invagination and are released into a structure known as a multivesicular body (MVB) [18]. The MVB then fuses with the plasma membrane, releasing its cargo of exosomes into the extracellular space. In the past few years, several groups have reported the secretion of exosomes by various cell types, and have discussed their potential biological functions [18].

Again, PMEVs and exosomes are morphologically distinct. A recent study reveals that protease-containing microvesicles shed from tumor-cell lines appear to be rather heterogeneous in size and shape as opposed to exosomes, which and are a more uniform population of vesicles [13]. The same study also showed that microvesicles sediment at lower speeds relative to exosomes, which pellet at 100,000 g. Scientists have however recently acknowledged the difficulty of separating exosomes from other types of extracellular vesicles (PMEVs), which precludes a clear attribution of a particular function to the different types of secreted vesicles [19].

2. FUNCTIONS OF PMEVS

The function of microvesicles appears to be dependent on the cargo they carry. This, in turn, is dependent on the cell type from which they originate [16]. The most frequently described characteristic of both *in vitro* and *in vivo* released PMEVs is their procoagulant activities [20]; [21] which contribute to haemostasis by stimulation of cytokine secretion and tissue factor expression in endothelial cells [22]. PMEVs contain several signalling proteins and bioactive lipids including sphingosine 1-phosphate (S1P) and arachidonic acid (AA) and are said to be involved in signal transduction. They can activate certain signalling pathways in human cells such as P38 and mitogen-activated protein kinase (MAPK) [23]. Other PMEV fractions were reported to induce cellular growth, chemotaxis, apoptosis and the outgrowth of transplanted haematopoetic stem cells as well as the inhibition of endothelium-dependent vasodilatation [22]; [24]; [25].

Plasma Membrane-derived Extracellular Vesicles can directly activate and stimulate cells to produce inflammatory substances or mediators such as cytokines [4] [26]. PMEVs bearing

antigens of their cell of origin can transfer these surface molecules to other cell types and in so doing they may alter the biological activity of the recipient cells [27]. In addition, at least *in vitro* microparticles mediate intercellular interactions [8]; [26]; [28]. Also, subpopulations of PMEVs isolated from human plasma expose C1q, C3 and C4, strongly suggesting their direct involvement in activation of the complement system [29]. Currently, the relation between cellular PMEVs and C-reactive protein (CRP) is being studied. This acute phase protein is known to bind to membranes and, in the membrane-bound form, may activate the classical pathway of the complement system, ultimately leading to vascular damage [30].

Although elevated levels of PMEV subpopulations are present in the circulation of patients with inflammatory disease, any causal link between PMEVs and inflammatory processes cannot readily be established. This is because cytokines trigger cells, thereby stimulating the release of PMEVs, whereas PMEVs trigger cells to produce and release cytokines [4]; [20]. Therefore, it is as yet unclear whether cellular PMEVs are a cause or a consequence of inflammatory processes and associated vascular damage. PMEVs however play a role in organ defence systems such as stress response, inflammation and regeneration as well as in modulation of vascular tone, angiogenesis and stem cell engraftment [24]. PMEVs may also expose adhesion-cell molecules, and specifically adhere to for example endothelial cells thereby stimulating these cells to produce various intermediates, such as E-selectin and tissue factor [10]; [24]; [26].

Phosphatidylserine (PS) acts as a marker for cells that are identified as injured and ready for phagocytosis. However because injured cells have a window of opportunity to be repaired, PMEVs have to be shed from the cells when the repair is successful by probably getting rid of the phagocytotic signal [5]; [31]. PMEVs help cells resist death by eliminating the membrane attack complex (MAC) of complement from their surface so inhibiting apoptosis of polymorphonuclear leukocytes [23]. Chemotactic responsiveness of human haematopoietic stem/progenitor cells as well as increased survival of these cells is enhanced by platelet-derived PMEVs [24]; [26]. The role of PMEVs in the inhibition of phagocytosis of apoptotic cells has also been demonstrated [32].

2.1. PMEVs as a Differentiation Agent (Differentiation Therapy)

The significance of the local effect of PMEVs on different cell types and in physiological conditions has recently attracted growing attention since a great variety of biological consequences of the action of PMEVs in the immune response and inflammation have been revealed [21]. For example, the presence and type of stimulatory signals determine whether promonocytes/monocytes acquire dendritic cell or macrophage characteristics and functions and in a study by Inal *et al* of the Cellular and Molecular Immunology Research Centre (CMIRC) of London Metropolitan University, UK [unpublished data] the effect of PMEVs on the induction of differentiation of promonocytes into macrophages was clear.

In recent times, much research has been carried out on differentiation agents as cancer therapies, whereby they are able to differentiate the immature promonocytic forms into mature ones to halt their proliferation and the leukaemia [33]. A work to find out how PMEVs induce

differentiation of promonocytes to macrophages, and so prevent their proliferation and whether this could provide the underlying principle by which PMEVs may be used for treatment of myeloid leukaemia has been undertaken by colleagues at CMIRC [unpublished data].

Since all-trans retinoic acid (ATRA), phorbol 12-myristate 13-acetate (PMA) and histamine are all involved in cellular differentiation, and therefore leukaemia treatment, their effect on the terminal differentiation of HL-60 promonocytic cells to monocytes/macrophages have been investigated [unpublished data]. The differentiation process was observed through a change of morphology, appearance of cell surface markers such as CD14 and CD11b, which are known typical macrophage markers. Nitro blue tetrazonium (NBT) assay with statistical analysis again confirmed these agents (two of which are already in use in cancer therapeutics) to be good inducers of differentiation.

Until recently, the idea of restoring normal differentiation in primitive leukaemic cells seemed unrealistic until the effect of ATRA in acute promonocytic leukaemia (APL) was shown [33]; [34]. This is because chemotherapy and haematopoietic stem-cell transplantation were the only therapeutic options available in acute leukaemia but most APL patients are now treated first with ATRA since it became the first differentiation agent found to be successful in APL treatment [33]; [34].

Experiments have shown that attachment of PMEVs to HL-60 cells is PS mediated, as with contact (and fusion) of monocyte-derived PMEVs with platelets, but the attachment/fusion is not a prerequisite for the observed differentiation [35]. However, contact with or phagocytosis of apoptotic cells and PMEVs by macrophages has been shown to lead to the release of TGF-β1by the macrophages, at levels of 80pg/ml and 350pg/ml respectively. Importantly, such release and autocrine-like action of TGF- β1 on the HL-60 cells results in reduction in proliferation, and consequent differentiation of the cells [12].

Differentiation therapy has shown a great deal of promise but has its shortfalls since ATRA and other agents with the capacity to induce differentiation of leukemic blasts *in vitro* have not shown efficacy *in vivo* in acute leukemias other than APL even though in many types of acute leukemia, disruption of genes involved in cell proliferation and differentiation has been observed [36]. The successful treatment of APL with differentiation therapy however, gives hope that agents (PMEVs) targeting those genes especially by down-regulating fusion proteins will be able to restore differentiation of other types of leukemic blasts in the near future.

2.2. PMEVs and Diseases

Although circulating basal level PMEVs can be found in the blood of normal individuals, increased numbers of circulating PMEVs have been identified in individuals with certain diseases, including hypertension, prothrombotic states such as thrombotic thrombocytopenic purpura, the antiphospholipid antibody syndrome, multiple sclerosis, cerebral malaria and many diseases associated with inflammation [20]; [22]. PMEVs can be taken as a sign of cellular dysfunction and serve as general indicators of cell injury, stress, thrombosis and inflammation although their role in the various diseases whether as direct contributors or merely a reflection of the disease

remains to be determined [20]; [23]. However the presence of PMEVs provides an important tool in measuring the protective effect of therapeutic intervention in a non-invasive manner as well as acting as a marker or indicator of severity of disease states [20].

The quantity, cellular origin and composition of PMEVs are dependent on the type of disease. For example, monocyte, platelet and endothelial-cells derived PMEVs are found in septic patients [37]. Platelet-derived PMEVs are increasingly present in patients with peripheral artery disease, myocardial infarction, atherosclerosis, diabetic retinopathy, paroxysmal nocturnal haemoglubinuria and those undergoing ischemic events [22]; [38]. Recent studies indicate that PMEVs are able to decrease nitric-oxide-dependent vasodilation, increase arterial stiffness, promote inflammation, and initiate thrombosis at their PS-enriched membrane, which highly co-expresses tissue factor [30]. PMEVs are also known to be elevated in acute coronary syndromes, end-stage renal disease and all conditions associated with endothelial injury or dysfunction.

Elevated levels of circulating platelet, monocyte, or endothelial-derived PMEVs are associated with most of the cardiovascular risk factors and appear indicative of poor clinical outcome [30] [25]. In addition to being a valuable hallmark of vascular cell damage, PMEVs are at the crossroad of atherothrombosis processes by exerting direct effects on vascular or blood cells [22]. Under pathological circumstances, circulating PMEVs would support cellular cross-talk leading to vascular inflammation and tissue remodeling, endothelial dysfunction, leukocyte adhesion, and stimulation [22].

At sites of vascular injury, P-selectin exposure by activated endothelial cells or platelets leads to the rapid recruitment of PMEVs bearing the P-selectin glycoprotein ligand-1 and blood-borne tissue factor (TF), thereby triggering coagulation [2]; [25]. PMEVs accumulating in the lipid core of the atherosclertotic plaque are thus a major determinant of its thrombogenecity [39]. In fact one of the main goals of research is to analyse PMEVs within the atherosclerotic plaque since it is believed sequestered PMEVs constitute the main reservoir of TF activity, promoting coagulation after plaque erosion or rupture [4].

Elevated levels of PMEVs have been observed in cerebral malaria (CM) where their procoagulant property helps in the sequestration of activated blood cells (notably monocytes/macrophages, parasitized erythrocytes, and platelets) in cerebral vessels consequent to immune responses in the host [40]. Experiments carried out with the ATP-binding cassette transporter A1 (*ABCA1*) knockout mice showed a reduction in the capacity of cells to vesiculate, resulting in complete resistance to cerebral malaria of the *ABCA1*$^{-/-}$ mice.

The finding that *ABCA1* deletion confers a complete protection against CM, associated to an impaired PMEVs production, orientates toward new therapeutic approaches to the search for candidate genes controlling vesiculation [41]. With vesiculation (PMEV release) being implicated in atherosclerosis and CM, one of the main goals of research is to prevent both PMEV release and PS exposure at the cell surface. Thus, lower PMEV levels are likely to reduce the incidence of CM and thrombotic diseases [23].

3. CONCLUSION

Although the prognostic potential of circulating PMEVs is still in its infancy, the different studies being carried out clearly demonstrate that their detection and quantification is an interesting and potentially valuable tool to appreciate in disease states [42]. Elucidation of the PMEV composition and the mechanisms involved in exertion of their effects (functions) will supply a lot of evidence that will enable us to develop intervention strategies for prevention and treatment of most diseases associated with PMEV release [3].

List of Abbreviations

AA	Arachidonic Acid
ABCA1	ATP-binding cassette transporter A1
APL	Acute Promonocytic Leukaemia
ATRA	All Trans Retinoic Acid
CM	Cerebral Malaria
CRP	C-reactive Proteins
IgM	Immunoglobulin M
MAC	Membrane Attack Complex
PMA	Phorbol 12-myristate 13-acetate
PMEVs	Plasma Membrane-derived Extracellular Vesicles
PS	Phosphotidylserine
S1P	Sphingosine 1-phosphate
TF	Tissue Factor
TGF – β1	Tissue Growth Factor – β1

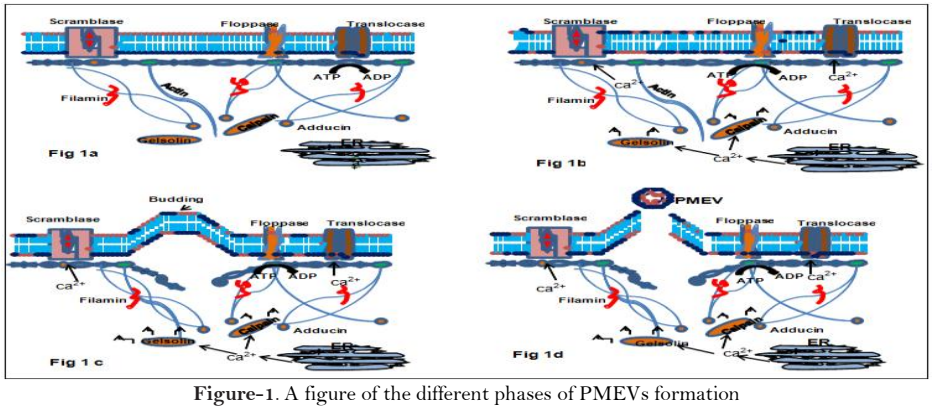

Figure-1. A figure of the different phases of PMEVs formation

Fig 1a: *Representation of the resting cell*: Scramblase is inactive while Translocase and Floppase are active maintaining membrane asymmetry. Fig 1b: *Cell Activation*: Scramblase, Calpain and Gelsolin are activated due to calcium release from ER. Calpain cleaves long actin filaments. Gelsolin cleaves actin-capping proteins. Translocase is inactivated. Membrane asymmetry is compromised. Fig 1c: *Cytoskeletal Disruption*: protein anchorage to the cytoskeleton is disrupted allowing membrane budding. Fig 1d: *Plasma Membrane-derived Extracellular Vesicles (PMEVs) formation*: PMEVs are formed and released with increased phosphatidylserine exposed on their external surface.

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