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Review

Microparticles and immunomodulation in pregnancy and pre-eclampsia

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Abstract

Cellular microparticles are ubiquitously shed from cell membranes or secreted as endocytic vesicles called exosomes. Shed microparticles are ≥100 nm in size and are generated during apoptosis or necrosis. In contrast, exosomes are smaller (<100 nm), express more limited protein content and are released from late endosomes. Both membrane particles and exosomes can be detected in the circulation in non-pregnant and pregnant women. In the former, they are increased in conditions associated with systemic inflammation such as sepsis or metabolic syndrome. During pregnancy, they are also associated with pre-eclampsia and include not only particles derived from platelets, endothelium and various leukocytes but also syncytiotrophoblast-derived microparticles. Syncytiotrophoblast membrane microparticles (often called STBMs) interact with both immune and endothelial cells. They may contribute to the systemic inflammatory response of both normal and pre-eclamptic pregnancies, although inhibitory activity has also been described. Moreover, trophoblast-derived exosomes may contribute to or cause the downregulation of T cell activity that has been repeatedly observed during pregnancy. Deletion of activate T cells which express Fas ligand by Fas-expressing exosomes derived from trophoblast may contribute to immunoregulation necessary for normal pregnancy.
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1. Introduction

Microparticles are cellular fragments ubiquitously shed into body fluids, under both physiological and pathological conditions. The term is generic and describes a range of membrane-bound, subcellular elements produced during apoptosis, cellular activation or by vesicle secretion. The particles are usually of the order of 100 nm in diameter. In general, the largest are necrotic fragments. Intermediate in size are those that are formed directly by blebbing of cell membranes after activation or apoptosis. They are sometimes called ectosomes (Gasser and Schifferli, 2004) to distinguish them from smaller exosomes (30–100 nm) (Théry et al., 2002), which are shed from intracellular multivesicular bodies (Fig. 1) when they fuse with the plasma membrane. In this paper, unless otherwise stated, the unqualified term microparticles (MPs) refers to ectosomes.

Microparticles or exosomes vary with respect to cellular origin, size and antigenic properties, and contain many proteins and lipids from the membranes and cytoplasm of the cells of origin, even mRNA. They may transmit infectious particles such as human immunodeficiency virus or prions, or even intact organelles such as mitochondria (Ratajczak et al., 2006).

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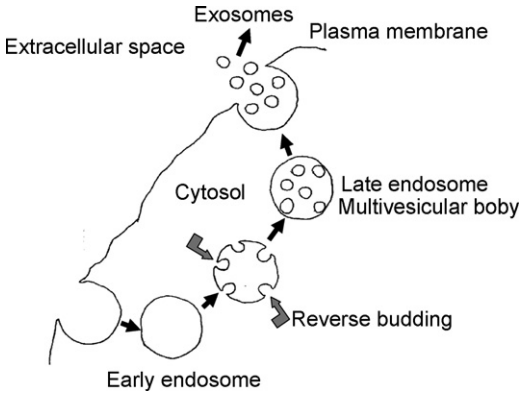

Fig. 1. Origin of exosomes from multivesicular bodies by exocytosis. Adapted from Morelli (2006).

Platelet MPs were the first to be detected by the persistence of platelet-like activity in serum and were then directly visualised by electron microscopy in 1967 (Wolf, 1967).

In the circulation, MPs may originate not only from platelets but also erythrocytes, granulocytes, leukocytes and endothelium (Ratajczak et al., 2006). Numerous reports of circulating dendritic cell particles appear to be mainly referring to exosomes.

2. Mode of formation

Cultured cells constitutively shed MPs, a process that is stimulated by various events, including inflammatory stimuli or calcium influx and is calpain-dependent (Yano et al., 1993). Inflammatory stimuli include cytokines such as tumour necrosis factor-alpha (TNF-α) or interleukin-1 (IL-1β), or laboratory reagents including fMLP, phorbol ester, ionomycin, phorbol myristate acetate (PMA), concanavalin A or activated complement C5a (see Distler et al., 2005, for further details). A key early event is reorganisation of the lipid asymmetry of the plasma membrane, with exteriorisation of phosphatidyl serine. Lipid rafts and their accompanying cholesterol and proteins are concentrated where the membrane buds so that MPs are enriched in cholesterol and raft-associated proteins. Calcium chelation inhibits apoptosis and MP generation. Increased levels of cytoplasmic calcium activate different cytosolic enzymes relevant to MP formation. Calpain is one of the most important and has several actions in microparticle generation including cleaving cytoskeletal filaments, facilitating microparticle shedding, and activating apoptosis through procaspase-3. Different mechanisms may contribute to the processes of MP formation in cell-specific ways and the type of MP may change depending on how its production is stimulated (Jimenez et al., 2003). For example, exosomes are produced by different mechanisms than other MPs (see next section), but also in response to cell activation (Théry et al., 2002). Both microparticles and exosomes are now considered to provide unconventional routes for protein secretion (Nickel, 2005).

3. Exosomes

This topic is comprehensively reviewed by Théry et al. (2002). Exosomes were first described nearly 25 years ago. They are smaller than MPs and formed by secretion of the contents of cytoplasmic multivesicular bodies. As are other MPs, they are rich in lipid rafts, express molecules characteristic of the cell of origin and convey some of their cytoplasmic contents. However, some plasma membrane proteins are excluded and some, such as tetraspanins, which contribute to the organization of large molecular complexes and membrane subdomains, are thought to be enriched. Exosomes do not contain any proteins of nuclear, mitochondrial, endoplasmic reticulum or Golgi apparatus origin and therefore are not simply fragments of the plasma membrane. Exosomal proteins include those that are found in the cytosol, the membrane of endocytic compartments or in the plasma membrane. Other markers include heat shock proteins, annexins, integrins and other adhesion molecules. The presence of classes I and II MHC antigens endows the exosomes with antigen-presenting capabilities (Zitvogel et al., 1998).

4. Measurement

Microparticles can be analysed by flow cytometry or ELISA. Centrifugation is essential, first to remove platelets and subsequently more vigorously to sediment the particles of interest. Standard protocols have not yet been agreed. Freezing is possible but undesirable. The great advantage of flow cytometry is that MPs of different cellular origins can be discriminated by their unique markers, concurrently, but as yet it is not sensitive enough to detect exosomes. Electron microscopy enables direct examination of morophology.

5. Microparticles and the systemic inflammatory response

We have previously summarised the evidence for a systemic inflammatory response in both normal pregnancy and pre-eclampsia (Redman et al., 1999; Sargent et al., 2006) and emphasised the role of the intravascular

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