View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by RERO DOC Digital Library

Semin Immunopathol (2011) 33:393–394
DOI 10.1007/s00281-011-0276-6

REVIEW

Microvesicles are messengers

Jürg A. Schifferli

Received: 25 April 2011 / Accepted: 4 May 2011 / Published online: 18 May 2011
© Springer-Verlag 2011

For years, we have rightly learned that communication in and between organisms depends on soluble mediators and cell-to-cell contact. The evidence that microvesicles released by one cell might provide information to another cell or is capable to modify the immediate and the distant environment emerged only over the last two decades (Fig. 1). Initially, such membrane-coated vesicles were considered as waste to be eliminated or to correspond to activating surfaces for coagulation. Only more recently did it became apparent that there was more to it. These vesicles transmitted messages—suppressive, activating and/or modifying messages. Interestingly, even bacteria release vesicles, which seem to bulge from the outer membrane. Most cells release microvesicles, spontaneously or after stimulation. Thus, this universal phenomenon may have two fundamental functions: get rid of unnecessary material and transmit messages. In this series of reviews, the second aspect will be mainly emphasized since many novel aspects have emerged and merit attention. There has been no attempt to cover the whole field, but rather to illustrate some fundamental aspects, which are presently under investigations.

First, bacteria produce vesicles. These outer membrane vesicles (OMV) of gram-negative bacteria have revealed a mechanism by which virulence factors can be concentrated and transmitted at a distance to other bacteria. Can Ünal and colleagues describe this phenomenon, discuss how these vesicles can vehicle toxins, serve as activators [1] or decoy for the immune system, but indicate as well, that it has been possible to use OMV to our advantage, i.e. by modifying and using them as vaccines. Indeed, the efficacy of the OMV-derived vaccine against the serotype B meningococci is around 90%; nothing similar has been obtained by other methods to date. The idea to use microvesicles as vaccines has also been taken up by tumour immunologists!

Eukaryotic cells release different type of vesicles. Without matrix vesicles released by mineralizing cells, we would be boneless and even teethless! The existence of such vesicles was over a longer period of time disputed, until it was realized that they were essential for calcification to take place. Ellis Golub describes the complex biological properties of matrix vesicles [2]. He indicates, however, not only the good side of these annexins and phosphatidyl-serine (PS) containing vesicles, but also that they are responsible for pathological calcifications as seen in atherosclerotic plaques.

But not all vesicles are shed from the cell surface as matrix vesicles. There has been an extensive series of studies on the formation of exosomes, a type of vesicle that is formed inside the cell and then secreted. Exosomes are produced/stored in multivesicular bodies, express specific proteins of the endosomal compartments, and have a characteristic size of around 50–100 nm. Initially described in reticulocytes, they were found in many cells, including immune cells—in particular dendritic cells—and in tumour cells as well. Many groups of researchers have explored these exosomes in depth, their formation, the expression of specific molecules on their surface and of course their possible functions. Very interesting are the studies, which define their immune response enhancing or blocking activities. The Paris team has for more than a decade explored the potential role of dendritic cells in immune

This article is published as part of the special issue on Small Vesicle as Immune Modulators [33:5]

J. A. Schifferli (✉)
Department of Medicine, University Hospital Basel,
Basel, Switzerland
e-mail: j.schifferli@unibas.ch

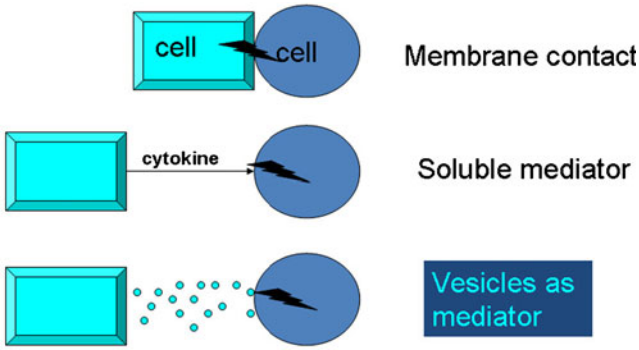

Fig. 1 Intercellular communication in an organism or between organisms

responses (Nathalie Chaput and Clotilde Théry) [3]. Douglas Taylor and Cicek Gercel-Taylor have defined exosomes of tumour cells and placenta [4] more than 20 years ago and provided much evidence concerning their capacity to modify their microenvironment. Both review present up to date knowledge in the field of exosomes.

Exosomes transmit messages by their surface proteins and lipids. However, the observation that intra-vesicular components might transmit not only proteins, but also different types of RNA and DNA has fascinating perspectives. Indeed, the cells taking up such materials might be modified profoundly. Tae Hon Lee and co-authors describe the "cargo" function of exosomes, and show thanks to recent data obtained in their own group how oncogenes are transmitted from tumour cells to cells around the tumour—an oncogenic field effect [5]. It is possible that such transfer of genetic material is part of normal biology and development as well.

One should not forget that much initial work on microvesicles has been performed with platelets. Activated platelets release a large number of microvesicles directly from the cell surface (shed microvesicles=microparticles, also called ectosomes) and exosomes. These microparticles express much PS, thus, allow coagulation to proceed. Olivier Morel and colleagues describe this interaction between vesicles originating from platelets and other cells found in blood and the coagulation cascade, a field, to which they have contributed extensively [6]. Evidently, there is more to it than just coagulation, binding to endothelial and inflammatory cells induces further reactions, which merit to be understood if we want to control pathological situations related to excessive platelet activation.

Salima Sadallah et al. review recent evidence that many circulating cells release ectosomes, i.e. vesicles budding directly from the cell surface. This has been known for a long time for platelets and erythrocytes when attacked by complement. Interestingly, ectosomes released by polymorphonuclear leukocytes, the very cells that enhance inflammation, have anti-inflammatory and immunomodulatory activities [7], probably because of the expression of PS similar to apoptotic cells.

Indeed, apoptotic cells and bodies show a change in the distribution of the membrane bi-layer phospholipids with PS being scrambled from the internal layer to the external surface. The high expression of PS and oxyPS induces their phagocytosis by macrophages but also by by-standard cells with induction of an anti-inflammatory/immunosuppressive reaction [8]. Benjamin Frey and Udo Gaipl recapitulate what is known about PS on apoptotic cells and microvesicles, so as to allow us to better understand the role of PS expression under different conditions [9].

References

1. Vidakovics ML, Jendholm J, Mörgelin M, Månsson A, Larsson C, Cardell LO, Riesbeck K (2010) B cell activation by outer membrane vesicles–a novel virulence mechanism. PLoS Pathog 15:e1000724
2. Kirsch T, Harrison G, Golub EE, Nah HD (2000) The roles of annexins and types II and X collagen in matrix vesicle-mediated mineralization of growth plate cartilage. J Biol Chem 275:35577–35583
3. Viaud S, Ploix S, Lapierre V, Théry C, Commere PH, Tramalloni D, Gorrichon K, Virault-Rocroy P, Tursz T, Lantz O, Zitvogel L, Chaput N (2011) Updated technology to produce highly immunogenic dendritic cell-derived exosomes of clinical grade: a critical role of interferon-γ. J Immunother 34:65–75
4. Sabapatha A, Gercel-Taylor C, Taylor DD (2006) Specific isolation of placenta-derived exosomes from the circulation of pregnant women and their immunoregulatory consequences. Am J Reprod Immunol 56:345–355
5. Magnus N, Garnier D, Rak J (2010) Oncogenic epidermal growth factor receptor up-regulates multiple elements of the tissue factor signaling pathway in human glioma cells. Blood 116:815–818
6. Morel O, Hugel B, Jesel L, Mallat Z, Lanza F, Douchet MP, Zupan M, Chauvin M, Cazenave JP, Tedgui A, Freyssinet JM, Toti F (2004) Circulating procoagulant microparticles and soluble GPV in myocardial infarction treated by primary percutaneous transluminal coronary angioplasty. A possible role for GPIIb-IIIa antagonists. J Thromb Haemost 2:1118–1126
7. Eken C, Martin PJ, Sadallah S, Treves S, Schaller M, Schifferli JA (2010) Ectosomes released by polymorphonuclear neutrophils induce a MerTK-dependent anti-inflammatory pathway in macrophages. J Biol Chem 285:39914–39921
8. Borisenko GG, Matsura T, Liu SX, Tyurin VA, Jianfei J, Serinkan FB, Kagan VE (2003) Macrophage recognition of externalized phosphatidylserine and phagocytosis of apoptotic Jurkat cells–existence of a threshold. Arch Biochem Biophys 413:41–52
9. Frey B, Munoz LE, Pausch F, Sieber R, Franz S, Brachvogel B, Poschl E, Schneider H, Rödel F, Sauer R, Fietkau R, Herrmann M, Gaipl US (2009) The immune reaction against allogeneic necrotic cells is reduced in Annexin A5 knock out mice whose macrophages display an anti-inflammatory phenotype. J Cell Mol Med 13:1391–1399