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Review

Immunomodulatory effects of exosomes produced by virus-infected cells

Juraj Petrik *

Scottish National Blood Transfusion Service and University of Edinburgh, Edinburgh, UK

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ABSTRACT

Viruses have developed a spectrum of ways to modify cellular pathways to hijack the cell machinery for the synthesis of their nucleic acid and proteins. Similarly, they use intracellular vesicular mechanisms of trafficking for their assembly and eventual release, with a number of viruses acquiring their envelope from internal or plasma cell membranes. There is an increasing number of reports on viral exploitation of cell secretome pathways to avoid recognition and stimulation of the immune response. Extracellular vesicles (EV) containing viral particles have been shown to shield viruses after exiting the host cell, in some cases challenging the boundaries between viral groups traditionally characterised as enveloped and non-enveloped. Apart from viral particles, EV can spread the virus also carrying viral genome and can modify the target cells through their cargo of virus-coded miRNAs and proteins as well as selectively packaged cellular mRNAs, miRNAs, proteins and lipids, differing in composition and quantities from the cell of origin.

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Abbreviations: CMV, cytomegalovirus; DC, dendritic cells; EBV, Epstein–Barr virus; ESCRT, endosomal sorting complexes responsible for transport; EV, extracellular vesicles; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HHV, human herpesvirus; HIV, human immunodeficiency virus; HPgV, human pegivirus (formerly known as GBV-C or hepatitis G virus); HPV, human papillomavirus; IFN, interferon; IL, interleukin; ILV, intraluminal vesicles; miRNA, micro RNA; MV, microvesicles; MVB, multivesicular bodies; SNARE, SNAP [soluble NSF (N-ethylmaleimid-sensitive factor) association protein] receptor; TCR, T-cell receptor; TLR, toll-like receptor.

* Scottish National Blood Transfusion Service and University of Edinburgh, Edinburgh, UK. Fax: +441313145583.
E-mail address: juraj.petrik@nhs.net.

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1. Extracellular vesicles

Practically all cells have been shown to release EVs under physiological conditions and to increase this release under various stress stimuli. This supports one of the main functions proposed for EVs – intercellular communication with neighbouring cells as well as more distant target cells which they can reach via their presence in body fluids. Among early descriptions of EVs were Wolf's paper on "platelet dust" [1], investigation of erythrocyte transferring receptor shedding [2] and vesicle formation during erythrocyte maturation [3].

Three main types of EVs are currently recognised: microvesicles, exosomes and apoptotic bodies. Apoptotic bodies are the largest EVs (1–5 μM). As their name suggests they are produced during programmed cell death. Apart from their size they can be distinguished from other vesicles by their higher density (1.24–1.28 g/ml) and DNA and histone content [4]. They are not a subject of this review. Microvesicles (MV; sometimes termed shedding microvesicles) are formed by blebbing from the plasma membrane. They are intermediate in density (1.16 g/ml) and size (100–1000 nm). Due to the process of their formation almost no general markers have been described for MV. Rather, the cargo corresponds to the cell of origin, albeit the content and quantities of molecules may not be identical to average content and quantities of the cell of origin. It may reflect local plasma membrane changes and environment, with particular molecular species accumulating at the sites of shedding. The exceptions seem to be some integrins and matrix metalloproteins, in particular MMP2 which can be considered a microvesicle (ectosome) marker [5]. Exosomes are the smallest among EVs (40–100 nm), many less dense than MV (1.10–1.19 g/ml). They also differ by their biogenesis, originating from internal membranes. Consequently, there are a number of specific markers in exosomes produced in different types of cells. Differential centrifugation of pre-cleared conditioned media, plasma, and other body fluids is the most frequently used way of preparation of MVs and exosomes. However, MV sedimentation at 15–20,000*g* and subsequent exosome sedimentation at 100–110,000*g* do not provide a perfect separation of the two types of EVs and same is true for the commercially available kits. Additional methods such as filtration, density gradient centrifugation, chromatography or affinity capture are therefore frequently used to obtain better defined EV subpopulations [6–8].

This review will focus on exosomes, with specific attention given to exosomes produced during viral infection.

2. Exosome biogenesis, content, sorting, release and uptake

As mentioned earlier, exosomes are the only EVs formed from internal membranes, by inward budding of endosomal membrane of multivesicular bodies (MVB; or late endosomes). They correspond to intraluminal vesicles (ILV) which can be destined either for degradation in lysosomes, for recycling or secretion after being trafficked to the plasma membrane and released into extracellular space upon fusion [9]. Then they are termed exosomes. Distinct subpopulations destined for different processing appear to differ in cholesterol content – high in MVB for exosome secretion, low in those for degradation [10], and lysobiphosphatidic acid which is missing in exosomes [11].

Exosome biogenesis is intertwined with the processes of the selective cargo transport between organelles. Four ESCRT (endosomal sorting complexes responsible for transport) were described for MVB destined for degradation: ESCRT 0, I, II and III. The first three recognise and sequester ubiquitinated membrane proteins, while ESCRT III takes part in ILV scission and budding [12]. For MVB destined for secretion, several parallel mechanisms seem to operate. In addition to the ESCRT pathway described above, an ESCRT-independent mechanism, dependent on ceramide producing enzyme sphingomyelinase, was described [13]. Another mechanism, independent of the first two, involves tetraspanins [14]. Functions of the ESCRT system may be different for lysosomal sorting and EV production. Based on the authors' unpublished data from a study of RNAi targeting 23 components of ESCRT 0/I/II/III and associated proteins, only a few involved in the EV production were identified: STAM (signal transducing adaptor molecule), TSG101, ALIX, HRS (hepatocyte growth factor-associated tyrosine kinase) and VPS4 [12].

Sorting signals in the cytoplasmic domains of transmembrane cargo proteins interact with vesicle "coats" – protein complexes coating the surface of vesicle (COP I, COP II, clathrin). Signals are quite diverse – from short hydrophobic sequences of two amino acids to 5–9 amino acid signals which may imply multiple binding sites on recognition proteins [9]. The composition of these coating proteins involving a number of adaptor molecules is rather complex and changes during the transport stages. The uncoating of clathrin vesicles is mediated by cytosolic chaperones (Hsc70, auxilin) and the association of membrane proteins with chaperones (Hsc70, hsp90, 14-3-3 epsilon, PKM2) in the process of recruitment of cytosolic proteins has been suggested for protein sorting during the exosome secretory pathway of vesicle production [15].

Less clear is the situation with sorting the RNA species into exosomes. Certain nucleotide patterns and hnRNPA2B1 interaction with target miRNA sequences were implicated in RNA sorting mechanisms [16,17]. They are unlikely to explain the presence of all RNA species in exosomes and further studies are necessary to decipher RNA targeting into exosomes.

SNARES (SNAP receptors) are mostly C-terminally anchored molecules with cytosolic N-terminal domain, containing the "SNARE motif" of 60–70 amino acids involved in coiled-coil formation [18]. They appear to have two main functions: to promote fusion and to ensure the specificity of membrane fusions. Or in general terms, they act to overcome the energy barrier to fusion. These are complex processes involving a number of additional proteins and factors. But the specificity comes from pairing of different v (vesicular) and t (target) SNARES. They form a four-helix bundle, with one alpha helix contributed by the monomeric v-SNARE and three by the oligomeric t-SNARE. This very stable complex brings the membranes together, facilitating fusion. The specificity of membrane fusion is partly mediated by different v- and t-SNARE pairing. However, it has been shown that they can pair promiscuously in vitro,

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