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Popular Article

Extracellular Vehicles (EVs): A Novel Approach for Treating and Diagnosing Diseases

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Introduction

Extracellular vehicles (EVs) are lipid bilayer-enclosed particles released from all types of cells and found in biological fluids such as blood, cerebrospinal fluid (CSF), urine, saliva, breast milk, seminal fluid and tears and that carry cargoes such as lipids, proteins and nucleic acids, protecting them from enzymatic degradation in the extracellular environment (Liu *et al*., 2021). The three main subtypes of EVs are microvesicles (MVs), exosomes and apoptotic bodies which are differentiated based upon their biogenesis, release pathways, size, content and function (Bongiovanni *et al*., 2021). EVs play an important role in the maintenance of tissue homeostasis and pathogenesis. Due to their small size, we are unable to see EVs by light microscopy, and some of them can only be visualized by electron microscopy, eventually with the use of immunogold labeling using specific EV markers. Several techniques have been developed for the collection and analysis of EVs from body fluids such as blood, but it remains extremely difficult to isolate them directly from tissues. Cells use extracellular vesicles (EVs) to interact with one another. EVs are essentially messages consisting of certain "words" (bioactive chemicals). Thus, the content of EVs is very specific and makes them a highly attractive research topic. A growing body of research aims to better elucidate the roles of EVs in tissue development, maintenance, and function, as well as in pathogenesis. Noteworthy, EV messages can have a local or distant effect: They can act as paracrine agents when they are released into the extracellular space or as endocrine agents when

they are released in the circulation and thereby affect distant organs and cells. The molecular content of EVs in the blood or in other body fluids can provide information about their tissue of origin, allowing them to be used as biomarkers. As EVs can target specific tissues and be taken up by specific cells, EVs can be exploited to convey and deliver therapeutic molecules.

EV Classification and Biology

Extracellular vehicles (EVs) are part of the complete secretome of the cell and there are no specific markers to distinguish EV subtypes and their subcellular origin. However, differences exist that enable categorization of EVs into distinct subclasses. There are 3 main classes of EVs – exosomes (30–100 nm), microvesicles (100-1000 nm) and apoptotic body (50-5000 nm) — that mainly differ in their mode of biogenesis rather than their size (Fig. 1). Exosomes are small EVs that arise in the endosomal system. The endosomal system consists of highly dynamic membrane compartments that actively interact to regulate the uptake of molecules or ligands, their recycling to the cell surface, and their degradation. Endosomes provide an intracellular environment where molecules can be sorted prior to determining their fate. Inward budding of the endosomal limiting membrane leads to the formation of multivesicular bodies that direct molecules to lysosomes for degradation or to the plasma membrane for release into the extracellular space. Intraluminal vesicles arise in multivesicular bodies through budding mediated by the endosomal sorting complex required for transport (ESCRT).

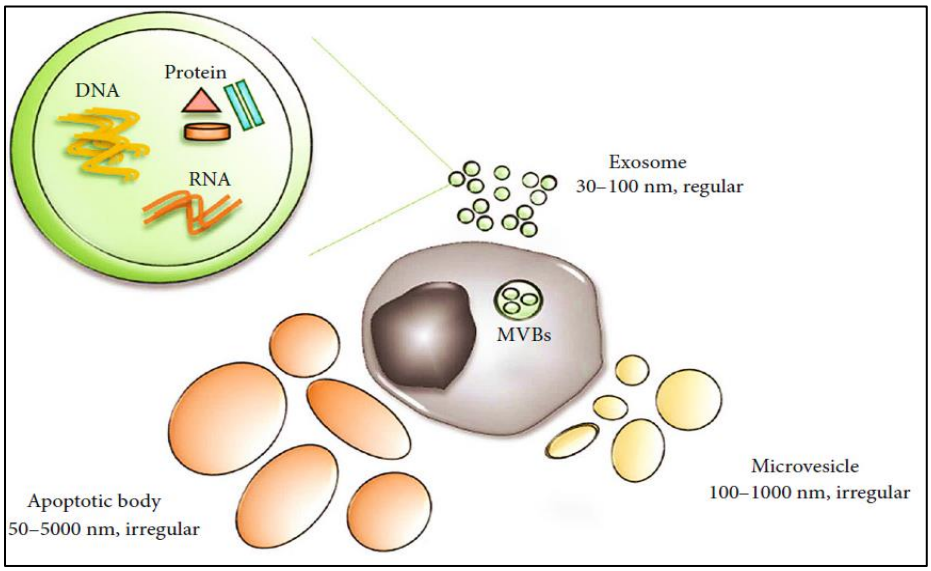

Fig 1: Three main classes of extracellular vesicles: micro vesicles, exosomes and apoptotic bodies

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Micro vesicles, also referred to as ectosomes, are larger EVs of 100 to 1000 nm diameter that are released into the extracellular space by direct budding from the plasma membrane. They also include microvesicles released from specific cell types, such as from apoptotic cells or tumor cells. In these circumstances they are typically referred to as apoptotic bodies and large oncosomes, respectively. The cargo sorting and outward plasma membrane budding resulting in microvesicle release is mediated by small GTPases as well as components of the endosomal sorting complex required for transport machinery.

After release by donor cells into the extracellular space, EVs reach their target cells. Many EVs are taken up by the recipient cells and degraded by their lysosomal system; in others, the EV contents induce phenotypic changes in the recipient cell. EVs can transmit information both at the recipient cell surface and after internalization. Uptake of EVs requires that EVs bind to specific receptors present on the surface of target cells. However, it is not known if binding of particular EV subtypes to recipient cells is target-specific or nonspecific and stochastic; it is likely that both mechanisms occur (Mathieu *et al*., 2019). The various mechanisms by which EVs are internalized into the recipient cell seem to be more dependent on the recipient cell type than on the EVs themselves. EVs can directly fuse to the plasma membrane of the recipient cells and then release their content into the cytoplasm. Alternatively, EVs can be internalized by phagocytosis or endocytosis. Endocytosis can be clathrin-dependent or clathrin-independent (lipid raft-mediated). The latter can require the presence of caveolins, which are proteins involved in the creation of small cave-like invaginations in the plasma membrane (French *et al*., 2017). Endocytosis can result in EV degradation in the lysosome or release of the EV cargo into the cytoplasm of the recipient cells by back-fusion with the endosomal membrane (Carter *et al*., 2018). However, investigation of this final step in EV uptake, namely, the delivery of EV contents into the recipient cell via EV degradation or re-secretion, is crucial to understand the functional consequences of EV-mediated transfer of bioactive molecules.

Field of Applications

Understanding the mechanisms of action of EVs provides new insights into pathogenesis and may lead to the development of new therapies for cancer, degenerative diseases and skin diseases. These innovative therapies are based on exploiting the cargo function of EVs to deliver drugs to target cells or blocking EV biogenesis, release, or uptake. EVs have the potential for various applications, such as delivery vehicles for small interfering RNA (siRNA) in tumor

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therapy, modulated exosomes for the treatment of pancreatic cancer, vaccines and as diagnosis markers. Furthermore, many studies have aimed to unravel the molecular profile of EVs and to map the EV content alterations that occur within cells under the influence of disease, with the aim of discovering new reliable biomarkers (Zhao *et al*., 2019). As EVs are released by diseased cells into the extracellular space and to the circulation, they can be isolated from many body fluids and their molecular cargo can yield information about the cells of origin. This is the driving factor behind research into the use of EVs as biomarkers, predominantly in humans but increasingly also in veterinary medicine. Liquid biopsies are minimally or noninvasive compared to tissue biopsies. Liquid biopsies based on EVs are still in an early stage of development and there are only a few EV-based tests currently approved by the Food and Drug Administration, mainly for cancer patients.

EVs contain different cargo derived from their donor cells including proteins, lipids, and the nucleic acids: DNA, messenger RNA, small noncoding RNA, such as miRNA and long noncoding RNA (Mateescu *et al*., 2017). These are candidate biomarkers because they reflect the state of the donor (diseased) cells at the time of formation, and this EV cargo can mirror variations in molecular expression over time. Several characteristics of EVs make it potentially advantageous to measure biomarkers in EVs rather than as free molecules in body fluids:

1. Biomarkers contained within EVs are more stable as they are shielded by the lipid bilayer from enzymatic degradation by (ribo)nucleases, proteases, and lipases, and from environmental and storage conditions, such as freezing, thawing, and pH.

2. Biomarkers may be enriched in these vesicles; that is, present in a higher concentration and therefore more readily detectable than in body fluids.

Cancer	EV biomarkers	Proteins
Breast cancer	miR-1246, miR-21 in plasma (↑)	HER2, CD47, DEL-1 and EpCAM (↑)
Pancreatic cancer	miR-17-5p, miR-21, miR-1246, miR-4644, miR-3976 (↑)	-
Ovarian cancer	miR-21, miR-141, miR-200a, miR-200b, miR-200c, miR- 203, miR-205 and miR-214 (↑)	-
Colorectal cancer	let-7a, miR-1229, miR-1246, miR-150, miR-21, miR-223 and miR-23a in serum (↑)	-

Table 1: Various EVs biomarkers for cancer diagnosis

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Species	Sample	Disease	Biomarker	References
Human and Mice	Serum	Pancreatic cancer	$GPC1^+$ circulating exosomes (crExos)	Melo *et al*., 2015
Human	Serum	Colorectal cancer	Circulating Long RNAs (lncRNAs (BCAR4)	Dong *et al*., 2016
Dog	Blood	Cancer	Platelet-derived extracellular vesicle (PEV) and leukocyte-derived EV	Zmigrodzka *et al*., 2019
Human	Plasma (neuronal exosomes)	Parkinson's disease	α-synuclein	Niu *et al*., 2020
Human	Bone Marrow	Treatment of COVID-19	Exosomes derived from allogeneic bone marrow mesenchymal stem cells	Sengupta *et al*., 2020
Mouse	Blood	Parkinson's disease therapy	Exosome-based catalase formulations	Haney *et al*., 2015

Table 2: Various studies related to EVs

Conclusions

Recent advances have shown the multiple roles of EVs in physiological and pathophysiological processes, highlighting their potential to serve as clinical biomarkers for disease diagnosis and monitoring. As EVs are derived from human cells, there is always the benefit of biocompatibility compared to other modalities of treatment. EVs are highly stable, non-toxic and non-immunogenic which makes them to be used as therapeutic delivery agents. Currently more than 100 EV-based ongoing clinical trials are available on www.clinicaltrials.gov. However, there is a long road ahead to the clinical usage of EVs based liquid biopsy, but its diagnostic potential still excites and drives scientists to further research on it.

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