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REVIEW ARTICLE OPEN

Extracellular vesicles as tools and targets in therapy for diseases

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Extracellular vesicles (EVs) are nano-sized, membranous structures secreted into the extracellular space. They exhibit diverse sizes, contents, and surface markers and are ubiquitously released from cells under normal and pathological conditions. Human serum is a rich source of these EVs, though their isolation from serum proteins and non-EV lipid particles poses challenges. These vesicles transport various cellular components such as proteins, mRNAs, miRNAs, DNA, and lipids across distances, influencing numerous physiological and pathological events, including those within the tumor microenvironment (TME). Their pivotal roles in cellular communication make EVs promising candidates for therapeutic agents, drug delivery systems, and disease biomarkers. Especially in cancer diagnostics, EV detection can pave the way for early identification and offers potential as diagnostic biomarkers. Moreover, various EV subtypes are emerging as targeted drug delivery tools, highlighting their potential clinical significance. The need for non-invasive biomarkers to monitor biological processes for diagnostic and therapeutic purposes remains unfulfilled. Tapping into the unique composition of EVs could unlock advanced diagnostic and therapeutic avenues in the future. In this review, we discuss in detail the roles of EVs across various conditions, including cancers (encompassing head and neck, lung, gastric, breast, and hepatocellular carcinoma), neurodegenerative disorders, diabetes, viral infections, autoimmune and renal diseases, emphasizing the potential advancements in molecular diagnostics and drug delivery.

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INTRODUCTION

Extracellular vesicles (EVs) represent a heterogeneous collection of lipid bilayer-enclosed particles, actively synthesized and secreted by a myriad of cell types into the extracellular milieu. Their secretion is a pervasive mechanism observed across all domains of life, encompassing both prokaryotes and eukaryotes, and it occurs under a range of conditions, from physiological to pathological states. While historically dismissed as mere cellular debris with limited relevance, current research has illuminated their pivotal role as bioactive carriers. These vesicles serve as conduits for transporting diverse cellular constituents, facilitating intricate cellular communication and mediating a plethora of biological processes.[1] EVs carry a wide range of cargo, including proteins such as cell surface receptors, signaling proteins, transcription factors, enzymes, and extracellular matrix proteins.[2] They also contain lipids and nucleic acids (such as miRNA, mRNA, and DNA) that can be transferred from parent to recipient cells, mediating intercellular communication and molecular transfer.[3] EVs have been found to contribute to pathological diseases such as heart disease, neurodegenerative diseases, and cancer.[4] EVs encompass various subtypes classified by their synthesis and release mechanisms, including exosomes, apoptotic blebs, and other EV subgroups.[5] They can also be classified based on the originating cell type, for example, platelet-derived, endothelial cell-derived, or the physiological state of the cells, e.g., "oncosomes" discharged from cancer cells; "prostasomes" originated from the prostate. Microvesicles, exosomes, and apoptotic bodies are the main entities of EVs (Fig. 1),[6,7] but recent research has identified additional types, such as large oncosomes, migrasomes,[8] ectosomes,[9] exomeres, supermeres, and membrane particles (Table 1). EVs are extensively distributed and have been detected in all human bodily fluids, including mother milk, cerebrospinal fluid, urine, saliva, and blood, both in healthy and pathological conditions (Fig. 2). Notably, the nature of the fluid, associated diseases, and the prevailing disease conditions correlate intricately with the EVs' quantity, tissue provenance, molecular composition, and inherent functional traits.

Profiling proteins and Extracellular RNA (exRNA) in biofluids, notably urine and blood, holds substantial diagnostic and prognostic value. This could provide insights into the manifestations of either systemic or localized diseases. Given the remarkable capacity of EVs to encapsulate and preserve the molecular signature of their parent cells, they have emerged as potential treasure troves for biomarker discovery.[10] A particular focus has been on human milk (HM), which is teeming with a spectrum of bioactive constituents pivotal for infant health. EVs in HM have

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