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Extracellular vesicles as personalized medicine

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Abstract

Extracellular vesicles (EVs) are released from all cells in the body, forming an important intercellular communication network that contributes to health and disease. The contents of EVs are cell source-specific, inducing distinct signaling responses in recipient cells. The specificity of EVs and their accumulation in fluid spaces that are accessible for liquid biopsies make them highly attractive as potential biomarkers and therapies for disease. The duality of EVs as favorable (therapeutic) or unfavorable (pathological) messengers is context dependent and remains to be fully determined in homeostasis and various disease states. This review describes the use of EVs as biomarkers, drug delivery vehicles, and regenerative therapeutics, highlighting examples involving viral infections, cancer, and neurological diseases. There is growing interest to provide personalized therapy based on individual patient and disease characteristics. Increasing evidence

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suggests that EV biomarkers and therapeutic approaches are ideal for personalized medicine due to the diversity and multifunctionality of EVs.

Keywords

Nanomedicine; Regenerative medicine; Cancer; Neurological disease; Viruses; Immune response

1. Introduction

Extracellular vesicles (**EVs**) are released from all cells and form a critical intercellular communication mechanism (Couch et al., 2021). The rich diversity of EVs supports a growing list of functions in maintaining health and promoting disease. EVs are defined and characterized by their size (nanoparticles), the presence of a phospholipid bilayer that contains certain distinguishing markers (e.g., tetraspanins CD9, CD63, CD81), and functional ability (e.g., anti-inflammatory), as described in the most recent guidelines from the International Society for Extracellular Vesicles (**ISEV**) (Thery et al., 2018). The EV membrane contains bioactive lipids, carbohydrates, and proteins, while nucleic acids, such as DNA and RNA, and proteins (for example, cytokines) can be present in the EV interior. These EV-associated biomolecules reflect the cell of origin, enabling diagnostic and therapeutic applications (Thery et al., 2018). Cells continuously release EVs using both intracellular endocytic pathways and direct budding from the plasma membrane. EVs circulate in the blood and extracellular space, where they act in a paracrine or long-distance manner on recipient cells (Rodrigues et al., 2018). Depending on the context, EVs can have favorable (therapeutic) or unfavorable (pathological) effects, and much remains unknown regarding the role of EVs in homeostasis and various disease states (Yates et al., 2022b). Understanding the contribution of EVs to disease is complicated by the heterogeneity of EVs in biological samples.

A variety of terms and definitions have been used over time for EVs, leading to some confusion in the field (Bazzan et al., 2021; Couch et al., 2021; Thery et al., 2018). Here, we use the term EVs to refer to all extracellular, lipid bilayer, sub-cellular particles and their functional contents with sizes ranging from 30 nm to 1 μm. This definition includes the widely recognized major subgroups termed exosomes, microvesicles, and apoptotic bodies (Fig. 1). Distinctions between these groups are based primarily on their origin (Rodrigues et al., 2018). Exosomes are released by endocytic pathways within cells and range from approximately 30 to 150 nm (DeLeo and Ikezu, 2018). Microvesicles or ectosomes are shed from the plasma membrane into the extracellular space and range from approximately 100 to 1000 nm (Colombo et al., 2014; Janas et al., 2016). Apoptotic bodies arise from degrading cells and range from approximately 100 nm to several micrometers, sometimes large enough to contain entire cellular organelles (Buzas et al., 2014; Gyorgy et al., 2011). The collective term EV is used in this article, as subtypes have overlapping size ranges and biomolecular content, and current technology is unable to accurately separate or distinguish exosomes from microvesicles (Bazzan et al., 2021; Crescitelli et al., 2013; Gyorgy et al., 2011; Khalaj et al., 2019; Rodrigues et al., 2018; Thery et al., 2018; Yates et al., 2022a).

Historically, the main role of EVs was thought to be as nano-sized “trash bags”, eliminating unwanted waste from the cell (Couch et al., 2021; Szwedowicz et al., 2022). Today, they are known to play vital roles in cellular communication (Yanez-Mo et al., 2015). Regardless of the origin of EVs (i.e., plasma membrane, intraluminal vesicle), the membranous and inner contents of EVs are influenced by the parent cell. Factors that may affect EV characteristics include donor sex, age, and cellular stress. All components of the lipid membrane and internal compartment of EVs can impact recipient cells (Thery et al., 2018). Larger EVs may contain sub-cellular contents such as mitochondria or other functional macromolecules that can affect recipient cells (Dean et al., 2009; Gasecka et al., 2019). EV-mediated transfer of functional products enables a signaling axis between donor and recipient cells that can be useful in a variety of situations to promote physiological homeostasis or pathology (e.g., stress responses, host cell responses to pathogens, and tumor microenvironment modulation) (Couch et al., 2021; Yanez-Mo et al., 2015; Yates et al., 2022a, 2022b). Once EVs are internalized by recipient cells, intracellular signaling cascades can be initiated by EV-associated biomolecules, such as microRNAs (**miRNAs**) and proteins, that are released into the cytoplasm (Pant et al., 2012; Rodrigues et al., 2018). In addition to intracellular uptake, EVs may also activate signaling cascades in recipient cells through surface interactions without subsequent uptake, that is, a “kiss-and-run” approach (Morris and Witwer, 2022).

All cells release EVs, which are present in biological secretions, excretions, and tissues (Fig. 1), (Robbins and Morelli, 2014) including ejaculate (Hoog and Lotvall, 2015), lipoaspirate (Tian et al., 2020; Wang et al., 2021), synovial fluid (B. Yin et al., 2022), breast milk (Zhong et al., 2021), amniotic fluid (Costa et al., 2022), saliva (Li et al., 2022; Yuana et al., 2015), urine (Barreiro and Holthofer, 2017; Minkler et al., 2021; Yuana et al., 2015), cerebrospinal fluid (Welton et al., 2017), blood/plasma (Yuana et al., 2015), lymph (Milasan et al., 2016), and mucus (Pastor et al., 2021). Other types of nanoparticles are also found in biofluids, such as lipoproteins (Feingold, 2000) and exomeres (H. Zhang et al., 2018). New sources of EVs continue to be characterized as technology limitations surrounding isolation and authentication improve; however, a comprehensive understanding of the functional properties of EVs in health and disease remains to be determined.

Difficulties in assigning a particular function to EVs stems from their heterogeneity. Without the technical ability to independently isolate subpopulations, it is challenging to accurately assess individual contributions of EVs to homeostasis and disease (Ramirez et al., 2018; Thery et al., 2018; Veerman et al., 2021; Yates et al., 2022a). Limitations in EV separation and subsequent characterization stem from overlapping biomolecular content and size ranges, which can also be affected by isolation methods, storage conditions, and measurement parameters (Ramirez et al., 2018; Thery et al., 2018; Veerman et al., 2021; Yates et al., 2022a). Although there are reports of EVs containing distinct cargo, leading to a specific response in a disease model, such findings are often difficult to replicate due to differences in characterization methods and/or isolation techniques (see Challenges below) (Raposo and Stoorvogel, 2013; Tans et al., 1991; Yates et al., 2022a).

Many of the qualities that make EVs difficult to characterize also imbue them with incredible versatility and applicability as promising candidates for personalized medicine. Because of their specificity for certain tissues and disease states, EVs can be used as

personalized diagnostic biomarkers and allogenic or autologous biotherapeutics and/or biogenic drug delivery vehicles. EVs offer promise for a personalized precision medicine approach to healthcare, where therapy can be tailored to the sex, age, and condition/disease of the individual.

2. EVs and personalized medicine

Personalized or precision medicine is based on using patient-specific information like genetic background or environmental and lifestyle factors to make decisions about the best course of treatment (Administration U. S. F. a. D., 2016; Piffoux et al., 2019; Shang et al., 2017). Many biologic patient-specific factors can be traced to blood or tissue biomarkers and many of those biomarkers can be found on/in EVs. Thus, EVs can be used to diagnose disease and ideally, if biomarkers can be identified early, for preventative medicine (Shang et al., 2017). Patient-specific biomarkers and early biomarkers using EVs allow tailored treatment decisions and individualized treatment regimens (Piffoux et al., 2019).

An accessible biopsy, termed the “liquid biopsy,” has long been awaited in various fields of medicine. This tissue-free approach to obtaining a ‘biopsy’ allows minimally-invasive screening, assessment, monitoring, and diagnosis, which is of high interest to all stakeholders (Lone et al., 2022; Shang et al., 2017). Because EVs accumulate in all body fluids and are known to contain biomarkers of cellular states, they are an important component of liquid biopsies (Shang et al., 2017). Use of EVs in liquid biopsies could be especially useful for conditions affecting vulnerable populations where tissue biopsies induce greater risk, such as pregnancy, and for diseases that are difficult to diagnose in early asymptomatic stages, like pancreatic cancer (Costa et al., 2022; Lone et al., 2022; Weingrill et al., 2021; Yates et al., 2022a). Aside from diagnosis, identifying EV-specific biomarkers that promote disease may provide opportunities to interrupt disease progression in patients via early treatment (Yates et al., 2022a).

As the field moves forward to utilize EVs as biomarkers and therapies for personalized medicine, it is important to realize that EVs play a role in normal homeostatic processes that protect against disease (Table 1) as well as promoting disease (Fig. 2) (Focosi et al., 2021; Yates et al., 2022b). Additionally, viruses and bacteria highjack EVs to promote infection. These dual roles of EVs need to be kept in mind in order to understand the communication context of EVs as biomarkers or therapeutic agents. The section below highlights three focus areas of EVs as personalized medicine: viral infection, cancer, and neurological disease, and briefly touches on other areas of growing research.

3. EVs in health and disease

3.1. EVs, viral infection, and immune activation

Launching a protective immune response against viruses is critical to host survival. In response to infection, cells of the immune system use EVs to enhance immunity (Nogueira et al., 2015; Rodrigues et al., 2018; Wen et al., 2017). EVs released from antigen presenting cells (**APCs**) including dendritic cells, macrophages, and B cells have been found to express MHC class I or II-antigen complexes that are able to directly activate $CD8^+$ or $CD4^+$ T cells,

respectively (Admyre et al., 2007; Hwang et al., 2003; Raposo et al., 1996; Thery et al., 2002). EVs released from APCs are also able to indirectly stimulate an immune response by transferring MHC I or II-antigen complexes to other APCs (Hwang et al., 2003). Another factor that is important for the ability of EVs to enhance immunity is binding to immune cells via expression of tetraspanins, including CD9, CD63 and CD81, and integrins (for example, CD11b) on the EV surface. However, many studies on the role of EVs in the immune response have been conducted on cultured cells, and much less is known about the capacity of immune cell-derived or other cell-derived EVs to activate the immune system *in vivo*. Recently, it was shown that different cell culture media supplements (i.e., presence or absence of lipoproteins) have opposing effects in terms of EV interactions with immune cells, highlighting the importance of mimicking physiological conditions (Busatto et al., 2020, 2022).

It is well established that many viruses such at HIV, coxsackievirus, hepatitis B and C, influenza, Epstein-Barr virus, and even SARS-CoV-2 highjack cellular (exosome ESCRT) and mitochondrial programs to enhance viral replication, package virus into EVs (capsid proteins, virions), and use EVs containing virus or viral products to subvert the immune response to obtain a replicative advantage in the host (Clough et al., 2021; Marcilla et al., 2014; Nogueira et al., 2015; Rodrigues et al., 2018; Sin et al., 2017; Yang et al., 2022). This includes SARS-CoV-2 RNA which has been detected inside EVs (Kwon et al., 2020). The mechanisms involved in exosome development and virus budding for enveloped viruses are very similar, and studies show that many viruses use the same cellular exocytosis machinery that produces EVs (ESCRT) to package viral capsid proteins and other pathogen-derived factors (Rodrigues et al., 2018). Viruses are able to hide from anti-viral antibody responses within EVs and also can use EV receptors for entry to host cells rather than their own viral receptors (Raab-Traub and Dittmer, 2017). Additionally, some viral receptor cargo co-localize with tetraspanins like CD81 on EVs and enhance or are required for viral infection of host cells (Pileri et al., 1998; J. Zhang et al., 2004). Some viruses, such as HIV, have been found to produce viral factors (Nef) that alter host cells causing them to create more EVs to enhance viral replication (Raymond et al., 2011). In contrast, EVs that contain ACE2 can block SARS-CoV-2 spike protein-dependent infection, indicating a protective anti-viral function of EVs (Cocozza et al., 2020; El-Shennawy et al., 2022), although $ACE2^{+}$ EVs that enhance SARS-CoV-2 replication have also been reported (Tey et al., 2022). Overall, viruses employ multiple EV-based mechanisms to suppress the immune response and to promote viral shedding and persistence that may often overwhelm the body's ability to defend against them (Rodrigues et al., 2018).

3.2. EVs and cancer

The role of EVs in promoting cancer is well established. EVs are a key mechanism that tumors use to influence the surrounding healthy microenvironment, allowing the tumor to create a niche for invasion and metastasis where they promote immunosuppression, which furthers cancer progression (Martellucci et al., 2020; Massaro et al., 2021). Tumor cells, with their constant growth and division, shed and release more soluble factors than healthy cells, and the EVs that they release have abnormal contents (Martellucci et al., 2020; Sun et al., 2018; Thind and Wilson, 2016). These EVs are involved with cellular communication

and disease promotion at every stage of cancer pathogenesis, from development and invasion, to progression and metastasis (Fig. 3) (Sun et al., 2018). The paracrine and long-distance effects of EV-based communication allow early signaling between cancerous and healthy cells, facilitating organotropic metastasis from the primary tumor (An et al., 2015; Urabe et al., 2021).

However, the many roles EVs play in the pathogenesis of cancer may provide equally important, novel therapeutic targets to prevent disease. This communication network can be targeted to reduce tumor burden, reduce or prevent metastasis or relapse, and circumvent drug resistance (Lopez de Andres, Grinan-Lison, Jimenez and Marchal, 2020; Sun et al., 2018). If EV-mediated immune suppression within tumors is blocked, natural antitumor immunity could help decrease progression (Massaro et al., 2021). EV inhibitors are being studied for their potential to change the effects that tumor EVs have on the microenvironment, making them more amenable to traditional therapies (Catalano and O'Driscoll, 2020; W. Sun et al., 2018). Moreover, EVs can be isolated from immune cells with natural antitumor capabilities and used as anticancer agents (Del Vecchio et al., 2021), or they can be used as drug vehicles for nanodelivery of chemotherapies (Sun et al., 2018).

As a step toward developing therapies, identification of altered EVs linked to specific tumor subtypes are being developed as biomarkers (Avendano-Vazquez and Flores-Jasso, 2020; Bondhopadhyay et al., 2021; Del Bene et al., 2022; Li et al., 2022; Martellucci et al., 2020; Ramirez-Garrastacho et al., 2022; Sun et al., 2018). These biomarkers come from various accessible liquid biopsy sources, including saliva for esophageal cancer (Li et al., 2022), urine for prostate cancer (Ramirez-Garrastacho et al., 2022), and blood (Belov et al., 2016; Hu et al., 2021). Early detection of cancers that are typically found in later stages is vital to improve survival rates and treatment responses (Thery et al., 2018). Additionally, metastatic monitoring via liquid biopsies could increase access to care and reduce disease burden for patients that often must travel to specialized centers annually to monitor cancer progression (Lone et al., 2022; Thery et al., 2018). Diagnosis of cancer with a liquid biopsy instead of a tissue biopsy would provide a less invasive alternative that may be more accurate than a tissue biopsy, which can miss focal, abnormal cells (Lone et al., 2022; Thery et al., 2018). Advances in sequencing have allowed robust molecular profiling, essential for these carriers of diverse functional macromolecules (Gonzalez-Kozlova, 2022). These trends towards easier, continuous monitoring and biomarker-driven prognosis and treatment decisions demonstrate the many ways EVs can be used in personalized medicine for cancer patients.

3.3. EVs and neurological disease

EVs have also been found to promote the pathogenesis of disease in many neurological diseases such as Alzheimer's dementia, Parkinson's disease, and prion diseases. These conditions have a pattern of aberrant protein accumulation (Soto and Pritzkow, 2018) that spreads throughout the brain over time as the disease progresses (Braak et al., 2003; DeLeo and Ikezu, 2018; Takeuchi, 2021; You and Ikezu, 2019). EVs have been identified that promote disease by carrying misfolded proteins or their coding material between neurons (Hill, 2019; Khalaj et al., 2019; Takeuchi, 2021; You et al., 2022). Specifically, EVs have

been found to spread RNA repeats in Huntington's disease (Khalaj et al., 2019), α-synuclein in Parkinson's disease (Khalaj et al., 2019; Takeuchi, 2021), prions in Prion disease (Fevrier et al., 2004; Khalaj et al., 2019), TDP-43 in amyotrophic lateral sclerosis (Feiler et al., 2015; Takeuchi, 2021), and phosphorylated tau in Alzheimer's dementia (Ruan et al., 2021; Takeuchi, 2021). In a process that is similar to cancer metastasis, transfer of this cargo transforms healthy cells into dysfunctional, diseased cells. Research has shown that EV-packaged, pathogenic macromolecules like TDP-43 are preferentially taken up by cells compared to non-packaged, free TDP-43 (Feiler et al., 2015). Additionally, EVs contribute to physical deposits within the brain, either by actively catalyzing aggregation driven by lipid membrane properties, as observed with α-synuclein (Grey et al., 2015; Khalaj et al., 2019), or by providing a "sticky surface" for accumulation due to outer membrane surface molecules, as observed with amyloid beta-containing plaques in Alzheimer's disease (Takeuchi, 2021). The severity of some neurodegenerative diseases have also been linked to levels of certain EVs in cerebrospinal fluid (Agosta et al., 2014; Hill, 2019; Muraoka et al., 2019, 2020), further indicating the association of EVs with the disease process.

Although new discoveries of the roles of EVs in neurological diseases are continuously being made, a similar number of studies are being published on the physiological and neuroprotective roles of EVs. For example, EVs have been found to increase synaptic activity, maintain and form myelin sheaths, and promote inflammatory regulation (Antonucci et al., 2012; Bakhti et al., 2011; Bianco et al., 2005). In addition to contributing to protein aggregates in the brain, there is also evidence that EVs actively prevent aggregate formation (Khalaj et al., 2019). EVs have also been found to actively scavenge and remove pathogenic molecules like amyloid beta, TDP-43, and α-synuclein from the intracellular space (Takeuchi, 2021). This is one of the reasons EVs were originally thought to be cellular 'garbage bags', which remains one of their most essential homeostatic roles (Takeuchi, 2021). Extracellularly, EVs also insulate aberrant proteins from interfering with synapse function (An et al., 2013). This selective externalization of pathogenic and/or misfolded proteins could help slow or suppress progression of neurodegenerative disease, revealing the dual role of EVs in the brain (Takeuchi, 2021). Furthermore, healthy neural cells can release protective molecules to other cells in the extracellular space via EVs, for example, transferring heat shock proteins in acute settings (Takeuchi, 2021). Therapeutically administered EVs can simulate neuroprotection, with *in vitro* models showing that EVs from healthy, non-CNS sources can reduce neurodegenerative disease and even promote restoration of proteostasis (Bonafede and Mariotti, 2017; Bonafede et al., 2016).

With the discovery of the role of EVs in the pathogenesis of many neurological diseases, a large number of therapeutic targets have arisen. Importantly, neural communication facilitated by EVs is not likely to be the sole means of propagation of disease, therefore, targeting or inhibiting pathogenic EVs has to be precise. For example, pharmacologic suppression of EV release or uptake has been suggested as a method to reduce progression of diseases linked to EV transmission of pathogenic molecules (Asai et al., 2015; Nath et al., 2012; Ruan et al., 2020; Sardar Sinha et al., 2018), although such approaches may have side effects due to the critical role of EVs in homeostasis.

Similar to the cancer field, there is interest in the neuroscience community to use liquid biopsies (Picca et al., 2022). Perhaps surprisingly, EVs in peripheral body fluids have been found to reflect cellular messaging from the brain, as EVs are capable of crossing the blood brain barrier to send peripheral signals (Thery et al., 2018). In disease states, this barrier is more compromised, facilitating greater transfer of EVs to the periphery (Tominaga et al., 2015). A number of studies are assessing whether EVs found in the blood of elderly individuals with neurodegenerative conditions, such as Alzheimer's disease (Eren et al., 2022; Picca et al., 2022) or Parkinson's disease (Calvani et al., 2020; Picca et al., 2022), can be used as biomarkers. EVs originating from the brain are isolated/detected based on neuron-specific markers, and higher Ab42 and synaptic molecule levels in neuron-derived EVs have been associated with improved cognitive function (Eren et al., 2022).

As communication tools, EVs provide both diagnostic and therapeutic opportunities for neurogenerative disease. Similar to viral infections and cancer, studies have primarily been conducted *in vitro* and it is yet unclear if EVs are direct drivers of neurodegenerative disease *in vivo* (Hill, 2019). More research is needed to determine the role of EVs in maintaining healthy neurons versus promoting disease (Hill, 2019). Additionally, the ability to identify EV subpopulations from specific neural cell types will be important for early diagnosis of neurological diseases and for tailoring personalized therapies (You et al., 2022).

3.4. EVs and other conditions

EVs have been found to contribute to health and disease in many other conditions. One area of focus of EV research has been on the urinary system, in part due to the ease of accessing urine. Urine is a source of early biomarkers of kidney diseases (Barreiro and Holthofer, 2017; Minkler et al., 2021) and EVs in urine have even been suggested as an alternative to kidney biopsy (Cricri et al., 2021). One major stumbling block to the potential use of urine EVs is the unknown effect of kidney filtration on EV populations. Specifically, it is unknown to what extent EV subpopulations from circulation change pre- and post-renal filtration and the ability to use urine-derived EVs to detect pathologies beyond kidney disease.

EVs have been linked to the development of a number of chronic diseases, especially those where the immune system is involved. In autoimmune diseases, EV signatures are altered, demonstrating their association with the pathogenesis of inflammatory disease (Grieco et al., 2021). In particular, autoimmune diseases with EVs as autoantigens or as contributors to pathology have been identified (Yates et al., 2022b). In joints, as in most tissues, EVs are important for maintaining the microenvironment; however, they can also mediate transport of proinflammatory molecules that contribute to cartilage degradation and osteoarthritis (Yin et al., 2022; Zhou et al., 2020). Conversely, EVs have been proposed as ideal therapies and diagnostic tools for osteoarthritis due to their regenerative capabilities in cartilage repair (Zhou et al., 2020) as well as diagnostic tools to track osteoarthritis progression, respectively (Yin et al., 2022). In type I and type II diabetes, EVs have been found to promote disease (Jayaseelan and Arumugam, 2019; Xiao et al., 2019). In inflammatory bowel disease, EV communication between gut microbiota and the host is affected (Gul et al., 2022). EVs are also implicated in pro-thrombotic diseases and conditions, where elevated EV levels increase the risk of dysregulated coagulation cascades (Curry et al., 2014). Similarly, in pregnancy,

EVs have been correlated with pre-eclampsia and pregnancy-induced hypercoagulability in patients, and found to be a direct cause of these conditions in mice (Chen et al., 2021). Taken together, the role of EVs is currently being studied in many different conditions.

4. EVs as personalized therapies

The past two decades have seen major advancements in technologies that enable improved understanding and characterization of EVs. Before EVs are released from cells, they acquire intracellular cargo that is often comprised of a mixture of proteins, metabolites, and nucleic acids (usually RNA). A variety of 'omic' analyses of EV populations isolated from patient blood in a number of disease conditions have revealed that EVs carry unique molecular signatures during disease (de Miguel Perez et al., 2020; Hendrix, 2021; Hood, 2019; Kinoshita et al., 2017; Marleau et al., 2012; Szabo and Momen-Heravi, 2017; Thompson et al., 2016; Wu et al., 2020; Xu et al., 2020). This has accelerated the scientific community's understanding of the significance of EVs in the context of disease and how these biogenic nanoparticles can be used to phenotype various disease conditions, treat degenerative conditions, or deliver drugs.

4.1. EVs as biomarkers

The contents of EVs change during the pathogenesis of disease, and technological advancements in the analysis of RNA, proteins, glycans, and lipid profiles allows more comprehensive signature detection than previously possible (Cheng et al., 2015; Saugstad et al., 2017; Walker et al., 2020). A biomarker is optimal if it is specific and sensitive to a particular disease, and EVs offer this opportunity in stable packaging (Bei et al., 2017; Rodrigues et al., 2018). Another advantage is that EVs are highly abundant in many bioavailable fluids, offering several sources from which to diagnose or track disease (El-Shennawy et al., 2022; Zhong et al., 2021). The heterogeneity of these populations present opportunities for truly tailored personalized medicine approaches, but are also extremely challenging to fully characterize (Zhong et al., 2021).

Emerging methods for more detailed characterization of EVs include multiplexed super resolution microscopy via directed stochastic reconstruction microscopy (**dSTORM**) (Fig. 4) and flow-cytometry that allow single EV analysis. These methods are not yet available for use clinically, but demonstrate progress in approaches to understand and characterize specific EV populations in the context of disease (Thery et al., 2018). Currently, some EV biomarker panels have been developed and approved by the Food and Drug Administration (**FDA**) for use in patients-the first for cancer reached the market in 2016 (Sheridan, 2016). While these panels show great potential, their use in the clinic is hindered by poor reproducibility, which is affected by the lack of widely accepted guidelines or standardized protocols for isolation, handling, and storage of EVs (Khalaj et al., 2019).

Choosing the appropriate biofluid to study is important in determining the mechanistic contribution of EVs to regeneration or disease; for example, urine may not be a good biofluid to identify EVs related to lung injury. Understanding the nuances of EV derivation is essential for appropriate biomarker characterization and development of clinical tests. Blood is the most common source of biofluid used for biomarker studies due in part to

accessibility. Studies characterizing pathogenic RNA and protein content of EVs from blood have been reviewed for several diseases such as hepatitis (Szabo and Momen-Heravi, 2017), cancer (de Miguel Perez et al., 2020; Hood, 2019; Kinoshita et al., 2017; Marleau et al., 2012; Nawaz et al., 2014), neurodegeneration (Thompson et al., 2016; You and Ikezu, 2019), autoimmune disease (Wu et al., 2020; Xu et al., 2020), and cardiovascular disease (Bei et al., 2017; Chong et al., 2019; Dickhout and Koenen, 2018; Fu et al., 2020). These studies represent the next generation of biomarker development.

Developing early and rapid detection of diseases using EVs has led to the concept of EV depletion as a potential therapeutic option (Marleau et al., 2012). Aethlon Medical Incorporated is in recruitment stages for an early feasibility study to use their Hemopurifier™ for EV depletion for patients with head and neck squamous cell cancers. The study is expected to be completed by 2023 (Clinical Trials.gov website). Side effects from a reduction in total EV numbers may impact underlying physiological processes that rely on them to maintain health or allow other disease conditions to emerge (Hill, 2019). Simple depletion may not be the answer; instead, targeting EVs from specific cell types or pathways has been suggested (Hill, 2019; Khalaj et al., 2019). This specific targeting strategy is limited by current technical ability/knowledge, as it is challenging to differentiate pathological and physiological EVs (Rodrigues et al., 2018). This issue is further complicated in early timepoints or stages of disease, when EV disease signatures can only be found in relatively rare EV populations compared to other physiological populations, which range in the trillions (Hill, 2019; Rodrigues et al., 2018). A potential solution to this rarity is being assessed in neurological disease settings where antibody-meditated pull down for non-pathogenic EVs is being performed on blood in the periphery, allowing more efficient isolation of rarer populations for biomarker discovery, a technique that could also be applied to pathogenic EVs for specific depletion of pathogenic messengers (Hill, 2019).

4.2. EVs and regenerative medicine

While stem cell therapy has traditionally dominated the regenerative space, there is increasing evidence that the restorative functions once assumed to be due to stem cells are mediated by released products from stem cells termed the ‘secretome’, which includes EVs (Ding et al., 2021; Tao et al., 2018; Whittaker et al., 2020). Some advantages to using the secretome or EVs instead of cells include easier handling and storage, for example, freeze-drying can be performed to produce an “off the shelf” product that is readily available when needed. Additionally, EVs are unable to form cancerous growths, which is a risk with cell therapy (Feng et al., 2020; Qi et al., 2020; Szwedowicz et al., 2022; Tao et al., 2018; Wan et al., 2022; Wellings et al., 2021; Willis et al., 2020). The small size of EVs compared to cells also makes vascular obstructions less likely following intravenous administration and results in different biodistribution profiles (Ali et al., 2020). Finally, cells are more responsive to environmental conditions than EVs, and can change characteristics, which may be advantageous or disadvantageous depending on the context. EVs can also be modified by altering surface and/or internal components, allowing modular component design (Tao et al., 2018), and several EV-based drug delivery applications have been developed (S. Walker et al., 2019; Witwer, 2021).

The reparative functions of EVs are numerous, for example, EVs are able to reduce the effects of aging on cells (Feng et al., 2020; Mensa et al., 2020; Prattichizzo et al., 2019; Y. Yin et al., 2021). EVs obtained from the plasma of young mice have been found to reduce aging when administered to old mice (Iannotta et al., 2021; Prattichizzo et al., 2019; Sahu et al., 2021; Yoshida et al., 2019). Cellular senescence that occurs with age has been linked to EV signaling, providing new targets to mitigate the deteriorative effects of aging (Yin et al., 2021).

Altering inflammatory responses (Grieco et al., 2021), tissue/wound healing (Bray et al., 2021; Costa et al., 2022), and brain remodeling (Gualerzi et al., 2021) are all active areas of research with EV products for both tracking and inducing regenerative processes (Gualerzi et al., 2021). Inhibiting inflammation is an avid area of EV research. EVs are known to participate in the cross-talk between the immune system and other cells of the body, and are altered in a variety of disease states (Grieco et al., 2021). Fibrosis often leaves scar tissue which is an endpoint of tissue damage that has been irreparable with medication or surgery. Thus, great interest has been placed on determining whether EVs are able to prevent or return scar tissue to a healthy state (Qi et al., 2020; Wan et al., 2022; Wellings et al., 2021). Complete tissue regeneration via EV therapy is being actively tested in bone, skin, and cardiac muscle (Kost et al., 2022; Pishavar et al., 2021; Thankam and Agrawal, 2020; Yin et al., 2021).

4.3. EVs as drug delivery vehicles

Aside from their capacity as biomarkers and endogenous therapeutics, EVs can also be used for delivery of exogenous therapeutic agents, including small molecules, peptides/proteins, and RNA. Nanodelivery improves the site-specific accumulation of free drugs, resulting in increased therapeutic efficacy and less side effects (Khalid et al., 2017; Shen et al., 2017; Wolfram et al., 2015). Additionally, nanoparticles enable protection of RNA and protein therapeutics that are sensitive to degradation by extracellular and intracellular enzymes (Shen et al., 2015). Nanoformulations also have advantages over micro-formulations, including larger surface area to volume ratio, which can improve interactions with targets, and reduced risk of vascular obstructions (Martin et al., 2005).

There has been considerable interest in the use of EVs as medication carriers, especially for chemotherapeutics (Busatto et al., 2019; S. Walker et al., 2019). Although laboratory-created simple nanocarriers, such as liposomes, can be easily made through well-established methods and have been in clinical use for decades (Gentile et al., 2013), biologically-derived nanoparticles like EVs have the potential to outperform conventional delivery systems. Currently, the recognition and clearance of intravenously injected EVs by the innate immune system is much faster than that of synthetic nanoparticles (Couch et al., 2021). However, studies in reporter mice indicate that endogenous EVs can avoid immunological clearance and reach target tissues over long distances (Luo et al., 2020). Therefore, selecting the optimal EV subtype, preserving endogenous characteristics (i.e., minimizing damage from isolation, drug loading, and labeling), and lowering the infusion rate could overcome rapid immunological recognition. Clinically approved nanoparticles have simple surfaces that lack protein and glycan decorations, and attempts to develop targeted delivery systems

have repeatedly failed in clinical trials (Wolfram and Ferrari, 2019). It is likely that the aforementioned failures are partially due to overly simplistic strategies (one surface ligand) to target highly complex biological surfaces with thousands of biomolecules. EVs demonstrate specificity for recipient cells through complex surface interactions that involve multiple molecules in optimal orientations, spatial arrangements, and ratios, and may therefore, be more equipped than synthetic nanoparticles to mediate site-specific delivery. Additionally, EVs have been shown to cross the blood brain barrier, a major roadblock for many neuro-therapies (Hill, 2019). EVs can also be harnessed in infectious diseases for their specificity and ability to target pathogens (Schorey and Harding, 2016). Many EV-based drug delivery systems are currently in the translational pipeline (Lener et al., 2015; Rodrigues et al., 2018), and the upcoming decade is likely to reveal the utility of these intercellular messengers as drug carriers.

4.4. Challenges

Many challenges need to be overcome before EVs can successfully be used as biomarkers or therapies for diseases in the clinical setting. A critical challenge is the multitude of isolation methods that vary widely in EV enrichment capabilities. Specifically, over 190 different isolation methods and over 1000 unique protocols have been reported for EV isolation (EV-TRACK Consortium et al., 2017). Isolation and storage methods substantially impact structure and function of EVs, which remains a fundamental issue in the field. Additionally, there is a lack of controls that can be used to standardize conditions between laboratories. There are a number of technical challenges in isolating EVs from biological samples, in particular, separation from similar sized contaminants. Improved tools, such as those based on flow cytometry and super resolution microscopy, are needed for an improved understanding of EV heterogeneity, which is also a limiting factor for clinical translation. Data derived from super-resolution microscopy, for example, can be altered based on the chemistry of the imaging mediums used (Arsic et al., 2020).

Although EVs have been studied for almost 60 years, many aspects of EV biology remain largely unknown (Couch et al., 2021; De Tkaczevski, 1968; Feller and Chopra, 1968; Sun, 1966; Wolf, 1967). The study of EVs is further complicated by host factors that alter the phenotype of EVs, including donor age, biological sex, current or previous pregnancy, menopause, pre/postprandial status (fasting/non-fasting), time of day of collection (circadian variations), exercise level and time of last exercise, diet, body mass index, specific infectious and noninfectious diseases, medications, and other factors (Thery et al., 2018). EV characteristics are also affected by sample collection conditions, such as collection volume, first tube discard, type of container(s), time to processing, choice of anticoagulant (for blood plasma), mixing or agitation, temperature (of both storage and processing), type of transport (if any), whether the tube remained upright before processing, exact centrifugation or filtration procedures, degree of hemolysis, possible confirmation of platelet and lipoprotein depletion prior to storage, and so on (Thery et al., 2018). Overall, there are a vast number of factors contributing to variation in EV characteristics and functions that need to be resolved in order to create a consistent product that can be used for personalized medicine.

5. Summary

EVs are promising biological nanoparticles for use as biomarkers to diagnose disease, to monitor progression of disease (or pre-disease) and to use as therapies to prevent or reverse disease. The ability of EVs to communicate directly with recipient cells in a cell/tissue, sex, age, and disease-specific manner places them at the forefront of candidates for personalized medicine. EV research over the past 60 years has laid the foundation and resulted in critical insights, yet a great deal remains to be understood. EV research holds the promise of changing how we understand, monitor, and treat disease, and researchers are racing forward to make those discoveries.

Acknowledgements

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Appendix

Supplemental Table 1

EVs in Pathology References from Fig. 2.

Cardiovascular System	Clotting disorders (Midura et al., 2015; Siljander et al., 1996; Tans et al., 1991; Yates et al., 2022b; Zubairova et al., 2015) Vascular injury (Yates et al., 2022b) Sepsis (Kerris et al., 2020; Yates et al., 2022b) Coronary artery disease (Y. Liu et al., 2019) Atherosclerosis (Badimon et al., 2016) Myocardial infarction (Loyer et al., 2018; Mortberg et al., 2019) B-thalassanemia (Kheansaard et al., 2018)
Immune System	Sjögren's' Syndrome (Huang et al., 2020) Systemic lupus erythematous (Ullal et al., 2011) Rheumatoid arthritis (Boilard et al., 2010; Tessandier et al., 2020) Systemic sclerosis (Maugeri et al., 2018) Response to viral or parasitic infection (Dias, Costa, & daSilva, 2018; Kerris et al., 2020; Zakeri et al., 2021) Immune suppression (C. Liu et al., 2006; Valenti et al., 2006) Over-active immunity (Yates et al., 2022b)
Neurological System	Stroke (Agouni et al., 2019; Yates et al., 2022b) Neurodegenerative disease (Lee et al., 2020; Yates et al., 2022b) Multiple sclerosis (Blonda et al., 2018; Casella et al., 2018; Kimura et al., 2018; Mallardi et al., 2018; Minagar et al., 2001; Saenz-Cuesta et al., 2014) Neuroinflammation (Kumar et al., 2017; Rong et al., 2018; Verderio et al., 2012; Yates et al., 2022b) Cognitive deficits (Lee et al., 2020)
Reproductive System	Polycystic ovarian syndrome (Amabile et al., 2005; Sang et al., 2013) Endometriosis (Khalaj et al., 2019; Yates et al., 2022b)
Urinary System	glomerular/tubular injury (Gildea et al., 2014) kidney inflammation (Kahn et al., 2017; Yates et al., 2022b) kidney fibrosis (X. Liu et al., 2020) disrupted fluid balance (Jella et al., 2016; Lv et al., 2018) renal failure (Amabile et al., 2005)
Gastrointestinal System	gut permeability disorders (Mitsuhashi et al., 2016; Yates et al., 2022b) obstructive sleep apnea (Jia et al., 2017) obesity (Esposito et al., 2006) diabetes (Bashratyan et al., 2013; Rahman et al., 2014; Sheng et al., 2011) pancreatic inflammation (Bashratyan et al., 2013; Rahman et al., 2014; Sheng et al., 2011) gut-brain axis disorders (e.g. autism, depression)(Fowlie et al., 2018; Skonieczna-Zydecka et al., 2018)
Pregnancy	gestational diabetes (James-Allan et al., 2020; J. Liu et al., 2018; Salomon et al., 2016) pre-eclampsia (Han et al., 2020) maternal-fetal tolerance disorders (Knight et al., 1998; Simon et al., 2018; Tong and Chamley, 2015)

Musculoskeletal system	cachexia (Yates et al., 2022b) Duchenne's muscular dystrophy (Yates et al., 2022b) Osteoarthritis (Kolhe et al., 2017; Yates et al., 2022b)

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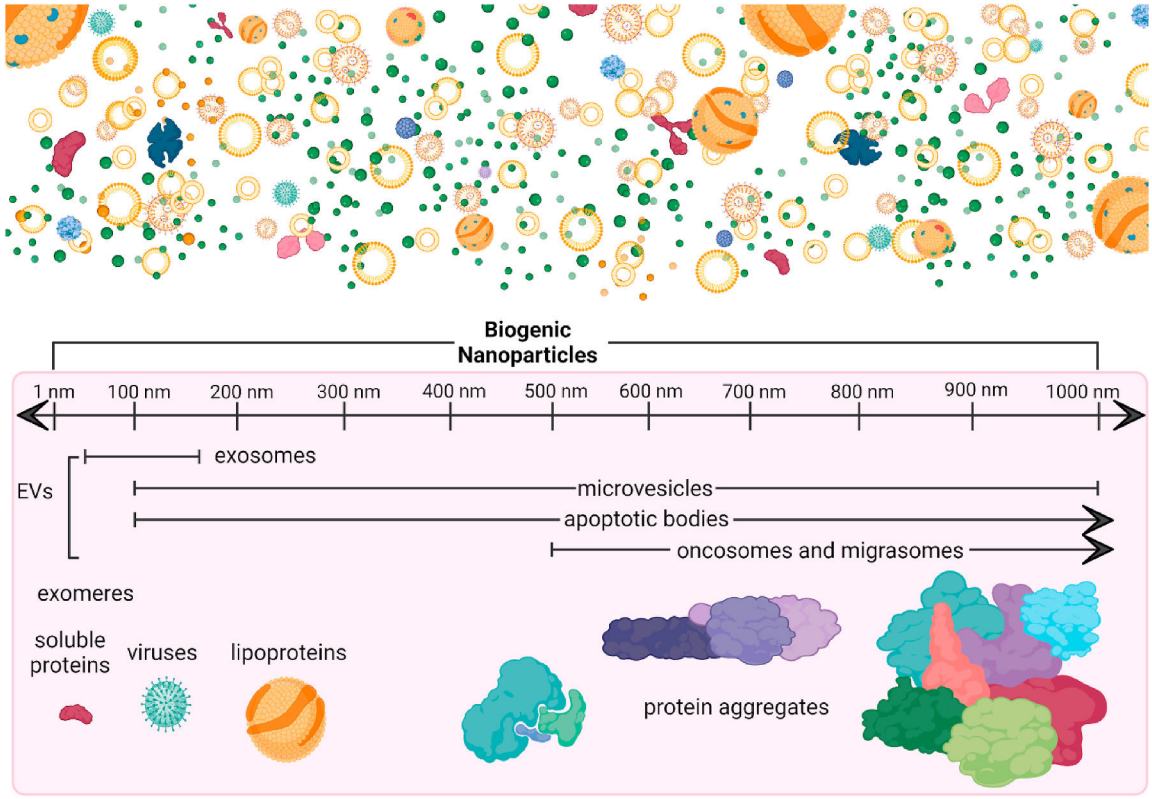

Fig. 1. Biogenic Nanoparticles.

Biogenic nanoparticles include extracellular vesicles (EVs) and other nanosized extracellular particles. Newer inclusions are exomeres: non-membranous nanoparticles smaller than 50 nm, with functional contents secreted by cells (H. Zhang et al., 2018), oncosomes: EVs released from cancer cells ranging between 100 nm and 4 μm (Meehan et al., 2016), and migrasomes: large nano- and microvesicles used for cell migration and intercellular signaling (da Rocha-Azevedo and Schmid, 2015; Ma et al., 2015). More well-established nanoparticles include lipoproteins (Feingold, 2000), viruses (Louten, 2016), and protein aggregates (Goodsell and Olson, 1993). This figure was created in ©BioRender-biorender.com.

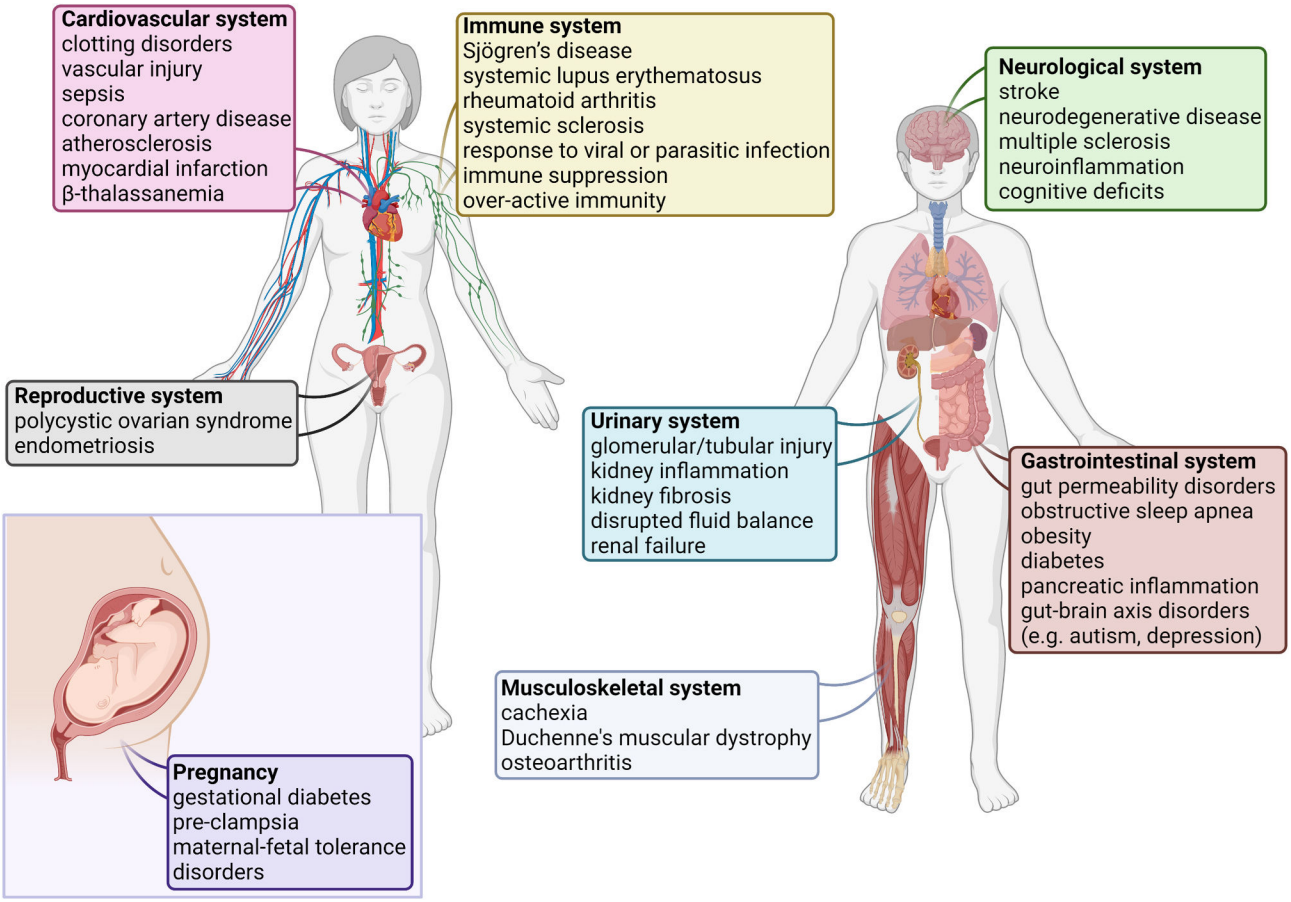

Fig. 2. EVs in Pathology.

Many studies have linked EVs to the pathogenesis of various diseases, references are listed in Supplement Table 1. The figure depicts a variety of these diseases, grouped by major organ system. This list is constantly growing. This figure was created in ©BioRender-biorender.com.

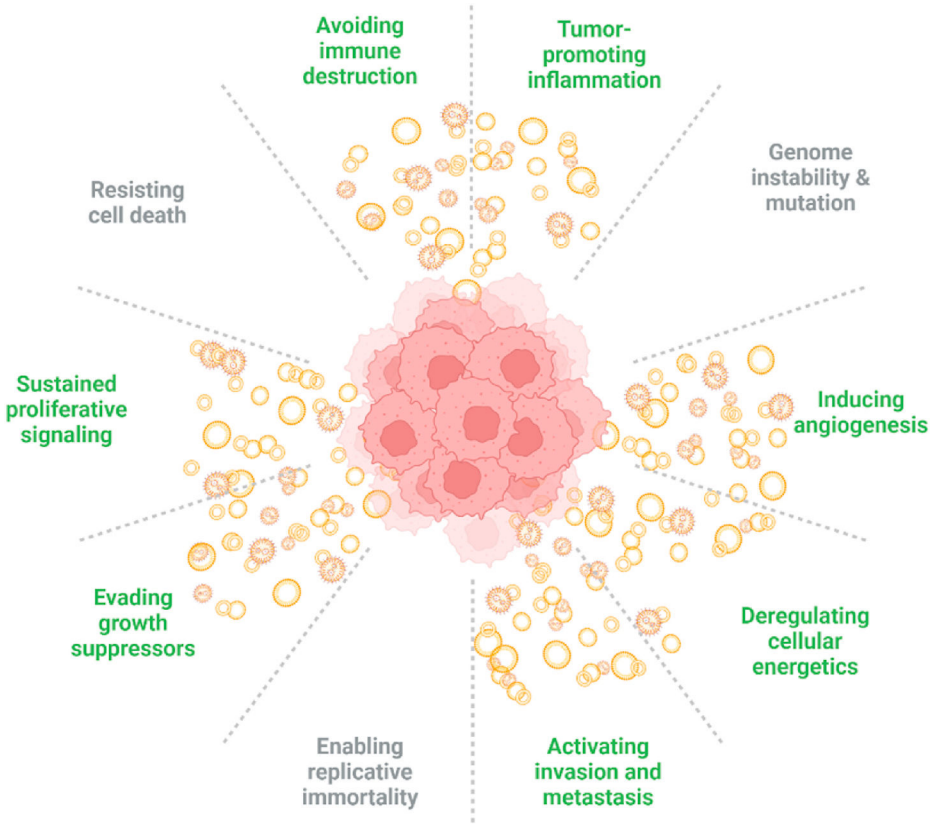

Fig. 3. EVs Impact the Hallmarks of Cancer.

Hallmarks of cancer promoted by EVs depicted in green, other cancer promoters in grey. Adapted from "Hallmarks of cancer (2011 update), including emerging hallmarks and enabling factors", by ©BioRender-biorender.com. Retrieved from https://app.biorender.com/biorender-templates.

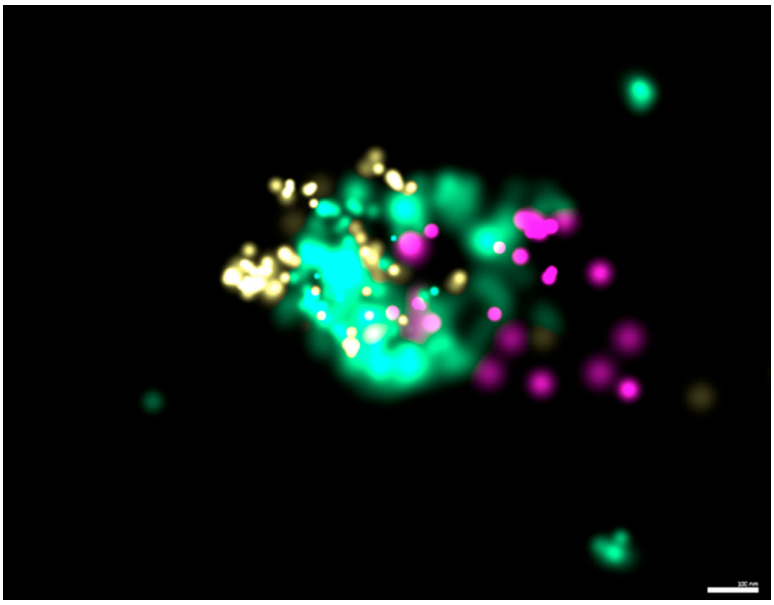

Fig. 4. Representative image of dSTORM tetraspanin profiling of an EV.
CD9 (yellow), CD81 (teal), CD63 (purple) using ONI EV profiling kit and precision depiction. Scale bar: 100 nm.

Table 1

Physiological relevance of EVs in major organ systems.

Immune System	initiation and resolution of inflammation (Buzas et al., 2014) innate immune system participants (Hong, 2018; Zhou et al., 2020) immune homeostasis (H. P. Chen et al., 2020; Rossaint et al., 2016) directly target antigen (Yates et al., 2022a) anti-microbial (Timar et al., 2013) enhance the immunological role of their parent cell (Yates et al., 2022a) antigen-presentation (Raposo et al., 1996) immune system inflammatory control (Karlsson et al., 2001) promote allergen tolerance (Karlsson et al., 2001) help activation or suppress immune functions when needed (Yates et al., 2022a)
Cardiovascular System	maintaining blood pressure (Good et al., 2020; Pironti et al., 2015)
Urinary System	fluid balance (Hiemstra et al., 2014) antimicrobial content carriers (Hiemstra et al., 2014) intra-nephron communication (Yates et al., 2022a)
Reproductive System	gamete development (Simon et al., 2018) sperm motility (Park et al., 2011) facilitate fertilization (Palmerini et al., 2003; Schuh et al., 2004) assist implantation (Greening et al., 2016; Nguyen et al., 2016; Simon et al., 2018) amniotic fluid signalling (Yates et al., 2022a) maternal-foetal communication and maternal tolerance of pregnancy (Knight et al., 1998; Simon et al., 2018; Tong and Chamley, 2015) early trophoblast development (Yates et al., 2022a) protect sperm from innate immune system of vaginal canal (Rooney et al., 1993) antibacterial (Carlsson et al., 2000)
Neurological System	assist intercellular communication for neurovascular unit (Yates et al., 2022a) regional development of the CNS(Yates et al., 2022a) contribute to the lateralization of the CNS(Yates et al., 2022a) communication across blood brain barrier (Dickens et al., 2017; Morales-Prieto et al., 2022) synapse maintenance and pruning (Lachenal et al., 2011; Paolicelli and Ferretti, 2017)
Musculoskeletal System	muscle homeostasis and myogenesis (Choi et al., 2016; Coenen-Stass et al., 2016; Forterre et al., 2014; Le Bihan et al., 2012; Romancino et al., 2013) metabolic regulation in muscles (Jalabert et al., 2016) muscle regeneration and repair (Choi et al., 2016; Fry et al., 2017) regulate fibrosis (Fry et al., 2017) bone cell communication (Deng et al., 2015) participate in osteogenesis (Weilner et al., 2016)
GI System	facilitate immune tolerance or activation towards gut microbiota (Nahui Palomino, Vanpouille, Costantini and Margolis, 2021) gut balance between microorganisms and between microorganisms and host (Yates et al., 2022a) facilitate symbiotic effects of gut microbiota (Yates et al., 2022a)

Abbreviations: CNS, central nervous system; GI, gastrointestinal.