International Journal of Nanomedicine

Dovepress
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REVIEW

Organoid-Derived Extracellular Vesicles: From Biogenesis and Cargo Mechanisms Toward Therapeutic Applications

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Abstract: Organoids are three-dimensional in vitro models that mimic the anatomical and functional complexity of biological tissues, evolving into a powerful platform for studying human development and disease. Organoid-derived extracellular vesicles have been revealed as important intercellular messengers within organoid systems. Participating in the transport of functional substances such as proteins, lipids, and nucleic acids, these lipid-coated nanometer-scale carriers play a role in regulating biological responses. Unlike extracellular vesicles derived from 2D culture, organoid-derived extracellular vesicles carry tissue-specific molecular information and offer unique advantages in terms of targeting precision and biocompatibility. Strategies for engineering organoid-derived extracellular vesicles-such as loading them with specific drugs, surface-modifying them with targeting ligands, or modulating the microenvironment governing vesicle secretion-are currently being extensively explored to enhance their therapeutic potential and targeting capabilities. At the same time, the specific genetic instructions carried by organoid-derived extracellular vesicles hold great promise for early disease diagnosis and prognosis assessment. However, urgent challenges remain, including the heterogeneity of organoids and their in vivo microenvironments, low efficiency in vesicle isolation and purification, and the lack of established standardized production and quality control systems. This paper focuses on two potential applications of organoid-derived extracellular vesicles: as novel therapeutic agents and as tools for improving disease models. It also explores their application prospects in targeted drug delivery, regenerative medicine, and biomarker identification, with the aim of providing insights and guidance for research on the use of organoid-derived extracellular vesicles as multifunctional platforms and carriers in precision medicine.

Keywords: organoids, drug delivery vehicle, engineering strategies, cell-free therapy

Introduction

Organoids, which are made from stem cells and self-assemble into three-dimensional structures that resemble tiny organs, have a number of advantages when it comes to simulating the structure and functioning of actual organs. A pioneering breakthrough was achieved in the field of gut organ simulation technology in 2009.[1] Subsequently, they successfully cultured a variety of organoids with important physiological structures and functions.[2] Organoids are a cutting-edge technology with enormous promise for use in developmental biology, disease pathology, cell biology, regenerative processes, precision medicine, and drug toxicity and efficacy testing, among other scientific fields. During the development and maintenance of organoids, there is precise and dynamic communication and interaction among various cell types, a process that relies heavily on the mediation of extracellular vesicles (EVs).

https://doi.org/10.2147/IJN.S610960
Received: 21 March 2026
Accepted: 30 May 2026
Published: 3 July 2026

EVs are phospholipid bilayer-structured nanoscale vesicles that range in size from 30 to 150 nm and are usually circular or elliptical in form. Exosomes, microvesicles, and apoptotic bodies are among the cell-derived membrane structures known as EVs.[3,4] In previous studies, researchers have typically focused on EVs secreted by monolayer cell lines. Compared to single-cell lines, organoids contain multiple cell types that structurally and functionally resemble their corresponding organs, more closely mirroring the characteristics of the in vivo microenvironment. Vesicles secreted through multicellular coordination can more comprehensively reflect organ-specific information. Organoid-derived extracellular vesicles (OEVs) possess unparalleled potential compared to traditional EVs in the construction of disease models and the development of biomarkers and therapeutic delivery vehicles.

In this review, we outline the advantages of OEVs in therapeutic applications and disease modeling, summarize key strategies for OEV engineering, and analyze the potential challenges and limitations that may arise when integrating emerging technologies into OEV research and applications.

Biogenesis and Molecular Composition

Following their formation through endocytosis, OEVs can either be internalized by early endosomes in neighboring cells or fuse with other endosomal structures.[5] Early endosomes then develop into late endosomes, whose membrane structures undergo further invagination to produce a large number of intraluminal vesicles. Together, these intraluminal vesicles form multivesicular structures inside late endosomes. Ultimately, mature multivesicular bodies fuse with the plasma membrane, releasing their intracellular vesicles as OEVs into the extracellular space.[6] Released OEVs can be internalized by target cells through endocytosis, membrane fusion, or receptor-mediated mechanisms, thereby completing intercellular signal transmission (Figure 1).

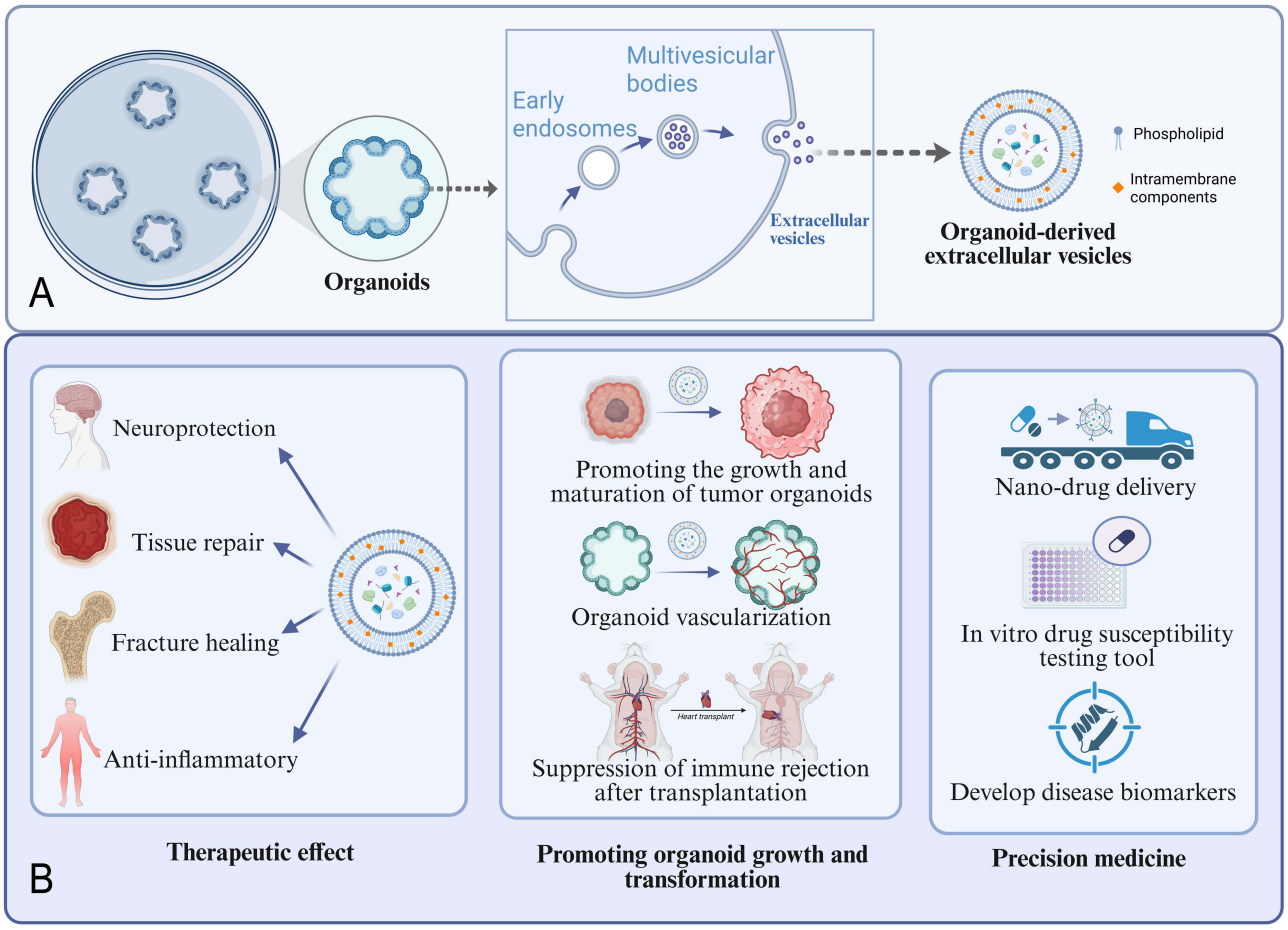

Figure 1 Emerging roles of OEVs in biogenesis, therapeutic delivery, and precision medicine.

Table 1 Common Methods for OEVs Isolation and Purification

Common Isolation/ Purification Method	Principle	Advantages	Limitations
Differential centrifugation	Separates based on particle size and density by gradually increasing centrifugal force, sequentially removing cells, debris, and large vesicles, finally pelleting target EVs	Simple operation, low cost, suitable for large volume samples	Low purity, prone to contamination by particles of similar size (eg., protein aggregates), poor reproducibility
Ultracentrifugation	Pellets EVs under centrifugal force >100,000×g (often combined with differential centrifugation). The most widely used method	Broad applicability, can process large sample volumes, one of the "gold standard" methods	May disrupt vesicle integrity, time-consuming, purity still affected by co-pelleting contaminants
Density gradient centrifugation	Uses media such as iodixanol or sucrose to form density gradients; EVs enrich in specific density layers	High purity, can separate different EV subtypes	Cumbersome operation, time-consuming, low yield, not suitable for large-scale preparation
Size exclusion chromatography	Based on molecular sieving effect; large molecules (EVs) elute first, small molecules (proteins, etc.) are retained	Preserves EV structure and activity, gentle, good reproducibility	Low throughput, dilutes sample, requires specialized columns
Immunoaffinity capture	Utilizes specific surface markers on EVs (eg., CD9, CD63, CD81) to bind with antibody-coated magnetic beads or chips	High specificity, can obtain highly pure subpopulations	High cost, efficiency depends on antibody affinity, elution may damage vesicles
Ultrafiltration	Uses membranes with specific molecular weight cut-off (eg., 100 kDa); molecules smaller than the pore size pass through, EVs are retained and concentrated	Fast, gentle, no special equipment required, can be combined with ultracentrifugation	Membrane clogging possible, purity not high enough, requires further purification with other methods

Differential centrifugation, ultracentrifugation, density gradient centrifugation, size exclusion chromatography, immunoaffinity capture, and ultrafiltration are just a few of the techniques that scientists have created over the last few decades to isolate and purify EVs. Notwithstanding the ongoing optimization efforts, ultracentrifugation remains the gold standard workhorse. Su et al[7] have now adapted this approach for OEVs. Organoid culture supernatants are collected and centrifuged at 4°C and 10,000 g for 20 minutes to exclude debris and dead cells. After that, a 0.22 μm membrane and a 100 kDa limit-exclusion membrane are used to filter the supernatant. To extract OEVs, the filtrate is centrifuged at 150,000 g for 90 minutes at 4°C. While stressing the use of EV-depleted serum to avoid contamination by exogenous EVs, recent research has suggested a unique technique for isolating and purifying OEVs (Table 1).

The Difference Between OEVs and EVs, PDEVs, BEVs

EVs were first classified as cellular byproducts based on their role in coagulation. However, this conception was revised after electron microscopic visualization of platelet-derived EVs in 1967, which offered seminal insight into their true nature.[8] For these membrane-bound vesicles, Johnstone coined the term "exosomes" in 1987.[9] Ambiguous definitions and divergent isolation criteria bred nomenclatural chaos in EV research. To curb the indiscriminate use of "exosome" the International Society for Extracellular Vesicles stipulated in 2018 that EVs <200 nm should be designated "small extracellular vesicles".[10] The Minimal Information for Studies of Extracellular Vesicles (MISEV) standards were further refined in 2023, resulting in a more accurate characterization of EVs.[4] Standardized characterization based on physical characteristics, biological makeup, and cellular origin was emphasized in this concept. EVs are described as particles that are expelled from cells, have a lipid bilayer, and cannot replicate themselves. Exosomes and other vesicular particles are included in this phrase. In this paper, unless otherwise specified, "EVs" refer to populations of nanoscale vesicles secreted by monolayer cells cultured in conventional adherent or suspension cultures, exhibiting a typical phospholipid bilayer structure. EVs from various biological sources, such as those released by 2D-cultured live cells, plant-derived extracellular vesicles (PDEVs), bacterial extracellular vesicles (BEVs), and OEVs, are the subject of current research (Table 2).

Table 2 Comparison of the Sources, Characteristics, Applications and Limitations of Various EVs

	Source and Generation	Biological Characteristics	Application	Limitation	References
PDEVs	Natural plants	High biological safety, widely available, rich in plant-derived bioactive compounds, low immunogenicity	Inflammation Treatment, Drug Delivery Systems, Skincare Product Development	Plant species exhibit significant variation and complex composition, research on biocompatibility and metabolic pathways within the human body remains insufficient.	[11]
BEVs	Gram-positive bacteria, Gram-negative bacteria	Natural immune adjuvant, carrying bacterial-specific antigens, with excellent stability.	Vaccine development, antimicrobial drug research and development, disease diagnostic biomarkers	Potential endotoxin contamination may exist, safety and targeted delivery control within the body require further validation.	[12]
EVs	Single-layered cell	Low acquisition cost, easy to standardize, limited by yield and activity	Disease diagnostic biomarkers, immunotherapy	Single source, making it difficult to mimic complex tissue microenvironments, Limited yield, with activity significantly affected by culture conditions.	[3]
OEVs	Organoids	High physiological relevance, rich in tissue-specific information, high cost, demanding organoid construction requirements.	Personalized medicine, disease mechanism research, drug development	Organoid cultures exhibit significant batch-to-batch variability and low source consistency, high cost, demanding organoid construction requirements.	[7]

PDEVs come from a variety of sources. According to recent studies, several PDEVs have therapeutic value as drug delivery vehicles because of their high biocompatibility and minimal immunogenicity, as well as their antioxidant and anti-inflammatory effects.[13] PDEVs have been shown to be devoid of viruses, MHC antigens, and human or animal diseases. They have been demonstrated to have low immunogenicity and little chance of causing human immunological rejection.[14] Because of their extensive sourcing potential and affordable production,[15] PDEVs are a topic of great interest. Strong biological qualities, such as anti-inflammatory, anti-cancer, antibacterial, antifungal, and antioxidant effects, have been shown by those produced from a variety of edible plants.[16] Additionally, it has been demonstrated that PDEVs load medications well, allowing for precise administration.

The Gram-negative bacterium was originally seen in 1965 releasing outer membrane vesicles that were between 20 and 250 nanometers in size through budding.[17] These vesicles serve as "decoys" to thwart phages or host-derived antimicrobial agents by carrying pathogen-associated genetic sequences. Additionally, a 2013 study found that outer-inner membrane vesicles, which are essential for pathogen stress tolerance, can be secreted by Gram-negative bacteria.[18] Researchers can accurately alter the characteristics and antigen presentation mechanisms of BEVs through genetic engineering, boosting immune responses and showing great promise for vaccine development.[19]

It has been shown that using stereoscopic culture can improve intercellular communication, expand the area of contact between cells, and better preserve the physiological characteristics of cells.[20] It has been shown that creating organoids from various cell subtypes produces extracellular vesicles with richer components and more complete architectures.[21] OEVs have greater diversity and tissue specificity in proteins, RNAs, and metabolites than EVs made exclusively from single cell lines.[22] Superior cellular absorption efficiency and functional activity, such as encouraging tissue regeneration, reducing inflammation, or boosting anticancer activities, are demonstrated in vitro.[23] OEVs are more similar to naturally occurring vesicles in living organisms, enabling precise delivery of bioactive compounds and facilitating interactions between them. It is widely acknowledged that 3D culture systems have a significant impact on the biosynthesis and secretion characteristics of EVs. In 3D culture, the yield of EVs from mesenchymal stem cells is approximately twice that obtained from 2D monolayer culture.[24] In gastric cancer cell models, 3D culture not only alters secretion flux but

Table 3 Characterization of the Effects of Different Cultivation Modes on the Yield, Molecular Composition, and Function of EVs

	EVs Derived from 2D Culture	EVs Derived from 3D Culture
Training structure	Monolayer planar growth; cells exhibit flattened, adherent morphology lacking vertical spatial organization	3D, self-assembled structure containing multiple cell types; recapitulates tissue layering and compartmentalization
Biochemical microenvironment	Cells uniformly exposed to static, high-concentration soluble factors; absence of gradients	Physiological gradients of oxygen, nutrients, and metabolites; mimics the heterogeneous in vivo microenvironment
Output and heterogeneity	Relatively low yield; fluctuates with cell passage number or culture conditions.High batch-to-batch variability; mainly due to heterogeneous cell states and culture limitations	Significantly higher yield; further enhanced by dynamic culture; more stable production.Relatively controllable heterogeneity; vesicle subpopulation distribution closely reflects in vivo conditions
Targeting and homing capabilities	Weak targeting capability; primarily relies on passive diffusion or non-specific uptake	Strong targeting capability; benefits from complex surface ligand repertoire derived from multiple cell types, enabling precise recognition and binding to diseased tissues
Molecular characteristics and functional expression	Molecular composition (RNA, protein, lipid) deviates from in vivo state; lacks tissue-specific signals	Molecular profile closely resembles native tissue; enriched with key signaling molecules reflecting tissue polarity, cell-cell communication, and microenvironment

also results in a widespread upregulation of the miRNA profile carried by EVs, while protein components are correspondingly downregulated.[25] Vesicles derived from 3D culture are more similar in molecular composition to their in vivo physiological state.[26] Changes in their secretion kinetics and the abundance of key signaling molecules suggest that the flat growth pattern of 2D monolayers may deviate from the cells' natural secretory state. Currently, significant differences remain among studies regarding culture system types, cell sources, detection time points, and isolation and purification methods, which to some extent limit the comparability of results and the generalizability of conclusions (Table 3).

In addition, this organoid platform resolves the bottlenecks of low yield and significant batch-to-batch variability inherent in conventional EVs manufacturing processes, supporting the standardization of large-scale EVs production. As a result, it accelerates the pathway from laboratory research to clinical application (Figure 2).

Functional Roles in Physiology and Disease

Mediating Neuroprotection Through OEVs

Several studies have documented that mesenchymal stem cells derived from human umbilical cord mesenchymal stem cells (hucMSCs) possess neuroprotective properties.[27,28] HucMSC-derived EVs have been shown to cross the blood-brain barrier, elevate substantia nigra dopamine levels, and attenuate neuronal apoptosis in Parkinson's models,[29] brain OEVs also exhibit similar neuroprotective properties.[30] In particular, it has been demonstrated that these OEVs lessen apoptosis and oxidative stress in brain astrocytes. Damage to brain tissue from an ischemic stroke results in serious neurological impairments. Utilizing isolated OEVs with human induced pluripotent stem cells (hiPSCs) to generate brain organoids, a recent study further demonstrated that these OEVs conferred significant protection in an ischemic stroke mouse model.[31] The observed benefits notably comprised the modulation of autophagy, clearance of reactive oxygen species, and reduction of inflammatory responses. When taken as a whole, these findings show how OEVs have neuroprotective effects and provide new information about how to treat neurodegenerative illnesses.

When studying brain OEVs, it is crucial to focus on whether the miRNA composition carried by OEVs undergoes alteration.[32] For instance, miR-133b carried by mesenchymal extracellular vesicles can bind to abnormally expressed gene mRNAs and inhibit their translation, thereby mitigating neuronal damage. Notably, endogenous exosomes secreted by neurons and glial cells may also carry pathological α-synuclein, potentially exacerbating neurodegenerative

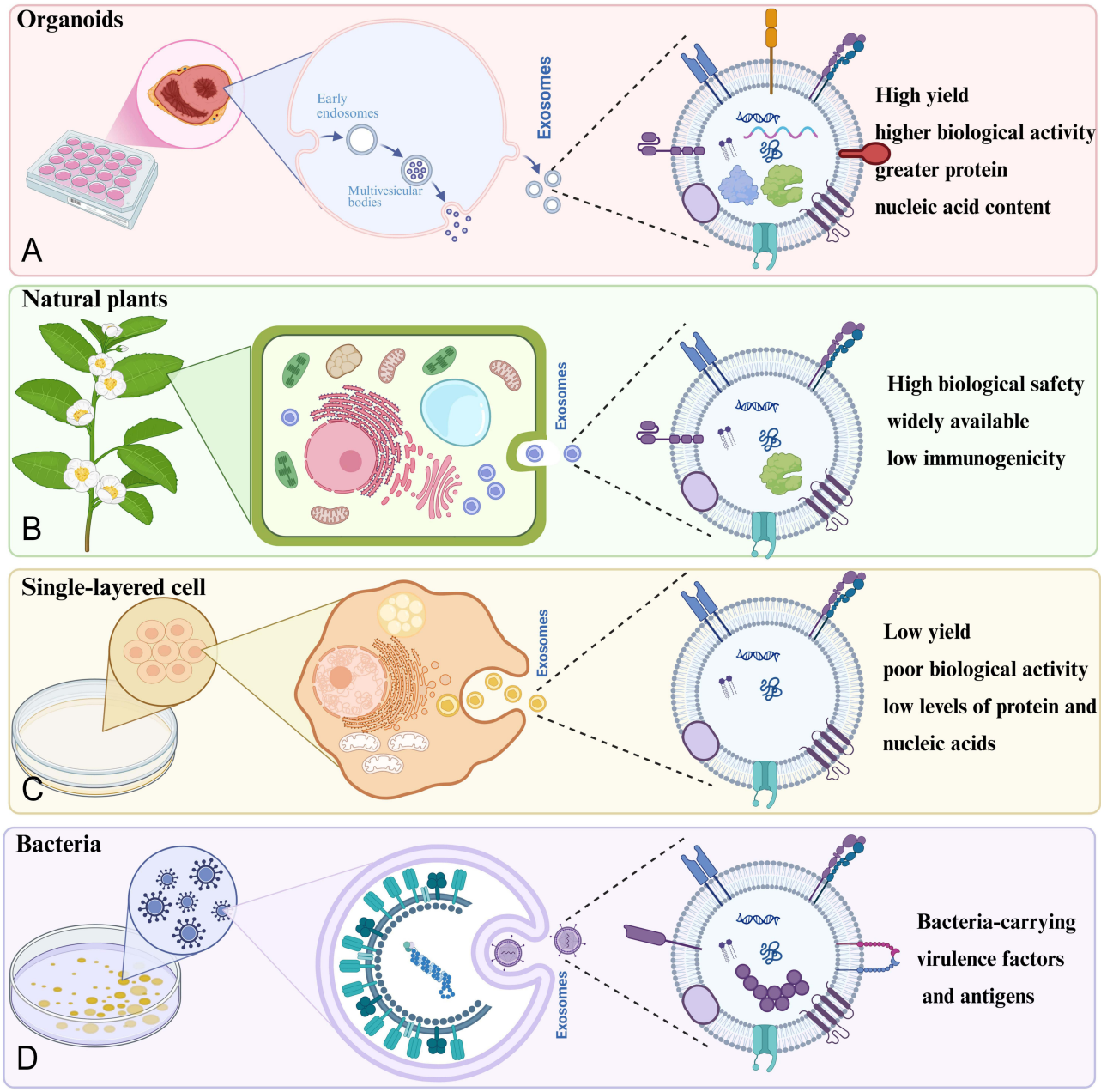

Figure 2 OEVs, PDEVs, EVs, BEVs generation diagram.

processes.[33] It also means that not all extracellular vesicles produce favorable impacts on disease outcomes, and their precise processes deserve additional exploration.

The Tissue Repair Function of OEVs

Researchers are investigating cell-free therapeutics for tissue repair, in which injured areas can be precisely targeted by bioactive molecules released by cells, hence increasing therapeutic efficacy.[34] Compared to EVs derived from embryonic stem cells, human retinal OEVs contain a richer array of immune-regulatory and retinal development-related proteins. They actively modulate fatty acid metabolism, effectively clearing abnormal lipid deposits and exerting antioxidant functions.[35] Further studies indicate that these human retinal OEVs can specifically target and inhibit the MAPK signaling pathway in retinal cells-particularly by downregulating the phosphorylation levels of p38 MAPK and JNK-

thereby alleviating oxidative stress and inflammatory responses.[36] This ultimately delays photoreceptor cell apoptosis and slows the progression of retinal degenerative diseases.

While Focusing on the salivary gland as an exocrine model, Ferreira et al[37] employed a magnetic 3D bioassembly platform to co-culture its organoids with human dental pulp stem cells, followed by salivary gland OEVs isolation from the conditioned medium. The salivary gland OEVs demonstrated improved tissue repair capabilities by successfully stimulating neuronal growth, epithelial progenitor cell proliferation, and epithelial expansion (up to 60%) in injured salivary glands. This method has broad application potential for common epithelial injuries like burns and radiation damage, even if it is currently only seen in damaged salivary glands. Long-term radiation exposure and aging are examples of chronic injury conditions that current models based on acute injury are unable to accurately replicate. It is still unclear whether salivary gland OEVs will be stable and effective in the long run in such circumstances. Clarifying their mechanisms of action and creating individualized treatments should be the main goals of future study.

Unlike traditional anti-adhesion strategies that rely solely on physical barriers, OEV-loaded superlubricant nanoskin reshapes the cytomatrical interaction network in the postoperative microenvironment through the synergistic action of physical barriers and biological regulation, thereby preventing adhesions while promoting physiological tissue repair.[38] By leveraging the natural nanoscale dimensions and surface molecular characteristics of OEVs, functional modification is achieved without compromising the mechanical properties of the superlubricant coating. Combining OEVs with nanostructured superlubricant nanoscale skin forms an innovative strategy that integrates "physical adhesion prevention with biological repair promotion."

Exploration of OEVs in the Treatment of Diabetic Non-Healing Wounds

In the pathological state of diabetes, the hyperglycemic environment severely impedes angiogenesis by inhibiting the HIF-1α/VEGF signaling pathway and disrupting endothelial cell function, thereby becoming a major bottleneck in wound healing. VEGF and pro-angiogenic miRNAs enriched in OEVs can effectively restart the inhibited angiogenesis program.[39] Furthermore, the antioxidant enzymes and anti-inflammatory factors they carry can scavenge reactive oxygen species (ROS) and reduce local inflammatory burden, thereby breaking the vicious cycle of "hyperglycemia-inflammation-hypoxia" in diabetic wounds.

Patients with diabetes frequently have poor wound healing, which can result in chronic ulcers and, in extreme situations, limb amputation.[40] A safer and more economical approach to treating diabetic wound healing is being investigated by researchers. Epidermal organoids (EpiOs) have become a cutting-edge model system for studying the physiological foundations of skin function and illness. In addition to having a population of differentiable epidermal stem cells, EpiOs share structural similarities with the epidermis. It was reported that epidermal OEVs, carrying substantial quantities of miRNAs and VEGF, promoted cell migration, proliferation, and angiogenic processes.[41] In individuals with diabetes, the hyperglycemic milieu inhibits angiogenesis, which prevents wound healing.

A production system using bioreactors to generate EVs derived from human adipose can reduce levels of inflammatory cytokines, stimulate collagen production, and activate the proliferation and migration of keratinocytes and fibroblasts.[42] In in vivo experiments, this approach promoted wound closure in excision wound models, increased keratinization and collagen deposition, and improved overall healing rates. In a clinical case study, complete wound closure and dermal regeneration were achieved following local treatment.

Anti-Inflammatory Effects of OEVs

Intestinal homeostasis and bone metabolism are closely linked. Inflammatory bowel disease (IBD) causes a systemic inflammatory environment to develop, leading to overactivity of proinflammatory factors such as TNF-α and IL-17, which stimulate bone-resorbing cells.[43] It disrupts immune homeostasis, resulting in bone loss. Existing treatments focus primarily on calcium supplementation and the administration of antiresorptive agents, often neglecting causal therapy in favor of symptom management. Su et al[44] stimulated intestinal organoids with lipopolysaccharides to mimic the inflammatory microenvironment in IBD. Intestinal OEVs directly target immune cells and suppress upstream signals of osteoclast activation at the source while improving intestinal inflammation and bone loss. Intestinal OEVs therapy not only functions as a bone-targeted drug delivery system but also reconstructs the inflammatory microenvironment. By

targeting the root cause of IBD inflammation, it prevents lasting skeletal damage and achieves causal treatment. Disease modeling using organoids from patients and tailored production of OEVs opens new avenues for the treatment of comorbidities.

A sustained-release technology was developed by mixing GelMA hydrogels with salivary gland OEVs.[45] Experiments demonstrated that GelMA hydrogels loaded with these salivary gland OEVs significantly enhanced angiogenesis, cell migration, proliferation, and collagen synthesis, effectively promoting wound healing. This technology also modulates immune homeostasis by inducing macrophage polarization toward the M2 phenotype, thereby reducing inflammatory responses. Numerous illnesses, such as tumors,[46] autoimmune disorders,[47] atherosclerosis,[48] and metabolic diseases,[49] are believed to be associated with macrophage polarization. During macrophage polarization, 2D-EVs exhibit an inhibitory effect on the proinflammatory cytokine IL-12β, whereas 3D-EVs demonstrate an enhancing effect on the anti-inflammatory cytokine IL-10.[50] Macrophage-derived EVs can directly regulate the activation status and effector functions of innate lymphoid cells, reshaping the network of immune cell interactions within the inflammatory microenvironment by delivering specific miRNAs and immunoregulatory proteins.[51] Future studies should investigate whether OEVs enhance the expression of anti-inflammatory-related miRNAs to achieve anti-inflammatory effects (Figure 3 and Table 4).

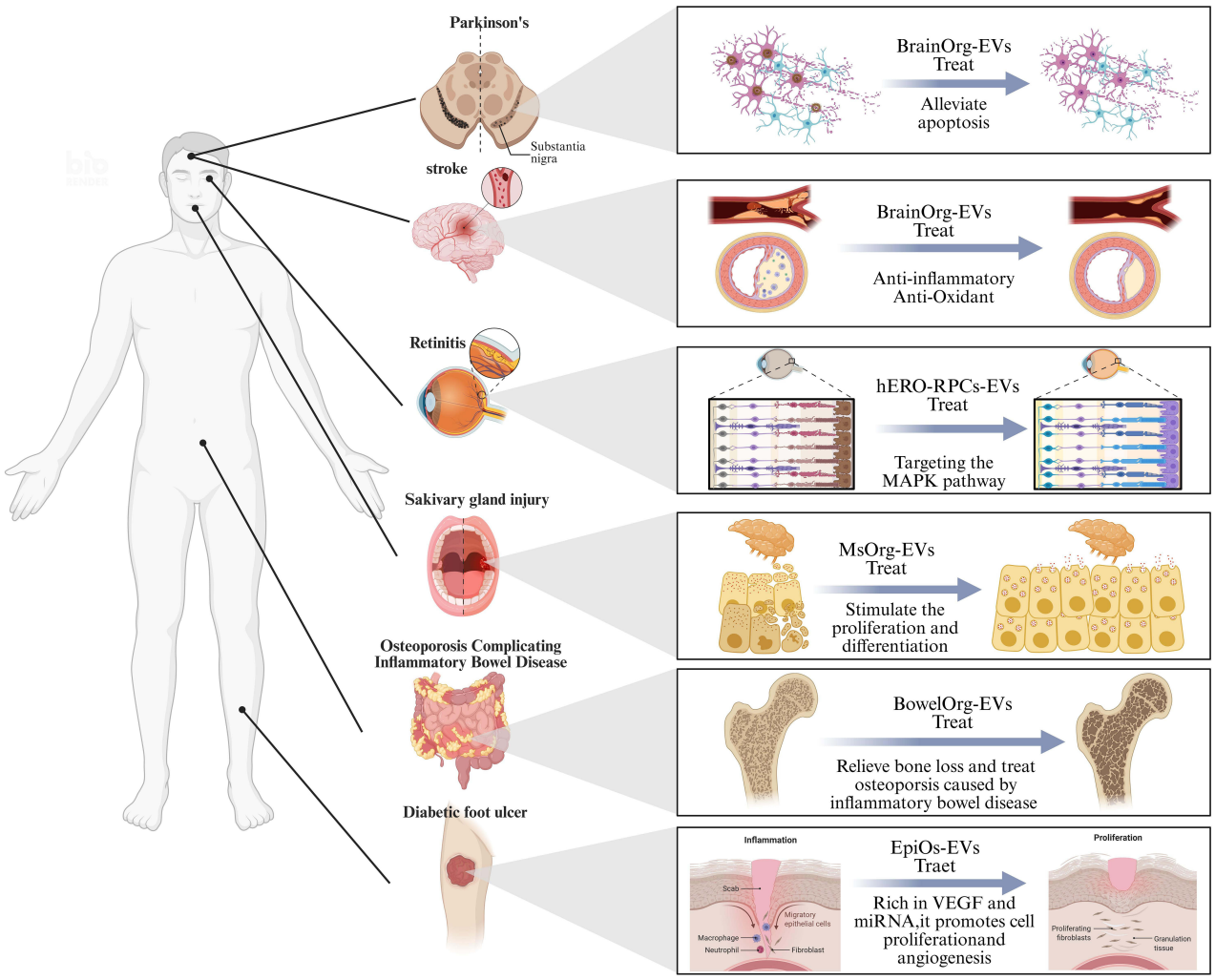

Figure 3 OEVs therapeutic effects and functional roles in physiology and disease.

Table 4 Summary of Therapeutic Effects of OEVs in Different Disease Models

Disease Model	Source of OEVs	Main Function	Mechanism of Action	References
Parkinson's disease	Brain organoids	Increase dopamine levels, inhibit neuronal apoptosis	Cross blood-brain barrier, regulate autophagy	[29, 30]
Ischemic stroke	Brain organoids	Clear ROS, reduce inflammation	Regulate autophagy, antioxidant	[31]
Retinal degeneration	Retinal organoids	Delay degeneration, clear lipid deposits	Target MAPK signaling pathway	[35, 36]
Diabetic wound	Epidermal organoids	Promote angiogenesis, cell migration	High expression of VEGF and miRNA	[41]
Inflammatory bowel disease and osteoporosis	Intestinal organoids	Reduce inflammatory factors, improve bone loss	Regulate immune response	[37, 44]
Wound healing	Salivary gland organoids	Promote collagen synthesis, M2 macrophage polarization	Macrophage polarization	[45]

Applications in Disease Modeling

OEVs Promote Tumor Organoid Growth

The dynamic balance of the tumor microenvironment depends not only on the regulation by immune cells and peripheral factors, but also on the tumor's own active remodeling of the microenvironment through the release of mediators such as EVs. As a key mechanism, this process cannot be overlooked. In the ovarian cancer microenvironment, tumor associated macrophages, regulatory T cells, and tumor cells are involved in a relationship of mutual inhibition, and the peripheral microenvironment can also attenuate the efficacy of immunotherapy through the secretion of factors.[52] Neither the tumor, the immune system, nor the peripheral microenvironment exists in isolation, but rather they are in a dynamic, mutually shaping state.

One technique for producing tumor organoids is currently building in vitro tumor tissues from patient derived tumor specimens.[53] An organoid library based on biopsy specimens from gastrointestinal tumor metastases was effectively established as early as 2018 by a London based research team.[54] They demonstrated the clinical translational utility of patient-derived organ tissues for pharmacological efficacy assessment and individualized precision treatment by performing assessments of chemotherapy and targeted drug sensitivity.[55] Meanwhile, using tumor organoid models, scientists found that these tumor OEVs can decrease immune cell activity, promote angiogenesis, and transform normal fibroblasts into cancer associated fibroblasts.[56] In order to facilitate tumor growth and metastasis, this mechanism modifies the tumor microenvironment.[57] Co-culturing extracellular vesicles generated from esophageal adenocarcinoma with stomach organoids increases the expression of cancer-associated miRNAs (such as miR-21 and miR-210) and triggers phenotypic alterations that impact the growth of co-cultured organoids.[58] Recent studies indicate that tumor OEVs enhance organoid proliferation capacity and elevate levels of cancer associated microRNAs.[59]

OEVs Promote Organoid Vascularization

Building functioning vascular networks makes it easier to supply nutrition and oxygen to tumor organoids, providing a deeper comprehension of the mechanisms behind tumor spread.[60] A patient-derived tumor organoid chip with vascularization and tumor microvasculature that efficiently evaluates tumor spread has been created by a research team.[61] An emphasis on customized treatment strategies is replacing a tumor-type-centered strategy in cancer treatment, marking a paradigm shift.[62]

EVs from adipose tissue reprogram static culture environments into pro-angiogenic microenvironments by delivering key bioactive molecules.[63] This microenvironmental transformation not only supports adipocyte precursor cell differentiation but also specifically activates the angiogenesis program, thereby synchronously enabling adipose tissue formation and vascular network construction within organoids.[64] This discovery offers novel therapeutic strategies for chronic vascularized wounds and burn wound healing (Figure 4).

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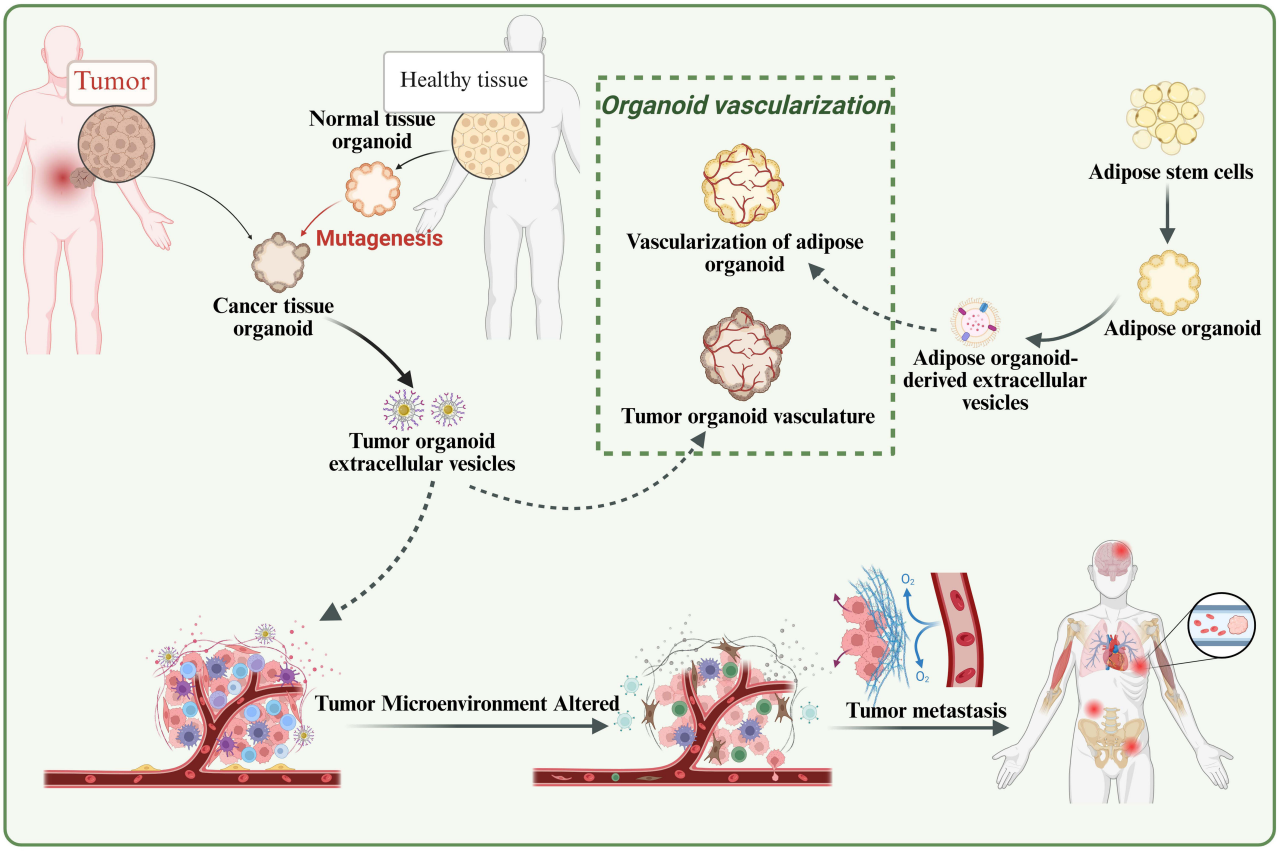

Figure 4 The Role of OEVs in vitro model construction.

Therapeutic Applications

OEVs as Highly Efficient Carriers for Targeted Drug Delivery

Through engineering modifications, drug molecules are loaded into the interior of OEVs. The integrins on the surface of OEVs specifically recognize fibronectin or vitellin ligands on the target cell membrane, triggering a cascade of adhesion signals. Transmembrane protein molecules abundant on the surface of OEVs promote the adhesion and fusion of OEVs with the target cell membrane. After the phospholipid bilayer of the OEVs fuses with the cell membrane, the drug is transported into the recipient cell via laminin-mediated endocytosis and laminin-dependent endocytosis. The membrane-fusion-mediated direct cytoplasmic delivery pathway avoids the risk of drug degradation by lysosomes, making it suitable for nucleic acid drugs and protein-based therapeutics that are susceptible to degradation in acidic environments.

Selective penetration into tumor tissues is made possible by OEVs with nanoscale diameters, which improve the enhanced permeability and Retention effect.[65] OEVs are great drug delivery vehicles because they resemble cell membranes in structure and have high biocompatibility and permeability. Jia et al[66] created organoids that resembled the original tumors by cultivating patient tumor tissues in vitro. They loaded medications into OEVs made from these organoids using microfluidic technology, exhibiting excellent targeting and great efficiency. Using the Folch method to treat endosomes produced from melanoma, their contents were removed, leaving only membrane components with targeting activities.[67] An artificial endosome delivery system was then successfully built by assembling them onto the surface of organosilicon nanoparticles. This biomimetic system exhibited preferential enrichment of tumor tissues inside animal models. Endosomal membranes are naturally able to target the lungs. Doxorubicin-loaded nanocages efficiently accumulated at the tumor site, greatly reducing the growth of the original tumor and the spread of its metastases.

Based on a multi-site Fc-conjugation strategy, OEVs can serve as multifunctional platforms capable of simultaneously carrying chemical drugs, nucleic acid therapeutics, and photosensitizers.[68] By linking different targeting molecules via Fc

fragments, synergistic targeting of multiple receptors can be achieved. Fc-fused ligands can be efficiently anchored to the surface of OEVs via chemically or biologically orthogonal reactions, enabling stable, directed multi-site conjugation using native or recombinant Fc receptors. This strategy overcomes the limitations of traditional single-site modification, such as low ligand density and uneven distribution significantly enhancing tumor cell recognition and uptake, and improving targeted delivery efficiency. Building on this foundation, we further incorporated the principles of liquid-liquid phase separation to design a novel drug delivery system.[69] By developing stimulus-responsive drug carriers, we achieved precise temporal and spatial control over the delivered drugs, thereby optimizing the therapeutic efficacy and safety of OEVs.

Combining vesicles from different sources to integrate their respective functional advantages is one of the key directions in the development of vesicular delivery systems. Through genetic engineering, we have engineered mixed vesicles derived from mesenchymal stem cells that can efficiently scavenge ROS and restore mitochondrial homeostasis, demonstrating significant protective effects in a model of hepatic ischemia-reperfusion injury. Delivery systems containing multiple active components enhance their synergistic therapeutic effects in complex pathological microenvironments.[70]

Engineering Strategies for OEVs

Natural OEVs have short half-lives and a limited capacity to carry drugs. The clinical translation of OEV-based medicines can be further advanced by molecular engineering of natural OEVs to obtain more accurate and effective treatment.[71] Engineered OEVs improve targeting, maximize loading efficiency, facilitate effective nanomedicine administration, and extend circulation time in vivo.[72] However, a thorough assessment is necessary for the long-term safety of modified OEVs.[73]

Engineering modifications of OEVs primarily fall into two categories: direct modification after isolation and indirect regulation via organoid modification. Direct engineering involves chemically or physically modifying OEVs isolated from organoid culture supernatants to enable them to carry specific functional molecules.[74] For example, leveraging the transmembrane properties of membrane-penetrating peptides, small-molecule drugs or siRNA can be passively loaded into the OEV lumen through co-incubation. Click chemistry's high efficiency and specificity enable the targeted peptide to be bound to the membrane surface of the OEV, thereby conferring functions such as targeting tumor angiogenesis.[75] In contrast, electroporation technology uses intense electrical pulses to create microscopic pores in the membrane, allowing hydrophilic drugs or nucleic acids to easily penetrate into the vesicle.[76] Such direct modification methods are relatively simple to implement and allow for controllable technical design. Their disadvantages, however, include unstable modification efficiency, difficulty in ensuring OEV uniformity, and the risk of damaging the vesicle surface structure, which can adversely affect its function.

Indirect engineering involves genetically or expression-regulating source cells within organoids to naturally secrete OEVs carrying specific molecules or functions.[5] For instance, gene editing techniques can be used to knock out or introduce point mutations in target genes, or plasmid transfection and lentiviral packaging can be employed to overexpress fusion proteins combining transmembrane proteins with targeting peptides.[77] This enables secreted OEVs to stably display targeting ligands on their surfaces, achieving precise delivery. Although these methods involve high technical barriers and extended timelines, the engineered OEVs obtained typically exhibit greater uniformity and stability, with more reliable functional performance (Figure 5).

The maturation stages of several brain areas, including the forebrain and hindbrain, can be replicated in vitro using human brain organoids. Mature tissue architectures can be produced by utilizing hiPSC to create forebrain and hindbrain organoids, respectively, and cultivating them for 30 to 45 days.[31] Different brain regions produce matrix-binding vesicles (MBVs), which transport region-specific signaling chemicals and control the destiny of recipient cells.[78] After ischemia-reperfusion injury, forebrain MBVs enriched with WNT3A further promote neuronal axon regeneration, while hindbrain MBVs containing SHH show more marked suppression of astrocyte proliferation. In an in vitro ischemia-reperfusion paradigm, knocking in the WNT3A-Lamp2b fusion gene in human-derived brain organoids naturally enriched WNT3A in OEVs, greatly improving neuronal survival. Nevertheless, in gene modification strategies, the overexpression of exogenous fusion genes may impose a significant metabolic and biosynthetic burden on the organoids themselves, such as increased oxidative stress, elevated endoplasmic reticulum stress, and energy metabolism dysregulation. Subsequently, this may affect the viability and proliferative capacity of the parental organoids and potentially reduce the yield and functional homogeneity of OEVs (Table 5).

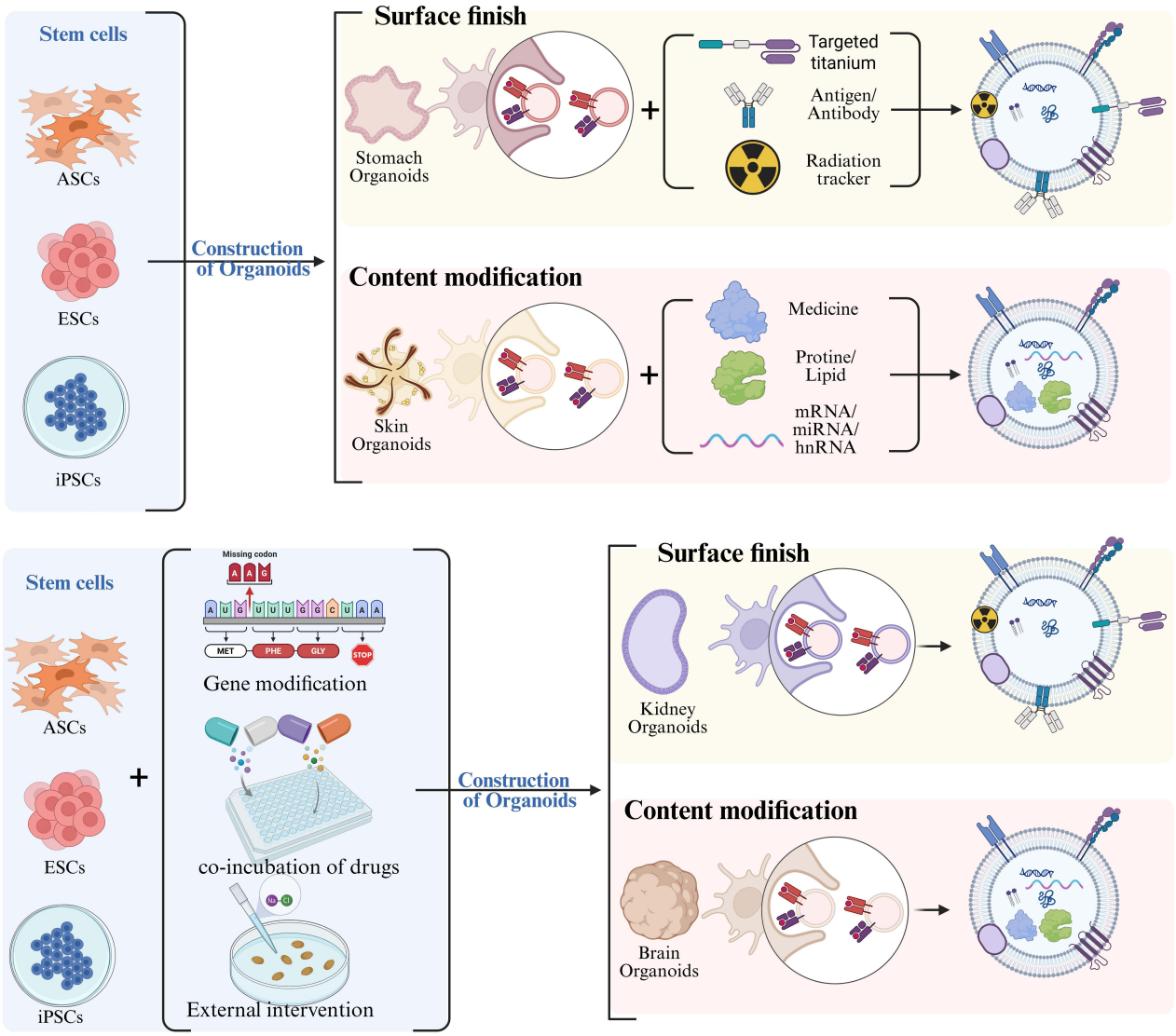

Figure 5 Engineered construction method for OEVs.

The Potential of OEVs Immunomodulatory Functions in Regenerative Medicine

Early studies have demonstrated that extracellular vesicles, owing to their low immunogenicity and immunomodulatory properties, can effectively improve graft survival rates. Concurrently, organoids, with their high physiological relevance, have been attempted for direct transplantation into patients with advanced diseases, showing tremendous potential for

Table 5 Engineering Strategies for OEVs and Their Applications

Engineering Strategy	Method	Application Scenario	Advantages
Secondary modification	Chemical/physical methods	Short-term drug delivery, targeted ligand loading	Simple operation, high flexibility
Gene editing	CRISPR activation/ repression	Regulate miRNA, lncRNA expression	Precisely control OEVs contents
Fusion gene knock-in	WNT3A-Lamp2b	Enhance neuronal survival	Naturally enrich target molecules
Engineered M2 EVs	Loading Static inhibitor	Treat secondary hyperparathyroidism	Promote autophagy, induce M2 polarization

clinical translation.[79] In a rhesus monkey model of chronic heart failure, engineered cardiac tissue derived from hiPSCs achieved six-month graft survival and significantly improved ventricular systolic function.[80] The left ventricular ejection fraction of a patient with severe heart failure then rose from 35% to 39% following surgery in the first human clinical trial. Patients with retinitis pigmentosa were given retinal organoids made from hiPSCs.[81] Postoperative observation revealed no adverse reactions or complications in any patient. After two years of follow-up, patients integrated safely and stably, and their sensitivity to light stimuli improved significantly. No evidence of immune rejection was observed, providing initial proof of the high safety and feasibility of temporary organ transplants.

However, the mechanism by which organoids secrete vesicles and exert their effects while "living" as grafts within recipients remains unknown.[82] At the level of immune regulation, exosome-mimetic nanovesicles exert a significant regulatory effect on CD4+ T cells. These vesicles may disrupt the balance between pro-inflammatory and anti-inflammatory responses in immune cells, as evidenced by a significant increase in pro-inflammatory cytokines and a significant decrease in anti-inflammatory cytokines, providing important insights into the potential regulatory role of OEVs in the immune microenvironment.[83] We hypothesize that these OEVs, generated in situ by transplanted organoids, may exert critical immunomodulatory effects locally and systemically through active intercellular communication. This could reduce rejection risks and promote long-term survival. Unraveling the post-transplant functions and mechanisms of OEVs represents a crucial frontier for advancing organoid transplantation technology and achieving breakthroughs in regenerative medicine.

Cell-Free Therapy Based on OEVs

Transplanting intact, viable cells into the body to replace damaged cells, regulate the immune system, and carry out other tasks is known as traditional cell therapy. Mesenchymal stem cell transplantation for the control of autoimmune diseases,[84] hematopoietic stem cell transplantation for the treatment of hematological disorders,[85] and the use of immune cells for anticancer therapy are other examples.[86] However, this strategy involves the risk of unchecked proliferation that results in cancer when applied to stem cells. Additionally, the patient's immune system may identify transplanted cells from allogeneic origins as "foreign," leading to immunological rejection reactions.[87] Furthermore, excessive immune cell activation might trigger severe inflammatory reactions that could be fatal. While eliminating the dangers of using live cells, cell-free therapies based on extracellular vesicles,[88] apoptotic bodies, or released cellular substances can maintain the therapeutic advantages of conventional cell therapies.[89]

OEVs do not have the ability to proliferate, carry a variety of bioactive compounds released by organoids, and are not carcinogenic. They are less immunogenic than living cells after purification, which lowers the possibility of immunological rejection.[90] Additionally, organoids can function as stable "production workshops" for extracellular vesicles, making it possible to produce stable and consistent vesicles in large quantities.[6] It should be noted that the carcinogenic substances carried by tumor OEVs theoretically pose a potential risk of inducing malignant transformation in recipient cells, this limitation should be fully taken into account in safety assessments. Standardized organoid construction protocols, unified purification processes, systematic evaluation of long-term safety, and in vivo/in vitro tracking to comprehend pharmacokinetics and biodistribution are all necessary to move OEVs toward clinical application as therapeutics.

In vitro Antimicrobial Susceptibility Prediction Tool

Extracellular vesicles released by drug-resistant cells have been shown in cellular models to transfer membrane proteins or miRNA to sensitive cells, giving the latter resistance to chemotherapy or targeted therapy.[91,92] In order to assess how hypoxia-induced extracellular vesicles containing PKM2 increase cisplatin resistance in non-small cell lung cancer (NSCLC) cells, Huang et al[93] subjected NSCLC cells to hypoxic conditions. They discovered that PKM2 increases glycolysis in NSCLC cells, producing reductive metabolites to counteract reactive oxygen species caused by cisplatin and inhibiting apoptosis through the PKM2-BCL2 pathway. Simultaneously, it reprograms cancer-associated fibroblasts to produce an acidic milieu, which eventually promotes NSCLC cell proliferation and cisplatin resistance in a combinatorial manner.

Additionally, there are no reports of resistance-associated molecules (such as particular miRNAs or drug efflux pump proteins) being secreted by organoid-derived extracellular vesicles and transferred to sensitive cells, thereby inducing population-wide resistance,[94] despite the fact that chemotherapy/targeted drug resistance models have been established using tumor organoids.[95,96]

Development of Disease Diagnostic Biomarkers

The clinical traits, genetic mutations, and heterogeneity of the original tissue are preserved in organoids made from patient-derived cells.[97] Compared to those from cell lines, the extracellular vesicles released by these organoids are more clinically relevant and more closely represent the actual condition of sick cells. OEVs function not only as carriers of bioactive molecules in intercellular communication but also as potential mediators of disease pathology.[98] The specific markers they carry are closely associated with the mechanisms driving disease initiation and progression. By employing a "modular structure" strategy to prepare nanoenzymes with artificial substrate binding sites and using them to construct a visual sensing platform for L-dopa, the core concepts in the fields of biosensing and diagnostics share an intrinsic connection with OEV-based biomarker discovery.[99]

After constructing disease-related organoids, machine learning, artificial intelligence, or multi-omics fusion models can process large volumes of OEVs data.[100] By automatically extracting and ranking large datasets of membrane or intracellular proteins highly or lowly expressed in OEVs along with their significance, these approaches uncover hidden patterns and correlations within the data, enabling more accurate identification of potential disease-related biomarkers, prediction of therapeutic responses, and optimization of OEVs engineering.[101] When hiPSCs with different genetic origins were differentiated into basal forebrain cholinergic neurons, different subtypes of disease-associated exosomal Aβ42 oligomers or tau proteins showed different conformations or contents. Precise patient subtyping may be made possible by these variations[102,103] (Figure 6).

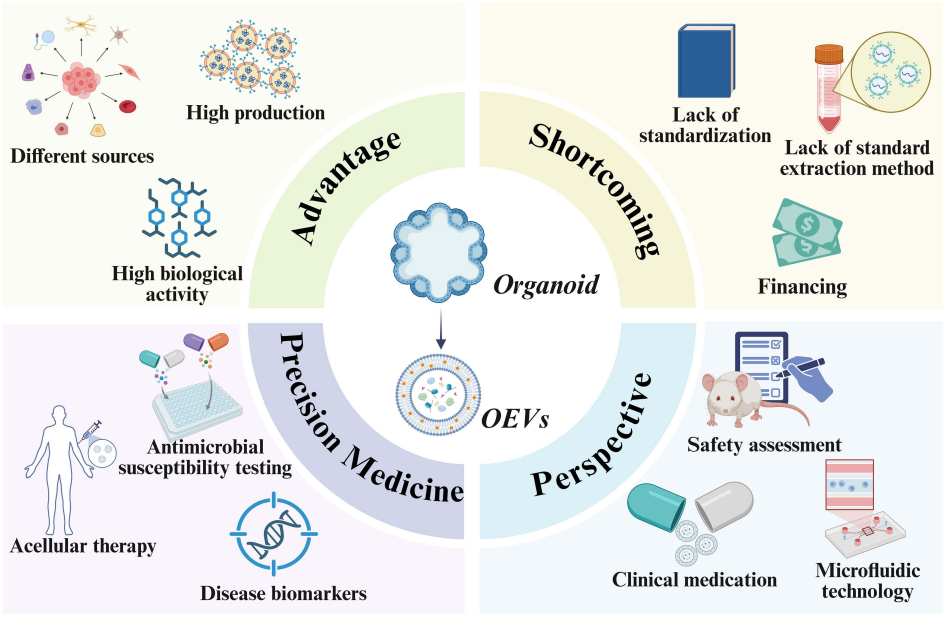

Figure 6 Advantages and limitations of OEVs for therapeutic applications.

Challenges and Limitations

Research on OEVs is currently in the exploratory phase, spanning from their biological mechanisms to clinical translation prospects. There are substantial research gaps concerning their impact on organoid formation as well as their therapeutic implications on illnesses. First, it's still unknown how exactly OEVs regulate disease. How precisely do OEVs alter the immune microenvironment in tumor models? How are target cells regulated by the particular miRNAs or proteins that OEVs carry? OEVs play a key mediating role in organoid self-renewal and maturation; however, the exact molecular mechanisms and regulatory networks underlying organoid morphogenesis, cell differentiation, and functional maturation remain unclear and require further investigation.

The current literature lacks rigorous head-to-head comparisons between OEVs and conventional EVs, specifically studies that compare the therapeutic activity and batch consistency of OEVs with those derived from 2D cultures or conventional 3D spheroids under uniform isolation and quantification standards within a single controlled experiment. Most existing evidence stems from cross-sectional comparisons across different laboratories, cell lines, and isolation methods, which may introduce systematic bias.

Various organoid culture methods exist, and different approaches have varying effects on the generation and molecular composition of OEVs. Matrix-embedding techniques often involve the addition of scaffolds, such as biohydrogels, during organoid culture to provide three-dimensional support and biological signals, thereby promoting the self-organization of organoids and protecting cells from damage caused by external mechanical shear forces. However, scaffold materials such as hydrogels share similarities with OEVs in terms of particle size distribution, surface charge, and protein composition. Conventional methods—such as differential centrifugation, size-exclusion chromatography, or polymer precipitation—struggle to effectively separate OEVs from degraded gel fragments, leading to reduced extraction purity and interference from false-positive signals. Researchers have attempted to use enzymatic digestion to release embedded organoids from the gel; however, enzymatic treatment may compromise the membrane integrity of OEVs or introduce exogenous vesicular contaminants. Furthermore, additional purification steps are required after enzyme removal, resulting in a significant reduction in sample recovery. The matrix-free suspension culture method utilizes the self-aggregation properties of cells to form self-organized organoids in low-adhesion microplates. Although this method can improve the extraction efficiency and purity of OEVs, the mechanical shear forces generated during organoid culture can affect the mechanically sensitive signals of the organoids. Furthermore, the total cell count in a single culture system is lower than that in the matrix-embedded method, often resulting in lower OEV yields. To address challenges such as high-throughput screening, complex structure construction, and the preservation of cellular components, and to enable large-scale production that meets clinical needs, diverse culture strategies have been developed. Introduction of bioreactors has provided a new platform for the large-scale production of OEVs. When human vascular organoids were cultured in vertical rotary bioreactors under low shear conditions of 40 rpm, EV yield increased by 2–3 times compared to the static control group, and the particles were comparable to those from static culture in terms of particle size, marker expression, and in vitro therapeutic activity.[104] Hydrodynamic bioreactor systems stimulate stem cell spheroids through fluid shear forces generated by alternating flow patterns, resulting in a significant 10–20 fold increase in EV yield compared to static culture.[105] Currently, an automated organoid preparation system based on microfluidic technology has been established and has been used to prepare human hepatocellular carcinoma organoids, liver organoids, and colorectal cancer organoids.[106] By reducing heterogeneity within the organoids, this method demonstrates significant advantages in terms of morphological consistency, transcriptomic fidelity, and reproducibility of cellular composition. Microfluidic chip technology integrates perfusion channels and cell culture chambers on micron-scale chips, precisely controlling liquid and fluid shear stress conditions. It enables the preparation of microspheres with uniform particle size and controllable structure, thereby influencing the number, size distribution, and content loading of OEVs, and consequently improving the consistency and functionality of OEVs in drug delivery and disease model construction. Multi-channel parallel designs enable high-throughput screening and analysis; however, the high manufacturing costs of microfluidic chips make large-scale, low-cost production challenging. 3D printing technology allows for precise control of organoid size, morphology, and internal 3D microenvironment by pre-setting cell numbers, spatial distribution, and the composition of the scaffold matrix. By printing organoids with specific surface modifications or functions, OEVs can be engineered to

express specific ligands or receptors on their surfaces, thereby enhancing targeting. However, the scaffold matrix and bio-ink can affect the efficiency of OEV extraction and purification. The limitations of individual technologies have led researchers to seek solutions through the integration of multiple technologies.[107] 3D-printed organoids can be embedded within microfluidic chip chambers, which, by optimizing the organoid microenvironment, can significantly improve the homogeneity, yield, and functional targeting of OEVs. With innovations in materials and processes, it is expected that low-cost, high-purity, large-scale production will be achieved, propelling OEVs from laboratory research toward standardized clinical biotherapeutic products.

Although OEVs demonstrate tremendous translational potential in the field of precision medicine, their practical clinical application still faces multiple obstacles. The first challenge is the standardization of preparation processes, particularly regarding the maintenance of structural integrity and functional activity during storage and transportation. The lack of effective preservation protocols directly leads to increased batch-to-batch heterogeneity and diminished therapeutic efficacy, severely hindering their industrialization as biological products. The addition of human albumin and trehalose to PBS can significantly improve the stability of EVs during two years of storage at −80°C and increase recovery rates after repeated freeze-thaw cycles, providing a foundational protocol for OEV storage.[108] Secondly, systematic in vivo safety data for OEVs remain limited.[109] Current evidence indicates that, at the cellular level and in some animal models, OEVs have demonstrated good functional activity and low cytotoxicity, providing valuable references for subsequent research.[110] However, to meet the safety requirements for clinical translation, more comprehensive animal studies will be needed in the future to systematically supplement and refine the evidence chain regarding the in vivo safety of OEVs.[111]

Conclusion and Perspectives

OEVs are derived directly from stem cells, which spontaneously assemble into organoids. Due to their multicellular nature, OEVs are better able to preserve the signaling networks of the organ microenvironment, and the biological information they convey exhibits stronger tissue polarity and organ specificity. OEVs demonstrate multifaceted functions and application potential in the biomedical field. At the fundamental mechanistic level, OEVs exhibit clear tissue repair and regenerative capabilities. By mediating neuroprotection, exerting anti-inflammatory effects, and regulating immune responses, they offer new intervention strategies for neurological diseases, chronic inflammation, and autoimmune-related damage. In disease treatment, OEVs have been explored for the management of diabetic non-healing wounds, accelerating tissue healing through synergistic anti-inflammatory and pro-angiogenic functions. Additionally, OEVs effectively promote vascularization and growth in disease models; however, it is worth noting that tumor OEVs also exert a certain promotional effect on tumor organ growth, suggesting that their bidirectional regulatory potential within the tumor microenvironment requires careful evaluation. At the translational application level, leveraging their inherent advantage of a natural multi-cellular signaling profile, OEVs have been developed as highly efficient carriers for targeted drug delivery to tumors. Combined with diverse engineering strategies, their targeting specificity, drug-loading capacity, and therapeutic efficacy can be significantly enhanced. In the diagnostic field, analyzing the contents of OEVs derived from Alzheimer's disease organoid models, in conjunction with the expression profiles of specific neuronal markers, glial cells, and other brain cell types, can reveal complex biological signals transmitted through intercellular communication.[112] As highly informative liquid biopsy biomarkers, the molecular characteristics of these pluripotent cells significantly improve the specificity and sensitivity of early-stage Alzheimer's disease diagnosis.

As OEVs transition from basic research to clinical translation, systematic breakthroughs are urgently needed in several key areas. The primary task is to establish internationally recognized standards for the isolation and detection of OEVs, which is a fundamental prerequisite for ensuring the comparability and reproducibility of research results across different laboratories and batches. Building on this foundation, it is essential to systematically conduct OEV-based drug delivery research using animal models to comprehensively evaluate their in vivo efficacy, pharmacokinetic characteristics, and long-term safety, thereby providing robust preclinical evidence for subsequent clinical trials. Concurrently, by leveraging the deep integration of novel biomaterials and bioengineering technologies, an automated, scalable OEV production and quality control system compliant with Good Manufacturing Practice requirements must be established to fundamentally address the current industrialization bottlenecks of low yield and significant batch-to-batch variability.[113] In the diagnostic field, the development

of OEV-based liquid biopsy products will transform the rich multicellular signals they carry into clinically applicable early-stage, non-invasive diagnostic biomarkers, providing a novel tool for the early screening, classification, and dynamic monitoring of various major diseases. OEVs will transition from laboratory proof of concept to a new phase of standardization, automation, and clinical application, truly realizing their translational value in precision medicine.

Abbreviations

BEVs, Bacterial extracellular vesicles; EpiOs, Epidermal organoids; EVs, Extracellular vesicles; hiPSCs, Human induced pluripotent stem cells; hucMSCs, Human umbilical cord mesenchymal stem cells; IBD, Inflammatory bowel disease; MBVs, Matrix-binding vesicles; MISEV, Minimal information for studies of extracellular vesicles; NSCLC, Non-small cell lung cancer; OEVs, Organoid-derived extracellular vesicles; PDEVs, Plant-derived extracellular vesicles.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 82360049) (NO.82460096), NHC Key Laboratory of Healthy Birth and Birth Defect Prevention in Western China Open Project (2024XBYSKF001) (2024XBYSKF007), National Clinical Key Specialty Cultivation Project Platform for Endocrinology Open Project (2024NMKFKT-04). Thanks for biorender.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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