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REVIEW

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Organoid-tissue extracellular vesicles

Han Liu[1,2,3,4] | Ting Cheng[1,2,3,4] | Guangfeng Li[1,2,3,4] | Zhidao Xia[5] | Chenglong Wang[6] | Ke Xu[1,2,3,4] | Jiacan Su[1,2,3,4,6]

[1]Institute of Translational Medicine, Shanghai University, Shanghai, China

[2]MedEng-X Insititutes, Shanghai University, Shanghai, China

[3]Organoid Research Center, Shanghai University, Shanghai, China

[4]National Center for Translational Medicine (Shanghai) SHU Branch, Shanghai University, Shanghai, China

[5]Centre for Nanohealth, Swansea University Medical School, Swansea University, Swansea, UK

[6]Department of Orthopedics, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Correspondence
Chenglong Wang, Ke Xu and Jiacan Su.
Email: wangorth@163.com, kexu@shu.edu.cn and drsujiacan@163.com

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Abstract

Extracellular vesicles (EVs) are lipid bilayer structures secreted by cells that act as intercellular messengers. Tissue-derived EVs (TEVs), harvested from the tissue interstitium, directly reflect the actual physiological or pathological state of the tissue microenvironment. However, the difficulty in tissue acquisition severely limits the development of TEVs. In contrast, organoids are 3D cell clusters cultured from stem cells, which have spatial structures and physiological functions that are highly similar to the source tissues. Although organoid-derived EVs (OEVs), isolated from culture supernatants, can reflect complex cellular interactions, they cannot directly reflect the state of the tissue microenvironment like TEVs. Building on the foundation of TEVs and OEVs, we introduce the innovative concept of organoid-tissue EVs (OTEVs), where residing in the organoid interstitium. Acting as a communication bridge between OEVs and TEVs, OTEVs can accurately represent the true microenvironment. They overcome the challenges associated with the limited availability of TEVs and the inability of OEVs to directly reflect the microenvironment. We believe that OTEVs will synergize with TEVs and OEVs to enhance the understanding of the pathogenesis of complex diseases, as well as to improve their diagnosis and treatment.

Abbreviations: 3D, three-dimensional; AD, Alzheimer's disease; Ad-EVs, adipose tissue-derived extracellular vesicles; BEVs, bacteria-derived EVs; EAT, Epicardial adipose tissue; EVs, extracellular vesicles; FGF10, fibroblast growth factor 10; hDPSC, human dental pulp stem cells; Hep-EVs, hepatocyte-derived extracellular vesicles; hERO-RPC, human retinal organoid-derived retinal progenitor cells; hESC, human embryonic stem cells; LPS, lipopolysaccharide; M3DB, magnetic 3D bioassembly; MEVs, mammalian cell-derived EVs; Mu-EVs, muscle-derived EVs; MVBs, multivesicular bodies; OEVs, organoid-derived EVs; OTEVs, organoid-tissue EVs; PBS, phosphate-buffered saline; PEVs, plant-derived EVs; RD, retinal degeneration; TEVs, tissue-derived EVs; TMJ OA, temporomandibular joint osteoarthritis.

Han Liu, Ting Cheng, and Guangfeng Li are contributed equally to this work.

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KEYWORDS
diseases diagnosis and treatment, extracellular vesicles, organoid extracellular vesicles, tissue extracellular vesicles

1 | INTRODUCTION

EVs are intricate lipid bilayer structures secreted by a wide variety of cells and play a critical role as intercellular messengers within the body.[1–4] These vesicles are capable of delivering a diverse array of biomolecules, including lipids, proteins, and nucleic acids, which are essential for cell-to-cell communication and contribute significantly to both physiological and pathological processes.[5–8] EVs are involved in numerous biological functions, such as immune response, tissue repair, and regulation of cellular functions, thereby influencing a range of outcomes from normal cellular processes to disease progression.[9–12] Among the various types of EVs, TEVs are particularly noteworthy.[13–15] These vesicles are harvested from the tissue interstitium, where they originate, and are considered valuable indicators because they can directly reflect the actual physiological or pathological state of the tissue microenvironment.[16] The presence of specific biomolecules in TEVs can provide insights into disease states, including cancers, inflammatory conditions, and other pathological processes.[17–19] However, the utility of TEVs is significantly hindered by the inherent difficulty in acquiring tissue samples. Obtaining adequate tissue without causing harm to the patient or disturbing the tissue architecture is a considerable challenge, which limits the availability of TEVs for both research and clinical applications.

In contrast to the limitations present with tissues, organoids represent an innovative approach in the field of biomedical research.[20] Organoids are three-dimensional (3D) cell clusters cultured from stem cells that exhibit complex spatial structures and physiological functions that closely resemble those of their original source tissues.[11,21] These multicellular constructs retain key characteristics of the tissue environment, including cell-to-cell interactions, signaling pathways, and tissue architecture, making them invaluable for investigating biological processes in a more realistic context compared to traditional 2D cultures.[22] In recent years, our team has focused on OEVs.[23,24] Our team proposed the concept of OEVs in the world and proposed a strategy to use OEVs to treat complex diseases.[10] We also systematically explored the applications of organoids and OEVs in disease treatment.[23,25] We hope that a thorough comprehension of OEVs will pave the way for novel therapeutic approaches to tackle intricate diseases. In addition, we explored the role of gut microbiota-derived EVs in regulating bone metabolism and proposed new osteoporosis therapies based on the gut-bone axis, including traditional metabolites and immune and endocrine pathways, as well as the potential applications of bacteria-derived EVs (BEVs)[26–28] and intestinal OEVs (IOEVs).[29] Unlike traditional 2D cell culture systems, 3D cell culture can form tissue structures similar to stem cell niches and has a physiological state closer to that of tissue.[30] Compared with EVs cultured in traditional 2D culture, OEVs have a larger number and better physiological effects.[24] However, while OEVs can be isolated from the culture supernatants and have been shown to reflect complex cellular interactions, they do not directly mirror the microenvironmental cues in the same way as TEVs.

To address this gap, EVs residing in the interstitium of organoids can be extracted and classified as OTEVs based on the principles of isolation.[31] This innovative approach allows OTEVs to serve as a vital communication bridge between OEVs and TEVs, possessing the potential to accurately represent the true microenvironment of the tissue from which the organoids are derived. By capturing the specific signatures of these organoid-tissue EVs, researchers can gain critical insights that more closely align with the native tissue environment. OTEVs effectively mitigate some of the significant challenges associated with the limited availability of TEVs while addressing the shortcomings of OEVs, particularly their inability to directly reflect the state of the tissue microenvironment. Through the study of OTEVs, researchers can delve deeper into the underlying mechanisms of various diseases, potentially elucidating the pathogenesis of complex conditions that have remained elusive. Consequently, the concept of OETVs emerges as a promising avenue for translational research, offering the potential to significantly advance our understanding of disease mechanisms. OTEVs will work together with TEVs and OEVs to support in-depth research into the causes, diagnosis and treatment of complex diseases (Figure 1).

2 | TISSUE-DERIVED EVS (TEVS)

2.1 | The biogenesis and structure of TEVs

Cell-derived EVs are phospholipid bilayer nanoparticles containing many bioactive molecules such as proteins,

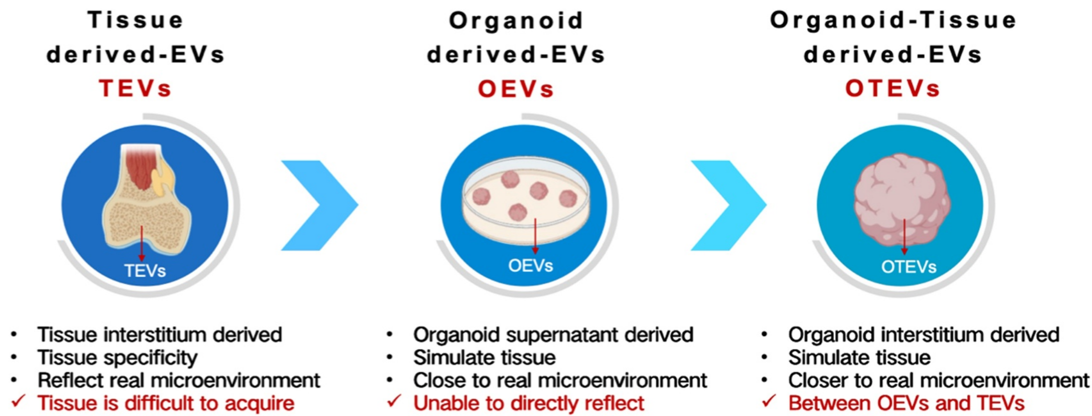

FIGURE 1 The relationship between TEVs, OEVs, and OTEVs. The characteristics and origins of three types of EVs are TEVs, OEVs, and OTEVs. TEVs are derived from the tissue interstitium, exhibit tissue specificity, and accurately reflect the real microenvironment, although tissue acquisition can be challenging. OEVs, sourced from the organoid supernatant, simulate tissue and closely approximate the real microenvironment but cannot directly reflect it. OTEVs, obtained from the organoid interstitium, also simulate tissue and are even closer to the real microenvironment, positioning them between OEVs and TEVs in terms of their properties. OTEVs are a compromise between OEVs and TEVs in terms of simulating tissues and reflecting microenvironments.

nucleic acids, and lipids.[32] Compared with EVs derived from cell culture or biological fluids, TEVs, isolated directly from tissue interstitial spaces, can more accurately represent the physiological and pathological conditions of the tissue microenvironment because they have a more realistic complex microenvironment than cell lines, a richer source of information, and a purer exclusivity than body fluid circulation (such as blood, pleural effusion, ascites, and urine).[33] This distinctive feature makes TEVs indispensable tools for deciphering disease mechanisms, enhancing diagnostic accuracy, identifying therapeutic targets, and advancing cell-free therapeutic approaches.[34]

TEVs are discovered within the interstitial spaces of tissues and released from various types of cells, such as epithelial cells, immune cells, macrophages, mesenchymal stem cells, fibroblasts, and granulocytes (Figure 2A). In fact, TEVs are a type of EVs derived from mammalian cell-derived EVs (MEVs).[35] Therefore, the biogenesis and structure of TEVs are similar to those of MEVs. Compared with the biosynthesis and secretion mechanism of cells in 2D culture, the EVs in tissues may be affected by multiple cell types and intercellular signals (Figure 2A). The formation process of TEVs is similar to that of cell-derived EVs (Figure 2B). It mainly involves the following three steps:

1) Endoplasmic reticulum-Golgi pathway: The biosynthesis process in the cell starts in the endoplasmic reticulum. After the biomolecules such as proteins and lipids are synthesized here, they are modified and packaged by the Golgi apparatus.
2) Formation of multivesicular bodies (MVBs): In the cytoplasm, the substances processed by the endoplasmic reticulum and the Golgi apparatus are encapsulated into the endoplasmic reticulum-Golgi apparatus intermediate, and then the early endosomes are formed. The early endosomes gradually mature into late endosomes through processes such as invagination and fusion, and finally form MVBs containing multiple small vesicles.
3) Fusion and release with the cell membrane: The multivesicular body fuses with the cell membrane and releases the small vesicles inside to the outside of the cell to form exosomes. This process is regulated by a variety of intracellular signaling pathways and molecules, such as the Rab protein family and the SNARE protein complex.

Moreover, TEVs possess a variety of nucleic acids, proteins, lipids, and metabolic byproducts (Figure 2C). TEVs also contain common MEV markers, such as CD9, CD63, CD81, flotillin, TSG101, and ALIX.[36] The formation of TEVs is a complex process that is influenced by many factors, including cell type, tissue microenvironment, cell physiological state, biosynthetic pathways, gene expression and transcriptional regulation, as well as extracellular matrix and mechanical factors. These factors interact with each other and jointly determine the formation, secretion and function of Ti-EVs.

2.2 | The isolation of TEVs

In 2021, Crescitelli et al.[31] published an efficient TEV isolation protocol in *Nature Protocols*. In short, the extraction scheme of TEV is shown in Figure 3. The TEV

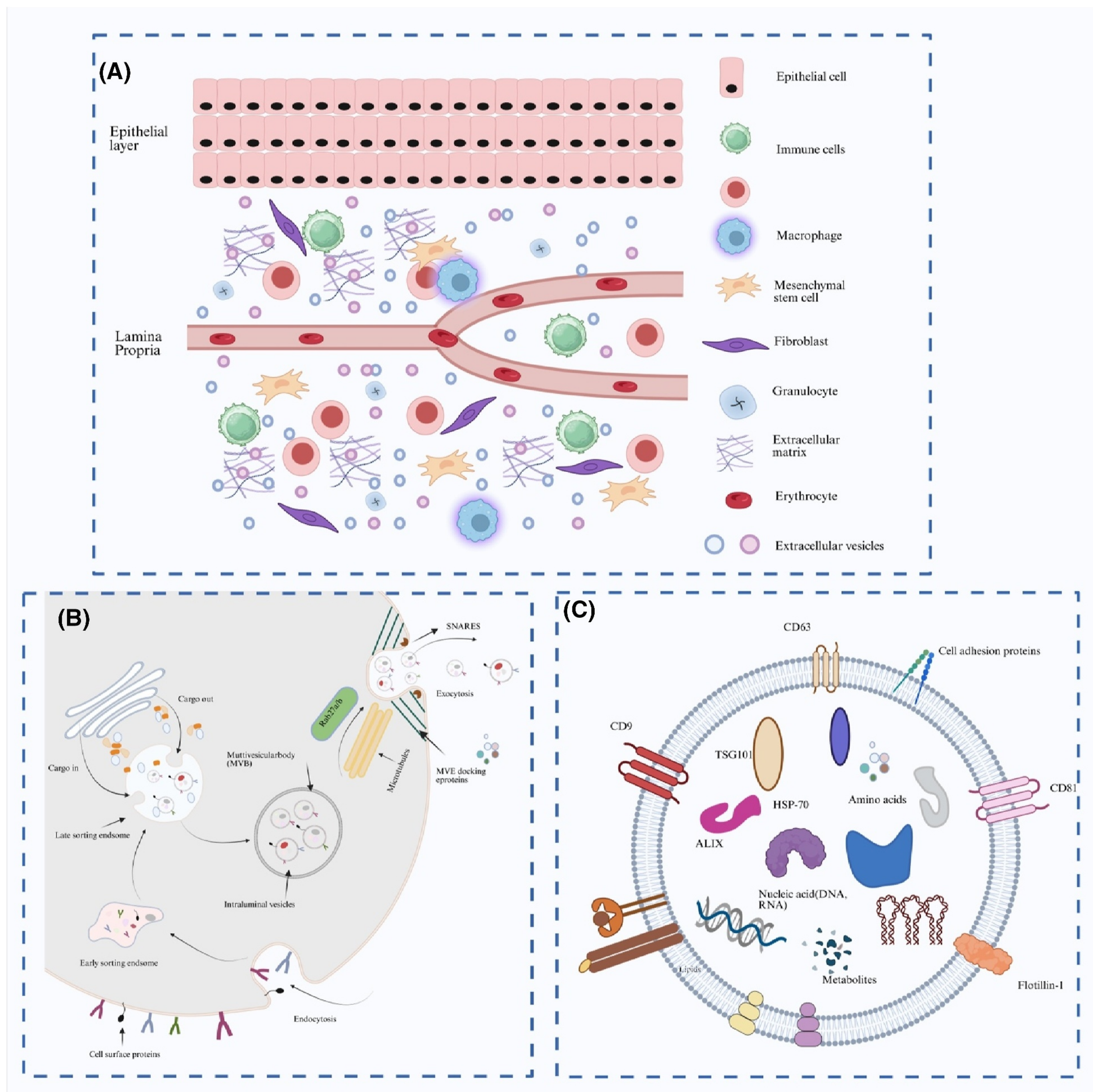

FIGURE 2 The biogenesis and structure of TEVs. (A) TEVs are found in the tissue interstitium. A variety of cells, such as epithelial cells, immune cells, macrophages, mesenchymal stem cells, fibroblasts, granulocytes, and erythrocytes can secrete TEVs. (B) The biogenesis of TEVs. (C) The structure and composition of TEVs. TEVs have a complex composition of nucleic acids, proteins, lipids, and metabolites. The figure was created using https://app.biorender.com/.

isolation protocol should be performed on fresh tissue samples to avoid excessive cell death. For blood-rich tissues, perfusion prior to TEV isolation is critical to reduce contamination with serum EVs and other particles. The tissue undergoes gentle dissociation through homogenization or enzymatic digestion at 37°C for less than 1 hour. Following dissociation, the tissue mixture was passed through a 70 μm pore-sized filter to separate tissue pieces and cell debris. The filtrate was then subjected to differential centrifugation at approximately 500–3000 × g at 4°C for 0–30 min to remove apoptotic bodies and large cellular debris or intact cells. Subsequent centrifugation at 10–14,000 × g at 4°C for over one hour helps to further clear the sample of contaminating microvesicles and any remaining cellular debris. The sample was then filtered through a 0.22 μm pore-sized filter to isolate larger EVs. To obtain small EVs, the sample undergoes ultracentrifugation at speeds greater than 100,000 × g at 4°C, repeated twice for over one hour each time. The extracted TEVs can be stored at −80°C for long-term preservation

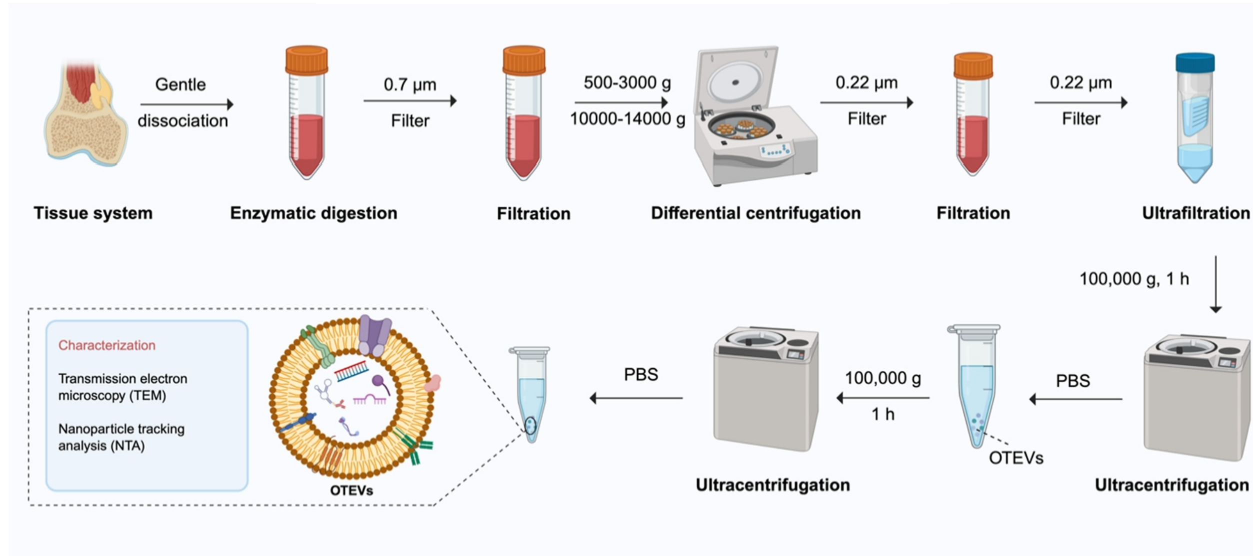

FIGURE 3 Isolation of TEVs. Tissue is first dissociated gently and then filtered through a 70 μm pore-sized filter. Differential centrifugation at 500–3000 × g and 10–14,000 × g removes debris and microvesicles. A 0.22 μm filter or 100 KDa ultrafiltration membrane isolates larger EVs, while ultracentrifugation at over 100,000 × g twice captures smaller EVs. The isolated Ti-EVs can be stored at −80°C or used immediately. The figure was created using https://app.biorender.com/.

or utilized immediately for various applications. This method ensures the isolation of TEVs with minimal contamination from other cellular components.

2.3 | The application of TEVs

EVs are crucial for cell-to-cell communication and offer new diagnostic opportunities and therapeutic targets.[37] TEVs, found in interstitial spaces, better reflect the complex microenvironments of multicellular tissues and contain diverse biomolecules that can influence recipient cells.[38] Li et al.[14] highlighted the advantages of TEVs over body fluid-derived or cell culture-derived EVs, such as tissue specificity and accurate reflection of the tissue microenvironment. Therefore, TEVs have a wide range of applications, including disease diagnosis and basic treatment.

2.3.1 | The disease diagnosis of TEVs

TEVs carry a variety of biomolecules, such as proteins, lipids, and nucleic acids, which can serve as biomarkers for disease diagnosis.[39] TEVs play an important role in tumor diagnosis. Dong et al.[40] identified four potential bladder cancer-specific mRNA biomarkers in small EVs derived from urine, tumor tissue, and adjacent normal tissue, suggesting that tissue-derived small EVs (sEVs) may better reflect tissue- or disease-specific biological features compared to those from biofluids. Non-invasive cancer diagnosis can be achieved by detecting TEVs in blood or other body fluids. TEVs released from tumor tissue can enter the blood circulation, and tumor-specific molecular markers can be detected by isolating and analyzing these TEVs.

In addition, TEVs also play a crucial role in the diagnosis of cardiovascular and neurological diseases. For example, Rizzuto et al.[41] explored epicardial adipose tissue (EAT)-derived EVs, which transport active biomolecules, are implicated in the pathogenesis of ischemia/reperfusion injury, coronary atherosclerosis, heart failure, and atrial fibrillation. Bodart-Santos et al.[42] found that TEVs derived from brain tissue of patients with Alzheimer's disease (AD) and frontotemporal dementia can trigger memory impairment in wild-type mice, and these TEVs all carry Tau protein. Muraoka et al.[43] isolated EVs from the gray matter of the cerebral cortex of 20 patients with AD and 18 controls and found that the levels of pS396 tau and Aβ1-42 in EVs of AD patients were significantly increased. They also identified ANXA5, VGF, GPM6A and ACTZ as new marker proteins of AD derived EVs through quantitative proteomics and machine learning techniques.

2.3.2 | The basic treatment of TEVs

TEVs are promising candidates for basic therapeutics due to their ability to carry bioactive molecules, tissue

specificity, low immunogenicity, drug delivery, promote tissue repair and regeneration, immunomodulate, and serve as disease markers.[44] For example, Ying et al.[45] demonstrated that hepatocyte-derived extracellular vesicles (Hep-EVs) play a crucial role in liver regeneration following partial hepatectomy by promoting hepatocyte proliferation through Cdk1 activity, and their supplementation shows potential to enhance liver regeneration, highlighting their therapeutic potential in organ regeneration.

TEVs also have great application scenarios in the field of bone aging, such as osteoporosis and osteoarthritis. For example, Ma et al.[46] demonstrated that skeletal muscle-derived EVs (Mu-EVs) can reach bones through the blood and be engulfed by BMSCs. Proteomics was used to analyze the key molecules that mediate communication between skeletal muscle and bone, fully revealing the important role of Mu-EVs in BMSC metabolic regulation and bone formation stimulation (Figure 4A). Li et al.[18] found that obesity exacerbates temporomandibular joint osteoarthritis (TMJ OA) by altering the composition of adipose tissue-derived extracellular vesicles (Ad-EVs), which induce chondrocyte apoptosis and cartilage degradation, and targeting miR-3074-5p in these vesicles may offer a therapeutic strategy for obesity-related TMJ OA (Figure 4B).

3 | ORGANOID-DERIVED EVS (OEVS)

3.1 | The biogenesis and structure of OEVs

Acquisition of TEVs is challenging due to the difficulty of obtaining tissue samples. In contrast, OEVs offer a promising alternative as they are derived from 3D cell clusters that mimic the structure and function of native tissues. Our team comprehensively summarized the concept of OEVs, and innovatively proposed a strategy for combining organoids and OEVs to treat complex diseases.[24] Similar to the EVs produced by traditional 2D cells, OEVs play a crucial role in facilitating communication and material exchange between organoid cells, acting as a vital medium for intercellular communication.[47,48] Compared with EVs derived from conventional 2D cultured cells, OEVs have higher yields and stronger biological functions.[23] Since OEVs are also derived from 3D cultured mammalian cells, they are essentially a type of MEV. Therefore, the biogenesis and structure of OEVs are similar to those of MEVs (Figure 5). Under 2D culture conditions, the biosynthesis and secretion mechanisms of cells are relatively simple and are mainly affected by the state of the cells themselves. However, the biosynthesis of OEVs may be more affected by cell-to-cell interactions and microenvironment due to the 3D structure of organoids.[49]

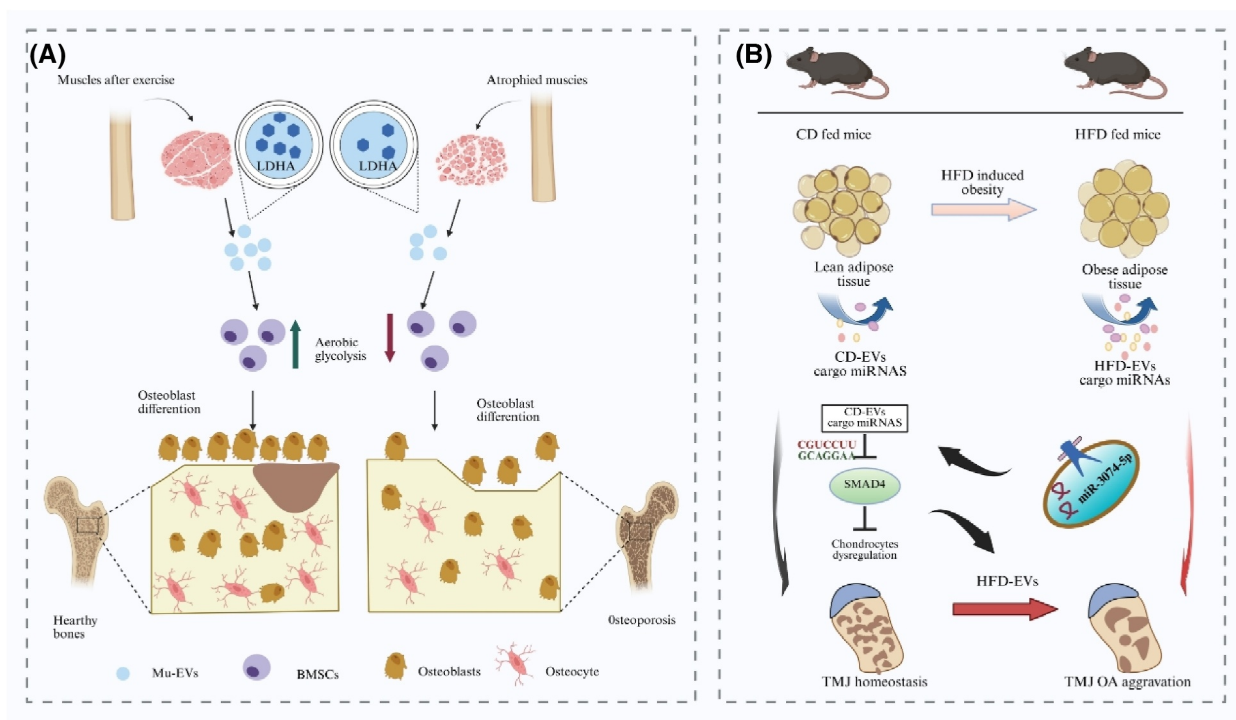

FIGURE 4 The application of TEVs. (A) Skeletal muscle-derived TEVs promote glycolysis in BMSCs by delivering glycolic profiles to enhance bone formation. (B) Adipose tissue-derived TEVs promote TMJ OA aggravation by delivering miR-3074-5p. The figure was created using https://app.biorender.com/.

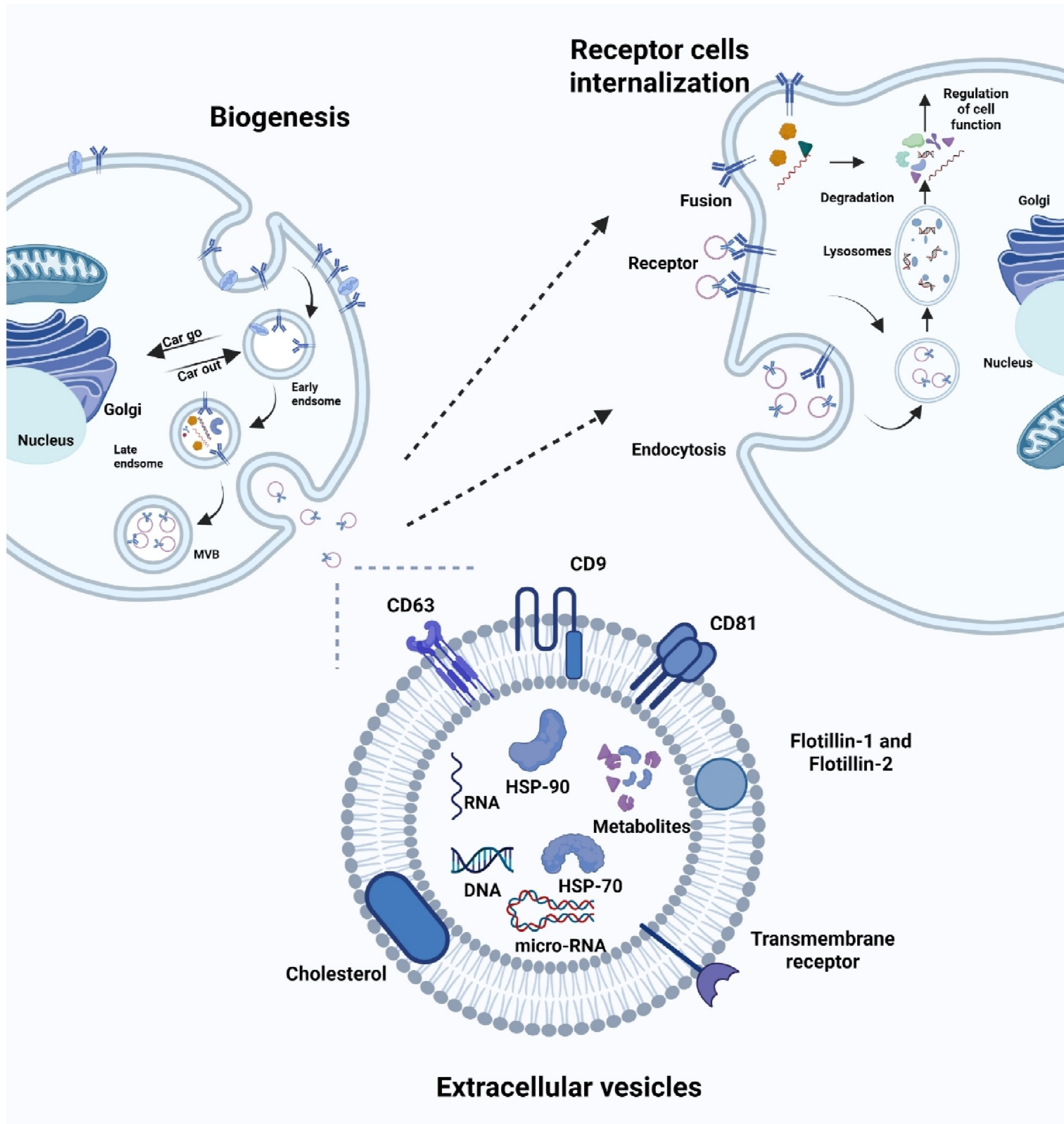

FIGURE 5 The biogenesis and structure of OEVs. Cells encapsulate substances from the extracellular environment into early endosomes through endocytosis, and early endosomes gradually mature into late endosomes through substance exchange with the Golgi apparatus. MVBs are formed in the membrane of late endosomes, which contain intraluminal vesicles. Subsequently, late endosomes can fuse with lysosomes for degradation or fuse with cell membranes to release intraluminal vesicles, which can be taken up by receptor cells through membrane fusion, endocytosis, and receptor-mediated signaling pathways. Their phospholipid bilayer membranes are rich in specific proteins, membrane receptors, as well as RNA, DNA, proteins, and cellular metabolites. The figure was created using https://app.biorender.com/.

3.2 | The isolation of OEVs

The isolation of OEVs, especially pretreatment methods, is different from that of TEVs due to their different sources. Currently, OEVs are derived from organoid culture supernatant.[49–51] Compared to traditional cell lines, organoid cultures are more intricate and typically require 3D scaffolds, such as Matrigel. This complexity poses additional challenges for the isolation of OEVs. For example, components in the culture medium can

interfere with the isolation process and matrix enzyme digestion may compromise the integrity of the EVs. Consequently, the isolation of OEVs necessitates more precise and gentle techniques to ensure the purity and functionality of the vesicles. Our team optimized and established a set of OEV isolation protocols.[24] During the isolation process, to prevent exogenous EV contamination, it is necessary to ensure that the organoid culture medium does not contain EVs. 24–48 h before collecting OEVs, the organoid culture medium was replaced with fresh culture medium to avoid interference from matrix components. Subsequently, the organoid culture supernatant was subjected to multiple differential centrifugation (300–10,000 g) and density gradient centrifugation (100,000 g) to harvest OEVs. If necessary, 100 KDa ultrafiltration membrane and 0.22 μm filter membrane can be added. The obtained OEVs are resuspended in sterile phosphate-buffered saline (PBS) and stored at −80°C until use (Figure 6).

3.3 | The application of OEVs

OEVs are gaining more attention as therapeutic drugs, biomarkers and drug delivery vehicles in various fields. EVs secreted by organoid-derived progenitor cells also have a more therapeutic potential than EVs secreted by stem cells. At present, the application of OEVs mainly focuses on immune regulation, epithelial repair, and retinal degeneration repair.

3.3.1 | OEVs for immune regulation

EVs are efficient mediators of intercellular communication between intestinal epithelial cells and immune cells.[52] OEVs can regulate immune responses because they are rich in bioactive molecules, can serve as mediators of intercellular communication, have targeted immunomodulatory properties, can mimic physiological environments, have low immunogenicity, and act through multiple mechanisms.[23] These characteristics make OEVs have great potential in immunomodulation and can be used to treat a variety of inflammatory diseases. Zhang et al.[53] demonstrated that OEVs derived from mouse and human intestinal organoids can modulate inflammatory responses in a variety of immune cells by inhibiting lipopolysaccharide (LPS)-induced cytokine production in these cells. Sequencing results indicated that multiple microRNAs, especially Let-7, were involved in OEV-mediated immune regulation.

3.3.2 | OEVs for epithelial repair

The application of OEVs in epithelial repair has shown significant potential. OEVs can regulate cell proliferation, migration, and repair capacity, thereby promoting the regeneration and functional recovery of epithelial tissue by carrying a variety of bioactive molecules. For example, Chansaenroj et al.[54] constructed a 3D culture system of SG organoids using the magnetic 3D bio-assembly

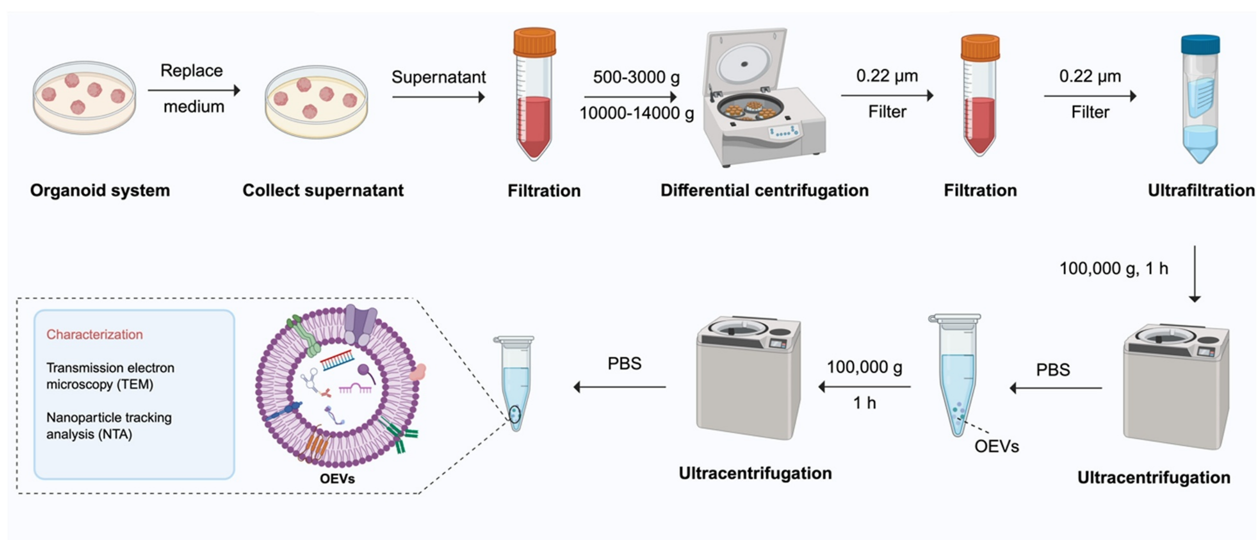

FIGURE 6 Isolation of OEVs. To ensure purity, the organoid culture medium was refreshed 24 h prior to collecting OEVs, eliminating potential interference from matrix components. Subsequently, the isolation of OEVs includes differential centrifugation and density gradient centrifugation. If necessary, ultrafiltration and filtration steps can be added. The figure was created using https://app.biorender.com/.

(M3DB) platform. SG OEVs significantly stimulated epithelial growth, mitosis, epithelial progenitor cells, and neural growth in damaged SGs. Proteomic analysis predicted that SG OEVs promoted cell growth, development, and signaling through molecular targets downstream of fibroblast growth factor 10 (FGF10).

Moreover, Kwak et al.[55] developed a pluripotent stem cell-based epidermal organoid that can produce efficient OEVs for skin regeneration. Shin OEVs have shown the ability to promote skin wound healing in both in vitro and in vivo experiments. Specifically, OEVs can significantly promote the proliferation and migration of epithelial cells, accelerate wound closure, and reduce inflammatory responses. In addition, OEVs can promote the regeneration and repair of skin tissue by regulating the composition of the extracellular matrix. These studies not only show the application prospect of OEVs in epithelial repair but also provide new ideas and methods for future clinical treatment.

3.3.3 | OEVs for retinal degeneration repair

OEVs secreted by late-stage retinal organoids expressed higher biomarkers than those of early-stage retinal organoids. Importantly, OEVs secreted by retinal organoids expressed higher differential expression of retinal function-related proteins and EV biogenesis proteins than that of hUCMSC-derived EVs, indicating their enhanced therapeutic potential in the treatment of ocular diseases.

Retinal degeneration (RD) involves irreversible vision loss due to retinal pigment epithelium or neuron damage. Gao et al.[56] demonstrated that OEVs secreted by human retinal organoid-derived retinal progenitor cells (hERO-RPC) showing unique capabilities in immune modulation, retinal development, and lipid metabolism regulation compared to human embryonic stem cells (hESC)-EVs (Figure 7A). Specifically, hESC-EVs contained higher levels of proteins linked to angiogenesis and cell cycle, whereas hERO-RPC-EVs were abundant in proteins related to immune regulation and retinal development. Notably, hERO-RPC-EVs showed less association with cell proliferation and exhibited a distinctive capacity to modulate lipid metabolism compared to hESC-EVs.

Furthermore, Huang et al.[51] found that hERO-RPC-sEVs, when transplanted into RCS rats, significantly protected retinal structure and function by suppressing Müller cell gliosis and promoting their early dedifferentiation (Figure 7B). The therapeutic effects were attributed to miRNAs within the sEVs, particularly miR-21-5p and miR-92a-3p, which downregulated the expression of NFIB, a gene critical for Müller cell fate determination. This discovery highlights the potential of hERO-RPC-sEVs as a novel cell-free therapy for retinal degenerative diseases.

4 | ORGANOID-TISSUE EVS (OTEVS)

4.1 | The biogenesis and structure of OTEVs

TEVs isolated from the interstitial space of tissues have a more realistic and complex microenvironment and a richer source of information than cell lines, so they can accurately represent the physiological and pathological conditions of the tissue microenvironment, becoming a hot direction for revealing disease mechanisms, improving diagnostic accuracy, identifying therapeutic targets, and advancing cell-free therapeutic methods.[24,46] However, the difficulty in obtaining tissues has hindered their rapid development. The development of organoids has made up for the limitations of tissue development and has become an innovative tool.[57–60] OEVs can be isolated from the supernatant of organoid culture and have been shown to be close to the real complex microenvironment, as well as a rich source of information.[51,56] Therefore, they can be widely used to represent the physiological and pathological conditions of the tissue microenvironment. Although OEVs are very close to TEVs and overcome the problem of tissue origin, they cannot directly reflect microenvironmental clues like TEVs. To solve this problem, we proposed the concept of OETVs, which are present in the interstitium of organoids. OTEVs effectively address the significant challenges associated with the limited availability of TEVs and also overcome the shortcomings of OEVs in not being able to directly reflect the state of the tissue microenvironment. OTEVs are also derived from mammalian cells, thus their biogenesis and structure are similar to those of MEVs.

4.2 | The isolation of OTEVs

OTEVs are derived from the organoid interstitium, which is different from OEVs derived from organoid supernatant. Therefore, OTEVs are a type of EVs that more directly reflect the state of the tissue microenvironment compared to OEVs. Here, we summarized a set of OTEV isolation methods based on the separation protocol of OEVs and TEVs (Figure 8). The process for isolating OTEVs begins with a fresh organoid system, followed by collection of the organoid tissue. Subsequent steps are

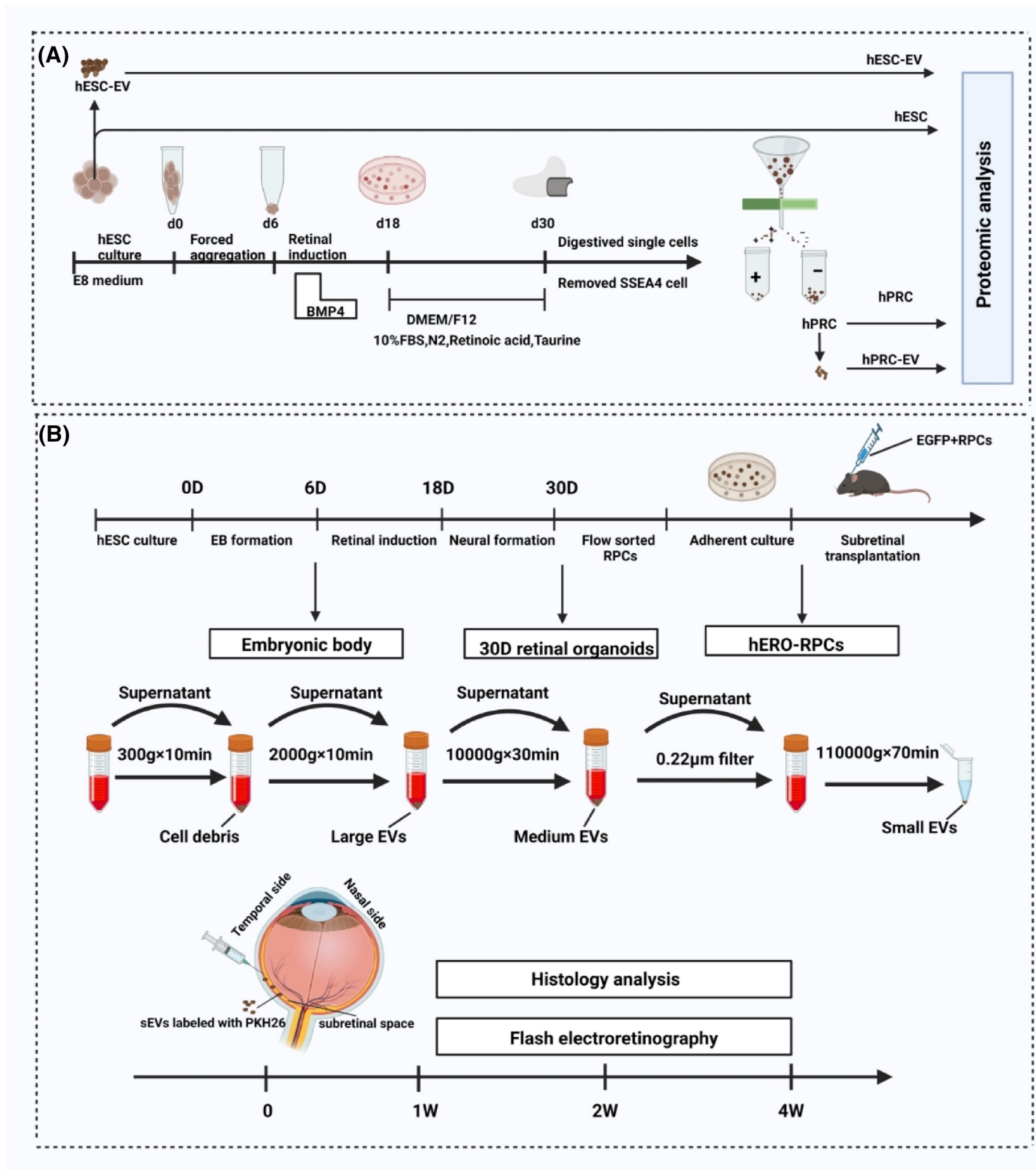

FIGURE 7 The application of OEVs. (A) Induction of retinal organoids and isolation of EVs derived from hESCs and hERO-RPCs. (B) Isolation of hERO-RPCs and hERO-RPC-sEVs, and the application of hERO-RPCs-sEVs on retinal. The figure was created using https://app.biorender.com/.

similar to those for extracting TEVs. In brief, a gentle dissociation is performed, which may involve homogenization or enzymatic digestion at 37°C for less than 1 hour. The mixture was then filtered through a 70 μm pore-sized filter and subjected to differential centrifugation at 4°C, first at approximately 500–3000 × g for 0–30 min, then at 10–14,000 × g for over one hour. Subsequently, the solution was filtered through a 0.22 μm pore-sized filter and/or a 100 KDa ultrafiltration membrane. Final purification was achieved by high-speed centrifugation at greater than 100,000 × g at 4°C, repeated twice for over more than 1 hour. The resulting OTEVs can be stored at −80°C or used immediately for various applications.

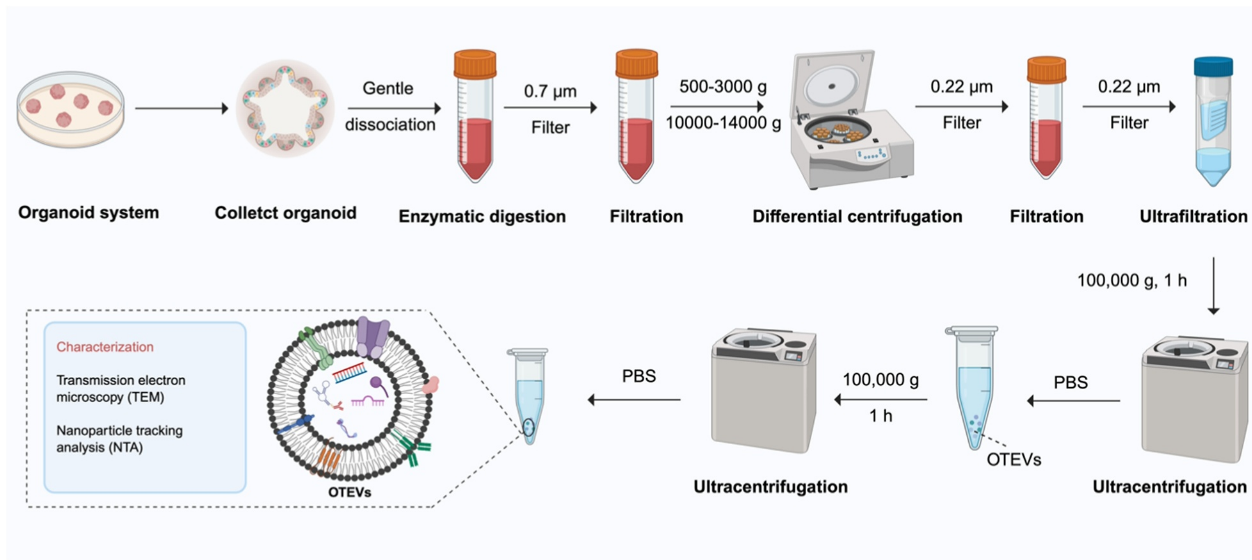

FIGURE 8 Isolation of OTEVs. The isolation of OTEVs starts with a fresh organoid, followed by tissue collection and a dissociation process at 37°C for under 1 hour. The mixture was filtered through a 70 μm filter, then subjected to differential centrifugation at 4°C. Further purification was done using a 0.22 μm filter or 100 KDa ultrafiltration membrane, and high-speed centrifugation at >100,000 × g. The purified OTEVs were either stored at −80°C or used right away for applications. The figure was created using https://app.biorender.com/.

4.3 | The significance of OTEVs

We have previously summarized the application of TEVs and OEVs (Table 1). Then, we introduced the concept of OTEVs. The proposed concept of OETVs marks a significant advancement in the field of biomedical research. This innovative approach may greatly enhance our ability to reveal the pathogenesis of complex diseases, guiding both diagnosis and treatment strategies with unprecedented precision. By harnessing the unique characteristics of OETVs, researchers and clinicians may be able to develop more personalized approaches to medical care tailored to individual patient needs and conditions. This could lead to a new era of precision medicine, where treatments are designed to target the specific genetic and molecular profiles of a patient's disease. The integration of organoid technology and EVs research promises to unveil a new dimension in biomedical science with far-reaching implications for the future of healthcare and disease management. This synergy could potentially lead to the development of novel therapeutic interventions that target specific disease processes, improving patient outcomes and quality of life.

The introduction of the concept of OTEVs does represent a major innovation in the field of EVs research. Specifically, OTEVs can not only enhance the understanding of disease mechanisms but also help to elucidate elusive and complex disease processes, thereby improving our understanding of disease pathogenesis. In addition, OTEVs can serve as more specific and sensitive biomarkers for various diseases, thereby improving the accuracy of disease diagnosis. OTEVs can also be used to develop more targeted and personalized treatments. By bridging the gap between basic research and clinical applications, OTEVs can promote the translation of laboratory discoveries into actual clinical solutions. In summary, the concept of OTEVs has the potential to have a significant impact on the field of EVs research by providing a more accurate representation of the tissue microenvironment. This innovation can enhance the understanding of disease mechanisms, improve diagnostic accuracy, target therapeutic strategies, and promote translational research. We believe that OTEVs will play a key role in future biomedicine and healthcare.

Importantly, the classification of EVs has been expanded to include a diverse range of sources and types[61] (Figure 8). Under the broad categorization of EVs, there are plant-derived EVs (PEVs),[62–66] BEVs,[67–71] and MEVs.[72] In the current system, MEVs can be further divided into TEVs, OEVs, and OETVs (Figure 9). This detailed classification system allows for a more nuanced understanding of the roles and functions of EVs in health and disease, paving the way for targeted therapeutic strategies and personalized treatment plans.

TABLE 1 Recent applications of TEVs and OEVs.

Classification	Source	Function	References
TEVs	Tumor tissue	Reflect molecular subtypes of bladder cancer	40
	Epicardial adipose	Reflect pathogenesis of cardiovascular diseases	41
	Alzheimer's disease brain	Reveal altered synapse-related proteome and induce cognitive impairment	42
	Alzheimer's disease brain	Reveal new marker proteins through quantitative proteomics and machine learning techniques	43
	Hepatocyte-derived tissue	Safeguard liver regeneration and support regenerative therapy	45
	Skeletal muscle	Transport glycolytic enzymes to treat disuse osteoporosis	46
	Adipose tissue	Aggravate temporomandibular joint osteoarthritis associated with obesity	18
OEVs	Intestinal organoids	Modulate inflammatory responses and inhibit LPS-induced cytokine production	53
	Salivary gland organoids	Ameliorate salivary glands epithelial damage	54
	Epidermal organoids	Improve wound healing by promoting cell proliferation, migration and angiogenesis	55
	Human retinal progenitor cells organoids	Regulating fatty acid metabolism to prevent retinal pigment epithelial damage caused by lipid overload	56
	Human retinal stem cells organoids	Protect retinal structure and function by suppressing Müller cell gliosis and promoting their early dedifferentiation	51

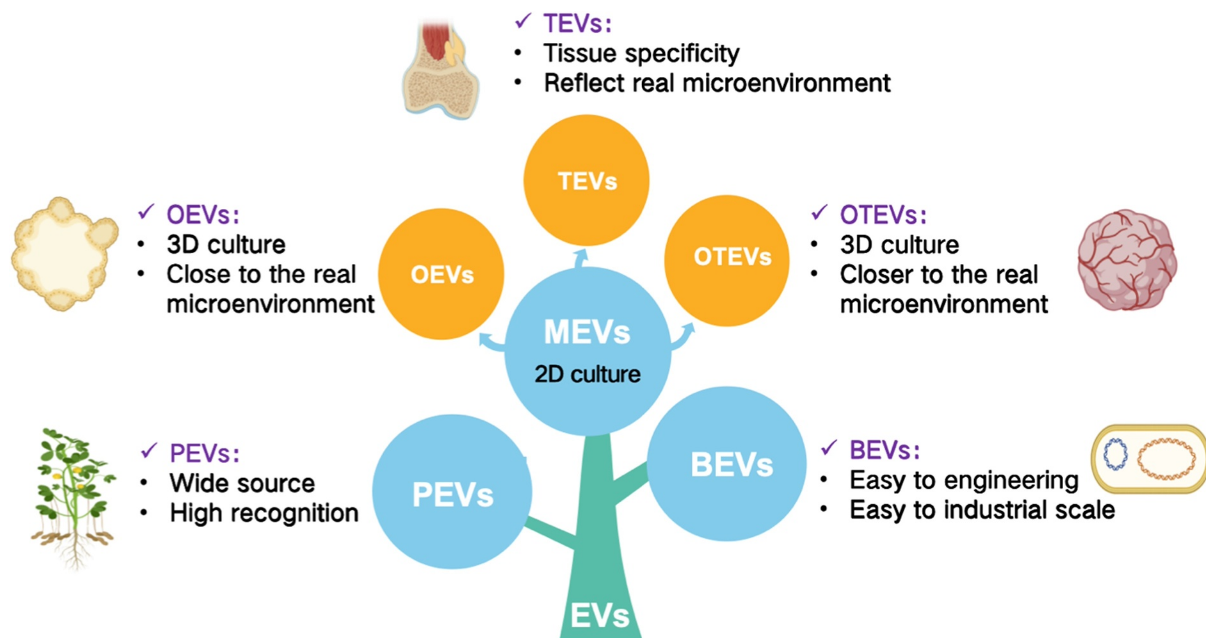

FIGURE 9 Classification of extracellular vesicles. Within the extensive classification of EVs, they are derived from various sources including PEVs, BEVs, and MEVs. MEVs are further categorized into three subtypes: TEVs, OEVs, and OTEVs.

5 | CONCLUSION

EVs play a crucial role in intercellular communication, influencing both physiological and pathological processes. While TEVs provide valuable insights into the tissue microenvironment, their utility is limited by the challenges associated with tissue sampling. In addition, OEVs offer a promising alternative, providing a more physiologically relevant model for studying disease mechanisms compared to traditional 2D cultures.

However, OEVs lack the direct reflection of the tissue microenvironment that TEVs provide. To bridge this gap, OTEVs have emerged as a novel approach, combining the advantages of both OEVs and TEVs. OTEVs offer a unique opportunity to accurately represent the tissue microenvironment, thereby enhancing our understanding of complex diseases and potentially leading to innovative therapeutic strategies. By integrating the strengths of TEVs, OEVs, and OTEVs, researchers can advance translational research and improve their ability to diagnose and treat complex diseases.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. X. Liu, Q. Wei, Z. Sun, S. Cui, X. Wan, Z. Chu, Y. Zhang, W. Zhong, L. Lu, L. Shi, X. Fu, C. Zhang, S. Wang, *Interdiscip. Med.* **2023**, *1*, e20230019.
2. H. Liu, Q. Zhang, S. Wang, W. Weng, Y. Jing, J. Su, *Bioact. Mater.* **2022**, *14*, 169.
3. H. Liu, Z. Geng, J. Su, *Extracell Vesicles Circ. Nucl. Acids* **2022**, *3*, 63.
4. H. Liu, M. Li, T. Zhang, X. Liu, H. Zhang, Z. Geng, J. Su, *Chem. Eng. J* **2022**, *450*, 138309.
5. X. Liu, Q. Wei, L. Lu, S. Cui, K. Ma, W. Zhang, F. Ma, H. Li, X. Fu, C. Zhang, *Front. Immunol.* **2023**, *14*, 1094685.
6. Q. Wei, X. Liu, J. L. Su, Y. X. Wang, Z. Q. Chu, K. Ma, Q. L. Huang, H. H. Li, X. B. Fu, C. P. Zhang, *Front. Bioeng. Biotechnol.* **2022**, *10*, 1083459.
7. H. Liu, H. Zhang, Y. Han, Y. Hu, Z. Geng, J. Su, *Theranostics* **2022**, *12*, 6576.
8. H. Liu, H. Zhang, S. Wang, J. Cui, W. Weng, X. Liu, H. Tang, Y. Hu, X. Li, K. Zhang, F. Zhou, Y. Jing, J. Su, *Compos. Part B Eng.* **2023**, *255*, 110610.
9. Q. Wei, J. Su, S. Meng, Y. Wang, K. Ma, B. Li, Z. Chu, Q. Huang, W. Hu, Z. Wang, L. Tian, X. Liu, T. Li, X. Fu, C. Zhang, *Adv. Sci.* **2024**, *11*, 2307761.
10. H. Liu, J. Sun, M. Wang, S. Wang, J. Su, C. Xu, *Chem. Eng. J* **2023**, *465*, 142842.
11. H. Liu, J. Su, *Interdiscip. Med.* **2023**, *1*, e20230011.
12. L. S. Holliday, J. K. Neubert, X. Yang, *Extracell Vesicles Circ. Nucl. Acids* **2025**, *6*, 158.
13. J. C. Lee, R. M. Ray, T. A. Scott, *Mol. Ther.* **2024**, *32*, 2950.
14. S. R. Li, Q. W. Man, X. Gao, H. Lin, J. Wang, F. C. Su, H. Q. Wang, L. L. Bu, B. Liu, G. Chen, *J. Extracell. Vesicles* **2021**, *10*, e12175.
15. K. S. Lee, J. Lee, H. K. Kim, S. H. Yeom, C. H. Woo, Y. J. Jung, Y. E. Yun, S. Y. Park, J. Han, E. Kim, J. H. Sul, J. M. Jung, J. H. Park, J. S. Choi, Y. W. Cho, D. G. Jo, *J. Extracell. Vesicles* **2021**, *10*, e12152.
16. B. Yin, J. Ni, C. E. Witherel, M. Yang, J. A. Burdick, C. Wen, S. H. D. Wong, *Theranostics* **2022**, *12*, 207.
17. P. Lou, S. Liu, Y. Wang, K. Lv, X. Zhou, L. Li, Y. Zhang, Y. Chen, J. Cheng, Y. Lu, J. Liu, *Adv. Mater.* **2023**, *35*, 2300602.
18. B. Li, Y. Jin, B. Zhang, T. Lu, J. Li, J. Zhang, Y. Zhou, Y. Wang, C. Zhang, Y. Zhao, H. Li, *Clin. Transl. Med.* **2024**, *14*, e70029.
19. Z. Ye, W. Chen, G. Li, J. Huang, J. Lei, *Cancer Metastasis Rev.* **2024**, *43*, 575.
20. R. Polak, E. T. Zhang, C. J. Kuo, *Nat. Rev. Cancer* **2024**, *24*, 523.
21. Z. Zhao, X. Chen, A. M. Dowbaj, A. Sljukic, K. Bratlie, L. Lin, E. L. S. Fong, G. M. Balachander, Z. Chen, A. Soragni, M. Huch, Y. A. Zeng, Q. Wang, H. Yu, *Nat. Rev. Methods Primers* **2022**, *2*, 94.
22. C. Corrò, L. Novellasdemunt, V. S. W. Li, *Am. J. Physiol. Cell Physiol* **2020**, *319*, C151.
23. H. Liu, J. Su, *Biomater. Transl* **2023**, *4*, 199.
24. G. Zhou, R. Li, S. Sheng, J. Huang, F. Zhou, Y. Wei, H. Liu, J. Su, *J. Nanobiotechnol.* **2024**, *22*, 679.
25. H. Liu, J. T. Triffitt, Z. Xia, J. Su, *Biomater. Transl* **2024**, *5*, 93.
26. N. Ji, F. Wang, M. Wang, W. Zhang, H. Liu, J. Su, *J. Control. Release* **2023**, *364*, 46.
27. H. Liu, P. Song, H. Zhang, F. Zhou, N. Ji, M. Wang, G. Zhou, R. Han, X. Liu, W. Weng, H. Tan, S. Wang, L. Zheng, Y. Jing, J. Su, *J. Extracell. Vesicles* **2024**, *13*, e12429.
28. H. Liu, Y. Wu, F. Wang, S. Wang, N. Ji, M. Wang, G. Zhou, R. Han, X. Liu, W. Weng, H. Tan, Y. Jing, W. Zhang, H. Zhang, Z. Shi, J. Su, *Compos. Part B Eng.* **2023**, *267*, 111047.
29. H. Liu, R. Li, H. Yang, B. Situ, G. Wang, K. Xu, J. Su, *Small Sci.* **2025**, *5*, 2400474.
30. M. Ravi, V. Paramesh, S. R. Kaviya, E. Anuradha, F. D. Solomon, *J. Cell. Physiol.* **2015**, *230*, 16.
31. R. Crescitelli, C. Lässer, J. Lötvall, *Nat. Protoc.* **2021**, *16*, 1548.
32. M. A. Kumar, S. K. Baba, H. Q. Sadida, S. A. Marzooqi, J. Jerobin, F. H. Altemani, N. Algehainy, M. A. Alanazi, A. B. Abou-Samra, R. Kumar, A. S. Al-Shabeeb Akil, M. A. Macha, R. Mir, A. A. Bhat, *Signal Transduct Target Ther.* **2024**, *9*, 27.
33. W. Li, J. Zhu, J. Li, Y. Jiang, J. Sun, Y. Xu, H. Pan, Y. Zhou, J. Zhu, *J. Cancer Res. Clin. Oncol.* **2024**, *150*, 184.
34. L. Jank, A. Kesharwani, T. Ryu, D. Joshi, D. C. Ladakis, M. D. Smith, S. Singh, T. Arab, K. W. Witwer, P. A. Calabresi, C. H. Na, P. Bhargava, *J. Neuroinflammation* **2024**, *21*, 154.
35. L. Debbi, S. Guo, D. Safina, S. Levenberg, *Biotechnol. Adv.* **2022**, *59*, 107983.
36. Y. Xia, J. Zhang, G. Liu, J. Wolfram, *Adv. Mater.* **2024**, *36*, 2403199.
37. Y. Li, H. Zhang, Y. Jiang, J. Yang, D. Cai, X. Bai, *Interdiscip. Med.* **2024**, *2*, e20230055.
38. J. Han, S. Kim, Y. H. Hwang, S. A. Kim, Y. Lee, J. Kim, S. Cho, J. Woo, C. Jeong, M. Kwon, G. H. Nam, I. S. Kim, *Adv. Sci.* **2024**, *11*, 2308662.
39. J. Dong, B. Wu, W. Tian, *Stem Cell Res. Ther.* **2023**, *14*, 67.

40. L. Dong, M. Feng, M. D. Kuczler, K. Horie, C. J. Kim, Z. Ma, K. Lombardo, H. Lyons, S. R. Amend, M. Kates, T. J. Bivalacqua, D. McConkey, W. Xue, W. Choi, K. J. Pienta, *J. Extracell. Vesicles* **2024**, *13*, e12402.
41. A. S. Rizzuto, G. Gelpi, A. Mangini, S. Carugo, M. Ruscica, C. Macchi, *iScience* **2024**, *27*, 109359.
42. V. Bodart-Santos, L. S. Pinheiro, A. J. da Silva-Junior, R. L. Froza, R. Ahrens, R. A. Gonçalves, M. M. Andrade, Y. Chen, C. L. Alcantara, L. T. Grinberg, R. E. P. Leite, S. T. Ferreira, P. E. Fraser, F. G. De Felice, *Alzheimers Dement* **2023**, *19*, 5418.
43. S. Muraoka, A. M. DeLeo, M. K. Sethi, K. Yukawa-Takamatsu, Z. Yang, J. Ko, J. D. Hogan, Z. Ruan, Y. You, Y. Wang, M. Medalla, S. Ikezu, M. Chen, W. Xia, S. Gorantla, H. E. Gendelman, D. Issadore, J. Zaia, T. Ikezu, *Alzheimers Dement* **2020**, *16*, 896.
44. I. Jeong, S. Park, J. Park, O. K. Kim, *Food Nutr. Res.* **2024**, *68*, 10545.
45. S. Q. Ying, Y. Cao, Z. K. Zhou, X. Y. Luo, X. H. Zhang, K. Shi, J. Y. Qiu, S. J. Xing, Y. Y. Li, K. Zhang, F. Jin, C. X. Zheng, Y. Jin, B. D. Sui, *J. Nanobiotechnol.* **2024**, *22*, 521.
46. S. Ma, X. Xing, H. Huang, X. Gao, X. Xu, J. Yang, C. Liao, X. Zhang, J. Liu, W. Tian, L. Liao, *Cell Metab.* **2023**, *35*, 2028.
47. A. F. Deng, F. X. Wang, S. C. Wang, Y. Z. Zhang, L. Bai, J. C. Su, *Mil. Med. Res.* **2024**, *11*, 37.
48. V. V. T. Nguyen, S. Ye, V. Gkouzioti, M. E. van Wolferen, F. Y. Yengej, D. Melkert, S. Siti, B. de Jong, P. J. Besseling, B. Spee, L. J. W. van der Laan, R. Horland, M. C. Verhaar, B. W. M. van Balkom, *J. Extracell. Vesicles* **2022**, *11*, e12280.
49. S. Abdollahi, *Biotechnol. Bioeng.* **2021**, *118*, 1029.
50. P. Arthur, S. Kandoi, L. Sun, A. Kalvala, S. Kutlehria, S. Bhattacharya, T. Kulkarni, R. Nimma, Y. Li, D. A. Lamba, M. Singh, *Pharm. Res.* **2023**, *40*, 801.
51. S. Huang, Y. Zeng, Q. Guo, T. Zou, Z. Q. Yin, *J. Control. Release* **2024**, *370*, 405.
52. L. Ye, Y. Wang, F. Xiao, X. Wang, X. Li, R. Cao, J. Zhang, T. Zhang, *Microb. Cell Fact.* **2023**, *22*, 235.
53. Y. Zhang, Y. Yan, J. Meng, M. Girotra, S. Ramakrishnan, S. Roy, *Mucosal Immunol.* **2021**, *14*, 887.
54. A. Chansaenroj, C. Adine, S. Charoenlappanit, S. Roytrakul, L. Sariya, T. Osathanon, S. Rungarunlert, G. Urkasemsin, R. Chaisuparat, S. Yodmuang, G. R. Souza, J. N. Ferreira, *Bioact. Mater.* **2022**, *18*, 151.
55. S. Kwak, C. L. Song, J. Lee, S. Kim, S. Nam, Y. J. Park, J. Lee, *Biomaterials* **2024**, *307*, 122522.
56. H. Gao, Y. Zeng, X. Huang, L. A, Q. Liang, J. Xie, X. Lin, J. Gong, X. Fan, T. Zou, H. Xu, *J. Extracell. Vesicles* **2024**, *13*, e12401.
57. B. S. Beydag-Tasöz, S. Yennek, A. Grapin-Botton, *Nat. Rev. Endocrinol.* **2023**, *19*, 232.
58. J. Wang, Y. Wu, G. Li, F. Zhou, X. Wu, M. Wang, X. Liu, H. Tang, L. Bai, Z. Geng, P. Song, Z. Shi, X. Ren, J. Su, *Adv. Mater.* **2024**, *36*, 2309875.
59. Y. Hu, H. Zhang, S. Wang, L. Cao, F. Zhou, Y. Jing, J. Su, *Bioact. Mater.* **2023**, *25*, 29.
60. L. Bai, Y. Wu, G. Li, W. Zhang, H. Zhang, J. Su, *Bioact. Mater.* **2024**, *31*, 525.
61. Y. Li, C. Zhou, H. Liu, T. Cai, H. Fan, *Biomolecules* **2024**, *14*, 312.
62. R. Han, Y. Wu, Y. Han, X. Liu, H. Liu, J. Su, *Nano Res.* **2024**, *17*, 2857.
63. R. Huang, B. Jia, D. Su, M. Li, Z. Xu, C. He, Y. Huang, H. Fan, H. Chen, F. Cheng, *J. Extracell. Vesicles* **2023**, *12*, e12361.
64. R. Han, D. Zhou, N. Ji, Z. Yin, J. Wang, Q. Zhang, H. Zhang, J. Liu, X. Liu, H. Liu, Q. Han, J. Su, *J. Nanobiotechnol.* **2025**, *23*, 41.
65. J. Feng, Q. Xiu, Y. Huang, Z. Troyer, B. Li, L. Zheng, *Adv. Mater.* **2023**, *35*, 2207826.
66. Y. Cao, Z. Wu, H. Li, J. Shen, D. Li, T. Qiu, Z. Chen, Q. Zhao, K. Zhao, *Extracell Vesicles Circ. Nucl. Acids* **2025**, *6*, 21.
67. Y. Chen, Z. Ou, M. Pang, Z. Tao, X. Zheng, Z. Huang, D. Wen, Q. Li, R. Zhou, P. Chen, B. Situ, C. Sheng, Y. Huang, X. Yue, L. Zheng, L. Huang, *J. Extracell. Vesicles* **2023**, *12*, e12328.
68. Z. Ou, B. Situ, X. Huang, Y. Xue, X. He, Q. Li, D. Ou, B. He, J. Chen, Y. Huang, L. Deng, M. Zhang, Q. Wang, L. Zheng, *J. Extracell. Vesicles* **2023**, *12*, e12395.
69. Y. Lin, J. Wang, F. Bu, R. Zhang, J. Wang, Y. Wang, M. Huang, Y. Huang, L. Zheng, Q. Wang, X. Hu, *Gut Microbes* **2025**, *17*, 2452229.
70. S. Wang, Y. Hu, P. Song, Q. Lin, X. Tang, Q. Gao, J. Wang, D. Zhou, J. Li, D. Huang, L. Bai, X. Chen, J. Gao, H. Liu, Z. Shi, J. Su, *Compos. Part B Eng.* **2025**, *297*, 112255.
71. M. Wen, J. Wang, Z. Ou, G. Nie, Y. Chen, M. Li, Z. Wu, S. Xiong, H. Zhou, Z. Yang, G. Long, J. Su, H. Liu, Y. Jing, Z. Wen, Y. Fu, T. Zhou, H. Xie, W. Guan, X. Sun, Z. Wang, J. Wang, X. Chen, L. Jiang, X. Qin, Y. Xue, M. Huang, X. Huang, R. Pan, H. Zhen, Y. Du, Q. Li, X. Huang, Y. Wu, P. Wang, K. Zhao, B. Situ, X. Hu, L. Zheng, *Interdiscip. Med.* **2023**, *1*, e20230017.
72. Y. Ma, S. Dong, A. J. Grippin, L. Teng, A. S. Lee, B. Y. S. Kim, W. Jiang, *Trends Biotechnol.* **2025**, *43*, 61.

AUTHOR BIOGRAPHIES

Han Liu is an associate professor at the Institute of Translational Medicine, Shanghai University. He received his doctoral degree from the State Key Laboratory of Bioreactor Engineering, East China University of Science and Technology. Then, he worked as a postdoctoral fellow under the guidance of Prof. Jiacan Su at the Institute of Translational Medicine, Shanghai University. His research focuses on synthetic biology-based bacterial extracellular vesicles, organoid extracellular vesicles, and transformation of bone/cartilage organoids.

Ting Cheng is a master's degree candidate at the Institute of Translational Medicine, Shanghai University. She obtained her bachelor's degree from Bengbu Medical University. Subsequently, she pursued her master's degree at the Institute of Translational Medicine, Shanghai University. She has been involved in research related to the transformation of synthetic

biology-based bacterial extracellular vesicles, organoid extracellular vesicles, and bone/cartilage organoids.

Guangfeng Li, Deputy Chief Physician of the Orthopedics Department at Shanghai MCC Hospital. He studied at the School of Medicine of Yangzhou University from 2009 to 2012 and obtained a Master's degree in Surgery. His professional expertise is in fundamental research in the application of minimally invasive techniques to treat joint injuries and cartilage degeneration.

Zhidao Xia served as a visiting scholar at the Wound Healing Research Institute, Churchill Hospital, University of Oxford in 1998. He obtained his doctoral degree from the University of Oxford in 2005 and subsequently held positions as a postdoctoral researcher, senior researcher, and doctoral supervisor at Oxford University. Since 2010, he has been a Senior Lecturer in Regenerative Medicine at the Medical School of Swansea University in the UK and the leader of the Regenerative Medicine Research Group. In 2016, he took up a part-time position as an Associate Professor at Oxford Brookes University. Since 2023, he has also served as a Visiting Researcher in the Department of Orthopedics at the Johns Hopkins University School of Medicine in the United States. His main research interests include bone tissue regeneration, the interaction between biomaterials and host tissues/cells at the interface, the application of mesenchymal stem cells, and the additive manufacturing of bone graft substitutes.

Chenglong Wang is an associate chief physician at Xinhua Hospital Affiliated to Shanghai Jiao Tong University. He specializes in minimally invasive treatments for shoulder and knee joints, including conditions such as frozen shoulder, rotator cuff injuries, acromial impingement, labral tears, meniscus injuries of the knee joint, anterior and posterior cruciate ligament ruptures, patellar subluxation, synovitis, plica syndrome, and loose bodies, which cause pain in the shoulder and knee joints.

Ke Xu is an associate professor at the Institute of Translational Medicine, Shanghai University. He graduated from the School of Pharmacy, East China University of Science and Technology, and completed his postdoctoral studies at Emory University in the United States. Subsequently, he conducted research on the molecular mechanisms and therapeutic strategies of aging-related diseases (bone-related diseases/cancer) at the Institute of Translational Medicine, Shanghai University. He also focuses on organoid extracellular vesicles and the transformation of bone/cartilage organoids.

Jiacan Su is the dean of the Institute of Translational Medicine of Shanghai University and the director of the Department of Orthopedics of Xinhua Hospital, Shanghai Jiao Tong University School of Medicine. He obtained his B.S. from Second Military Medical University in 1999. He continued his successive postgraduate and doctoral programs of study at the Second Military Medical University from 1999 to 2004. His research focuses on the basic and clinical research of bone and joint degenerative diseases, the development and application of new biomaterials, and the development and transformation of bone/cartilage organoids.

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