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Blebbisomes: isolation, characterization, and functional role of organelle-rich giant vesicles

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ABSTRACT

Cells secrete a diverse array of extracellular vesicles (EVs) to mediate intercellular communication, profoundly influencing both physiological and pathological processes through the transfer of proteins, lipids, and genetic material. Among these, blebbisomes have recently emerged as a novel, large (up to 20 μm), organelle-rich EV subtype, distinguished by their dynamic membrane blebbing and active release from cells. Blebbisomes harbor a spectrum of intact organelles, including functional mitochondria and multivesicular endosomes, yet notably lack a nucleus. Their enrichment with immune checkpoint proteins in cancer underscores a potential role in immune regulation and tumor progression, positioning them at the forefront of research into disease mechanisms. The unique structural and functional attributes of blebbisomes highlight their potential significance as a crucial way of communication and promising targets for therapeutic innovation. This review synthesizes current advances in isolation, characterization, and functional understanding of blebbisomes, illuminating their emerging roles in health and disease.

Introduction

Extracellular vesicles (EVs) are membrane-bound particles released by most of the cell types into the extracellular milieu, serving as critical mediators of intercellular communication. Once considered mere cellular debris, EVs have emerged as pivotal players in both physiological and pathological processes, facilitating the transfer of proteins, lipids, and nucleic acids between cells and even across distant organs.[1,2] EVs encompass a heterogeneous group of membrane-bound structures, including exosomes, microvesicles, and apoptotic bodies, which differ in their size, biogenesis, and molecular content.[3–5] Exosomes typically range from 30 to 200 nm in diameter and originate from the endosomal pathway (Fig. 1), while microvesicles (100–1000 nm) are shed directly from the plasma membrane. Apoptotic bodies, formed during programmed cell death, are generally larger (1–5 μm).[3,6,7] The field of EV research has expanded rapidly, with growing recognition of their diverse functional roles and potential clinical applications in diagnostics and therapeutics.[1,3,8]

EVs are now recognized as essential vehicles for cell-to-cell and cell-to-environment communication, mediating the horizontal transfer of messenger RNAs, microRNAs, proteins, and lipids.[3,9,10] By delivering these molecular cargos, EVs influence the behavior and fate of recipient cells, modulating immune responses, tissue repair, and homeostasis.[11–13] In the central nervous system, for example, EVs support neuron survival and regulate inflammation, while in other tissues, they contribute to organ homeostasis and the maintenance of physiological balance.[14,12] Pathologically, EVs can propagate disease by transferring pathogenic proteins, such as prions or aggregated proteins in neurodegenerative diseases, and by facilitating tumor progression and metastasis through the transfer of oncogenic factors.[4,15,16]

The EV landscape is highly heterogeneous, with emerging subtypes such as migrasomes, mitovesicles, and exophers adding complexity to the field.[17,18] This diversity reflects the multiple origins, sizes, and molecular compositions of EVs, which enable them to perform a wide range of functions (Table 1). In physiological contexts, EVs maintain tissue homeostasis, mediate immune surveillance, and participate in processes such as angiogenesis and wound healing.[19,20] Conversely, in pathological states, EVs can promote disease progression by transferring deleterious cargo, modulating the tumor microenvironment, and evading immune detection.[21,22] Their presence in biofluids also positions EVs as promising for biomarker studies for various diseases, including cancer and neurodegenerative disorders.[11,12,23]

Recent advances in EV research have led to the identification of blebbisomes (Fig. 1), a previously unrecognized class of exceptionally large, organelle-rich EVs.[8,24,25] The biogenesis of blebbisome is driven by a retraction event powered by non-muscle myosin IIB, which generates contractile force, while actin dynamics facilitate membrane deformation and severing via a nanotube connected to the cell. Unlike

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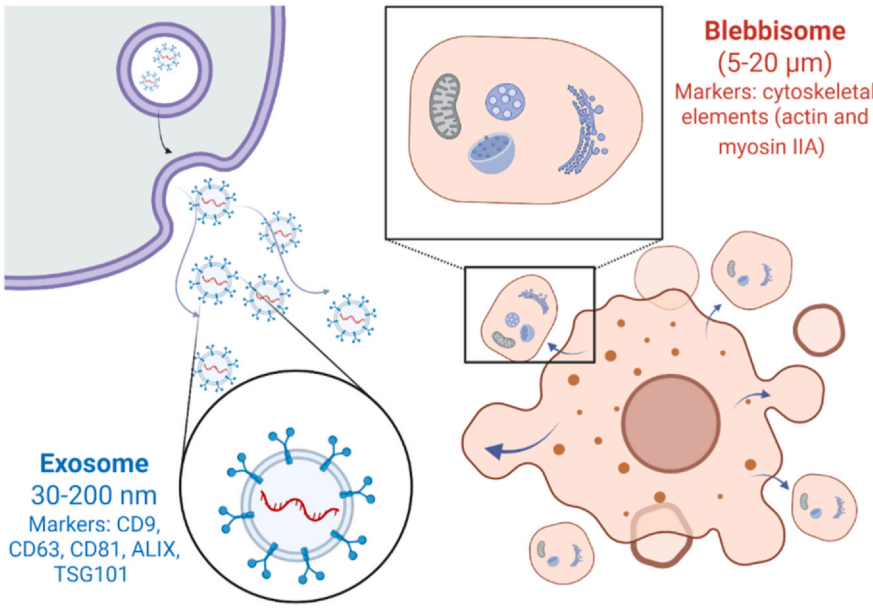

Fig. 1. Difference between exosomes and blebbisomes. Mammalian cells release vesicles ranging from 30 nm to several micrometres. Large EVs (> 200 nm) arise from the plasma membrane and contain various organelles, including blebbisomes (5–20 μm). Small EVs (< 200 nm), such as exosomes, originate within multivesicular endosomes (MVEs) before secretion.

migrasomes and exophers, which rely on different cytoskeletal or autophagy-related pathways, blebbisomes uniquely retain functional mitochondria and organelles, enabling prolonged motility and autonomous secretion of vesicles. This mechanistic distinction separates blebbisomes from other large EVs. Particularly, exosomes, a widely studied extracellular vesicle type, are marked by tetraspanins (CD9, CD63, CD81), ALIX, TSG101, and syntenin, while blebbisomes show organelle-rich content with specific markers such as that of mitochondria, Golgi, PD-L1, and B7-H3. Both types facilitate intercellular communication and immune regulation, influencing disease processes in cancer, cardiovascular, and neurological disorders.[24] As we move forward, various aspects of blebbisomes will be unfolded in detail.

Blebbisome: a new member in the field of EVs

Blebbisomes represent a significant departure from classical extracellular vesicles (EVs) due to their large size, unique content, and active behavior. They are defined as membrane-enclosed vesicles with diameters averaging 10 μm and reaching up to 20 μm, making them the largest EVs described to date. Blebbisomes are distinguished by their continuous membrane blebbing, rich organelle content—including functional mitochondria and multivesicular endosomes—but notably lack a defined nucleus (Fig. 2**a-c**). Formation of blebbisomes involves their temporary connection to the cell body via a thin membrane nanotube. Advanced imaging techniques have shown that the scission of this nanotube releases the blebbisome as an independent, organelle-rich vesicle containing cytoplasm and intracellular organelles. Both blebbisomes and tunneling nanotubes play roles in intercellular communication, but in distinct ways: blebbisomes function as autonomous extracellular vesicles, while tunneling nanotubes are F-actin-based structures that connect cells directly for cargo transfer. Blebbisomes are also capable of both secreting and internalizing smaller EVs, suggesting a dynamic role in cellular interaction.[24]

Present in both normal and cancerous cells, blebbisomes are broadly relevant in biology. Their occurrence in bone marrow suggests potential involvement in hematopoiesis or immune regulation, while in cancer, they have been visualized in vivo and are implicated in modulating the tumor microenvironment. Notably, blebbisomes may be enriched with immune checkpoint proteins such as PD-L1 and B7-H3, implicating them in immune modulation and tumor immune evasion. Their ability to interact with other EV populations highlights their potential significance in processes like cancer progression, metastasis, and therapy resistance.[24]

Blebbisome Isolation Technique: Critical Consideration and Potential Optimization

Blebbisomes are isolated via a meticulously optimized protocol prioritizing structural preservation and functional viability.[24] The procedure initiates with cell culture in Dulbecco's Modified Eagle Medium (DMEM) supplemented with EV-depleted fetal bovine serum (FBS) to eliminate confounding vesicular contaminants. Cells are cultured at 37°C under 5% CO_2 until reaching 30–50% confluence, a density that balances high blebbisome yield with minimal stress from overcrowding. Post-culture, cells are rinsed with phosphate-buffered saline (PBS) to remove medium residues, followed by trypsinization to detach both cells and blebbisomes, which are collected in conical tubes. Initial centrifugation at 1000 × *g* for 5 min separates intact cells (pellet) from blebbisome-containing supernatants, which are then sequentially filtered through 10 μm and 5 μm pluriStrainer sieves to exclude residual cellular debris. The clarified supernatant undergoes centrifugation at 2000 × *g* for 10 min to pellet blebbisomes, which are washed in PBS and re-pelleted to enhance purity by removing soluble contaminants. Post-isolation handling is tailored to downstream applications: blebbisomes destined for functional assays or live microscopy are maintained at 37°C to sustain metabolic activity, while those intended for proteomic analysis are immediately lysed in ice-cold buffer supplemented with protease inhibitors to prevent protein degradation. Key protocol refinements include the use of EV-depleted FBS to avoid co-isolation of EVs, room temperature processing to prevent temperature-sensitive structural damage, and optimized centrifugation forces that ensure efficient pelleting without disrupting blebbisome integrity.[24] This method ensures high purity isolates suitable for exploring blebbisome roles in cellular mechanics, apoptosis, or pathological processes, with adaptability for molecular, imaging, or biochemical analyses.

Key considerations include using EV-depleted FBS to prevent co-isolation of EVs,[26,27] room-temperature processing to avoid structural damage from thermal stress, and centrifugation parameters (low-speed spins to preserve blebbisome integrity, higher speeds for efficient pelleting). Challenges arise from blebbisome fragility, as excessive force during centrifugation or filtration risks structural disruption. Size overlap with smaller EVs (e.g., exosomes) and cellular debris complicates purification, necessitating precise filtration (e.g., 5–10 μm sieves).[26,27] Residual contaminants from incomplete cell removal or lysed cells further reduce purity, requiring iterative washing steps. Maintaining functional viability during isolation demands strict temperature control and rapid processing to prevent degradation.

Table 1
Major characteristics of different types of small and large EVs including blebbisome.

Type of EV	Size Range	Biogenesis Pathway	Key Markers	Content/Features	Remark or Functions
Exosome	30–200 nm	Endosomal (multivesicular endosome)	CD63, CD9, CD81, TSG101, Alix	Proteins, RNAs, lipids	Classical small EV; intercellular communication
Ectosome/Microvesicle	~150–1000 nm	Direct budding from plasma membrane	Annexin A1, ARF6	Proteins, lipids, nucleic acids	Large EV; overlaps with sEVs in size
Migrasome	500–3000 nm	Formed on retraction fibers during migration	TSPAN4, integrins	Cytosolic proteins, organelles	Involved in cell migration, signaling
Apoptotic Body	1–5 µm	Apoptosis (cell fragmentation)	Annexin V, phosphatidylserine	Cell organelles, DNA fragments	Large EV; removal of dying cell debris
Exopher	3.5–4 µm	Cellular extrusion (stress response)	Not well defined	Organelles, aggregated proteins	Disposal of damaged cell components
Large Oncosome	1–10 µm	Plasma membrane shedding (tumor cells)	Annexin A1, ARF6	Oncogenic proteins, DNA, lipids	Tumor-derived; very large EV
Blebbisome	Up to 20 µm	Membrane blebbing/retraction (myosin IIB-dependent)	Exosome markers (TSG101, ALIX, RAB27A/B), organelle markers	Organelles, exosomes, microvesicles	Motile, can secrete and internalize sEVs
Exomere	~35–50 nm	Non-vesicular particle (not a true EV)	HSP90, HSPs	Proteins, nucleic acids	Lacks membrane, distinct from vesicles
Supermere	< 50 nm	Non-vesicular particle	Not well defined	Diverse proteins, RNAs	Lacks membrane; distinct from exomeres and EVs

In my opinion, the future holds a huge promise for developing potential microfluidic devices for capturing single blebbisomes via immunoaffinity principle. In addition, unlike smaller EVs, blebbisomes could be characterized via regular flow cytometry without the need of microbead-based capture.

Characterization of Blebbisomes

Morphological and structural features

Blebbisomes are exceptionally large, membrane-enclosed EVs, reaching up to 20 µm in diameter, which distinguishes them from other EV subtypes (Table 1). Their defining morphological feature is dynamic membrane blebbing, a process driven by intracellular hydrostatic pressure and regulated by actomyosin contractility, particularly involving non-muscle myosin IIB.[24,25] This blebbing behavior is continuous and long-lived, enabling blebbisomes to be readily identified by light and electron microscopy due to their pronounced and persistent membrane protrusions. Structurally, blebbisomes are characterized by the presence of actin-rich protrusions, reflecting their origin from the plasma membrane and the underlying actin cortex.[28] The actin cytoskeleton plays a crucial role in both the initiation and retraction phases of bleb formation, where localized disruption or detachment of the cortex from the membrane allows cytoplasmic pressure to drive membrane expansion, followed by actin repolymerization that stabilizes the bleb.[24,28] Unlike smaller vesicles, blebbisomes retain various cellular organelles, including functional mitochondria, and can maintain autonomous blebbing and metabolic activity for extended periods after release. Their unique size, persistent blebbing, and actin-based protrusions make blebbisomes not only morphologically distinct but also functionally versatile, potentially serving as major communication agent within tissues.[24,25]

Organelle and molecular composition

Blebbisomes are distinguished by their rich organelle and molecular composition, containing a diverse array of intact cellular organelles such as mitochondria, Golgi apparatus, endoplasmic reticulum (ER), lysosomes, endosomes, peroxisomes, and autophagosomes or amphisomes. High-resolution imaging and proteomic analyses confirm the presence of these organelles, with mitochondria and ER structures readily observable and lysosomal and endosomal markers consistently detected. Notably, blebbisomes lack a defined nucleus, as evidenced by the absence of nuclear proteins and nuclear staining, setting them apart from intact cells.[24,25] Despite this, they retain ribosomes and RNA, as shown by the detection of ribosomal proteins and positive fluorescence in situ hybridization for RNA, indicating that blebbisomes may support some level of protein synthesis or RNA-based activity. This organelle-rich environment, coupled with the absence of a nucleus, gives blebbisomes a unique profile more like cells than to other EVs, yet distinct in their lack of nuclear material. The presence of multiple organelles and molecular machinery suggests that blebbisomes are not only structurally complex but may also be functionally versatile, potentially capable of metabolic activity, intercellular communication, and uptake or secretion of other vesicles.[24,25]

Protein content

The protein content of blebbisomes reflects their complex cellular origin and functional diversity. Immunofluorescence microscopy and transmission electron microscopy (TEM) are routinely employed to visualize and confirm the presence of organelle-specific protein markers within blebbisomes, such as those for mitochondria, Golgi apparatus, and endoplasmic reticulum, supporting their organelle-rich nature. In cancer-derived blebbisomes, advanced protein analysis techniques, including western blotting and mass spectrometry, have identified a suite

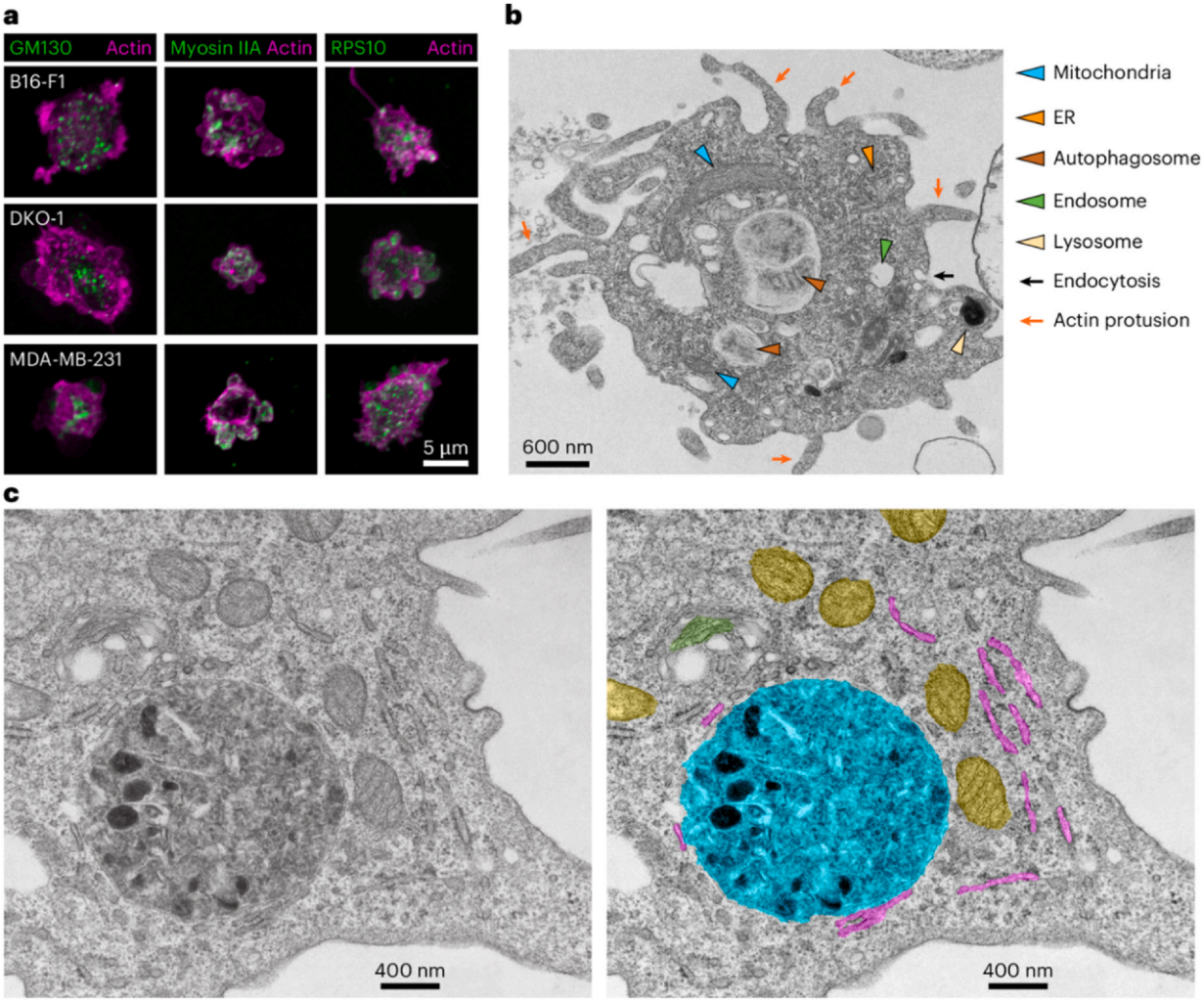

Fig. 2. Blebbisomes are membrane-bound vesicular structures that encapsulate a diverse array of intracellular organelles. (a) Immunofluorescence imaging of GM130, myosin IIA and RPS10 in B16-F1, DKO-1 and MDA-MB- 231 blebbisomes stained for actin by iSIM. The images are representative of three independent experiments. (b) TEM imaging of purified MDA-MB-231 blebbisome. The coloured arrowheads indicate organelles or ultrastructures as indicated, the black arrows show endocytosis, and the red arrows show actin protrusions. (c), A TEM image of a purified MDA-MB-231 blebbisomes (left) and a colour-coded (false colour) image (right). Yellow, mitochondria; green, Golgi apparatus; purple, ER; and turquoise, autophagosome–lysosome. Example micrographs from $n = 2$ independent blebbisome purifications are shown. Reproduced from Dennis K. Jeppesen et al.[24] published by Springer Nature under CC-BY 4.0 International license (http://creativecommons.org/licenses/by/4.0/).

of immune checkpoint proteins—such as PD-L1, PD-L2, B7-H3, VISTA, PVR, and HLA-E—within their protein cargo.[24,25] The detection of these immunomodulatory proteins suggests that blebbisomes may play a role in tumor immune evasion and intercellular signaling. Protein extraction from isolated blebbisomes involves lysis in specialized buffers with protease and phosphatase inhibitors, followed by quantification and identification using techniques like SDS-PAGE, western blotting, and mass spectrometry. This molecular profiling underscores the unique protein landscape of blebbisomes, distinguishing them from other EVs and highlighting their potential significance in both physiological and pathological contexts.[24,25]

Interestingly, the protein composition of blebbisomes is not simply a passive reflection of their cell of origin. Proteomic analyses show that blebbisomes, although similar to cells in having abundant mitochondrial, ER, Golgi, cytoskeletal, and ribosomal proteins, are selectively depleted in nuclear proteins, indicating active protein sorting. Furthermore, sorting mechanisms involve cytoskeletal dynamics—particularly myosin IIB contractility—and the selective packaging of proteins from specific organelles like mitochondria and endosomes, distinct from other extracellular vesicles.

These findings suggest that protein sorting mechanisms target specific proteins—such as those involved in immune modulation and vesicle trafficking—into blebbisomes, rather than simple bulk transfer reflective of the parent cell's total composition.

Functional properties of blebbisomes

Functionally, blebbisomes are not merely passive carriers of cellular material; they exhibit both the uptake and secretion of other EVs, such as exosomes and microvesicles. This bidirectional exchange allows blebbisomes to act as both recipients and donors of molecular cargo, facilitating the transfer of proteins, lipids, and nucleic acids within the extracellular space. Such interactions suggest that blebbisomes serve as a major agent in cellular communication, integrating and relaying signals between cells and their environment. Their large size and organelle-rich composition further enable them to participate in complex signalling events, potentially modulating the behaviour of neighbouring cells and influencing tissue dynamics.[24,25]

Blebbisomes also display pronounced cell-like properties. They contain multiple intact organelles—including mitochondria, endoplasmic reticulum, Golgi apparatus, lysosomes, endosomes, peroxisomes, and autophagosomes—but notably lack a nucleus.[24,25] This organelle complement equips blebbisomes with the capacity to perform

processes independently of their parent cells, such as energy production, protein synthesis, and vesicular trafficking. Intriguingly, blebbisomes can undergo apoptosis, a programmed cell death process, further emphasizing their functional autonomy and resemblance to living cells.[24,25] This apoptotic capability may serve as a mechanism for regulated turnover and clearance within tissues.

In terms of functional roles, blebbisomes are implicated in a variety of processes. Their ability to interact with and modulate the extracellular environment positions them as key mediators of intercellular communication and signal integration. In normal physiology, they may contribute to tissue homeostasis, immune surveillance, and the orchestration of multicellular responses. Pathologically, blebbisomes have been observed in cancer, where they are released by tumor cells and can contain a suite of immune checkpoint proteins—including PD-L1, PD-L2, B7-H3, VISTA, PVR, and HLA-E implicating them in immune regulation and potentially in the evasion of immune responses by tumors. This suggests that blebbisomes could play a role in cancer progression by modulating the tumor microenvironment and facilitating immune escape.[24,25] Moreover, the presence of functional mitochondria and other organelles within blebbisomes distinguishes them from other large EVs, such as exophers and migrasomes, which are primarily involved in the removal of damaged cellular components (Table 1). Instead, blebbisomes retain healthy organelles and remain metabolically active for extended periods after release, allowing them to continue interacting with their surroundings and participating in extracellular processes. Apparently, blebbisomes represent a unique class of motile, organelle-rich EVs with cell-like properties, capable of independent movement, complex interactions with other EVs, and autonomous functional activities. Their distinctive mechanism of release, dynamic behavior, and involvement in both physiological and pathological processes underscore their significance as major communication centers in the extracellular environment, with emerging roles in immune regulation, cancer biology, and intercellular signalling.[24–26]

Potential of blebbisomes as diagnostic and therapeutic tool

As the concept of blebbisome has been recently introduced, it lacks any concrete paper demonstrating the precise theranostic tool using blebbisome, therefore, it warrants further research to explore diagnostic and therapeutic potential of blebbisomes. Given that blebbisomes encapsulate functional organelles, including mitochondria, they represent a promising avenue for assessing the physiological or pathological status of their parent cells.[24] This property holds significant potential for advancing liquid biopsy approaches, enabling non-invasive diagnostics for chronic conditions such as gliomas and Alzheimer's disease. Additionally, the relatively large size of blebbisomes (in the micrometer range) facilitates their analysis in an intact state, reducing the risk of structural compromise typically associated with electron microscopy sample preparation. This characteristic may allow for their application in advanced biosensing technologies, such as surface plasmon resonance and atomic force microscopy,[7] to investigate the surface protein composition of blebbisomes with high fidelity. Importantly, the therapeutic potential of blebbisomes is also noteworthy. By virtue of carrying intact, functional mitochondria,[24] blebbisomes could be harnessed to modulate cellular energy metabolism in recipient cells. This opens new possibilities for developing novel treatments targeting metabolic dysfunction in diseases such as cancer and neurodegenerative disorders, positioning blebbisomes as both diagnostic and therapeutic tools in precision medicine.

In the context of clinical translation, blebbisome research requires addressing various critical challenges, including safety concerns, scalable production, and regulatory compliance. Safety issues emphasize immune compatibility and potential off-target effects, requiring thorough preclinical and clinical evaluation. Scalable production methods are needed to generate clinical grade blebbisomes with consistency and purity. Regulatory frameworks for extracellular vesicles are evolving, demanding rigorous quality control and characterization standards. Aligning blebbisome research with precision medicine principles involves defining patient-specific vesicle profiles and therapeutic targeting to maximize efficacy and minimize adverse effects. Integrating these aspects will enable safer, reproducible, and personalized blebbisome-based diagnostics and therapies, fostering their clinical acceptance and maximizing translational potential. Continued interdisciplinary research is essential for overcoming these hurdles and achieving practical clinical applications of blebbisomes.

Future perspectives

The discovery of blebbisomes as large, organelle-rich EVs with cell-like properties has opened an exciting new chapter in the study of intercellular communication and disease mechanisms. As research into these unique structures accelerates, several promising future directions and implications for both fundamental biology and clinical applications are emerging.

One of the most compelling avenues for future research lies in the comprehensive molecular and functional characterization of blebbisomes. While initial studies have established their ability to both secrete and internalize exosomes and microvesicles, the full spectrum of their cargo—encompassing proteins, lipids, and nucleic acids—remains to be elucidated.[24,25] High-resolution proteomic and transcriptomic analyses will be essential to map the signaling pathways and functional networks mediated by blebbisomes. Furthermore, investigating the biogenesis and regulation of blebbisome release across different cell types, physiological states, and microenvironments will provide critical insights into their roles in health and disease. Advanced imaging and *in vivo* tracking technologies could be leveraged to observe blebbisome dynamics and interactions in real time, deepening our understanding of their motility, cargo exchange, and fate in tissues.

The involvement of blebbisomes in disease, particularly cancer and immune disorders, is a rapidly developing area of interest. In cancer, blebbisomes have been shown to carry a diverse array of immune checkpoint proteins, such as PD-L1, PD-L2, B7-H3, VISTA, PVR, and HLA-E, which are known to facilitate tumor immune evasion.[24,25] Their release by cancer cells *in vivo* and presence in tumor microenvironments suggest that blebbisomes may serve as important vehicles for immunosuppressive signals, contributing to the suppression of anti-tumor immune responses and potentially promoting metastasis.[24,25] Beyond oncology, the potential involvement of blebbisomes in immune regulation raises the possibility that they may also play roles in autoimmune diseases, where dysregulated EV signaling is implicated in pathogenesis.[29] Understanding how blebbisomes interact with immune cells and modulate immune checkpoints could reveal new targets for therapeutic intervention in both cancer and immune-mediated disorders.

The unique properties of blebbisomes present both exciting therapeutic opportunities and significant challenges. On one hand, their ability to carry and deliver bioactive cargo—including immune checkpoint proteins—positions them as potential targets for novel immunotherapies. Inhibiting the formation, release, or function of cancer-derived blebbisomes could attenuate tumor immune evasion and enhance the efficacy of existing immunotherapies.[24,25] Conversely, harnessing engineered blebbisomes as delivery vehicles for therapeutic agents, such as small molecules, RNAs, or proteins, may offer new strategies for targeted treatment. However, the development of blebbisome-based therapies will require overcoming challenges related to their large size, heterogeneity, and complex composition. Specific targeting, efficient delivery, and avoidance of off-target effects will be critical considerations in translating blebbisome research into clinical applications.

Key research questions, which would require further investigation, include whether blebbisomes can serve as reliable liquid biopsy biomarkers for early disease detection, how to overcome their inherent

fragility and purification challenges, and if therapeutic inhibition of tumor-derived blebbisomes could improve immunotherapy outcomes. Addressing these could advance clinical use by enabling non-invasive diagnostics, enhancing biomarker stability, and potentially boosting cancer treatment efficacy through immune modulation. In addition, the integration of machine learning (ML) models including classical and quantum ML models with internet of things (IoT) can be employed for mining of various properties of blebbisomes, which could also be extended to other EVs including exosomes, potentially contributing to liquid biopsy of various diseases.[30,31]

Conclusions

Blebbisomes have emerged as a unique class of autonomous, organelle-rich EVs with remarkable functional properties, including independent motility, dynamic membrane blebbing, and the ability to both uptake and secrete other EVs. Their potential capacity to act as cellular communication agent, coupled with the presence of intact organelles but absence of a nucleus, allows them to perform select cellular processes outside the parent cell. In cancer, their enrichment in immune checkpoint proteins implies them in immune evasion and tumor progression, while their presence in normal tissues suggests broader roles in tissue homeostasis and immune surveillance. The discovery of blebbisomes challenges traditional views of intercellular communication and adds complexity to the extracellular signaling network. As research advances, blebbisomes hold promise as novel biomarkers and therapeutic targets, offering new opportunities for disease diagnosis, prognosis, and treatment. Their study is poised to significantly impact both basic cell biology and clinical medicine.

Declarations

Not applicable.

CRediT authorship contribution statement

Abhimanyu Thakur: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Abhimanyu Thakur has read and agreed to the published version of the manuscript and give their consent for publication in this journal.

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