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INVESTIGATION ON THE ROLE OF EXOSOMES IN CELL COMMUNICATION AND THEIR POTENTIAL THERAPEUTIC STRATEGIES IN DIABETES

Surabhi S. M.[1], Pinki Verma[2*]

[1]Research Scholar, Department of Pharmacology, Aditya Bangalore Institute of Pharmacy Education & Research, Rajiv Gandhi University of Health Sciences, Yelahanka, Bengaluru, 560064 Karnataka, India.

[2]Associate Professor, Department of Pharmacology, Aditya Bangalore Institute of Pharmacy Education & Research, Rajiv Gandhi University of Health Sciences, Yelahanka, Bengaluru, 560064 Karnataka, India.

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***Corresponding Author**

Pinki Verma

Associate Professor, Department of Pharmacology, Aditya Bangalore Institute of Pharmacy Education & Research, Rajiv Gandhi University of Health Sciences, Yelahanka, Bengaluru, 560064 Karnataka, India.

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ABSTRACT

Background: Exosomes, nanosized extracellular vesicles (30–150 nm), are critical mediators of intercellular communication, transferring bioactive cargo (proteins, lipids, RNA) to modulate cellular functions. In diabetes mellitus (DM), a metabolic disorder affecting over 500 million globally, exosomes exhibit dual roles: they contribute to disease pathogenesis by exacerbating β-cell dysfunction, insulin resistance, and vascular complications, while offering therapeutic promise as drug delivery vehicles or regenerative tools. Despite advancements in diabetes management, current therapies often fail to address underlying molecular mechanisms or prevent complications, underscoring the need for innovative strategies. Exosomes inherent biocompatibility, low immunogenicity, and capacity to cross biological barriers position them as transformative candidates for precision diagnostics and therapeutics in DM. Main Text Exosomes play a dual role in diabetes, serving as both mediators of disease progression and vehicles for innovative therapies. In T2DM, adipose and liver-derived exosomes transfer insulin-resistance-inducing miRNAs (miR-34a, miR-155) and pro-inflammatory cytokines,

disrupting metabolic homeostasis. For T1DM, β-cell exosomes deliver autoantigens that trigger autoimmune destruction, while immune cell exosomes propagate inflammation through miR-21 and other mediators. These vesicles also drive diabetic complications by shuttling pathogenic cargo - fibrotic factors in nephropathy, angiogenic miRNAs in retinopathy, and neurotoxic proteins in neuropathy. Therapeutically, engineered exosomes show remarkable promise. MSC-derived exosomes promote β-cell regeneration, while CRISPR-edited exosomes enable precise drug/gene delivery. Advances in nanotechnology allow tissue-specific targeting, and AI helps optimize exosome design. However, challenges like production scalability, cargo consistency, and long-term safety must be addressed before clinical translation. Future research should focus on standardizing isolation methods, improving targeting efficiency, and developing personalized approaches through multi-omics profiling. With their ability to modify disease processes rather than just manage symptoms, exosome-based therapies represent a paradigm shift in diabetes treatment. Realizing their full potential will require overcoming technical hurdles through interdisciplinary collaboration, paving the way for transformative therapies that restore metabolic health. **Conclusion:** Exosomes represent a paradigm shift in diabetes management, both as biomarkers of early disease and as versatile therapeutic platforms. Future innovation lies in overcoming biological and technical barriers through interdisciplinary collaboration. By harnessing exosome biology, next-generation therapies could reverse insulin resistance, regenerate β-cells, and prevent complications, transforming diabetes care from symptomatic treatment to disease modification.

KEYWORDS: Extracellular vesicles, Exosome biogenesis, Intercellular communication, β-cell dysfunction, MicroRNAs (miRNAs), Long non-coding RNAs.

BACKGROUND

Exosomes have emerged as essential mediators of intercellular communication, playing pivotal roles in both normal metabolic processes and the pathophysiology of diabetes. Their unique ability to transport bioactive molecules, including proteins, lipids, and microRNAs, between different metabolic tissues positions them as key contributors to the onset of insulin resistance, dysfunction of β-cells, and the progression of diabetic complications.[1,2] At the same time, these characteristics make exosomes promising candidates for therapeutic applications in diabetes treatment. They hold potential not only for their natural biological

effects, particularly those derived from mesenchymal stem cells (MSCs), but also as delivery systems for therapeutic agents such as drugs, genes, and proteins.[3,4]

The diverse functions of exosomes in diabetes—ranging from their involvement in disease pathogenesis to their use in regenerative therapies—underscore this field's complexity and immense potential. Despite ongoing challenges in the standardization, scalability, and targeted delivery of exosome-based therapies, these approaches offer significant promise for more effective treatments. Such treatments may address the root causes of diabetes, including β-cell destruction and insulin resistance, rather than merely managing its symptoms.[5] As research in this area advances, exosome-based strategies could significantly change the landscape of diabetes care by enabling solutions that regenerate pancreatic β-cells, reverse insulin resistance, and prevent the long-term complications associated with this chronic disease.[6]

Future advancements in exosome biology, combined with innovations in bioengineering and delivery mechanisms, will be essential to fully harness their therapeutic potential in diabetes management. Over the coming years, the translation of exosome-based therapies from preclinical models to clinical settings is expected to offer new hope for millions affected by diabetes globally.[7,8]

Main Text

Overview of extracellular vehicles (EVs): Exosomes, microvesicles, and apoptotic bodies

Extracellular vehicles (EVs) are membrane-bound nanoparticles released by cells into the extracellular environment, playing vital roles in intercellular communication, disease progression, and waste disposal. They are broadly categorized into three main types: exosomes, macrovesicles (MVs), and apoptotic bodies, each differing in biogenesis, size, and biological functions.[9]

Exosomes (30–150 nm) originate from the endosomal pathway, where multivesicular bodies (MVBs) fuse with the plasma membrane to release their intraluminal vesicles. Their formation depends on the endosomal sorting complex required for transport (ESCRT) machinery or ESCRT-independent mechanisms involving tetraspanins (CD9, CD63, CD81) and ceramide. Exosomes carry proteins, lipids, and nucleic acids (miRNA, mRNA) and are crucial in immune regulation, cancer metastasis, and neurodegenerative

diseases. Due to their stable nature and specific cargo, they are promising biomarkers and drug delivery systems.[10]

Macrovesicles (100–1,000 nm), also called ectosomes, form through direct outward budding of the plasma membrane. Their release involves calcium-dependent cytoskeletal remodelling and phosphatidylserine (PS) exposure. Unlike exosomes, MVs often retain surface markers from parent cells and participate in coagulation, inflammation, and tumor progression. Elevated levels are associated with cardiovascular diseases and cancer, making them potential diagnostic tools.[11]

Apoptotic bodies (500–5,000 nm) are the largest EVs, produced during programmed cell death (apoptosis) via membrane blebbing. They contain cellular debris, including fragmented DNA, histones, and organelles, which are cleared by phagocytes to prevent inflammation. Defective clearance can trigger autoimmune responses, linking them to diseases like systemic lupus erythematosus (SLE).[12]

The study of EVs has expanded rapidly due to their roles in cancer, neurodegeneration, and regenerative medicine. Exosomes, in particular, are being explored for liquid biopsies and therapeutic applications, while MVs and apoptotic bodies provide insights into thrombosis and immune regulation. Future research may uncover novel EV-based treatments and diagnostic strategies.[13]

Importance of exosomes in intercellular communication and disease modulation

Exosomes are nanoscale vesicles (approximately 30–150 nanometers in diameter) released by numerous cell types, and they are increasingly recognized as key facilitators of communication between cells. They serve as carriers of a diverse array of molecules, including proteins, lipids, messenger RNAs, microRNAs, and DNA fragments, which can influence the activity and behavior of recipient cells.[14,15] These vesicles can enter target cells through processes like membrane fusion, receptor binding, or endocytosis, subsequently modulating signaling pathways and gene expression involved in various biological functions such as immunity, tissue regeneration, and neuronal signaling.[16] In pathological conditions, exosomes play a central role in disease progression. For example, in cancer, tumor-derived exosomes contribute to malignancy by enhancing processes like angiogenesis, metastasis, and immune evasion through the transfer of tumor-promoting factors.[17, 18] In neurological diseases such as Parkinson's and Alzheimer's, they are believed to facilitate the intercellular

spread of neurotoxic proteins like α-synuclein and amyloid-beta, thus accelerating neurodegeneration.[19,20] Furthermore, in cardiovascular disorders, exosomes are involved in healing damaged heart tissue and promoting new blood vessel growth after injury.[21] During infections, pathogens can exploit exosomal pathways to transport viral components and evade immune responses.[22] Due to their stable presence in body fluids and their cargo's reflection of the originating cell's condition, exosomes are being explored as non-invasive biomarkers for early diagnosis and disease monitoring.[23] Additionally, their natural compatibility and targeting ability make them promising candidates for delivering therapeutic agents. Altogether, exosomes are not only crucial for maintaining normal physiological communication but also represent innovative tools for diagnosing and treating various diseases.

Biogenesis and Composition of Exosomes

Exosomes are extracellular vesicles that originate from the endosomal system and are released into the extracellular space when multivesicular bodies (MVBs) fuse with the plasma membrane. Their formation begins with the inward budding of the endosomal membrane, resulting in the generation of intraluminal vesicles (ILVs) within MVBs. These ILVs, once secreted, are termed exosomes.[24] The biogenesis process is tightly regulated and involves several molecular pathways, notably the Endosomal Sorting Complex Required for Transport (ESCRT)-dependent mechanism, which facilitates cargo sorting and vesicle budding through a series of protein complexes (ESCRT-0, -I, -II, and -III).[25] Additionally, ESCRT-independent pathways, involving tetraspanins (such as CD63, CD81, and CD9) and lipid molecules like ceramides, also contribute to exosome formation.[26] The molecular composition of exosomes is highly specific and reflects the physiological state of their parent cells. They typically contain a complex mixture of proteins (e.g., heat shock proteins, Rab GTPases, Alix, TSG101), lipids (e.g., sphingomyelin, cholesterol, phosphatidylserine), and nucleic acids, including mRNA, microRNA, long non-coding RNA, and occasionally DNA fragments.[27,28] This diverse cargo enables exosomes to participate in intercellular communication and modulate a range of biological processes. Furthermore, certain surface markers such as tetraspanins and integrins facilitate exosome targeting and uptake by specific recipient cells.[29] The selective packaging of molecules into exosomes is thought to be a controlled process, governed by signalling and sorting mechanisms within the donor cells. As such, exosomes serve not only as messengers but also as biomarkers, providing insight into the molecular and functional status of their originating cells.

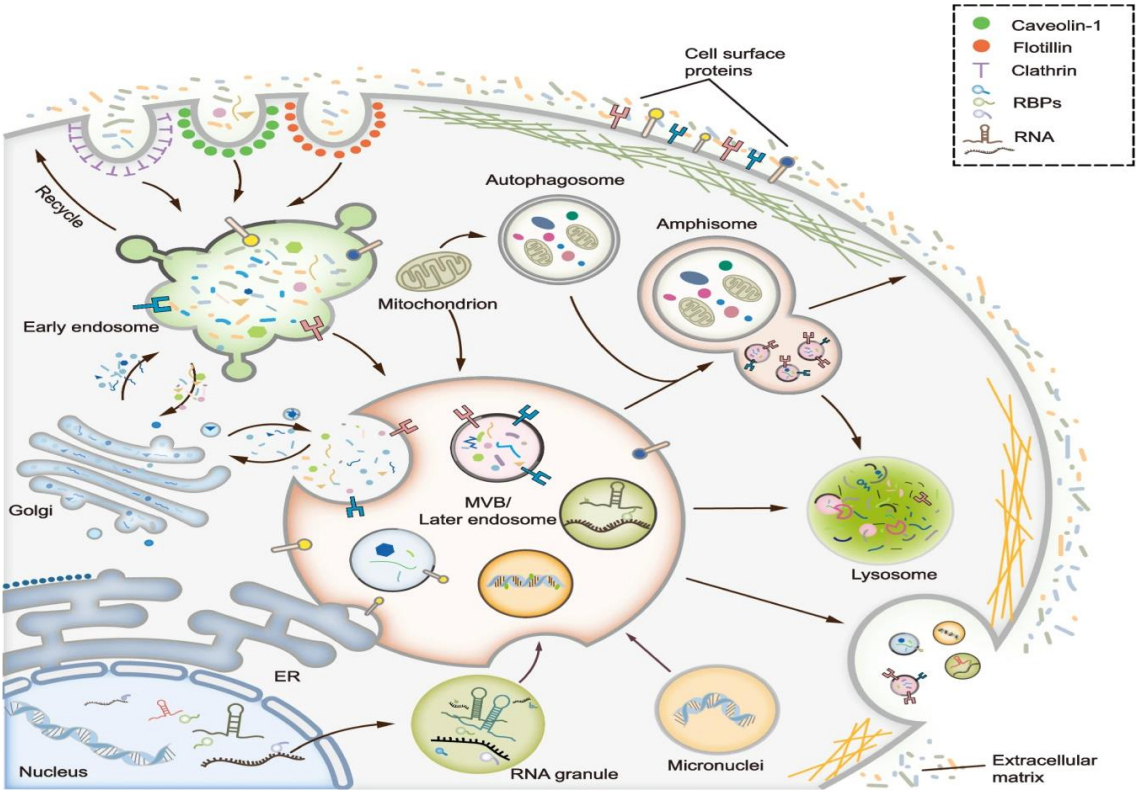

Figure 1: Biogenesis of Exosomes.

Mechanisms of Exosome Formation

Exosome formation is a multistep process that begins within the endosomal system and involves both ESCRT-dependent and ESCRT-independent pathways. The process is initiated by the inward budding of the limiting membrane of early endosomes, forming intraluminal vesicles (ILVs) within multivesicular bodies (MVBs). These ILVs are later secreted as exosomes upon the fusion of MVBs with the plasma membrane.[30] The Endosomal Sorting Complex Required for Transport (ESCRT) machinery, composed of four main complexes—ESCRT-0, I, II, and III—plays a critical role in membrane deformation and cargo sorting. ESCRT-0 recognizes and sequesters ubiquitinated cargo, while ESCRT-I and -II initiate membrane budding, and ESCRT-III is responsible for vesicle scission.[31] Accessory proteins such as ALIX and TSG101 further assist in these processes.[32] Alternatively, ESCRT-independent mechanisms also contribute to exosome biogenesis. These rely on lipid-based mechanisms, particularly ceramide generation, and the involvement of tetraspanins like CD9, CD63, and CD81, which assist in cargo selection and vesicle formation.[33] The fate of MVBs is regulated by Rab GTPases (e.g., Rab27a/b), which mediate their transport and fusion with the plasma membrane, thereby allowing exosome release.[34] Together, these mechanisms ensure the selective packaging and secretion of molecular cargo that enables exosomes to function as vital mediators of intercellular communication.

Molecular Composition of Exosomes

Exosomes are composed of a selective and highly organized set of biomolecules that reflect their cellular origin and functional purpose. Their lipid bilayer structure is enriched in specific lipids such as cholesterol, sphingomyelin, ceramide, and phosphatidylserine, which contribute to membrane stability and vesicle formation.[35] The protein content of exosomes includes a variety of molecules involved in membrane trafficking, vesicle formation, and intercellular signalling. Commonly identified proteins include tetraspanins (CD9, CD63, CD81), heat shock proteins (HSP70, HSP90), ESCRT-associated proteins (Alix, TSG101), and Rab GTPases, which assist in vesicle movement and secretion.[36,37] Exosomes also carry nucleic acids, most notably mRNAs, microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and occasionally DNA. These nucleic acids can be functionally active and influence gene expression in recipient cells, making exosomes important agents of epigenetic communication.[38] Additionally, surface adhesion molecules such as integrins and ICAMs facilitate cell targeting and uptake, contributing to the specificity of exosome-mediated interactions.[39] The composition of exosomes is not random; instead, cargo selection appears to be a tightly regulated process governed by sorting mechanisms within the parent cell. This selective packaging makes exosomes valuable biomarkers for disease diagnostics and potential tools for targeted therapeutic delivery.

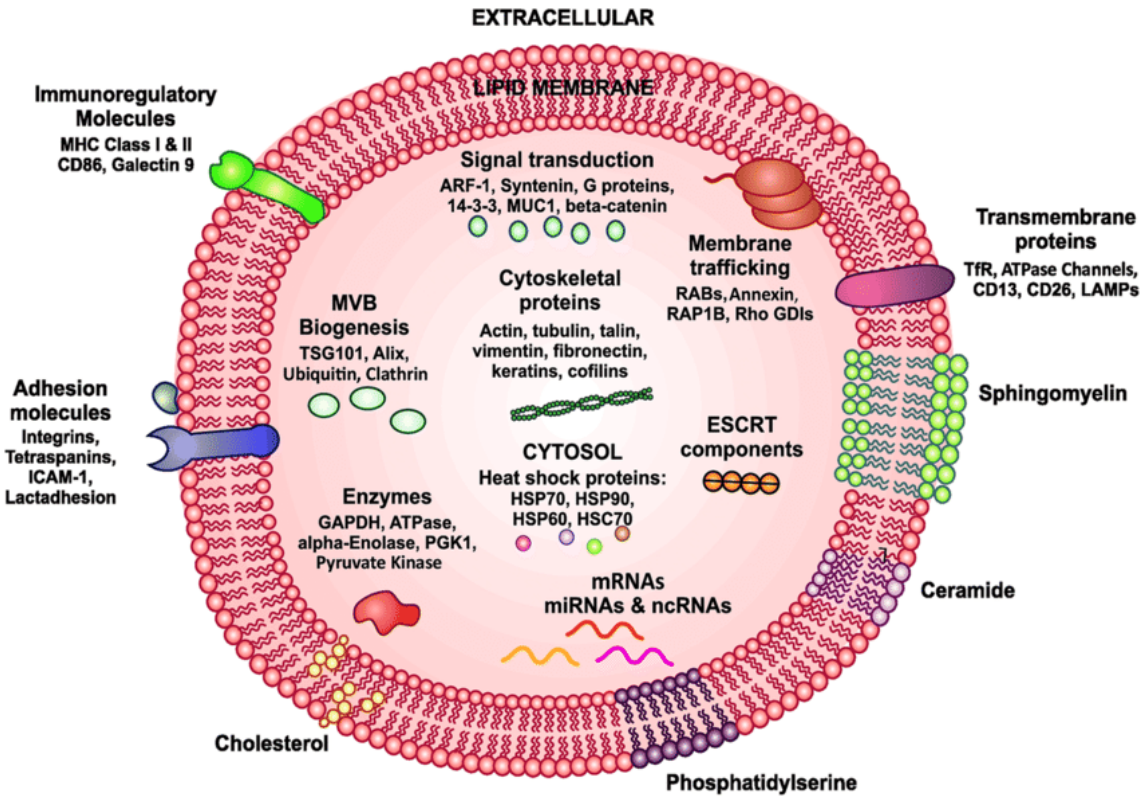

Figure 2: Composition of Exosomes.

Exosomes in Intercellular Communication

Exosomes play a critical role in intercellular communication by acting as vehicles for the transfer of biologically active molecules between cells. These nanovesicles carry a complex cargo—including proteins, lipids, and nucleic acids such as mRNAs and microRNAs, which can be delivered to recipient cells through mechanisms like membrane fusion, endocytosis, or receptor-ligand interactions.[40,41] Once internalized, the molecular contents of exosomes can modulate signalling pathways, gene expression, and even the phenotype of the recipient cell. This form of communication is vital in both physiological and pathological contexts. For example, in the immune system, exosomes facilitate antigen presentation and modulate immune responses by transferring MHC molecules and cytokines between cells.[42] In the nervous system, they contribute to synaptic plasticity and neurogenesis by exchanging signalling molecules and genetic material.[43] In cancer, tumour-derived exosomes can reprogram stromal or immune cells to support tumour growth and metastasis by transferring oncogenic factors or suppressive RNAs.[44] Similarly, exosomes participate in tissue repair by promoting angiogenesis and coordinating the responses of different cell types in wound healing.[45] This broad functionality underlines the importance of exosomes as messengers in both local and systemic communication networks, making them a central element in the regulation of cell behaviour and a promising target for therapeutic intervention.

Mechanisms of Exosome-Mediated Signalling

Exosomes mediate intercellular communication primarily through surface ligand-receptor interactions and the delivery of molecular cargo. On their surface, exosomes express various proteins such as integrins and immunomodulatory molecules that can bind to receptors on target cells, initiating downstream signalling that influences cellular functions. For instance, tumour-derived exosomes expressing PD-L1 can suppress T-cell activity and promote immune evasion, while specific integrins on exosomes can determine tissue tropism.[46,47] Furthermore, exosomes transport bioactive molecules like microRNAs (miRNAs), mRNAs, and proteins into recipient cells through mechanisms such as endocytosis or membrane fusion. These cargos can modulate gene expression and cell behaviour, particularly through post-transcriptional regulation by exosomal miRNAs.[48,49]

Role in Physiological Processes

Exosomes contribute significantly to various physiological processes. In immune regulation, exosomes from dendritic cells or other antigen-presenting cells carry MHC-peptide

complexes to influence T-cell activation, while tumour-derived exosomes can dampen immune responses by delivering checkpoint molecules like PD-L1.[50,51] In tissue repair, exosomes secreted by mesenchymal stem cells (MSCs) are known to enhance regeneration through angiogenesis, proliferation, and extracellular matrix remodelling. Moreover, they play a role in maintaining metabolic homeostasis by transporting signalling molecules that regulate glucose and lipid metabolism in target organs, including the liver and adipose tissue.

Dysregulation in Disease

Exosomal dysfunction has been implicated in a wide array of diseases. In cancer, tumour-derived exosomes facilitate metastasis, neovascularization, and immune suppression by delivering oncogenic miRNAs, immunomodulatory proteins, and adhesive integrins.[52,53] In neurodegenerative diseases, exosomes may carry toxic proteins such as tau or α-synuclein, contributing to disease propagation (1). Cardiovascular disease is also linked to exosomal imbalance, with changes that impair endothelial function and promote fibrosis or inflammation (5). Furthermore, in metabolic disorders like type 2 diabetes and obesity, altered exosome content can disrupt insulin signalling and lipid metabolism.[54,55]

Implications for Chronic Inflammation and Metabolic Disorders like Diabetes

Exosomes play a significant role in the development and progression of chronic inflammation and metabolic disorders, including type 2 diabetes mellitus (T2DM). In individuals with metabolic syndrome, adipose tissue-derived exosomes are enriched with pro-inflammatory cytokines, microRNAs, and signalling proteins that can promote systemic inflammation and disrupt insulin signalling pathways. These exosome cargos may influence macrophage polarization towards a pro-inflammatory (M1) phenotype, exacerbating insulin resistance in target tissues such as skeletal muscle and the liver.[56,57] Moreover, pancreatic β-cell-derived exosomes under diabetic conditions have been shown to carry stress-related molecules and autoantigens, potentially contributing to β-cell dysfunction and immune-mediated damage.[58] In T2DM, circulating exosomes have also been associated with altered miRNA profiles, such as reduced levels of miR-126, a regulator of vascular integrity, further linking exosomal dysregulation to endothelial dysfunction and diabetic complications.[59] Therefore, exosomes act not only as mediators of intercellular communication but also as biomarkers and potential therapeutic targets in chronic metabolic diseases.

Exosomes in Diabetes Pathophysiology

Exosomes have emerged as key contributors to the underlying mechanisms of both type 1 and type 2 diabetes mellitus. These small extracellular vesicles mediate cellular communication by transferring functional molecules—including proteins, lipids, and microRNAs (miRNAs)—between cells. In type 2 diabetes (T2DM), exosomes derived from insulin-resistant fat cells and pro-inflammatory macrophages often contain miRNAs and cytokines that interfere with insulin signaling in organs like the liver and skeletal muscle, thereby aggravating insulin resistance.[60,61] Specifically, exosomal miR-29 and miR-155 released from adipose tissue have been shown to suppress insulin receptor substrates and trigger inflammatory pathways, respectively. In type 1 diabetes (T1DM), exosomes secreted from damaged or stressed pancreatic β-cells may transport autoantigens such as insulin peptides and GAD65, potentially triggering an immune response that leads to β-cell destruction.[62,63] Additionally, exosomes circulating in the bloodstream of diabetic individuals often show dysregulated miRNA patterns, such as a drop in miR-126 and elevation of miR-21, both of which are linked to vascular impairment and complications including nephropathy and cardiovascular disease.[64] As a result, exosomes are not only critical to the disease process but also offer promise as diagnostic markers and novel therapeutic targets in diabetes management.

Exosomes in Autoimmune β-Cell Destruction

In type 1 diabetes (T1D), the autoimmune destruction of pancreatic β-cells is closely associated with the dysregulated immune recognition of self-antigens. Exosomes play a pivotal role in this process by acting as carriers of β-cell-derived antigens, such as insulin, glutamic acid decarboxylase 65 (GAD65), and heat shock proteins. These exosomes, released from stressed or dying β-cells, are internalized by antigen-presenting cells (APCs) like dendritic cells and macrophages. Once processed, the antigens are presented on major histocompatibility complex (MHC) molecules to naïve or autoreactive T cells, triggering an adaptive immune response against the β-cells. Moreover, immune cell-derived exosomes themselves can also amplify this process by facilitating cross-presentation of β-cell antigens and by delivering pro-inflammatory cytokines or microRNAs that exacerbate immune activation 3. This exosome-mediated communication not only accelerates β-cell damage but may also serve as a mechanism for antigen spreading during disease progression, underscoring their potential as biomarkers and therapeutic targets in autoimmune diabetes.

Role of Immune Cell-Derived Exosomes in Promoting Inflammation

Exosomes secreted by immune cells are potent mediators of inflammatory responses and contribute significantly to the progression of chronic inflammatory and autoimmune diseases. These vesicles, derived from T cells, B cells, macrophages, and dendritic cells, carry pro-inflammatory cytokines, signalling molecules, and regulatory microRNAs that modulate immune activity in target cells. For instance, macrophage-derived exosomes can enhance inflammation by transferring tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and miR-155 to recipient cells, thereby amplifying inflammatory signalling cascades such as the NF-κB pathway.[65] Similarly, exosomes from activated T cells have been shown to promote the release of additional cytokines from other immune cells, reinforcing the local immune response and tissue inflammation.[66] These immune-derived exosomes not only serve as vehicles for intercellular signalling but also help sustain and propagate inflammation over time, playing critical roles in diseases like rheumatoid arthritis, type 1 diabetes, and atherosclerosis.

Exosome-Mediated Insulin Resistance: Adipocyte- and Hepatocyte-Derived Exosomes

Exosomes derived from adipocytes and hepatocytes have been shown to play pivotal roles in the development of insulin resistance, a hallmark of metabolic disorders like type 2 diabetes. In obesity and insulin resistance, adipocyte-derived exosomes are enriched with pro-inflammatory molecules, including cytokines and microRNAs, that contribute to systemic inflammation and impair insulin signalling in target tissues such as the liver and muscle. For instance, exosomes from adipocytes can carry miRNAs such as miR-29, which targets insulin receptor substrates, and miR-155, which promotes inflammatory responses through NF-κB activation.[67,68] These exosomes may also promote endothelial dysfunction and vascular inflammation, further exacerbating insulin resistance.[69] Similarly, hepatocyte-derived exosomes have been shown to carry inflammatory cytokines and stress-related proteins that disrupt insulin receptor signalling in the liver, contributing to hepatic insulin resistance and glucose metabolism dysregulation.[70,71] By mediating communication between adipose tissue, liver, and other organs, these exosomes facilitate the development of systemic insulin resistance and are emerging as important players in metabolic diseases.

β-Cell Dysfunction and Apoptosis Triggered by Exosomal miRNAs

Exosomal microRNAs (miRNAs) have been identified as crucial regulators of β-cell dysfunction and apoptosis in diabetes. These small RNA molecules, packaged in exosomes,

are transferred between cells, influencing cellular behaviour and contributing to the progressive decline of pancreatic β-cell function. In type 1 diabetes (T1D) and type 2 diabetes (T2D), exosomes derived from immune cells or stressed β-cells themselves contain miRNAs that promote apoptosis and impair insulin secretion. For instance, miRNAs such as miR-29 and miR-155, which are found in exosomes from immune cells or inflammatory sites, target proteins involved in β-cell survival and insulin synthesis, triggering cell death pathways.[72,73] The delivery of these exosomal miRNAs to β-cells leads to their functional impairment and contributes to the autoimmune destruction of β-cells in T1D, while also exacerbating β-cell apoptosis in T2D due to chronic inflammation and insulin resistance. This highlights the role of exosome-mediated communication in the pathogenesis of diabetes and underscores their potential as biomarkers and therapeutic targets for preserving β-cell function.

Exosomes in Diabetic Complications: Nephropathy, Retinopathy, and Neuropathy

Diabetic complications, including nephropathy, retinopathy, and neuropathy, are major contributors to morbidity and mortality in diabetes. Exosomes play a key role in the development and progression of these complications by mediating intercellular communication and facilitating the spread of pathological signals. In diabetic nephropathy, for example, exosomes derived from glomerular cells, tubular cells, and immune cells are involved in the transfer of inflammatory cytokines and fibrotic factors, which promote renal damage and fibrosis.[74] Similarly, in diabetic retinopathy, exosomes from retinal cells and immune cells transport miRNAs and pro-inflammatory mediators that exacerbate retinal vascular permeability and angiogenesis, leading to vision impairment.[75] Furthermore, exosomes secreted by Schwann cells, macrophages, and other peripheral nerve cells in diabetes contribute to neuropathy by promoting inflammation and oxidative stress, which damage nerve fibers and impair nerve function.[76] Thus, exosomes not only serve as vehicles for biomarker discovery but also as potential therapeutic targets in managing diabetic complications.

Diagnostic Potential: Exosomal Biomarkers for Early Diabetes Detection

Exosomes have shown great promise as diagnostic tools for early detection of diabetes due to their ability to carry a wide range of bioactive molecules, including microRNAs (miRNAs) and proteins, that reflect the physiological and pathological states of various tissues. These small vesicles are easily detectable in bodily fluids, such as blood, urine, and saliva, making them non-invasive biomarkers for diabetes. Specific miRNAs, such as miR-29 and miR-146,

have been found to be significantly altered in exosomes from diabetic patients, correlating with insulin resistance and β-cell dysfunction.[77] Additionally, exosomal proteins, including insulin receptor substrates and markers of oxidative stress, may provide insights into the progression of both type 1 and type 2 diabetes. As a result, exosomes offer a promising approach for the early detection of diabetes and its complications, allowing for more timely interventions.[78]

Therapeutic Strategies

Engineering Exosomes for Antidiabetic Drug Delivery

Exosomes can be engineered to serve as effective drug delivery vehicles for the treatment of diabetes. Their natural ability to transport bioactive molecules makes them ideal candidates for delivering therapeutic agents such as insulin or glucagon-like peptide-1 (GLP-1) analogy to specific tissues. Researchers have successfully loaded exosomes with insulin and GLP-1 analogy, enhancing their stability and targeted delivery to insulin-sensitive tissues like skeletal muscle and liver.[79] This exosome-based approach not only improves drug bioavailability but also minimizes the side effects associated with traditional delivery methods. The development of exosome-based drug delivery systems is an emerging area of research, offering a potential therapeutic strategy for achieving better glycaemic control in diabetic patients.[79,80]

MSC-Derived Exosomes for β-Cell Regeneration

Mesenchymal stem cell (MSC)-derived exosomes are gaining attention in regenerative medicine, particularly in β-cell regeneration for diabetes treatment.[81] MSCs, known for their regenerative properties, release exosomes that contain proteins, lipids, and miRNAs capable of promoting tissue repair and regeneration. When applied to diabetic models, MSC-derived exosomes have been shown to stimulate the proliferation and function of pancreatic β-cells, offering a potential strategy for reversing β-cell loss in type 1 and type 2 diabetes. These exosomes can also modulate the immune system to reduce inflammation, further supporting their therapeutic potential in diabetes.

Immune Modulation: Exosomes Loaded with Immunosuppressive miRNAs/Proteins

In type 1 diabetes (T1D), where autoimmune destruction of pancreatic β-cells is a central feature, exosomes loaded with immunosuppressive microRNAs (miRNAs) or proteins offer a potential therapeutic approach. By transferring miRNAs such as miR-146 or proteins that suppress pro-inflammatory cytokines, exosomes can help modulate the immune response and

prevent β-cell destruction. This immunomodulatory effect could help in treating autoimmune diseases like T1D by inducing tolerance and curbing the overactive immune system, thus offering a novel approach to immunotherapy.[82,83]

Clinical Trials and Preclinical Advances: Summary of Current Exosome-Based Therapies Under Investigation

Exosome-based therapies are in the early stages of clinical and preclinical investigation for diabetes treatment. Several studies have shown promising results in using exosomes as diagnostic tools and therapeutic agents for both type 1 and type 2 diabetes. Clinical trials are exploring the potential of MSC-derived exosomes in regenerating β-cells, while others are testing the use of engineered exosomes for drug delivery (such as insulin or GLP-1) to improve glycaemic control. Additionally, preclinical studies have demonstrated the ability of exosomes to modulate immune responses in T1D, offering hope for long-term immune tolerance and prevention of β-cell destruction. While more research is needed to confirm the safety and efficacy of these therapies, exosome-based approaches represent an exciting frontier in diabetes treatment.

Technical Hurdles

Exosome Isolation, Standardization, and Scalability Despite the promise of exosomes in therapeutic applications, significant technical challenges remain. One of the major hurdles is the efficient isolation and purification of exosomes from biological fluids. Current methods, such as ultracentrifugation, size-exclusion chromatography, and immunoaffinity-based techniques, face limitations in terms of yield, purity, and reproducibility.[84] Standardization of these techniques is essential to ensure consistent exosome quality and functionality across studies and clinical applications. Additionally, the scalability of exosome production remains a challenge, as large-scale isolation methods must be developed that preserve exosome integrity and bioactivity while being cost-effective.[85] These technical issues must be addressed to enable the widespread use of exosomes in clinical settings**.**

Biological Challenges

Target Effects, Immune Clearance, and Stability

Exosome-based therapies also face biological challenges that could limit their clinical utility. One concern is off-target effects, where exosomes might deliver their cargo to unintended cells, potentially leading to adverse outcomes. This challenge highlights the need for precise targeting mechanisms to guide exosomes to specific tissues or cells.[86] Another issue is the

immune clearance of exosomes. The body's immune system may recognize exosomes as foreign particles, leading to their rapid removal, thus reducing their therapeutic efficacy. To overcome this, strategies to camouflage exosomes, such as surface modification with biocompatible molecules, are being explored.[87] Furthermore, exosome stability is a critical concern, as their cargo must remain intact during circulation and storage. Ensuring that exosomes retain their functional properties in the bloodstream and under storage conditions is crucial for their effectiveness in therapeutic applications.[88]

Ethical and Regulatory Considerations for Clinical Translation

The clinical translation of exosome-based therapies is also subject to ethical and regulatory challenges. Exosome production from human cells, such as mesenchymal stem cells or adipocytes, raises concerns regarding donor consent, safety, and potential genetic modification. Regulatory bodies require rigorous testing and validation of exosome-based therapies to ensure their safety, efficacy, and lack of contamination with harmful pathogens.[89] Additionally, the use of exosomes in immunotherapy and regenerative medicine necessitates careful consideration of long-term safety, particularly concerning unintended immune responses or tumorigenesis. Ethical issues surrounding the use of exosome-based therapies, including their potential commercialization and accessibility, must also be addressed to ensure fair distribution and minimize disparities in healthcare access.[90.91]

Advances in Exosome Engineering: CRISPR-Edited Exosomes

Recent advancements in exosome engineering hold immense potential for improving the therapeutic efficacy of exosome-based treatments. One notable development is the use of CRISPR-Cas9 technology to edit the contents of exosomes, allowing for the targeted delivery of specific therapeutic molecules. By genetically modifying exosomes to express or carry tailored cargo, such as proteins, miRNAs, or gene-editing components, researchers can enhance the precision and effectiveness of exosome-based therapies. For example, CRISPR-edited exosomes can be used to directly correct genetic defects in target cells or modulate immune responses in autoimmune diseases like type 1 diabetes.[92] This technology provides a powerful tool for advancing personalized medicine and improving the specificity of exosome-based drug delivery systems.

Integration with Nanotechnology and Artificial Intelligence for Personalized Therapies

The integration of exosome-based therapies with nanotechnology and artificial intelligence (AI) could revolutionize diabetes treatment. Nanotechnology can be used to enhance the functional properties of exosomes, such as improving their stability, optimizing drug loading, and enabling targeted delivery to specific tissues. Additionally, AI and machine learning algorithms can assist in identifying the most effective exosome formulations by analyzing complex biological data and predicting patient responses to exosome-based treatments. This personalized approach, combining exosome engineering with AI, could allow for the development of tailored therapies that are more effective and less invasive, opening new doors for managing both type 1 and type 2 diabetes.[93] By leveraging these technologies, the future of diabetes treatment could shift towards highly individualized and precise interventions.

Unanswered Questions: Exosome Heterogeneity and Long-Term Safety in Diabetes

Despite the significant progress in exosome-based therapies, several critical questions remain unanswered. One of the major challenges is the inherent heterogeneity of exosomes. Exosomes vary in size, composition, and content depending on the source cell, which complicates their standardization and application in clinical settings.[94] Understanding the mechanisms behind exosome heterogeneity is crucial for optimizing their use as therapeutic tools. Additionally, the long-term safety of exosome-based therapies in diabetes remains unclear. While exosomes are generally considered biocompatible, concerns about their potential for triggering immune responses, causing off-target effects, or inducing tumorigenesis over extended periods need further investigation.[95] Comprehensive studies on the long-term effects and safety profiles of exosome therapies are essential before they can be widely adopted in clinical practice.

CONCLUSION

Exosomes have emerged as key players in cellular communication, offering significant therapeutic promise in the management of diabetes. These nanoscale vesicles, secreted by various cell types, facilitate the transfer of bioactive molecules such as proteins, lipids, and microRNAs, influencing critical biological processes like immune modulation, insulin resistance, and β-cell function. In both type 1 and type 2 diabetes, exosomes have demonstrated their potential in mediating intercellular communication, contributing to disease pathogenesis, and offering new avenues for diagnostics and targeted therapies. Notably,

exosome-based drug delivery, regenerative medicine using mesenchymal stem cell-derived exosomes, and immune modulation in autoimmune diabetes present exciting strategies for improving patient outcomes.

Despite these advancements, challenges remain in terms of technical, biological, and regulatory hurdles, as well as concerns over the heterogeneity and long-term safety of exosome therapies. To fully realize the potential of exosomes in diabetes treatment, interdisciplinary collaboration is crucial. Bridging the gaps between basic research, nanotechnology, clinical applications, and regulatory frameworks will accelerate the translation of exosome-based therapies from the laboratory to the clinic. By fostering collaboration among biologists, chemists, engineers, and clinicians, we can address these challenges and unlock the full therapeutic potential of exosomes in diabetes care.

List of abbreviations

EVs: Extracellular vehicles

MVBs: multivesicular bodies

ESCRT: Endosomal Sorting Complex Required for Transport

PS: Phosphatidylserine

SLE: Systemic Lupus Erythematosus

ILVs: Intraluminal Vesicles

TGN: Trans-Golgi Network

ER: Endoplasmic Reticulum

HSP: Heat Shock Proteins

T2DM: Type 2 Diabetes Mellitus

T1 DM: Type 1 Diabetes

GAD: Glutamic Acid Decarboxylase

APCs: antigen-presenting cells

MHC: major histocompatibility complex

TNF-α : Tumour Necrosis Factor-α

IL-1β : Interleukin-1β

GLP-1: glucagon-like peptide-1

AI: artificial intelligence

DECLARATIONS

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

No datasets were generated or analysed during the current study.

Competing interests / Conflict of Interest

The authors declare that they have no competing interests.

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Authors Contributions

All authors have reviewed and approved the final manuscript.

1. Surabhi KS contributed to the conceptualisation and writing of the review.

2. Pinki Verma was responsible for drafting and making significant revisions to the manuscript, providing guidance, and conducting thorough proofreading to ensure the quality of the work.

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Author Information

Department of Pharmacology, Aditya Bangalore Institute of Pharmacy Education & Research, Rajiv Gandhi University of Health Sciences, Yelahanka, Bengaluru.

Corresponding Author

Pinki Verma.

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