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Narrative Review

Eukaryotic Cellular Products as Therapeutic Agents for Gram-Negative Bacterial Wound Infections

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Abstract

Wound infections by Gram-negative bacteria are a significant challenge for medical trials, in part because of antibiotic resistance and robust immune evasion mechanisms. Such infections often cause extended hospitalizations, increased healthcare costs, and high morbidity and mortality rates. Biofilms and endotoxins from Gram-negative bacteria, contributing to chronic inflammation and delayed wound healing, further complicate their management. Most conventional therapeutic approaches, including broad-spectrum antibiotics and wound debridement, are often inadequate and thus represent a critical demand for novel and effective strategies. Eukaryotic extracellular vesicles (EVs), involving microvesicles and exosomes, have emerged as promising therapeutic tools because of their natural biocompatibility and multifunctional properties. EVs play a pivotal role in wound healing through mechanisms such as immune modulation, promotion of angiogenesis and tissue regeneration, antimicrobial action, and the activation of paracrine signaling pathways. EVs offer a holistic approach to infections and tissue repair by delivering bioactive molecules such as cytokines, growth factors, miRNAs, and antimicrobial peptides. Their potential to disrupt bacterial biofilms, neutralize endotoxins, and stimulate regenerative processes positions them as transformative agents in addressing Gram-negative bacterial infections. This mini-review, therefore, discusses the therapeutic mechanisms and clinical implications of eukaryotic EVs in wound healing, with their promise to revolutionize infection management by reducing dependence on antibiotics.

Keywords: Eukaryotic, Gram-negative bacteria, Wound Infections

Introduction

Gram-negative bacterial infections are the most difficult to manage in chronic and acute wound care because they resist standard therapies and cause tissue injury. They are multi-layered pathogens with potent mechanisms of resistance to antibiotics that are often associated with delayed wound healing, morbidity, and healthcare expenses. Infections from bacteria like *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae* especially concern antibiotic survival and the possibility of creating biofilms, complicating therapeutic outcomes.[1,2] The conventional treatments - which mostly involve systemic or topical antibiotics, debridement, and antiseptics - are very restricted. Antibiotics, though typically promising in the short run, become more and more subject to the dangers of multidrug resistance (MDR). What's more, wound debridement is intrusive and doesn't often remove sub-underlying microbial problems (such as biofilm-based infections).[3] These limitations make the demand for novel therapeutic interventions to meet both the issue of infection control and tissue regeneration even more pressing. Traditional approaches to managing such infections- mainly relying on systemic or topical antibiotics, wound debridement, and antiseptics- have prominent limitations. Antibiotic therapies, while often effective in the short term, face the growing challenge of multidrug resistance (MDR), which diminishes their efficacy. Moreover, wound debridement is invasive and may not fully address underlying microbial challenges, particularly in biofilm-associated infections.[3] These constraints accentuate the need for innovative therapeutic strategies that can address the dual challenges of infection control and tissue regeneration.

Recent biotechnological developments have raised the possibility of eukaryotic cellular products as therapeutics, and extracellular vesicles (EVs) are one

candidate on the cusp. These nanoscale structures – which eukaryotic cells naturally release – facilitate intracellular communication and contain active molecules such as proteins, lipids, and nucleic acids. These EVs from stem cells, immune cells and other eukaryotic sources are antimicrobial, immune modulating and tissue repair-inducing, which make them a viable, novel replacement for traditional wound therapy.[4,5] Here, we seek to learn about the potential therapeutic use of eukaryotic cell products (most recently, extracellular vesicles) in wound healing from Gram-negative bacteria. In reviewing recent findings, we try to show their antimicrobial potential, regenerative properties and possible clinical applications as well as areas of need and potential research.

Characteristics of Eukaryotic EVs

Eukaryotic extracellular vesicles (EVs) are small, membrane-bound particles released by cells into the extracellular environment. These vesicles play key roles in intercellular communication, immune modulation, and tissue repair (Figure 1).

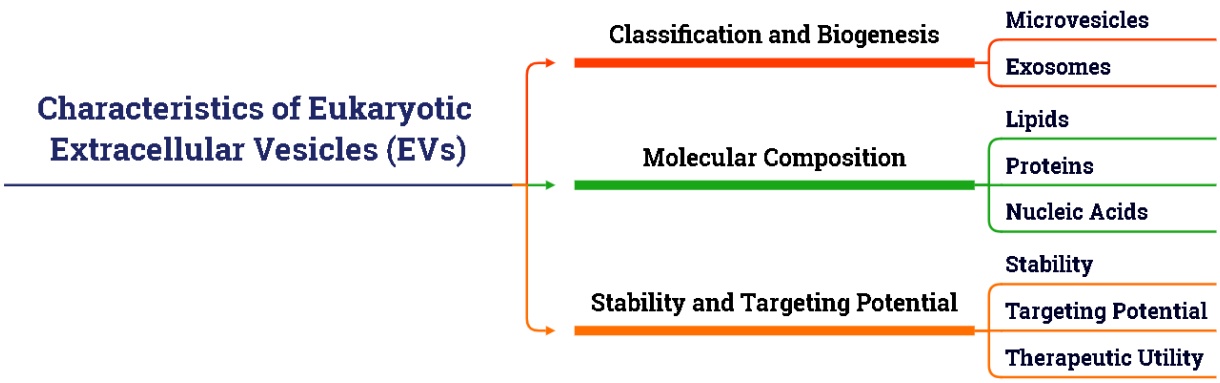

Figure 1. Overview of the Characteristics of Eukaryotic Extracellular Vesicles (EVs), Including their Classification, Molecular Composition, and Potential Applications.

Classification and Biogenesis

EVs are lipid bilayer-bound structures secreted by eukaryotic cells that play a central role in intercellular communication. Based on their size and biogenesis, they are broadly classified into two main types: microvesicles and exosomes. Microvesicles, typically ranging from 100 to 1000 nm in size, are formed by direct budding of the plasma membrane. This process involves cytoskeletal rearrangements and the outward budding of membrane regions, often influenced by cellular signaling pathways and stress conditions.[6] Exosomes are smaller vesicles ranging from 30 to 150 nm in diameter and originate from the endosomal system. Their biogenesis involves the inward budding of the endosomal membrane, resulting in the construction of multivesicular bodies (MVBs). The MVBs fusion with the plasma membrane leads to the release of exosomes out to the extracellular environment. This distinct mode of generation allows exosomes to carry specific cargo reflective of their cellular origin and function, making them highly specialized mediators of cellular signaling.[7]

Molecular Composition

What makes EVs unique is the molecular nature of how they talk to each other and what they can do to heal us. They carry a wide variety of lipids, proteins, and nucleic acids, including mRNAs and miRNAs. The membranes of EVs contain lipids that not only give them structure but also help them communicate with their targets. Proteins within EVs include those responsible for cargo sorting, membrane trafficking, and cell signaling, including tetraspanins, heat shock proteins, and integrins.[6] By controlling gene expression in the target cell, nucleic acids (in particular miRNAs and mRNAs) regulate biological functions. These molecules are packaged carefully into EVs to ensure that their cargo reflects the physiology of the host cell. Collectively, the molecular nature of EVs allows them to act as mediators of immune control, tissue repair, and antimicrobial activity – they are potent therapeutic agents.[8]

Stability and Targeting Potential

The primary strength of eukaryotic EVs is that they

remain intrinsically stable in biological systems. Their lipid bilayer lining protects encapsulated cargo against enzymatic degradation and body circulation.[9] This stability is essential for their therapeutic utility, especially in hostile environments like infections. Furthermore, EVs have innate targeting abilities via surface molecules like integrins, tetraspanins, and adhesion molecules. These molecules allow EVs to reach particular cells and tissues, sending their cargo to the places of action they are designed to perform. In wound healing, this targeting capability can bring bioactive molecules to the site of the wound for their antimicrobial, anti-inflammatory, and regenerative effects.[10] This stability and tuning are the reasons for the increasing need for EVs as potential wound-healing agents.

Pathophysiology of Gram-Negative Bacterial Wound Infections

Gram-negative bacteria are a major cause of wound infections because of their distinctive molecular structure, ability to avoid immune detection, and resistance to antimicrobial treatment. Among the most common Gram-negative bacteria responsible for chronic and acute wounds are *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae*. Their infections are associated with poor clinical results, such as chronic inflammation, slow healing, and vulnerability to systemic complications (Figure 2).[1]

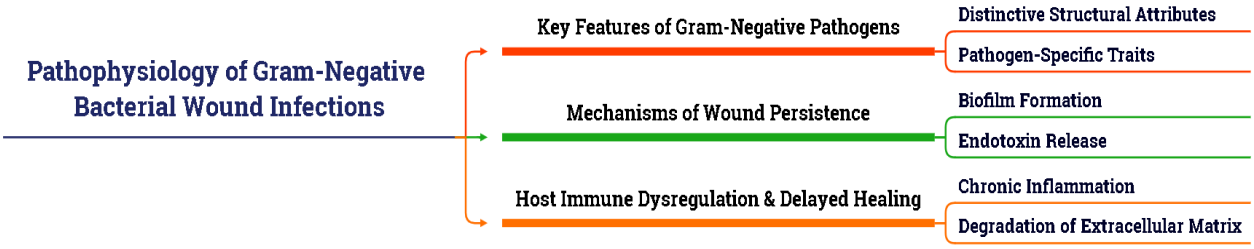

Figure 2. Overview of the Pathophysiology of Gram-Negative Bacterial Wound Infections. Key features of Gram-negative pathogens include distinctive structural attributes and pathogen-specific traits. Mechanisms of wound persistence are characterized by biofilm formation and endotoxin release, which contribute to infection resilience. Additionally, host immune dysregulation and delayed healing are driven by chronic inflammation and the degradation of the extracellular matrix, further complicating wound resolution.

Key Features of Gram-Negative Pathogens

Gram-negative bacteria possess a distinctive double-membrane cell envelope with an outer membrane rich in lipopolysaccharides (LPS). This structure provides inherent resistance to many antibiotics and antiseptics while enhancing the bacteria's capacity to adhere to and invade host tissues. Each of these pathogens has specific traits that exacerbate wound infections. For example, *P. aeruginosa* is very versatile and produces different kinds of virulence factors like elastases and exotoxins, which degenerate host tissues and impair immune responses. *E. coli* is well-documented for its rapid wound colonization and ability to form biofilms, whereas *K. pneumoniae* has been very effective in developing multi-drug resistance, which creates difficulties in managing the infection.[11]

Mechanisms of Wound Persistence

One of the most common ways Gram-negative bacteria keep themselves alive in a wound is through biofilms. Biofilms are polymathic, multicellular communities that tangle together in an extracellular polymer matrix made from themselves that adheres to wound surfaces. This architecture guards bacteria from antibiotics and attacks by immune cells and makes it easy to infect over time. Among bacteria in biofilms, the message goes through quorum sensing, making virulence factors and resistance genes more coordinated.[12]

The other primary mechanism that aids wound repair is endotoxins, in particular LPS, which spill out from the surface of Gram-negative bacteria. LPS produces powerful pro-inflammatory effects via Toll-like receptor 4 (TLR4) signaling pathways in host cells. Although this is supposed to limit infection, overexposure to LPS causes tissue damage, immune dysfunction, and delayed wound healing.[13]

Host Immune Dysregulation and Delayed Healing

Infections by Gram-negative bacteria often disrupt the balance of the host's immune response. Persistent activation of immune cells by bacterial components like LPS leads to chronic inflammation, which impairs

the wound-healing process. Besides, Gram-negative bacterial virulence factors, such as proteases and toxins, degrade extracellular matrix components, further impeding tissue repair. Biofilm-mediated immune evasion and excessive inflammatory responses together make a microenvironment unfavorable for wound closure and regeneration.[14]

Importance of Innovative Solutions for Treating Antibiotic-Resistant Strains

The rise of antibiotic-resistant Gram-negative strains, such as carbapenem-resistant *K. pneumoniae* and multidrug-resistant *P. aeruginosa*, has rendered traditional treatment strategies increasingly ineffective. These pathogens exploit their structural and genetic adaptations to survive in the presence of even the most potent antibiotics, highlighting the urgent need for innovative therapeutic solutions. Novel approaches in the use of EVs derived from eukaryotic cells are thus highly promising alternatives, which effectively exploit their immune-modulating, biofilm-disruptive, and tissue regenerative properties.[15,16] Such innovative strategies will be important in addressing the pathophysiology of Gram-negative wound infection, improving clinical outcomes, and reducing the global burden of these challenging infections.

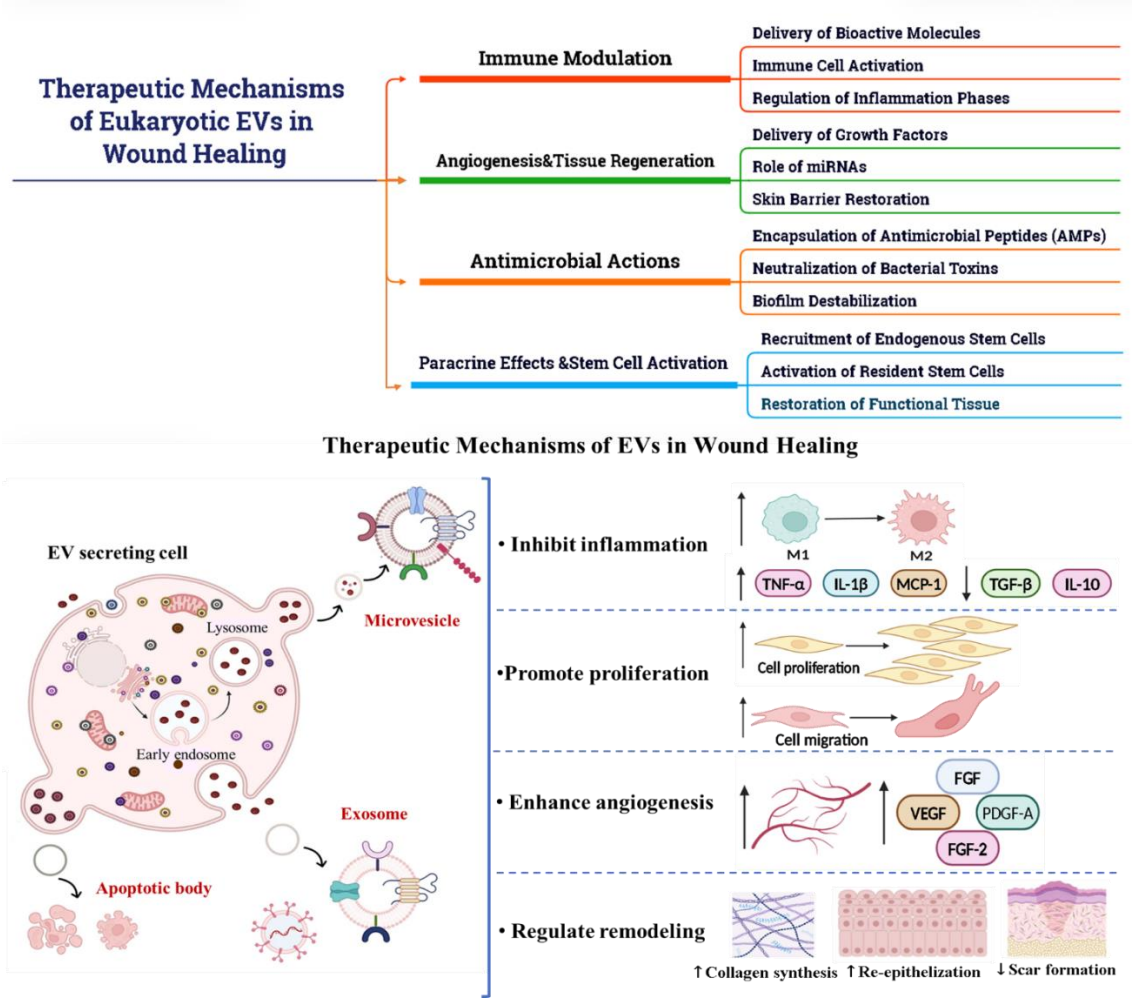

Figure 3. Illustration of Extracellular Vesicle (EV) Subtypes and their Functional Roles in Intercellular Communication. EV-secreting cells release three main types of vesicles: microvesicles, exosomes, and apoptotic bodies. These EVs regulate immune responses by modulating macrophage polarization (M1 to M2), influencing cell proliferation, promoting fibroblast migration and differentiation, enhancing angiogenesis through factors like VEGF, FGF, and PDGF-A, and contributing to tissue regeneration and repair by affecting extracellular matrix remodeling and epithelial restoration.

Therapeutic Mechanisms of Eukaryotic EVs in Wound Healing

Eukaryotic EVs have emerged as powerful therapeutic agents for wound healing, particularly in addressing challenges posed by Gram-negative bacterial infections. These nanoscale vesicles facilitate wound repair

through multifaceted mechanisms, including immune modulation, promotion of angiogenesis and tissue regeneration, antimicrobial activity, and activation of paracrine signaling pathways. The inherent bioactivity of EVs makes them innovative tools for combating infection and fostering tissue repair and regeneration[17] (Figure 3).

Immune Modulation

Modulating immune responses is a critical function of eukaryotic EVs during wound healing. By delivering bioactive molecules such as anti-inflammatory cytokines (e.g., IL-10 and TGF-β), EVs help to attenuate excessive inflammation, which is a hallmark of Gram-negative bacterial infections. This controlled immunosuppression prevents tissue damage caused by prolonged inflammation.[18] Moreover, EVs activate immune cells such as macrophages and neutrophils, which play a dual role in clearing bacterial infections and triggering the wound repair process. Notably, EVs modulate the balance between pro-inflammatory and anti-inflammatory responses, promoting the shift from the inflammatory phase toward the proliferative phase of healing. This regulation diminishes the risk of chronic inflammation and prevents wound stasis.[19]

Angiogenesis and Tissue Regeneration

Eukaryotic EVs significantly contribute to angiogenesis and tissue regeneration through the delivery of growth factors such as VEGF, FGF, and TGF-β. These factors are very important in neoangiogenesis, supplying oxygen and nutrients to the healing wound.[19,20] EVs further enhance the regenerative processes with their miRNA content. For example, miR-21 and miR-126 promote fibroblast activation, extracellular matrix remodeling, and epithelialization, thus collectively accelerating wound closure. These miRNAs influence the proliferation and migration of keratinocytes, which are important steps in the restoration of the skin barrier.[21,22]

Antimicrobial Actions

The intrinsic antimicrobial properties of EVs make them particularly valuable for Gram-negative bacterial infections. They can encapsulate and deliver antimicrobial peptides (AMPs), such as defensins and cathelicidins, which directly target and disrupt bacterial membranes. This targeted delivery minimizes off-target effects and ensures efficient bacterial clearance at the wound site.[23] Besides, EVs are known to neutralize bacterial toxins, such as LPS, mitigating immune overactivation and subsequent tissue damage. Moreover, there has been documentation of the potential role of EVs in destabilizing biofilms, one of the major determinants of chronic wound infection. They may destabilize biofilms by influencing quorum sensing or degrading extracellular polymeric substances; in both ways, they enhance the efficacy of antimicrobial interventions.[24]

Paracrine Effects and Stem Cell Activation

EVs, through paracrine signaling, recruit endogenous stem cells to the wound site and promote their differentiation into major cell types involved in tissue repair, such as keratinocytes and fibroblasts. This approach accelerates the regenerative process and improves the structural integrity of the healed tissue.[25]

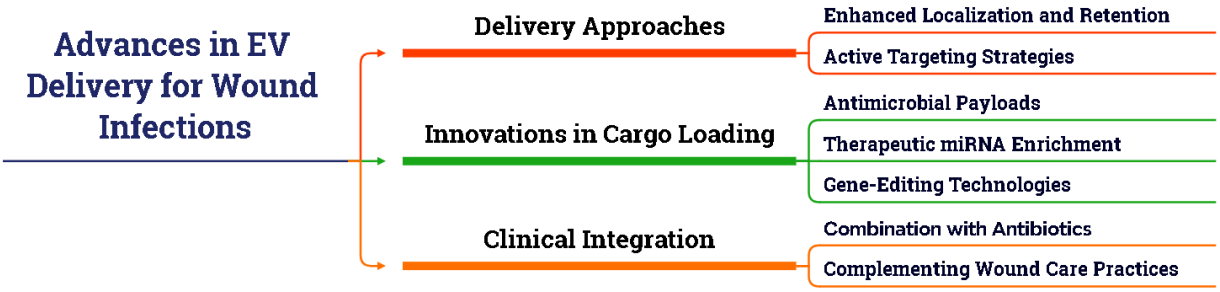

Figure 4. Overview of the Advances in EV Delivery for Wound Infections, including their Delivery Approach, Innovations in Cargo Loading, and Clinical Integration.

Additionally, EVs can activate resident stem cells by delivering specific miRNAs, proteins, and lipids that signal cellular proliferation and differentiation. These paracrine effects are pivotal in restoring functional tissue architecture and achieving complete wound healing.[26]

Advances in EV Delivery for Wound Infections

Recent advances in the delivery of EVs have considerably augmented their therapeutic potential against wound infections, especially those caused by Gram-negative bacteria. Innovation in delivery systems, cargo engineering, and clinical integration has made EV-based therapies more effective and applicable in the real world to solve key challenges in wound management (Figure 4).[27]

Delivery Approaches

Advanced strategies developed so far have improved methods for better localization and longer retention of EVs at the wound site, thereby maintaining their therapeutic activity. Incorporated EVs in wound dressings or hydrogels represent a particularly attractive approach. These materials work like a reservoir that permits a gradual release of EVs into the wound environment. Hydrogels are biocompatible and moisture -retentive, so they provide an ideal matrix for enhancing EV stability and prolonging their bioavailability.[28] In addition to passive delivery, active targeting strategies have emerged. Engineering EVs with surface ligands that bind specifically to infected tissues or bacterial biofilms enables targeted delivery of their cargo. For example, the functionalization of EVs with antibodies or peptides recognizing bacterial surface markers or inflammation-specific receptors ensures precision in targeting to maximize therapeutic efficacy while limiting off-target effects.[29]

Innovations in Cargo Loading

Enhancing the therapeutic payload of EVs has been one focus in the development of their utility in wound infections. One approach is loading exosomes with antimicrobial agents, like peptides or small molecules, to fight bacterial pathogens. Alternatively, EVs are enriched with therapeutic miRNAs that modulate the host immune response or those that favor tissue repair. For example, miRNAs targeting bacterial survival pathways or those upregulating the functions of fibroblasts and keratinocytes could be loaded into EVs to achieve antibacterial effects with simultaneous regeneration.[30] Emerging technologies such as CRISPR-Cas9 have expanded the scope of EV cargo engineering further. Encapsulating gene-editing tools in EVs can perform tasks like silencing bacterial resistance genes or modifying host cells to increase their antimicrobial defenses.[31] Thus, a new concept in the therapy of antibiotic-resistant Gram-negative infections was born, one that also promotes wound healing.

Clinical Integration

The EV-based therapies integration into current clinical practices can revolutionize wound management. One promising avenue lies in using EVs along with antibiotics to overcome resistance mechanisms. EVs could enhance drug penetration and the effectiveness of antibiotics by either disrupting biofilms or delivering antimicrobial peptides directly into bacterial colonies; this could also reduce antibiotic dosages and side effects.[32] Combination therapies are another area of focus. EVs can complement traditional wound care practices, such as debridement and advanced dressings, to provide a multifaceted approach in the control of infection and tissue regeneration. For example, the combination of EV-loaded hydrogels with mechanical debridement can optimize bacterial clearance while simultaneously accelerating the healing process.[33,34]

Clinical Implications and Challenges

The clinical translational impact of EVs in the management of wounds due to Gram-negative bacterial infection is huge. However, there are some critical issues concerning scalability, standardization, and bioengineering issues that remain challenges to taking the promotion into clinical practice.[35]

Potential Applications

EVs are promising in several clinical uses for gram-negative bacterial infections. The most relevant uses for such clinical scenarios are the treatment of diabetic wounds and burns, whose complications nowadays result mainly from infection with these multidrug-resistant pathogenic forms, such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. EVs' dual capacity to combat bacterial infections and promote tissue regeneration makes them particularly suitable for these conditions, where traditional treatments often fail.[36] Beyond therapy, EVs are even a tool in diagnosis. Indeed, the cargo composition of EVs reflects the cell of origin and physiological status of the wound and thus provides information about the infection's seriousness and follow-up. For example, the detection of specific miRNAs or proteins in EVs may

indicate noninvasive biomarkers to follow up on therapy and improve patient treatment.[37]

Current Challenges and Future Directions

Despite their promise, several challenges must be overcome to ensure the successful clinical translation of EV-based therapies.

1. Scaling up EV Production: Large-scale production for clinical use of EVs remains a bottleneck. Isolation methods used, like ultracentrifugation and size-exclusion chromatography, are labor-intensive and low-yielding. In this respect, the development of scalable, high-yield production systems is required either through the use of bioreactor-based culture systems or through the use of engineered cell lines.[38,39]
2. Cost-Effectiveness and Reproducibility: The high cost of isolation and purification of EVs is an important obstacle to widening their use. Besides, batch-to-batch variability of the manufactured EVs may affect their therapeutic effects. Such issues can only be resolved by innovating cost-effective and reproducible manufacturing processes.[40]
3. Standardizing EV Characterization and Regulatory Approval: EVs' high complexity and heterogeneity complicate their characterization and further regulatory approval. Common standards have to be elaborated to define EV properties, such as size, cargo composition, and bioactivity. Regulatory guidelines tailored for EV-based therapies will have to balance innovative aspects with safety and efficacy requirements.[41]
4. Bioengineering for Specificity and Multifunctionality: Bioengineering can enhance EV specificity and functionality. Engineering EVs to display targeting ligands or carry customized therapeutic cargoes will be important to enhance their precision in the treating infected wounds. This is a very exciting field where the generation of multifunctional EVs can target both infection and tissue repair concomitantly.[42,43]
5. Exploring Therapies for Multidrug-Resistant Infections: The dissemination of multiresistant Gram-negative bacteria urges the need for alternative therapeutic options. Since EV-based therapies disrupt biofilms, neutralize bacterial toxins, and deliver antimicrobial agents, they could be of paramount importance in coping with such difficult-to-treat infections.[44]

There are few studies underscore the diverse origins and mechanisms by which eukaryotic EVs can exert antimicrobial effects against Gram-negative bacteria, offering promising avenues for novel therapeutic strategies (Table 1).

Future Perspectives

The future of EV research and applications has immense potential, especially with its prospects regarding wound management and antimicrobial resistance.[56] Integrating recent developments in EV technologies with a trend toward more personalized and integrative medicine, therapeutic approaches for infections by Gram-negative bacteria will likely shift.

Advancements in EV Isolation and Engineering for Therapeutic Scalability

Scalable therapy remains one of the most important to be achieved with EV-based therapies. Innovations in the area of isolation technologies, namely microfluidics, tangential flow filtration, and affinity-based capture systems, are foreseen to improve yield and purity while reducing production costs.[57] These will enable large-scale manufacturing that facilitates wide clinical applicability of EV therapies. Meanwhile, bioengineering approaches may broaden the EVs' versatility. Instantly, genetic and chemical modifications can increase the efficiency of cargo loading and targeting specificity and improve stability in biological environments.[58] Engineered EVs could also be designed to carry tailor-made therapeutic payloads, such as specific miRNAs or antimicrobial agents, for highly targeted and effective treatment against Gram-negative bacterial infections.[59]

Integration of EV-Based Therapies into Personalized Medicine Approaches

Integration of EV therapies into personalized medicine, therefore, ensures its research in the future. These natural carriers of biomolecular cargo can be engineered to meet the particular pathophysiological conditions of every patient. For example, profiling the molecular composition of EVs derived from patient-specific cells could guide their therapeutic use, ensuring compatibility and efficacy. Because of the diagnostic potentiality of EVs, real-time monitoring of the course of infection development and dynamics of the wound-healing process is enabled. The personalized

Table 1. Studies Underscore Eukaryotic EVs Can Exert Antimicrobial Effects Against Gram-Negative Bacteria

	Source of EVs	Target G- Bacteria	Key Findings	Year	Ref.
1	Hepatocellular carcinoma cells (HepG2)	*E. coli*	Developed multifunctional therapeutic agent for bacterial sepsis control. Enhanced antibacterial activity and biocompatibility of coated extracellular vesicles.	2024	45
2	Nasal mucosa–exosomes (NMDEs)	*P. aeruginosa*	LPS exposure increases NMDE secretion and antimicrobial activity. Exosomes enhance nitric oxide production in epithelial cells.	2019	46
3	Dental follicle cells	*Porphyromonas gingivalis*	D-sEV inhibit *P. gingivalis* growth and biofilm formation. Reduced pathogenicity and inflammation in experimental periodontitis model.	2022	47
4	Human B-lymphoid cells	*Shigella flexneri*	Vesicles loaded with ciprofloxacin showed lower toxicity in zebrafish larvae. Effective against enteropathogenic Shigella with increasing antibiotic resistance.	2023	48
5	Human macrophages	*Salmonella Typhimurium*	*Salmonella Typhimurium* induces ER stress in macrophages. Extracellular vesicles sequester iron, inhibiting bacterial growth.	2023	49
6	Vascular endothelial cells	*Rickettsia parkeri*	Rickettsial infection increases release of endothelial exosomes. Exosomes induce dysfunction in brain microvascular endothelial cells.	2021	50
7	Human Mesenchymal Stem Cells (MSCs)	*Vibrio cholerae*	Human mesenchymal stem cells secretome inhibits *Vibrio cholerae* growth. Effective against biofilm formation by *Vibrio cholerae*.	2020	51
8	Adipose-Derived MSCs	*E. coli* and *Klebsiella pneumoniae*	ASC-derived exosomes improved bacterial clearance and reduced alveolar permeability.	2022	52
9	Neutrophils	*E. coli*	LL-37 enhances ectosome levels and reduces bacterial load. Ectosomes from LL-37 improve survival in septic mice.	2020	53
10	Human Mesenchymal Stem Cells (MSCs)	*E. coli*	MSC EVs enhance antimicrobial activity in bacterial pneumonia by transferring miR-145 to target cells, which suppresses MRP1 activity.	2019	54
11	Rat Mesenchymal Stem Cells (MSCs)	*E. coli*	While MSC-EVs lack direct antibacterial effects, they confer neuroprotective benefits through anti-apoptotic, anti-gliosis, and anti-inflammatory mechanisms	2022	55

formulation of EVs can adapt the treatment strategy, in accordance with biomarker analyses, to the dynamic needs of the wound environment for the best outcome with minimal detrimental effects.[56,60]

Potential for EVs to Reduce Reliance on Traditional Antibiotics

An increase in multidrug-resistant Gram-negative bacteria underlines the need for the identification of antibiotic alternatives. EV-based therapies may lower reliance on conventional antibiotics by utilizing their antimicrobial, anti-inflammation, and regenerative potential. EVs might serve as vehicles delivering either antimicrobial peptides or disrupting biofilms via natural or engineered modes of action that do not contribute to the rise of resistant bacterial infections.[61] The combination of EVs with lower doses of antibiotics will further enhance therapeutic efficacy due to the reduced selection pressure driving towards resistance. This will be in congruence with global efforts to preserve antibiotic efficacy and combat the emerging challenge of antimicrobial resistance.[62]

Conclusion

Eukaryotic EVs are being reported as multi-functional and potent tools in wound healing and infection management. Their unique ability to modulate the immune response, promote tissue regeneration, and specifically deliver antimicrobial therapies justifies their prime potential in the management of wounds complicated with Gram-negative bacterial infections. EVs indeed address all critical challenges in wound care, such as disrupting biofilm, regulating the immune response, and promoting epithelialization, hence providing a multi-approach profile toward both acute and chronic infections.[18] EVs are a novel class of therapeutic agents with the potential to revolutionize current treatments of Gram-negative bacterial infections, particularly those by multidrug-resistant pathogens. Their ability to synergize with existing therapies and reduce the use of antibiotics makes them an important intervention in modernizing wound care and preventing AMR.[32,59] Continuous research and development efforts could not translate most of these promising preclinical study outcomes into clinical use. Many challenges are

to be met in scalable production, cost-effectiveness, regulatory approval, and therapeutic standardization before EV-based therapies realize their full potential. Rigorous clinical trials will be needed to establish safety, efficacy, and practicality in various patient populations.[58,63]

In conclusion, eukaryotic EVs represent a paradigm shift in the treatment of wounds and infections and a new frontier in attaining better results in recalcitrant and resistant Gram-negative bacterial infections. More innovation and collaboration will be needed to ensure that preclinical insight is translated into accessible, effective, and impactful therapies that can be delivered to the world.

Conflict of Interest

The authors declare no conflicts of interest.

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