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REVIEW

Unveiling the Pathological Landscape of Intrauterine Adhesion: Mechanistic Insights and Exosome-Biomaterial Therapeutic Innovations

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Abstract: Intrauterine adhesion (IUA) is a fibrotic disorder caused by endometrial injury, characterized by structural damage and functional impairment of the endometrium, which severely impacts female reproductive health. The core pathology of IUA revolves around aberrant fibrosis, driven by intricate interactions among inflammation, epithelial-mesenchymal transition (EMT), and dysregulated cellular processes such as autophagy and ferroptosis. Inflammation acts as a pivotal initiator, directly activating fibrotic pathways or inducing EMT, thereby exacerbating fibrosis. Recent studies highlight the dual roles of autophagy and ferroptosis in IUA progression, where their dysregulation either mitigates or aggravates fibrotic outcomes, underscoring the complexity of its pathogenesis. Current treatments, such as transcervical resection of adhesions (TCRA), offer short-term anatomical restoration but fail to address high recurrence rates and insufficient endometrial regeneration. Exosomes have emerged as a promising cell-free therapeutic strategy, leveraging their bioactive cargo to modulate fibrosis, inflammation, and EMT. However, research on exosome-based therapies for IUA remains limited, particularly in targeting autophagy, ferroptosis, and their integration with biomaterials. Biomaterial-assisted exosome delivery systems, such as hydrogels and scaffolds, enhance therapeutic efficacy by enabling sustained release and localized action. Despite preclinical progress, clinical translation faces challenges, including standardized protocols and long-term safety validation. This review synthesizes the pathological mechanisms of IUA, explores the therapeutic potential of exosomes and biomaterials, and discusses future directions to bridge the gap between mechanistic insights, therapeutic strategy development and clinical applications.

Keywords: intrauterine adhesion, pathological mechanism, exosomes, biomaterials

Introduction

Intrauterine adhesion (IUA) is a pathological condition characterized by abnormal fibrosis of the endometrium caused by tissue damage, resulting in uterine structural disruption, menstrual abnormalities, infertility, and recurrent pregnancy loss.[1–3] This condition poses a significant threat to women's reproductive health and overall quality of life. The incidence of IUA significantly increases following uterine procedures, such as curettage or abortion, affecting approximately 19% to 45% of patients, with recurrent surgeries or infections further exacerbating the risk.[4,5] Severe IUA often leads to uterine cavity obliteration and loss of endometrial function, causing substantial impairments in fertility.[6] The complex pathological features and high recurrence rates of IUA represent significant challenges for both patients and healthcare systems.

Transcervical resection of adhesions (TCRA) is the current standard treatment for IUA. By mechanically separating intrauterine adhesions, TCRA can restore uterine anatomy and improve short-term reproductive outcomes.[7] However, its long-term efficacy is limited, particularly in severe cases, where recurrence rates can reach up to 62.5%.[1] Repeated

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surgical interventions may further damage the endometrium, exacerbate fibrosis, and hinder endometrial regeneration. Postoperative complications and increased risks of infection also undermine therapeutic outcomes and patient prognosis. These limitations underscore the urgent need for innovative regenerative strategies to address the complexity of IUA.

Advancements in regenerative medicine have offered new therapeutic prospects for IUA, particularly through the development of biomaterials and cell-based therapies. Biomaterials, such as hyaluronic acid gels and decellularized extracellular matrix scaffolds, have been utilized to improve the intrauterine microenvironment, prevent adhesion recurrence, and support cell proliferation.[8,9] However, their efficacy in promoting long-term endometrial regeneration remains limited. Meanwhile, stem cell-based therapies, especially mesenchymal stem cells (MSCs), have demonstrated significant potential in endometrial repair due to their multipotent differentiation capabilities and immunomodulatory functions. MSCs are particularly effective in anti-fibrosis and angiogenesis; however, challenges such as low post-transplant survival rates, poor engraftment efficiency, and potential tumorigenic risks hinder their widespread clinical application.[10,11]

In recent years, exosomes have emerged as a promising cell-free therapeutic tool for IUA treatment. Exosomes, small extracellular vesicles secreted by cells, carry various bioactive molecules, including proteins, microRNAs (miRNAs), and lipids, that modulate intercellular communication. These vesicles exert potent antifibrotic and tissue repair effects. Compared to stem cell-based therapies, exosomes offer higher safety profiles and operational ease, eliminating risks of tumorigenicity and immune rejection.[6,12,13] Additionally, combining exosomes with biomaterials, such as hyaluronic acid hydrogels and porous scaffolds, enables sustained release and targeted delivery, significantly prolonging local therapeutic effects and enhancing efficacy.[14–16] This exosome-biomaterial synergistic strategy has shown great promise in preventing adhesion recurrence and promoting endometrial regeneration, making it one of the most prospective approaches for IUA treatment.

Notably, exosomes have shown the capacity to target key pathological pathways involved in IUA, including fibrosis, inflammation, and epithelial-mesenchymal transition (EMT). However, current studies investigating exosome-based interventions in IUA remain sparse. The hallmark pathological alteration in IUA is endometrial fibrosis, with inflammation and EMT identified as two central mechanisms. Inflammation serves as a primary trigger, either directly activating fibrotic cascades or indirectly promoting fibrosis by inducing EMT. The interplay and mutual reinforcement among fibrosis, inflammation, and EMT form a complex pathological network underlying IUA progression. Emerging evidence further suggests that dysregulation of biological processes such as autophagy and ferroptosis also contributes to the development of IUA. Despite recent advances in mechanistic understanding, targeted therapeutic strategies leveraging exosomes are still underdeveloped and face considerable challenges in addressing the intricate pathophysiological environment of IUA. Moreover, the integration of exosomes with biomaterial-based systems for IUA therapy remains largely unexplored. To drive translational progress, several key challenges must be addressed, including the standardization of exosome isolation protocols, optimization of delivery systems, and robust clinical validation on a large scale.

This review provides a comprehensive summary of the pathological mechanisms of IUA, with a particular focus on fibrosis, immune dysregulation, and EMT (Figure 1). It underscores the limitations of conventional treatment modalities and highlights the latest advancements in regenerative medicine. Special attention is given to the multifunctional role of exosomes in reversing fibrosis and promoting endometrial regeneration, especially in the context of their combination with biomaterials (Figure 2). In addition, the review discusses the current progress in emerging mechanisms such as autophagy and ferroptosis, the insufficiency of targeted therapeutic development, and the gap in clinical translation—offering forward-looking insights into the next-generation therapies for IUA. Finally, we outline future research priorities, emphasizing the need for deeper mechanistic exploration, advanced delivery platform design, and rigorous clinical evaluation. With continued technological innovation and interdisciplinary collaboration, IUA treatment is expected to evolve toward more precise and effective regenerative solutions, ultimately delivering sustained therapeutic benefits and improved reproductive outcomes for affected patients.

Pathophysiological Mechanisms Underlying IUA

Central Pathological Feature: Tissue Fibrosis

Activation of Fibroblasts and Myofibroblast Transdifferentiation

The hallmark pathological feature of intrauterine adhesion (IUA) is endometrial fibrosis, primarily characterized by the aberrant deposition of extracellular matrix (ECM) components such as collagen. This fibrotic process is predominantly

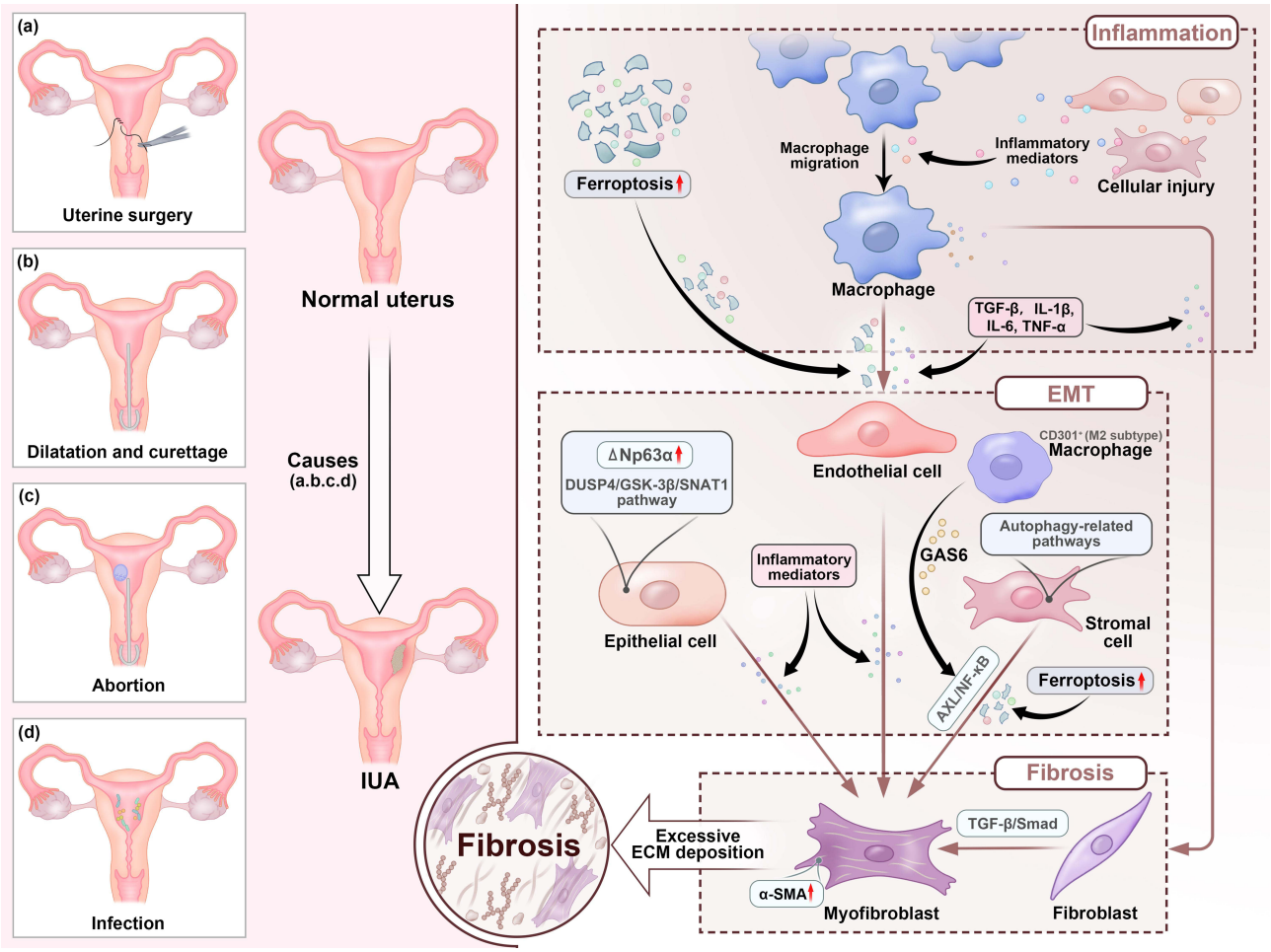

Figure 1 Causes, symptoms, and pathological mechanisms of IUA. Intrauterine adhesions (IUA) are fibrotic lesions caused by endometrial injury, characterized by endometrial tissue destruction and dysfunction. The core pathological feature of IUA is endometrial fibrosis, marked by abnormal deposition of extracellular matrix (ECM), such as collagen. The activation of fibroblasts into myofibroblasts serves as a pivotal step in this process. Additionally, endometrial epithelial cells, endothelial cells, stromal cells, and macrophages within the local microenvironment can also differentiate into fibroblasts under specific conditions. Autophagy, ferroptosis, and local inflammation play crucial roles in the activation of myofibroblasts.

driven by the excessive activation of fibroblasts and their transdifferentiation into myofibroblasts. Among the key regulatory mechanisms, the TGF-β/Smad signaling pathway plays a central role by inducing the differentiation of fibroblasts into highly secretory myofibroblasts. These cells produce large amounts of type I collagen and fibronectin, thereby disrupting the normal architecture of the endometrium, reducing uterine elasticity, and ultimately impairing fertility.[6,17,18] In addition, macrophage-derived growth arrest-specific 6 (GAS6) protein has been shown to promote stromal cell transdifferentiation through activation of the GAS6/AXL/NF-κB signaling axis.[19,20] Within the fibrotic microenvironment, endometrial stromal cells also exhibit elevated expression of α-smooth muscle actin (α-SMA), further enhancing type I collagen accumulation and contributing to increased tissue stiffness.[21–23]

Impaired Autophagy in Fibrosis Progression

Autophagy, a highly conserved intracellular degradation and recycling mechanism, plays a crucial role in maintaining cellular homeostasis by degrading damaged organelles, misfolded proteins, and other biomolecules via lysosomal pathways.[24] Under normal conditions, autophagy is essential for cell survival and function. However, its role in fibrosis is context-dependent, as it can either suppress or exacerbate fibrotic processes depending on the pathological conditions. Moderate autophagic activity facilitates the clearance of pro-fibrotic mediators, such as oxidative stress products and senescent cells, thereby mitigating fibrosis.[25] Conversely, dysregulated autophagy, whether impaired or excessively activated, disrupts this balance and contributes to pathological progression.

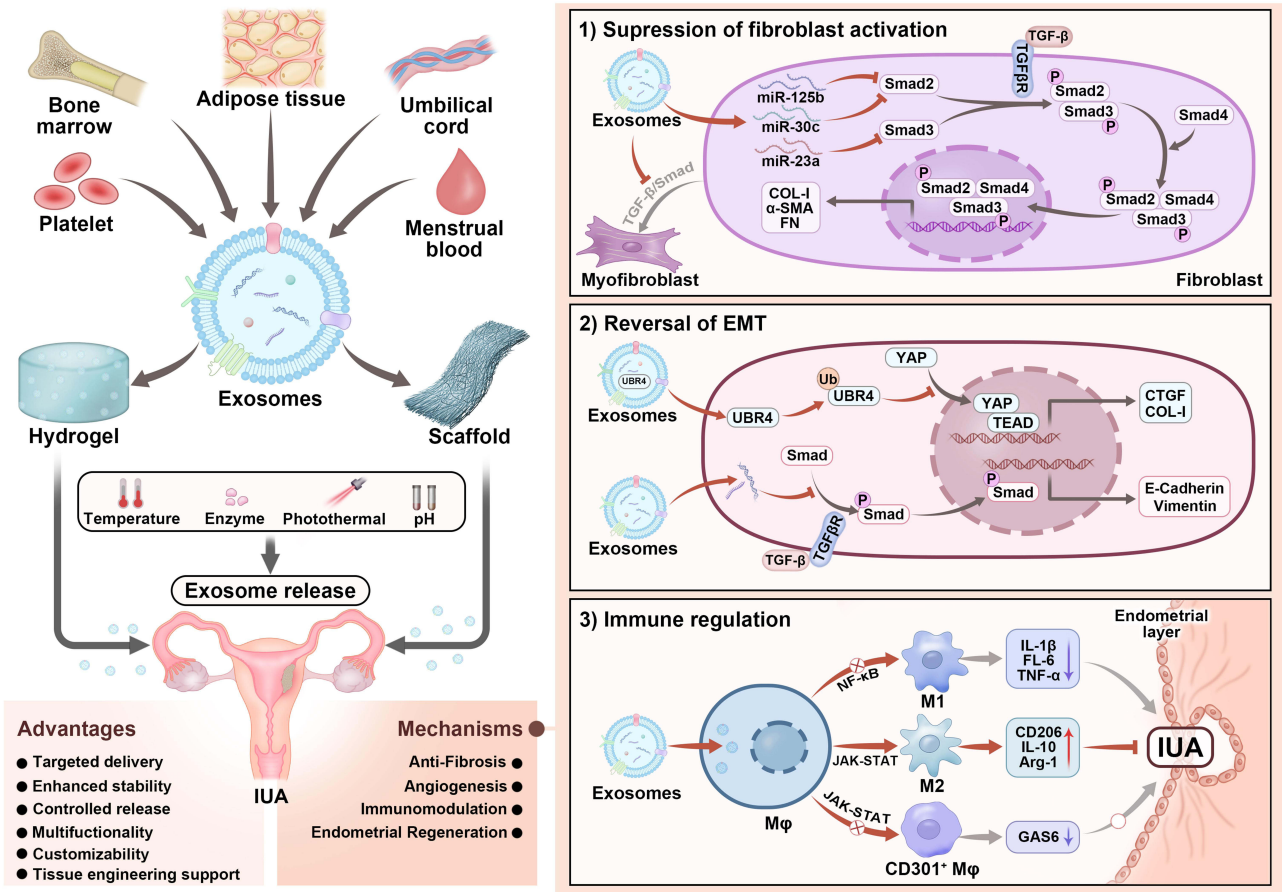

Figure 2 Sources of exosomes, mechanisms for treating IUA, and advantages of combining exosomes with biomaterials. The primary mechanisms by which exosomes treat IUA include: inhibiting fibroblast activation into myofibroblasts; suppressing EMT; and modulating the local immune microenvironment of the endometrium. Furthermore, the combination of exosomes with biomaterials offers enhanced therapeutic efficacy.

In the context of IUA, studies have shown that autophagy levels are significantly reduced in endometrial tissues, leading to abnormal ECM accumulation and exacerbation of fibrosis.[26,27] On the other hand, excessive autophagy may induce premature cell death, further impairing endometrial regeneration and exacerbating pathological damage.[26] Autophagy dysregulation in IUA is mediated through several key signaling pathways. The WNT/β-catenin signaling pathway, a well-known driver of fibrotic processes, becomes hyperactive when autophagy is impaired, leading to upregulation of fibrotic markers such as α-SMA and type I collagen.[28,29] The loss of DKK1, a WNT signaling inhibitor, further reduces autophagic activity, driving stromal cells to differentiate into myofibroblasts and promoting ECM accumulation.[26] Similarly, the PI3K/AKT/mTOR pathway, a negative regulator of autophagy, is persistently activated in IUA, suppressing autophagosome formation and impairing the cell's ability to clear damaged components.[27] This hyperactivation not only inhibits autophagy but also exacerbates cell adhesion loss and matrix stiffness.[27,30] Additionally, the Sonic Hedgehog (SHH) pathway, when aberrantly activated, suppresses autophagy through the AKT-mTOR axis, increasing the number of myofibroblasts and enhancing the expression of fibrotic markers.[27] Experimental studies have demonstrated that pharmacological inhibition of the SHH pathway, such as with GANT61, can restore autophagic activity and alleviate fibrotic lesions in animal models.[27]

In summary, the fibrotic pathology of IUA involves intricate signaling pathways and multifaceted molecular regulation. The activation of fibroblasts and impairment of autophagy are central to the progression of fibrosis in IUA. Future in-depth studies focusing on these mechanisms will not only enhance our understanding of the disease's pathogenesis but also provide critical insights for the development of targeted therapeutic strategies.

Inflammatory Response as a Central Driver of Fibrotic Progression

Role of Inflammation in IUA Development

Inflammation is an early response to endometrial injury, primarily aimed at clearing damaged tissue and initiating repair. However, persistent or dysregulated inflammation disrupts the local microenvironment, driving fibrosis.[31] In the context of IUA, excessive activation of inflammatory cells, particularly macrophages, along with sustained release of pro-inflammatory cytokines like TNF-α and IL-6, activates fibrotic signaling pathways and impairs endometrial regeneration.[32]

Unlike other tissues, the endometrium undergoes cyclic, reversible inflammatory episodes associated with menstruation and repair.[33] Under normal conditions, balanced inflammation facilitates debris clearance and tissue regeneration. In IUA, however, this cyclical homeostasis is disrupted, leading to chronic inflammation and irreversible fibrosis.[1] Furthermore, inflammation-induced cell death, particularly ferroptosis, exacerbates tissue damage and sustains fibrosis initiation.[34,35]

Dual Roles of Macrophages in Inflammation and Fibrosis

Macrophages play a pivotal role in maintaining uterine immune homeostasis, tissue clearance, and post-injury remodeling. Under normal conditions, they dynamically polarize between M1 (pro-inflammatory) and M2 (anti-inflammatory /repair) phenotypes. However, in IUA, this polarization becomes dysregulated, often skewing towards M2 subtypes.[36] While M2 polarization is intended to resolve inflammation and promote tissue repair, in the context of chronic inflammation, it paradoxically contributes to fibrosis.[37] Macrophages in IUA may adopt a mixed M1/M2 phenotype, retaining pro-inflammatory functions while simultaneously secreting profibrotic factors, which drive fibrosis. Particularly, $CD301^+$ M2 macrophages, enriched in the fibrotic endometrium, secrete GAS6, activating the AXL/NF-κB signaling pathway in stromal cells, promoting their transdifferentiation into myofibroblasts and ECM accumulation.[38] This forms a uterine-specific fibrotic loop, where macrophages not only resolve inflammation but also facilitate maladaptive repair, driving fibrosis progression.

Therapeutically, mesenchymal stem cells (MSCs) have demonstrated anti-fibrotic potential by modulating macrophage function. MSCs secrete stanniocalcin-1 (STC-1), which enhances the phagocytic ability of large peritoneal macrophages (LPMs), enabling them to clear ferroptotic debris and suppress the release of pro-fibrotic signals.[39] This macrophage-centered regulatory axis, involving the dynamic polarization between M1 and M2 phenotypes, plays a central role in both inflammation resolution and fibrosis promotion. Targeting the molecular mechanisms that regulate macrophage polarization, such as cytokine signaling pathways (eg, IL-6, TNF-α) and transcription factors (eg, STAT3, NF-κB), offers a promising strategy for IUA intervention. Additionally, modulating metabolic pathways like ferroptosis may help further regulate macrophage function and attenuate fibrosis.

Ferroptosis as a Bridge Linking Inflammation and Fibrosis

Ferroptosis, a programmed cell death mechanism driven by iron-dependent lipid peroxidation, is characterized by elevated lipid peroxidation and decreased activity of glutathione peroxidase 4 (GPX4).[40,41] In fibrosis, ferroptosis serves as a critical link between inflammation and fibrotic progression. Studies have demonstrated its essential role in fibrosis across various tissues, including the lungs, liver, kidneys, and ovaries.[42–46] In IUA, ferroptosis exacerbates inflammation by releasing cytokines such as IL-6 and IL-8, which activate macrophages and stromal cells, thereby intensifying the inflammatory response.[47] Additionally, cell debris from ferroptosis, including iron ions and oxidized lipids, acts as a "fuel" for fibrosis initiation by directly activating stromal cells and enhancing ECM deposition.[48] Furthermore, epithelial cells undergoing ferroptosis can signal neighboring stromal cells through paracrine pathways, accelerating myofibroblast transdifferentiation.[49] Inhibitors of ferroptosis, such as ferrostatin-1 (Fer-1), have been shown to significantly reduce fibrosis in IUA mouse models by alleviating lipid peroxidation and oxidative damage.[34] Combining ferroptosis inhibitors with MSC therapy or autophagy activators may exhibit synergistic effects, mitigating inflammation while effectively suppressing fibrosis progression.[39]

In IUA, the inflammatory response deviates from its physiological, cyclically resolved pattern into a persistent and dysregulated process that fuels fibrosis. This pathological shift is mediated by aberrant macrophage polarization and

sustained ferroptotic activity, both of which contribute to the disruption of immune homeostasis in the endometrial microenvironment. Understanding these mechanisms may inform the development of targeted and more effective anti-fibrotic strategies.

EMT: A Key Mechanism of Structural and Functional Disruption

Contribution of EMT to IUA Pathogenesis

Epithelial-mesenchymal transition (EMT) is a pivotal biological process in which epithelial cells lose their polarity and intercellular adhesion, acquiring mesenchymal characteristics such as enhanced migratory capacity and increased ECM production.[50] Accumulating evidence indicates that inflammation acts as a crucial upstream driver of EMT, forming a pathological positive feedback loop that drives the initiation and progression of endometrial fibrosis in IUA.[51,52] Following endometrial injury, pro-inflammatory cytokines such as IL-6, TNF-α, and TGF-β are abundantly released, which subsequently activate canonical EMT-inducing pathways, including the NF-κB and TGF-β/Smad signaling axes. These inflammatory signals disrupt epithelial homeostasis by downregulating epithelial markers such as E-cadherin, while upregulating mesenchymal markers including N-cadherin and α-SMA, thereby facilitating the epithelial-to-mesenchymal phenotypic transition.[53,54] As inflammation-driven EMT progresses, the resulting mesenchymal-like cells acquire a profibrotic secretory profile, releasing fibrogenic cytokines and ECM components that stimulate the differentiation of stromal fibroblasts into myofibroblasts. This cascade accelerates collagen synthesis and deposition, promoting the establishment of a fibrotic microenvironment.[55] Collectively, these findings suggest that inflammation and EMT function synergistically as a reinforcing axis that drives the pathological fibrotic remodeling observed in IUA.

In the normal endometrium, EMT follows a cyclical and reversible pattern, governed by hormonal rhythms. Estrogen stimulates epithelial proliferation and inhibits EMT through ERβ signaling, while progesterone modulates key EMT transcription factors, such as SNAI1 and ZEB1, via the progesterone receptor (PR).[56] During menstruation, the withdrawal of progesterone triggers transient EMT activation to facilitate tissue repair. Under physiological conditions, this process is swiftly reversed during the regenerative phase to prevent fibrosis.[57] However, in IUA, this finely regulated mechanism is disrupted, leading to persistent EMT activation, the loss of epithelial barrier integrity, and excessive collagen deposition.[2] Further research has highlighted the pivotal role of endometrial-specific transcription factors in the aberrant activation of EMT. For instance, ΔNp63α, a transcriptional regulator critical for epithelial stemness, is significantly upregulated in IUA and promotes sustained EMT by activating the DUSP4/GSK3β/SNAI1 signaling pathway, thereby disrupting endometrial homeostasis.[58] Additionally, key uterine developmental regulators such as Hoxa10, Hoxa11, and Wnt7a are frequently dysregulated in fibrotic endometria, further amplifying the mesenchymal transition process.[59,60]

Furthermore, oxidative stress induced by ferroptosis has been identified as a powerful trigger for EMT. Lipid peroxidation products and inflammatory mediators generated during ferroptosis activate the TGF-β signaling pathway, which further drives EMT in endometrial epithelial cells.[34] EMT-transformed cells contribute to fibrosis by secreting TGF-β, matrix metalloproteinases (MMPs), and fibronectin, all of which promote the transdifferentiation of stromal cells into myofibroblasts and increase ECM stiffness.[55] This creates a vicious cycle within the fibrotic microenvironment, perpetuating fibrosis and further disrupting endometrial function.

Crosstalk Between Autophagy and EMT in Fibrotic Remodeling

Emerging evidence suggests that reduced autophagy levels are closely associated with the occurrence of EMT in IUA. Autophagy plays a critical role in regulating EMT by degrading cellular damage-associated factors, thereby maintaining epithelial homeostasis and inhibiting mesenchymal transition. Key mechanisms include the regulation of the DIO2-MAPK/ERK-mTOR and SHH signaling pathways. DIO2, a key enzyme involved in thyroid hormone metabolism, is significantly downregulated in IUA. The loss of DIO2 suppresses MAPK/ERK-mTOR pathway activity, inhibiting autophagy and promoting EMT progression, with a marked increase in fibrosis markers such as α-SMA and fibronectin.[30] Furthermore, hyperactivation of the SHH signaling pathway inhibits autophagy, accelerating the expression of EMT-associated molecules. In mouse models of IUA, pharmacological inhibition of the SHH pathway restores autophagic activity and reduces EMT-related marker expression.[27] Moderate activation of autophagy exhibits protective

effects against EMT through multiple mechanisms. Autophagy clears oxidative stress products, including damaged organelles and lipid peroxidation byproducts, reducing the inflammatory microenvironment's stimulation of EMT. Additionally, autophagy preserves epithelial polarity and cell-cell junctions, mitigating the loss of epithelial homeostasis during EMT.[30] These findings suggest that therapeutic strategies targeting autophagy regulation may effectively alleviate EMT and its associated fibrotic processes in IUA.

EMT is a critical mechanism in the structural and functional disruption associated with fibrosis in IUA. By promoting the loss of epithelial homeostasis, mesenchymal transition, and the formation of a fibrotic microenvironment, EMT drives the progression of fibrosis through multiple signaling pathways. Meanwhile, autophagy interacts closely with EMT, with reduced autophagy further exacerbating EMT pathology. Future research should focus on developing novel therapeutic strategies targeting the autophagy-EMT axis, providing new directions and targets for the prevention and treatment of IUA.

Current Treatment Strategies for IUA

Conventional Treatment Approaches and Their Limitations

Over the past few decades, the primary therapeutic strategies for IUA have included transcervical resection of adhesions (TCRA), adjunctive pharmacological therapies, stem cell transplantation, and the application of biomaterial-based physical barriers. These interventions have shown a degree of success in restoring uterine anatomy and improving functional outcomes, particularly in cases of mild to moderate IUA. However, their long-term efficacy in patients with severe adhesions remains unsatisfactory. A systematic evaluation of these conventional approaches reveals significant limitations in their ability to promote sustained endometrial regeneration and restore reproductive function.

TCRA

TCRA is currently the first-line treatment for IUA, widely applied in clinical practice due to its minimally invasive nature and direct visualization capability.[7] In patients with mild to moderate adhesions, TCRA effectively separates fibrotic bands, improves menstrual abnormalities, and in some cases enables spontaneous pregnancy.[61] The use of advanced instruments, such as cold scissors and bipolar electrodes, has further enhanced the safety and precision of the procedure.[62]

However, TCRA is challenged by high recurrence rates and limited functional recovery. Studies have reported that in patients with severe IUA, the recurrence rate can reach up to 62.5% after surgery, primarily due to persistent fibrosis and insufficient angiogenesis during endometrial repair.[1] Additionally, the surgical procedure itself may cause new trauma to the endometrium, inducing secondary inflammation and re-adhesion.[63] Although adjuvant treatments like estrogen administration and physical barriers may offer short-term benefits, retrospective studies have shown that even with multiple surgeries combined with drug interventions, the live birth rate in severe cases remains below 40%, highlighting the limited regenerative potential of TCRA in advanced disease.[64,65]

Pharmacological Treatments

Hormonal therapies—especially estrogen—are widely used to promote endometrial proliferation and tissue repair after surgical intervention. Estrogen stimulates the regeneration of basal layer cells, improves endometrial thickness, and may help reduce the recurrence of adhesions.[66] Aspirin, as an antiplatelet agent, has shown potential in improving local microcirculation and regulating the TGF-β/Smad signaling pathway, thereby exerting anti-fibrotic and pro-angiogenic effects.[67]

Nevertheless, the efficacy of pharmacological treatments is limited by several factors. Firstly, there is no consensus on optimal dosage or administration protocols, resulting in inconsistent clinical outcomes across studies. Secondly, while such therapies may offer modest benefits in non-severe cases, they are generally insufficient to reverse basal membrane disruption or structural damage in patients with severe fibrosis. In one study, the improvement rate of endometrial thickness after high-dose estrogen therapy in severe IUA was reported to be less than 30%, and some patients developed thromboembolic complications.[68,69] Moreover, long-term use of aspirin may induce gastrointestinal side effects, further restricting its prolonged application.[67]

Stem Cell-Based Therapies

MSCs, derived from sources such as bone marrow (BMSCs) and umbilical cord (UCMSCs), have demonstrated significant potential in promoting endometrial regeneration due to their paracrine signaling, anti-fibrotic effects, and angiogenic capabilities.[70,71] Animal studies have shown that MSCs can suppress fibroblast activation and promote endothelial cell proliferation through the secretion of cytokines and exosomes, thereby improving both structural and functional recovery.[10]

Despite these promising findings, stem cell therapy remains in the preclinical stage and faces numerous translational challenges. Safety concerns, including tumorigenicity and ectopic tissue formation, remain unresolved.[72] Additionally, MSC harvesting often involves invasive procedures, and their processing, storage, and transportation require stringent conditions, reducing clinical accessibility. Lack of standardization in preparation protocols and cell potency variability across donors further complicate clinical implementation. Moreover, clinical observational studies have indicated that MSC-based treatments fail to significantly improve pregnancy outcomes in some patients with severe IUA, suggesting that cell viability and bioactivity are still limited by individual variation.[70]

Physical Barriers and Biomaterial Applications

Physical barriers, such as hyaluronic acid gels, intrauterine balloons, and intrauterine devices (IUDs), are commonly used postoperatively to prevent re-adhesion by physically separating the anterior and posterior uterine walls.[73] In recent years, biomaterials such as collagen scaffolds, polyethylene glycol (PEG), and decellularized extracellular matrix (dECM) have been explored as delivery vehicles for stem cells or exosomes. These biomaterials aim to combine structural support with bioactivity to facilitate tissue regeneration.[9,73,74]

However, their clinical efficacy is also limited. Traditional physical barriers primarily provide mechanical isolation without modulating the local uterine microenvironment.[3] Meanwhile, issues related to degradation kinetics, mechanical properties, and biocompatibility of biomaterials remain unsolved. A multicenter study reported that hyaluronic acid gels could reduce adhesion recurrence rates to below 20% in mild IUA, but the rate increased to approximately 60% in severe cases, indicating that barrier-based strategies alone are insufficient to effectively address advanced fibrotic conditions.[75]

Exosomes as Emerging Therapeutic Agents in Endometrial Regeneration

Given the limitations of conventional IUA therapies—particularly the high recurrence rates and insufficient endometrial regeneration—exosomes have gained increasing attention as a novel, cell-free regenerative strategy. Exosomes are nano-sized extracellular vesicles secreted by various cell types, carrying functional cargos such as miRNAs, proteins, and lipids that mediate intercellular communication and tissue repair.[76] In the context of IUA, exosome-based therapy represents a promising alternative that addresses many of the challenges associated with current treatments.

Recent studies have shown that MSC-derived exosomes improve the uterine microenvironment through paracrine mechanisms. For instance, exosomes derived from BMMSCs and UCMSCs regulate the TGF-β/Smad signaling pathway, thereby reducing fibrosis, promoting angiogenesis, and enhancing the proliferation of endometrial cells.[77] Beyond reducing adhesion recurrence, exosomes offer a novel and efficient therapeutic avenue by actively supporting endometrial regeneration, particularly in improving long-term pregnancy outcomes for IUA patients.

Compared to traditional treatments, exosome-based therapies offer several distinct advantages. Their extracellular action and biological origin eliminate the risks of immune rejection and ethical controversies associated with cell transplantation. Additionally, their potent bioactivity enables targeted repair of damaged tissues. When combined with advanced delivery systems, such as hydrogels or nanoparticles, exosomes demonstrate enhanced therapeutic efficacy by prolonging retention within the uterine cavity, ensuring precise delivery, and achieving functional sustained release.

To conclude, exosomes represent an innovative tool in regenerative medicine, paving new directions for IUA treatment. Future advancements in the optimization of exosome isolation and purification techniques, the development of intelligent delivery systems, and their integration with other innovative therapies hold the promise of providing IUA patients with more precise, efficient, and long-lasting therapeutic solutions.

Mechanistic Insights into Exosome-Based Therapy for IUA

Key Bioactive Components of Exosomes

Exosomes are nanoscale extracellular vesicles secreted by cells, with diameters ranging from 30 to 150 nm. Enclosed by a bilayer phospholipid membrane, they carry diverse bioactive molecules, including proteins, lipids, and nucleic acids (eg, DNA, mRNA, miRNA, and lncRNA). By mediating intercellular communication, these molecules play pivotal roles in tissue repair, antifibrotic processes, and immune regulation.[12] Due to their unique composition and multifunctional mechanisms, exosomes have emerged as a promising research focus in tissue engineering and regenerative medicine. As highly efficient carriers of biological signals, exosomes exhibit significant potential for promoting tissue repair and therapeutic applications, particularly in treating IUA.

The protein components of exosomes, such as heat shock proteins, integrins, and angiogenesis-related factors, can modulate inflammatory responses, promote angiogenesis, and enhance cell adhesion, thereby improving the local microenvironment and facilitating IUA repair.[74,78] Lipid molecules on the exosomal membrane not only serve as critical mediators of cellular recognition but also enhance the stability and delivery efficiency of exosomes, further underscoring their value in therapeutic applications.[79] Among the nucleic acid components, miRNAs have garnered particular attention for their roles in fibrosis inhibition and tissue repair. For instance, miR-125b-5p, miR-30c-5p, and miR-23a-3p can effectively mitigate fibrosis by targeting the TGF-β/Smad signaling pathway.[80] miR-29 plays a key role in reducing the abnormal deposition of ECM by inhibiting collagen expression.[81–83] Furthermore, miR-21 significantly promotes cell proliferation through activation of the AKT signaling pathway, thereby accelerating endometrial regeneration and repair.[84]

Collectively, the diverse and functional molecular composition of exosomes underscores their extensive therapeutic potential. The synergistic actions of their protein, lipid, and nucleic acid components effectively contribute to inflammation suppression, tissue remodeling, and fibrosis reversal. These characteristics highlight the pivotal role of exosomes in IUA treatment and provide a robust theoretical foundation for their development as next-generation therapeutic carriers, paving the way for future clinical translation.

Exosome-Mediated Anti-Fibrotic Mechanisms

Endometrial fibrosis, a central pathological feature of IUA, is marked by aberrant fibroblast activation, excessive ECM deposition, EMT, and sustained inflammation. These interconnected processes collectively accelerate fibrotic progression and critically impair endometrial regenerative capacity. In recent years, exosomes have emerged as potent modulators of fibrosis, owing to their cargo of functional miRNAs, proteins, and other regulatory molecules. This section synthesizes the principal antifibrotic mechanisms of exosomes, emphasizing their roles in cellular reprogramming, ECM regulation, and gene-level signaling modulation.

Regulation of Fibroblast Activation and EMT

The aberrant activation of fibroblasts and the initiation of EMT represent key early events in fibrotic remodeling. Exosomes exert multifaceted regulatory effects on these processes, effectively attenuating myofibroblast differentiation and reversing EMT-associated phenotypic shifts. For instance, miR-125b-5p, miR-30c-5p, and miR-23a-3p—enriched in exosomes derived from placental mesenchymal stem cells (PMSCs)—directly target Smad2 and Smad3, thereby inhibiting the TGF-β/Smad signaling pathway and markedly reducing α-SMA expression and myofibroblast activation.[80,85] Additionally, TSG6-modified exosomes have been shown to induce macrophage polarization toward the M2 phenotype, which suppresses inflammation-driven fibroblast activation and further mitigates fibrogenesis.[86] Menstrual blood-derived mesenchymal stem cell (MenSC)-derived exosomes also inhibit fibroblast activation through the Hippo/TAZ signaling pathway, resulting in the downregulation of fibrosis-associated gene expression.[22,87] At the EMT level, exosomes from BMSCs block TGF-β1-induced phosphorylation of Smad2/3, restoring epithelial characteristics (eg, E-cadherin expression) while downregulating mesenchymal markers such as Vimentin.[85] Moreover, MenSC-derived exosomes promote the ubiquitination and degradation of YAP, thereby suppressing its interaction with EMT transcriptional regulators and inhibiting EMT gene expression.[88] Similarly, exosomes derived from UCMSCs suppress EMT progression by downregulating the TGF-β/Smad axis.[89]

Modulation of Collagen Deposition and ECM Remodeling

Excessive ECM deposition, especially of collagen types I, III, and V, is a hallmark of endometrial fibrosis. Exosomes from PMSCs have been shown to downregulate COL1A1, COL5A2, and Vimentin, thereby mitigating collagen accumulation and preserving tissue architecture.[13] Additionally, exosomal miR-29a and miR-340 target and suppress the TGF-β signaling pathway, leading to significant attenuation of fibrotic matrix deposition in endometrial tissues.[81,90] Exosomes also deliver regulatory proteins such as UBR4, which facilitate YAP ubiquitination and degradation, further inhibiting the overproduction of fibrosis-related collagens.[88]

Beyond inhibiting collagen synthesis, exosomes enhance ECM turnover by promoting matrix degradation. This is achieved through the upregulation and activation of matrix metalloproteinases MMP-2 and MMP-9, enzymes essential for ECM remodeling and fibrosis resolution.[91] Notably, exosome delivery systems incorporating thermosensitive hydrogels have been developed to increase intrauterine retention and bioavailability, thereby amplifying the ECM-modulating effects of exosomes and preventing fibrotic protein aggregation.[92]

Gene-Level Control of Fibrotic Signaling Pathways

In addition to modulating cellular behavior and ECM dynamics, exosomes exert gene-level regulatory control over fibrotic signaling networks. Exosomes derived from PDGF-BB-preconditioned MenSCs activate the AKT/NF-κB signaling axis, enhancing the expression of antifibrotic mediators while simultaneously suppressing key profibrotic genes such as CTGF and TGF-β.[93] Furthermore, exosomal miRNAs have been shown to modulate core components of the Wnt signaling pathway, effectively inhibiting fibrosis-associated cellular programming.[94] Of particular interest, MenSC-derived exosomes downregulate the expression of COL1 and CTGF via YAP ubiquitination and degradation, highlighting the precision with which exosomes can reprogram the fibrotic transcriptome.[88] These findings underscore the potential of exosome-based therapies to target multiple nodes of fibrotic signaling cascades at the genetic level. These mechanistic insights suggest that exosomes do not act through isolated pathways, but rather coordinate a broad-spectrum regulatory network that spans cellular, extracellular, and transcriptional levels. By targeting early fibroblast activation, suppressing EMT progression, regulating ECM composition, and modulating fibrotic signaling cascades at the genetic level, exosomes engage in a multifaceted biological strategy to disrupt fibrotic remodeling within the endometrium.

Exosome-Driven Mechanisms of Endometrial Repair

Endometrial repair is a highly coordinated biological process encompassing cell proliferation, tissue remodeling, angiogenesis, immunoregulation, and the re-establishment of endometrial receptivity. This process relies not only on the regenerative potential of resident cells but also on the orchestration of signaling events within the uterine microenvironment. As extracellular vesicles rich in bioactive molecules, exosomes have emerged as promising therapeutic agents capable of modulating diverse aspects of endometrial repair. This section summarizes the multifaceted mechanisms through which exosomes facilitate regeneration and functional recovery of the endometrium.

Promotion of Cell Proliferation and Survival

Cell proliferation and survival are foundational to endometrial regeneration, driving the restoration of stromal cell populations and re-establishing endometrial thickness and function. Exosomes significantly enhance these processes via the delivery of miRNAs and proteins that regulate the cell cycle and apoptosis. Notably, miR-21-5p and miR-7162-3p, enriched in exosomes, modulate Cyclin D1 and p21 expression, promoting G1/S phase transition and stromal cell proliferation.[95,96] In parallel, exosome-mediated activation of the PI3K/Akt pathway suppresses apoptosis-related effectors such as Caspase-3, thereby improving cell viability and tissue integrity.[97] Further enhancing this regenerative effect, exosomes derived from PDGF-BB-preconditioned MenSCs activate the NF-κB pathway, augmenting antioxidant defenses and reducing the expression of apoptotic factors, which collectively improves cell survival under oxidative and inflammatory stress.[93] These findings illustrate the central role of exosomes in promoting stromal renewal through synchronized modulation of proliferative and anti-apoptotic signaling.

Modulation of Vascularization and Immune Microenvironment

Revascularization and immune balance are critical for effective endometrial repair. Exosomes support angiogenesis by delivering pro-angiogenic proteins and miRNAs to endothelial cells. For instance, UCMSC-derived exosomes are enriched in vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), both of which enhance endothelial cell proliferation and migration, thereby promoting neovascularization.[98] Additionally, miR-126 packaged in exosomes targets SPRED1 and PIK3R2, facilitating VEGF pathway activation and accelerating angiogenic response.[99] Similarly, PDGF-BB-conditioned MenSC-derived exosomes enhance vascular stability via AKT/NF-κB signaling activation.[93]

Equally important is the immune environment. While a transient inflammatory response is essential for initiating tissue regeneration, persistent inflammation impairs repair outcomes. Exosomes modulate immune cell phenotypes and cytokine profiles to fine-tune this response. TNF-α-preconditioned MSC-derived exosomes enriched in Galectin-1 induce macrophage polarization toward the anti-inflammatory M2 phenotype and suppress the M1 phenotype, thereby reducing the production of pro-inflammatory cytokines.[100] Moreover, exosomal miR-223-3p targets STMN1, downregulating TNF-α and IL-1β while upregulating anti-inflammatory mediators such as TGF-β and VEGF.[101] At the signaling level, exosomes downregulate NF-κB and STAT1 activity, curbing chronic inflammatory gene expression and restoring immunological homeostasis.[102,103] PDGF-BB-preconditioned exosomes also activate STAT3, reinforcing anti-inflammatory signaling and further improving the reparative microenvironment.[93] Together, these mechanisms underscore the pivotal role of exosomes in simultaneously promoting vascularization and mitigating inflammation during endometrial repair.

Structural and Functional Remodeling of the Endometrium

As repair progresses, restoring the structural and functional properties of the endometrium is essential for fertility. Exosomes contribute to late-stage tissue remodeling by modulating ECM dynamics, promoting glandular regeneration, and enhancing hormone responsiveness. PMSCs-derived exosomes downregulate collagen genes such as COL1A1 and COL5A2, limiting ECM overaccumulation and alleviating fibrosis.[13] Concurrently, PDGF-BB-preconditioned MenSC exosomes stimulate glandular regrowth, increasing both the number and complexity of functional secretory glands necessary for implantation and support of early pregnancy.[93]

In addition to structural reconstitution, exosomes influence hormonal receptivity. Exosomal treatment upregulates estrogen receptor (ER) and progesterone receptor (PR) expression, enhancing the endometrium's responsiveness to endocrine cues critical for embryo implantation.[10,104] These results indicate that exosomes act not only as morphological remodelers but also as functional enhancers of the endometrial niche, preparing it for reproductive success. Importantly, these multi-tiered effects are not isolated but function in concert throughout the repair process, linking early regenerative events with late-stage tissue specialization. Evidence from in vitro and in vivo studies supports the notion that exosomes act as functional mediators of endometrial repair, coordinating proliferative responses, vascular development, immune balance, and microstructural reconstruction. Their ability to simultaneously influence both structural and functional aspects of regeneration positions them as biologically integrative agents within the endometrial healing process.

Variations in the Functions of Exosomes from Different Sources

The source of exosomes significantly influences their molecular composition, mechanisms of action, and therapeutic efficacy. In the treatment of IUA, exosomes derived from different origins, including MenSCs, UCMSCs, BMSCs, adipose-derived stem cells (ADSCs) and other sources, exhibit distinct functional characteristics and potential advantages. These exosomes act through diverse molecular mechanisms, making them a focal point of research for IUA treatment. Their specific roles in inhibiting fibrosis, promoting angiogenesis, and improving the endometrial microenvironment offer valuable theoretical support for their clinical application (Table 1).

Future research should focus on several key directions. First, optimizing delivery strategies, such as developing targeted delivery carriers, could further enhance the retention time and therapeutic efficiency of exosomes at the lesion site. Second, in-depth exploration of the specific mechanisms by which exosomes function at different stages of endometrial repair will provide a solid foundation for their clinical translation. Additionally, combining exosomes with

Table 1 Summary of the Functions and Mechanisms of Exosomes from Different Sources in Intrauterine Adhesion Treatment

Source	Primary Mechanisms	Therapeutic Features	References
MenSC-Exos	-Targeting YAP ubiquitination to downregulate fibrosis-related genes (COL1A1, COL5A2) -Regulating TGF-β/Smad pathway to reverse EMT	-Effective antifibrotic action -Safe and easily accessible treatment option	[85,88]
UCMSC-Exos	-Enriched with VEGF and miR-126, promoting angiogenesis via the PI3K/Akt pathway -Balancing M1/M2 macrophage ratio to regulate inflammation	-Strong angiogenesis and immune modulation capacity -Hydrogel systems enhance efficacy and retention time	[92,99]
BMSC-Exos	-miR-29a suppressing fibrosis-related genes and collagen deposition -Reversing EMT by downregulating Vimentin and enhancing E-cadherin expression	-Comprehensive antifibrotic and tissue repair capability -High clinical safety for multiple fibrotic diseases	[81,82,85]
PMSC-Exos	-Targeting TGF-β/Smad pathway via miR-125b-5p to reduce Smad2/3 activity	-Significant reduction in fibrosis -Effective in increasing endometrial thickness	[80]
ADSC-Exos	-Anti-inflammatory effects via regulation of inflammatory factors (eg, TNF-α, IL-1β)	-Strong anti-inflammatory and tissue remodeling capacity	[86]
Delivery Systems	-Hydrogel-based systems enhance retention and therapeutic efficacy -Improve bioavailability and reduce dosage needs	-Increased therapeutic efficiency and reduced side effects	[92]

other regenerative medicine technologies, such as bio-scaffolds or hydrogels, holds great potential to further enhance their therapeutic efficacy. Through these efforts, exosomes could emerge as a safe, efficient, and precise tool for endometrial repair, offering innovative solutions for the treatment of IUA and other related conditions. This progress would represent a significant step forward in advancing the field of regenerative medicine to new heights.

Future Directions in Exosome-Based IUA Therapy

Although current research highlights the significant potential of exosomes in treating endometrial fibrosis, their precise mechanisms and optimization strategies require further investigation. Future studies should focus on key areas such as targeted regulation of core fibrotic pathways, autophagy modulation, and multi-target combinatory therapies to achieve more precise and effective outcomes.

Targeted Regulation of Core Fibrotic Pathways

Fibrosis is the hallmark pathological change in IUA, making the regulation of key fibrotic pathways a research priority. Exosomes are instrumental in reversing both fibroblast activation and the transdifferentiation of myofibroblasts, as well as in remodeling the ECM. For example, designing exosomes enriched with antifibrotic miRNAs, such as miR-29a and miR-125b-5p, could target pathways like TGF-β/Smad and WNT/β-catenin, effectively inhibiting fibrosis progression. Gene-editing technologies could enhance the specificity of exosomes toward myofibroblasts, reducing α-SMA and type I collagen expression and alleviating fibrosis. Additionally, optimizing the activity of ECM-degrading enzymes like MMP-2 and MMP-9 within exosomes and developing long-lasting delivery carriers may further enhance ECM degradation, achieving comprehensive fibrosis remodeling.

Autophagy Regulation: A Core Mechanism for Fibrosis and Repair

The interplay between exosomes and autophagy plays a vital role in maintaining tissue homeostasis and promoting pathological repair. Autophagy, a core mechanism of cellular degradation and renewal, is essential not only for maintaining endometrial stability but also for regulating fibroblast activation and ECM accumulation, which are pivotal in the progression of fibrosis. Although studies on exosome-mediated regulation of autophagy are still in their early stages, existing findings provide a strong theoretical foundation for further exploration in this field. Research has shown that specific miRNAs and proteins carried by exosomes can significantly influence autophagy by modulating related signaling pathways.[105] For example, exosomes derived from MSCs, enriched with miR-125b-5p, target TRAF6 to inhibit the NF-κB signaling pathway, alleviating intervertebral disc degeneration. Similarly, miR-125b-5p in macrophage-derived exosomes has been shown to regulate liver fibrosis by suppressing fibrotic gene expression and mitigating pathological damage.[106]

However, there remains a notable gap in understanding the precise mechanisms through which exosome-mediated autophagy regulation impacts endometrial fibrosis. In particular, the specific therapeutic window, degree of autophagy activation, and its coordinated role in both anti-fibrotic action and tissue regeneration have not been adequately

elucidated. Current evidence suggests that autophagy plays a dual role: moderate activation supports cellular homeostasis by clearing damaged organelles, suppressing inflammation, and reducing ECM deposition, thereby inhibiting fibrosis. Conversely, excessive autophagy may trigger apoptosis, ultimately impairing endometrial regeneration and repair.[26] This paradoxical function of autophagy—balancing fibrotic suppression and regenerative inhibition—has not yet been thoroughly characterized in the literature.

Hence, precise modulation of autophagy through exosomes to balance fibrosis reversal and tissue regeneration is a critical and underexplored therapeutic strategy. Future research may pursue two key directions. First, enhancing autophagy to suppress fibrosis by identifying autophagy-regulating miRNAs or proteins within exosomes via high-throughput screening, or engineering exosomes to deliver AMPK activators or PI3K/AKT/mTOR pathway inhibitors to restore autophagic function and reduce ECM deposition. Second, mitigating the adverse effects of excessive autophagy to promote tissue regeneration—for example, by combining exosomes with autophagy modulators to reduce apoptosis triggered by hyperactive autophagy and enhance endometrial regenerative capacity. Moreover, the concept of an "autophagic threshold"—a fine-tuned range of activity that promotes anti-fibrotic effects without triggering detrimental apoptosis—may serve as a novel therapeutic target. Advances in exosome engineering, such as CRISPR-based gene editing to enrich exosomes with specific autophagy-related components, or integrating long-acting delivery systems to prolong tissue retention, could further optimize clinical efficacy.

Taken together, the lack of mechanistic clarity surrounding the threshold-dependent effects of autophagy represents a key research gap. Addressing this will be vital for translating exosome-based autophagy modulation into precise and effective treatments. This multifaceted strategy not only holds promise for improving IUA therapy but also provides broader insight into the application of exosomes in fibrotic diseases. Although the study of exosome-autophagy interactions is still in its infancy, highlighting such knowledge gaps and proposing mechanistic frameworks will accelerate the clinical translation of basic findings and advance precision medicine approaches in fibrosis.

Multi-Targeted Regulation: Integrative Therapy for Fibrosis and EMT

EMT plays a critical role in the progression of fibrosis in IUA. While current research on exosomes has primarily focused on the TGF-β/Smad pathway, future studies should expand to other EMT-driving factors. For example, exosomes targeting multiple pathways, such as TGF-β, WNT/β-catenin, and SHH, could effectively mitigate EMT-induced fibrosis. Furthermore, integrative strategies that combine antifibrotic and anti-inflammatory approaches could prove highly effective. For instance, pairing exosomes with anti-inflammatory agents like IL-10 or antioxidant enzymes could inhibit the fibrotic microenvironment, preventing fibrosis progression at its source. Developing composite exosome therapies that integrate multi-level signaling pathway regulation may represent a breakthrough in IUA treatment.

Overall, future research should prioritize the development of more targeted and comprehensive exosome-based therapeutic strategies. Combining the targeted regulation of core fibrotic pathways, autophagy modulation, and multi-targeted integrative therapies could enable precise intervention and holistic repair of IUA-associated fibrosis. These advancements would significantly enhance the clinical applicability of exosomes, paving the way for innovative solutions in the treatment of endometrial fibrosis and other fibrotic diseases.

Combined Applications of Biomaterials and Exosomes in IUA Treatment

Current Status of Biomaterials in the Treatment of IUA

The application of biomaterials in the treatment of IUA has garnered significant attention in recent years, offering innovative solutions to address fibrosis and tissue regeneration. Among various biomaterials, hydrogels and scaffold materials stand out due to their excellent properties and demonstrate substantial potential in IUA therapy.

Therapeutic Potential of Hydrogels

Hydrogels, characterized by their injectability, plasticity, excellent biocompatibility, and biodegradability, have become a focal point of contemporary research.[107,108] Hydrogel-based therapeutic strategies are particularly promising for IUA treatment, as demonstrated in the following aspects: Firstly, hydrogels can form physical barriers within the uterine cavity, preventing tissue adhesions and promoting endometrial regeneration. For example, antifouling granular hydrogels

(PHEAA gel) effectively block the deposition of fibrinogen and fibroblasts, reducing excessive ECM accumulation and thereby lowering the risk of adhesion recurrence.[109] Additionally, self-healing hydrogels, owing to their shear-thinning properties, adapt to the irregular structures of the uterine cavity and rapidly restore volume and adhesiveness post-injection, enabling efficient application.[110] Hydrogels also serve as delivery carriers for various therapeutic agents. For instance, HA/Gel hydrogels loaded with UCMSCs significantly enhance endometrial thickness and function by promoting angiogenesis and suppressing inflammatory responses.[111] Similarly, platelet-rich plasma (PRP)-enriched double-network hydrogels inhibit the TGF-β1/SMAD2/3 pathway, reducing collagen deposition and improving uterine function and regeneration capacity.[112] Moreover, novel hydrogels incorporating antioxidant enzymes or antifibrotic agents demonstrate excellent antioxidant and antifibrotic properties. For example, Ru single-atom nanozyme (Ru-SAN) hydrogels scavenge reactive oxygen species (ROS) and regulate ferroptosis pathways, thereby mitigating fibrosis and promoting angiogenesis.[113] Another hydrogel containing extracellular adipose-derived extracts (CEFFE-Cu-PEG) not only increases endometrial thickness and receptivity but also significantly reduces the expression of fibrosis markers.[114]

Innovation and Application of Scaffold Materials

Scaffold materials provide mechanical support and promote cellular proliferation and differentiation, creating an ideal microenvironment for damaged endometrial regeneration. For example, collagen scaffolds combined with stem cells provide a favorable regenerative microenvironment, effectively enhancing endometrial repair.[16] Additionally, oxidized hyaluronic acid-gelatin scaffolds, known for their excellent degradability and biocompatibility, deliver stem cells to damaged sites while gradually releasing therapeutic agents.[115] As delivery system carriers, scaffolds not only enhance the stability and retention time of drugs and stem cells but also exhibit tremendous potential in improving therapeutic efficacy.

Despite significant advances in the use of biomaterials for IUA treatment, challenges remain, including meeting individualized treatment needs, ensuring long-term safety, and improving delivery efficiency and stability. Future research should focus on integrating hydrogels, scaffold materials, and novel delivery platforms to develop multi-functional, intelligent, and responsive materials capable of addressing varying degrees of IUA pathology. Moreover, optimization of drug-loading capacities and controlled-release mechanisms should be prioritized, along with large-scale clinical trials to validate their safety and efficacy. Additionally, the integration of emerging biotechnologies, such as gene editing and precision medicine, could expand the application prospects of these materials in managing complex cases. In conclusion, innovative biomaterial-based therapeutic strategies hold great promise for providing more precise and effective solutions for IUA patients, significantly improving their quality of life.

Synergistic Applications of Exosomes and Biomaterials: Advantages and Opportunities

Limitations of Exosome Monotherapy in Regenerative Medicine

As a cell-free therapeutic strategy, exosomes have emerged as promising candidates in regenerative medicine due to their inherent capacity to mediate intercellular communication and deliver functional biomolecules. By transporting miRNAs, proteins, and lipids, exosomes play critical roles in modulating cellular processes such as proliferation, anti-inflammatory responses, angiogenesis, and inhibition of fibrosis. These properties render them highly attractive for tissue repair applications, including IUA.

Although exosomes demonstrate great therapeutic potential in tissue repair, their in vivo application still faces several challenges. In particular, systemic administration often results in rapid clearance, low bioavailability, and poor targeting specificity.[116,117] However, it is important to note that such systemic pharmacokinetic limitations are not the primary concern in the context of IUA. This condition is typically managed through localized delivery approaches, such as intrauterine injection or biomaterial-assisted implantation, which naturally bypass systemic clearance mechanisms and allow for targeted accumulation at the lesion site.

Despite this localized advantage, critical obstacles remain. Most notably, limited retention time in the uterine cavity and rapid degradation of exosomal content may significantly impair therapeutic efficacy. Without appropriate delivery systems, exosomes may diffuse away from the target tissue or undergo enzymatic degradation, reducing their ability to maintain sustained interaction with endometrial cells.[118] Furthermore, due to their nanoscale size, the cargo-loading

capacity of exosomes is inherently restricted, which can limit the quantity and duration of active molecular signals.[119] In regenerative tasks such as anti-fibrosis or angiogenesis, rapid release of miRNAs may trigger short-term effects but fail to maintain long-lasting therapeutic outcomes.[120]

Additionally, the natural surface proteins of exosomes exhibit low receptor-binding specificity, even under localized conditions, which may reduce target affinity.[121] Crosstalk with extracellular matrix components or other competing biomolecules in the uterine microenvironment may further hinder their therapeutic performance.[122]

Taken together, these limitations underscore the need to develop advanced exosome delivery platforms capable of enhancing retention, protecting bioactive cargo, and enabling controlled release. Among emerging solutions, the integration of exosomes with engineered biomaterials has attracted particular attention. These composite systems offer not only mechanical stability and localized delivery but also dynamic responsiveness to the uterine microenvironment—an essential feature for improving therapeutic precision, durability, and efficacy. This biomaterial-assisted strategy presents a promising direction for enhancing uterine regeneration and expanding the clinical utility of exosome-based regenerative medicine.

Current Strategies Combining Exosomes and Biomaterials in IUA Treatment

In recent years, increasing attention has been directed toward the use of composite exosome-biomaterial systems for the treatment of IUA. Exosomes, as natural nanovesicles with anti-fibrotic, immunomodulatory, and regenerative capacities, have emerged as promising candidates in IUA therapy. Nevertheless, their clinical application is hampered by rapid clearance, limited tissue targeting, and suboptimal bioavailability.[12,116,117] To address these challenges, recent advances have explored the integration of exosomes with biomaterials, forming composite delivery systems that significantly enhance therapeutic performance.

The incorporation of biomaterials—such as hydrogels, nanoparticles, and porous scaffolds—has proven effective in prolonging exosome retention at the lesion site, protecting their bioactive contents, and enabling controlled release in response to local microenvironmental cues.[120,123,124] This synergistic strategy not only improves therapeutic efficacy but also offers spatiotemporal precision in delivery, marking a pivotal advancement in IUA treatment (Table 2). Among various biomaterials, thermosensitive hydrogels like PCLA-PEG-PCLA exemplify promising carriers that undergo sol-gel transition at body temperature, allowing in situ gelation and sustained exosome release for over seven days, thereby enhancing endometrial regeneration outcomes (Figure 3A).[92] Nanoparticle-based systems further enable microenvironment-responsive release and protection against enzymatic degradation. For instance, exosome-loaded nanozymes have demonstrated the ability to scavenge ROS, thus mitigating fibrosis progression.[125,126] Additionally, sodium alginate hydrogels (SAH), with their three-dimensional porous architecture, provide a favorable uterine repair microenvironment while ensuring gradual exosome release (Figure 3B).[127]

Targeted delivery capabilities are further enhanced by surface functionalization with targeting molecules or specific ligands. For instance, TSG6-modified exosome composites have demonstrated significantly improved specificity toward target tissues, enhancing therapeutic precision (Figure 3C).[86] Moreover, stimuli-responsive systems triggered by environmental factors such as temperature, pH, or enzymatic activity ensure efficient delivery of exosomes to target sites while maximizing their therapeutic efficacy.[120,129] Beyond serving as exosome carriers, biomaterials also provide physical support structures, facilitating cell adhesion, migration, and proliferation, and creating a stable environment for tissue regeneration. For example, sodium alginate hydrogels not only stabilize exosome loading but also promote cell migration and tissue repair, laying a strong foundation for antifibrotic effects and tissue regeneration.[127] These advancements open possibilities for more complex combination therapies in the future.

In summary, the integration of exosomes and biomaterials offers significant advantages in delivery efficiency, local microenvironment optimization, and therapeutic efficacy. Future advancements will require further integration of intelligent, responsive materials and multifunctional designs to broaden the applications of this technology in regenerative medicine.

Table 2 Application of Exosomes and Biomaterials in the Treatment of IUA

Exosome	Biomaterial	Combination Method	Mechanism of Action	In vivo Therapeutic Effects	Reference
UCMSC-Exos	Thermosensitive hydrogel (PCLA-PEG-PCLA)	Exosomes directly embedded in hydrogel to form composite	-Hydrogel enables sustained exosome release -Inhibits TGF-β/Smad signaling pathway -Reduces fibrosis -Anti-inflammatory effects -Promotes angiogenesis and endometrial cell proliferation	-Endometrial thickness significantly restored (approaching normal levels)	[92]
Decidual stromal cells (DSCs) -Exos	Sodium alginate hydrogel (SAH)	Exosomes encapsulated in SAH for in situ injection	-Promotes angiogenesis, mesenchymal-epithelial transition (MET), extracellular matrix remodeling -Enhances endometrial receptivity	-Endometrial thickness significantly increased	[127]
ADSCs-Exos	Chitosan/ glycerophosphate (CS/GP) thermosensitive hydrogel	TSG6-modified exosomes combined with CS/GP to form sustained-release system	-Inhibit M1 macrophage activation -Modulate macrophage polarization -Reduces endometrial fibrosis -Promotes tissue repair	-Endometrial thickness improved	[86]
Fe_3O_4-Se nanoparticles (Non-exosomal)	Alginate/GelMA double-network hydrogel	Nanoparticles encapsulated in microcapsule hydrogel shell	-Exert anti-inflammatory, antioxidant, and antibacterial effects -Promote tissue regeneration -Inhibit fibrosis by scavenging ROS to facilitate endometrial repair	-Endometrial thickness increased from 183.1 μm to 723.3 μm (improvement rate 99%)	[128]
PMSC-Exos	None	Direct injection	-Inhibit TGF-β/Smad signaling pathway via miR-125b-5p, miR-30c-5p and miR-23a-3p to reduce fibrosis	-Endometrial thickness increased from 193 μm to 427 μm (improvement rate 121%)	[80]
MenSCs-Exos	None	Direct injection	-UBAP1 mediates YAP ubiquitination degradation to inhibit fibrosis -P65 transcriptionally activates UBAP1 expression	-Endometrial thickness significantly increased -Fibrotic area reduced	[88]

Comparative Analysis of Biomaterial Types and Their Compatibility with Exosomes

The integration of exosomes with biomaterials has unlocked new possibilities in the treatment of IUA, yet the success of such combination therapies is deeply influenced by the physicochemical properties, degradation behaviors, and biological compatibilities of the carrier materials.

Among these, hydrogels are the most widely studied exosome delivery vehicles. Synthetic hydrogels, such as PEG-based or polyvinyl alcohol (PVA)-based matrices, are highly tunable and exhibit controllable degradation profiles and mechanical strength, which make them particularly suitable for sustaining the release of exosomal contents in vivo. However, their bioinert nature often necessitates functionalization to improve cell-material interactions and ensure effective integration with regenerating tissue.[73] By contrast, natural hydrogels such as those derived from hyaluronic acid, gelatin, or chitosan offer intrinsic bioactivity and promote cell adhesion, proliferation, and differentiation, which enhances the regenerative microenvironment. Nevertheless, their rapid degradation rates and mechanical fragility pose

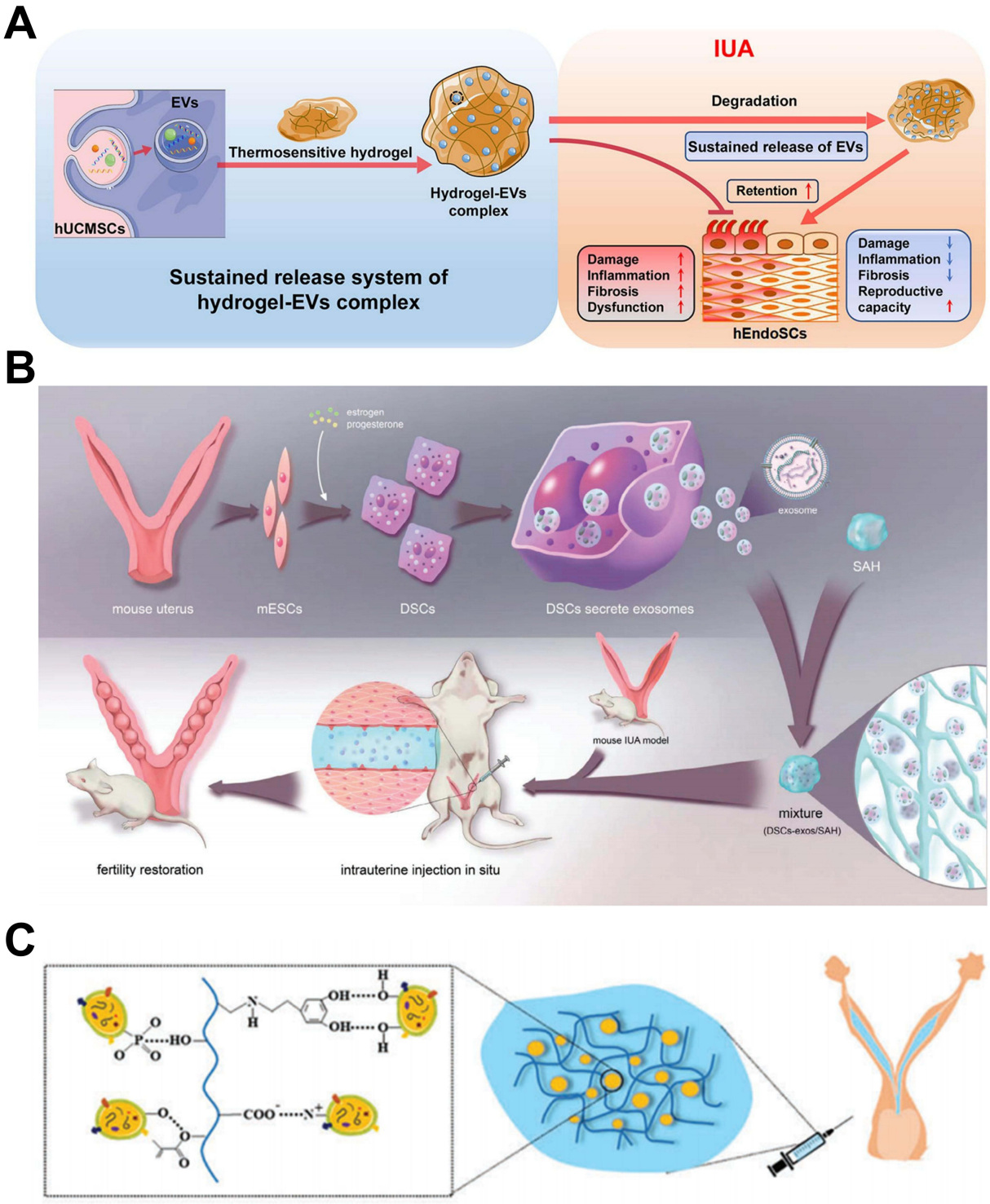

Figure 3 Application of exosomes and biomaterials in the treatment of IUA. (**A**) Thermosensitive hydrogel enhances retention and therapeutic effects of UCMSC-Exos in IUA, promoting endometrial repair and fertility restoration. Reproduced with permission from Yu S, Zhang X, Li W, et al. Thermosensitive hydrogel as a sustained release carrier for mesenchymal stem cell-derived extracellular vesicles in the treatment of intrauterine adhesion. *J Nanobiotechnology.* 2024;22(1):570.[92] (**B**) Schematic of decidual stromal cell (DSC)-derived exosomes encapsulated in SAH scaffold for intrauterine injection, promoting endometrial regeneration, angiogenesis, MET, and fertility restoration in IUA through miRNA-mediated repair. Reproduced with permission Liang Y, Shuai Q, Zhang X, et al. Incorporation of decidual stromal cells derived exosomes in sodium alginate hydrogel as an innovative therapeutic strategy for advancing endometrial regeneration and reinstating fertility. *Adv Healthc Mater.* 2024;13(13):e2303674. © 2024 Wiley-VCH GmbH.[127] (**C**) Schematic representation of chitosan/glycerophosphate (CS/GP)-loaded ADSC-Exos, and non-covalent interactions (hydrogen bonds) between CS/GP and ADSC-Exos. Reproduced with permission from Sun H, Dong J, Fu Z, et al. TSG6-Exo@CS/GP attenuates endometrium fibrosis by inhibiting macrophage activation in a Murine IUA model. *Adv Mater.* 2024;36(21):2308921. © 2024 Wiley-VCH GmbH.[86]

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significant challenges for achieving long-term exosome retention and controlled release, often requiring chemical crosslinking or blending strategies to enhance stability and function.[130]

In terms of delivery strategies, injectable hydrogels have gained popularity due to their minimal invasiveness and ability to conform to the irregular geometry of the uterine cavity, making them especially appropriate for localized exosome administration. Thermosensitive or shear-thinning hydrogels not only facilitate efficient intraluminal injection but also form in situ depots that sustain exosome presence at the lesion site.[92] However, the mechanical support they provide is limited, particularly in severe cases of endometrial fibrosis. In contrast, three-dimensional (3D) printed scaffolds offer higher architectural precision, mechanical robustness, and spatial control over pore distribution, which allow for greater customization and potentially enhanced endometrial tissue regeneration. These scaffolds can also be preloaded with exosomes and fabricated to enable temporally controlled release under physiological conditions.[3] Yet, their implantation typically involves surgical procedures, making them less desirable for patients requiring conservative treatment approaches.

The compatibility between biomaterial types and exosome therapy is thus a key determinant of therapeutic efficacy. Natural hydrogels may be more suitable for early-stage IUA or cases requiring bioactive scaffolding, while synthetic hydrogels and 3D-printed materials offer superior tunability for complex pathological contexts or where mechanical reinforcement is needed. Recent experimental models further underscore this distinction. For example, Lin et al developed a silver-ion-crosslinked PEGDA hydrogel delivering adipose-derived stem cell exosomes, demonstrating improved epithelial integrity and angiogenesis in an IUA model.[77] Similarly, Gu and colleagues employed 3D-printed collagen–chitosan scaffold embedded with BDNF-stimulated stem cell-derived exosomes, showing enhanced neuroregeneration and long-term functional restoration, suggesting that structurally robust scaffolds may be particularly beneficial for severe adhesion cases requiring prolonged exosome retention.[131] Altogether, a nuanced understanding of biomaterial–exosome compatibility is vital for optimizing therapeutic strategies in IUA. Material selection should be aligned with disease severity, regenerative goals, and exosome characteristics.

Potential Therapeutic Mechanisms of Combined Applications of Exosomes and Biomaterials in IUA Treatment

The integration of exosomes and biomaterials represents an emerging and versatile strategy for the treatment of IUA, addressing multiple pathological processes such as fibrosis, impaired angiogenesis, immune dysregulation, and insufficient endometrial regeneration. This combined approach not only enhances therapeutic specificity and efficacy but also enables localized and sustained delivery, while modulating the uterine microenvironment to facilitate tissue repair.

However, despite encouraging preclinical findings, mechanistic studies and the development of corresponding therapeutic strategies remain in their early stages. Integrating the latest insights into the pathogenesis of IUA with advances in exosome-based interventions from other disease contexts, it becomes evident that research on exosome applications in IUA is still limited—particularly with regard to understudied mechanisms such as autophagy and ferroptosis, as well as the design of exosome–biomaterial composite systems. Within this context, a systematic elucidation of the current therapeutic mechanisms underlying exosome-biomaterial synergy in IUA not only bridges existing knowledge gaps but also lays the groundwork for the development of more precise and effective regenerative treatments.

Anti-Fibrotic Mechanisms

Fibrosis is a central pathological feature of IUA, characterized by excessive ECM deposition and disruption of normal endometrial architecture. Integration of MSC-derived exosomes with scaffold biomaterials has been shown to attenuate fibrosis by downregulating key profibrotic genes (COL1A1, COL5A2, and α-SMA) through inhibition of the TGF-β/Smad and YAP/TAZ signaling pathways.[85] For instance, a study using MSC-derived exosomes loaded onto a heparin-poloxamer hydrogel demonstrated significant suppression of Smad2/3 phosphorylation, thereby reversing EMT and preventing further fibrotic progression.[13] Moreover, sustained delivery systems, such as collagen–chitosan composite scaffolds, facilitate prolonged exposure of the lesion site to therapeutic exosomes, amplifying anti-fibrotic effects and promoting matrix remodeling in situ.[132] Recent studies have also highlighted the role of specific miRNAs carried by

exosomes in modulating fibrotic pathways. For example, exosomes enriched with miR-122-5p have been shown to alleviate endometrial fibrosis by inhibiting the TGF-β/Smad signaling pathway.[133]

Pro-Angiogenic Mechanisms

Restoring vascular supply is critical for endometrial regeneration. Exosomes are rich in angiogenic miRNAs (eg, miR-126, miR-132, miR-21) and growth factors (eg, VEGF, FGF2) that activate endothelial proliferation and migration. When exosomes are encapsulated within thermosensitive hydrogels or self-assembling peptide nanogels, they provide a controlled and localized release of angiogenic signals.[134] These systems stimulate the PI3K/Akt, ERK1/2, and SDF-1/CXCR4 pathways to enhance capillary density and vessel maturation in damaged endometrial tissue.[135] Furthermore, low-oxygen preconditioning of exosome-producing cells (eg, hypoxia-induced ADSC-EVs) significantly boosts VEGF content, resulting in superior vascular network formation.[136] Additionally, exosomal tRF-1003 has been identified to induce angiogenesis via regulating the HIF1α/VEGF signaling pathway through MAPK1, providing a novel perspective on the mechanisms driving angiogenesis.[137]

Immunomodulatory Mechanisms

Chronic inflammation and dysregulated immune responses play pivotal roles in the formation and persistence of IUA. TSG-6-modified exosomes have shown potent anti-inflammatory properties. By inhibiting NF-κB signaling, these exosomes reduce the secretion of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) while enhancing anti-inflammatory mediators (TGF-β1, IL-10).[86] In animal models, such engineered exosome-biomaterial systems have been shown to reprogram local macrophage phenotypes from M1 (pro-inflammatory) to M2 (pro-regenerative), further supporting tissue repair. Additionally, integration with hyaluronic acid-based hydrogels enhances CD44-mediated immune regulation and cell-matrix interactions.[14] Moreover, exosomes derived from LPS-preconditioned bone marrow MSCs have been demonstrated to accelerate wound healing by transferring TSG-6 to modulate the NF-κB/NLRP3 signaling pathway, resulting in the switch of macrophages to an M2-like subtype.[138]

Mechanisms Enhancing Endometrial Regeneration and Receptivity

The ultimate goal of IUA treatment is to restore a receptive endometrial environment capable of supporting embryo implantation. Exosome-loaded biomaterials have been shown to increase endometrial thickness, gland density, and the expression of hormone receptors including ER and PR.[10,104] Exosomes carrying miR-205-5p have been reported to enhance epithelial proliferation and suppress fibrotic gene expression by targeting ZEB1, thereby promoting endometrial epithelial remodeling and increasing receptivity.[139] Moreover, histological analyses confirm that exosome-based therapies result in organized glandular architecture, enhanced vascular density, and improved epithelial integrity, all crucial for functional endometrial recovery.[13] Additionally, exosomes derived from CTF1-modified bone marrow stem cells have been shown to mediate efficient repair of injured endometrial tissues by promoting enhanced angiogenesis and consequent improvements in endometrial receptivity.[140]

Emerging Mechanisms: Roles of Autophagy and Ferroptosis

Despite progress in anti-fibrotic and regenerative strategies, other cellular mechanisms like autophagy and ferroptosis remain underexplored in the context of IUA. Autophagy has dual roles in tissue repair. Recent studies suggest that MSC-exosomes can modulate autophagic flux in endometrial stromal cells by delivering autophagy-related miRNAs and proteins, thus balancing degradation and regeneration processes.[26] Ferroptosis, an iron-dependent form of programmed cell death, has been implicated in endometrial damage. The inhibition of ferroptosis using Fer-1 reduces ROS accumulation and EMT activation in IUA models. It is speculated that exosomes could carry GPX4-regulating miRNAs to modulate ferroptosis-related pathways, opening new therapeutic avenues.[34] Additionally, studies have demonstrated that extracellular vesicles, especially exosomes, could expel intracellular iron when stimulated by ferroptosis, which is an important mechanism driving ferroptosis resistance.[141]

Taken together, the integration of exosomes with biomaterials provides a comprehensive therapeutic strategy for IUA, engaging multiple cellular processes such as fibrosis resolution, angiogenesis, immune modulation, and endometrial regeneration. Meanwhile, emerging insights into autophagy and ferroptosis offer promising mechanistic dimensions yet

to be fully explored. Further research should aim to deepen our understanding of these pathways and refine exosome-biomaterial systems for translational application.

Future Perspectives and Translational Directions

Optimization of Biomaterial–Exosome Systems: Engineering and Design Challenges

Despite the growing success of biomaterial–exosome platforms in regenerative medicine, significant challenges remain in system optimization to ensure consistent and effective clinical outcomes. One major area of focus lies in the engineering of controlled release profiles. Exosomes, when delivered alone, are rapidly cleared from the site of injury; thus, integrating them into responsive biomaterials that provide spatiotemporal control is essential. Smart hydrogels that respond to internal stimuli such as pH or ROS have emerged as promising carriers.[142] These materials enable on-demand release in the fibrotic microenvironment characteristic of IUA, thereby improving therapeutic precision. Furthermore, the biomechanical compatibility of biomaterials must be tailored to match endometrial tissue, particularly in the case of scaffold systems. Achieving an optimal balance between biodegradability and structural integrity is critical, as premature degradation can limit therapeutic duration, while overly persistent scaffolds may interfere with tissue remodeling. Incorporating functional domains such as cell-adhesive ligands or enzymatically cleavable sequences can support both tissue integration and exosome retention. Recent advancements in nanostructured composite hydrogels, injectable elastomers, and self-healing scaffolds underscore the growing capability to customize material behavior to align with regenerative needs.[143] These engineering strategies collectively point to a new generation of bioresponsive exosome delivery systems tailored for uterine repair.

AI and Bioinformatics in Precision Design of Regenerative Therapies

To advance beyond empirical trial-and-error development, the integration of artificial intelligence (AI) and bioinformatics offers a transformative paradigm for rational design in exosome-biomaterial systems. With the availability of high-throughput sequencing and proteomic data from patients with endometrial fibrosis, machine learning algorithms can identify key molecular targets, such as miRNAs involved in TGF-β/Smad or PI3K/Akt signaling, that may serve as high-efficacy exosome cargo.[144] Deep learning frameworks trained on expression profiles have been applied to optimize exosome contents for disease-specific interventions, enabling intelligent customization of therapeutic payloads.[145,146] Concurrently, AI-driven materials informatics platforms are being developed to predict the physicochemical properties of biomaterials, such as degradation kinetics, viscoelasticity, and drug diffusion profiles, based on polymer composition and structural parameters. These tools facilitate inverse design processes, wherein therapeutic goals determine the material blueprint.[147] On the fabrication side, microfluidics technologies integrated with AI-controlled feedback systems are now used to encapsulate exosomes into hydrogel droplets with unprecedented precision and scalability. These microfluidic platforms allow real-time control of flow rates, crosslinking, and particle size, resulting in highly uniform and reproducible constructs suitable for clinical translation.[148,149] Looking ahead, the convergence of AI, systems biology, and materials science holds the potential to produce exosome-biomaterial composites that are both disease-specific and patient-specific. These advances pave the way for precision regenerative therapies tailored to uterine microenvironmental heterogeneity.

Clinical Translation of Exosome–Biomaterial Therapies: Barriers, Benchmarks, and Strategic Pathways

Regulatory and Manufacturing Challenges in Exosome Therapies

The translation of exosome-biomaterial systems into clinical applications is constrained by significant regulatory ambiguities and technical inconsistencies. Regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have yet to provide specific guidance for exosome-based therapeutics, resulting in an unclear classification that straddles biologics, cell-derived products, and combination medical devices. This regulatory ambiguity affects not only clinical trial design and quality control but also the fundamental definitions of product identity, purity, potency, and the acceptable degree of cargo heterogeneity.

On the manufacturing side, current exosome isolation methods—ultracentrifugation, size-exclusion chromatography, and polymer-based precipitation—are typically not compatible with large-scale, Good Manufacturing Practice (GMP)-compliant production.[150] Their scalability is further complicated when exosomes are combined with hydrogels or scaffold materials, which require additional control over encapsulation efficiency, release kinetics, and material degradation profiles under clinical conditions. The absence of standardized protocols introduces variability that undermines reproducibility and hinders progression toward clinical-grade batch production. Without convergence on regulatory definitions and robust manufacturing workflows, exosome–biomaterial therapeutics risk remaining in the experimental stage, regardless of their biological promise.[151,152]

Preclinical Evidence and Challenges in Clinical Translation

In recent years, exosome-biomaterial combination systems have shown significant promise in animal models of IUA, demonstrating robust regenerative potential for endometrial repair. However, clinical translation remains challenged by heterogeneity in study design, lack of long-term follow-up data, and unresolved issues related to scalability and standardization of exosome production.

In various rodent IUA models—including those induced by mechanical injury, chemical ablation, thermal cauterization, or cryogenic damage—exosomes derived from MSCs have been locally delivered via injectable hydrogels or biodegradable scaffolds to promote structural and functional recovery of the endometrium.[13,153] Studies have reported marked increases in endometrial thickness (by approximately 45–60%), glandular density, angiogenic marker expression (eg, CD31, VEGF), and Ki-67-positive cell proliferation.[154] Additionally, fertility restoration has been observed, with pregnancy rates recovering to 60–75% in previously infertile animals.[155] Despite these encouraging findings, most studies are limited by small sample sizes (typically 6–10 animals per group), inconsistent model induction methods, and a lack of rigorous randomization, blinding, or power analysis. Follow-up periods are generally short (≤4 weeks), limiting assessment of long-term endometrial receptivity or fibrotic relapse.[156] These limitations reduce the reproducibility and translational applicability of current preclinical evidence.

From a translational standpoint, large-scale manufacturing and product consistency of MSC-derived exosomes remain key obstacles. The most commonly used MSC sources include umbilical cord (UCMSC), menstrual blood (MenSC), placenta, and bone marrow. While MenSCs are ethically accessible and easily collected, they exhibit significant donor variability and limited yield, restricting their suitability for standardized production.[157] UCMSCs, on the other hand, offer strong expansion capacity and low immunogenicity, making them a frequently used source in preclinical studies. However, challenges remain in the context of allogeneic applications, including cold-chain logistics, immune compatibility, and regulatory compliance.[158]

To address these issues, current efforts are focused on standardizing donor selection criteria, establishing serum-free culture systems, and developing master cell banks to ensure the consistency of raw materials. At the same time, GMP-compliant protocols for upstream and downstream processing—including sterile manufacturing, batch traceability, and critical quality attribute (CQA) monitoring—are being implemented. The downstream phase also requires cold-chain storage and validated thawing and administration protocols to preserve exosome bioactivity throughout the clinical workflow.[159] An integrated manufacturing and delivery framework is therefore essential for enabling the clinical-grade application of exosome therapeutics.

Notably, early clinical investigations have also provided preliminary support for the therapeutic potential of exosomes and their parent cells in IUA. Several small-scale, open-label studies have reported that intrauterine infusion of autologous BMSCs or MenSCs significantly improves endometrial thickness (from <5 mm to >7 mm), reduces adhesion scores, and restores fertility through spontaneous or assisted pregnancies.[70,160] In addition, allogeneic UCMSC-loaded collagen scaffolds have been implanted into the uterine cavity via hysteroscopy in patients with recurrent IUA, resulting in improved menstrual volume, restoration of endometrial morphology, and upregulation of receptivity-related markers.[161] A recent prospective randomized controlled trial further demonstrated that, compared with blank scaffolds, the UCMSC-loaded scaffold group achieved higher cumulative clinical pregnancy (45.5% vs 7.7%) and live birth rates (27.3% vs 7.7%) within one year. Although the differences did not reach statistical significance due to the limited sample size, the findings provide initial evidence supporting both the safety and

efficacy of this therapeutic strategy.[161] Reported adverse events were limited to mild, transient allergic reactions, indicating a favorable safety profile.

In summary, exosome-biomaterial platforms demonstrate strong regenerative potential in IUA animal models and have shown preliminary safety and efficacy in early-phase clinical studies. Nevertheless, successful clinical translation will require well-powered, rigorously designed preclinical and multi-center clinical trials to evaluate long-term therapeutic outcomes, including sustained endometrial function, pregnancy success, and safety. Concurrently, the establishment of scalable GMP-compliant production systems and unified quality control standards is essential for realizing the clinical utility of this emerging therapeutic approach.

Integrative Pathways Toward Clinical Translation

Moving beyond isolated innovations in material design or exosome engineering, a successful translation pathway will require a systems-level framework that coordinates biological insight, materials science, regulatory foresight, and manufacturing readiness. A growing number of development programs now integrate systems biology models and AI-assisted design to match disease-specific molecular profiles with rationally selected exosome cargo and delivery matrices.[162] This alignment enables closed-loop feedback between therapeutic need and material performance—a necessary evolution beyond one-size-fits-all models.

Rather than presenting a rigid translational roadmap, the field is converging toward a dynamic architecture wherein adaptive material screening, modular microfluidic manufacturing, and multiparametric in vivo assays co-evolve with regulatory consultation. For example, microfluidic-based encapsulation platforms now offer scalable, reproducible, and sterile production lines for exosome-hydrogel constructs, while preclinical models incorporate histological, molecular, and reproductive endpoints to simulate real-world clinical scenarios. Regulatory engagement is also shifting upstream, with early-phase dialogue increasingly guiding product design and batch-release criteria.[163,164]

This integrative trajectory reflects a broader paradigm shift—from treating translation as a downstream process to embedding translatability as a design principle from the outset. In this model, biomaterial–exosome systems are not simply engineered for efficacy, but architected for deployment—biologically, technically, and regulatorily. As mechanistic understanding deepens and validation platforms mature, these therapies are poised to redefine the regenerative landscape for uterine disorders and beyond.

Conclusion

The treatment of IUA is undergoing a significant shift from traditional surgical interventions to innovative regenerative medicine-based approaches. Among these emerging therapies, exosomes, as a cell-free therapeutic tool, have demonstrated immense potential in anti-fibrosis, immune modulation, and tissue repair. Rich in bioactive molecules, exosomes effectively mediate intercellular communication, suppress fibrosis, promote endometrial regeneration, and optimize the local microenvironment. Furthermore, the combination of exosomes with biomaterials extends their retention time in target tissues, enables sustained release, and significantly enhances therapeutic outcomes, offering IUA patients a durable treatment option beyond the reach of conventional methods. However, advancing the clinical translation of exosome-based therapies and their combination strategies requires substantial progress in understanding underlying mechanisms, optimizing delivery systems, and evaluating long-term safety. With continued interdisciplinary collaboration and the integration of innovative technologies, IUA treatment holds the promise of remarkable breakthroughs. These advancements are expected to deliver more effective and sustainable therapeutic solutions, ultimately improving patients' quality of life and restoring their reproductive potential.

Data Sharing Statement

No datasets were generated or analysed during the current study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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