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Progress of mesenchymal stem cells affecting extracellular matrix metabolism in the treatment of female stress urinary incontinence

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Abstract

Stress urinary incontinence (SUI) is a prevalent pelvic floor dysfunction in women post-pregnancy. Currently, conservative treatment options have low success rates, while surgical interventions often result in multiple complications. The altered state of the extracellular matrix (ECM) is a pivotal factor in the onset of various diseases and likely plays a significant role in the pathogenesis of SUI, particularly through changes in collagen and elastin levels. Recent advances in mesenchymal stem cells (MSCs) therapy have shown considerable promise in treating SUI by modulating ECM remodeling, thereby enhancing the supportive tissues of the female pelvic floor. MSCs exhibit substantial potential in enhancing urethral sphincter function, modulating connective tissue architecture, and stimulating fibroblast activity. They play a pivotal role in the reconstruction and functional recovery of the ECM by influencing various signaling pathways, including TGF-β/SMAD, JAK/STAT, Wnt/β-catenin, PI3K/AKT, and ERK/MAPK. We have reviewed the advancements in MSC-mediated ECM metabolism in SUI and, by integrating the functions of ECM in other diseases and how MSCs can ameliorate conditions through their impact on ECM metabolism, we have projected the future trajectory of SUI treatment development.

Keywords Stress urinary incontinence, Mesenchymal stem cells, Extracellular matrix, Elastin, Collagen, Connective tissue, Fibroblasts, Signaling pathways

Introduction

Stress urinary incontinence (SUI) is a global health challenge predominantly affecting women, usually triggered by increased abdominal pressure from various activities (e.g., sneezing, coughing, and physical movements) [1]. As the most prevalent form of urinary incontinence, recent data indicates that the overall prevalence of SUI among women in mainland China is 24.5% [2], with the risk of developing SUI increasing progressively with age, reaching a 50% prevalence among women over 40 [3]. The quality of life for women is inversely correlated with the severity of their condition; the frequency and volume of incontinence, as well as the compulsory use

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of urinary pads in daily life, significantly impact women's self-esteem and confidence [4]. The median annual management cost for women with urinary incontinence at baseline approaches $500 [5], imposing a substantial financial burden on patients. Histologically, SUI is characterized by pelvic tissue dysfunction and alterations in connective tissue composition [6, 7], with pregnancy and childbirth being primary causative factors due to damage to pelvic floor muscles, pubic nerves, and periurethral tissues [8]. Preferred conservative treatments include pelvic muscle exercises, medications, and urethral fillers, though they often fail to achieve success [9]. Surgical treatment is a therapeutic approach taken when conservative treatment is ineffective, including various types of slings and artificial urethral sphincter implantation. Among them, the retropubic mid-urethral sling (RMUS) and transforaminal mid-urethral sling (TMUS) have been measured to have the highest level of evidence for the feasibility and safety of treating SUI [10]. Despite the substantial evidence level supporting their feasibility and safety, surgeries are frequently complicated by issues like poor healing, nerve trauma, bladder damage, and postoperative voiding disorders [11, 12].

In recent years, regenerative medicine, particularly cellular therapies, has advanced as a potential alternative to surgical interventions for treating urinary incontinence, potentially expanding the range of treatment options. Mesenchymal stem cells (MSCs) are a prevalent type of stem cell utilized in the treatment of SUI. These multipotent stem cells are derived from various tissues, including bone marrow [13], peripheral fat [14], muscular tissue [15], umbilical cord [16], dental pulp [17], and urine [18]. In clinical applications, MSCs are predominantly harvested from sources such as bone marrow, umbilical cord blood, and adipose tissue [19]. These MSCs have shown significant efficacy in the treatment of SUI [20–23], by modulating immune functions and facilitating the repair of damaged tissues through both differentiation and paracrine effects [24, 25]. Paracrine mechanisms, primarily involving the secretion of growth factors (GFs), cytokines, chemokines, and extracellular vesicles (EVs), are believed to be central to the reparative actions of MSCs [26, 27]. These vesicles aid in regulating immunity, promoting cell proliferation, angiogenesis, and differentiation by transferring proteins, mRNAs, and microRNAs (miRs) to target cells [28]. EVs exhibit a wide range of diversity, with the three most extensively studied categories being exosomes(Exos), microvesicles, and apoptotic bodies(ABs) [29]. Among these, Exos are the smallest, typically measuring 30–150 nm in diameter [30]. MSC treatments have demonstrated safe and effective outcomes in phase I and II clinical trials [31], with minimal ethical concerns, promising a substantial therapeutic future in SUI management.

Inadequate urethral closure due to impaired pelvic floor support structures is the main etiology of SUI [4], with alterations in the ECM serving as a significant pathogenic mechanism [32]. The ECM constitutes a complex, three-dimensional network surrounding cells that facilitates intercellular biosignal transmission and regulates cell proliferation, differentiation, and migration, among other functions [33]. In pathological conditions, extensive remodeling of the ECM is a crucial driver of disease progression [34]. Stem cell therapy has been shown to stimulate ECM remodeling in urethral injuries in SUI, thereby improving urinary incontinence [18, 35]. However, the molecular mechanisms by which MSCs regulate the ECM of pelvic floor tissues to enhance SUI treatment remain unexplored. In this context, we review and propose a prospective study on how MSCs influence ECM metabolism in the treatment of female SUI.

Effect of MSCs on ECM metabolism

MSCs are a class of pluripotent, differentiable stromal cells [36] with therapeutic roles that include proliferation, differentiation, pluripotency, homing/migration, nutrition, and immunomodulation [37]. These functions vary according to the stem cell type and the extracellular environment. In 2006, MSCs were first proposed as mediators of therapy through their secretory effects [38], involving GFs, cytokines, chemokines, and EVs as paracrine mediators [39]. Recent preclinical studies have confirmed that MSC treatments primarily operate through these mediators [40–42], addressing diseases such as cirrhosis, psoriasis, and pulmonary fibrosis. One study on the role of adipose-derived stem cells (ADSCs) in heart valve tissue engineering found that ADSCs secrete ECM components like collagen and elastin [43], marking a significant advancement in treating ECM-related diseases. MSCs modulate ECM metabolism in various diseases, including fibrosis [44], cancer [45], wound healing [46], neuroinflammation [47], and SUI [48], suggesting that MSCs not only differentiate but also regulate ECM through secreted factors, providing a new direction for female SUI treatment.

It has been shown [18, 35] that stem cells facilitate SUI recovery by modulating ECM metabolism, primarily enhancing urethral function, with the ECM playing a pivotal role in maintaining the integrity and functionality of pelvic floor support structures. Collagen and elastin are crucial components of the ECM. Collagen, abundant and diverse, is predominantly found in pelvic floor support tissues like the vaginal wall and fascia, with types I, III, and to a lesser extent, V being most prevalent. Type I collagen plays a role in regulating cellular activity and promoting growth, contributing to tissue support and strength, while type III collagen is linked to tissue elasticity, and type V's role remains poorly understood [32].

During tissue healing, collagen III is prevalent in the initial stages of ECM formation, transitioning to collagen I during the maturation and remodeling phases [49]. Preclinical studies have shown a significant reduction in collagen types I and III in the anterior vaginal wall of SUI rats, whereas increased pelvic floor collagen has alleviated urinary incontinence [50, 51]. Elastin, the primary component of tissue elastic fibers, facilitates contraction and stretching, playing a vital role in maintaining normal pelvic floor function [52, 53]. Moreover, elastin is an essential element of pelvic floor connective tissue, with abnormalities associated with dysfunction, particularly in SUI and pelvic prolapse [54]. Elastin fiber dysfunction leads to a loss of elasticity, impeding urethral sphincter contraction and disrupting the urethral closure mechanism, leading to SUI [55]. In treating SUI, MSCs can act directly or influence other cells, such as fibroblasts, to remodel the ECM of pelvic floor support structures (Fig. 1). and regulate ECM metabolism signaling pathways.

MSCs remodeling pelvic floor support structure ECM

The normal urethral sphincter, intact anterior vaginal wall, and periurethral connective tissue are crucial pelvic floor support structures that regulate urethral opening and closing in response to abdominal pressure changes [56], along with the anorectal muscle, which also plays a supportive role [57]. The urethra is mainly anchored by the anterior vaginal wall, enriched with a dense ECM produced by fibroblast regulation [58]. In addition, connective tissue contains essential pelvic floor support components, with collagen and elastin fibers being crucial elements of the matrix [50]. MSCs' remodeling of the ECM in pelvic floor support structures in women with SUI primarily focuses on the connective tissue surrounding the urethral sphincter and the anterior vaginal wall, predominantly enhancing incontinence management by regulating the collagen and elastin levels that maintain tissue stability and relaxation. (Table 1).

ECM around the urethral sphincter

The urethral sphincter, a vital part of the urethral support structure, comprises the internal urethral sphincter (IUS) and external urethral sphincter (EUS). These structures are intrinsic to urethral closure and typically function in conjunction with secondary exogenous closure structures (such as the anal retractor and puborectalis muscles) [56]. Damage to the urethral sphincter or weakening of support structures can cause the urethra to fail to close under increased intra-abdominal pressure, leading to urine leakage [59]. The balance of forces between elastic and collagen fibers is critical for maintaining normal urethral sphincter function, with abnormal collagen remodeling of periurethral tissues and a loss of functional elastic fiber network observed in a rat model of SUI [60]. Therefore, the degradation of collagen and elastin in periurethral tissues is closely linked to the development of urinary incontinence. MSCs are capable of repairing the damaged urethral sphincter and performing injectable

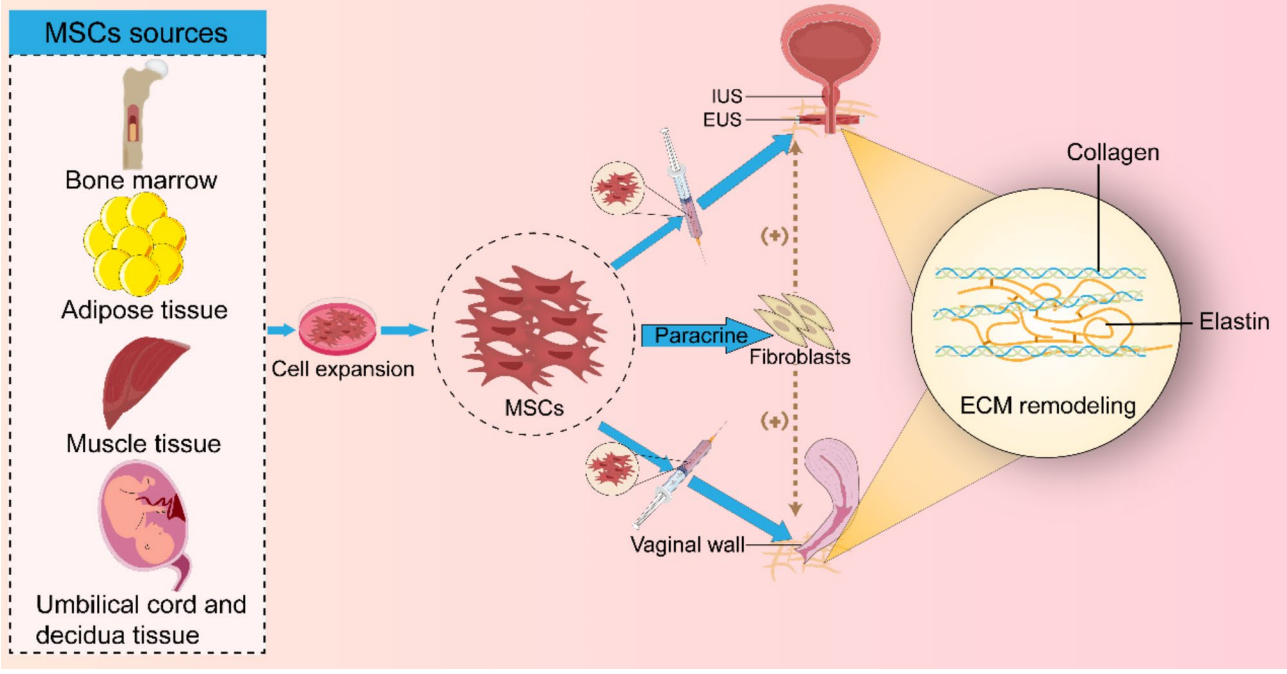

Fig. 1 Remodeling of pelvic floor support tissue ECM by MSCs from different tissue sources

Table 1 Preclinical trial of MSCs injection for SUI in Women

Study	Animals/Model	Stem cell source	Cell count (/mL)/reagent volume	Route of injection	Compositional changes in periurethral/vaginal ECM after injection	Measurement situation
Lin et al. [59]	Rat / VD + ovariectomy	Rat ADSCs	1×10^6	Intravenous injection into the urethra or tail vein	Significant increase in periurethral elastin content	LPP was significantly elevated
Dissaranan et al. [60]	Rat /VD	Rat BMSCs, CCM	2×10^6	Lateral caudal vein injection	Significant increase in elastin fibers around the urethra	LPP significantly elevated, EUS EMG not improved
Deng et al. [61]	Rat /VD + PNC	Rat BMSCs, CCM	2×10^6	Tail vein injection	Periurethral elastin fibers are reoriented, and density increases near EUS.	LPP and PNSBP accelerated recovery, but EUS EMG did not improve significantly
Bilhar et al. [62]	Rat /VD	Rat MDSCs	1×10^6	Medial tail vein injection	Increased expression of type I collagen and type III collagen around the urethra	unmeasured
Janssen et al. [63]	Rat /VD + PNC	Rat BMSCs	$2/4/6\times10^6$(private injection)	Lateral caudal vein injection	Thickening of elastin fibers around the urethra	LPP was significantly elevated, with no significant effect of EUS EMG or PNENG
Zhang et al. [64]	Rat / Abdominal urethral lysis	Rat BMSCs	2×10^6	Wall of the urethra injection	Increased levels of periurethral elastin, type I collagen, and type III collagen	LPP was significantly elevated
Jiang et al. [65]	Rat /VD + PNC	Rat BMSCs-CCR1 + CCL7	2×10^6	Intravenous injection	Significant increase in the percentage of collagen around the urethra	LPP, EUS EMG, and PNMBP were all significantly elevated
Paz et al. [23]	Rat /VD	Human DMSCs	Two injections of 2×10^6 each (one week apart)	Bilateral injections into the periurethral area	The presence of larger elastic fibers around the urethra	LPP was significantly elevated
Sadeghi et al. [66]	Rat /VD	Human BMSCs	1×10^6	Periurethral or intravenous injection	The ratio of total urethral connective tissue area to total urethral tissue area was significantly elevated.	LPP was significantly elevated
Janssen et al. [67]	Rat /VD + PNC	Human BMSCs	2×10^6	Intravenous injection	Increased elastic fiber density and decreased collagen deposition in the vaginal wall	LPP, EUS EMG were not significantly elevated
Jiang et al. [68]	Rat /VD	Human BMSCs, CCM	0.4 ml	Periurethral injection	Significantly increased collagen content in tissues of the mid-urethra and adjacent anterior vaginal wall	LPP was significantly elevated

VD: Vaginal Dilatation, PNC: pudendal nerve crush, EUS EMG: external urethral sphincter electromyography, PNENG: pudendal nerve electroneurogram, PNSBP: pudendal nerve sensory branch potential, PNMBP: pudendal nerve motor branch potentials, ADSCs: adipose mesenchymal stem cells, BMSCs: bone marrow mesenchymal stem cells, DMSCs: decidual mesenchymal stem cells, LPP: leak point pressure, CCM: concentrated conditioned medium

treatments that differentiate into smooth muscle cells for direct repair [61, 62], but also indirectly affect the urethral sphincter and peripheral ECM through paracrine effects [35].

As early as 2010, Lin et al. [61] administered urethral injections of ADSCs using a vaginal balloon dilatation and bilateral ovariectomy-induced SUI model in postpartum rats. Histological analysis revealed significantly higher elastin levels in the treated group compared to the model group, suggesting that ADSCs mediate tissue recovery, including elastin, through cytokines. Subsequently, Dissaranan et al. [63] performed vaginal dilatation (VD) in sprague-dawley (SD) female rats to simulate birth injury, injecting the model rats intravenously with autologous bone marrow mesenchymal stem cells (BMSCs). Measurements indicated that, compared to the control group, VD rats exhibited an increase in elastin and fibers in the peripheral matrix of the EUS, along with a significant improvement in leak point pressure (LPP). Although there was no significant change in external urethral sphincter electromyography (EUS EMG), MSCs demonstrated a remodeling effect in the ECM through paracrine secretion, potentially enhancing EUS function. It is important to note that no specific paracrine factors were identified in this experiment. The following year, Deng et al. [64] developed a similar rat model of birth injury induced by dual vaginal dilatation plus pudendal nerve crush (VD + PNC) injury, treating it with BMSCs via tail vein injection, and reported similar results. Additionally, fewer animal experiments have utilized myogenic stem cells (MDSCs); however, Bilhar et al. [65] explored MDSCs effects on urethral recovery in

female SUI model rats. After MDSC treatment, observed were neogenesis, urethral muscle regeneration, and a significant increase in collagen type I alpha 1 (Co1α1) and collagen type III alpha 1 (Col3α1) gene expression, indicating sustained recovery of urethral tissue. This underscores the significant potential of MSCs and their secretions for ECM repair in the treatment and prevention of SUI.

All aforementioned studies focused on the effect of a single MSC dose in a rat SUI model. Janssen et al. [66] explored the impact of multiple MSC doses on maintaining urethral function, employing a VD + PNC double injury SD female rat model. This injury model revealed thinner and more susceptible elastic fibers in the urethral sphincter, particularly in the internal urethral sphincter (IUS). Treatment with single and multiple doses of MSCs significantly improved elastin production and fiber thickening, and somewhat prevented disruption of the EUS. Although the three-dose treatment groups showed significant improvement in LPP relative to the control group, differences among these groups were minimal, likely due to multiple comparisons and the small sample size. Notably, peak bladder pressure was significantly higher in the maximum dose MSC-treated group compared to others, offering another metric for assessing urethral function. This study suggests that MSC treatment enhances urethral integrity by increasing periurethral elastin and restoring neuromuscular function, with higher doses amplifying this effect.

In recent years, BMSC-derived small extracellular vesicles (sEV) have been reported to increase the synthesis of ECM proteins such as elastin, collagen I, and collagen III around the urethral sphincter, enhancing the length and thickness of elastic and collagen fibers [67]. sEV, also known as Exos. In a novel study, the combinatorial therapy of MSCs overexpressing chemokine receptor 1 (CCR1) and the chemokine (C-C motif) Ligand 7 (CCL7) was found to more effectively promote collagen synthesis and muscle fiber thickening around the EUS [68]. Utilizing a VD + PNC rat model, these MSCs were genetically modified to overexpress CCR1 and administered via tail vein injection prior to treatment with BMSCs, followed by the periurethral injection of CCL7. Recently, Paz et al. [23] extracted decidua mesenchymal stem cells (DMSCs) from the maternal layer of the human placenta, known as the decidua. These DMSCs were injected periurethrally into VD-treated rat models, and histological analysis revealed an increase in elastic fibers around the EUS, coincident with improved urinary incontinence. Furthermore, they isolated myofibroblasts from the suburethral tissue of SUI patients and observed a significant reduction in senescence-associated secretory phenotype (SASP) components, such as monocyte chemoattractant protein (MCP-1) and MCP-3, post-treatment, suggesting that the pathogenesis of SUI may also involve the senescence of pelvic tissue cells.

These studies have investigated cell-free therapies, combination therapies, and stem cells from various tissue sources for SUI treatment, enhancing EUS function through regenerative processes and likely by modulating collagen and elastin synthesis. However, differences between animal models and human diseases necessitate further investigation into MSC treatments in humans.

ECM in connective tissue

The connective tissue surrounding the urethra and vaginal wall is a critical component of the urethral support structure, assuming both supportive and connective roles [69]. Rich in ECM, connective tissue maintains functional integrity as a physical scaffolding for cells, tissues, and organs, significantly contributing to the biomechanical properties of tissues, crucial for elasticity and strength [70, 71].

Impairment of functional ECM in connective tissue is a key change in the pathophysiology of SUI. Altered ECM metabolism in periurethral connective tissue has been reported in patients with SUI [32, 72]. Human umbilical cord mesenchymal stem cells (huc-MSCs) have been found to enhance SUI by augmenting urethral connective tissue [73], possibly through paracrine and anti-inflammatory effects. Some researchers have observed that in vivo injection of MSCs into rats with periurethral connective tissue hemorrhage following VD restored both urethral and systemic connective tissue and vascularity [74]. This effect may extend to the vaginal wall organization, as Janssen et al. [75] noted that BMSCs improved the biomechanical properties of the vaginal wall, possibly through ECM remodeling. After VD + PNC, while elastin in the vaginal wall was reduced and collagen deposition increased, intravenous MSC administration resulted in an increase in elastin fiber density and a return to normal collagen levels, accompanied by a recovery of vaginal fibrosis and improved urethral function. Increased expression of matrix metalloproteinase-9 (MMP-9) following vaginal injury degrades ECM components, but MSCs can reverse MMP-9 expression and reduce ECM loss, significantly benefiting the pelvic floor support structures [76] and presenting excellent potential for restoring SUI caused by pelvic floor disorders.

MSCs modulate fibroblast remodeling of the ECM

The relationship between ECM formation and fibroblasts is well-established, highlighting mechanisms associated with MSC treatment of SUI involving fibroblast-driven ECM metabolism.(Fig. 2).

Fibroblasts, the primary cellular component of connective tissue, secrete collagen, elastin, and glycoproteins, which are integral to ECM composition and remodeling

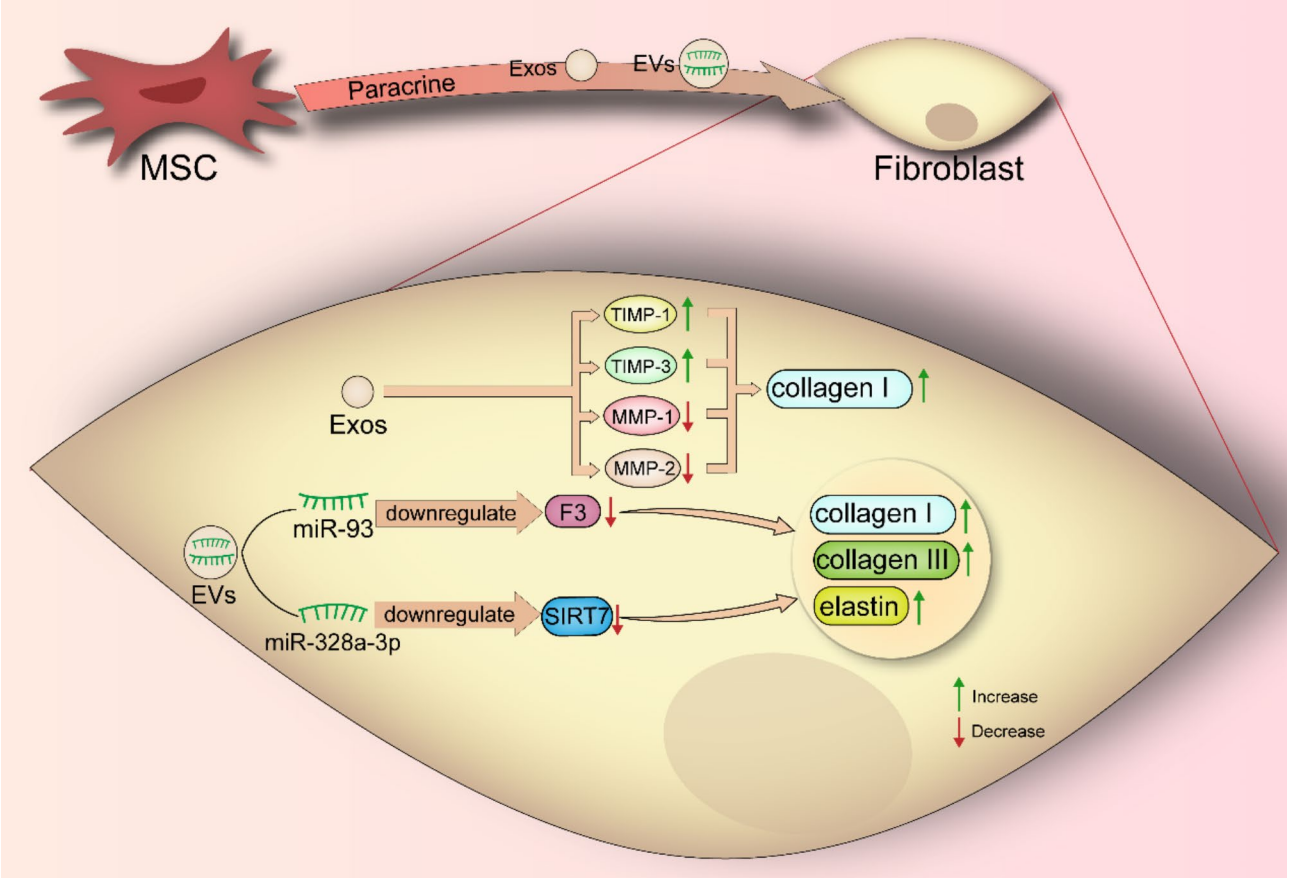

Fig. 2 MSCs regulate fibroblasts through paracrine effects. After MSCs-secreted EVs and Exos are internalized by fibroblasts, their loads of miR-93, miR-328-3p, and other substances regulate fibroblast remodeling of the ECM

[77]. Their dysfunction is linked to the development of SUI. Excessive mechanical stress, such as childbirth, damages fibroblasts, increasing intracellular levels of reactive oxygen species (ROS) and apoptosis [78, 79]. It has been reported [80] that female vaginal fibroblasts can secrete sEV, and increased secretion of fibroblast-sEV during SUI impairs the normal function of fibroblasts to express collagen. Differential analyses suggest this may be related to tissue inhibitor of metalloproteinase-2 (TIMP-2), transforming growth factor-beta (TGF-β), and ATP-binding cassette subfamily C member 4 (ABCC4), among other mechanisms. Regulation of ECM by fibroblasts has also been associated with non-coding RNAs such as miR-34a, miR-93, and miR-328a-3p [48, 51, 67, 81]. miR-34a down-regulates nicotinamide phosphoribosyltransferase (Nampt) expression, miR-93 suppresses coagulation factor III (F3) and calpain-2 expression, and miR-328a-3p down-regulates sirtuin7(SIRT7) expression, reductions in these substances could promote collagen synthesis to regulate ECM remodeling. Non-coding RNAs, including miRs, negatively regulate gene expression at the transcriptional level by binding to their target RNAs [82].

MSCs are closely associated with fibroblasts, able both to differentiate into fibroblasts for repairing damaged connective tissues after injury [83] and to regulate fibroblasts and thus ECM remodeling through the secretion of EVs [84]. MSCs-derived Exos were shown in skin healing studies to be taken up by fibroblasts, stimulating cell migration, proliferation, and collagen synthesis [85]. In SUI treatment, this mechanism was demonstrated by Jiang et al. [86], who used BMSCs-conditioned medium (CM) to culture vaginally isolated adventitial fibroblasts, treated with increased proliferation, migration rate, and production of collagens I and III, facilitating recovery in rats with simulated SUI after VD. Liu et al. [87] assessed the effect of ADSCs-Exos on collagen metabolism in cultured fibroblasts from women with SUI. They isolated fibroblasts from periurethral vaginal wall tissues of women with SUI who had no severe pelvic disease or prior pelvic surgery, noting significantly reduced collagen levels compared to controls. After treating these fibroblasts with ADSC-Exos medium for 6 h, they found down-regulation of MMP-1 and MMP-2, up-regulation of tissue inhibitor of TIMP-1 and TIMP-3, and

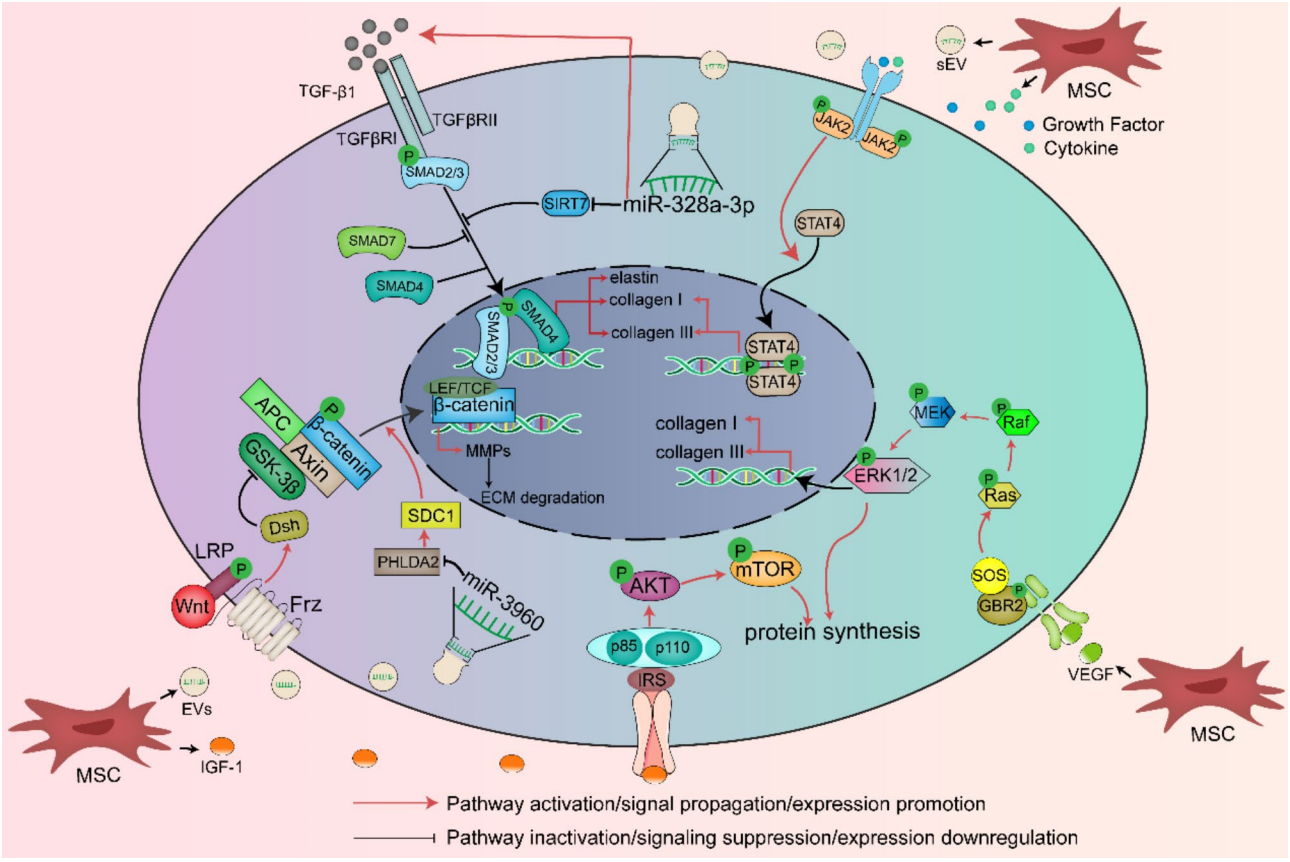

Fig. 3 Signaling pathways of MSCs-driven intracellular ECM. Signaling pathways of MSCs-driven intracellular ECM. In the TGF-β/SMAD pathway, BMSCs-EVs load miR-328a-3p into fibroblasts. miR-328a-3p downregulates SIRT7 expression, which in turn promotes the binding of phosphorylated SMAD2/3 to SMAD4 into the nucleus and promotes the expression of elastin, collagen I, and III. In the JAK/STAT pathway, cytokines and GFs secreted by BMSCs bind to target cell receptors and activate JAK2-STAT4 phosphorylation, and p-STAT4 forms a dimer to enter the nucleus and promote collagen I and III expression. In the Wnt/β-catenin pathway, miR-3960 loaded by MSCs-EVs entered the target cells and down-regulated PHLDA2, inhibiting ECM degradation induced by this substance. In the PI3K/AKT pathway, IGF-1 secreted by MSCs activated PI3K-AKT-mTOR phosphorylation and regulated intracytoplasmic protein synthesis. In the ERK/MAPK pathway, VEGF secreted by MSCs can activate Ras-Raf-MEK-ERK1/2 phosphorylation, which promotes the expression of collagen I and III in the nucleus and regulates protein synthesis in the cytoplasm

significantly higher collagen I content than in the phosphate buffer-treated group.

Wang et al. [48] demonstrated that ADSCs-EVs could regulate fibroblasts to contribute to pelvic floor tissue ECM remodeling in SUI. They explored the specific mechanism of the miR-93/F3 axis involved in SUI in ADSCs-EVs: after ADSCs-EVs carrying miR-93 were engulfed by fibroblasts, the expression of the target gene F3 was suppressed. In another similar study [67], miR-328a-3p was found to downregulate SIRT7 in human primary fibroblasts and SUI rats, promoting elastin and collagen I production. The downregulation of F3 and SIRT7 in fibroblasts in both studies promoted ECM metabolism.

MSCs activate intracellular ECM-related signaling pathways

The potential mechanisms through which MSCs influence ECM metabolism are extensive and form a complex regulatory network, with some key signaling pathways now well-defined. This study details the cytokine networks involved in ECM production by MSC-activated cells and several major signaling pathways that may contribute to ECM formation, either independently or interactively.(Fig. 3).

TGF-β/SMAD signaling pathway

The TGF-β superfamily consists of structurally related cytokines that are crucial within cells. The TGF-β/SMAD pathway is the principal route regulating collagen synthesis in fibroblasts [88] and plays a vital role in activating fibroblasts that promote ECM synthesis in skin and other organ tissues [89]. This pathway is intimately linked with ECM gene expression and fibrosis, encompassing heart,

liver, kidney, lung, and skin fibrosis [88], and extends to ECM-associated disorders such as SUI, urge incontinence, and pelvic prolapse [90]. TGF-β, a pleiotropic cytokine, regulates cellular behavior and plasticity across various tissues. Its myriad cellular responses are primarily mediated through the classical SMAD signaling pathway, although it also employs non-classical pathways like PI3K/AKT to regulate collagen and ECM homeostasis efficiently [91]. TGF-β1/SMAD is pivotal in ECM metabolism, implicated in the pathogenesis of mechanical injury-induced SUI, though the specific effects and underlying mechanisms remain poorly defined [92]. Classically, TGF-β activates the type I receptor (TGFβRI), which phosphorylates SMAD2/3; these then bind to SMAD4 and translocate into the nucleus to influence gene expression, a process inhibited by SMAD7 [93].

Zhang et al. [67] explored the specific impact of BMSCs-derived sEV on the TGF-β1 signaling pathway in urothelial function and ECM remodeling both in vivo and ex vivo. sEV are readily absorbed and internalized by fibroblasts and tissues surrounding the urethra. They discovered that miR-328a-3p carried by BMSCs-sEV is a crucial upstream regulator of ECM, antagonizing the expression of SIRT7. SIRT7 is a nucleolar-dependent deacetylase that opposes TGF-β1 signaling and total SMAD2/3 protein phosphorylation, thus regulating ECM [93]. Therefore, the remodeling of the urethral sphincter ECM by BMSCs is facilitated by the secretion of sEV containing miR-328a-3p, which is internalized by periurethral tissue cells and down-regulates SIRT7 to enhance ECM secretion. This mechanism improves the ECM of the damaged urethral sphincter and represents a novel approach to treating SUI.

In recent years, efforts have increased to enhance SUI management by modulating the ECM through TGF-β/SMAD signaling. Liu et al. [94] discovered that dimethyl fumarate (DMF) upregulated nuclear factor erythroid 2-related factor 2 (Nrf2) levels, activating the TGF-β1/SMAD3 pathway to regulate collagen and elastin in the pelvic floor, thereby improving incontinence. Li et al. [95] found that puerarin might serve as a therapeutic agent for SUI, with its mechanism involving the regulation of collagen metabolism in mouse L929 fibroblasts by promoting the Nrf 2/TGF-β1 signaling pathway while also protecting fibroblasts from mechanical traction injury. Nrf2, a critical antioxidant gene inducer, can be modulated by huc-MSCs in some cells in vivo via EVs [96, 97]. Therefore, Nrf2 emerges as a potential therapeutic target for MSCs in SUI treatment to mitigate fibrosis and inflammation. Future studies may reveal MSCs' ability to reduce ECM damage in pelvic floor tissues through activation of Nrf2/TGF-β/SMAD, aiming to ameliorate or prevent SUI.

JAK/STAT signaling pathway

The janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway, while relatively straightforward, is crucial for cell proliferation, differentiation, apoptosis, and immune response. The classical STAT pathway involves cytokine binding to its receptor, leading to tyrosine phosphorylation and activation of receptor-associated JAK, followed by phosphorylation and activation of STAT. Once activated, tyrosine-phosphorylated STAT (p-STAT) forms a dimer that translocates to the nucleus, binds to target DNA sequences, and regulates gene expression. In the non-classical pathway, unphosphorylated STAT also forms a dimer that enters the nucleus to regulate transcription [98]. The JAK family includes JAK1, JAK2, JAK3, and Tyrosine kinase 2 (Tyk2), with seven identified STAT family members (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, STAT6) [99].

Studies on JAK/STAT in SUI are limited. Jiang et al. [86] found that BMSCs enhanced SUI treatment by promoting fibroblast proliferation, migration, and collagen production in the anterior vaginal wall of rats via the JAK2/STAT4 pathway. Utilizing the properties of BMSCs-secreted proteome, they cultured fibroblasts from the vaginal tissue of SUI model rats with BMSCs-CM, observing significantly higher levels of phosphorylated janus kinase 2 (p-JAK2) and p-STAT4 compared to controls. GFs and cytokines binding to membrane receptors in BMSCs-CM elevated p-JAK2 and p-STAT4 levels in fibroblasts, with JAK2 inhibitor treatment reversing these effects. This led to a notable increase in LPP, enhancing vaginal antrum fibroblast survival and collagen fiber regeneration in the treated group. In addition, a study [100] on self-healing biomaterials discovered that a novel basic fibroblast growth factor (bFGF)/stromal cell-derived factor (SDF-1)/hydrogel cross-linking material effectively induced BMSCs homing and enhanced collagen production in vaginal tissues, with kyoto encyclopedia of genes and genomes (KEGG) enrichment analysis confirming that the JAK-STAT signaling pathway plays a key role associated with collagen production, though more specific mechanisms need further exploration. Therefore, MSCs play a broad role in treating diseases like SUI caused by ECM injury in pelvic floor tissues through regulation of the JAK/STAT signaling pathway.

Wnt/β-catenin signaling pathway

The Wnt/β-catenin signaling pathway is central to various biological processes, including cell proliferation, differentiation, apoptosis, stem cell self-renewal, tissue homeostasis, and wound healing. It is an evolutionarily conserved pathway, typically divided into β-catenin-dependent and independent types [101]. Classical pathway transduction primarily involves extracellular Wnt protein binding to frizzled(Frz) protein and co-receptor

low-density lipoprotein receptor-related protein 5/6 (LRP5/6). This triggers phosphorylation of disheveled protein (Dsh), transmitting signals into the cytoplasm to inhibit glycogen synthase kinase 3 β (GSK-3β) activation, leading to accumulation of intracellular cytoplasmic free β-catenin. Subsequently, β-catenin enters the nucleus and binds to lymphocyte enhancer factor/T cell factor (LEF/TCF) to promote downstream gene expression [102].

Indeed, the Wnt pathway plays various roles in ECM-related diseases such as fibrosis but is considered a challenge for therapeutic targeting [103]. Identifying potent and specific Wnt pathway inhibitors for the treatment of cancer and other diseases remains one of the most significant challenges for future research in this field [104]. In recent years, the Wnt protein signaling pathway has been recognized for its key roles in various diseases, including tumors [105], fibrosis [106], pelvic prolapse [107], and SUI [108, 109]. Studies involving the ECM have shown that activation of β-catenin can be involved in both the synthesis and degradation of the ECM by secreted substances such as MMPs. In pelvic floor disorders, reduced β-catenin expression in vaginal fibroblasts may be associated with pelvic organ prolapse. One reason for this association is that a significant reduction in collagen I expression by vaginal fibroblasts was found in cases of pelvic organ prolapse, which was reversed with the use of Wnt/β-catenin activators [107]. This partially reflects the link between Wnt/β-catenin and pelvic floor dysfunction. Fewer studies have shown that MSCs improve SUI by modulating Wnt/β-catenin to regulate ECM. In other diseases, some researchers have found that EVs secreted by BMSCs, like ABs, can regulate the Wnt/β-catenin pathway to ameliorate endometrial fibrosis, though the specific molecular mechanism has not been explored [110]. Furthermore, in a study exploring chondrocyte damage in arthritis, it was found that MSC-derived EVs could load miR-3960 into cartilage tissue cells to down-regulate pleckstrin homology-like domain family a member 2 (PHLDA2) proteins, thereby inhibiting the syndecan-1 (SDC-1)/ Wnt/β-catenin axis and reducing ECM degradation [111]. In conclusion, based on the effect of β-catenin activation on collagen production in vaginal fibroblasts and its regulation by paracrine secretions from MSCs, we hypothesized that this signaling pathway may play a key role in the treatment of SUI in MSCs and may represent a promising therapeutic target.

PI3K/AKT signaling pathway

Akt, a serine/threonine kinase also known as protein kinase B (PKB), is activated by a variety of growth factors, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), insulin-like growth factor (IGF), and TGF-β. Upon activation, Akt phosphorylates numerous downstream effectors crucial for apoptosis, transcription, and carcinogenesis regulation [112]. The most prevalent activation pathway for Akt is the phosphatidylinositol 3-kinase (PI3K)-dependent route, involving two subunits, the regulatory p85 and the catalytic p110, which together activate Akt. The mammalian target of rapamycin (mTOR) is a major downstream target of Akt, completing the primary nodes of this pathway [113].

The PI3K/AKT pathway plays a significant role in ECM synthesis regulation. Recent findings suggest that silk fibroin (SF) can activate the integrin/PI3K/AKT signaling pathway in MSCs, either directly or indirectly, enhancing their paracrine function and promoting collagen production [114]. Studies focusing on the PI3K/AKT pathway in MSCs for improving SUI are limited. It has been reported that MSCs can secrete insulin-like growth factor-1 (IGF-1) [114, 115], which activates the Akt signaling pathway, accelerating pelvic floor nerve and tissue recovery in rat-induced SUI models [116, 117]. While IGF-1 is known to influence a variety of cellular processes, such as growth, motility, and differentiation, the impact of Akt activation by IGF-1 on pelvic floor ECM has not been thoroughly investigated. However, other studies have shown that IGF-1 can promote collagen synthesis in tendon tissues [118], though this effect is not direct but mediated through the co-regulation of the PI3K/Akt and ERK pathways [119]. It remains to be determined whether MSCs can regulate pelvic floor collagen synthesis via the IGF-1/PI3K/AKT axis. Consequently, the PI3K/AKT signaling pathway could be a promising therapeutic target for treating SUI.

ERK/MAPK signaling pathway

The mitogen-activated protein kinase (MAPK) signaling pathway, commonly mediated by protein kinase-coupled receptors, is evolutionarily conserved and involves receptors like the epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), and vascular endothelial growth factor receptor (VEGFR) in a receptor tyrosine kinase (RTK) signaling cascade [120]. The well-characterized MAPK family includes extracellular signal-regulated kinase 1/2 (ERK1/2), c-Jun amino-terminal kinase (JNK), p38, and ERK5. The ERK/MAPK pathway involves a multilayered kinase cascade activated by receptor-ligand binding, initiating the MAPK signaling pathway through Ras protein activation. This leads to the phosphorylation of Raf, MEK1/2, and ERK1/2 target proteins. Phosphorylated ERK1/2 activates various transcription factors to regulate gene expression and can also affect subcellular responses within the cytoplasm [121].

The MAPK pathway significantly influences ECM synthesis, degradation, and remodeling, controlling ECM dynamic stability by regulating ECM-related gene expression, such as MMPs [122]. In a study examining the

relationship between ERK1/2 and SUI in periurethral support tissue fibroblasts, the use of an ERK kinase inhibitor was shown to influence the expression of mRNAs and proteins for collagen I and III in vaginal fibroblast cultures, suggesting that the ERK/MAPK pathway affects pelvic floor collagen tissue and may be implicated in SUI pathogenesis [123]. Additionally, ADSCs were found to potentially improve SUI by activating ERK1/2 through vascular endothelial growth factor (VEGF) [124], which binds to receptor proteins and triggers a series of responses in target cells. Tissue analysis reveals an increase in collagen I/III ratios (enhancing urothelial tensile strength [125])and more dense and organized elastin. Therefore, MSCs may regulate the ERK/MAPK signaling pathway to affect ECM remodeling, offering a potential treatment for SUI and a key target for future therapeutic strategies.

Discussion

The preceding discourse has methodically delineated the impact of MSCs on female SUI from the perspectives of tissue structure, cellular function, and molecular mechanisms. Current research is predominantly confined to preclinical experiments, employing MSCs in animal models via intravenous or periurethral injections to investigate histological and molecular changes in the periurethral tissues, while monitoring parameters such as LPP, EMG, PNSBP, PNMBP, and PNENG to assess the recovery from SUI, yielding promising outcomes. However, clinical trials that delve into histological and molecular studies are scarce, focusing primarily on symptomatic improvement due to the inability to obtain post-treatment tissue samples from patients. Additionally, the administration route, therapeutic dosage, in vivo survival time, and therapeutic mechanisms of these treatments necessitate confirmation through large-sample studies. Moreover, within the realm of research concerning the molecular underpinnings of the extracellular matrix associated with MSCs in the treatment of SUI, the TGF-β/SMAD signaling cascade emerges as the predominant pathway orchestrating collagen homeostasis, with Nrf2 potentially representing a therapeutic target. Although the JAK/STAT, Wnt/β-catenin, and PI3K/AKT pathways have been identified, their precise roles in therapeutic regulation remain enigmatic. In the ERK/MAPK signaling axis, VEGF is capable of activating ERK1/2, thereby ameliorating SUI symptoms. Collectively, MSCs are posited to enhance ECM metabolism across a spectrum of signaling pathways, primarily modulating the expression of collagen I and III, as well as elastin. However, the elucidation of specific target genes or molecular targets necessitates further investigation, underscoring a critical challenge and focal point for forthcoming research endeavors.

Embryonic stem cell (ESC) therapy is widely debated due to ethical concerns. To mitigate these disputes, researchers are continuously seeking stem cell types that align with ethical standards and offer optimal efficacy, with induced pluripotent stem cells (iPSCs) emerging as a viable alternative that significantly reduces the risk of teratoma formation [126]. Additionally, since their initial extraction from bone marrow in 1974 [127], MSCs have been extensively utilized in preclinical studies for the treatment of various diseases, particularly in rodents, with their safety and efficacy being evident. Concomitantly, in the systematic review of clinical trials by Lalu et al. [128], it was observed that, aside from transient pyrexia, no other adverse effects were identified following MSC therapy. MSCs, derived from a variety of adult tissues, possess the unique capability to differentiate into endodermal, mesodermal, and ectodermal lineages, akin to the properties of embryonic stem cells, yet they circumvent the ethical dilemmas associated with human embryonic involvement [129]. Consequently, ethical controversies surrounding MSCs are virtually nonexistent. However, the primary limitations of MSCs may lie in their heterogeneity and the efficiency of their differentiation processes [130].

Conclusion

The molecular pathogenesis of SUI is not yet fully understood, with a growing body of evidence suggesting that pathological changes in the ECM of pelvic floor support tissues play a role in its pathogenesis. To date, the modulation of ECM metabolism by MSCs has been increasingly investigated in the treatment of various conditions, including SUI. Our review indicates that MSCs exhibit significant potential in enhancing urethral sphincter functionality, modulating connective tissue structure, and stimulating fibroblast activity, thereby reconstructing the ECM and restoring aberrant pelvic floor support structures through the influence on ECM-related signaling pathways such as TGF-β/SMAD, JAK/STAT, Wnt/β-catenin, PI3K/AKT, and ERK/MAPK. However, these studies are often limited by small sample sizes and are conducted exclusively in animal models, which to some extent restricts the extrapolation of findings to human conditions and heightens the uncertainty of their clinical application in humans.

Within the bounds of ethics, future research on the modulation of ECM by MSCs for the treatment of SUI may progressively employ primate models to investigate the histological changes in pelvic floor tissues induced by MSC therapy in humans, while also exploring optimal routes, dosages, and long-term effects, with the aim of providing more effective treatment regimens for clinical SUI patients. Additionally, in recent years, the technology of MSCs improving damaged tissues by secreting

Exos to regulate relevant signaling pathways in target cells has gradually matured. Nevertheless, studies involving signaling pathways within cells related to pelvic floor support tissues remain scarce, with most research being confined to macroscopic histological changes, which significantly limits the understanding of underlying mechanisms. Therefore, research on MSCs regulating target cell signaling pathways to reshape ECM in the treatment of SUI may emerge as a mainstream direction with broad prospects.

In summary, MSCs hold the potential to cure SUI, and the underlying mechanisms are likely to be progressively elucidated.

Abbreviations

SUI	Stress urinary incontinence
RMUS	Retropubic mid-urethral sling
TMUS	Transmural mid-urethral sling
MSCs	Mesenchymal stem cells
ECM	Extracellular matrix
GFs	Growth factors
EVs	Extracellular vesicles
sEV	Small extracellular vesicles
ABs	Apoptotic bodies
Exos	Exosomes
ADSCs	Adipose-derived stem cells
IUS	Internal urethral sphincter
EUS	External urethral sphincter
VD	Vaginal dilation
VD + PNC	Vaginal dilation + pudendal nerve crush
SD	Sprague-dawley
EUS EMG	External urethral sphincter electromyography
PNENG	Pudendal nerve electroneurogram
PNMBP	Pudendal nerve motor branch potentials
PNSBP	Pudendal nerve neurosensory branch potentials
LPP	Leak point pressure
BMSCs	Bone marrow mesenchymal stem cells
DMSCs	Decidual mesenchymal stem cells
USCs	Urine-derived stem cells
MDSCs	Myogenic stem cells
IUS	Internal urethral sphincter
EUS	External urethral sphincter
CCR1	Chemokine (c-c motif) receptor 1
CCL7	Chemokine (c-c motif) ligand 7
SASP	Senescence-associated secretory phenotype
MCP-1	Monocyte chemoattractant protein
huc-MSCs	Human umbilical cord mesenchymal stem cells
TGF-β	Transforming growth factor-β
ABCC4	ATP-binding cassette subfamily C member 4
MMP-9	Matrix metalloproteinase-9
TIMP-2	Metalloproteinase tissue inhibitor-2
EGFR	Epidermal growth factor receptor
FGFR	Fibroblast growth factor receptor
PDGFR	Platelet-derived growth factor receptor
VEGFR	Vascular endothelial growth factor receptor
VEGF	Vascular endothelial growth factor
IGF	Insulin-like growth factor
IGF-1	Insulin-like growth factor-1
RTK	Receptor tyrosine kinase
LEF	Lymphocyte enhancer factor
TCF	T cell factor
CM	Conditioned medium
CCM	Concentrated conditioned medium
DMF	Dimethyl fumarate
ROS	Reactive oxygen species
bFGF	Basic fibroblast growth factor
Frz	Frizzled
Tyk2	Tyrosine kinase 2
p-JAK2	Phosphorylated Janus kinase 2
SDF-1	Stromal cell-derived factor-1
KEGG	Kyoto encyclopedia of genes and genomes
PHLDA2	Pleckstrin homology-like domain family a member 2
SDC-1	Syndecan-1
LRP5/6	Low-density lipoprotein receptor-related protein 5/6
SCs	Satellite cells
MAPK	Mitogen-activated protein kinase
STAT	Signal transducer and activator of transcription
p-STAT	Phosphorylated signal transducer and activator of transcription
SIRT7	Sirtuin7
GSK-3β	Glycogen synthase kinase 3β
JNK	c-Jun amino-terminal kinase
PKB	Protein kinase B
ERK1/2	Extracellular signal-regulated kinase 1/2
SF	Silk fibroin
ESC	Embryonic stem cell
iPSCs	Induced pluripotent stem cells

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