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REVIEW

Stem Cell and Neural Progenitor Cell Therapy for Neurogenic Bladder—Where Are We in 2023?

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Abstract

Purpose of Review This review aims to consolidate the currently available literature regarding the treatment of neurogenic bladder (NGB) with stem cells or neural progenitor cells (NPCs).

Recent Findings Several promising studies published in the past 5 years suggest therapeutic potential of stem cells in treating NGB. In vitro models of NGB have demonstrated the efficacy of stem cells from varying sources to induce nerve regeneration while simultaneously improving bladder function parameters. Additionally, mesenchymal stem cells (MSCs) were found to inhibit fibrosis through the TGF-β1 signaling pathway while their effects were potentiated by elevated levels of BDNF or SDF-1. Among induced pluripotent stem cells (iPSCs), it was noted that autophagy inducers improved regenerative effects. NPCs, in a recent clinical trial, also underscored the potential for translating stem cell therapies into practice.

Summary Stem cells offer a potentially revolutionary regenerative medicine strategy for treatment of NGB. Many in vivo trials are promising, but there is a distinct shortage of clinical trials attempting to translate this success into human subjects. In the future, research should be directed towards understanding the complex mechanisms of stem cell-based therapy while moving towards the clinical applications of the technology.

Keywords Neurogenic bladder · Stem cells · Neural progenitor cells · Regenerative medicine

Abbreviations

CNS	Central nervous system
NGB	Neurogenic bladder
MSC	Mesenchymal stem cell
BM-MSC	Bone marrow derived mesenchymal stem cell
SCI	Spinal cord injury
α-SMA	Alpha smooth muscle actin
TGF-β1	Transforming growth factor beta 1
imMSC	Immortalized stem cells
BDNF	Brain-derived neurotrophic factor
TrκB	Tropomyosin receptor kinase B
CREB	CAMP-response element binding protein
PMSC	Placental stem/stromal cells
hAFSC	Human amniotic fluid stem cells
PGP9.5	Protein gene product 9.5
mRNA	Messenger ribonucleic acid
GAP-43	Growth-associated protein-43
NGF	Nerve growth factor
PNT	Pelvic nerve transection
hUC-MSC	Human umbilical cord mesenchymal stem cells
qPCR	Quantitative polymerase chain reaction
FGF	Fibroblast growth factor
TRPV1	Transient receptor potential vanilloid 1
TLR4	Toll-like receptor 4
NF-κB	Nuclear factor kappa B
MAPK	Mitogen-activated protein kinases
ADSC	Adipose-derived stem cells
iPSC	Induced pluripotent stem cells
mTOR	Mammalian target of rapamycin
NSC	Neural stem cells
SDF-1 (CXCL12)	Stromal cell-derived factor 1 (C-X-C motif chemokine ligand 12)
nNos	Neuronal nitric oxide synthase
VEGF	Vascular endothelial growth factor
bFGF	Basic fibroblast growth factor

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PI3K	Phosphoinositide 3-kinases
NPC	Neural progenitor cells

Introduction

Micturition is a complex process driven by both mechanical and physiological mechanisms. Under standard conditions, the central nervous system (CNS) coordinates a variety of neural activities to guarantee the appropriate function of the urinary system [1]. Neurogenic bladder (NGB) may emerge as a consequence of nervous system damage, leading to bladder dysfunction that manifests clinically as urinary incontinence, retention, or infections [2]. The incidence of NGB increases markedly among individuals affected with neurological conditions, including multiple sclerosis, Parkinson's disease, and spinal cord injuries [3]. Therapeutic options for management of NGB include conservative measures, medical management, minimally invasive procedures such as injection of botulinum toxin, and surgical interventions [4].

Regenerative medicine aims to create and implement new treatments to repair tissues and organs, restoring function across various medical conditions including congenital diseases, cancer, trauma, and inflammation [5]. In the context of NGB, regenerative approaches could be applied either locally, at the bladder level, or in higher-order centers such as the CNS [6]. Quintessential facets of regenerative medicine, stem cell and neural progenitor cell therapies offer potential therapeutic value in neurological disorders [7]. For instance, it has been postulated that stem-cell therapy, when employed in patients who have Parkinson's disease, could also address the NGB dysfunctions observed in these individuals [8]. By leveraging the potential of regenerative medicine, a novel therapeutic paradigm could be established, offering comprehensive and potentially curative interventions for patients with NGB and other neurologically driven urological dysfunctions. This review strives to aggregate the recent literature examining regenerative methodologies for managing NGB within the preceding 5 years.

Methodology

An English-language literature review was conducted utilizing PubMed and Google Scholar to identify articles pertinent to regenerative medicine methodologies in the treatment of NGB. The search terms employed included "regenerative medicine," "stem cells," "neural progenitor cells," and "neurogenic bladder," with the results being confined to articles published post-2018. The identified studies were reviewed, and full-text English papers on NGB and regenerative medicine approaches were thoroughly examined. Article titles and abstracts underwent manual review to ascertain their inclusion. Given the narrative nature of this review, a systematic review of the literature and abstracts was not executed, but it was rather tailored based on the question of interest.

Results

Bone Marrow-Derived Mesenchymal Stem Cells (BM-MSCs)

Mesenchymal stem cells (MSCs) represent a type of adult stem cell endowed with self-renewal properties while being able to differentiate into diverse lineages [9]. These multipotent stem cells can be derived from a great degree of sources, including bone marrow, adipose tissues, synovial fluids, ligaments, muscle, umbilical cord, and placenta [10]. The employment of BM-MSCs has gained attention in the regenerative management of NGB. In in vivo models of NGB created by either complete or incomplete spinal cord injury (SCI), Salehi-pourmehr et al. [11] observed a notable improvement in urinary dysfunction subsequent to the administration of BM-MSCs sourced from rats directly into the bladder wall. Noteworthy, statistically significant changes in bladder compliance and residual volume were noticed in the hemi-SCI group at the study's conclusion, albeit these metrics did not fully revert to pre-SCI levels. Furthermore, histological analysis showed a reduction in collagen deposition in groups treated with BM-MSCs. The BM-MSCs mitigated bladder dysfunction in the SCI model, notably in the hemi-SCI group, when transplanted during chronic injury phases. The transplantation of BM-MSCs into the bladder wall might present a novel therapeutic avenue for alleviating bladder dysfunction in SCI patients during the chronic phase of healing, particularly those afflicted with NGB disorder [11]. In a comparable study, Shen et al. [12] administered BM-MSCs into the bladder wall of rats subjected to bilateral pelvic nerve crush. Subsequently, a similar improvement in urodynamic parameters and a reduction in collagen deposition were observed. Western blot analysis showed that the injured rats, post-MSC treatment, exhibited a rise in α-SMA expression while manifesting a decline in TGF-β1, Smad2/3, and collagen type I and III expression in contrast to the control injured rats [12]. Given the association of the TGF-β1 pathway with tissue fibrosis [13], the treatment with BM-MSCs seems to exhibit anti-fibrotic attributes in the bladder. Additionally, the authors propose that BM-MSCs might foster nerve regeneration, as delineated by the enhanced expression of cholinergic neuron biomarkers in the MSC-treated animals. This study suggested that therapy with BM-MSCs could inhibit detrusor fibrosis, enhance intravesical pressure and voiding efficiency, and

partially improve voiding function in rats subjected to bilateral pelvic nerve crush [12].

Immortalized Stem Cells (imMSCs)

Tian et al. [14] suggested that an environment rich in brain-derived neurotrophic factor (BDNF) increases the regenerative effects observed with stem cell therapy. Injecting imMSCs into the bladder wall led to functional improvements of the lower urinary tract post-bilateral major pelvic ganglion injury. However, MSCs engineered to exhibit high BDNF expression showed significantly superior improvements. In cohorts treated with BDNF overexpressing MSCs, the recovery of muscle and nerve tissue was expedited. The authors hypothesized that the BDNF/TrκB/CREB signaling pathway was essential in neural tissue regeneration, as MSCs expressing BDNF resulted in a marked rise in phosphorylation levels. In a rat model of NGB instigated by nerve injury, the impact of MSCs was evident on nerve tissue repair, contributing positively to functional recovery and tissue repair of the NGB. Concurrently, it was demonstrated that enhanced expression of BDNF, which holds a specific reparative effect on nerve injury, could more efficaciously repair the injured major pelvic ganglion in the local microenvironment. This mechanism might be correlated with the activation of the BDNF/TrκB/CREB signaling pathway and the mitigation of apoptosis by the highly expressed BDNF [14].

Placental Stem/Stromal Cells (PMSCs)

Yao et al. [15] developed a rat model of NGB deriving from SCI. On the ninth day post-injury, nerve cells derived from PMSCs were administered at the injury site. Subsequent urodynamic examination revealed partial restoration of bladder function, and an apparent improvement in detrusor muscle cell morphology was observed. The authors suggested that the post-injury recovery was improved by the MSCs' capacity to differentiate into neurons, providing a protective barrier against apoptosis of cells, thereby aiding in maintaining bladder functionality. The findings of this study demonstrate that the transplantation of PMSCs could rapidly differentiate into nerve cells to compensate for the extensive apoptosis of cells [15].

Human Amniotic Fluid Stem Cells (hAFSCs)

Amniotic fluid stem cells have been explored for potential utilization in NGB therapy. In an in vivo model employing unilateral and bilateral pelvic nerve transection (PNT), Liang et al. [16] administered stem cells collected from amniotic fluid to the injury site. A cytometric assessment revealed improvements in pelvic nerve damage with hAFSCs. Moreover, both groups exhibited recovery of neurofilament density and PGP9.5 mRNA following the administration of hAFSCs. Expressions of GAP-43, p75, and NGF were diminished, while encephalins were elevated back to control levels after the treatment, indicating their involvement in this process. In summary, bladder dysfunction triggered by pelvic nerve transection could see improvement following hAFSC transplantation, with PGP9.5, GAP-43, neurotrophins, and encephalin potentially playing roles in nerve regeneration [16].

Human Umbilical Cord Mesenchymal Stem Cells (hUC-MSCs)

Human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) facilitate revascularization, reduce inflammation, and enhance the microenvironment for SCI treatment [17•]. To decipher the mechanism underlying hUC-MSC-based NGB treatment, Li et al. [18] administered the cells to rats. Through Western blot and qPCR analyses, it was observed that following SCI, the levels of collagen type I/III, FGF2, p-p38, TRPV1, TLR4, and p-NF-κB increased. However, post-MSC treatment, the levels of the proteins mentioned above were significantly decreased. It was assumed that bladder function improvement was attributed to the inhibition of the p38 MAPK/NF-κB pathway by MSCs. Animals treated with MSCs exhibited increased neuronal cell survival alongside reduced edema, inflammatory cell presence, fibrosis, and collagen deposition. In conclusion, hUC-MSCs aid in restoring bladder function post-SCI by inhibiting the p38 MAPK/NF-κB pathway [18].

Adipose-Derived Stem Cells (ADSCs)

A study by Tien et al. [19] assessed the impact of autologous adipose-derived stem cell (ADSC) transplantation on acute SCI. Forty-seven SCI patients were divided into intervention and control groups, with ADSCs cultured and transplanted in the intervention group. Post-transplantation assessments revealed improvements in motor function, bladder function, and daily living activities for all patients, with no reported side effects. All patients experienced enhanced quality of life, with 80% expressing satisfaction with the treatment outcomes. The findings suggest that ADSC transplantation may be a safe and effective therapeutic approach for SCI patients while resulting in a significant improvement in muscle function [19].

Induced Pluripotent Stem Cells (iPSCs)

Being less differentiated compared to multipotent MSCs, pluripotent stem cells have been explored for similar applications in treating NGB. Shao et al. [20] employed an in vivo SCI-based NGB model to delve into the role of autophagy in treatment with neural stem cells derived from induced pluripotent stem cells (iPSCs). The study

highlighted that the autophagy induction agent rapamycin facilitated the differentiation of iPSCs into neural stem cells by inhibiting the mTOR pathway. Additionally, upon implantation of autophagy-induced iPSCs, bladder tissue repair was noticed, while autophagy-inhibited cells yielded the reverse effect. These findings reveal that transplanting iPSC-derived neural stem cells (NSCs) can alleviate NGB following SCI, whereas autophagy inhibition results in exacerbated bladder tissue damage in SCI-affected rats, manifesting as bladder wall thickening and collagen deposition. These outcomes imply that autophagy acts as a self-repair, renewal, and protective mechanism in the transplantation of iPSC-derived NSCs for NGB treatment [20].

Stromal Cell-Derived Factor-1 (SDF-1) Mediated MSC Recruitment

SDF-1 is a highly potent chemoattractant signal involved in stem cell homing [21••]. Several studies propose that SDF-1 might play a role in the regenerative properties of BM-MSCs in treating NGB models. In a study by Zhu et al. [22••], rats with bilateral pelvic nerve damage were treated using upregulated and downregulated SDF-1 BM-MSCs. Notably, a significant improvement of NGB symptoms was observed in the groups treated with high SDF-1 MSCs, alongside enhancements in nerve repair and smooth muscle recovery. A high SDF-1 environment correlated with elevated expression levels of nNos, VEGF, and bFGF. The PI3K/AKT/mTOR and MAPK signaling pathways might be crucial to nerve recovery, as the upregulated and downregulated SDF-1 MSCs triggered their activity. Specifically, the high SDF-1 group exhibited the most explicit expression of mediators related to these pathways [22••]. In a study by Cho et al. [23], high SDF-1 expressing BM-MSCs were administered to rats subjected to bilateral pelvic nerve crush procedures. The researchers observed enhanced smooth muscle recovery associated with an upregulation of α-SMA expression in the bladder wall. Additionally, nerve recovery in the high SDF-1 group was increased, as evidenced by elevated beta-III-tubulin expression. Collectively, these investigations emphasized a promising association between SDF-1 and the tissue regenerative capacities of MSCs in the context of NGB. The authors suggest stem cell treatment may improve NGB function and recover atrophic bladder by promoting angiogenesis, tissue regeneration, and nerve recovery [23].

Neural Progenitor Cells (NPCs)

In a recent phase I clinical trial (NCT01933802), Harris et al. [24•] explored the treatment of multiple sclerosis utilizing NPCs derived from BM-MSCs. Out of the 20 participants enrolled in the trial, half exhibited enhanced bladder function following the administration of NPCs. Among the two participants diagnosed with NGB, both experienced alleviation of NGB symptoms following the treatment. Additionally, post-intrathecal NPC treatment, 70% and 50% of the participants exhibited enhanced muscle strength and bladder function, respectively. The observed potential reversal of disability in a subset of patients advocates for a larger phase II placebo-controlled study to ascertain the efficacy of intrathecal NPC treatment in individuals with multiple sclerosis [24•]. A summary of included studies in this review can be found in Table 1 and Fig. 1. Figure 2 indicates the remodeling process of NGB mediated by inflammation and growth factors.

Discussion

The multifaceted exploration of various stem cell types in the context of NGB offers a promising approach to regenerative medicine. The opposing origins of these stem cells provide a rich selection of therapeutic modalities, each with unique mechanisms of action and potential benefits. Bone marrow is a reservoir of diverse stem cell populations, with MSCs being the most significant among them. MSCs should possess the capacity for self-renewal and demonstrate tri-lineage differentiation potential into cell types such as adipocytes, chondroblasts, and osteoblasts [25]. BM-MSCs represent a notable stride in this realm, demonstrating significant improvements in bladder function in animal models of SCI. Inhibition of detrusor fibrosis is one of the crucial treatments for NGB, and the TGF-β1 signaling pathway has been closely associated with tissue fibrosis [26]. The reduction in collagen deposition and the possible anti-fibrotic properties of BM-MSCs, as exhibited in the studies by Salehi-pourmehr et al. [11] and Shen et al. [12], illuminate a promising avenue for mitigating fibrotic changes post-SCI.

The neurotrophic factor BDNF plays a crucial role in neuron development and growth, primarily by binding to tyrosine kinase B receptors [27]. In scenarios of neurodegenerative diseases, a common occurrence is the downregulation of BDNF expression [27]. In line with the findings of this review regarding high BDNF expressing MSCs, Wu et al. demonstrated that the upregulation of BDNF in stem cells enhances their therapeutic potential in addressing Alzheimer's disease [28]. Therefore, BDNF might be vital in developing stem cell-centric treatments for neurogenic disorders. The proposed BDNF/TrκB/CREB signaling pathway by Tian et al. [14] could be a central mechanism fostering neural tissue regeneration, thereby opening avenues for targeted molecular therapies in synergy with stem cell transplantation.

Stem cells obtained from amniotic fluid and membranes exhibit differentiation capacities akin to embryonic stem

Table 1 Key findings of the studies are included in this review

Reference	Year	Study	Methodology	Main findings
Yao et al. [15]	2021	Rat	Placental MSC-derived nerve cells implanted on injury site 9 days post-op	Stem cell-derived nerve cells improved bladder function after SCI
Zhu et al. [22••]	2020	Rat	imMSCs/eSDF-$1^{+/-}$ pelvic nerve perineural injection 1 week post-op	SDF-1 recruited MSCs to restore nerve tissue and improved bladder function
Salehi-pourmehr et al. [11]	2019	Rat	Bone marrow MSC implanted in bladder muscle 4 weeks post-op	MSC treatment in bladder wall improved bladder function after SCI
Tian et al. [14]	2021	Rat	imMSCs and high BDNF imMSCs implanted in bladder wall 1 week post-op	Higher BDNF expression resulted in greater repairs to major pelvic ganglion tissues
Liang et al. [16]	2020	Rat	hAFSCs were injected at transection site immediately after injury	hAFSC implantation resulted in improvement of bladder dysfunction
Shen et al. [12]	2022	Rat	Bone marrow MSCs implanted in bladder detrusor layer following injury	Bone marrow MSCs improved bladder function and reduced detrusor fibrosis
Shao et al. [20]	2021	Rat	iPSC-derived neural stem cells with autophagy inducer and inhibitor implanted on injury site 1 week post-op	Bladder function was improved by iPSC-derived neural stem cells treated with autophagy inducer
Tien et al. [19]	2019	Human	ADSC transplantation immediately following spinal cord surgery, then 30, 45, and 75 days post-op	ADSC transplantation for spinal cord injury was safe in humans, and neurogenic bladder improvements were noted
Li et al. [18]	2022	Rat	Human umbilical cord MSC were transplanted into the spinal cord 8 days post-op	Human umbilical cord MSCs resulted in improvement of neurogenic bladder induced by spinal cord injury
Cho et al. [23]	2020	Rat	Human bone marrow MSCs with up/downregulated of SDF-1 were transplanted to the pelvic nerve and bladder wall 1 week post-op	Upregulated SDF-1 MSCs resulted in more nerve repair and neurogenic bladder improvement
Harris et al. [24•]	2018	Human	Bone marrow MSC-derived neural progenitor cells intrathecally, three doses 3 months apart	Half of the patients showed improvements in bladder function

cells. Additionally, similar to mesenchymal stem cells, they can regulate the local immune response [29]. Their lower immunogenicity alongside immunomodulatory characteristics facilitates their utilization in both allo- and xeno-transplantation scenarios [30]. The rapid differentiation of PMSCs into nerve cells, as illustrated by Yao et al.

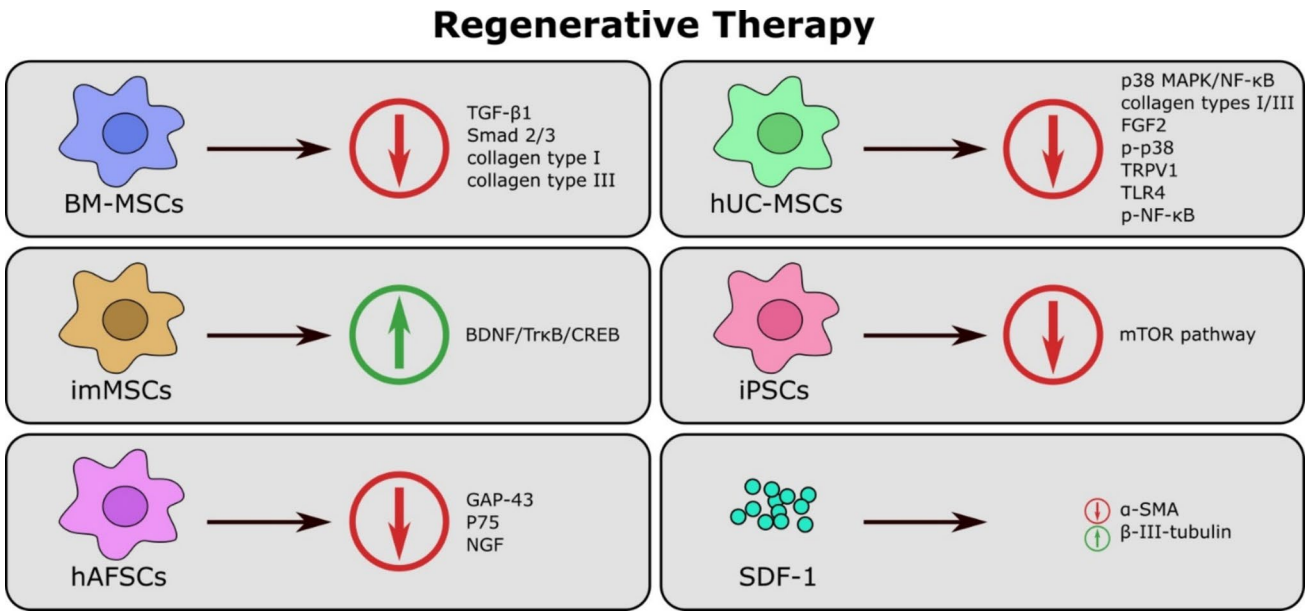

Fig. 1 An overview of selected articles in the review paper

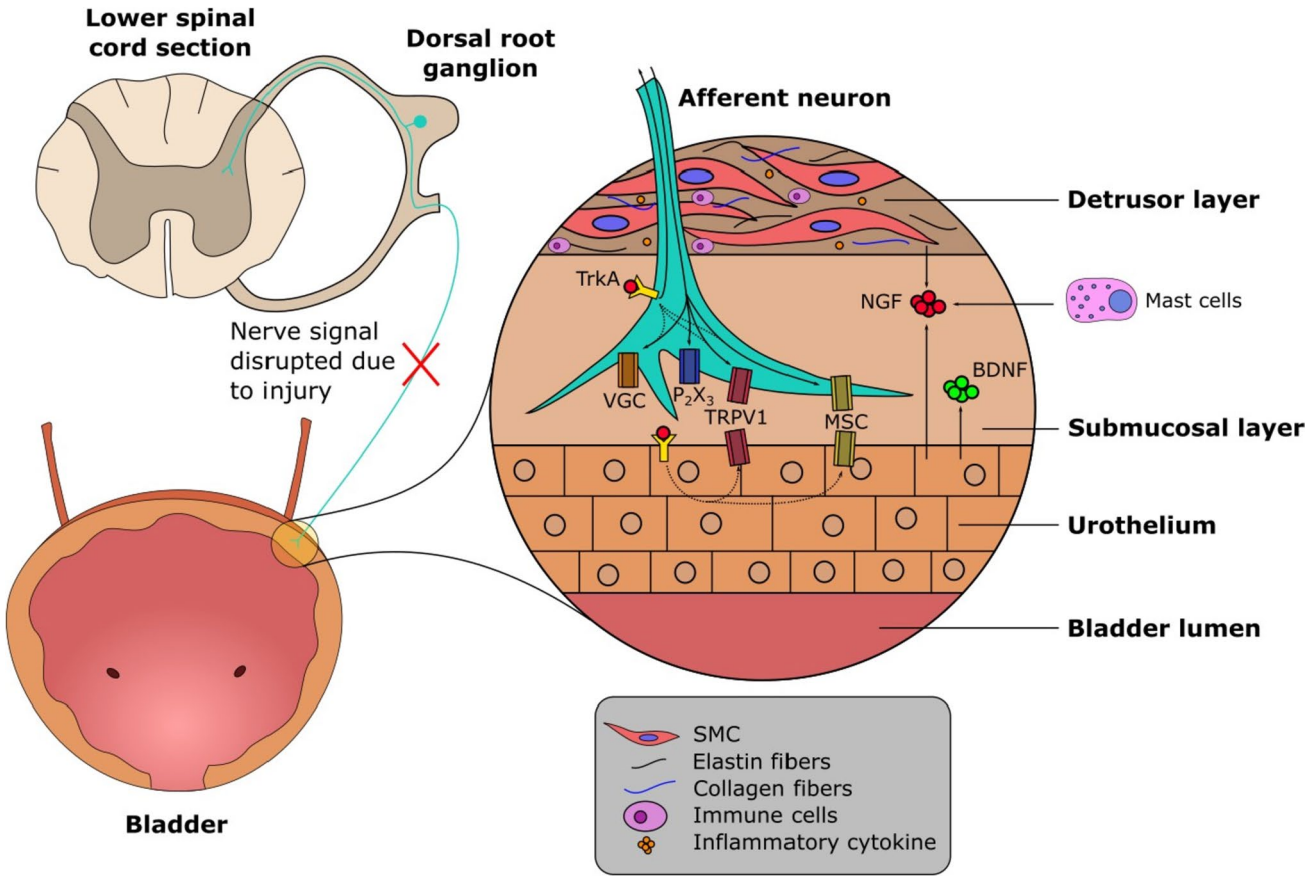

Fig. 2 A summary of neurogenic bladder remodeling process driven by inflammation and growth factors

[15], coupled with the improvement in neurofilament density and other nerve regeneration markers in the study by Liang et al. [16], establishes a compelling justification for future investigations into the neuro-regenerative capacities of these stem cell types.

iPSCs represent a novel class of pluripotent cells attainable through the reprogramming of differentiated cells from both animal and human origins [31]. Particularly in iPSCs, autophagy is essential for reprogramming, as it facilitates mitochondrial clearance. In the absence of autophagy, the proliferation of iPSCs is markedly impacted [32]. The interplay between pluripotent stem cells and autophagy underscores a complex relationship between cellular mechanisms and stem cell therapy. The manipulation of the mTOR pathway, as investigated by Shao et al. [20], reveals a refined approach to augment the effectiveness of stem cell therapy in NGB by facilitating the differentiation of iPSCs into neural stem cells.

SDF-1, also known as CXCL12, plays a vital role in the central nervous system, especially within the dorsal corticospinal tract and meninges [33]. The role of SDF-1 in mediating MSC recruitment underscores the potential of molecular signaling in facilitating stem cell homing and tissue regeneration [34]. The variance in therapeutic outcomes based on SDF-1 modulation in MSCs, as outlined by Zhu et al. [22••] and Cho et al. [23], provides a basis for exploring targeted molecular therapies alongside stem cell transplantation.

NPCs are precursor cells within the CNS that can differentiate into numerous glial and neuronal cell types that constitute the CNS [35]. Unlike embryonic stem cells, NPCs are not capable of generating non-neural cells found in the CNS, such as immune system cells. While predominantly observed in the CNS of developing embryos, NPCs are also present in both neonatal and adult brains; hence, they are not exclusively categorized as embryonic stem cells [36]. NPCs, as explored in a recent clinical trial by Harris et al. [24•], extend the discussion into the clinical realm, underscoring the translational potential of stem cell therapies in treating neurogenic disorders. The preliminary evidence of enhanced bladder function and the potential reversal of disability warrant further exploration in more extensive, well-designed clinical trials to ascertain the safety and efficacy of NPC transplantation in individuals with neurologic disorders.

This review, aggregating recent advancements in regenerative medicine for NGB, presents certain limitations. A

primary constraint is the sparse number of studies exploring stem cell applications in NGB over the past 5 years, which narrows the scope of understanding and potentially leaves specific innovative approaches unexplored. Additionally, the included studies exhibit variation in the methodologies employed to induce NGB, adding a layer of complexity when synthesizing the findings. The different methods of inducing spinal cord and nerve injuries across the studies may lead to varying manifestations of NGB, which could influence the observed efficacy and mechanisms of cell-based interventions. The lack of a standardized injury model makes it challenging to better understand the relationship between the different methods of injury induction and the resultant manifestations of NGB. Moreover, the heterogeneity in stem cell types and treatment protocols utilized across the studies compounds the challenge of drawing definitive conclusions. The myriad of stem cell types, each with unique properties, alongside varying protocols for their cultivation, delivery, and assessment, presents a broad spectrum of variables that could significantly impact the observed outcomes. Despite these limitations, this review serves as a valuable summary of recent developments in regenerative medicine for NGB, providing insights that can guide future research in this domain.

Numerous studies discussed in this review underscore the potential of stem cells in restoring bladder function in vivo. Yet, a broader spectrum of clinical trials is essential to determine the efficacy of stem cell implantation in humans. Moving forward, research endeavors should pivot towards evaluating the cellular mechanisms in enhanced bladder function in vivo and extrapolating these insights to human clinical trials. This translation of findings from in vivo models to human trials is paramount in bridging the knowledge gap and advancing regenerative solutions for NGB in clinical settings.

Conclusions

In conclusion, exploring diverse stem cell types and their respective mechanisms of action in the context of NGB may offer a promising yet complex therapeutic approach. The combination of molecular, cellular, and clinical approaches, as evidenced in the discussed studies, underscores the potential of regenerative medicine in advancing the treatment paradigms for NGB and possibly other neurogenic disorders. Future studies requiring robust design, larger sample sizes, and long-term follow-up are imperative to validate these findings and to explore the long-term safety and efficacy of cell therapies in the clinical setting.

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Declarations

Conflict of Interest The authors declare no competing interests.

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- • Of importance
- •• Of major importance

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