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Review Article

Mechanisms of prostatic inflammation-mediated male lower urinary tract symptoms

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Abstract: Lower urinary tract dysfunction (LUTD) is prevalent in aging men. It is characterized by urinary symptoms such as weak stream and more frequent urination, and is linked to a variety of prostate and urethral pathologies. While the leading medical therapies for male LUTD aim to reduce the tone and volume of the prostate and urethra, no current therapies target two prominent emerging mechanisms of male LUTD: prostate inflammation and fibrosis. LUTD arises and progresses over decades of a man's life, making it difficult to pinpoint disease mechanisms. Non-human research models, including mice, have been useful for investigating slow-progressing diseases of aging. Research involving mouse models of lower urinary tract dysfunction is surging due to a growing suite of genetic, pharmacological and immune-based tools for manipulating mouse prostate histopathology, cell signaling and phenotyping mouse urinary voiding. Current research is focused on understanding how macrophages, fibrocytes, mast cells and other cells are recruited to the prostate and how these cells are activated to drive prostate inflammation and fibrosis. This review highlights recent mouse studies to investigate the cellular and molecular underpinnings of prostate inflammation and fibrosis, and the molecular mechanisms that have emerged from these studies as potential therapeutic targets

Keywords: LUTD, prostate, inflammation, collagen, fibrosis

Introduction

Male LUTD affects over 4 billion individuals worldwide [1] and is characterized by a disorders of the bladder, urinary sphincter, urethra, and the prostate. LUTD can vary in severity and is often accompanied by lower urinary tract symptoms (LUTS) such as incomplete bladder emptying, hesitancy and intermittency, weak stream, and frequent urination, especially at night [2, 3]. Male LUTS becomes more frequent and severe with age [4-7]. The worldwide geriatric population is expected to nearly double over the next three decades, increasing the medical burden for male LUTS and making the quest for new and more effective therapies urgent [8, 9].

Male LUTS can arise from a multitude of pathologies, making it difficult to pinpoint effective treatment options that extend across the population. A historical cause and clinical predictor of male LUTS has been urethral obstruction due to benign prostatic hyperplasia (BPH). Steroid 5α-reductase inhibitors (5ARIs) are given to patients who have BPH, with the goal of shrinking the prostate by blocking the enzymatic conversion of testosterone into its more potent androgen receptor agonist, dihydrotestosterone [10]. Smooth muscle dysfunction of the prostate and bladder neck are also contributors to LUTS development, usually through hypertonia [11]. Men with smaller prostate volumes and LUTS are generally prescribed α-adrenergic receptor antagonists (α-blockers), which reduce smooth muscle tone in the prostate and bladder neck [11]. 5ARIs and α-blockers are more effective in combination than as monotherapies [11], but even in combination do not alleviate symptoms in all men [11, 12]. Recent developments in drug therapy have introduced several promising new options for treating LUTS, including beta-3 adrenoceptor agonists, which increase bladder capacity by relaxing smooth muscle [13]; phosphodiester-

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ase five inhibitors, whose exact mechanisms are still unknown but are believed to promote smooth muscle relaxation by increasing cyclic guanosine monophosphate [14]; and anticholinergic agents, which relax bladder smooth muscle by reducing the effects of acetylcholine [15]. Although medical therapies and surgery have been effective in improving symptoms in some men, some men do not experience improvement from these treatments. In some cases, symptoms may persist, recur or worsen and can cause lasting and irreversible damage to bladder function [11, 16-19].

It is necessary to look beyond smooth muscle dysfunction and BPH to uncover additional mechanisms that drive male LUTD. Understanding the additional drivers of LUTD is crucial in the development of new therapies that are effective across a broader cohort of men. Inflammation-mediated prostate fibrosis is a prominent candidate in the mechanism for clinical progression of LUTS. Inflammation is caused by a multitude of factors, and involves the infiltration of both pro- and anti-inflammatory cells that promote tissue repair through collagen synthesis [3]. Clear evidence links inflammation to prostatic collagen deposition and LUTS [2, 4, 5, 20-22]. Around 50% of men with chronic prostatitis experience LUTS [23], which may be due to swelling and irritation of the prostate and urethra, thereby interupting urine flow, or to prolonged inflammation, which can cause collagen accumulate in the prostate. Inflammation is a driver of collagen accumulation in the mouse prostate [24]. Collagen deposition on the prostate leads to tissue stiffening, urethral constriction, and voiding dysfunction [20, 24-26]. Prostatic collagen content in men, particularly in the transition zone, positively correlates with LUTS severity [27]. A study comparing the prostates of men with LUTS, who were being treated with both 5ARIs and α-blockers but without significant symptom relief, with prostates of men without LUTS, found higher periurethral collagen content in the prostates of men with LUTS [27]. Additionally, these studies provide evidence that prostatic fibrosis contributes to LUTS development independently of BPH or smooth muscle dysfunction.

While connections between inflammation, prostatic collagen content, and voiding dysfunction have been established, further pre-clinical research is needed to identify key cell types, mediators, and mechanisms. This is crucial for the development of new targeted therapies for the treatment of prostate fibrosis.

Evaluating the role of mouse models in the study of male urinary voiding dysfunction

Non-malignant prostate pathologies that contribute to LUTS arise and progress over decades, making it difficult to pinpoint disease mechanisms. Non-human research models offer an opportunity to study disease progression in a more rapid timeline and under controlled conditions. Mouse models have been used to study non-malignant male urinary voiding dysfunction but not without controversy [28, 29]. One criticism is based on anatomical differences between human and mouse prostate. The human prostate features a thick fibromuscular capsule surrounding glandular tissue that was initially divided into zones based on where histological diseases are most prevalent. Prostate cancer primarily affects the peripheral zone, while benign hyperplastic nodules typically occur in the transition and sometimes central zone [30, 31]. Interestingly, a recent single cell RNA sequencing analysis demonstrates that each human prostate zone is populated by a unique distribution of fibroblasts [32]. It has been proposed that the capsule surrounding the human prostate confines the prostate in a limited space and that the growth of benign prostatic nodules place increasing pressure on the urethra, impeding expansion of the urethra and bladder emptying [33, 34]. The concept is supported by the effectiveness of surgical prostate enucleation procedures such as transurethral resection of the prostate, holmium laser enucleation, and others that improve voiding function [33]. It is important note that prostatic collagen is dense and expands with age in the periurethral region [35], the region enucleated by surgical procedures for treating LUTS.

Mouse prostate anatomy differs from that of humans in that it features four distinct lobes (anterior, dorsal, lateral, and ventral) that are not confined by a substantial fibromuscular capsule. While the distal tips of the mouse prostate (acini) are not confined, the proximal ductal segments are restrained in a space between the striated muscle rhabdosphincter and urethral epithelium, and course parallel to the urethral epithelium for some distance before draining into the urethral lumen. It was initially be-

Table 1. Mouse models of prostatic inflammation which show accumulation of collagen

Mouse model of prostatic collagen accumulation	References
Transurethral instillation of *E. coli*	[22, 48, 138]
Sustained exposure to exogenous testosterone and 17β estradiol	[49, 131]
Aged mice	[21, 100]
High fat diet/Diabetes	[50, 51]
Experimental autoimmune prostatitis	[52, 53, 116]
Environmental contaminant exposure	[56-58]
Genetic gain and loss of function	[53-55]

lieved that only dogs and humans develop prostate-related voiding dysfunction with age; However, a recent study demonstrated that when male mouse urinary voiding patterns are monitored across lifespan, aging male mice also develop urinary voiding dysfunction [21]. Clinically relevant urodynamic testing and validated measurements of spontaneous urinary voiding activity in mice have revealed numerous similarities between urinary voiding dysfunction in mouse models with voiding dysfunction experienced by human men [36-45]. There are also histological similarities among human, canine and mouse prostate cells that give rise to inflammatory pathologies [35, 46, 47].

Several mouse models accumulate prostatic collagen (**Table 1**). Transurethral infection of male mice with uropathogenic *Escherichia coli* (*E. coli*) yields histological changes to the mouse prostate that resemble, in part, histological changes to the inflamed human prostate [22, 48]. *E. coli* induced prostatic inflammation and collagen accumulation also elicits urinary voiding dysfunction that resembles voiding dysfunction in humans with LUTS [22, 25, 48]. Mice exposed to exogenous testosterone and 17β estradiol accumulate prostatic collagen and void more frequently over time [49]. The prostates of 24-month-old (aged) male mice feature a denser collagen network and more cellular proliferation than 2-month-old mice [21]. The prostates of male mice fed a high fat diet (HFD) or of mice with diabetes feature immune cell infiltration, increased collagen content and urinary voiding dysfunction [50, 51]. Autoimmune prostatitis has been linked to prostate fibrosis in mice [52], along with increased abundance of prostatic interferon regulatory factor 7, enhanced prostatic cell glycolysis, and an increased density of M1 polarized macrophages [53]. A reduction in interferon regulatory factor 7 reduced prostatic collagen content in this mouse model [53]. A genetic approach to hyperactivate phosphoinositide 3-kinase (PI3K) signaling in prostatic epithelial cells of mice resulted in inflammation and prostate fibrosis starting at 4-months of age and progressing until at least 12-months of age [54]. Additionally, a model with E-cadherin deficiency promoted increase immune cell infiltration and inflammation in aged mice [55]. Mice exposed to common environmental contaminants (cigarette smoke, bisphenol A, and cadmium) also develop prostate inflammation and fibrosis [56-58].

Despite the challenges of recapitulating human LUTS in mice, mice have contributed to our understanding of prostate fibrosis mechanisms and potential therapies.

Cytokines and chemokines linked to prostate inflammation and fibrosis

Transforming growth factor (TGFB)

TGFB is a pro- and anti-inflammatory cytokine, depending on environmental context and cellular landscape, that binds the TGFB receptor and drives phosphorylation of SMAD family members 2 & 3 (SMAD2/3) to initiate collagen transcription or to differentiate inflammatory cells [59]. TGFB is associated with, and in some cases required for fibrosis across many tissues [60-64]. The TGFB pathway has been pharmacologically targeted using small molecule inhibitors, and recent phase 1 clinical trials for the TGFB receptor kinase inhibitor, vactosertib, has been shown to be safe and effective [65]. Targeting TGFB function in animal models of renal and idiopathic pulmonary fibrosis is sufficient to alleviate fibrosis and associated symptoms [62, 66]. Few studies have focused on the role of TGFB in prostate inflammation, fibrosis, and LUTS. Since TGFB has been an effective target

in alleviating collagen accumulation in fibrotic diseases, it most likely has a similar role in the inflamed prostate. Connective tissue growth factor (CTGF) is a downstream target of TGFB, and its activity has been targeted by the CTGF blocking antibody FG-3019 for treating idiopathic pulmonary fibrosis, which was generally well-tolerated with a safety profile like placebo, but did not meet the study endpoints in phase 3 clinical trials [67]. Similarly, the CTGF blocking antibody RXI-109 for treating subretinal fibrosis also showed effectiveness with no significant side effects of toxicity as of stage 2 clinical trials [68].

Nuclear factor-kappaB (NF-κB) and related inflammatory cytokines

Several other inflammatory cytokines have been implicated in prostate inflammation, some of which are potential targets for new LUTS therapies [69, 70]. Interleukin 1B (IL1B) and tumor necrosis factor (TNF) are expressed in mouse models of prostate inflammation [26, 71] and in human clinical specimens [72, 73] and can function in concert to promote NF-κB activation, driving cytokine/chemokine expression. Many males with LUTD and ranging from ages 50-80 years have elevated levels of TNF [74], and TNF blockade significantly decreases epithelial hyperplasia, macrophage-mediated inflammation, and BPH incidence [71]. IL1B is highly expressed both in the prostates of patients with chronic prostatitis and patients with BPH [72, 75]. High fat diets induce urinary voiding dysfunction in mice, a phenotype linked to higher levels of oxidative stress/NADPH oxidase deregulation, which elevate prostate inflammatory cytokines via NF-κB activation [25, 76-78].

Studies involving men with BPH [79] and abdominal obesity [80], connected elevated low-density lipoprotein-cholesterol and HFDs with increased systemic inflammation/LUTS. NF-κB activation is likely to play a strong role in starting or increasing the initial inflammation response via TNF and IL1B, especially in LUTD pathologies involving HFDs. NF-κB mediated inflammation has also been linked to prostate cell proliferation [81, 82]. NF-κB regulates cyclooxygenase-2 (COX2), which drives cell proliferation and inflammation [83, 84]. COX2 is necessary for ROS-dependent activation of NF-κB [85] and *in vitro* inhibition of NF-κB with an isoliquirtigenin, a licorice root extracted flavonoid with anti-inflammatory properties [86], decreases COX2 expression and reduces inflammation [87]. In the prostate, COX2 contributes to inflammation by converting arachidonic acid into pro-inflammatory prostaglandins [88]. COX2 activity is elevated in inflamed and enlarged prostates and is a target for nonsteroidal anti-inflammatory drugs (NSAIDs) [88, 89]. NSAIDs have been evaluated for therapeutic use in patients with male LUTS, but do not clearly offer long-term benefits, despite some short-term benefits for patients with nocturia [89-91]. However, NSAIDs have provided better short-term benefits in combination with 5ARIs and α-blockers [92-94]. NSAIDs may be available as an adjuvant to 5ARIs, particularly in the early phase of 5ARI therapy, as 5ARIs take a few months to exert symptom improvement [95, 96].

Notably, in a recent study that examined prostates of human patients with and without BPH, and of mice, treatment with celecoxib and/or finasteride decreased the abundance of NADH: ubiquinone oxidoreductase core subunit S3 (NDUFS3) without significantly changing the density of inflammatory cells [97]. The authors also reported that BPH prostates had less NDUFS3 than prostates without BPH [97]. The authors concluded NSAIDs may have a potential negative drug interaction with mitochondrial complex I [97], interrupting ATP synthesis by uncoupling mitochondrial oxidative phosphorylation [98], a mechanism recently shown to cause hepatotoxicity in rats [99]. A recent study gives further support to the hypothesis that mitochondrial dysfunction is a mechanism of non-malignant prostate disease, as age-related decreases in C1 mitochondrial proteins were observed in BPH/LUTS patients [100], but this connection requires further investigation. Uncontrolled NF-κB regulation of COX2 promotes BPH and prostate inflammation, and while inhibitors of COX2 have shown some benefits, though further testing is needed to understand if there is a significant negative interaction with mitochondrial CI function.

The chemokine ligand C-C motif chemokine ligand 2 (CCL2) and its receptor C-C motif chemokine receptor 2 (CCR2)

CCL2/CCR2 has a key role in fibrosis by modulating the recruitment of immune cells, includ-

ing dendritic cells, monocytes, and T cells [101], but may also activate mast cells and basophils [102]. CCL2 can be secreted by several cells including monocytes, macrophages, dendritic cells, endothelial cells, and fibroblasts, and is induced by TNF, TGFB, IL4, and IL1B [102]. CCL2/CCR2 signaling mediates macrophage involvement in testicular and colon fibrosis [103, 104] and fibrocyte recruitment in the kidney and prostate (discussed in more depth in fibrocyte section) [35, 105]. Functional blockades of CCL2/CCR2 partially alleviate fibrosis of the liver, kidney, and lung [106-108]. In the prostate, CCL2/CCR2 plays a significant role in mediating inflammation and fibrosis. CCL2/CCR2 is elevated in prostatic fluid of men with chronic pelvic syndrome [109] and in urine specimens of BPH/LUTS patients [110], correlating with obesity and prostatic inflammation [111]. CCR2+ monocytes and macrophages drive the prostate fibrotic response in mice implanted with slow-release implants of exogenous testosterone and estradiol [49]. Additionally, CCR2 is an essential mediator of autoimmune prostatitis in a mouse model of chronic pelvic pain [112]. Fibrosis was also shown to be mediated in part by CCL2/CCR2, as *Ccr2* null mice infected with uropathogenic *E. coli* to induce prostate inflammation accumulated significantly less collagen than infected wild type mice [35].

The stromal cell-derived factor-1 (CXCL12)/C-X-C receptor 4 (CXCR4) axis

The CXCL12/CXCR4 axis promotes ECM changes and fibroblast activation [50, 113, 114], and CXCR4 inhibitors are in development as anti-inflammatory therapies [115]. CXCL12/CXCR4 has pro-inflammatory properties and promote M1 macrophage polarization and cytokine production [116, 117]. CXCL12/CXCR4 signaling promotes the activation and proliferation of CD4+ cells [118, 119], which are involved in BPH/LUTS disease progression (see Leukocyte section). CXCL12 drives fibrosis of several tissues [120, 121], including the prostate [50, 116]. These prostate studies identified CXCR4 as a mediator of pro-inflammatory M1 macrophages; while blocking CXCR4 inhibits fibroblast activation in chronic prostatitis mouse models [116]. Additionally, inhibiting CXCR4 activity leads to decreased fibrosis and voiding dysfunction in high fat diet mouse models of prostate inflammation [50]. CXCL12/CXCR4 signaling drives phenoconversion of prostate fibroblasts into myofibroblasts *in vitro* [122], but more studies are needed to confirm a similar action *in vivo*.

The CX3C chemokine receptor type 1 and its ligand CX3CL1

CX3CF1 and CX3CL1 activate several signaling cascades, including PI3K [123], which in turn simulates NF-κB signaling, cytokine production, production of extracellular matrix components by intestinal epithelial cells [124], and fibroblasts [125]. CX3CR1 can also activate TNF, leading to signal transducer and activator of transcription 3 (STAT3) pathway activation [123]. Genetic deletion of CX3CR1 in mice reduces collagen production by 50% in granulation tissues injected with TGFB and CTGF [126] and reduces kidney fibrosis by halting expansion of pro-fibrotic macrophages [127]. CX3CR1 activation also drives M2 macrophage differentiation [128], cells which are implicated as major drivers of prostate inflammation and urinary voiding dysfunction [129-132]. CX3CR1 has not been a target in preclinical studies of prostate related voiding dysfunction but has been related to prostate cancer and metastasis [133, 134].

Cells implicated in prostate inflammation, fibrosis and urinary voiding dysfunction (Summarized in Figure 1)

Mast cells

Mast cells are histamine producing immune cells that derive from the yolk sac (YS) and seed tissues during embryogenesis or derive from bone marrow and seed tissues later in life [135, 136]. Erythromyeloid progenitors populate adipose, pleural cavity, and connective tissue, while bone marrow derived mast cells populate mucosal tissues including the prostate and urethra [136]. Mast cells have also been reported in endocrine glands and in perivascular tissues near nerve termini [137]. Definitive hematopoietic stem cells have the potential to differentiate into all blood lineage cells, while it is currently thought that the differentiation potential for YS-derived mast cells is limited to erythrocytes, megakaryocytes, and macrophages [135]. Definitive adult mast cells express CCR2/CCL2 and embryotic YS-derived mast cells selectively express CX3CR1 [135]. In the

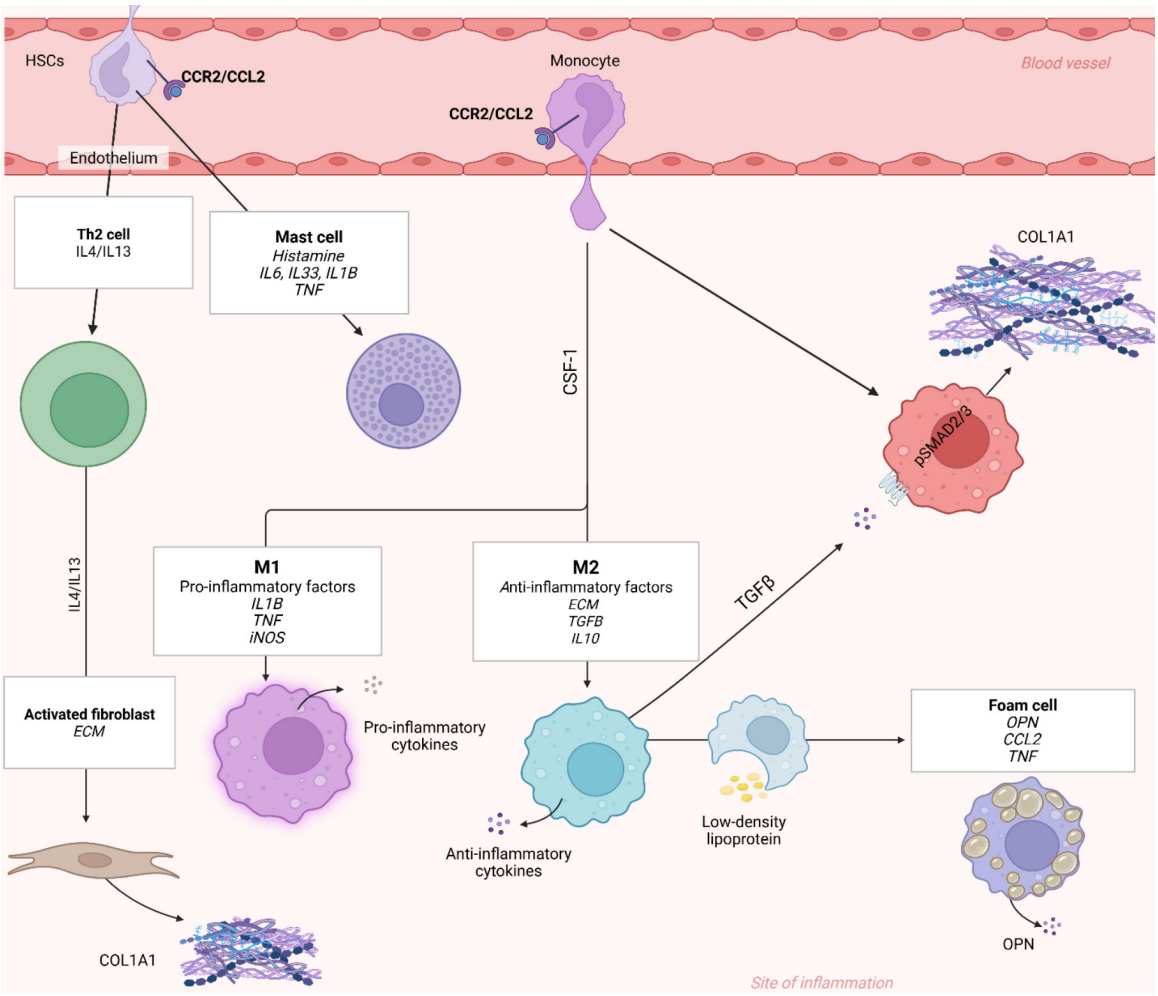

Figure 1. Summary of cells reported in prostate inflammation, fibrosis, and voiding dysfunction.

prostate, mast cell can produce interleukin 6 (IL6) to stimulate STAT3/Cyclin D1 signaling in epithelial cells, driving their proliferation [138]. This has been demonstrated *in vitro* by exposing BPH-1 epithelial cells to IL6 [139]. Mast cells have been implicated in prostate inflammation through secretion of pro-inflammatory cytokines like TNF, IL1B and interleukin 33 [137]. Mast cell inhibition reduces CD3+/CD8+ T cells and CD11b+ macrophages, while alleviating prostate fibrosis/LUTS in mice with bacterial infections of the prostate [138]. Mast cells are also more numerous in inflamed prostate tissue resulting from exposure to exogenous testosterone and 17β estradiol [131]. Additionally, mast cells are observed in prostate tissues of men with chronic pelvic pain syndrome and LUTS [140-143] and abolishing mast cell activity in bladder autoimmune inflammation models alleviates bladder inflammation and LUTD [144]. Identifying additional characteristic roles for mast cells in prostate inflammation and fibrosis mediation could reveal new mechanistic targets for LUTD treatments.

T lymphocytes

T lymphocytes are white blood cells that mediate the acquired or antigen-specific immune response. Mast cells may play a role in activating T cells since inactivation of mast cells reduces CD3+ and CD8+ T cells in the prostate of mice with bacterial infections [138]. Early studies involving T cells and their role in BPH/LUTS report conflicting roles of T cells. A 2009 study showed that prostate-localized CD8+ and CD4+ T cells were more frequent than other inflammatory cells in BPH biopsies of 282 men undergoing open prostatectomy or transurethral resection [145]. A different study conducted in

2011 did not support that T cells are reliable predictors of clinical progression of LUTS in BPH patients, implied through the lack of immunostaining evidence in 96 BPH biopsy tissues [146]. However, a more recent study also cast doubt on the importance of CD8+ cells in prostate inflammation but instead raised the hypothesis that CD4-Th1 cells drive autoimmune prostate inflammation [147]. Looking back at some supporting older studies, CD4+ cells were seen to make up 70% of the inflammatory infiltrate in transurethral prostate tissues from men with LUTS [148], while the CD4 subset, Type 2 (Th2) cells, were seen promoting interleukin 4/interleukin 13 (IL4/IL13) axis signaling in BPH tissue [149]. Increased Th2 cell densities were observed in the periurethral region of BPH patients [150], an area known for increased collagen density and disease progression. Pro-fibrotic IL4/IL13 signaling [151] has been implicated in LUTS progression by promoting T cell activation through STAT3 signaling and subsequent fibroblast activation [114]. Inhibition of STAT3 and the IL4/IL13 axis attenuated fibrosis in bacterial-inflamed mouse prostate [20]. CD4+ cells and specifically their Th2 subtype have been shown to be present and active in prostate inflammation, mediated through IL4/IL13 axis signaling [20, 114].

Macrophages

Macrophages have been associated with inflammation and fibrosis, including inflammation-mediated prostatic collagen accumulation [48, 104, 116, 130, 132, 152-154]. Macrophages are derived from monocytes, recruited via CCR2/CCL2 or CX3CR1 [128] and differentiated through macrophage colony stimulating factor [155]. M1 or classically activated macrophages secrete pro-inflammatory factors like IL1B and TNF. M2, or alternatively activated macrophages, are better recognized for their roles in tissue wound healing, fibrosis and resolution of inflammation though secreting of growth factors like TGFB, fibroblast growth factor, and tissue inhibitor of matrix metalloproteinase 1 [156-158]. In autoimmune prostatic inflammation, macrophages secrete TNF and stimulate fibroblast proliferation, leading to BPH and inflammation [71]. In bacterial models of prostate inflammation, M1 macrophages can be activated by bacterial lipopolysaccharide and promote pro-inflammatory signaling through the NF-κB pathway [159, 160]. M2 macrophages secret TGFB, which promotes collagen production [160] and are abundant in the collagen-dense periurethral region of men with BPH [129, 161, 162]. M1 and M2 macrophages are necessary for early prostate inflammation (M1 macrophages) and fibrosis (M2 macrophages). Identifying the specific mechanisms by which macrophages contribute to prostate inflammation, fibrosis and LUTS is an invaluable focal point in developing targeted treatments.

Foam cells

Foam cells are a subset of macrophages deriving from activation of the CXCL12/CXCR4 axis, which promotes phagocytosis of low-density lipoprotein [163, 164]. Phagocytosis of low-density lipoproteins gives rise to lipid-laden cells with a M2 macrophage-like phenotype. Foam cells drive osteopontin (OPN) production [48, 131] and production of cytokines such as TNF and chemokines like CCL2 [165]. A mouse model of urinary voiding dysfunction driven by slow-release implants of testosterone and 17β estradiol features periurethral accumulation of OPN+ foam cells, increased urinary frequency, increased prostatic collagen deposition, increased densities of macrophages in the ventral lobe and mast cells in the dorsal lobe [131]. Genetic deletion of OPN prevented each of these testosterone and estradiol-dependent histological and physiological changes in mice [131]. In the same study, testosterone and estradiol increased the prostatic density of M1 macrophages in an OPN-dependent fashion, while OPN deletion increased the density of M2 macrophages [131]. The results suggest a role OPN+ foam cells in the regulation of M1/M2 macrophage differentiation and fibrosis.

Myofibroblasts

Myofibroblasts are activated fibroblasts that co-express α-smooth muscle actin and the intracellular collagen marker proCOL1 [166]. Myofibroblasts contribute to the pathogenesis of fibrotic diseases in several organs, including the lungs, heart, skin, and kidney [151, 167-169]. Myofibroblast activity in LUTS/BPH development has been controversial and many studies have stated or implied their role in LUTD development without histological evidence, especially *in vivo* [2, 170, 171]. There is more evidence of prostate fibroblasts to myofibroblasts phenocoversion *in vitro*, especially in response

to TGFB and/or CXC-type chemokines [120, 130, 172, 173]. One study using single cell analysis of mouse and human prostate tissue shows an increase of myofibroblast populations in BPH, but the authors noted this was not evidence due to the phenotype potentially being part of cell culture conditions [46]. It has been recently reported that many of the cells that populate and contribute to collagen deposition in the prostates of mice, dogs, and humans are not positive for α-smooth muscle actin [22, 35].

Additionally, it was recently shown that fibroblasts activated by IL4/IL13 expressed ECM proteins but do not differentiate completely into myofibroblasts, showing a lack of α-smooth muscle actin expression or contractile activity [114]. However, an *ex vivo* study suggests that TGFB-induced fibroblast to myofibroblast conversion in the prostate is dependent on elevated IGF binding protein 3 mediated by cancerous cells [174], while a different *in vivo* study using hormone-accelerated BPH tissue but excluding any tissue with prostatitis or infection, made similar conclusions [175]. This could suggest that myofibroblasts mediate fibrosis in some hyperplastic fibromuscular stroma, but the precise *in vivo* conditions for this phenomenon are unknown.

Fibrocytes

Fibrocytes have been described as mesenchymal progenitors arising from myeloid precursors [176]. Fibrocytes express markers associated with hematopoietic cells (CD45 and LYZ) but possess characteristics typical of mesenchymal cells or fibroblasts (collagen production, occasional spindle-shaped morphology, S100A4 expression), making them difficult to track *in vivo* [35, 177-179]. Fibrocytes express collagen and expand when faced with bacterial-induced prostate inflammation [35]. They are also implicated as a contributor to inflammation in fibrotic conditions including cystic, pulmonary, liver, corneal, and prostatic fibrosis [35, 177, 180-183]. Fibrocytes can be activated by TGFB, promoting SMAD2/3 phosphorylation and collagen transcription [184]. Specifically in the prostate, *Ccr2* null mice faced with uropathogenic *E. coli* prostate infection had significant decreases in both overall collagen density and fibrocyte population, suggesting a CCR2- dependent mechanism where fibrocytes synthesize the majority of collagen when faced with bacterial infection [35]. Additionally, fibrocytes labeled with CD45 and vimentin are denser in the prostates of mice with type 1 diabetes and bacterial-induced inflammation [24, 51]. Fibrocytes are promising as targets for LUTS therapy as they have both pro- and anti-inflammatory properties but have been difficult to work with. Most agree that additional specific fibrocyte markers are needed to confirm and further investigate the role of these cells in inflammation-mediated prostatic collagen accumulation.

Discussion and conclusion

The connection between prostatic collagen accumulation and LUTS has prompted significant efforts to identify key cellular mediators, underlying mechanisms, and potential therapeutic targets. While mouse models of human urinary dysfunction were once met with skepticism, they have become indispensable tools for understanding the pathophysiology of LUTS. Using these models, recent studies have highlighted several mechanisms, cell types, cytokines, and chemokines as central players in the development of prostate inflammation and collagen accumulation, with each contributing uniquely to disease progression. All of the cell types discussed in this review have a role to play in inflammation mediated prostatic collagen accumulation and LUTD development, which warrants the need for further investigation. Some of these cells, including fibrocytes, macrophages, and mast cells have been shown to have direct roles in inflammation and fibrosis, mainly through the release of mediating cytokines, like TGFB, or direct transcription of procollagen. The studies involving these cells highlight their potential as new targets for therapeutic drugs [50, 114, 131, 138, 185]. Future research should focus on identifying specific markers for each respective cell type to improve *in vivo* tracking and exploring the potential interaction between other cell populations.

Moreover, the cytokines and chemokines discussed in this review each have a specific role in promoting prostate inflammation and fibrosis. Inhibition of TGFB has shown promise in other fibrotic disease treatments and investigating the role TGFB has in LUTD development may be an optimal start for the development of targeted treatments. However, each one should

be considered for further investigations because painting a more complete picture of each respective mechanism will improve our understanding of their specific interactions, which may lead to the information needed to develop new therapies.

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Disclosure of conflict of interest

None.

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