Minireview

The contribution of the immune system to genitourinary fibrosis

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Impact Statement

This review examines evidence for the contribution of the immune system to the pathophysiology of genitourinary fibrosis, including urethral and ureteral strictures, retroperitoneal fibrosis, and Peyronie's disease. These diseases are difficult to manage, and their causes are incompletely understood; however, they may share an underlying autoimmune etiology that begins with impaired wound healing. The immunologic contributors to these diseases have not been completely characterized and few reviews address the role of the immune system in their pathogenesis. Defining the role of the immune system in the development of genitourinary fibrosis will improve our understanding of how immunologic dysfunction contributes to these and other fibrotic diseases.

Abstract

Fibrotic diseases of the genitourinary tract are devastating and incompletely understood pathologies. These diseases include urethral and ureteral strictures, retroperitoneal fibrosis, and Peyronie's disease. They can contribute to obstructive uropathy and sexual dysfunction. Poor understanding of the pathophysiology of these diseases severely limits our ability to prevent and treat them. Genitourinary fibrotic diseases likely represent related pathologies that share common underlying mechanisms involving wound healing in response to injury. These diseases share the common feature of extracellular matrix abnormalities—such as collagen deposition, transforming growth factor-β accumulation, and dysregulation of collagen maturation—leading to abnormal tissue stiffness. Given the association of many of these diseases with autoimmunity, a systemic pro-inflammatory state likely contributes to their associated fibrogenesis. Herein, we explore the immunologic contribution to fibrogenesis in several fibrotic diseases of the genitourinary system. Better understanding how the immune system contributes to fibrosis in these diseases may improve prevention and therapeutic strategies and elucidate the functions of immunologic contributors to fibrosis in general.

Keywords: Genitourinary fibrosis, inflammation, retroperitoneal fibrosis, urethral stricture, ureteral stricture, Peyronie's disease

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Introduction

Genitourinary fibrotic diseases are morbid conditions that are difficult to manage and generally lack specific therapies to prevent and reverse the process of fibrotic transformation. Diseases involving genitourinary fibrosis include urethral and ureteral strictures, retroperitoneal fibrosis, and Peyronie's disease. These are devastating conditions whose pathophysiologies are poorly understood. These diseases share abnormalities in pro-fibrotic signaling, but how these contribute to their pathogenesis remains incompletely characterized. Like other scarring diseases that exhibit imbalances in the immune system, studies of these disease states suggest that robust immune signaling may contribute to their pathology.[1] In this review, we will evaluate the known contributions of the immune system to genitourinary fibrosis and focus on how a shared pathology may underlie these seemingly disparate diseases.

Wound healing and fibrosis—a delicate balance

Wound healing in the urinary tract is thought to be similar to healing in other tissues (Figure 1).[2] Following tissue injury, clotting factors and platelet activation form a hemostatic clot, initiating a signaling cascade that begins the process of wound healing.[3,4] Neutrophils and macrophages are recruited to the injured site and serve in both host defense and tissue remodeling.[4] Neutrophils defend against pathogen entry as the wound starts to heal.[4] Macrophages phagocytose pathogens and recruit fibroblasts, which subsequently proliferate and deposit collagen and other extracellular matrix (ECM) proteins.[3–5] Interactions between the ECM and cells within the wound mediate wound contraction, allow for epithelial cells to migrate into the wound, and ultimately lead to wound repair.[4] Immune cells (e.g. B and T lymphocytes) and cytokines further contribute to

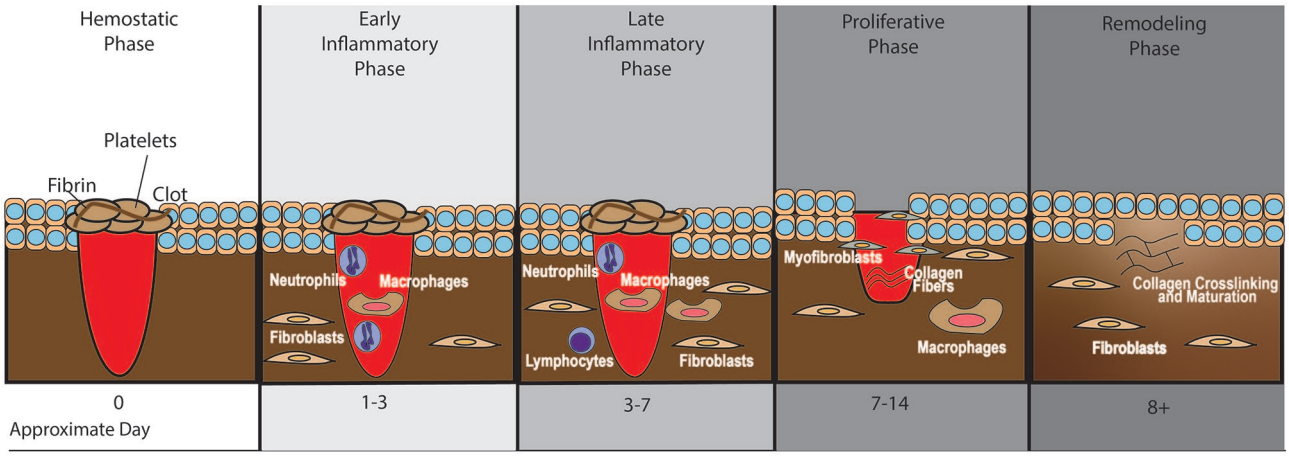

Figure 1. Normal wound healing. After an injury, platelets and clotting factors coalesce at the wound forming a scab to provide hemostasis and protection of the wound site. Immune cells, beginning with neutrophils and then macrophages appear at the wound to clear debris and prevent infection. Fibroblasts then cover the wound and deposit collagen to aid in wound closure. After this, collagen cross-linking and remodeling occurs. (A color version of this figure is available in the online journal.)

healing.[4,6–9] T lymphocytes increase the strength of wounds by promoting collagen deposition and producing growth factors.[6,7] In mice, B lymphocytes appear around 5 days after injury and produce interleukin 6 (IL-6), helping to initiate fibrosis; however, their presence and role in human wound healing remains unclear.[8]

One key factor impacting wound healing is transforming growth factor β (TGF-β), which is produced by both macrophages and fibroblasts. This cytokine recruits cellular mediators of wound healing including neutrophils, macrophages, and fibroblasts to initiate and propagate the inflammatory signaling cascade required for tissue repair. TGF-β also promotes the production of collagens and other ECM components, which are then remodeled throughout the healing process.[4,10–12] TGF-β has 3 isoforms and 3 receptors, and combinations of each of these promote different pro- and anti-fibrotic wound healing phenotypes in different contexts.[13] For example, TGF-β signaling via the TGF-β-receptor 2 (TGF-βR2) promotes an anti-inflammatory macrophage phenotype that may help reduce fibrosis.[14] Conversely, in a model of diabetic-related degenerative myopathy, production of TGF-β1 by pro-inflammatory macrophages contributed to muscle fibrosis.[15] Thus, tight balance of the cellular and ECM mediators of wound repair are indispensable for appropriate healing.

Fibrotic diseases of the genitourinary tract likely begin with an insult requiring healing (e.g. infection or trauma) which then goes awry.[3] Wound healing failure occurs when there is insufficient collagen matrix deposition or dysregulation of normal immune activation during healing. Thus, fibrosis and subsequent remodeling is critical for normal wound healing.[16–18] Over zealous activation of wound healing pathways, however, results in excess ECM production or inappropriate remodeling, producing a dense fibrous scar.[1,4,16]

Scar formation may play a role in promoting urinary tract fibrosis. In other settings, chronic inflammation is associated with activation of fibroblasts and myofibroblasts, which then deposit excess ECM, leading to the formation of scar tissue.[1] Excess acute immune activation can also create a pro-inflammatory environment to further increase fibrosis.[4] Wound infections can lead to inflammation and scarring mediated by toll-like receptor (TLR) activation.[19,20] Inappropriate TGF-β signaling has also been associated with scar formation.[11,21–23] The result of scarring within the urinary tract is poor tissue plasticity, which can alter its function or narrow the lumen through which urine flows and increase pressure within the urinary system. Thus, a delicate balance is needed to ensure proper tissue healing without excess fibrosis to maintain urinary tract function following an insult.

Urinary tract scarring is a complex process that likely involves not only the extent, type, and location of injury, but also genetic and environmental factors.[24–27] For example, while pelvic trauma is a well-known risk factor for urethral stricture development, some individuals do not develop strictures despite extensive trauma while others with minimal trauma develop severe strictures.[28] Similarly, not all patients undergoing radiation therapy or retroperitoneal surgery later develop fibrosis.[29] Thus, better understanding the host response to injuries and the environmental contributors, especially as they relate to immune activation, may help identify modifiable risk factors and therapeutic targets for these devastating and difficult to manage diseases.

Fibrosis initiators: innate immune contributors

The innate immune system plays a role in normal wound healing and the initiation of fibrosis through a variety of nonspecific pathways. Damage-associated molecular patterns (DAMPs) are produced in response to proinflammatory stimuli, including infection, tissue injury, and autoimmune disease.[30] TLRs and Rig-like receptors (RLR) coordinate the immune response to DAMPs.[30] These danger-sensing receptors increase inflammation to promote fibrosis and proinflammatory cell infiltration.[20,30] Nuclear factor κB (NFκB) has been implicated in fibrosis and is a downstream signaling molecule for numerous proinflammatory pathways, including the TLR pathways.[31] The complement system, another danger-sensing mechanism, consists of a protein cascade that is activated in response to infections or tissue damage. The complement system promotes debris

opsonization and pathogen lysis and may play a role in immune activation at wound sites.[32] Neutrophils—phagocytic cells that remove debris and aid in recruiting other immune cells—are one of the first immune cells recruited to sites of injury.[4] Macrophages, arrive shortly after neutrophils and are antigen-presenting cells that aid in debris removal, tissue remodeling, and the initiation of adaptive immunity (see below). When activated, macrophages develop different phenotypes depending on the surrounding cytokine milieu, which are broadly classified as either M1 or M2.[33] M1 macrophages, which are proinflammatory, promote antibacterial responses that are stimulated by interferon γ (IFN-γ) and danger-associated signaling.[33] M2 macrophages are promoted by IL-4 and -10 and are associated with allergic responses, although they also have anti-inflammatory properties in some settings.[33] Numerous studies demonstrate that macrophages contribute to fibrosis, but the exact macrophage phenotypes found in wounds are still debated and likely depend on the local environment.[5,14,34,35] In addition, activation of immune cells in the innate immune system produces interleukins such as IL-1, -2, and -6, as well as TGF-β, which have all been shown to promote inflammation and fibrosis in a variety of models, including genitourinary fibrosis.[14,36–40] Eosinophils and mast cells, which promote allergic responses, have also been implicated in fibrogenesis.[38,41] Thus, numerous innate factors can contribute to fibrosis throughout the body and likely play a role in fibrosis within the genitourinary tract.

Continued fibroinflammation is coordinated by adaptive immune contributors

In contrast to the innate immune system, the adaptive immune system produces profibrotic cytokines as part of an antigen-specific system to target disease-causing agents.[1] When foreign materials are encountered, antigen presentation occurs via major histocompatibility complexes (MHC), referred to as MHC I or MHC II in most vertebrates and human leukocyte antigen (HLA) I and HLA II in humans.[42] MHC I is found on most cells and presents a sampling of antigens manufactured within the cell's protein production machinery, a mechanism by which cells producing viral particles or abnormal proteins can be targeted. MHC II is found on professional antigen presenting cells, including macrophages, dendritic cells, and B lymphocytes. MHC II primarily presents antigens phagocytosed by these cells during pathogen recognition and removal.[42] Antigens on MHCs are presented to T lymphocytes (MHC I interact with cluster of differentiation (CD) 8+ cytotoxic T cells (CTL) and MHC II with CD4+ T helper (TH) cells). CTL are responsible for coordinating the lysis of cells that present foreign antigens, such as viral particles.[43] TH cells interact with B lymphocytes to promote antibody production.[44] There are multiple subsets of TH cells, including TH_1 cells (important for defense against intracellular pathogens), TH_2 cells (defense against parasites and in allergic responses), and TH_{17} cells (fight bacterial and fungal infections).[44] B cells interact with TH cells and proliferate, some of which become antibody-producing plasma cells.[45] Antibodies play a role in pathogen recognition, neutralization, and removal.[45] The regulation of innate and adaptive immunity remains to be fully characterized in the context of fibrosis, especially as it occurs in the genitourinary tract.

Urethral strictures—fibroinflammatory contributors

Urethral strictures are characterized by concentric narrowing of the lumen of the conduit through which urine travels out of the bladder, potentially leading to lower urinary tract obstruction.[46] These strictures impact roughly 0.6% of the male population and occasionally also occur in women.[47] Obstruction due to urethral strictures can cause symptoms including incomplete bladder emptying, weak urinary stream, suprapubic pain, urinary frequency, and urinary urgency.[48] In addition, increased pressure due to obstruction can lead to bladder decompensation and contribute to diminished renal function even after the stricture has been addressed.[47] Urethral strictures can be induced by iatrogenic causes, trauma, inflammation, and infection, but may also occur without a clear initiating event.[46] Up to 25% of individuals experiencing a pelvic fracture have a concomitant urethral injury, with 22.7–100% of those urethral injuries resulting in stricture formation.[28] The determinants underlying whether or not a stricture forms are likely multifactorial.[28] Urethral strictures have no specific laboratory biomarkers.

Treatment of urethral stricture disease is primarily surgical. Minimally invasive surgical options to open the urethra include dilation or cutting the tissue by direct visual internal urethrotomy (DVIU).[49,50] A more invasive option is urethroplasty, in which the scarred area is either removed and the two ends of the urethra are reconnected (i.e. primary anastomosis) or the stricture is opened longitudinally and a graft (e.g. buccal mucosa) is interposed to increase the size of the lumen.[46,48] Success of surgical management varies, with the reported long-term success of DVIU being roughly 20–30% and urethroplasty being around 85–90%.[49] Management of stricture recurrence after prior operative management can be very challenging so a successful initial surgery is paramount; thus, better understanding of their pathophysiology could reduce rates of recurrence, identify targets for medical management, or prevent them from developing.[49,50]

Contribution of the innate immune system

Studies of urethral strictures suggest that excessive inflammation contributes to their pathogenesis and recurrence. Chronic inflammation was identified in 44% of specimens collected during urethroplasty.[51] While another human study failed to demonstrate inflammatory cells in the area of long-standing urethral strictures, this does not exclude the possibility that inflammatory infiltrates contribute to early urethral stricture formation.[52] Individuals with lichen sclerosis with recurrent urethral strictures demonstrate a different immunologic profile compared with subjects with lichen sclerosis without recurrent strictures, suggesting that immunologic behavior may impact stricture recurrence.[53] A study of TGF-β1 and CXC chemokine receptor (CXCR) 3 in isolated human urethral fibroblasts

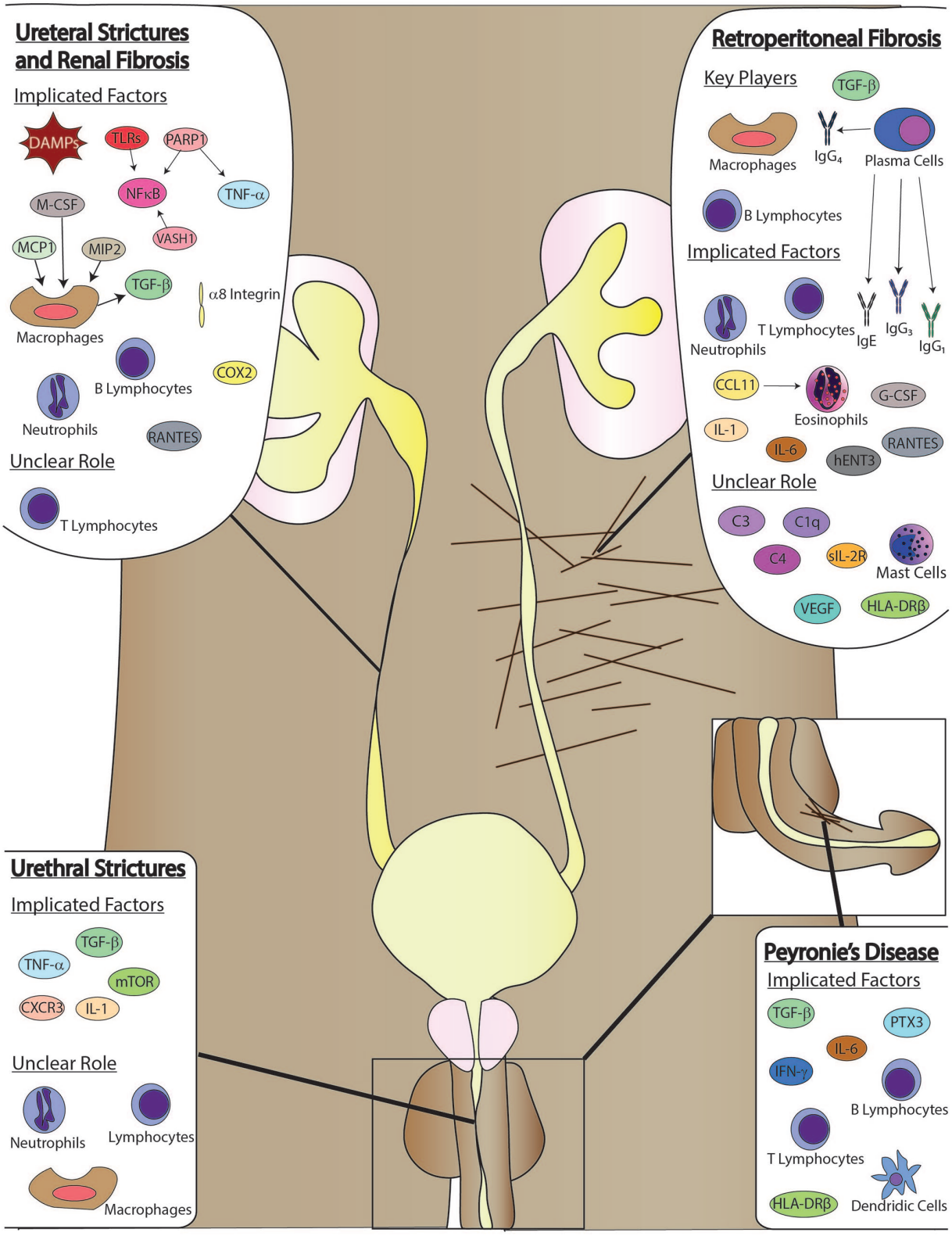

Figure 2. Immunologic contributors to various genitourinary fibrotic diseases, including urethral strictures, ureteral strictures, retroperitoneal fibrosis, and Peyronie's disease. (A color version of this figure is available in the online journal.)

demonstrated reductions in fibroblast viability and migration after induction of TGF-β signaling (Figure 2).[23] TGF-β1 levels were higher and CXCR3 levels lower in individuals with recurrent urethral strictures compared with healthy controls and TGF-β1 blockade increased CXCR3 expression.[23] The authors, therefore, theorized CXCR3, which is a receptor for multiple chemokines, may serve as a feedback mechanism exerting an anti-inflammatory effect in the setting of urethral healing.[23]

Understanding the timing and nature of immune cell recruitment and cytokine signaling following injury may yield insights into the role of inflammation in stricture formation following urethral trauma. A study of porcine urethral injury demonstrated infiltration by inflammatory cells roughly 1 week after injury.[52] By 8 weeks, the inflammatory cell infiltrate began to disappear while fibrotic tissue began appearing.[52] This study indicates that inflammation precedes scar formation following urethral injury but stopped short of demonstrating the mechanism underlying this process. Interestingly, losartan, a competitive inhibitor for angiotensin II, attenuated stricture formation in rabbits by reducing TGF-β and collagen types I and III, and increasing matrix metalloprotease (MMP) 1.[54] Other authors have demonstrated that angiotensin II, acting via the angiotensin receptor 1 (AT1), triggers immune cell proliferation and thereby promotes inflammation, which may explain this study's success in utilizing angiotensin II blockade to prevent strictures.[55]

TGF-β has been shown to induce inflammation via the Akt/mammalian target of rapamycin (mTOR) pathway.[56] One *in vitro* study of fibroblasts isolated from individuals with urethral strictures demonstrated that rapamycin, an inhibitor of mTOR, reduced cell growth and collagen production.[57] Of note, rapamycin reduced expression of SMAD2 protein, a known downstream effector of TGF-β signaling.[57] Another similar study demonstrated that inhibition of the Akt/mTOR pathway also reduced TGF-β-induced autophagy, which has the potential to reduce scar formation.[56] Thus, targeting the mTOR pathway may be a potential therapeutic strategy for stricture prevention and treatment.

The plasma neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are nonspecific markers of systemic inflammation.[58–60] Given that platelet, neutrophil, and lymphocyte counts are often included as routine lab work for patients, there has been significant interest in evaluating these markers in the setting of urethral strictures.[58,60] One study demonstrated higher absolute neutrophil count and NLR in subjects with recurrent urethral stricture after undergoing DVIU, suggesting that chronic inflammation may contribute to stricture recurrence.[60] PLR, but not NLR, was predictive of stricture development in individuals undergoing transurethral resection of the prostate (TURP), a common procedure for management of benign prostatic hyperplasia that carries a small risk of associated urethral strictures.[58] NLR was found not to predict stricture recurrence in patients undergoing urethroplasty.[61] Thus, while there has been significant interest in utilizing NLR and PLR to predict strictures in various clinical populations, the results have been mixed and more specific markers are needed to identify patients at risk.

Evidence for adaptive immune involvement in urethral strictures

Few studies have addressed the contribution of the adaptive immune system to urethral strictures.[51] It is possible that the lymphocytes found in some urethral stricture specimens are coordinating an antigen-specific response, particularly given the association between infection and stricture formation.[51] Studies to characterize these cells have not been performed and further studies are needed to evaluate the contribution of the adaptive immune system to the pathogenesis of urethral strictures.

Potential immunologic therapies in urethral strictures

Given the evidence for the contribution of the immune system to stricture pathogenesis, the utilization of stem cells to reduce inflammation during surgical urethral stricture management has been promising. Synthetic scaffolds containing bone marrow-derived stem cells (BMSC) in a rat model of substitution urethroplasty demonstrated significant reductions in inflammatory markers, including IL-1β, tumor necrosis factor-α (TNF-α), neutrophil myeloperoxidase and the macrophage marker CD68 compared with scaffolds without BMSC.[35] Indeed, almost all rats treated with this scaffold urethroplasty with or without BMSC had good urine flow following their procedure, indicating surgical success of this type of urethroplasty in this model along with the possible benefit of the reduction in inflammation when BMSC were utilized.[35] Injection of adipose-derived stem cells in a rat urethral stricture model reduced collagen deposition through an anti-inflammatory mechanism, although a reduction in stricture recurrence was not demonstrated.[62] Thus, the anti-inflammatory properties of stem cells in the context of urethral fibrosis warrants further investigation.

Future research directions

Significantly more research is needed to understand the inflammatory causes of urethral stricture disease to better identify those at risk for developing them and elucidate targetable pathways to better treat and prevent the disease. There may be yet unidentified host factors that impact the occurrence or natural history of this disease state. For example, the overall inflammatory state in individuals who develop strictures is incompletely understood. NLR and PLR are inconsistent in their ability to predict urethral stricture behavior but given the ease of collection of these markers, further evaluation may be warranted.[58,60] In addition, degree of pelvic trauma is not consistently associated with urethral stricture formation.[47] Further investigation is needed, given the potential for bladder dysfunction and subsequent renal failure as well as the patient morbidity associated with repeated surgeries following failure of initial management.[28,49]

Ureteral strictures—evidence of inflammatory damage in both the ureter and the kidney

Ureteral strictures represent another fibrotic disease of the genitourinary system in which unbalanced inflammation incites fibrosis. Ureteral strictures can lead to renal fibrosis and failure by obstructing the flow of urine from the kidney to the bladder.[63,64] Thirty-five percent of ureteral strictures are iatrogenic (most often due to surgery near but not intending to involve the ureters) and 20% are idiopathic.[63] The remainder are associated with benign and malignant pathology

such as urinary tract infections, tuberculosis, impacted calculi and urinary tract cancers.[63,65,66] Patients may present with signs of urinary tract obstruction (e.g. flank pain or impaired renal function) or with infection. Imaging is used to confirm the diagnosis and define stricture length.[67] There are no serum biomarkers currently available to test for the presence or pathophysiology of ureteral strictures. Management typically involves mechanical opening of the stricture utilizing endoscopic balloon dilation and stent placement, or surgical ureteral reconstruction in which the damaged segments are either removed or surgically widened.[67]

Innate immune contributors to ureteral fibrosis

Most studies of the immunological findings associated with ureteral strictures have focused on post-obstructive fibrosis in the kidney, with relatively few evaluating the strictures themselves. In one study, ureteral stricture specimens demonstrated increased expression of cyclooxygenase 2 (COX2), a proinflammatory enzyme, compared with healthy control ureteral segments from individuals undergoing transplant nephrectomy.[68] In a porcine model of ureteral obstruction, COX2 rose 6 h after obstruction and remained elevated through 48 h postobstruction; however, the effects of COX2 enrichment in ureteral tissue were not investigated further.[68] A separate study demonstrated elevated expression of TGF-β in both macrophages and fibroblasts in obstructed porcine ureters, which remained 28 days after the initiation of obstruction.[69] Interestingly, treatment with injured fibroblasts induced macrophage TGF-β production.[69] Thus, there is limited evidence to suggest that ureteral strictures have an underlying inflammatory cause, but further confirmation is needed.

Renal fibrosis secondary to obstructive uropathy

Renal cellular infiltrate in ureteral obstruction

As indicated above, most studies of ureteral strictures have focused on the impact on the kidneys, likely due to the greater availability of tissue and the interest in the renal effects secondary to urinary tract obstruction. Nonetheless, it is possible that similar processes are occurring in both the damaged ureter and the kidney during and following stricture formation. Inflammation of the kidneys secondary to ureteral obstruction can contribute to renal failure, which occurs through renal cell apoptosis and renal fibrosis in both the tubular and interstitial components of the kidney.[66,70]

While macrophages are recruited to the kidneys following ureteral obstruction and are well-established contributors to postobstructive renal fibrosis, the role of lymphocytes is less well-understood.[71] A study of labeled leukocytes evaluated the sequence of immune cell response *in vivo* in both the ipsilateral and contralateral kidneys following unilateral ureteral obstruction.[71] In the obstructed kidneys, polymorphonuclear (PMN) cells, which represent both neutrophils and macrophages, peaked at 6 h and slowly disappeared while lymphocytes peaked at 24 h and remained present through 72 h.[71] The contralateral kidney did not experience a significant immune cell infiltrate.[71] These studies demonstrate that the timing and order of immune cell entry into obstructed kidneys are similar to wound healing in other contexts, such as cutaneous or cardiac injuries (Figure 1).[2,72] Leukocyte depletion through bone marrow irradiation prior to ureteral obstruction in rats reduced obstruction-induced fibrosis in the kidney.[73] Conversely, another study utilized severe combined immunodeficiency (SCID) mice, which lack both T and B lymphocytes, to study the contribution of lymphocytes to renal fibrosis seen with ureteral obstruction.[74] While both SCID and control mice developed a macrophage infiltrate in their kidneys following ureteral obstruction, wild-type (WT) mice developed a lymphocytic infiltrate primarily composed of T-lymphocytes that was not present in SCID mice.[74] Despite the lack of lymphocytic infiltrate, SCID mice demonstrated similar degrees of fibrosis and inflammation as controls, suggesting that lymphocytes play a minor role in fibrosis secondary to obstructive uropathy and may be more reactive than causative.[74] Thus, like other fibrotic diseases of the genitourinary tract, macrophages may represent the major contributor to obstructive renal fibrosis and may be an attractive therapeutic target.

The role of cytokines in the obstructed kidney

Multiple chemotactic factors, including monocyte chemoattractant protein 1 (MCP1), macrophage colony stimulating factor (M-CSF), and osteopontin, are implicated in attracting macrophages and other immune cells into obstructed kidneys and promoting fibrosis (Figure 2).[34,75–77] Human renal cortical epithelial cells produce MCP1 *in vitro* in response to a variety of proinflammatory factors, including TNF, lipopolysaccharide (LPS), IFN-γ, and IL-1β.[75] MCP1 recruits macrophages to tissues. Obstructed rat kidneys demonstrate peak MCP1 mRNA expression between 12 and 96 h after obstruction, which corresponds with the timing of macrophage infiltration.[34,77] Likewise, ureteral obstruction in the mouse increases MCP1 and other leukocyte chemotactic factors such as regulated upon activation normal T cell expressed and presumably secreted (RANTES), and macrophage inflammatory protein 2 (MIP2), promoting infiltration of immune cells into the kidney.[78] Obstruction increases TGF-β expression, which is likely secreted by macrophages in the kidneys to augment myofibroblast behavior.[77,79] Ureteral obstruction is associated with increased expression of M-CSF, which appeared to be produced by the renal tubular epithelial cells and correlated with macrophage infiltration.[76] In culture, renal epithelial cells produce M-CSF in response to IL-1 treatment, indicating that inflammation can induce M-CSF production.[76] Osteopontin, an important chemoattractant for immune cells, is enriched in kidneys, beginning about 4 h after obstruction.[77,80] Macrophages and monocytes in the obstructed kidneys localize to areas of osteopontin expression.[77] In addition, integrin α8 knockout (KO) mice had increased inflammatory infiltrate and renal fibrosis after unilateral obstruction, indicating a role for integrin α8 in attenuating the immune response in the setting of obstructive nephropathy.[81] Thus, multiple proinflammatory and anti-inflammatory signaling pathways may coalesce to promote or prevent renal fibrosis by coordinating immune cell recruitment during ureteral obstruction.

The factors that initiate renal damage and fibrosis in ureteral strictures remain unclear. Ureteral obstruction increases renal expression of IFN-γ, TLR4, and MyD88 (a downstream signaling molecule for multiple TLR pathways).[31] Genetic loss of TLR2, TLR4, or MyD88 in mice reduces collagen accumulation in obstructed kidneys compared with WT, demonstrating that TLR signaling contributes to fibrogenesis.[31] In addition, MCP1 expression was reduced in the obstructed ureters of both TLR2-KO and MyD88-KO mice.[31] Loss of MyD88 signaling following experimental ureteral obstruction reduced TH_2 accumulation and promoted an M1 type macrophage infiltration, suggesting that MyD88 and TLR signaling increase fibrogenesis through promotion of the M2 phenotype and TH_2 signaling.[31] Thus, it is likely that TLRs activated by DAMPs mediate obstruction-induced renal fibrogenesis. It should be noted, however, that not all DAMPs have been found to contribute to renal fibrosis. For example, macrophage-specific KO of High Mobility Group B1 (HMGB1, an established DAMP) did not affect postobstructive renal fibrosis.[82] Identifying which DAMPs and downstream signals are involved in fibrogenesis may help explain the variability in fibrotic phenotype observed during injuries and reveal novel therapeutic targets.

NFκB-mediated inflammation has also been further implicated in fibrosis in the obstructed kidney. In poly-adenosine diphosphate-ribose polymerase 1 (PARP1) KO mice, ureteral obstruction resulted in reduced NFκB signaling and expression of other inflammatory markers.[83] Vasohibin 1 (VASH1), a proangiogenic factor, has also been implicated in reducing renal fibrosis and inflammation in ureteral obstruction.[84] A study of ureteral obstruction in VASH1 heterozygous KO mice demonstrated that these mice had increased inflammatory markers compared with controls, including phosphorylated NFκB, C-C motif chemokine 2 (CCL2), TGF-β1, and phosphorylated Smad3.[84] miRNA-21—and especially the mature form miRNA-21-5p, which is phosphorylated by methyltransferase-3—stimulates renal fibrosis by NFκB and ERK1 pathway activation.[64] Both *in vitro* in cultured human kidney cells and *in vivo* in a mouse ureteral ligation model, miRNA-21-5p upregulation activated NFκB and ERK1 promoting fibrosis and TNF-α enrichment.[64] Thus, NFκB impacts renal fibrosis via multiple pathways.

Oxidative stress in the obstructed kidney

Expression of important antioxidant enzymes, such as superoxide dismutase and glutathione peroxidase, is reduced in obstructed kidneys in rats resulting in oxidative stress that is associated with tissue damage, apoptosis, and inflammation.[85] Several studies have evaluated the effects of antioxidants on obstructive pathology in the kidney. Oleuropein, an olive-derived antioxidant, attenuated these changes, indicating that this may be a useful therapeutic.[85] Another antioxidant, dermatan sulfate reduced renal MCP production, macrophage infiltration, and TGF-β content, indicating an ability to reduce inflammation during ureteral obstruction.[86] Treatment with ulinistatin, a protease inhibitor with antioxidant and anti-inflammatory properties found naturally in urine, reduced fibrosis, TGF-β, collagen, TNF-α, IL-1, and NFκB protein levels in obstructed rat kidneys compared with untreated controls, although these levels were not reduced to the level of sham procedure animals.[87] *Nigella sativa* extract, another potential anti-inflammatory and antioxidant therapy, reduced fibrosis, renal cell apoptosis, MCP1, TNF-α, and multiple markers of oxidative stress in a rat model of ureteral obstruction.[88] While promising, more work is needed to better understand how obstruction leads to oxidative stress and to improve our ability to target therapeutics to specific immune pathways that become dysfunctional in ureteral obstruction.

Future directions for study of ureteral obstruction

The ureteral and renal inflammatory response that leads to fibrosis in obstructive uropathy have, to our knowledge, not been directly compared despite potentially sharing pathologic mechanisms. It is unclear whether renal inflammation following ureteral obstruction is reflective of the same process as in the ureteral stricture. Furthermore, the relationship between ureteral strictures and fibrosis in other areas of the urinary tract has not been explored but is a potential next step as similarities between pathologies may help us better understand others. Thus, further evaluation of the inflammatory processes occurring at ureteral stricture sites is warranted to better understand and determine treatment strategies for this poorly understood disease entity.

Retroperitoneal fibrosis—external inflammation that impacts the ureter

Retroperitoneal fibrosis is an inflammatory disorder causing fibrotic change throughout the posterior compartment of the abdomen, extrinsically compressing the kidneys and ureters, leading to obstructive uropathy.[26,89] It affects roughly 1–2 per 500,000 people and known etiologies include autoimmune diseases, medications, malignancy, retroperitoneal surgery, infections, and radiation exposure.[90,91] It can also be present as a component of other disease states, including Erdheim–Chester disease or immunoglobulin (Ig) G4-related diseases (discussed later).[36,92] In up to 75% of cases, however, no cause is identified.[90,93] Presenting symptoms include abdominal pain, back pain, fatigue, and ureteral obstructing resulting in hydronephrosis, which is often bilateral.[89,90,93] Despite the contribution of the immune system to its pathology, there is no established biomarker to identify retroperitoneal fibrosis. Immunomodulatory drugs are the mainstay of medical management for retroperitoneal fibrosis.[94] Surgical management includes the placement of ureteral stents or nephrostomy tubes to manage obstructive uropathy, which can often be removed following immunomodulatory therapy.[29,93] In some cases, however, more invasive surgeries are necessary to free the ureters from the surrounding tissues.[29,93–95] There have been cases of spontaneous remission but usually this disease follows a progressive or relapsing-remitting course.[93]

Both innate and adaptive immune cells play a role in retroperitoneal fibrosis

Several studies have used immunohistopathology to identify immune cells within retroperitoneal fibrosis specimens.[96,97] The bulk of the retroperitoneal fibrosis tissue

consists of collagen bundles and spindle cells, which stain positive for macrophage-associated markers such as CD13 and CD86 (Figure 2).[89,96–98] A broad variety of immune cells are present, including T lymphocytes, polyclonal B lymphocytes, plasma cells, follicular dendritic cells, eosinophils, and mast cells.[38,89,96–99] Plasma cells encountered are more likely to be IgG+ than IgM+.[97] B and T lymphocytes appear to form perivascular aggregates composed of a central area of B cells surrounded by CD4+ T cells; both B and T lymphocytes appear to be proliferating and activated.[41,97] HLA-DR staining is present in many of the specimens and has been attributed to both macrophages and B lymphocytes.[96,97] Thus, multiple immune cells are present within retroperitoneal fibrosis tissues and characterizing their roles and interactions may yield insight into the etiology and improve therapy for this disease.

Evidence of innate immune system involvement in retroperitoneal fibrosis

Nonspecific systemic inflammatory markers, including platelet counts, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), are often elevated in individuals with retroperitoneal fibrosis.[100,101] Treatment with immunomodulatory medications, including corticosteroids, azathioprine, or cyclophosphamide, can lead to remission in up to 80% of individuals.[102] Nonetheless, nonspecific autoimmune markers are often elevated in retroperitoneal fibrosis patients, highlighting the likelihood that a systemic proinflammatory state is contributing to this pathology.

The complement system remains understudied in retroperitoneal fibrosis and data linking the innate immune system to the disease remains sparse. One case report demonstrated elevated serum C1q and reductions in serum C3 and C4 complement factors in a patient with retroperitoneal fibrosis.[103] In another study, 2 of 13 subjects with retroperitoneal fibrosis had low complement levels.[100] Another case study reported a reduction in C3 and C4 complement factors in an individual with IgG4-related disease.[104] Further study is needed to determine whether these changes are causal for retroperitoneal fibrosis. If so, this could be a promising therapeutic target given the availability of targeted immunomodulatory drugs.[32] In addition, systemic complement dysregulation could link retroperitoneal fibrosis to other fibrotic diseases, but this remains to be established.

Cytokine signaling may also impact retroperitoneal fibrosis. One study identified elevated levels of CCL11 (also known as eotaxin, an eosinophilic chemotactic factor) in individuals with retroperitoneal fibrosis, compared with healthy controls, with the degree of CCL11 elevation correlating with disease severity.[38] CCL11 was localized to inflammatory aggregates and several CCL11 haplotypes were more common in affected subjects.[38] These subjects also had elevations in RANTES, granulocyte-CSF (G-CSF), and platelet-derived growth factor (PDGF), and infiltrates of eosinophils and mast cells in retroperitoneal biopsies.[38] These findings suggest that abnormal CCL11-mediated recruitment of eosinophils and mast cells plays a role in retroperitoneal fibrosis. Another study found elevated serum IL-6 in individuals with retroperitoneal fibrosis and treatment.[40] Treatment with tocilizumab, an anti-IL-6 therapy, resulted in improvement of disease manifestations and reductions in inflammatory markers and serum levels of soluble IL-6 receptor.[40] Together, these results suggest that circulating cytokines may correlate with retroperitoneal fibrosis.

The adaptive immune system in retroperitoneal fibrosis

Autoantibodies, including antinuclear antibody (ANA) and antineutrophil cytoplasmic antibodies (ANCA), are also frequently positive in patients with retroperitoneal fibrosis, implicating the adaptive immune system in the disease process.[100,101,105] One study found 3 of 13 individuals with retroperitoneal fibrosis to have positive ANA titers.[100] One patient had a speckled pattern and one had a nucleolar pattern of distribution for these ANAs.[100] The final patient had lupus nephritis with markedly elevated ANA titers and a speckled ANA pattern.[100] Retroperitoneal fibrosis was reported in 26.3% of individuals with positive ANCA titers.[102]

Abnormalities in antigen presentation may contribute to the pathophysiology of retroperitoneal fibrosis. One study compared the genetics of 327 subjects with retroperitoneal fibrosis to 2,443 unaffected controls to identify genes that contribute to retroperitoneal fibrosis.[26] *HLA-DR*β variations were associated with retroperitoneal fibrosis in this study, specifically the *HLA-DRB1*0301* and *HLA-DRB1*0302* alleles.[26] These alleles have a substitution of arginine at position 74, which is associated with tighter T-cell receptor binding to the HLA–peptide complex and could explain how this allele promotes autoimmunity.[26] The *HLA-DRB1*0405* and *HLA-DQB1*0401* alleles have been associated with IgG4-related diseases, but have not specifically been associated with retroperitoneal fibrosis.[92] More evaluation of the relationship of HLA polymorphisms and retroperitoneal fibrosis may yield insights into both HLA function and its relationship to fibrotic diseases.

Retroperitoneal fibrosis as a component of other autoimmune diseases

Retroperitoneal fibrosis can also occur as part of other known autoimmune diseases. Retroperitoneal fibrosis is present in up to 59% of individuals with IgG4-related diseases, which also include autoimmune pancreatitis, renal fibrosis, and vasculitis.[91,98,106–108] One hallmark of IgG4-related retroperitoneal fibrosis is monoclonal IgG4 + plasmacytes, which represent more than 40% of retroperitoneal plasmacytes.[99] In a study comparing retroperitoneal fibrosis with associated multifocal sclerosis, idiopathic isolated retroperitoneal fibrosis, and retroperitoneal fibrosis with known etiology, the strongest association with serum IgG4 level was seen in multifocal sclerosis, compared with the other groups.[98] Another study of IgG4-related diseases demonstrated increased TGF-β in some of the fibrotic tissues; however, the TGF-β content of retroperitoneal tissue from the one individual in the series with retroperitoneal fibrosis was not specifically examined.[39] IgE, IgG1, IgG3, and free light-chains have also been implicated in IgG4-related retroperitoneal fibrosis, which may implicate plasma cell dysfunction in the disease.[104] B-cell depletion therapy with rituximab is associated with

remission of IgG4-related retroperitoneal fibrosis.[109] Thus, it appears that, in addition to IgG4, other immunoglobulins are likely involved with the development of IgG4-related retroperitoneal fibrosis through the action of plasma cells and B lymphocytes; however, the complete mechanism underlying this disease state remains to be elucidated.

Retroperitoneal fibrosis has been associated with disorders other than IgG4-related diseases, including H-syndrome, a protein-losing nephropathy in which IgG light chains are found in the urine, and Erdheim–Chester disease.[36,103,110] H-syndrome, an autosomal recessive disorder due to mutations in the *SLC29A3* gene, presents with retroperitoneal fibrosis and other fibrotic and autoimmune manifestations and is associated with elevated serum vascular endothelial growth factor (VEGF), TGF-β, and soluble IL-2 receptor (sIL-2R) levels.[110] Erdheim–Chester disease is a sclerotic disease in which individuals develop areas of bone fibrosis as well as inflammatory fibrosis of the pituitary gland and the retroperitoneum.[36] One study found that treating these patients with the IL-1 receptor antagonist anakinra improved their retroperitoneal fibrosis and other disease manifestations, thus implicating IL-1 in its pathogenesis.[36] Thus, retroperitoneal fibrosis is associated with a wide variety of systemic fibroinflammatory disease states, strongly implicating the immune system in its pathogenesis.

Immunologic therapeutic targets for treating retroperitoneal fibrosis

Treatment of retroperitoneal fibrosis typically begins with corticosteroids, which are subsequently transitioned to other immunomodulatory agents; however, there is wide variation in treatment regimens and limited clinical data to guide intervention.[89,93,102] There has been significant interest in targeting the immunologic changes associated with retroperitoneal fibrosis given the success of various immunotherapies in treating the disease. Retroperitoneal fibrosis secondary to non-Hodgkin's lymphoma responds to rituximab, an anti-CD20 antibody that is cytotoxic to B lymphocytes, thus implicating these cells in this disease process.[90] Mycophenolate mofetil (MMF) is an immunosuppressant that inhibits purine synthesis and reduces lymphocyte proliferation. Given the presence of lymphocytes in specimens of patients with retroperitoneal fibrosis, Scheel et al. prospectively treated a cohort of subjects with combination prednisone and MMF.[95] In this study 25 of 28 subjects had improvement of their fibrosis with few complications.[95]

Future directions for research in retroperitoneal fibrosis

Despite the clear immune contribution to retroperitoneal fibrosis, our understanding of the behavior of the immune system in this disease state remains rudimentary and warrants further investigation. Retroperitoneal fibrosis is often initially managed with nonspecific corticosteroid therapy. Better understanding the disease process that underlies retroperitoneal fibrosis may reveal more targeted therapies with fewer side effects. Therefore, more specific evaluation and characterization of the disease is needed to fully elucidate the roles of each immune player and better determine the most important contributors to this disease state. In addition, to our knowledge, there have not been studies evaluating fibroinflammatory changes within the ureter in the context of retroperitoneal fibrosis, and correlation of these processes could further enhance our management of this heterogeneous disease. Furthermore, retroperitoneal fibrosis may share pathogenetic characteristics with other urinary tract fibrotic diseases such as ureteral and urethral strictures, so these processes could be compared.

Peyronie's disease—a penile manifestation of excess fibrosis due to inflammation

Peyronie's disease is characterized by the development of a fibrotic plaque in the penis causing acute penile curvature and painful erections.[111] Average age of onset is 53 years with prevalence of 3.4/1,000 and annual age-adjusted incidence of 0.3/1,000, although the incidence is much higher in certain populations.[111] The pathophysiology of Peyronie's disease is largely thought to be driven by fibrosis caused by trauma to the penis resulting in a fibrotic plaque of the tunica albuginea, the fibrous sheath covering the erectile bodies.[111] This fibrosis prevents that section of the penis from expanding during erection, resulting in curvature toward the direction of the scar. Not all traumas result in the development of fibrosis and not all Peyronie's disease results from clear traumatic events.[24,111,112] In Peyronie's disease, inciting events typically trigger molecular and immunologic processes that result in an acute phase and a chronic phase of disease. Most studies define the transition between the acute and chronic phase as resolution of painful erection and stabilization of the curvature.[59,113–115] Peyronie's disease lacks laboratory tests to identify the disease itself or to mark the transition between the acute and chronic phases of the disease. Clinical management of Peyronie's disease is generally deferred until a patient's disease stablizes.[112] Depending on the severity, less invasive treatment options may include observation, penile stretching, and injection of IFN-α_{2b}, verapamil, or collagenase.[112] Patients with severe deformities, large calcifications, or medically refractory erectile dysfunction (ED) may be treated surgically, with placement of plication stitches to straighten the penis, plaque excision with or without grafting, and/or penile prosthesis placement.[116]

The innate immune system contribution to Peyronie's disease

Current understanding of the acute phase of Peyronie's disease is derived from animal models. In an excisional punch biopsy model of penile injury, healing occurs in a manner-like wound healing in other contexts (Figure 1). The injury response starts with coagulation within minutes and tissue infiltration by inflammatory cells (neutrophils then macrophages) over 1-2 days.[117] Over the next several days, epithelial cells are organized along the border of the site of injury, the site fills with fibrin, fibronectin, and collagens, and new blood vessels extend into the site of injury.[117] In well-regulated wound healing, these wound patches are remodeled by MMPs and other fibrinolytic proteins to repattern the tissue to be more similar to baseline tissue organization with little

scar formation.[118] In a Peyronie's disease model, however, cytomodulin injection into the tunica albuginea triggers TGF-β1 production and results in fibrotic plaque development.[119] After injection, tissues initially show expected wound healing but profibrotic factors (e.g. fibrin, fibrinogen, collagen) persist with increased expression of TGF-β1, significantly longer than seen during typical wound healing.[119]

In Peyronie's disease, the healing sequence deviates toward fibrosis, likely due to excess inflammation, and results in scar (i.e. plaque) formation. When remodeling should start, Peyronie's disease tissues shift to a cycle of profibrotic and proinflammatory signaling with inhibition of fibrinolysis and collagen remodeling. Excised fibrotic Peyronie's disease plaques show increased expression of TGF-β1, which promotes the development of myofibroblasts.[25,120] Myofibroblasts further increase the deposition of collagen, which, in conjunction with further deposition of fibrin and crosslinking by fibronectin, results in fibrosis.[117,120] In addition, TGF-β injection into the penises of rats induces plaque formation which is ameliorated by MMF.[121] Analysis of plaques from humans and rodents indicate that Peyronie's disease is associated with increased collagens, especially collagen type I, as well as TGF-β.[25,120] Interestingly, MMP2 and MMP9, which are associated with collagen remodeling, are also increased in Peyronie's disease plaques indicating that some remodeling is occurring but that it is not proceeding normally.

During the acute phase of Peyronie's disease, serum inflammatory markers are elevated in approximately 75% of patients, although no single inflammatory factor has been shown to reliably identify Peyronie's disease.[113] One study identified elevated serum levels of pentraxin-3 (PTX3) and IL-6 during the acute phase of the disease, and IL-6 was particularly associated with subjects experiencing painful erections.[114] Another study reported increased serum TGF-β1 and IFN-γ and decreased TNF-α in subjects with Peyronie's disease.[122] NLR and PLR are elevated in the acute phase of disease with PLR declining in a time-dependent fashion.[59,115]

Peyronie's disease is usually treated surgically only after the stabilization of the fibrotic plaque, so the acute remodeling phase of Peyronie's disease is difficult to study in humans. Once stabilized, the chronic phase of Peyronie's disease is characterized by a persistent fibrosis maintained by permanent tissue remodeling. Several previous reviews highlight that inhibition of fibrinolysis by plasminogen activation inhibitor 1 (PAI-1), inhibition of collagen remodeling by MMP inhibition, and reactive oxygen and nitrogen species (ROS/RNS) imbalance with nitric oxide (NO) are associated with fibrosis in Peyronie's disease.[27,123,124] Thus, it could be postulated that failure to terminate inflammation during wound healing promotes Peyronie's disease and that propensity to develop Peyronie's plaques is driven by host factors that may also promote fibrosis in other contexts.

The adaptive immune response in Peyronie's disease

Evidence exists that CD8+ cytotoxic T cells, B cells, and dendritic cells, as well as more specialized monocyte-derived CTL and mucosa-associated invariant T (MAIT) cells are present in Peyronie's plaques and continue to stimulate an inflammatory response (Figure 2).[125] The presence of these cells may serve as evidence of adaptive immune system involvement in Peyronie's disease pathogenesis. However, further exploration of the role of adaptive cellular immunity is required to characterize the role of these and other adaptive immune cells in this diseases state.

Associations with certain HLA types have frequently been cited as evidence of adaptive immune system involvement in the pathogenesis of Peyronie's disease. HLA-B7 cross-reacting groups were present in most subjects with Peyronie's disease in several studies.[126,127] This HLA-B7-related susceptibility to Peyronie's disease is transmitted in an autosomal dominant fashion and is associated with a high rate of co-occurrence with Dupuytren's contractures, a fibrotic disease of the palmar fascia.[127] However, a larger study of 51 patients showed that only HLA-B27 was significantly associated with Peyronie's disease, and neither individual B7 group members (HLA-B40, -B22, -B7) or the B7 group as a whole were significantly associated with Peyronie's disease.[128] Further reanalysis of several studies showed Peyronie's disease HLA types were consistent with population prevalence, although prevalence of Peyronie's disease in particular HLA groups has not been fully evaluated.[129] There is evidence that HLA-B type is associated with familial, but not sporadic, Peyronie's disease, which may explain some of the discrepancies in studies evaluating HLA types in this disease.[24]

Epigenetic regulation of the immune system in Peyronie's disease

Epigenetic changes may play a role in the pathogenesis of Peyronie's disease. Development of a myofibroblast phenotype (identified by increased α-smooth muscle actin on histology and SMAD2 and 3 gene expression) in cells isolated from Peyronie's plaques can be prevented *in vitro* with histone deacetylase (HDAC) 2 inhibition by siRNA suggesting epigenetic remodeling during the chronic disease phase.[120,130] Another study demonstrated that the mRNA expression of multiple HDACs was higher in fibroblasts isolated from Peyronie's plaques compared with non-Peyronie's control tissue and that inhibiting HDAC7 reduced TGF-β expression and myofibroblast differentiation.[131] These results demonstrate that epigenetic mechanisms such as histone modifications may play a role in driving the profibrotic phenotype and that stabilization of usually transient myofibroblasts by epigenetic regulation and inflammatory stimulation reinforces fibrotic changes. While the drivers of these epigenetic changes have not been determined, a better understanding of this mechanism may reveal novel mediators of fibrotic responses in healing.

The association of Peyronie's disease with other autoimmune diseases

Several systemic diseases are associated with Peyronie's diseases including Paget's disease,[132] systemic sclerosis,[133] scleroderma,[134] idiopathic pulmonary fibrosis, and autoimmune diseases in general.[135] There is evidence of both local and systemic inflammation in Peyronie's disease. Systemic inflammation and genetic susceptibility may explain why relatively mild penile trauma may result in Peyronie's disease in some individuals, but complete disruption of the

tunica albuginea (i.e. penile fracture) may not in others. Thus, like other fibroinflammatory diseases of the genitourinary tract, there may be individuals who are more prone to fibrosis in whom a traumatic event leads to overexuberant wound healing coordinated by immune overactivation. Studies associating Peyronie's disease with other disease states, including Dupuytren's contracture, scleroderma, and other autoimmune fibrotic diseases, may indicate a common underlying pathology for these diseases. More evaluation is needed to further understand the role of inflammation in Peyronie's disease, which may improve treatment for this psychologically disturbing and functionally debilitating disease entity.

Conclusion and further questions

Numerous fibrotic diseases of the genitourinary tract have immunologic components to their pathogenesis, which may be shared across disease processes. The association of many of these diseases with other fibrotic processes, such as the association of Peyronie's disease with Dupuytren's contracture and systemic sclerosis and the association of urethral strictures with lichen sclerosis indicates that they may be different manifestations of a common pathogenic process.[24,53,59,115,127,133] Research in genitourinary fibrosis is sparse and studies often lack a mechanistic evaluation of the findings. Overall, the study of genitourinary fibrosis has been hampered by a lack of animal models that fully recapitulate the human disease states. Thus, the immune system remains underexplored in these diseases, and significant questions remain. It is unclear the extent to which infections, impaired wound healing, and/or autoimmunity are contributing to these disease states. The exact contributions of the innate and adaptive immune components are incompletely characterized in all the pathologies outlined herein. However, the immune system has been extensively explored in other models of scar formation and fibrosis, and extrapolation of these findings to genitourinary fibrosis may help us better understand these conditions. Contributors to the immune response including TGF-β, IL, macrophages, and B lymphocytes have all been implicated in both genitourinary fibrosis and other fibrotic diseases.[11,23,69,98,99,114] Identification and characterization of the immunologic drivers of genitourinary fibrosis may reveal novel therapeutic targets for these disease states as well as improve treatment of other fibrotic diseases. In addition, many of the surgical treatments for these diseases, such as urethroplasty, mechanical dilations of the ureter or urethra, or removal of Peyronie's plaques, are pro-inflammatory and thus may be suboptimal therapies for inflammation-based diseases; however, without better understanding of the immunologic factors contributing to these diseases, their medical management is relatively limited. Thus, much more work is needed to better understand these disease states and their potentially shared immunopathogenesis.

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All authors contributed to the literature review and writing of the manuscript. KMD was primarily responsible for the figures.

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