Animal Models for Interstitial Cystitis/Painful Bladder Syndrome (IC/PBS)

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The etiopathogenesis of IC/PBS has not yet been elucidated. Several different theories have been proposed for the underlying pathology of IC/PBS. Advancement in addressing this disease has been painfully slow due to lack of understanding of the underlying pathophysiology. A main limitation in IC/PBS research has been the lack of an appropriate animal model. In this review, we focused on the current animal models for IC/PBS disease.

Key words: Interstitial cystitis, painful bladder syndrome, IC animal model

Animal Models For Interstitial Cystitis/Painful Bladder Syndrome

The International Continence Society has defined IC/PBS as “the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology” (1). IC is a chronic inflammation of the urinary bladder in the absence of verified infection and/or irritation in the bladder and lower urinary tract (LUT), necessitating the addition of the new terminology painful bladder syndrome (PBS) (3-5). Complete diagnostic criteria for epidemiological studies of IC/PBS have not been established. Earlier diagnostic criteria proposed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) included a cystoscopic finding of glomerulations upon bladder distension or Hunner’s ulcer, in addition to bladder pain or urinary urgency, along with several criteria to exclude other diseases (6). However, 10% to 34% of patients with urinary urgency due to bladder pain do not exhibit glomerulations upon bladder distension and only 10% of patients diagnosed with IC present with Hunner’s ulcer (7-10).

Depending on the diagnostic criteria used, the prevalence of IC/PBS has been estimated as between 0.03% to 2.0% of adults (11-13). The prevalence of IC/PBS among women is estimated to be 2 to 5 times higher than in men (3, 13). The recent Rand Epidemiology study of IC/PBS in women in the United States identified the prevalence of IC/PBS as 6.5% and 2.7% based on high sensitivity and high specificity diagnostic criteria, respectively, which translates to 3.3 to 7.9 million women suffering from IC/PBS symptoms (14). According to the NIDDK diagnostic criteria, IC/PBS occurs 17 times more frequently in relatives of IC/PBS patients than in the general population in the United States (15). The medical costs have been estimated at more than $100 million per year in the United States (16).

IC/PBS patients suffer considerable morbidity over the course of their lives, especially during their most productive years. Advancement in addressing this disease has been painfully slow due to a lack of understanding of the underlying pathophysiology.

Etiology of IC/PBS

The etiopathogenesis of IC/PBS has not yet been elucidated. Several different theories have been proposed for the underlying pathology of IC/PBS (17), including defects of the barrier glycosaminoglycan layer, infection induced, mast cell activation (18-20) autoimmunity, increased production of antiproliferative factor (21), decreased sialylation and glycosylation of Tam Horsfall Protein (THP) (22), increased TNF-related apoptosis-inducing ligand (TRAIL) receptor 4 (23), elevated transient receptor potential subtype 1 vanilloid receptor in nerve fibers (24), and neuroendocrine and neuroimmune mechanisms (25).
Animal Models For IC/PBS
Numerous animal models for cystitis have been generated in different ways, such as through intravesical administration of chemical irritants or immune stimulants, systemic or environmentally impelled inflammation, a naturally occurring model, and experimentally induced autoimmunity models, which include systemic immunization with bladder homogenate or recombinant uroplakin II protein, and induction of bladder autoimmunity in transgenic URO-OVA mice by ovalbumin (OVA)-specific T cells.

Intravesical Irritant Instillation Models
Instillation of urine from IC patients into the bladder of rabbits resulted in histological inflammatory changes that resembled human IC bladders, but did not yield statistically significant differences in 24-hour urinary frequency and volume (26). Intravesical instillation of acetone solutions induced transient IC in rats, monkeys, and rabbits that included markedly increased voiding frequency and decreased volume per void (27-29). Moreover, intravesical administration of an acidic solution resulted in increased levels of neutrophil chemotactic factors, accumulation of neutrophils, and edema in the bladder of rabbits (30). Intravesical instillation of mustard oil and electrical stimulation of pelvic ganglia activated bladder afferent fibers and produced high levels of plasma extravasation in the bladder of rats (31). Instillation of xylene into the bladder in rats induced inflammation that involved irritation of capsaicin-sensitive sensory nerves in the bladder wall (32).

Intraperitoneal administration of the antineoplastic drug cyclophosphamide has been used extensively for induction of cystitis in animals. It damages the bladder mucosa and causes edema, accumulation of leukocytes in bladder tissue, and hemorrhage (33-35).

Immune Stimulant-Induced Cystitis Models
Intravesical administration of substance P or the bacterial endotoxin LPS resulted in cystitis characterized by neutrophil invasion, hemorrhage and edema in the bladder in two strains of mice (36). Of those responses, only slight hemorrhage was observed in congenic mast cell knockout mice (37). In another model, neurogenic bladder inflammation was induced in rats by injection of pseudorabies virus (PRV) into the adductor caudae dorsalis tail muscle (38). In the equivalent model in mice, PRV induced tumor necrosis factor alpha-dependent mast cell infiltration into the lamina propria along with pelvic pain mediated by histamine (39-42). In addition, the cathelicidin LL-37, an antimicrobial peptide, was used to generate bladder inflammation in mice (43).

Stressful Environmental Stimulus-Induced Cystitis Models
Exposure of animals to various physical and psychological stress factors has been shown to induce cystitis in the bladder. In one study, restraint stress induced activation of mast cells in the bladder, which was attenuated by neonatal depletion of sensory nerve terminals (44). Another group subjected rats to acute cold and restraint stress, which resulted in edema, leukocyte invasion, and mast cell degranulation in the bladder (45). In another study, moderate stress induced by exposing mice to constant illumination for 96 hours resulted in desquamation of superficial and intermediate urothelial cells (46-48).

Naturally Occurring Cat Model for IC/PBS
Idiopathic IC has been observed in domestic cats, with symptoms similar to human IC/PBS such as increased urinary frequency and pain (49). Also similar to human IC/PBS, cats with feline IC exhibit reduced urinary excretion of total and GP-51 glycosaminoglycan, increased bladder wall permeability, and elevated density of neurokinin-1 receptors in the bladder (50-54). In addition, increased substance P immunoreactivity has been found in feline IC and some human IC/PBS studies (52, 54). The major advantage of feline IC is its occurrence in the absence of external stimulants. A disadvantage of this model is its dissimilar gender distribution compared with human IC/PBS, with equal distribution among male and female cats, compared with 2- to 5-fold greater prevalence of human IC/PBS in women (55). Also, the etiology of cystitis development in cats is unknown. Other issues include handling problems that require veterinarian involvement and expensive care in animal facilities (56).

Experimental Autoimmune Cystitis Induced by Immunization with Bladder Homogenate
In different mouse strains such as BALB/cAN and SWXJ, experimental autoimmune cystitis (EAC) was generated by immunization with bladder homogenate from syngeneic animals and showed some of the physiopathological features of cystitis (57, 58). The initial EAC model was developed in BALB/cAN mice immunized with a syngeneic bladder homogenate that induced edema, fibrosis, perivascular lymphocytic infiltrations and deposition of mast cells in the detrusor muscle of the bladder (57). Cell-mediated autoimmunity was confirmed in this model by adoptive transfer of spleen cells from bladder homogenate-immunized mice into naïve mice, thereby recapitulating the disease (57). In another study, SWXJ mice that are prone to the generation of autoimmune diseases were immunized with bladder homogenate and developed EAC showing the symptoms of increased urination frequency and decreased volume per void, along with histopathological alterations such as increased infiltration of lymphocytes and mast cells, and thickened lamina propria (59). Bladder homogenate was also obtained from Lewis rats and used to induce EAC in syngeneic animals, demonstrating increased urinary frequency, mast cell accumulation and vascular congestion (60). It was suggested that T helper cells could play a role in the immune response in the bladder to bladder homogenate-induced EAC (61, 62).

EAC Induced by Immunization with Recombinant UPK2 Protein
A potentially more organ specific EAC model was generated by targeting the abundantly expressed urothelial membrane-specific protein uroplakin II (UPK2) (63). SWXJ mice immunized with recombinant murine UPK2 exhibited symptoms of significantly increased urination frequency and decreased volume per void, along with increased infiltration of T cells in the bladder. However, as in the bladder homogenate EAC models, visceral pain was not assessed in this model.

Sensitization to Ovalbumin and URO-OVA Mice
An experimental cystitis model was generated by sensitizing guinea pigs to ovalbumin (OVA) by multiple intraperitoneal injections of the antigen, followed by injection of OVA into the bladder. Those animals exhibited permeability of the urothelium (64-66).

In a parallel study in mice, transurethral instillation of OVA yielded bladder inflammation experimental cystitis in wild type mice, but not in congenic mast cell deficient mice (67).
Another EAC model has been created using transgenic URO-OVA mice, which produce a membrane form of OVA, driven by the urothelial-specific uroplakin II gene promoter, as a self-antigen on the urothelium. URO-OVA mice are susceptible to induction of bladder inflammation by adoptive transfer of activated OVA-specific CD8+ T cells. In addition, crossbreeding URO-OVA mice with transgenic mice that express an OVA-specific CD8+ T cell receptor (OT-I mice) yielded mice that spontaneously developed autoimmune cystitis (68, 69). However, OVA is not an endogenous antigen of the bladder, and bladder urodynamic changes and pain correlated with the IC/PBS phenotype have not been characterized in this model.

**Conclusion**

The earlier animal models of IC/PBS were developed through different approaches such as inducing inflammation by transurethral application of irritants or immune stimulants into the urinary bladder and systemic and environmentally caused irritations. Although systemic cyclophosphamide-induced bladder inflammation is a well-described and broadly studied model of chronic cystitis, its pathogenesis does not fit that of human IC/PBS (70). A spontaneous model of IC/PBS described in cats has not been applied extensively in the scientific community due to cost and handling problems (56, 71).

The transgenic URO-OVA mouse model of EAC fabricated a urothelial membrane-specific form of OVA as a self-antigen, and then bladder autoimmune cystitis was generated through the transfer of OVA-specific CD8+ T cells to this mouse (68, 69). The disadvantage of this model is that OVA is not an endogenous antigen of bladder, and urodynamic assessment of the bladder or bladder dysfunction, as well as pelvic pain associated to IC/PBS phenotype, have not been demonstrated.

The models of autoimmune-mediated cystitis in SWXJ mice generated by immunization with bladder homogenate or the urothelial membrane-specific protein UPK2 faithfully reproduced the urodynamic aspects of human IC/PBS and exhibited inflammatory T cell responses to the targeted bladder tissues (59, 63). The disadvantage of immunization with bladder homogenate is the possible induction of nonspecific and systemic immune reactions along with the bladder-specific responses, due to the inclusion of tissue-nonspecific antigens in the homogenate. The EAC mice immunized with bladder-specific recombinant UPK2 protein exhibited bladder-specific T cell mediated autoimmunity and clear evidence of IC-related bladder dysfunction, as indicated by significantly increased frequency of urination and decreased urine output per void (59, 63). However, this EAC mouse model did not exhibit pelvic pain responses to noxious stimulation with von Frey filaments, thus failing to reproduce one of the major symptoms of human IC/PBS. In view of that, the need remains for an animal model that expresses all of the major phenotypical properties observed in human IC/PBS, namely urinary frequency/urgency and pelvic pain, along with bladder specificity and a high induction rate of the phenotype.

It is evident that IC/PBS influences millions of people. However, no successful therapies have been presented. The present treatment applications merely alleviate the storage or voiding bladder symptoms by different agents and applications. There has been no significant treatment or preventive strategies for IC/PBS for the last several decades. Failure of clinical researches to discover successful therapies for IC/PBS has led the scientific community to develop animal models that could provide a valuable step to jump start translational research in which the clinical studies have been hindered. Thus, it is valuable to develop an animal model that demonstrates all of the major phenotypical features of IC/PBS.

**Conflict of Interest**

No conflict of interest was declared by the author.

**Authors’ contributions:** Conceived and designed the experiments or case: Kl, FD. Performed the experiments or case: Kl, FD. Analyzed the data: Kl, FD. Wrote the paper: Kl, FD. All authors read and approved the final manuscript.

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Çıkar Çatışması

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