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# Experimental murine models of interstitial cystitis/bladder pain syndrome: A review

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**Summary.** Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic enigmatic disease of the urinary bladder characterized by persistent bladder/pelvic pain in conjunction with lower urinary tract symptoms. IC/BPS is categorized as either Hunner-type IC (HIC) or BPS based on the presence/absence of the Hunner lesion, a reddish mucosal lesion in the bladder. HIC and BPS present with similar symptoms, however, the etiologies are completely different. Recent evidence suggests that HIC is an immune-mediated inflammatory disease of the urinary bladder. In contrast, BPS, other forms of HIC lacking Hunner lesions, is a minimally inflamed condition comprising various clinical phenotypes. Based on this evidence, basic research into IC/BPS has shifted to target each subtype of IC/BPS. Today, experimental murine models of autoimmune cystitis are used for HIC research, whereas models related to neurophysiological and psychosocial dysfunctions have been developed for BPS research. This emerging concept of a subtype-tailored approach may contribute to a better understanding of the full picture of IC/BPS, thereby improving current clinical management strategies and the development of novel therapies.

**Key words:** Interstitial cystitis, Bladder pain syndrome, IC/BPS, Hunner, Animal, Model, Murine

## Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a rare, debilitating disorder of the urinary bladder characterized by irritable pain and discomfort in conjunction with lower urinary tract symptoms (LUTS), such as increased urinary frequency and urgency (Homma et al., 2020; Clemens et al., 2022). The detailed pathophysiology, and thus, the full picture of IC/BPS remains unknown, which renders the condition enigmatic and ill-defined. Today, IC/BPS is considered a complex disease comprising miscellaneous conditions manifesting similar clinical symptoms such as irritable bladder pain and LUTS (Hanno and Dmochowski, 2009; Homma et al., 2020). IC/BPS is classified roughly as either Hunner-type IC (HIC) or BPS based on the cystoscopic presence or absence of the Hunner lesion (a characteristic reddish mucosal lesion in the bladder) (Homma et al., 2020). Growing evidence suggests that HIC is a more specific condition, characterized by histological chronic inflammatory changes in the bladder, whereas BPS remains an ill-defined, enigmatic symptom syndrome complex with minimal inflammatory changes in the bladder (Akiyama and Hanno, 2019; Akiyama et al., 2019b, 2020; Fall et al., 2020; Lai et al., 2020).

To date, the etiology of IC/BPS is thought to comprise urothelial alterations, autoimmunity against bladder components, upregulated expression of nociceptive receptors in the bladder mucosa, urinary toxins, and infection by microorganisms (Akiyama, 2020; Masterson et al., 2023). Previously, we found that bladder histology of HIC specimens revealed an accumulation of plasma cells and frequent expansion of light chain-restricted B cells (Maeda et al., 2015; Akiyama et al., 2019a). Our RNA-seq analysis showed that HIC and BPS have different gene expression patterns; genes involved in biological pathways related to cell proliferation, immune system, and infectious disease are upregulated specifically in HIC (Akiyama et al., 2019b). Recently, we conducted a genome-wide association study in Japanese patients with HIC and identified risk-associated genetic variants for HIC in the major histocompatibility complex (MHC) region, which were further fine-mapped to reveal amino acid variants of MHC class II genes (Akiyama et al., 2023b). Intriguingly, the identified risk amino acid variants are located in the antigen-binding grooves of MHC classIImolecules, suggesting that alterations in antigen-presentation may underlie the pathophysiology of HIC.

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Collectively, these findings indicate that HIC is an immune-mediated inflammatory disease of the urinary bladder potentially associated with aberrant immune responses and B-cell abnormalities. The demographics of patients with HIC support a connection between HIC and autoimmunity. Patients with HIC show a higher incidence of comorbid systemic autoimmune diseases, such as Sjogren's syndrome, rheumatoid arthritis, and systemic lupus erythematosus than the general population (Boye et al., 1979). Patients with HIC also show a female preponderance (a common, known epidemiological feature of autoimmune disorders) (Homma et al., 2020), the presence of anti-urothelial auto-antibodies in serum and bladder tissues (Jokinen et al., 1972; Ochs et al., 1994), and a favorable response to corticotherapy (Soucy and Gregoire, 2005; Akiyama et al., 2023a). Meanwhile, studies report a higher prevalence of positive urine cultures in female patients with IC, and that most patients experience bacteria-mediated acute cystitis before the onset of IC symptoms (Keay et al., 1995; Haarala et al., 1999). This evidence suggests a potential association between infection and initiation of dysregulated immune responses in IC (i.e., infection is known to drive aberrant autoimmune responses) (Rose, 1998).

By contrast, BPS is a non-inflammatory disorder comprising various clinical phenotypes represented by bladder-centric, pelvic floor-centric, or widespread pain phenotypes (Lai et al., 2017). Some studies suggest a connection between the widespread pain BPS phenotype and conditions related to somatoform disorders and functional somatic syndrome (Warren, 2014; Chen et al., 2017).

Based on this evidence, the International Consultation on Incontinence (2018) proposed that HIC and BPS should be clearly defined as different conditions (Abrams et al., 2018). Subsequently, the East Asian guidelines for IC/BPS were updated to define IC/BPS with Hunner lesions as HIC, and other forms of IC/BPS as simply BPS (Homma et al., 2020).

The crucial problem related to the clinical management of IC/BPS is that, despite the completely different underlying etiologies, HIC and BPS manifest similar symptoms (i.e., bladder/pelvic pain and lower urinary tract symptoms), which may lead to difficult differential diagnoses (Doiron et al., 2016; Watanabe et al., 2021). To better understand the pathophysiology of IC/BPS, and develop novel treatments, it is essential to establish precise subtype-specific animal models and identify their phenotypic characteristics. In this article, we review the current murine models of each subtype of IC/BPS and discuss future strategies for basic research aimed at revealing the pathogenesis of this enigmatic disease.

## Autoimmune cystitis models

Previously, we showed that HIC is associated with aberrant immune responses in the bladder tissue, characterized by B-cell abnormalities and genetic susceptibility determined by MHC gene risk variants (Fig. 1) (Maeda et al., 2015; Akiyama et al., 2023b). Based on this evidence, it is reasonable to explore murine models for HIC that exhibit bladder inflammation and voiding dysfunction mediated via an autoimmune mechanism. Past studies demonstrated that autoimmune responses of the bladder mucosa, primed by homogenized mouse bladder tissue antigens, cause stromal edema, and increase urothelial permeability, lymphocytic infiltration, suprapubic pain, and bladder dysfunction (Jin et al., 2017; Liu et al., 2019). These models are also characterized by having longer-lasting bladder symptoms (lasting for several months) than other bladder inflammation models developed by induction of bladder irritation (Bullock et al., 1992; Luber-Narod et al., 1996). Bladder urothelial antigens, such as uroplakin (UPK) (Altuntas et al., 2012), Transient Receptor Potential Melastatin (TRPM) 8 (Zhang et al., 2017), and UPK3A-derived immunogenic peptide (Izgi et al., 2013), have been used to create experimental autoimmune cystitis (EAC) models for IC/BPS research. These models exhibit bladder inflammation characterized by T cell-dominant infiltration, increased urinary frequency, and increased suprapubic pain, thereby replicating the clinico-pathological features of human IC/BPS.

We endeavored to develop novel EAC models using URO-OVA mice that express the well-defined model antigen ovalbumin (OVA) as a "self" antigen derived from the urothelium (Liu et al., 2007; Kim et al., 2011; Liu et al., 2011; Wang et al., 2016; Kogan et al., 2018; Cui et al., 2019; Akiyama et al., 2021, 2023c). Adoptive transfer of OVA-specific $CD8^+$ T cells from OT-I mice expressing the transgenic $CD8^+$ T-cell receptor specific for the $OVA_{257-264}$ epitope peptide ($H2\text{-}K^b$) into recipient URO-OVA mice induced bladder inflammation. This was characterized by dense cellular infiltration, stromal edema, mucosal hyperemia, and upregulated expression of genes encoding tumor necrosis factor (TNF)-α, nerve growth factor (NGF), substance P, interleukin (IL)-6, interferon-γ and monocyte chemoattractant protein-1 (Liu et al., 2007; Kim et al., 2011). In parallel with bladder inflammation, cystitis-induced URO-OVA mice showed increased pelvic nociceptive responses and voiding dysfunction (Cui et al., 2019). These findings indicated that our URO-OVA mouse model reproduces the key clinicopathological features of HIC. Furthermore, we generated URO-OVA/OT-I mice by crossing URO-OVA with OT-I mice. The F1 generation acquired both urothelial OVA expression and endogenous OVA-specific $CD8^+$ T cells. The model spontaneously developed bladder inflammation over time during the normal aging process (Liu et al., 2007; Kim et al., 2011; Kogan et al., 2018). In that model, bladder inflammation began at four weeks, with a peak at eight weeks, and was sustained for up to 20 weeks. Like the URO-OVA mice, the URO-OVA/OT-I mice showed pelvic nociceptive

responses and voiding dysfunction after EAC development (Kogan et al., 2018), providing valuable insight into the mechanism(s) underlying the initiation and persistence of chronic cystitis and associated symptoms.

In addition to T cells, B cells are also implicated and may play a pivotal role in the pathophysiology of HIC, as described above. To evaluate the role of B cells in the EAC models, we generated antigen OVA-specific B cells, along with antigen OVA-specific T cells, by immunizing C57BL/6 mice with adjuvant-emulsified OVA protein. We observed that URO-OVA mice developed EAC after the adoptive transfer of splenocytes (a mixture of T and B cells) from the OVA-immunized C57BL/6 mice (Akiyama et al., 2021). The bladder showed marked chronic inflammatory changes, including mononuclear cell infiltration, increased stromal vascularity, and hyperemia and edema, which were maintained for up to 28 days. Notably, to the best of our knowledge, we were the first to demonstrate CD19-positive B-cell infiltration in the bladder tissue of the EAC model (Fig. 2). Thus, our EAC model is a unique animal model that closely mimics human HIC disease.

Taken together, these novel EAC murine models may help us to better explore the specific roles of the immune cells and receptors potentially involved in the pathophysiology of human HIC.

### Bladder Inflammation models

As mentioned above, bladder inflammation is observed in HIC, whereas BPS is associated with minimal inflammatory changes in the bladder. Thus, bladder inflammation models could also be used as animal models of HIC. These can be created by intravesical or systemic administration of exogenous stimuli (Bjorling et al., 2011), and have long been used in IC/BPS research. In parallel with the chronic histological inflammatory changes, these bladder inflammation models exhibit lower urinary tract dysfunctions such as increased urinary frequency and bladder pain (Bjorling et al., 2011). Hydrogen peroxide (HP) is a reactive oxygen species that causes lipid

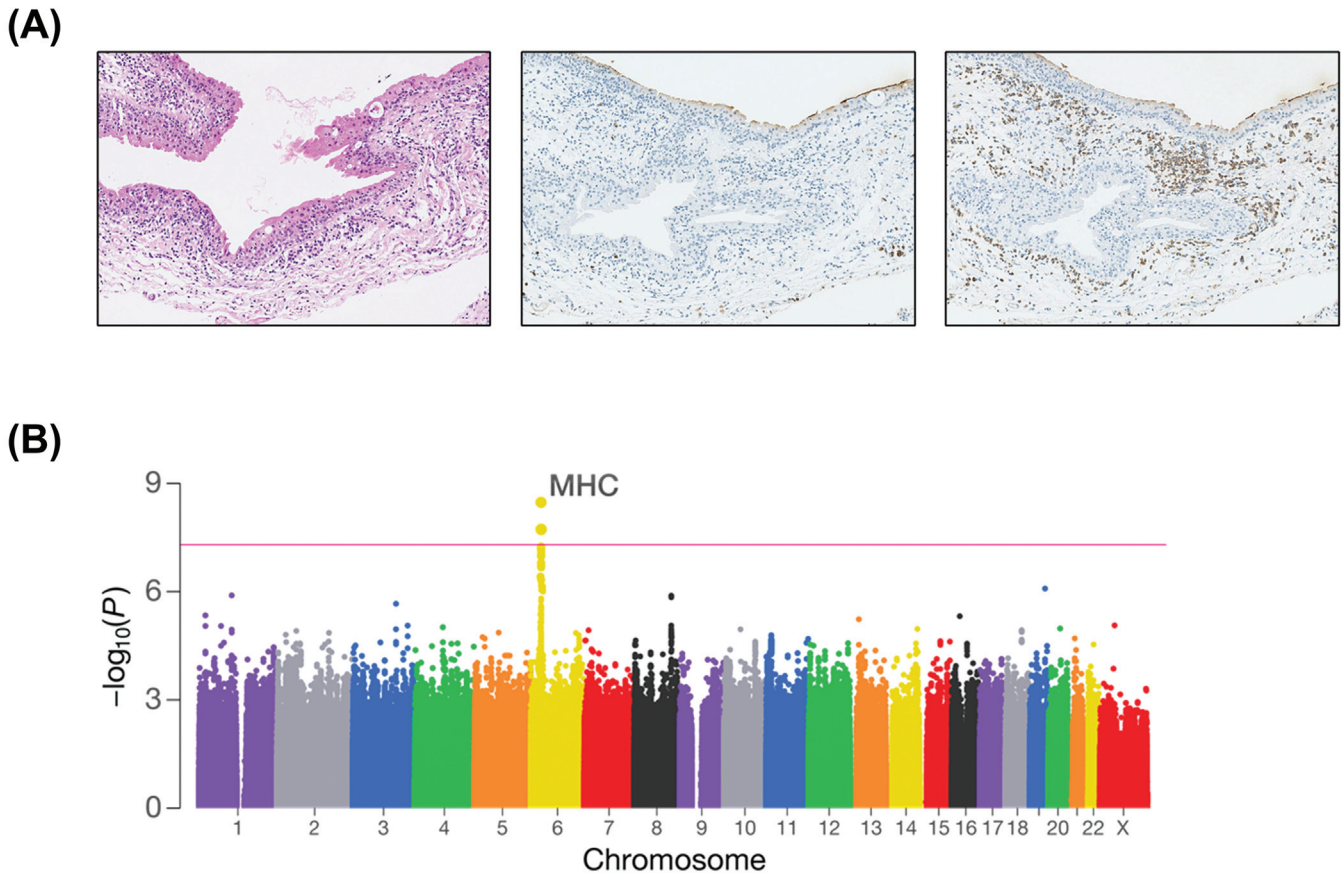


**Fig. 1. A.** *Left.* Hematoxylin and eosin staining. Note the dense plasma cell infiltration in the subepithelial layer. *Middle, right. In situ* hybridization to detect the kappa (*middle*) or lambda chain (*right*). Most plasma cells express the lambda chain. **B.** Genome-wide association study of HIC. The pink horizontal line indicates the genome-wide significance threshold of $p$=5.0×10$^{-8}$. MHC, major histocompatibility complex. cited from Akiyama et al. (2023) x 100.

peroxidation and oxidation of DNA and proteins. Studies in rat models demonstrated that a single intravesical administration of HP causes sub-chronic bladder inflammation along with voiding dysfunction lasting for two weeks (Homan et al., 2013; Dogishi et al., 2017). This model also shows increased levels of NGF, a well-known neurotransmitter involved in bladder hypersensitivity, in the bladder mucosa (Majima et al., 2017).

Deficient glycosaminoglycan (GAG) layers and urothelial alterations are also major hypotheses explaining the pathophysiology of HIC (Akiyama et al., 2020). Hyaluronidase, a subtype of endoglycosidase, hydrolyzes the GAG layers in the extracellular matrix (Meuwese et al., 2010; Lv et al., 2014). Degrading the GAG layers contributes to increased permeability of the urothelium, leading to long-term subepithelial inflammation (Lee et al., 2015). By contrast, protamine sulfate (PS) increases apical membrane permeability, leading to bladder inflammation and voiding dysfunction (Shioyama et al., 2008). High concentrations of PS cause strong inflammatory responses accompanied by severe bladder dysfunction. Meanwhile, low concentrations of PS selectively affect dysregulated bladders, such as hypersensitive bladder, but they do not affect bladder pathology and/or symptoms under normal conditions (Chuang et al., 2003). Low, but not high amounts of PS can penetrate the bladder urothelium, leading to epithelial denudation and subsequent subepithelial inflammation (Chuang et al., 2003), similar to the conditions in human HIC bladders. Lipopolysaccharide (LPS), a bacterial product, is also used to trigger bladder inflammation. Intravesical instillation of LPS induces bladder inflammation, along with bladder dysfunction and suprapubic pain, via Toll-like receptor 4-related signaling pathways (Kogan et al., 2018; Jerde et al., 2000). In the URO-MCP-1 transgenic mouse model, the bladder epithelium secrets MCP-1, leading to bladder inflammation, pelvic pain, and voiding dysfunction, as well as increased urothelial permeability (confirmed by magnetic resonance imaging) and elevated levels of IL-1β, IL-6, substance P, NGF, and claudin-2; in this model, much lower threshold levels of a single, intravesical, sub-noxious dose of LPS are required to evoke these changes when compared with that needed by wild-type C57BL/6 mice (Xu et al., 2016; Smith et al., 2020). These results are clinically relevant to human IC/BPS characterized by hypersensitivity to minor bladder irritants; indeed, subclinical infection can be attributed to symptom flares, suggesting the important role of environmental factors in exaggerating IC/BPS symptoms in addition to *in situ* inflammatory conditions. A rat model developed by adenoviral transduction of claudin-2, a pore-forming tight junction-associated protein, exhibits increased ionic permeability of the urothelium and develops bladder inflammation characterized by stromal edema and lymphocytic infiltration in conjunction with reduced bladder capacity and voiding dysfunction (Montalbetti et al., 2015, 2017). These models reproduce the clinicopathological features of HIC and provide further insight into the relationship between urothelial barrier dysfunction and subepithelial chronic inflammation in IC/BPS.

Other studies demonstrated that a transgenic mouse

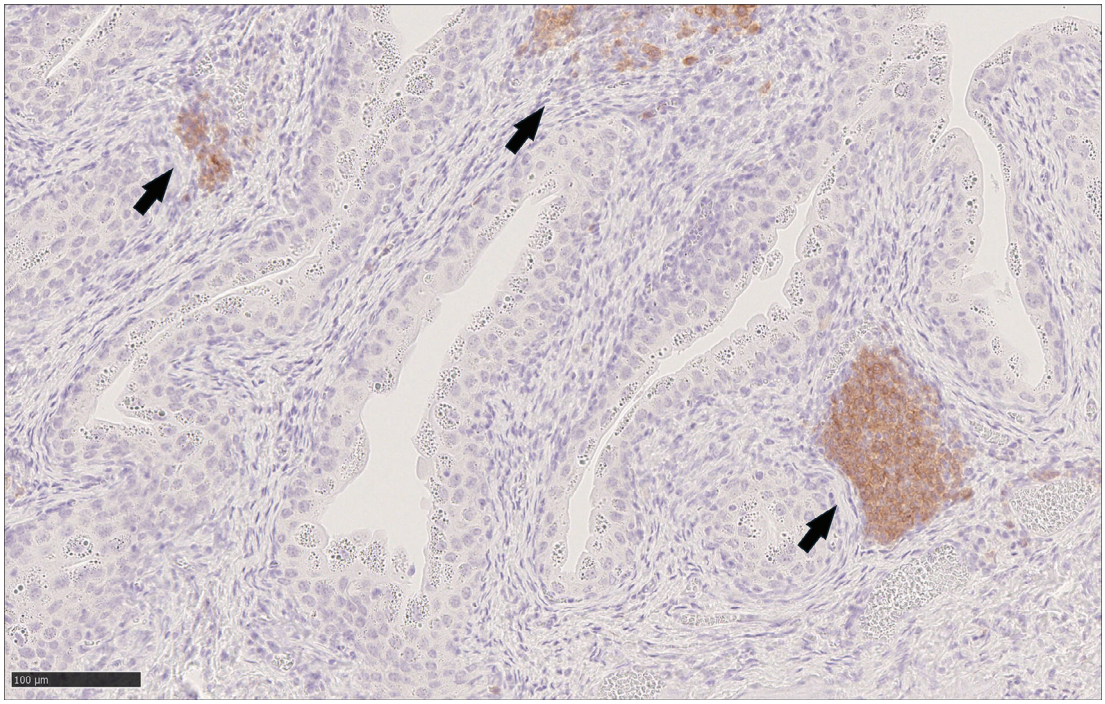


**Fig. 2.** Persistent histological bladder inflammation at 20 weeks post-induction of cystitis by adoptive transfer of splenocytes from OVA-immunized C57BL/6 mice to URO-OVA mice. Note the CD19-positive B-lymphocyte aggregates (arrows). Scale bar: 100 µm.

model overexpressing TNF-α in the urothelium exhibits urothelial denudation in conjunction with pelvic pain and voiding dysfunction, mimicking the characteristics of human HIC (Ogawa et al., 2010; Yang et al., 2018). A recently conducted randomized clinical trial of TNF-α for patients with IC/BPS demonstrated that an anti-TNF-α monoclonal antibody significantly improves pain and LUTS in patients with IC/BPS (Bosch, 2018). This evidence supports an important role for TNF-α in the pathophysiology of IC/BPS.

### Pelvic organ cross-sensitization models

The pelvic organ neural cross-talk model may be an optimal animal model for BPS. Previous studies identified neural cross-talk (bidirectional cross-sensitization) among pelvic organs (Yoshikawa et al., 2015; Kawamorita et al., 2016). For example, in a rat model, acute colonic inflammation induced by 2,4,6-trinitrobenzenesulfonic acid (TNBS, a colonic irritant) increases bladder pain behavior by activating the *in situ* C-fiber afferent pathways through colon-to-bladder neural cross-sensitization; indeed, a percentage of the afferent neurons originating from the colon and bladder are shared within the spinal cord (Pezzone et al., 2005; Qin et al., 2005; Christianson et al., 2007; Yoshikawa et al., 2015; Kawamorita et al., 2016). Neural cross-talk is also observed between the bladder and uterus, which

**Table 1.** Murine models of interstitial cystitis/bladder pain syndrome.

| Types of models | Induction method | Bladder inflammation (Ref.) | Pelvic/bladder pain | Voiding dysfunction | Urothelium denudation |
|---|---|---|---|---|---|
| Autoimmune cystitis models | Bladder tissue homogenization | Bullock et al., 1992; Luber-Narod et al., 1996; Jin et al., 2017; Liu et al., 2019 | Jin et al., 2017; Liu et al., 2019 | Bullock et al., 1992; Luber-Narod et al., 1996; Jin et al., 2017; Liu et al., 2019 | |
| | Uroplakin antigen | Altuntas et al., 2012 | | Altuntas et al., 2012 | |
| | Transient receptor potential melastatin 8 antigen | Zhang et al., 2017 | Zhang et al., 2017 | Zhang et al., 2017 | |
| | UPK3A-derived immunogenic peptide antigen | Izgi et al., 2013 | Izgi et al., 2013 | Izgi et al., 2013 | |
| | URO-OVA | Liu et al., 2007; Kim et al., 2011; Cui et al., 2019 | | Cui et al., 2019 | |
| | URO-OVA/OT-I | Liu et al., 2007; Kim et al., 2011; Kogan et al., 2018 | Kogan et al., 2018 | Kogan et al., 2018 | |
| | OVA-immunization | Akiyama et al., 2021 | Akiyama et al., 2021 | Akiyama et al., 2021 | |
| Bladder inflammation models | Lipopolysaccharide | Jerde et al., 2000; Xu et al., 2016; Kogan et al., 2018 | Jerde et al., 2000; Xu et al., 2016; Kogan et al., 2018 | Jerde et al., 2000; Xu et al., 2016; Kogan et al., 2018 | |
| | Protamine sulfate | Chuang et al., 2003; Shioyama et al., 2008 | Chuang et al., 2003; Shioyama et al., 2008 | Chuang et al., 2003; Shioyama et al., 2008 | Chuang et al., 2003; Shioyama et al., 2008 |
| | TNF-α overexpression | Yang et al., 2018 | Yang et al., 2018 | Yang et al., 2018 | Yang et al., 2018 |
| | Hydrogen peroxide | Homan et al., 2013; Dogishi et al., 2017; Majima et al., 2017 | Homan et al., 2013; Dogishi et al., 2017; Majima et al., 2017 | Homan et al., 2013; Dogishi et al., 2017; Majima et al., 2017 | Homan et al., 2013; Dogishi et al., 2017; Majima et al., 2017 |
| | Hyaluronidase | Meuwese et al., 2010; Lv et al., 2014 | Meuwese et al., 2010; Lv et al., 2014 | Meuwese et al., 2010; Lv et al., 2014 | Meuwese et al., 2010; Lv et al., 2014 |
| | Adenoviral transduction claudin-2 | Montalbetti et al., 2015, 2017 | Montalbetti et al., 2015, 2017 | Montalbetti et al., 2015, 2017 | |
| Pelvic organ cross-sensitization model | Uterine tissue fragment implantation | | Morrison et al., 2006; Nunez-Badinez et al., 2021; Hayashi et al., 2023 | Morrison et al., 2006; Nunez-Badinez et al., 2021; Hayashi et al., 2023 | |
| | Colon irritation by 2.4.6-TNBS | | Yoshikawa et al., 2015; Kawamorita et al., 2016 | Yoshikawa et al., 2015; Kawamorita et al., 2016 | |
| Psychological stress model | Water avoidance stress | Smith et al., 2011; Hurst et al., 2015; Ackerman et al., 2016; Chen et al., 2016; Matos et al., 2017; Wang et al., 2017; Gao et al., 2018 | Hurst et al., 2015; Ackerman et al., 2016; Chen et al., 2016; Matos et al., 2017; Wang et al., 2017; Gao et al., 2018; Dias et al., 2019; Saito et al., 2024 | Smith et al., 2011; Hurst et al., 2015; Ackerman et al., 2016; Chen et al., 2016; Matos et al., 2017; Wang et al., 2017; Gao et al., 2018; Dias et al., 2019; Saito et al., 2024 | Cetinel et al., 2005; Saito et al., 2024 |

may explain the high incidence (reportedly as high as 65-69%) of comorbid endometriosis in patients with IC/BPS (Paulson and Delgado, 2005; Wu et al., 2018). Indeed, studies show that implantation of uterine tissue fragments to the peritoneum or abdominal wall of rodents induces pelvic pain and bladder hypersensitivity symptoms (Morrison et al., 2006; Nunez-Badinez et al., 2021). Another study also reported that implantation of uterine tissue into the mesocolon and pelvic peritoneum evokes bladder overactivity via upregulation and activation of transient receptor potential ankyrin 1 (TRPA1) channels, suggesting that upregulation of the TRPA1 pathway induced by endometriosis enhances neural activity in the bladder via neural cross-talk between the bladder and uterus, which may explain the mechanism of the pelvic floor-centric etiology of IC/BPS (Hayashi et al., 2023).

### Psychological and physical stress models

Psychological and physical stress can evoke systemic hyperalgesia without obvious bladder inflammation, making it another potential model for BPS (Smith et al., 2011; Gao et al., 2018). Psychological stress exacerbates the symptoms of functional somatic syndromes such as fibromyalgia and irritable bowel syndrome (IBS) (Hunter et al., 2015; Leue et al., 2017; Powell et al., 2017). Likewise, it is clinicopathologically known that psychological stress exacerbates bladder symptoms in patients with IC/BPS (Kanter et al., 2016; Birder and Andersson, 2018; McKernan et al., 2019) via increased neural activity in brain regions involved in pain perception (Birder and Andersson, 2018), autonomic dysregulation of mitochondrial function in the urothelium (Kullmann et al., 2019), sensitization of C-fibers and mechanoreceptors (Gao et al., 2018), and alpha-1A adrenoceptor stimulation (Matos et al., 2017).

Among the stress-induced lower urinary tract dysfunction models, the water avoidance stress (WAS) paradigm is widely used to investigate the detailed mechanism underlying the relationship between psychological stress and bladder hypersensitivity (Hurst et al., 2015; Ackerman et al., 2016; Chen et al., 2016; Matos et al., 2017; Wang et al., 2017; Gao et al., 2018; Dias et al., 2019; Kullmann et al., 2019; Saito et al., 2021, 2024; de Rijk et al., 2022). The mechanism is not fully understood, however, psychological stress has been suggested to contribute to aberrant neurophysiological functions, such as altered sympathetic autonomic nerve activity and increased NGF and TRPV1 levels in the urothelium (Birder and Andersson, 2018), as well as upregulation of mast cell-nerve interactions (Smith et al., 2011). Alternatively, stress may increase the distance between adjacent urothelial cells (Cetinel et al., 2005). Furthermore, our recent study showed that WAS-induced bladder hypersensitivity and urothelial damage are enhanced by the intravesical application of low-dose PS, which does not affect bladder function under normal conditions, in a rat model, suggesting the etiological interaction between stress and bladder-centric manifestations in BPS (Saito et. al., 2024). The WAS model also presented with irritable gastrointestinal symptoms; thus, it could also serve as an animal model for IBS (Qin et al., 2014; Lee et al., 2015, 2017). Based on the potential association of BPS with somatoform disorders (as mentioned above), the WAS model may be a potential animal model for BPS, and provide a platform for examining the relationship between psychological stress and bladder dysfunction.

### Summary and Future Perspectives

In this review article, we summarized the current murine models for IC/BPS. While a wide variety of animal models have been developed, it is important to use those that are optimal for research in each subtype of IC/BPS. HIC and BPS have different bladder pathologies and thus need separate animal models. At present, an EAC model that manifests both subepithelial B cell-dominant inflammatory cell infiltration and epithelial denudation is the closest to human HIC, and the psychological stress-induced bladder hypersensitivity model and the neural cross-talk model between uterus and bladder seems to be optimal for human BPS. However, no EAC models have been shown to reproduce epithelial denudation, which is another important pathological feature of HIC. Likewise, no psychological stress models or neural cross-talk models have been shown to reproduce mucosal hyperemia after bladder overdistension (glomerulations), which has been considered a clinicopathological feature of BPS. If there are murine models that could thoroughly represent clinicopathological correlates of HIC and BPS, they would greatly contribute to the progress in the research of IC/BPS pathogenesis. Based on recently emerging omics analyses, such as genomics, proteomics, and lipidomics of human samples, animal models are essential to investigate the pathophysiology of IC/BPS and will pave the way for the development of novel treatments for this intractable disorder.

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