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A central role for toll-like 4 (TLR4) receptors in interstitial cystitis?

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Interstitial cystitis/bladder pain syndrome (IC/BPS) remains a clinical enigma. Estimated to affect over 8 million women globally (3, 19), it is a challenge to diagnose and to treat effectively, due to an unknown etiology and complex, poorly understood pathophysiology. Clinical diagnosis is symptom-based, with patients experiencing debilitating chronic pelvic or bladder pain, pressure or discomfort, along with urinary storage symptoms including frequency and urgency(10). IC/BPS is also associated with depression and anxiety(8).

Current treatments for IC/BPS are varied, and include diet and lifestyle changes, intravesical instillations directly into the bladder, oral medications, and as a last resort surgery. Generally, success rates for therapeutic interventions are modest at best and there is little consensus with respect to which is the most effective. Intravesical dimethyl sulfoxide therapy has been widely used for decades, alone or as part of a cocktail in combination with other agents such as local anesthetics(15). However, long-term outcomes are poorly documented. In a recent study intravesical DMSO/heparin/hydrocortisone therapy was only moderately effective for treatment of IC/BPS, with only half (56%) of patients well or significantly improved at 5 years(13). A better understanding of the pathophysiology of this condition could potentially lead to the identification of novel pharmacological targets and the development of more successful treatments. As such there has been extensive research focused on unravelling the underlying mechanisms of IC/BPS. Locally within the bladder wall, known key pathological changes include urothelium disruption, impaired barrier function and inflammation. These, in addition to sensitized peripheral and central neural pathways, all contribute to pain and urinary symptoms(15). There is also convincing epidemiological evidence supporting the link between IC/BPS and a history of urinary tract infection(16) and activation of the innate immune system.

Toll-like receptors (TLR) are a family of membrane glycoproteins expressed primarily on cells of the immune system that act as pattern recognition molecules. They can bind pathogen-derived molecules and mediate signaling cascades leading to an inflammatory response(12). Our understanding of TLRs has expanded greatly from their role in immune cells into their role in non-immune cells and tissues, and they have become an area of recent interest in inflammatory disorders of the lower urinary tract. Whilst there has been some focus on TLR7 in IC/BPS, where TLR7 expression was found to be upregulated in bladder biopsies from Hunner-type (ulcerative) IC patients, and a TLR7 agonist increased expression of TLR7 mRNA and induced cystitis in mice(11), the field is not well researched. TLR4 is expressed on urothelial cells(21) and it's role in mediating inflammation following infection of the bladder has been well established for some time(2). Schrepf and colleagues have shown that TLR4 inflammatory responses in PBMCs are a marker of widespread pain in IC/BPS(22). However, until now the role of TLR4 in IC/BPS was not well understood.

In a recent issue of the American Journal of Physiology-Renal Physiology, de Oliveira et al. (2018) elegantly demonstrate for the first time, and at both a molecular and functional level, that TLR4 plays a central role in initiating cyclophosphamide-induced bladder dysfunction and inflammation(9). In this study, convincing evidence is provided that genetic deletion, using $TLR4^{-/-}$ mice, or pharmacological inhibition of TLR4 with the selective antagonist resatorvid, prevents dysfunction in micturition and inflammatory events associated with cystitis. This data directly demonstrates for the first time important etiological information regarding CYP-induced–cystitis, in the increased expression of TLR4 downstream signaling MyD88 and TRIF, which supports an important role for this receptor.

A key finding, that is possibly somewhat underplayed in the manuscript, is the identification of a role for TLR4 in normal bladder function, shown in the untreated $TLR4^{-/-}$ mice, which displayed different voiding profiles with increased frequency of non-voiding contractions. This suggests that TLR4 signaling impacts the afferent arm of micturition, and it will be interesting in future studies to determine whether this is via a direct effect on afferent nerves *per se* or an indirect effect via the release of mediators from the urothelium, which is a source of inflammatory peptides and cytokines(14). Since other endogenous ligands can activate TLR4, including ECM components, heat shock proteins and β-defensins(18), other physiological roles for TLR4 in normal bladder control may yet be uncovered.

A confounding factor in our progress in understanding the pathophysiology of IC/BPS has been the limitations of the different animal models employed, recently brought to the forefront in an excellent review by Birder and Andersson(4). IC/BPS is complex and there are, as yet, no animal models available that mimic all aspects of the human experience. In the study by de Oliveira *et al.* the well-established cyclophosphamide (CYP)-induced mouse model of acute cystitis was used, in which urotoxicity results in pain-related behavior, altered micturition patterns and bladder overactivity, as well as inflammation(5, 6), all traditional features of ICS/BPS. Whilst it is important to acknowledge the limitations of such animal models, they remain important for the elucidation of important pathological and mechanistic information, contributing to the big picture of IC/BPS. Interestingly, it is becoming more widely acknowledged that IC and BPS are two separate disorders, cystitis as an inflammatory disease and BPS as a pain syndrome, and, as such, information gleaned from the different animal models may aid this differentiation, to the benefit of future diagnosis and treatments.

Overall, the article by de Oliveira *et al.* makes a significant contribution to our knowledge of IC/BPS and potential treatment of the condition. Whilst several immunosuppressive agents are under investigation as potential treatments for IC/BPS, and some have been trialed(1), this research opens up an alternative avenue in a field where is a limited arsenal. Blockade of TLRs is still in the experimental phase, but has great potential, especially given that the selective TLR4 antagonist used in the de Oliveira *et al.* study, TAK-242 (resatorvid), has already been as far as phase III clinical trials for the treatment of severe sepsis(17). This study provides solid rationale for the use of TLR4 antagonists for IC, and if the positive findings in the mouse model can be translated into the clinical setting this may be an attractive treatment in an IC cohort. However, many other agents have failed clinically due to systemic adverse effects, thus intravesical treatment using an innovative delivery system such as liposome-based administration may be an attractive avenue to investigate in the basic setting and clinically. Conversely, systemic factors may play a role in the pathology of some patients or some types of IC/BPS, particularly BPS, which is now being considered more of a pain syndrome linked to other co-morbidities such as irritable bowel syndrome(7). The question that now addressing is whether TLR4 is involved in central pain pathways of BPS and whether blockade of TLR4 will be effective in patients with these phenotypes. TLR4 have been shown to activate TRPV1 receptors(20), and given the sensory/urgency aspects of IC/BPS, new agents that target the afferent limb of micturition would be welcome.

Thus IC/BPS is a debilitating condition, yet we have only a limited understanding of the pathophysiology involved. This has resulted in the current treatments lacking efficacy in many patients and the need for new treatments acting via novel mechanisms. The demonstration

of a role for TLR4 in IC/BPS opens up possible new avenues for drug development for this condition.

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