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Review Article

Cellular and Molecular Aspect of Bladder Pain Syndrome: An Entry Point to Exploration of Its Pathogenesis

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Abstract

Background: Bladder pain syndrome/interstitial cystitis (BPS/IC) can cause pelvic pain, frequent urination, and a strong urge to urinate. These symptoms can significantly reduce quality of life, causing psychological distress, sexual dysfunction, poor sleep quality, decreased work productivity, and increased morbidity. Despite the prevalence of this condition, determining the most effective treatment guidelines for BPS/IC remains a challenge due to the complexity of its pathogenesis. *Objective:* Understanding cellular and molecular aspects is essential to explore different cell types in changes in function and sensitivity of the urothelial layer and chronic inflammation. *Main Ideas:* Cellular aspects in the pathogenesis of BPS/IC include Umbrella Cells, Basal and Intermediate Cells, Paraneuron Cells, Myofibroblasts and Telocytes, Detrusor Smooth Muscle Cells, Nerve Cells, Astrocytes, Microglia, CD68+ Macrophages, CD74+ Lymphocytes, Eosinophils, and Mast Cells. Disruption of these cells leads to altered urothelial barrier function, sensitivity, and chronic inflammation. Molecular aspects include chronic inflammation with increases in p38-mitogen activated protein kinase (p38 MAPK), Interleukin-1β (IL-1β), Interleukin-6 (IL-6), Tumor Necrosis Factor-α (TNF-α), Nerve Growth Factor (NGF), Brain-Derived Neurothropic Peptide (BDNF), and other molecules. *Conclusion:* Changes in the urothelial barrier and bladder wall sensitivity are also significant. Complex interactions between the immune and nervous systems contribute to chronic inflammation through positive feedback. Therefore, this article aims to understand the cellular and molecular aspects that play a role in the pathogenesis of BPS/IC and help provide appropriate treatment.

Keywords

Bladder Pain Syndrome, Interstitial Cystitis, Inflammation

1. Introduction

Interstitial cystitis (IC), also known as bladder pain syndrome (BPS), is a chronic condition characterized by persistent bladder pain, increased urinary frequency, urgency, and pelvic pain. The diagnosis can be made through cystoscopic evaluation by identifying the presence of Hunner ulcers [1]. Other symptoms, such as urinary symptoms (LUTS) that cannot be recognized as a result of infection, may also occur for six weeks or more in BPS/IC patients [2]. BPS/IC is a condition that affects a higher proportion of women, especially those between the ages of 50 and 69, with an estimated prevalence of around 400,000 patients in the UK [3].

Researchers have also linked the condition to several dis-

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eases, including fibromyalgia, rheumatoid arthritis, systemic lupus erythematosus, vulvar vestibulitis, vulvodynia, Sjogren's syndrome and asthma [1, 4, 5]. Chronic urgency and frequency in patients diagnosed with BPS/IC who experience LUTS can also be triggered by certain foods or stressful conditions [1, 6]. These symptoms can significantly reduce their quality of life, causing psychological stress, sexual dysfunction, poor sleep quality, decreased work productivity, and increased morbidity [7]. The complexity of the pathogenesis of this condition is one of the challenges in determining the most effective treatment guidelines for this disease [4].

Interstitial cystitis is a multifaceted condition believed to arise from various factors, such as pelvic wall dysfunction, bacterial cystitis, autoimmune responses, neurogenic inflammation, bladder trauma, and distension [8]. Recent studies indicate that the primary causes of BPS/IC involve compromised urothelial barrier function, urothelial hypersensitivity, heightened bladder wall sensitivity, and central sensitization [4, 9, 10]. Chronic inflammation plays a crucial role in BPS/IC development, marked by elevated levels of pro-inflammatory cytokines like IL-1β, IL-2, IL-6, and TNF-α [10, 11].

Senescent cells secrete many of these cytokines, known as SASPs [12]. In BPS/IC, glomerulisation observed after hydrodistention is also an important clinical sign. This condition is associated with higher concentrations of proangiogenic agents such as Hypoxic-inducible Factor 1α (HIF-1α), Epidermal Growth Factor (EGF), and Vascular Endothelial Growth Factor (VEGF) [13]. The SASP releases these various proangiogenic factors, including EGF, VEGF, Heparin-binding Epidermal Growth Factor (HB-EGF), and Fibroblast Growth Factor 7 (FGF7), which are important for tumor growth [14, 15]. In addition, the clinical symptom of BPS/IC is Hunner's ulcer, which is characterized by increased Apurinic/apyrimidinic endonuclease 1 (APE1) activity and decreased levels of Zonula Occluden-1 (ZO-1), E-cadherin, and Uroplakin (UP) [16, 17].

Understanding the multifaceted nature of interstitial cys-titis is essential for developing effective treatment strategies and improving the quality of life for affected individuals.

2. Cellular Aspect of BPS/IC

Every component of the bladder, including the neural pathways, may play a role in the onset of BPS/IC. The bladder is composed of four layers: the outermost adventitia layer, the detrusor muscle layer, the suburothelial or lamina propria layer, and the urothelial layer [18]. Specifically, the urothelial layer comprises transitional epithelium and includes three types of cells: the surface or umbrella cells, intermediate cells, and basal cells [19]. The lamina propria layer contains several interstitial cells, such as telocytes, interstitial cells of Cajal, myofibroblasts, and fibroblasts. This layer also includes many collagen fibres in its extracellular matrix [18, 20, 21]. The detrusor layer comprises groups of smooth muscle cells and other cells such as interstitial cells of Cajal, fibroblasts, and telocytes in the bladder [18, 21]. Adipocytes and their extracellular matrix component make up the adventitia layer [18]. The bladder's neuronal pathway consists of neuroglia cells and three types of neurons. Sensory neurons in the dorsal root ganglia near the spinal cord (L1-L2 and L6-S1) connect the spinal cord and bladder tissue through specific cells. Two types of neurons are involved in this connection: preganglionic neurons with cell bodies in the intermediolateral nucleus and postganglionic neurons with cell bodies in the mixed pelvic ganglia [22]. Glial cells wrap around the axons of neurons in the bladder tissue, creating a free-ending shape [22, 23]. These glial cells do not come in contact with each other. The central neuroglial cells in the spinal cord are astrocytes and microglial cells, which play a significant role in normal and pathological conditions [24-26]. Possible alterations in the arrangement or dysfunction of these cells could contribute to the development of BPS/IC and the invasion of inflammatory cells into the bladder, as described in Table 1.

Table 1. *Cellular Aspect in Pathogenesis of BPS/IC.*

Type of cell	Location	Role in BPS/IC	References
Umbrella cells	Bladder urothelial surface	The urothelial barrier, which is composed of the E-cadherin protein, tight junction [*Zonula occludin*], apical surface protein [*Uropakin*], and trafficking mechanism, can be affected by disruptions in cell structure. Apoptosis of cells can also alter the barrier function.	[27-29]
Basal and intermediate cells	Bladder urothelial	Disruption of umbrella cells can fail cytodifferentiation	[28, 30]
Paraneuron cells	Bladder neck and proximal urehtrae urothelial	Increased sensitivity to potentially harmful stimuli in the urethral lumen can lead to reflexive voiding and bladder pain	[31, 32]
Myofibroblasts and telocytes	More prevalent in lamina propria layer of bladder, but also found in detrusor	Enhanced sensitivity in the afferent pathway of *Overactive Bladder/Detrusor Overactivity* and *Interstitial Cystitis* is characterized by increased Piezo1-channel and HCN1 chan-	[33-35]

Type of cell	Location	Role in BPS/IC	References
	layer	nel expression	
Detrusor smooth muscle cells	Detrusor layer	Injecting Botulinum Toxin A and using leukotriene-1 receptor antagonists can inhibit muscle contractions, potentially resolving symptoms in BPS/IC treatment	[36-38]
Neuron cells	Urothelial and muscular layer of bladder	BPS exhibits heightened density and activity of these peripheral sympathetic fibres	[39-41]
Astrocytes and microglias	Spinal dorsal horn	The activation of these cells causes allodynia and bladder hyperactivity in cyclophosphamide-induced cystitis and colitis in rat models through the action of IL-1β and BDNF	[42, 43]
Macrophage CD68+	Bladder wall and adventitia layer	In the rat model of cyclophosphamide-induced cystitis, there is an increase in the expression of these cells	[44, 45]
Lymphocyte CD74+	Bladder wall and adventitia layer	On days 7 and 14, these cells have enhanced expression in both cyclophosphamide- and H2O2-induced cystitis rat models	[44, 46]
Eosinophils	Lamina propria, bladder wall, and adventitia layer	A few of these cells were seen in a rat model of cystitis induced by H2O2 on days 7 and 14, as well as in a clinical biopsy specimen	[44, 46]
Mast Cells	Prominent in detrusor layer but also found in lamina propria layer	The infiltration of bladder tissue was observed in a rat model of cystitis induced by H2O2 on days 1 and 14, and also in a clinical biopsy specimen	[44, 47]

BDNF: Brain-Derived Neurothropic Peptide; HCN-1: Hyperpolarization-activated cyclic nucleotide gated

Table 1 displays a cellular component that may have links with molecular substances that have contributed to the pathogenesis of BPS/IC, as presented in Table 2.

3. Molecullar Aspect of BPS/IC

As previously mentioned, four primary pathological conditions emerge in BPS/IC: alteration of the urothelial barrier, urothelial hypersensitivity, hypersensitivity of the bladder wall, and central sensitization. There is mounting evidence that chronic inflammation may be linked to these pathological conditions. Patients with BPS/IC have demonstrated increased activation of p38-mitogen-activated protein kinase (p38-MAPK) and TNF-α, as well as elevated levels of pro-apoptotic proteins such as Bax, Bad, phosphorylated p53, and Caspase-3 in the mucous membrane of the bladder [48]. Phosphorylated p53 can lead to an increased expression of Antiproliferative Factor (APF) in urine. This protein is excreted in urinary specimens of patients with BPS/IC and is known to inhibit the growth of human urothelial cells [49]. Patients diagnosed with BPS/IC displayed elevated levels of IgE in their serum, as well as increased levels of Leukotriene E4, Eosinophil Protein X, and tryptase in their urine. These proteins, typically elevated in allergic conditions, suggest a well-established chronic inflammatory state is present [46, 48, 50]. In bladder tissue from interstitial cystitis model rats and clinical biopsy samples from BPS/IC patients, there is a notable decrease in barrier proteins found in the umbrella cells, specifically E-cadherin, uroplakin (UP), Chondroitin Sulphate (CS), and zonula occluded-1 (ZO-1) [28, 48].

Some studies suggest that chronic inflammation in the suburothelial layer might lead to alterations in the urothelial barrier. Clinical samples and in vitro studies have shown increased levels of noradrenaline, ATP, NGF, alpha-1, and TRPV-1 expression in the suburothelial layer, along with mast cell infiltration [4, 41, 51]. These findings suggest a possible association between suburothelial chronic inflammation and urothelial hypersensitivity. Bladder tissue from interstitial cystitis rat models has shown increased NGF, BDNF, and TrK expression [39, 40, 52]. In rat models of interstitial cystitis induced by cyclophosphamide and peroxide, the bladder wall contains inflammatory cells such as macrophages, eosinophils, mast cells, and lymphocytes, indicating a potential link between bladder wall inflammation and detrusor hypersensitivity [44, 45, 47]. Additionally, these models exhibit increased spinal Fos, NGF, and BDNF expression, and activated astrocytes and microglia release cytokine IL-1β and chemokine CCL3 [41-43, 53]. This suggests that neural inflammation may contribute to central sensitization in the development of BPS/IC.

Table 2. Molecular Substances That Contributed in the Pathogenesis of BPS/IC.

Pathologic Process	Molecular Substances	Reference
Chronic inflammation	Increased of: p38 MAPK, IL-6, IL-1β, IL-2, HIF-1α, CRP, TNF-α, VEGF, CXCL10, EGF, IgE, eosinofil protein x, leukotrien E4, and triptase Decreased of: GP51	[10, 11, 13, 46, 48, 50, 54, 55]
Urothelial barrier alteration	Increased of: pro apoptotic protein and APF [phosphor-p53, Caspase 3, Bax, Bad] Decreased of: E-Cadherin, CS, UP, ZO-1, Ki-67, IL-8, and HB-EGF	[16, 17, 27, 28, 48, 56]
Urothelial hypersensivitiy	Increased of: ATP, stretch-activated ATP, alpha-1, TRPV-1, NA, and NGF	[4, 41, 48, 51]
Bladder wall hypersensitivity	Increased of: NGF, BDNF, TrK	[39, 40, 52]
Central Sensitization	Increased of: NGF, BDNF, and spinal Fos	[41, 42, 43, 53]

p38MAPK: p38-mitogen activated protein kinase; CCXL1: Chemokine ligand 1; EGF: Epidermal Growth Factor; VEGF: Vascular endothelial growth factor; HIF-1α: Hypoxia-inducible factor 1α; TrK: Tyrosine Kinase; CRP: C-reactive protein; GP51: Glicoprotein 51; APF: Antiproliferative factor; ZO-1: Zonula Occludin1; UP: Uroplakin CS: Chondroitin Sulphate; HB-EGF: Heparin-Binding Epidermal Growth Factor; TRPV1: transient receptor potential cation channel subfamily V member 1; NA: Noradrenalin; ATP: Adenosine Triphosphate; NGF: Nerve Growth Factor; BDNF: Brain-Derived Neurothropic Peptide.

The complex interaction of the immune and neural systems within the body influences the development of BPS/IC. Experts believe that BPS/IC has an autoimmune component due to its high prevalence in individuals with other autoimmune conditions such as Rheumatoid Arthritis, Sjogren's Syndrome, and SLE. While the exact mechanism is not yet fully understood, compelling evidence suggests that BPS/IC involves both immune and neural components. Researchers believe the immune and nervous systems play a role in BPS/IC. The immune system increases the levels of various cells and chemicals, including B and T lymphocytes, mast cells, IL-4, IL-6, IL-7A, IL-33, and MDC. Meanwhile, the nervous system produces higher levels of NGF and TRPV1. Research indicates that NGF is linked to the activation of pro-inflammatory cytokines and mast cells, suggesting that NGF might sustain chronic inflammation in BPS/IC through a self-perpetuating feedback loop mechanism [5].

4. Conclusion

This entity is widely acknowledged for its persistent changes and core characteristic of inflammation. Despite this, the inflammation is considered to have significant potential for pathogenesis. Understanding these key aspects is crucial for advancing our knowledge and treatment strategies.

Abbreviations

BPS	Bladder Pain Syndrome
IC	Interstitial Cystitis
BDNF	Brain-Derived Neurothropic Peptide
HCN-1	Hyperpolarization-Activated Cyclic Nucleotide Gated
p38MAPK	p38-Mitogen Activated Protein Kinase
CCXL1	Chemokine Ligand 1
VEGF	Vascular Endothelial Growth Factor
EGF	Epidermal Growth Factor
HIF-1α	Hypoxia-Inducible Factor 1α
CRP	C-reactive Protein
GP51	Glicoprotein 51
APF	Antiproliferative Factor
ZO-1	Zonula Occludin1
UP	Uroplakin
CS	Chondroitin Sulphate
HB-EGF	Heparin-Binding Epidermal Growth Factor
NA	Noradrenalin
NGF	Nerve Growth Factor
ATP	Adenosine Triphosphate
TRPV1	Transient Receptor Potential Cation Channel Subfamily V Member 1
BDNF	Brain-Derived Neurothropic Peptide
TrK	Tyrosine Kinase
p38 MAPK	p38-Mitogen Activated Protein Kinase
IL-1β	Interleukin-1β
IL-6	Interleukin-6
TNF-α	Tumor Necrosis Factor-α

Author Contributions

Kuni Zakiyyah Sumargo: Conceptualization, Writing – original draft, Funding acquisition

Abdi Dzul Ikram Hasanuddin: Resources, Writing – review & editing, Validation

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Conflicts of Interest

The authors declare no conflicts of interest.

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Biography

Kuni Zakiyyah Sumargo is a undergraduate student at the Faculty of Medicine, Universitas Negeri Gorontalo. She is actively involved in an organization focused on research, the Association of Scientific Medical Research. She is currently in her final semester of the preclinical stage and will next undertake clinical education to earn his medical degree.

Abdi Dzul Ikram Hasanuddin is currently a lecturer in Histology for the Medical Education Study Program at the State University of Gorontalo. He earned his Bachelor's degree in Medicine from the Faculty of Medicine at Brawijaya University, Malang (2009-2013), his Medical Doctor degree from the Faculty of Medicine at Brawijaya University, Malang (2013-2015), and his Master's degree in Biomedical Science with a concentration in Histology and Cell Biology from the Graduate Program at Hasanuddin University (2019-2021). His professional experience includes working as a contract doctor at Bulango Ulu Community Health Center, Multazam General Hospital, and Tombulilato Regional Hospital from 2017 to 2019. Additionally, he served as a contract lecturer in Biomedical Science at STIKES Bakti Nusantara (2016-2019).

Research Field

Kuni Zakiyyah Sumargo: Histology, Biology, Animal Laboratory, Biotechnology, Medical Education.

Abdi Dzul Ikram Hasanuddin: Histology and Cell Biology, Translational Medicine, Animal Laboratory, Urology, Medical Education.