

Interstitial Cystitis: *Preventing Flares and Producing Clinical Remissions for IC Patients through Translational Research*

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Interstitial cystitis is a chronic painful bladder disorder that affects approximately 1 million Americans whose curable treatment depends on establishing the etiology of this disease. While diverse in symptomatic presentations, the most consistent histological finding of the bladder is the loss or thinning of the bladder uro-epithelial layers. These findings suggest that the clinical and pathological presentation of interstitial cystitis may be caused by an inhibition of bladder uroepithelial cell regeneration, proliferation and/or apoptosis with resulting loss of the normal urothelial barrier and functions that leads to the development of pain from underlying sensory nerve dysfunction. Whether or not urothelial cells undergo proliferative repair, survival, or apoptosis following a bladder insult in IC patients appears to involve a balance between anti-apoptotic and apoptotic mechanisms regulated by the transcription factor NF- κ B signaling activation.

We have identified transcription factor NF- κ B activation in bladder biopsy material from IC patients and have further characterized an aberrant loss of sustained NF- κ B signaling activation over time in cell cultures of IC urothelium in comparison to normal urothelial controls upon exposure to TNF- α . Using an *in situ* apoptotic assay, exposure to TNF- α produces a dysfunctional activation pattern in IC urothelial cells that leads to cellular apoptosis when compared to normal controls. Furthermore, incubation of normal urothelial cells with conditioned media from IC cell cultures changes its NF- κ B activation signaling into a phenotype observed for IC cell cultures when challenged with TNF- α ; suggesting that something may be produced by this dysfunctional signaling such as APF, a newly characterized biomarker of IC.

Aberrant NF- κ B signaling activation may be responsible for the imbalance of apoptotic and survival mechanism of the bladder epithelium that gives rise to the pathogenesis of IC. Not only is the aberrant signaling of NF- κ B a potential biomarker, but development of therapies to produce sustained functional NF- κ B activation in the IC bladder urothelium may produce uroepithelial survival and subsequent remission of this disease. To this end, we are doing two things clinically in response to our basic science findings. First, we are asking all IC patients to avoid aspirin or aspirin-like products such as NSAIDs that block normal NF- κ B signaling as many cases of IC may be iatrogenic causes of using this class of medication. Second, we are providing patients with off-labeled use of misoprostol given as oral and/or instillation therapy as a mean to provide rapid uroepithelium healing. While the bladder lining may take weeks to months to heal, the regeneration of the urothelial lining must take place first to produce a remission of pain and chronic voiding symptoms which are the hallmark signs of IC.