Inhibition of NLRP3 inflammasome to treat bladder inflammation

Duke LICENSING & VENTURES

Unmet Need

Benign prostatic hyperplasia, also known as prostate gland enlargement, commonly results in bladder outlet obstruction, BOO, and affects tens of millions of older men globally. Over 14 million men in the United States have benign prostatic hyperplasia and it is seen histologically in 90% of men over the age of 85. Enlarged glands squeeze the urethra and thickens the bladder wall. Over time the bladder weakens and can no longer empty fully, leading to common symptoms of benign prostatic hyperplasia, such as, incomplete emptying, increased frequency to urinate and weak stream flow. Age is the primary cause, however, other diseases like diabetic bladder dysfunction, can also contribute to pathogenesis. Pharmacotherapy, such as alpha-blockers and 5-alpha reductase inhibitors, treat moderate symptoms but do not completely eliminate high intravesical pressure. The elevated pressure produces a chronic inflammatory state in the bladder that is triggered through a multimeric structure known as the NLRP3 inflammasome. This leads to fibrosis and decompensation, for which there is currently no treatment. There is an unmet need to treat the underlying inflammation to prevent or delay the progression of bladder dysfunction in BOO.

A similar inflammatory component is seen in diabetic patients where urinary dysfunction is the most common of all disease complications. Diabetic metabolites activate the NLRP3 inflammasome in the bladder which provokes an inflammatory response leading to urinary problems and bladder damage. Considering the epidemic of diabetes in the USA and globally, the absence of any specific treatment for diabetic bladder dysfunction represents a glaring unmet need.

Technology

Duke inventors have developed a potential therapeutic target that would prevent inflammation in bladder outlet obstruction cases and diabetics with diabetic bladder dysfunction. This discovery is intended to prevent disease progression in the bladder of patients with benign prostatic hyperplasia and improve patient quality of life. Specifically, the inventors have found NLRP3, an inflammasome, when inhibited, prevents bladder obstruction induced inflammation and urinary

Duke File (IDF)

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Inventor(s)

- Purves, Todd
- Hughes, Francis "Monty"

Links

- From the lab of Dr. J Todd Purves
- From the lab of Dr. Monty Hughes Jr.
- The potential repertoire of the innate immune system in the bladder: expression of pattern recognition receptors in the rat bladder and a rat urothelial cell line (MYP3 cells) (International Urology and Nephrology, 2015)
- Inflammasomes in the urinary tract: a disease-based review (American Journal of Physiology-Renal Physiology, 2016)

College

School of Medicine (SOM)

dysfunction. NLRP3 also plays a central role in diabetic complications and is a crucial element in the development of diabetic bladder dysfunction. The inventors have shown that activation of the NLRP3 inflammasome, due to diabetic metabolites, underlies bladder dysfunction and can serve as a critical pharmacological target for combating this physiological complication in humans. Anti-diabetic drugs play an important role in modulating NLRP3 inflammasome activity. Further studies have confirmed inhibition of NLRP3 with the FDA approved drug, glyburide, prevents obstruction induced inflammation and urinary dysfunction. The inventors demonstrated, using a rodent model of diabetic bladder dysfunction that pharmacological inhibition of NLRP3 prevents inflammation and urinary dysfunction in these models.

Advantages

- A novel therapeutic target to improve urinary function and protect against bladder damage in bladder outlet obstruction cases and improve overall quality of life
- NLRP3 inflammasome was tested *in vitro* and *in vivo* to confirm its activation is responsible for sterile bladder inflammation
- Inhibition of NLRP3 is able to prevent inflammation and urinary dysfunction in bladder outlet obstruction and in diabetes

Publications

- Inflammasomes are important mediators of cyclophosphamide-induced bladder inflammation (American Journal of Physiology, Renal Physiology, 2014)
- The NLRP3 Inflammasome Mediates Inflammation Produced by Bladder Outlet Obstruction (J Urol., 2016)
- The NACHT, LRR and PYD Domains-Containing Protein 3 (NLRP3) Inflammasome Mediates Inflammation and Voiding Dysfunction in a Lipopolysaccharide-Induced Rat Model of Cystitis (J Clinical Cell Immunology, 2016)
- U.S. Patent Application (16/879,693)

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