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MACROPHAGE MIGRATION INHIBITORY FACTOR (MIF) AS MARKER FOR UROLOGICAL INFLAMMATORY DISEASE

CROSS REFERENCE TO RELATED APPLICATIONS

This claims the benefit of U.S. Provisional Application No. 60/532,899, filed Dec. 30, 2003.

FIELD OF THE INVENTION

The present disclosure relates to the association between detecting and quantifying the presence of macrophage migration inhibitory factor (MIF) in urine, bladder and prostate tissues for the purpose of urological inflammatory disease diagnosis and prognosis. In addition, methods to inactivate MIF activity by use of antibodies or specific MIF inhibitors can be used to treat these diseases. For instance, such diseases as chronic pelvic pain syndrome, non-bacterial prostatitis, and interstitial cystitis may be mediated by MIF release. Periodic assays for MIF could be conducted for a patient to determine if the patient's MIF urine levels are high or increasing. In addition, intravesical MIF antibodies or other MIF-specific inhibitors would reduce or ameliorate these pelvic diseases.

BACKGROUND OF THE INVENTION

MIF is a regulator of inflammation and innate, as well as adaptive, immune responses. However, current research suggests an even greater role for MIF, as it is present in a variety of immune and non-immune cells (Baugh et al., *Crit. Care Med.* 30: Suppl. S27-S35, 2002). MIF is constitutively expressed in tissues such as the anterior pituitary, prostate epithelia (Meyer-Siegler et al., *Diag. Mol. Path.* 7:44-50, 1998; and Meyer-Siegler, *Cytokine* 12:914-921, 2000), gastric, small intestinal and colonic epithelia (Maaser et al., *Gastroenterology* 122:667-680, 2002), neuronal and non-neuronal cells in the brain (Bacher et al., *Mol. Med.* 4:217-230, 1998).

As a proinflammatory cytokine, MIF counter-regulates the effects of glucocorticoids (Baugh et al., *Crit. Care Med.* 30: Suppl. S27-S35, 2002; and Lue et al., *Microbes and Infection* 4:449-460, 2002). Therefore, MIF has been proposed to play a critical role in immune and inflammatory diseases including septic shock (Bernhagen et al., *Nature* 365:756-793, 1993), rheumatoid arthritis (Leech et al., *Arthritis & Rheumatism* 42:1601-1608, 1999), delayed-type hypersensitivity (Brown et al., *Transplantation* 71:1777-1783, 2001), Crohn's disease (De Jong et al., *Nature Immunology* 2:1061-1066, 2001), gastric ulcer formation (Vera et al., *Brain Res. Bulletin* 29:651-658, 1992), and prostate cancer (Meyer-Siegler et al., *Diag. Mol. Path.* 7:44-50, 1998; and Meyer-Siegler, *Cytokine* 12:914-921, 2000). Treatment with anti-MIF antibodies has been reported to prevent experimental colitis and treat established colitis in experimental animals (De Jong et al., *Nature Immunology* 2:1061-1066, 2001). Therefore, anti-MIF therapy might represent a potentially useful therapeutic tool in the treatment of different inflammatory conditions.

As a new and novel finding we have determined that the urothelium is a rich source of pre-formed MIF. MIF is released from the bladder epithelium upon induction of inflammation and inactivation of released MIF by intravesical anti-MIF antibody reduces inflammation in the bladder, prostate and the spinal cord. These results suggest that this knowledge may have commercial application.

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MIF was first described thirty years ago and was designated as a cytokine, a chemical mediator, which regulates cell growth by inducing the expression of specific target genes. The initial described function of MIF was as a regulator of inflammation and immunity. It is expressed in the brain, and eye lens, is a delayed early response gene in fibroblasts, and it has been reported that this protein can be found in prostate tissues. MIF has been shown to be a pituitary, as well as macrophage cytokine and a critical mediator of septic shock. Recent studies also suggest that MIF may have an autocrine function for embryo development and is produced by the Leydig cells of the testes. Thus, it appears that this cytokine may play a fundamental role in cell growth regulation and possibly development.

U.S. Pat. No. 6,043,044 discloses the use of prostate tissue extracts as a patient sample to determine the amount of MIF. Immuno- and RNA blot analysis performed using homogenized tissue that contains variable proportions of epithelial and stromal cells still determined significant differences in the levels of MIF protein produced by metastatic tissue (490.3+/-71.3 ng/mg total protein). In practice this test was unreliable and difficult to perform because of contamination with surrounding connective and stromal tissue. It does not have utility in patient diagnosis or prognosis. Further, the patent does not mention or correlate urine, bladder tissue, and/or prostate tissue MIF levels with urological inflammatory disease. Therefore, a need exists for an improved assay with commercial application that is less invasive than that of the prior art.

SUMMARY OF THE INVENTION

The present invention provides methods for detecting or diagnosing or prognosticating urological inflammatory disease. The methods comprise determining the levels of macrophage migration inhibitory factor (MIF) in an individual's urine, bladder tissue, and/or prostate tissue.

The present invention further provides methods for monitoring the treatment of an individual with urological inflammatory disease. The methods comprise administering a pharmaceutical composition to an individual and determining the levels of MIF in the urine, bladder tissue, and/or prostate tissue.

The present invention further provides methods for screening for an agent capable of modulating the onset or progression of urological inflammatory disease. The methods comprise exposing an individual to the agent and determining the levels of MIF in the individual's urine, bladder tissue, and/or prostate tissue.

In embodiments of the present invention, levels of MIF are determined by detecting MIF gene product in the urine, bladder tissue, and/or prostate tissue using immunoassays or nucleic acid analysis, preferably mRNA. Gene products as recited herein can be nucleic acid (DNA or RNA) and/or proteins. In the case of DNA and RNA, detection occurs through hybridization with oligonucleotide probes. In the case of proteins, detection occurs through various protein interaction. Because MIF in urine is measured, the present invention can provide a non-invasive test for urological inflammatory disease.

The urine, bladder tissue, and/or prostate tissue test of the present invention can be used alone or in conjunction with commonly used methods diagnosis.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Many biological functions are accomplished by altering the expression of various genes through transcriptional (e.g.,