Blocking TWEAK: New Strategy Against Lupus Organ Damage

October 07, 2014
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The oddly named cytokine, which regulates response to tissue damage, has turned up in recent research as an important factor in lupus comorbidities. Phase 2 studies targeting TWEAK are now under way.

Source: Rheumatology Network

TNF-like weak inducer of apoptosis — better known as TWEAK — is a member of the TNF family of cytokines. It has only one confirmed receptor, TWEAKR, encoded by a gene called Fn14.

The TWEAK/Fn14 pathway has become an intense focus of investigation, partly because of the growing evidence that it is involved in human autoimmune/chronic inflammatory diseases (AICIDs) such as systemic lupus erythematosus (SLE), rheumatoid arthritis, and multiple sclerosis.\(^1\)\(^2\) The TWEAK/Fn14 pathway regulates tissue responses after acute injury. Although transient activation of this pathway may be beneficial for tissue repair after acute injury, excessive or sustained TWEAK/Fn14 activation due to repeated injury or chronic diseases such as AICIDs may lead to significant tissue damage and pathological tissue remodeling.

Recent evidence supports the hypothesis that blocking the TWEAK/Fn14 pathway may be an effective treatment option for AICIDs, and clinical trials with anti-TWEAK-blocking antibodies are in progress.

Lupus, Organ Damage, and TWEAK

Linda Burkly PhD and Fei Shih MD PhD of Biogen Indec, Inc., in Cambridge MA are two of the nation’s leading researchers on the association between the TWEAK/Fn14 pathway and SLE.

“Our preclinical research has shown that the TWEAK/Fn14 pathway is activated locally in diseased organs where it acts as a common driver of tissue inflammation and damage, notably fibrosis,” they write.\(^3\) “Therefore our research suggests that blocking TWEAK with anti-TWEAK antibody may potentially alleviate the manifestations of SLE in multiple organs.” The company is currently conducting a phase 2 study to evaluate the efficacy and safety of anti-TWEAK antibody in SLE patients with lupus nephritis.

Lupus, Psychiatric Conditions, and TWEAK

Researchers at the Albert Einstein College of Medicine in New York City have linked the TWEAK/Fn14 pathway to neuropsychiatric SLE (NPSLE).\(^4\) Sometimes the initial presenting symptom, NPSLE occurs in 30-40% of SLE patients, associated with acute neurological events such as seizures, cerebrovascular accidents, and delirium, as well as psychiatric conditions including depression, anxiety, and psychosis, and cognitive decline.

Based on their extensive studies in a murine model of NPSLE, these researchers concluded that TWEAK/Fn14 signaling compromises the integrity of the blood-brain barrier in SLE to trigger the neurological sequelae.

“We recently found that lupus-prone MRL/lpr Fn14 knockout (KO) mice display a markedly attenuated neuropsychiatric phenotype, as revealed by a significant reduction in depressive-like behavior and improved cognitive function,” says study co-author Jing Wen PhD. These mice lacking essential components of the TWEAK pathway have better blood brain barrier integrity and less inflammatory mediators such as RANTES and C3 in the brain, he adds. Further, they show less antibody activity against double-stranded DNA, a "potential neurotoxin," in their cerebrospinal fluid.

Lupus Nephritis, Renal Protection, and TWEAK

In newly published research, the same team suggests that targeting the TWEAK/Fn14 pathway may protect against lupus nephritis.\(^5\) In that study, female mice of a lupus-prone strain genetically engineered to lack the TWEAK receptor had significantly lower levels of proteinuria and glomerular immunoglobulin deposition — as well as substantial preservation of podocytes in glomeruli — at 26 to 38 weeks of age, compared with wild-type females of the same strain.

If lacking the receptor "significantly improves renal disease in a spontaneous lupus nephritis model through prevention of the direct injurious effects of TWEAK" on kidney cells, they conclude, blocking
it could offer a new strategy for preventing lupus nephritis in humans.

References:


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