

Research suggests targeted treatment strategies for lupus

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New research provides clues about the causes of lupus symptoms and suggests specific new targeted treatment strategies, according to Nilamadham Mishra, M.D., from Wake Forest University Baptist Medical Center, in presentations this week at the American College of Rheumatology in Boston.

The studies looked at premature atherosclerosis in lupus patients as well as accelerated cell death that seems to be behind many of the disease's symptoms. Lupus is an autoimmune disorder that can involve the joints, kidneys, heart, lungs, brain and blood. An estimated two million Americans have a form of lupus.

In one study, Mishra and colleagues looked at the potential mechanisms of premature atherosclerosis, which is one of the leading causes of death and disability in lupus patients. Even when they take drugs to lower their cholesterol, lupus patients still develop fatty buildups in their vessels, which can lead to heart attack and stroke.

Previous research by Mishra found that a new class of drugs being developed (histone deacetylase inhibitors) were effective at preventing atherosclerosis in mice prone to develop the disease. In the current study, Mishra and colleagues explored whether it is a specific histone deacetylase, number 9 (HDAC9), that causes the problem.

Histones are considered the master regulators in gene expression, and Mishra was the first to establish an association between abnormal histone

codes and the complications of lupus in a mouse model of lupus.

In the current study, the researchers found that in atherosclerosis-prone mice, there is more HDAC9 than usual in the macrophages, which are cells within the artery walls that collect cholesterol and can lead to atherosclerosis. They found that these increased levels of HDAC9 increase inflammation in the arteries as well as the buildup of fatty tissue that may break off and cause a heart attack or stroke.

In mice macrophages that were genetically engineered to have no HDAC9, the researchers found the production of chemicals that promote inflammation were reduced and levels of cholesterol deposits were reduced compared to mice that produced normal levels of HDAC9.

“With the drug that inhibits HDAC9, we were able to decrease inflammation and remove cholesterol at the same time,” said Mishra. “This study suggests that specifically targeting HDAC9 without inhibiting other histone deacetylases will be helpful for atherosclerosis.”

In a separate study, scientists found a potential explanation for why cells in lupus patients die at an increased rate and accumulate in tissues. This accumulation of cells is believed to trigger the inflammation that causes symptoms.

“We have not previously understood why cells die at an increased rate,” said Mishra. “This new study suggests both a possible mechanism and treatment.”

The study examined microRNAs, chains of ribonucleic acid that are involved in cell proliferation and cell death. The goal was to explore the possibility that aberrant expression of microRNAs is responsible for the abnormal cell death in lupus patients.

The scientists analyzed blood samples from five patients with lupus and seven healthy people of the same ages and sex at two points during a three-month period. A particular microRNA, miR-16, was consistently increased in lupus patients compared to the healthy participants. The scientists suspect that having too much miR-16 inhibits genes that control cell death and may also inhibit natural cell progression – resulting in the accumulation in tissues.

“Understanding this connection may lead to targeted treatments to decrease levels of miR-16,” said Mishra.

Source: Wake Forest University

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