Scientists find new genetic mutation that halts the development of lupus

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The new study was published in the January 18 edition (Volume 28, Issue 1) of the journal *Immunity*.

The lupus-suppressing action is the result of what is known as a nonsense mutation of the Coronin-1A gene (Coro1a) required for the development of the disease. A nonsense mutation causes the gene to produce proteins that no longer function. The Coronin-1A gene is a multifunctional regulator of the cytoskeleton, a network of protein fibers or filaments in the cell that helps maintain cell shape and is the key contributor to cell movement.

“The mutation reduced symptoms of the disease by interfering with the development and activation of T cells and other immune responses,” said Dwight Kono, an associate professor at The Scripps Research Institute. “These findings solidify the critical role of Coronin-1A in normal immune responses, and identify it as a potential therapeutic target for lupus.”

Two Sides of Lupus Genetics

Systemic lupus erythematosus is a serious autoimmune disease that affects approximately 1.5 million Americans. It is influenced by genetic, environmental, and hormonal factors, although genetic predisposition appears to be the single greatest contributor to its onset.

There has been considerable interest in defining the genetics of systemic lupus erythematosus in recent years, not only for gaining a better understanding of the fundamental causes of the disease but also for the development of potential therapies.

“We were searching for a lupus susceptibility gene,” Kono said. “After mapping and cloning the Coronin-1A gene, we discovered this spontaneous mutation in a single strain of mice-those that don’t get severe or systemic lupus-like disease. More than likely, the mutation had existed undetected in our mouse colony for years.

“We ended up cloning a disease-resistance gene when we were thinking about doing the opposite,” he continued. “Suppressive genes may, in fact, play an important role in lupus susceptibility.”

The study suggests genetic-mapping studies need to adequately distinguish between predisposing or suppressive alleles or alternate gene forms, and that other lupus-related loci might also be associated with suppressive alleles. In addition to traditional predisposing genes, disease-suppressing genes and spontaneous mutations, as in the case for CoroLmb3, are likely to be important contributors to an entire repertoire of genetic variations that could help alter the onset and severity of the disease in lupus patients.

“Obviously, these types of variations will further complicate the identification of susceptibility genes,” Kono added. “However, as in the case of disease-suppressing genes such as we found in our study, their identification can provide important clues to pathogenesis and possibly therapy.”

Pointing to New Possibilities

The Scripps Research scientists found the mutation on a single genetic

locus-the position of a gene on a chromosome-called Lmb3 that plays a major role in modulating autoimmunity in transgenic mice. The cloned version of the Lmb3 mutation resulted in developmental and functional alterations in T cells, including reduced migration, survival, and activation. The study also showed that the Lmb3 autoimmune-suppressing phenotype could be transmitted only through Coro1aLmb3 T cells.

“The fact that its action appears to be somewhat specific for T cells is unusual,” Kono said. “Because we were able to show that blocking CoroLmb3 has specific effects, this work suggests other cytoskeleton proteins might prove to be good targets. This opens up an area that hasn’t really been considered, and gives more impetus to study these genes for autoimmunity.”

Because the actin cytoskeleton is essential for many crucial cellular functions and involves complex regulatory mechanisms in specific cell types, these new findings highlight the importance of actin regulation in lupus pathogenesis. They also suggest that alteration of an actin-regulatory protein can have limited but important effects on specific immune system functions.

“There may be quite a few regulatory proteins that can be used as targets,” Kono said. “We really don’t know right now. What we would like to do is identify all the genes that block autoimmunity one way or another. Finding these suppressing genes may be important in identifying future therapeutic targets.”

Source: Scripps Research Institute