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Researchers identify new enzyme that acts as innate immunity sensor

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Two studies by researchers at UT Southwestern Medical Center could lead to new treatments for lupus and other autoimmune diseases and strengthen current therapies for viral, bacterial, and parasitic infections.

The studies identify a new enzyme that acts as a sensor of innate immunity – the body's first line of defense against invaders – and describe a novel cell signaling pathway. This pathway detects foreign DNA or even host DNA when it appears in a part of the cell where DNA should not be. In addition, the investigations show that the process enlists a naturally occurring compound in a class known to exist in bacteria but never before seen in humans or other multicellular organisms, said Dr. Zhijian "James" Chen.

Dr. Chen, professor of molecular biology and a Howard Hughes Medical Institute (HHMI) investigator at UTSW, is senior author of both studies available online and published in today's print edition of *Science*. Although the immune-boosting response of DNA has long been recognized, the mechanism underlying that response remained a mystery, he said.

"In his 1908 Nobel acceptance speech, Ilya Mechnikov noted that surgeons in Europe treated patients with nucleic acids – the building blocks of DNA – to boost their patients' immune responses. That observation came four decades before scientists showed that DNA was the carrier of genetic information," Dr. Chen said.

Dr. Chen credits a uniquely biochemical approach for solving the longstanding puzzle. The approach used classical protein purification combined with a modern technology called quantitative mass spectrometry to identify the mysterious compound at the heart of the discovered process.

Under normal conditions, DNA is contained within membrane-bound structures such as the nucleus and mitochondria that are suspended within the cell's soupy interior, called the cytoplasm, he said. DNA in the cytoplasm is a danger signal that triggers immune responses, including production of type-1 interferons (IFN).

"Foreign DNA in the cytoplasm is a sign of attack by a virus, bacteria, or parasite," Dr. Chen said. "Host DNA that somehow leaks into the cytoplasm can trigger autoimmune conditions, like lupus, Sjogren's syndrome, and Aicardi-Goutiere's syndrome in humans."

In these studies, UTSW researchers identified a new sensor of innate immunity – the enzyme cyclic GMP-AMP synthase (cGAS) – that sounds a cellular alarm when it encounters DNA in the cytoplasm. After the enzyme detects and binds to the DNA, it catalyzes the formation of a compound called cyclic GMP-AMP (cGAMP), the compound never before seen in humans, Dr. Chen said.

The cGAMP functions as a second messenger that binds to an adaptor protein called STING, which activates a cell signaling cascade that in turn produces agents of inflammation: interferons and cytokines.

"Normally this pathway is important for immune defense against infections by microbial pathogens. However, when the immune system turns against host DNA, it can cause autoimmune diseases," Dr. Chen said. "Our discovery of cGAS as the DNA sensor provides an attractive target for the development of new drugs that might treat autoimmune

diseases."

Provided by UT Southwestern Medical Center