Scientists find mechanism that triggers immune responses to DNA

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(Medical Xpress)—Free-floating pieces of DNA in a cell's watery interior can mean bad things: invading viruses, bacteria, or parasites, ruptured cellular membranes, or disease. Genetic material is meant to be contained in a cell's nucleus or key organelles, and when it's loose, it's a sign for the immune system that something is wrong. Now, Howard Hughes Medical Institute scientists have discovered the molecular pathway responsible for detecting loose bits of DNA outside a cell's nucleus in the cytosol and setting off the resulting immune reaction.

The findings, published December 20, 2012, in two papers in the journal *Science*, could lead to treatments for autoimmune diseases such as lupus, in which ongoing immune reactions are often set off by loose pieces of DNA.

The cytosol of a cell is often passed over, its importance seemingly dwarfed by other parts of a cell. But in fact, says HHMI investigator Zhijian "James" Chen of the University of Texas Southwestern Medical Center, every molecule in the cytosol is carefully controlled and invaders are not welcome.

"The cytosol has to be very clean," says Chen. "If DNA gets in, that is actually very dangerous to cells."

Doctors have known since the early 20th century (even before they knew DNA's role of in carrying genetic information) that nucleic acids—DNA or RNA—could boost the activity of a person's immune system. And in

recent years, Chen and other scientists have discovered some of the immune molecules key to this response. However, the known molecules are not responsible for detecting DNA, and Chen wanted to find out the molecules that are.

So his group, which includes lead authors of the Science papers Lijun Sun, a HHMI research specialist, and Jiaxi Wu, a graduate student at UT Southwestern, developed a biochemical assay to isolate the unknown molecules that sensed loose DNA. They isolated cytosol from cells that had been invaded by free bits of DNA and divided the liquid into different fractions. Each fraction of the total mix was added individually into other, fresh cells to test whether an immune reaction was set off, which would suggest that portion of the original cytosol contained the DNA sensor. Once they narrowed down the cytosolic fractions, Chen and his colleagues used mass spectrometry, a method of analyzing the chemical characteristics of a compound, as well as classical biochemistry to learn more about the molecules. They eventually narrowed their focus to two key players and worked out their roles.

One was a small molecule called cyclic GMP-AMP (cGAMP), which binds to and turns on one of the molecules already known to carry out the immune reaction against DNA, STING. cGAMP belongs to a class of compounds called cyclic di-nucleotides, which were known to function as signaling molecules in bacteria. Until now, however, they were not known to exist in multicellular organisms.

The other player was the enzyme that produces cGAMP, dubbed cGAMP synthase (cGAS). Chen's team found that cGAS bound directly to DNA in the cytosol, and the binding turned on its activity as an enzyme to catalyze the cGAMP synthesis.

"The cGAS enzyme recognizes all double-stranded DNA without any apparent sequence specificity," says Chen. "Which makes sense because

an organism wants to recognize all sorts of DNA from different sources. As long as DNA gets into the wrong place, which is the cytosol, cGAS is there to detect it and sets off the immune reaction."

The discovery by Chen's group outlines the entire response of the cell from detecting free DNA in the cytosol to activating the STING-mediated immune response. But there are still details that need to be worked out.

"One of the things we need to do next is solve the structure of cGAS and try to understand how DNA binding activates the enzyme," says Chen. And understanding the structure can help with his next goal: designing compounds that can block the enzyme. In autoimmune diseases including lupus and Sjögren's syndrome, the immune system is put into overdrive attacking a person's own cells. One factor that sets off this immune response is loose DNA in these cells, so it's likely that cGAMP and cGAS play a role. By blocking a cell's response to its own DNA, the constant immune response in affected individuals could be dampened.

"We hope we can go on to identify chemical inhibitors of this enzyme," says Chen. "Such inhibitors could be developed into therapies for autoimmune diseases."

Provided by Howard Hughes Medical Institute

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