When DNA is out of place

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When DNA that turns up in the wrong place in mammalian cells, the innate immune system reacts by secreting interferons. The structure and mode of action of the enzyme that mediates this response have now been elucidated.

In animal cells, DNA molecules are normally restricted to the cell nucleus and the mitochondria. When DNA appears outside these organelles – in the so-called cytosol - it most probably originates from a bacterial pathogen or a DNA virus. This is why cytosolic DNA triggers a strong response by the innate immune system. However, various types of insult can also lead to the release into the cytosol of the cell's own DNA. In this case, the resulting immune response may precipitate an autoimmune disease.

The innate immune system is the body's first line of defense against invasive pathogens. It reacts to intruders by inducing the production of interferon proteins that alert the adaptive arm of the immune system. However, the protein that recognizes DNA which is "out of place" in the cytosol resisted identification until a short time ago. "It was only recently discovered that the enzyme cGAS serves as the sensor," says Professor Karl-Peter Hopfner of LMU's Genzentrum. Hopfner and his colleagues have now determined the three-dimensional structure of this DNA detector.

Cytosolic DNA activates enzyme

Indeed, as they report in the journal *Nature*, the LMU researchers not only delineated the structure of the cGAS molecule itself, they also elucidated the conformation of the complex formed when it binds to DNA. Careful analysis of both structures, together with further functional studies carried out in collaboration with Professor Veit Hornung of Bonn University, enabled the scientists to work out how cGAS recognizes, and is activated by, cytosolic DNA. Binding of the DNA alters the structure of cGAS, enabling the enzyme to catalyze the synthesis of a cyclic dinucleotide. This molecule then activates a transmembrane protein, which in turn stimulates the production of interferon. "In a second study, published simultaneously in *Nature*, we also determined the structure of the dinucleotide, and show that it represents a previously unknown form of this class of signaling molecule," Hornung adds.

To their surprise, the researchers also found that cGAS is structurally and mechanistically related to an antiviral enzyme that triggers an immune response upon detection of foreign RNA in the cytosol. "With this finding we have the first evidence for a mechanistic and evolutionary link between DNA- and RNA-induced immune reactions," Hopfner comments.

The new results are also very interesting from a clinical standpoint, as a better understanding of the interferon response could have implications for therapy, in two respects. On the one hand, targeted stimulation of interferon production could enhance immunotherapies directed against tumors. Conversely, the ability to attenuate misdirected immune responses against the body's own antigens could lead to better treatments for autoimmune conditions.

More information: Structural mechanism of cytosolic DNA sensing by cGAS, *Nature* (2013) doi:10.1038/nature12305

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