A left turn that kills: New mechanism triggering cell death and inflammation

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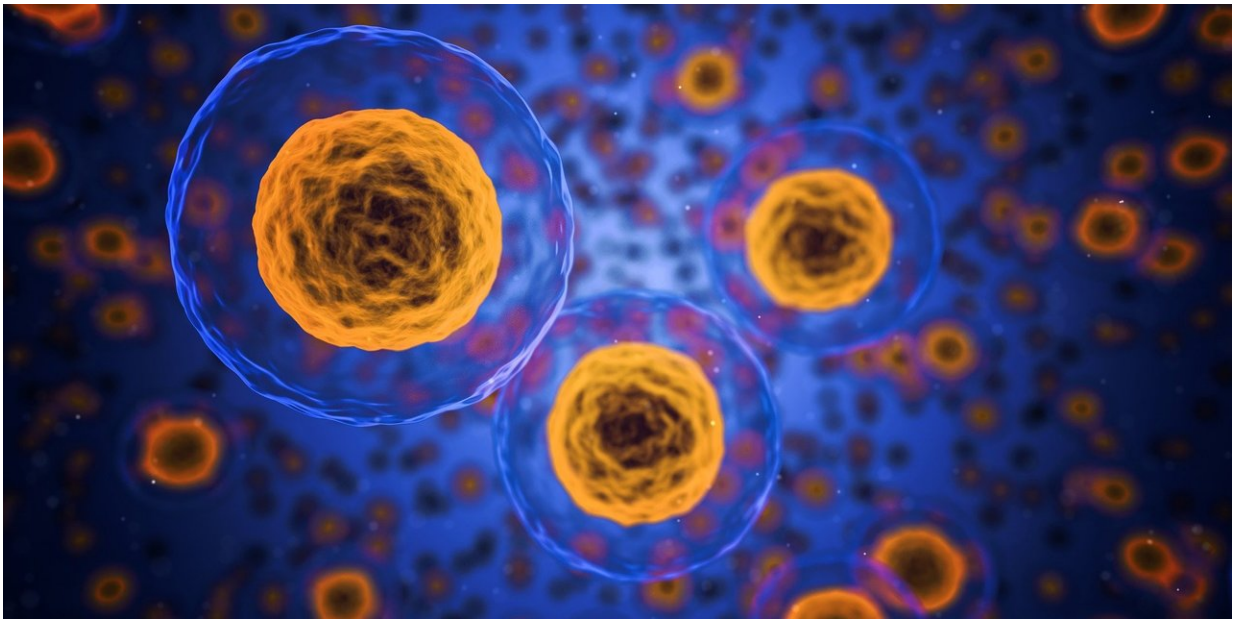

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Writing in *Nature*, researchers from Cologne, Texas and London describe their discovery of a new mechanism that could contribute to the pathogenesis of inflammatory diseases.

The scientists found that ZBP1, a protein best known for defending against incoming viruses, is activated by sensing an unusual form of cellular genetic material (Z-nucleic acids), leading to cell death and

inflammation.

Z-form nucleic acids are double-stranded DNA and RNA molecules with an unusual left-handed double helix structure, as opposed to the classical right-handed Watson-Crick double helix. Z-nucleic acids were discovered more than 40 years ago, but their biological function has remained poorly understood. The group of Professor Manolis Pasparakis at the CECAD Cluster of Excellence in Aging Research of the University of Cologne cooperated with scientists from the University of Texas Health Science Center and the Francis Crick Institute in London to study the role of Z-DNA Binding Protein 1 (ZBP1), one of only two proteins in mammals that senses Z-nucleic acids. ZBP1 was previously shown to sense the genetic material of certain viruses and induce the death of the infected cells to prevent viral spread.

Curiously, in their earlier studies, the researchers obtained evidence that ZBP1 can also cause cell death and inflammation in the absence of viral infection. They had found that when the function of RIPK1—a protein inhibiting ZBP1—was compromised, ZBP1 was activated and triggered an inflammatory type of cell death, called necroptosis. A key question behind the current study was how ZBP1 can be activated in the absence of incoming viral infection. Using experimental mouse models, the scientists found that the proinflammatory activity of ZBP1 depended on its ability to bind Z-nucleic acids, suggesting that it is activated by Z-form nucleic acids that existed within the cell. The next question was what type of endogenous nucleic acids are bound by ZBP1.

"We could show that ZBP1 binds to double-stranded RNA," Pasparakis said. "Although we currently lack the experimental methodology to demonstrate that this has the Z-conformation, based on all available structural studies, our interpretation of our results is that ZBP1 binds to endogenous Z-RNA via its Z□ domains."

Double-stranded RNA (dsRNA) is uncommon in cells but forms during the replication of certain viral genomes, and is thought to provide the ligand activating ZBP1 during viral infection. The scientists hypothesized that cellular dsRNA could be produced by endogenous retroelements, which are forms of parasitic DNA derived either from ancient retroviral infections or from active retrotransposons or "jumping genes," which constitute over half of the human and mouse genomes. To address the possible role of endogenous retroelements as sources of dsRNA, the team of Manolis Pasparakis collaborated with George Kassiotis' Retroviral Immunology Laboratory at the Francis Crick Institute. Indeed, computational analysis of RNA sequencing data from mouse skin showed that most complementary, putatively double-stranded, RNA was derived from particular groups of endogenous retroelements. These findings suggested that sensing of cellular dsRNA, most likely derived from endogenous retroelements, activates ZBP1, inducing cell death and inflammation. This mechanism may be relevant for the pathogenesis of inflammatory pathologies in humans, particularly in patients with mutations of proteins inhibiting ZBP1 such as RIPK1.

"Z-form nucleic acids have remained mysterious for so many years," Pasparakis remarked. "Currently, our only means to investigate their function is by studying the proteins that sense them. We made some progress, but the challenge ahead would be to understand why, where and how they form within a cell and what the purpose of this is."

A particularly fascinating aspect is the link to endogenous retroelements. "We currently understand very little about how these genomic parasites affect our health. It appears that over the course of evolution, some retrotransposons, which can mimic viral infection, have been recruited as useful partners in the response of our cells to damage, stress or true infection, but this partnership can also go wrong, causing disease," Kassiotis commented.

"Just like during viral infection, sensing of Z-RNA produced by endogenous retroelements by ZBP1 could provide a potent trigger for cell death and inflammation, and cause disease. These are early days and we have a long way to go, but understanding the underlying mechanisms may one day lead to novel therapies for human diseases," Pasparakis concluded.

More information: Huipeng Jiao et al. Z-nucleic-acid sensing triggers ZBP1-dependent necroptosis and inflammation, *Nature* (2020). DOI: 10.1038/s41586-020-2129-8

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