

Study finds that regulatory protein prevents signaling that triggers cell death

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The team studying the regulation of innate immune response includes (front row, from left) Yang Zhao, Ph.D., Antiana Richardson, (back row, from left) William Dunker, Xiang Ye, Ph.D., and John Karijolic, Ph.D. Credit: Susan Army

A protein implicated in neurodegenerative diseases including amyotrophic lateral sclerosis (ALS) prevents the activation of an innate immune response that leads to cell death, Vanderbilt researchers have discovered.

The protein, called TDP-43, regulates the accumulation of double-stranded RNA—genetic material found in both pathogens and in our own cells. The findings, published in the journal *Cell Reports*, reveal an intricate relationship between innate immune responses and control of [gene expression](#), said John Karijolic, Ph.D., assistant professor of Pathology, Microbiology and Immunology.

Karijolic and his team are interested in how cells discriminate between self and non-self, and the signaling pathways that are activated to protect against pathogens.

"Every day, we come into contact with microbes and viruses, and we have to make sure that we

don't allow those pathogens to establish an infection," Karijolic said.

His group has focused on the RIG-I-like receptors (RLRs), which detect double-stranded RNA and are important for responding to RNA viruses including SARS-CoV-2. Activation of RLRs triggers an antiviral response, including the production of interferon and other proinflammatory cytokines.

In previous studies, Karijolic and his colleagues made the surprising discovery that misprocessed cellular RNAs could also activate RLRs and trigger the innate immune response. The findings suggested to the team that gene expression itself, which can produce double-stranded RNA, might be "inherently dangerous," Karijolic said.

The investigators pursued the idea that RNA-binding proteins might act as controls to prevent the accumulation of "immunostimulatory" double-stranded RNA. They identified a collection of potential regulatory proteins and focused on TDP-43 because of its connection to neurological diseases such as ALS and frontotemporal lobar dementia (FTLD).

TDP-43 is essential for cell viability (without it, [cells](#) die), and the researchers found that reducing TDP-43 levels resulted in the accumulation of double-stranded RNA, activation of RLR signaling, and robust interferon production.

Interestingly, Karijolic noted, some patients with ALS and FTLD have elevated levels of interferon in their [cerebrospinal fluid](#), supporting a link between TDP-43, RLR pathway activation and neurological dysfunction.

"If reducing interferon is beneficial for the patients, then exploring the RLR pathway might point to novel therapeutic options," Karijolic said.

The team will continue to examine the RLR

pathway and the intriguing connection between control of gene expression and innate immune responses.

"Sensing nucleic acid (RNA or DNA) to distinguish self versus non-self poses a very big challenge" he said. "How do you impart specificity or selectivity? If the cell makes a mistake in gene expression, it activates the same pathway as if the cell is infected with a virus, leading to interferon-mediated [cell death](#)."

More information: William Dunker et al. TDP-43 prevents endogenous RNAs from triggering a lethal RIG-I-dependent interferon response, *Cell Reports* (2021). [DOI: 10.1016/j.celrep.2021.108976](https://doi.org/10.1016/j.celrep.2021.108976)

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