Study rewrites dogma of adenovirus infection and double-stranded RNA

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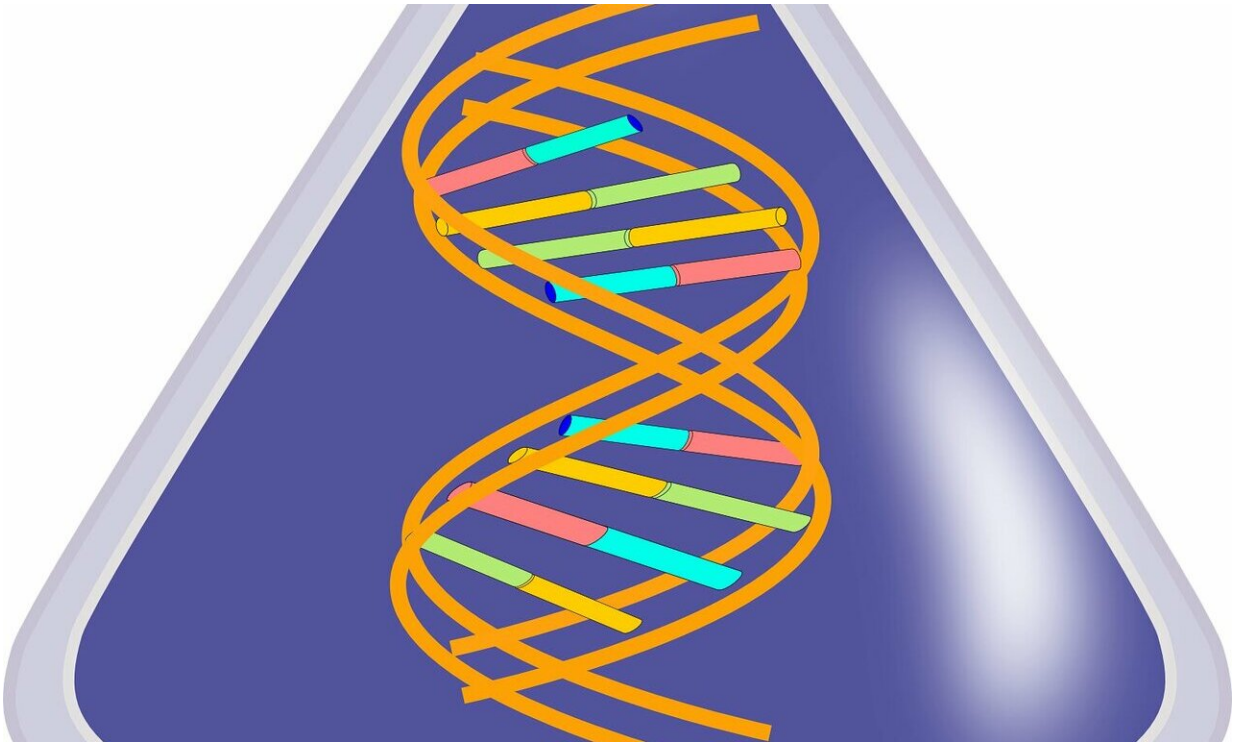

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Challenging the dogma of what scientists thought they understood about DNA viruses, a team of researchers led by Children's Hospital of Philadelphia (CHOP) has shown that adenovirus uses its own efficient RNA splicing mechanisms to prevent the formation of double-stranded RNA, which otherwise would trigger a host immune response. By

splicing its RNA transcripts in a way that prevents them from pairing with other viral messages, adenovirus evades host sensors that activate the immune system in the presence of double-stranded RNA. The findings were published today as a "Breakthrough Article" in *Nucleic Acids Research*.

Prior to this work, researchers had assumed DNA viruses produced double-stranded RNA during infection, given that transcription occurs symmetrically on both top and bottom strands of viral DNA; most DNA viruses also encode proteins that inhibit host pathways that recognize double-stranded RNA as foreign. However, despite this assumption, there was no direct evidence that DNA viruses like the adenovirus produce double-stranded RNA.

To investigate this theory, the research team, led by Matthew D. Weitzman, Ph.D., an investigator in CHOP's Department of Pathology and Laboratory Medicine, and Alexander Price, Ph.D., a post-doctoral fellow in the Weitzman Laboratory, used imaging by microscopy with two independent monoclonal antibodies to establish whether adenovirus produces double-stranded RNA. To their surprise, they found no detectable levels of double-stranded RNA following adenovirus infection. In contrast, they found abundant double-stranded RNA in cells infected with adenovirus mutants that were defective for viral RNA processing. When this occurred, host sensors for double-stranded RNA were activated, launching the host immune system into action.

"Through highly collaborative work, this study highlights a novel mechanism by which viruses can escape innate immune recognition by modulating host factors to promote efficient viral RNA production," Weitzman said. "Future research will need to account for this new discovery and investigate factors like small viral RNAs that were thought to block double-stranded RNA responses, but as these findings indicate, must exist for some other reason."

More information: Alexander M Price et al, Adenovirus prevents dsRNA formation by promoting efficient splicing of viral RNA, *Nucleic Acids Research* (2021). DOI: 10.1093/nar/gkab896