A synthetic approach to helping the immune system thwart infections

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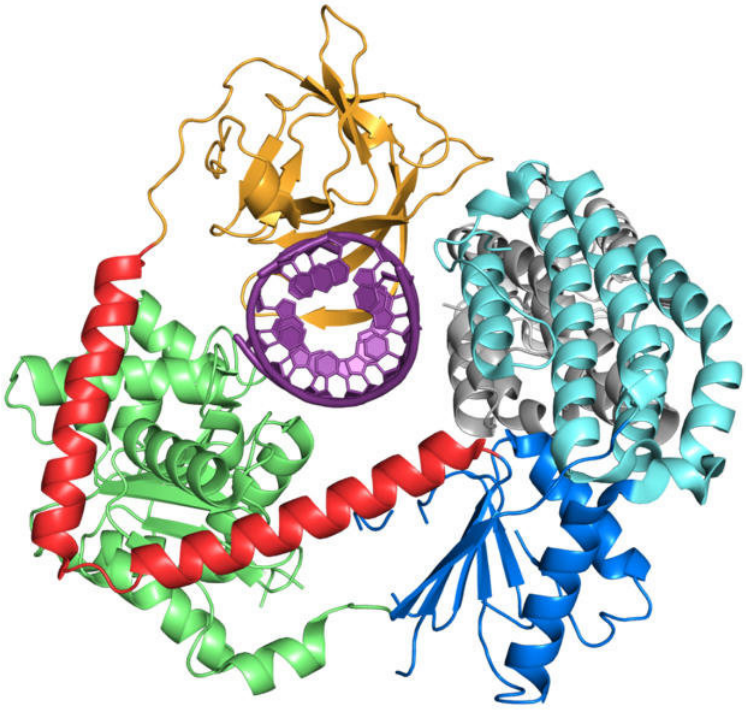

A diagram of the RIG-I protein. Credit: Yale University

Yale researchers have developed a set of synthetic molecules that may help boost the strength of a key, virus-fighting protein.

The protein, RIG-I, is an important sensor in the immune system of humans and other animals. It recognizes and responds to viral RNA by

surrounding it, latching onto it, and launching the immune system into action.

The Yale team, led by biologists Anna Pyle and Akiko Iwasaki, has designed molecules that jump-start the process. These synthetic, stem-loop RNA (SLR) molecules can be visualized as short cords with a knot at one end. The configuration enables the SLRs to bind with RIG-I molecules in a way that prompts an aggressive response.

"When you tickle RIG-I with this small, RNA hairpin, it alerts the body that it's time to respond," said Pyle, professor of molecular, cellular, and developmental biology, and of chemistry, at Yale, and co-corresponding author of a study published online Feb. 21 in the journal *Science Advances*.

"This gives us a tool that can help with everything from the design of better vaccines to better antivirals and anti-cancer therapies," Pyle said.

The new study represents the first time scientists have been able to specifically manipulate and analyze the RIG-I biosensor in a living animal—in this case, mice. The Yale researchers said further study is needed in order to gauge the potential for developing new drugs for everything from flu to various forms of cancer.

"I was shocked to see how potent this small RNA molecule is in stimulating antiviral interferon responses in mice. For its specificity and potency, we now use SLR for all of our RIG-I research in the lab," said Iwasaki, professor of immunobiology and of molecular, cellular, and developmental biology, and co-corresponding author of the study.

More information: Melissa M. Linehan et al. A minimal RNA ligand for potent RIG-I activation in living mice, *Science Advances* (2018). DOI: 10.1126/sciadv.1701854

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