# Link uncovered between viral RNA and human immune response

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(PhysOrg.com) -- In its fight against an intruding virus, an enzyme in our immune system may sense certain types of viral RNA pairs, according to scientists.

The key lies in a virus' RNA -- a long molecular chain often used to make proteins -- and how it regulates an enzyme called protein kinase R (PKR), according to researchers from Penn State, the University of Connecticut and the University of Beijing.

"PKR plays an important role in the human immune system," said Laurie Heinicke, graduate student of chemistry and first author for the paper. "It is activated by long stretches of double-stranded RNA. As a part of our built-in immune response, PKR can recognize viral double-stranded RNAs and inhibit their production."

Viral RNA enters human cells when attacking viruses inject their genetic material into the cells and force them to manufacture future generations of viruses. By latching on to specific sites on viral RNA, PKR can interrupt this process.

Or, according to Heinicke, "once activated by certain RNAs, PKR stops protein synthesis in the infected cell and ultimately causes cell death."

One way for this to happen is for the viral RNA to first form linked pairs called dimers. These RNA dimers then allow separate sets of PKR to bind with themselves, also forming dimers, a state where the paired

PKR is most effective against a viral onslaught.

"We showed that a small region of the HIV-1 genome termed TAR can regulate PKR," Heinicke continued. "The caveat, however, is that this RNA must form a dimer in order to be an activator."

The extra length that dimer RNA provides is critical in encouraging PKR to pair up and function properly.

"The length needed for one PKR to bind to RNA is fifteen base pairs," said Philip Bevilacqua, professor of chemistry, Penn State, one of the lead scientists on the project along with James Cole, associate professor, University of Connecticut. "To get two PKRs to bind and dimerize, you need an RNA strand that is twice as long." Cole's laboratory provided evidence of dimerization of RNA and PKR.

In their experiments at Penn State, the scientists found the dimer RNA activated PKR from 9 to 118 times more than the single strand RNA, depending on the RNA type. TAR RNA dimerization activated the most PKR when the TAR did not exhibit structural defects. The researchers report their findings in a recent issue of the *Journal of Molecular Biology*.

"Adding these defects decreases the number of places where PKR can bind to the RNA," Heinicke explained.

RNAs that showed the greatest degree of symmetry are more potent PKR activators than ones with defects. "It appears as though length is a necessary, but not sufficient condition for activation," said Bevilacqua.

The scientists constructed RNAs to remove TAR defects. Dimers of these RNAs increased PKR activity, compared to more asymmetric "wild-type" TAR dimers. Single strands of these RNAs did not activate

PKR. This is in contrast to previous work, which reported that the single strand wild-type TAR showed a 50-fold increase of activation over more symmetric variants.

"This helps us find what the actual molecular structure is that activates PKR," said Bevilacqua. "It is still basic research for now, but finding the cause for this may ultimately lead to understanding disease."

Source: Pennsylvania State University (news : web)