Respiratory virus infection triggers new class of biomolecules

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Dr. Michael Katze, UW professor of microbiology and head, Center for Systems and Translational Research on Infectious Disease, directed a study that found a new class of biomolecules are triggered inside mammalian cells in response to respiratory virus infection.

(PhysOrg.com) -- For the first time, scientists have discovered that a poorly understood class of RNA produced in a mammal's cells during a respiratory virus attack may affect the outcome of the infection. Their findings are reported today in *mBio*, a journal of the American Society for Microbiology.

RNA (ribonucleic acid) contains information transcribed from the cell's instruction manual, its DNA. The best known of these RNAs translate

sections of DNA code into building blocks for proteins.

Most studies of how animals' cells respond to virus infection typically look at protein-coding genes, which produce germ-fighting or inflammation-producing substances. However, mammalian cells also transcribe thousands of other RNAs that don't code for proteins.

"The role of most of these non-protein-coding RNAs remains an enigma," noted lead author of the study Dr. Xinxia Peng. computational research scientist, UW Department of Microbiology. Dr. Michael Katze, professor of microbiology at the University of Washington (UW) in Seattle, directed the project. Katze heads the Center for Systems and Translational Research on Infectious Disease (STRIDE).

"Some attention," Katze said, "has been given to small RNAs, like microRNAs, in host-virus interactions, but now it's becoming apparent that many long -non-protein coding RNAs -- bigger than 200 nucleotides -- are also biologically important."

Researchers are learning that long non-protein-coding RNAs have a wide variety of functions. A few examples are modifying chromosomes, regulating genes, influencing cell structure, and serving as precursors for small RNAs and microRNAs, which are involved in virus-host interactions.

The library of RNA transcripts inside of a cell is called its transcriptome, and is a reflection of gene activity. Many different RNAs can be read from a single gene. That is why a transcriptome contains much more complex instructions than seems possible from the DNA code. Unlike the genome, the transcriptome varies in different types of cells in the body and in accordance with ever-changing conditions inside and outside the cell.

Peng recalled, "There were intensive discussions about what value the new whole-transcriptome analysis would add to our understanding of viral pathogenesis. After several exploratory analyses, we realized that many long non-protein coding RNAs also responded to SARS virus infection. We were so excited. The response had just been overlooked by people. "

"People have not seriously looked at these long-non-protein coding RNAs during viral infection," Peng noted, "because so little is known about these RNAs in general and this type of RNA can't be monitored easily with typical technologies." Katze and his research team were able to use highly advanced technologies, namely next generation sequencing, to perform a whole-transcriptome analysis of the host response to severe acute respiratory syndrome coronavirus (SARS-CoV) infection. The study was conducted in four strains of mice, some more susceptible to this virus or to the flu virus than others.

Through a comprehensive computational analysis of the data, the researchers observed that virus infection triggered about 500 long non-protein coding RNAs transcribed from known locations on the genome and about 1,000 from previously unspecified genomic regions.

"Using this approach," Katze noted, "we demonstrated that virus infection alters the expression of numerous long non-protein coding RNAs. These findings suggest that these RNAs may be a new class of regulatory molecules that play a role in determining the outcome of infection."

The long non-protein coding RNAs may be helping to manage the infected animal's response to the virus, including the basic, first-line defense against infection -- the animal's innate, or inborn, immunity.

Another important finding was that the strains of more susceptible mice

had a common profile showing distinct rates of genetic activity. This profile contained unique "signatures" of non-protein coding RNA activity. These signatures were associated with lethal infection. Test-tube studies show that more that 40 percent of the long non-coding RNAs and genomic regions activated in a SARS infection were also activated in response to both influenza virus infection and interferon treatment.

This finding further pointed to a signature profile associated with pathogenicity -- the power of a virus-host interaction to cause disease.

"The relevance of long-non-protein coding RNAs to viral infections has not been systematically studied," said Dr. Paulene Quigley, program manager of the STRIDE center. "But now, with our ability to do whole-transcriptome analysis using next generation sequencing, we can systematically catalog and compare these long non-protein coding RNA in response to infection. What we are finding is very promising for infectious disease research."

These results, to the best of the scientists' knowledge, are the first to clearly demonstrate the widespread production and activation of long non-coding RNAs in response to virus infection. Their success opens new avenues for investigating the roles of long-non-protein coding RNAs in innate immunity to infection.

Exactly how the long-non-protein coding RNAs perform these functions is not yet known. It's possible that they might interact with protein complexes that modify gene expression during a viral infection. They might also modulate the host's response by regulating neighboring protein-coding genes.

"The functions of non-protein coding RNAs remain largely unexplored, but we now have the tools to study them," Katze said. "Such studies are critical, because non-protein coding RNAs may represent a whole new

class of innate immunity signaling molecules, interferon-dependent regulators, or modulators of the host response during viral infection. They could also be a new class of biomarkers for infectious disease and for diagnostics development. Identifying similar profiles in response to lethal respiratory infections may even provide clues into the 'high-path' viral infection, one of the holy grails of virology. That's a big deal any way you slice it."

Highly pathogenic viruses causing life-threatening illnesses, like SARS or West Nile or pandemic flu, continue to emerge. Looking forward, a detailed knowledge of non-protein coding RNA regulation and function likely will be necessary for a full understanding of how viruses cause disease and how the body defends against or succumbs to viruses.

More information: mbio.asm.org/

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