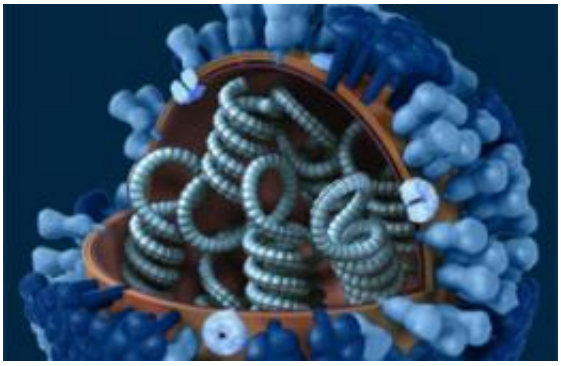
Influenza 'histone mimic' suppresses antiviral response

March 14 2012



The influenza virus, like all viruses, is little more than coils of genetic material enclosed by a membrane. New research shows how influenza's DNA packaging proteins mimic those of its host in order to gain access to critical gene-regulating machinery. (Image from CDC.)

(Medical Xpress) -- For a virus like influenza, the key to success isn't in overpowering the immune system, it's in tricking it. A team of researchers led by scientists at The Rockefeller University has identified a novel mechanism by which influenza viruses hijack key regulators of the human body's normal antiviral response in order to slip by it undetected. The finding, reported recently in *Nature*, shows that the immunosuppressive NS1 protein of the influenza A virus mimics a core component of gene regulating machinery in order to block antiviral gene function. The results they describe have major implications for our understanding of the biology of the seasonal influenza virus and its

pathogenesis. The research also suggests a possible target for a new class of antiviral and anti-inflammatory drugs.

The researchers, led by Alexander Tarakhovsky, head of the Laboratory of Lymphocyte Signaling, showed that the NS1 protein of the H3N2 strain of influenza — the "seasonal" flu — contains the same sequence of amino acids as the "tail" domain of a DNA packaging protein in humans called histone H3. The histones are present in the cell nucleus and play an important role in gene activation. Chemical modifications of the histone "tails" allow recruitment of effector proteins that, in turn, determine which genes are switched on or off. Chemical modifications of histones were first identified by Rockefeller scientist Vincent G. Allfrey in the early 1960s. Decades later, Rockefeller University's C. David Allis proposed the "histone code" theory that describes the importance of histone tails in regulating a wide array of cellular functions.

"By mimicking the histone H3 tail, the NS1 tail gives the virus access to the core of gene regulating machinery," says first author Ivan Marazzi, a postdoctoral fellow in the Tarakhovsky lab. "Through this mimicry the virus targets a set of proteins in the nucleus of the infected cells and impairs the antiviral host cell response."

Marazzi, working with graduate student Jessica Ho, discovered the ability of the NS1 protein to track and target a protein complex called PAF1C, which has been previously studied extensively by Robert G. Roeder's lab at Rockefeller. Together with Roeder's lab, the Tarakhovsky lab revealed the ability of NS1 to interfere with the activity of PAF1 complex. This complex turned out to be essential for the expression of the genes that are responsible for antiviral response.

"NS1 is hijacking PAF1C and using its similarity with the H3 'tail' to gain access to a position in the genome that helps the virus to block

antiviral genes," says Ho. "This finding extends the known ability of pathogens to reveal key regulatory processes and to use them for the pathogen's advantage."

The current study bears several major implications for influenza research and treatment. The NS1 protein varies from strain to strain and the NS1 "tail" specifically appears to be one of the most diverse parts of the NS1 protein. Some flu strains such as H1N1, which was responsible for the 2009 pandemic, do not contain an NS1 "tail" at all. Together with their collaborator, prominent flu researcher Adolfo Garcia-Sastre of Mount Sinai School of Medicine, the Tarakhovsky lab plans to test if diversification of the NS1 "tail" helps the influenza virus to maintain a long-term presence within human or animal populations. If so, it could explain how the influenza virus, which has no history of integration into animal or human DNA, has "learned" about the functional benefits of the histone "tail."

Finally, by identifying PAF1C as a NS1 target, the researchers may have found a promising new target for attenuation of inflammatory responses. In collaboration with GlaxoSmithKline, previous efforts of the Tarakhovsky lab in this direction yielded a synthetic "histone mimic" called I-BET. By binding to BET proteins that control inflammatory gene expression, I-BET suppresses inflammation. I-BET and the related compound JQ1, which has been identified by Jay Bradner at the Dana-Farber Cancer Institute at Harvard Medical School, are now considered a new generation of so called "epigenetic" drugs, i.e., drugs that control DNA function without interfering with it directly.

The current discovery is proof and validation of the functional importance of "histone mimicry," Tarakhovsky says, a phenomenon that was first discovered by Srihari Sampath, a Rockefeller M.D.-P.hD. student in Tarakhovsky's lab.

"Mimicry is a general biological phenomenon that facilitates adaptation of living beings to changes in their environment," says Tarakhovsky. "In the case of pathogens, we are 'locked' in a constant race. As we change, pathogens adapt to us and we keep adapting to each other in order to maintain a status quo in the race. By displaying histone mimicry, the flu virus may have found the most optimal approach to adapting to host response and using it to the maximum advantage of the virus. It will be fascinating to watch the future evolution of the histone mimic and our response to it."

More information: Suppression of the antiviral response by an influenza histone mimic, Ivan Marazzi, Jessica S. Y. Ho, Jaehoon Kim, Balaji Manicassamy, Scott Dewell, Randy A. Albrecht, Chris W. Seibert, Uwe Schaefer, Kate L. Jeffrey, Rab K. Prinjha, Kevin Lee, Adolfo García-Sastre, Robert G. Roeder and Alexander Tarakhovsky, *Nature* 483: 428–433 (March 14, 2012). www.nature.com/nature/journal/ … abs/nature10892.html

Provided by Rockefeller University