Histones Wreaking Havoc

A CLOSE LOOK AT INFECTED BLOOD SAMPLES REVEALS HOW SEPSIS SPIRALS OUT OF CONTROL.

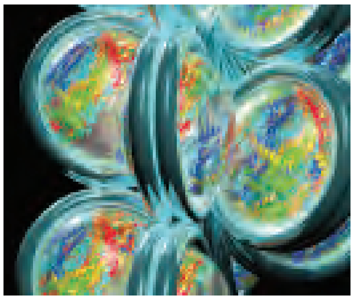
The proteins that keep DNA wound tightly inside a cell's nucleus—called histones—have no place outside the cell. New research suggests that when they land in the bloodstream, they encourage sepsis, the potentially deadly response of the immune system to severe infection. Destabilizing histones that escape the cell can halt the spiral of events that make sepsis lethal.

HHMI investigator Charles T. Esmon's lab group at the Oklahoma Medical Research Foundation previously showed that a compound called activated protein C (APC) could block sepsis. Although a commercial drug, Xigris, was developed from APC, its mechanism remained unclear, and it didn't work in all cases. Esmon was determined to further unravel the molecular basis of sepsis.

The idea that histones might play a role in sepsis came serendipitously. Jun Xu, a postdoctoral fellow in Esmon's lab noticed histones in cultures where macrophages—a type of immune cell—had become inflamed and cleaved and their toxic activities neutralized by APC.

"People had seen histones in the blood before," says Esmon, "but assumed they leaked out of cells as a side effect of the major damage caused by sepsis. No one ever guessed they had a more central role."

To determine whether the chopped up histones were more directly related to sepsis, the researchers exposed blood vessel cells—normally damaged during sepsis—to histones and to histone fragments. The intact histones killed cells while the histone fragments did not.



Normally, histones act as spools for DNA to wrap around, as shown in this artist's rendering.

Esmon's team also looked at mice, baboons, and humans with sepsis—they all had free-floating histones in their blood. When the researchers gave a histone-blocking protein to septic mice, which were expected to die, many of the mice survived.

The data, published in the November 2009 issue of *Nature Medicine*, suggest a new theory on sepsis: Initial cell damage, from widespread inflammation due to an infection, lets histones leak into the bloodstream. These histones kill more cells, which release more histones, in a vicious cycle. APC, scientists now know, cleaves those histones to stop sepsis. The severe side effects of APC, however, make it a last resort drug. Other histone blockers, which may cause fewer side effects, can now be tested on sepsis. ■ –SARAH C.P. WILLIAMS

IN BRIEF

TAKING SIDES

It's a myth that some people are "right-brained" and others "left-brained," but it is true that the brain divvies up jobs between sides. An imaging technique developed by HHMI investigator Randy L. Buckner reveals just how complex this division is.

Researchers use functional magnetic resonance imaging (fMRI) to link brain regions to certain tasks. fMRI measures blood flow—increased blood flow in an area indicates neuron activity. In a typical fMRI experiment, researchers ask a participant to perform a task—like watching images or memorizing a list—and then observe what brain area becomes active.

But Buckner's lab group, at Harvard University, wanted to know how the brain divides its baseline activity, unrelated to any task. So they asked each participant to lie still and stare straight ahead while they monitored the brain's constant chatter. The scientists tracked areas on both sides of the brain that spontaneously fired at the same time—indicating that they were doing matching or complementary jobs—and measured which side showed greater activity.

When the neurons that fired on each side were in areas known to be linked to language, the activity tended to be stronger on the left side; neurons in regions linked to vision and spatial awareness were stronger on the right. But not in everyone. In some people, the pattern was reversed, and in others the sides were less lopsided.

Now that Buckner has shown the links between sides of the brain can be observed in a resting brain, as reported in the *Proceedings of the National Academy of Sciences* on December 1, 2009, he hopes to investigate further how genes control the division of labor between the two sides of the brain, a question relevant to developmental disorders such as autism and schizophrenia.

TARGETING TICK SALIVA

Blocking a protein in tick saliva reduces the risk of a mouse becoming infected with Lyme disease, researchers have found.

HHMI investigator Erol Fikrig at Yale University discovered the protein, Salp15, in 2005. He found that the Lyme disease pathogen, *Borrelia burgdorferi*, ramps up the tick's production of Salp15. The bacterium then coats itself in the protein, hiding from the tick's immune system. Fikrig wondered whether a protein that blocked Salp15 could block Lyme disease.

His team injected mice with a Salp15 antiserum and then a day later with Salp15-coated *B. burgdorferi*, as it would be if the bacteria were transmitted from a tick. Three weeks later, 40 percent of these mice remained free of Lyme disease. All the control mice, which received an inactive antiserum before the bacteria, contracted the disease.

Previously developed Lyme disease vaccines have been dropped from the market. Fikrig's team tested whether combining those vaccines with Salp15 would increase their efficiency. The combination was a winner—only 25 percent of mice receiving both compounds showed signs of Lyme disease. The results appear in the November 19, 2009, issue of *Cell Host & Microbe*.

DOUBLE HELIX, REVISED

A half century after Francis Crick and James Watson discovered the famous double-helix shape of DNA, scientists are only beginning to fully understand its subtleties. New research by HHMI investigator Barry Honig has shown that slight variations in the helix shape allow DNA-binding proteins to differentiate between regions.

Honig, at Columbia University, became interested in the nuances of DNA shape

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