

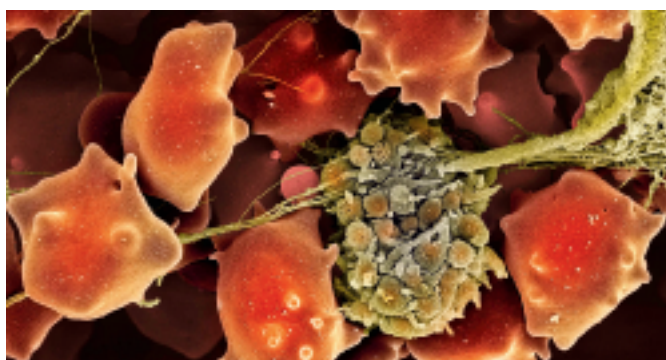
Mysterious Protein Protects Against Sepsis

RESEARCHERS FIND A LINK BETWEEN A LIVER RECEPTOR AND BLOOD CLOTTING.

One of the most deadly consequences of an infection is sepsis—a drastic, full-body response characterized by inflammation and blood clotting.

A study led by HHMI investigator Jamey D. Marth of the University of California, San Diego, reveals that a protein whose function has mystified scientists for decades helps protect against this extreme response.

The protein—a receptor named after biochemist Gilbert Ashwell—coats liver cells in vertebrates (organisms with a backbone), and binds to a specific type of glycoprotein. But its role during health or illness had not been defined. Mice engineered to lack the receptor appeared healthy.



Platelets and red blood cells clump together to form a blood clot, one dangerous consequence of sepsis.

Marth's team traced the origin of the receptors' function by first showing that a change in that specific glycoprotein decreases platelets in the blood. Marth realized that the pathogen *Streptococcus pneumoniae* also causes the same glycoprotein change, outside of the bloodstream, on its way to infecting cells.

To figure out whether there was a link between the Ashwell receptor and the pathogen, the researchers infected normal mice and those lacking the receptor with *S. pneumoniae*. They saw that the bacteria caused glycoprotein alterations in two factors that lead to blood clotting—von Willebrand Factor and platelets. The Ashwell receptors then recognized the modified glycoproteins and signaled the liver to remove them from circulation.

Mice without Ashwell receptors could not remove these coagulation factors and underwent more severe clotting and tissue damage, which increased the likelihood of death.

Clinicians have assumed that a low platelet count during sepsis was the result of platelets being used up by the extreme blood clotting, but Marth's research suggests something different.

"It's an adaptive response by the liver," he says, "enabled by the Ashwell receptors."

The finding, published in the June 2008 issue of *Nature Medicine*, clears up many questions about the Ashwell receptor, but raises others, says Marth. "Does its protective response extend to other pathogens? Can it be employed to increase the chance of human survival in severe sepsis?" ■ —SARAH C.P. WILLIAMS

IN BRIEF

May 1, 2008, issue of *Nature*, all nine genomes were different, while in others just one or a few people had variants.

"What's exciting to me," Eichler says, "is that we now have, in essence, eight new reference human genomes." And, understanding their variations—which are primarily caused when DNA misaligns during the process that produces sperm and eggs—could lead to a better understanding of diseases.

NOVEL GENE THERAPY IMPROVES VISION

By introducing a genetic vector into the cells of the retina of the eye, researchers have created a way to partially restore vision to people with an inherited disease.

Leber congenital amaurosis (LCA), which can be caused by a missing enzyme vital to regenerating rhodopsin in the eye after exposure to light, causes blindness early in life. The team of scientists, led by HHMI investigator Katherine High at the Children's Hospital of Philadelphia, reasoned that if they could get the gene for the missing enzyme into the cells that needed

it, the blindness would be reversed.

They used a viral vector that infects cells and introduces a gene into the nucleus of the cells it enters. Because retinal cells don't divide or get replaced, they didn't have to worry about the gene being copied—they just needed it to enter the nucleus.

It worked in a first, small clinical trial, the results of which appeared in the *New England Journal of Medicine* on May 22, 2008. Three patients—ages 19 to 26—received injections of the gene-carrying vector into the subretinal space. All three experienced improved vision. "They went from only being able to see a hand moving in front of them, to being able to read a few lines on an eye chart," explains High.

The next steps, she says, are to increase dosage and to try the treatment in younger children.

NEW NEURAL MODE OF INFORMATION STORAGE

It's not just the junction between two neurons, called the synapse, that gets stronger as information is repeatedly transmitted from one cell to the next. The

branches within an individual neuron, known as dendritic branches, can also become stronger, HHMI researchers have shown, offering a new complexity to how information in the brain is stored.

Jeffrey C. Magee and his colleagues at HHMI's Janelia Farm Research Campus created a way to observe how a single neuron responds to stimuli. They exposed only a small portion of a highly branched neuron to neurotransmitters and saw a spike of localized activity within the stimulated dendritic branch.

With continued stimulation the branch's activity got stronger, the scientists reported in the March 27, 2008, issue of *Nature*. Over time, they observed, the localized activity became so strong that it propagated to the main part of the neuron—the axon—and caused a nerve impulse. This behavior—stemming from the strengthening of a signal in the synapse. The next step, Magee says, is to study living animals to determine whether changing the environment of an animal leads to changes in the dendritic branches.