UCSD Researchers Boost White Blood Cells' Ability to Kill Bacteria

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Scientists at the University of California, San Diego have determined how white blood cells up the ante against invading bacteria, a finding that may lead to new treatments for infections including those caused by invasive-"flesh-eating"- Streptococcus bacteria.

The findings, which are published in the July, 2005 issue of *The Journal of Clinical Investigation,* represent a collaborative effort between the laboratories of Randall Johnson, UCSD professor of biology and Victor Nizet, associate professor of pediatrics at the UCSD School of Medicine.

The research team discovered that white blood cells respond directly to Streptococcus, Staphylococcus, Salmonella, and other bacteria that cause disease in humans, by increasing their levels of a protein known as hypoxia inducible transcription factor-1, or HIF-1. The protein, in turn, stimulates white blood cells to release antimicrobial compounds that kill bacteria. The team also found that treating white blood cells with chemicals to increase HIF-1 levels could enhance the cells' capacity to kill bacteria.

"These findings suggest a potential novel approach to treatment of difficult infections such as those produced by antibiotic resistant bacteria or those affecting patients with weakened immune systems due to chronic disease, cancer chemotherapy or AIDS," said Nizet. "Rather than designing drugs to target the bacteria, medications that promote HIF-1 activity could be used to boost the bacterial killing ability of white blood cells and promote the resolution of infection through the actions of our natural immune defenses."

Previous work by Johnson and colleagues showed that low oxygen levels, such as those found at the site of an infection, activate HIF-1 in macrophages and neutrophils-white blood cells that ingest and destroy microorganisms. In the current study, the researchers compared how well macrophages in which HIF-1 levels were elevated, normal or zero could kill bacteria, including Streptococcus isolated from a patient with flesh-eating disease. They found that the greater the HIF-1 levels in white blood cells, the greater their bacterial killing power. They also found that mice lacking HIF-1 in their macrophages and neutrophils were less able to combat skin infections than normal mice.

"A direct correlation was established between the levels of HIF-1 present in the mouse macrophages and neutrophils and how efficiently the cells were able to kill the bacteria," said lead author Carole Peyssonnaux, a postdoctoral researcher with biology professors Johnson and Nizet.

The HIF-1 protein is known to bind to cellular DNA and activate specific genes to help cells function is a low oxygen environment. The researchers found that in white blood cells, HIF-1 stimulates the production of small proteins, enzymes and nitric oxide, which work together to kill invading bacteria.

"The placement of essential microbial killing functions of white blood cells under regulation of HIF-1 represents an elegant controlled response system," explained Johnson. "The white blood cells are in a resting state as they circulate in the oxygen-rich bloodstream, but can then be activated in response to the declining oxygen gradient encountered upon migration to sites of infection. Direct encounter with the bacteria then activates the neutrophils

and macrophages maximally. Under HIF-1 regulation, antimicrobial genes are expressed only in infected tissues and not in healthy tissues where they could produce unwanted inflammatory damage."

Recognition of the essential role for HIF-1 in the bacterial killing ability of white blood cells led the researchers to explore potential medical implications of this discovery. With the assistance of Emmanuel Theodorakis, UCSD professor of chemistry and biochemistry, a group of pharmacologic agents that act to increase cellular HIF-1 levels was selected. These compounds significantly enhanced the capacity of macrophages to kill bacteria.

"Our findings offer proof of concept that small molecules can have a beneficial effect by modulating the production of HIF-1 protein in white blood cells," said Theodorakis.

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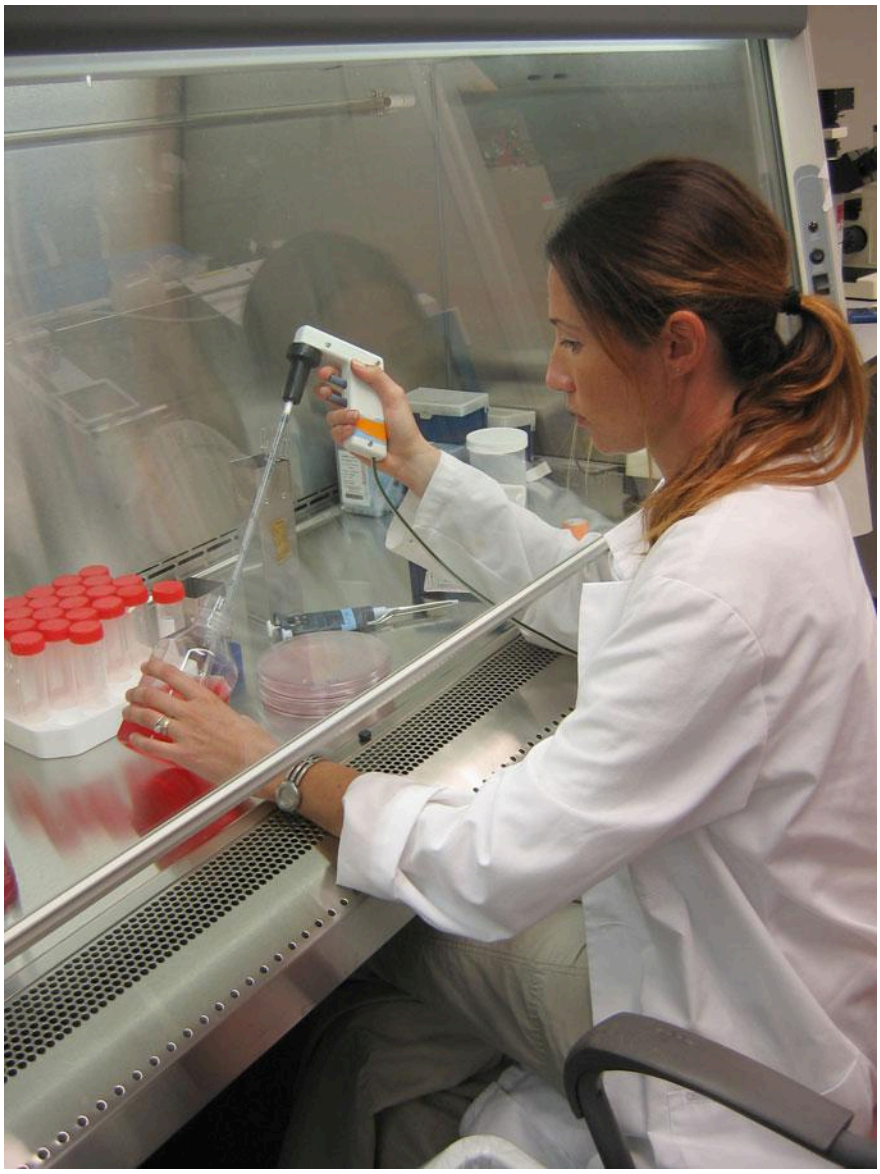
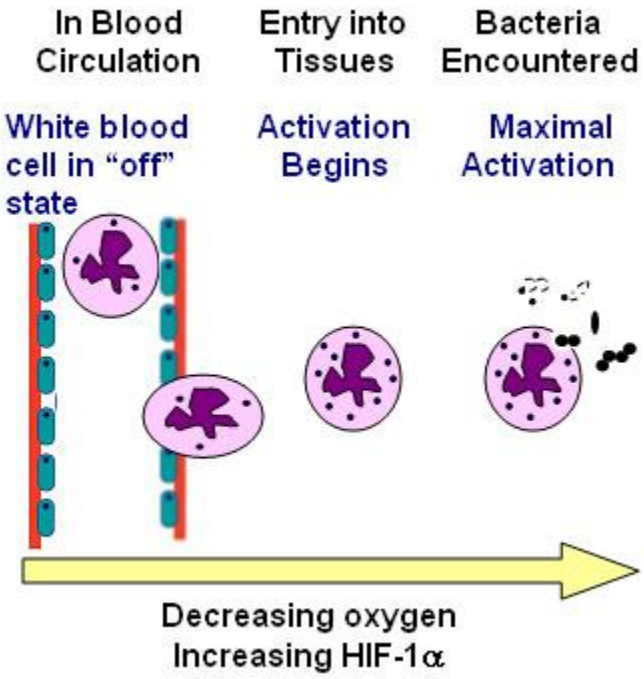
Image of Carole Peyssonnaux, postdoctoral researcher who spearheaded the research, and graphic depicting HIF-1 control of white blood cells' bacterial killing efficiency at: http://ucsdnews.ucsd.edu/newsrel/science/simmune.asp Credit: Laurent Rivierre, UCSD Victor Nizet, UCSD




In Blood Circulation
Entry into Tissues
Bacteria Encountered
White blood cell in "off" state
Activation Begins
Maximal Activation
Decreasing oxygen
Increasing HIF-1α