Macrophages: The 'defense' cells that help throughout the body

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The term "macrophage" conjures images of a hungry white blood cell gobbling invading bacteria. However, macrophages do much more than that: Not only do they act as antimicrobial warriors, they also play critical roles in immune regulation and wound-healing. They can respond to a variety of cellular signals and change their physiology in response to local cues.

David Mosser, Professor of Cell Biology and Molecular Genetics at the University of Maryland's College of Chemical and Life Sciences, will discuss the three primary duties of macrophages at the 2010 American Physiological Society conference, Inflammation, Immunity, and Cardiovascular Disease, in Westminster Colorado, August 25-28.

"There has been a huge outpouring of research about host defense that has overshadowed the many diverse activities that these cells do all the time," said Dr. Mosser. "We'd like to dispel the narrow notion that most people have that macrophages' only role is defense, and expand it to include their role in homeostasis."

Monocyte Differentiation

Macrophages exist in nearly all tissues and are produced when white blood cells called monocytes leave the blood and differentiate in a tissue-specific manner. The type of macrophage that results from monocyte differentiation depends on the type(s) of cytokines that these cells

encounter. Cytokines are proteins produced by immune cells that can influence cell behavior and affect interactions between cells. For example, macrophages that battle microbial invaders arise in response to interferon-γ, a cytokine that is produced during a cellular immune response involving helper T-cells and the factors they produce. These macrophages are considered to be "classically activated."

However, when monocytes differentiate in response to stimuli such as prostaglandins or glucocorticoids, the resulting macrophages will assume a "regulatory" phenotype. Alternately, wound-healing macrophages arise when monocytes differentiate in response to interleukin-4, a cytokine which is released during tissue injury.

According to Dr. Mosser, macrophages can change their physiology and switch types. For example, in healthy, non-obese people, macrophages in fat tend to function as wound-healing macrophages. They are also thought to maintain insulin sensitivity in adipose cells. However, should an individual become obese, macrophages in fat will instead promote inflammation and cause the adipose cells to become resistant to insulin.

Immune Regulation

Immune-regulating macrophages produce high levels of the cytokine interleukin-10, which helps suppress the body's immune response. Suppressing an immune response may seem counter-intuitive, but in the later stages of immunity it comes in handy because it limits inflammation.

According to Dr. Mosser, immune-regulating macrophages may hold the key to developing treatments for autoimmune diseases such as multiple sclerosis or rheumatoid arthritis. The focus of new research is on reprogramming the macrophages to assume a regulatory phenotype and prevent autoimmunity, he said.

There is broad potential for exploiting different stages of macrophage activation, Dr. Mosser added. "It might be possible to manipulate macrophages to make better vaccines, prevent immunosuppression, or develop novel therapeutics that promote anti-inflammatory immune responses."

Wound Healing

The release of interleukin-4 in response to tissue injury not only results in macrophages that specialize in wound-healing, it allows the macrophages to convert arginine to ornithine, which is a precursor of polyamines and collagen. Both polyamines and collagen are instrumental to the formation and maintenance of extracellular matrix, the material between cells that gives them structural support.

Certain harmful microbes, such as the tropical parasite *Leishmania spp.*, can exploit wound-healing macrophages, said Dr. Mosser. "If you have a macrophage whose job it is to promote wound-healing, that macrophage will not be capable of killing microbes," he said. "The microbe can enter the macrophage and survive inside, which is not good for the human host."

Infection with *Leishmania spp.* causes leishmaniasis, which is characterized by skin sores and ulcers and can enlarge the spleen, damage the liver, and cause anemia. At worst, it can decrease immunity and leave victims vulnerable to potentially fatal opportunistic infections. Survivors can suffer from immune reconstitution inflammatory syndrome, in which their recovering immune systems go overboard in response to infection and create an inflammatory response that makes symptoms even worse. Understanding how Leishmania exploits macrophages has led to a better understanding of how macrophages function in health and disease. It has also stressed the importance of treating infections early, before the bugs can wreak havoc on the

immune system.

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