How do white blood cells detect invaders to destroy?

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Scientists at Cedars-Sinai Medical Center have discovered how a molecular receptor on the surface of white blood cells identifies when invading fungi have established direct contact with the cell surface and pose an infectious threat.

The receptor called Dectin-1, studied in the laboratory of David Underhill, PhD, an associate professor in Cedars-Sinai's Inflammatory Bowel and Immunobiology Research Institute, detects fungi and instructs white blood cells whether to expend the energy needed to devour the invading pathogens. The findings are featured as the cover story in the April 28 edition of *Nature*.

Although scientists long have theorized how immune cells recognize microbial debris sloughed from invading organisms at some distance from themselves, this study establishes a model to explain how immune cells determine when pathogens are directly in contact with their surface and thus pose a significantly greater risk, demanding rapid destruction.

The study is important because it moves scientists one step closer to understanding the mysteries of how our bodies mount an immune response to fight disease.

In early stages of infection, white blood cells patrol the body looking for invading pathogens. Dectin-1, a receptor on the surface of white blood cells, recognizes specific components of fungal cell walls, and alerts or "switches on" the immune cells to prepare to fight the infection.

"Our lab has been studying Dectin-1, which directs white blood cells to eat and kill the fungi that they encounter directly, but to ignore soluble material sloughed off of the fungal surface which does not pose an immediate threat," said Helen Goodridge, PhD, first author on the study and a researcher in the laboratory headed by Underhill. "This is important because phagocytosis and anti-microbial defense responses are energy-intensive and destructive, and should only be used when absolutely necessary."

During phagocytosis, a white blood cell encounters a microbe, engulfs it, and eats it. Once inside the cell, the microbe can be killed using a combination of degradative enzymes, highly reactive chemicals, and an acidic environment.

A molecular structure that the Underhill lab calls a "phagocytic synapse" forms at the surface of the white blood cell when Dectin-1 detects fungi. As a phagocytic synapse forms, two inhibitory proteins that block transmission of signals inside the white blood cell are pushed aside. This allows Dectin-1 to instruct the cell to respond. The phagocytic synapse does not form when Dectin-1 encounters soluble fungal debris, so the white blood cell does not respond.

"The phagocytic synapse resembles another molecular structure, the 'immunological synapse.' It is critical at later stages of an immune response," said Underhill. "It appears that the phagocytic synapse may be an evolutionary precursor of the immunological synapse."

Provided by Cedars-Sinai Medical Center