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Cell surface receptors are all 'talk' in T cell stimulation

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Understanding the mechanisms that drive healthy immune responses is important when it comes to combating autoimmune diseases, which occur when cells that should attack invading organisms turn on the body instead.

In a study published in the June 13, 2008, issue of *Immunity*, Tufts researcher Stephen Bunnell, PhD, describes how cell surface receptors cooperate to generate immune responses in a process referred to as costimulation. To reveal how these receptors communicate, Bunnell, assistant professor of pathology at Tufts University School of Medicine and a member of the immunology program faculty at the Sackler School of Graduate Biomedical Sciences, formulated a fluorescent imaging technique that reveals the dynamic movements of proteins within living T cells.

T cells play an essential role defending the body against viruses and bacteria. To mount these defenses, T cells must sense these pathogens via cell surface receptors known as antigen receptors. T cells are much more likely to 'see' the invading organisms when a second group of proteins, known as integrins, becomes involved. Integrins are also cell surface receptors, and act as adhesive hooks that allow the T cell to latch onto its environment. "What we are providing here is insight into how these receptors collaborate, or 'talk' to one another," says Bunnell.

First author Ken Nguyen, a graduate student in immunology in Bunnell's laboratory, found that a particular integrin, VLA-4, influences how

cellular structures known as SLP-76 microclusters move within the responding T cell. These structures, which were first discovered by Bunnell, are assembled by the antigen receptor and relay information that is essential for T cell activation. "SLP-76 is a molecular building block that is employed by both antigen receptors and integrins. When VLA-4 is not involved, SLP-76 microclusters move away from the antigen receptor, which causes them to fall apart. We discovered that VLA-4 prevents the separation of SLP-76 microclusters from the antigen receptor. This keeps each SLP-76 microcluster intact for a longer time, and favors the transmission of stimulatory signals," says Bunnell.

Actin filaments are a major component of the 'skeleton' that enables cells to move. In activated T cells, many actin filaments grow at one end and fall apart at the other. These actin filaments 'flow' away from the growing end, much like a treadmill. Nguyen and colleagues showed that these flows drive SLP 76 from the antigen receptor, but are slowed when VLA-4 is engaged. "By altering the movement of actin within the cell, the integrin is collaborating with the antigen receptor to immobilize these complexes and make them survive over time," says Bunnell.

"We have known for some time that integrin signaling and T cell costimulation contribute to autoimmunity. Bunnell's images allow us to see that these can be related phenomena: integrins sensitize the immune system to antigens," says Naomi Rosenberg, PhD, dean of the Sackler School of Graduate Biomedical Sciences and vice dean for research at Tufts University School of Medicine.

In previous research, integrins and antigen receptors were thought of as working individually, in terms of geography and mechanism. Earlier studies by Bunnell, and recent studies by other investigators, have led researchers to believe that antigen receptors are most effective when located near integrins. Importantly, this study indicates that integrins

influence the transmission of signals through the same complexes used by the T cell antigen receptor.

"You need to understand the communication between the receptors in order to intelligently intervene and enhance the response to a virus or bacteria, or inhibit a destructive response," says Bunnell.

Bunnell's future research will examine how integrins alter the mechanical properties of activated T cells. By studying how integrins influence the SLP-76 complex, Bunnell will gain insights into the costimulatory processes that enable normal immune responses, and go awry in autoimmune diseases.

Source: Tufts University