The secret life of proteins: Researchers discover dual role of key player in immune system

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Northwestern University Feinberg School of Medicine researchers have identified a new and unusual role for a key player in the human immune system. A protein initially believed to regulate one routine function within the cell has proven vital for another critical step in the activation of the immune system.

That protein, STIM1, was previously known to sense a change in calcium within immune cells, a process that occurs when the body confronts a pathogen. Upon sensing this change, STIM1 opens a type of pore in the cell membrane, called a CRAC channel, to allow the flow of calcium ions — a vital step in activating the immune system.

The Feinberg team, led by Murali Prakriya, assistant professor of molecular pharmacology and biological chemistry, discovered that STIM1 not only opens these pores but is responsible for determining the exquisite selectivity for calcium ions within the CRAC channels, a critical factor in kick starting the body's immune system. These findings were recently reported in the journal *Nature*.

"People have generally thought that selectivity of ion channels is fixed and that selectivity and opening are separate processes; this is a fundamental shift in the way scientists believe ion channels operate," says Prakriya, referring to the 'pores' that STIM1 regulates. "CRAC channels and STIM1 are absolutely vital to activating the immune

system. As is observed in some human patients, you can block key parts of the system by blocking these molecules in immune cells. These finding reveal not only a novel mechanism by which CRAC channels operate, but also new ways in which it encodes biological information. This represents exciting new possibilities to develop therapeutics to treat a broad range of conditions."

To determine that STIM1 is responsible for selectivity and opening, the researchers created a mutated CRAC channel designed to keep the pore open without the assistance of STIM1. When the channel was opened without STIM1, multiple types of ions were passed through the pore, including sodium and potassium. When STIM1 was added back in, the channel became very selective for calcium ions again, like the normal channel. Even at low doses of STIM1, the unmutated channel lost its normally high calcium selectivity, allowing the entry of multiple types of ions.

Conditions that might benefit from immune suppression are likely targets for future CRAC channel targeted therapy, including autoimmune diseases and many types of allergies. Additionally, targeting CRAC channels could provide improvements for existing immune suppression therapies such as those used during transplantation.

"The CRAC channel is emerging to be incredibly important for the immune system," says Prakriya. "But we have been solely focused on its calcium conducting mode that occurs in response to STIM1. It is certainly possible that there could be other players in the cell that open the CRAC channel pore to permit the flux of other ions to stimulate different cell functions. That's the next question."

Also in the *Nature* article, Prakriya's team identified the location of the barrier, or gate, within the CRAC channel that controls its opening and closing.

"The identification of the molecular and structural regions of the pore that controls opening and closing is highly valuable for facilitating drug design targeting CRAC channels for the treatment of immune disorders," he adds.

Provided by Northwestern University