A single protein regulates 2 immune pathways

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Unchecked, the natural or innate immune system can run out of control - like a stuck accelerator on a car. Eventually, it will kill the host it is supposed to protect.

Much scientific attention is directed at understanding how this innate immune system is turned on, but little to how it is cooled down or regulated. That is important because the innate immune system is associated with inflammation. In turn, unchecked inflammation is associated with cancer, heart disease, autoimmune diseases and other chronic ailments.

A team of researchers led by Baylor College of Medicine has identified a protein called NLRC5, a member of the NOD-like protein family, that is involved in inhibition of protein complexes key to critical pathways of innate immunity called NF-κB and type I interferon signaling. A report on their work appears in the current issue of the journal *Cell*.

"Understanding the molecular mechanisms that hold innate immunity in check could provide clues to better treatments for cancer and autoimmune diseases associated with inflammation," said Dr. Rong-Fu Wang, professor in the Center for Cell and Gene Therapy, the department of pathology and immunology at BCM and a senior author of the report.

Think of the innate immune system as a rushing cascade, blocked in places by chunks of rock or landscape and forced through natural

cavities in a particular direction. Protein complexes such as the protein IKK complex in NF-κB pathway, and RIG-I and MDA5 as pathogen sensors in type I interferon pathways, act like these natural forces to control and direct the cascade of events that result in innate immunity.

NLRC5 interacts with two subunits of IKK to prevent their activation through blocking addition of a phosphate molecule (phosphorylation). This in turn, inhibits NF-κB activation and innate immune responses. NLCRC5 also interacts with innate immune receptors RIG-I and MDA5 to block type I interferon response.

When Wang and his colleagues "knocked down" or reduced the amount of the NLRC5 protein, both NF-κB and type 1 interferon activity increased, resulting in increased innate immune responses and antiviral immunity.

"Our findings identify NLRC5 as a key negative regulator that blocks two central components of the NF-κB and type I interferon pathways," said Wang. That makes it a key element in keeping the innate immune system running at just the right level.

Provided by Baylor College of Medicine