Study shows humans and plants share common regulatory pathway

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In findings that some might find reminiscent of science fiction, scientists at the Scripps Research Institute have shown for the first time that humans and plants share a common pathogen recognition pathway as part of their innate immune systems. The data could help shed fresh light on how pathogen recognition proteins function and the role they play in certain chronic inflammatory diseases.

The study was published in an advance online edition of the *Proceedings of the National Academy of Sciences* during the week of April 9, 2007.

The study provides new evidence that Nod1, a member of the Nod-like Receptor (NLR) protein family, is activated by the protein SGT1, which also activates Resistance (R) proteins in plants; R proteins protect plants from various pathogens. The study also confirms structural similarities between the Nod1 protein, which plays a pivotal role in the innate immune system's recognition and response to bacterial infection and members of the R protein family.

"There has been a great deal of speculation that R proteins and Nod1 are related, but our study provides the first direct link between plants and humans," said Richard Ulevitch, the Scripps Research scientist whose laboratory conducted the study. "Plants have Nod-like receptors and similar immune responses to bacteria and other pathogens-the R proteins evolved to counteract these pathogenic effects. Our study provides a new perspective on the Nod1 pathway in mammalian cells as well as the value of drawing on plant studies of R protein pathways to better understand

the pathogen recognition functions of these proteins."

The Nod proteins recognize invasive bacteria, specifically distinct substructures found in Gram-negative and Gram-positive organisms. Once activated, Nod1 produces a number of responses that include activation of intracellular signaling pathways, cytokine production and apoptosis or programmed cell death. Despite the fact that various models of Nod1 activation have been described, little has been known about other proteins that might affect the protein's activation. In contrast, a number of additional proteins have been linked to the activation pathways of the R protein in plants.

"The NLR family has clear links to human disease," Ulevitch said. "Out of the more than 20 proteins in the NLR family, several mutations are linked to diseases that involve chronic inflammation or autoimmune consequences. Up to now, there has been a limited understanding of the regulatory pathways of Nod1. By identifying SGT1 as a positive regulatory protein, our study offers new insights into the entire family."

SGT1 is a protein found in yeasts, plants, and mammals in both the nucleus and the cytosol. It functions in several biological processes through interaction with different multi-protein complexes. A large body of evidence also suggests that the protein plays a role in regulating pathogen resistance in plants. Various genetic studies have identified SGT1 as a crucial component for pathogen resistance in plants through regulation of expression and activities of some R proteins

Although there is a significant genetic crossover between plants and mammals, very little is known about this common human-plant regulatory pathway. Ulevitch speculated that certain protein regulatory structures might exist in both plants and humans simply because they do the same thing in much the same way.

"In reality," he said, "there are only so many ways to accomplish related biological responses."

The study also showed that a heat shock protein, HSP90, helped stabilize Nod1.

"Inhibiting HSP90 resulted in a significant reduction of Nod1 protein levels," Ulevitch said. "That clearly suggests that this protein plays a key role in stabilizing Nod1 and protecting it from degradation. In contrast, turning off SGT1 did not alter levels of Nod1."

In an earlier study, Ulevitch's laboratory reported that Nod1 also interacted with the COP9 complex, a multiprotein complex that is known to play a role in a number of development pathways in plants and that has a mammalian counterpart. This interaction, Ulevitch noted, provides a second link between Nod1 and plant R protein pathways.

"The association of Nod1 with SGT1 and the COP9 complex suggests that one possible role of SGT1 could be to target resistance-regulating proteins for degradation," he added. "In this hypothesis, the target protein would be a negative regulator of immune responses."

Future studies, Ulevitch said, will focus on the extensive literature that exists describing the R protein dependent immunity in plants to better understand human NLR pathways, especially those dependent on Nod1.

Source: Scripps Research Institute