Researchers discover how natural drug fights inflammation

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Researchers at the Virginia Bioinformatics Institute at Virginia Tech have discovered how abscisic acid, a natural plant hormone with known beneficial properties for the treatment of disease, helps fight inflammation. The results, which are published in the November 2010 *Journal of Biological Chemistry*, reveal important new drug targets for the development of treatments for inflammatory and immune-mediated diseases.

The scientists had reported some of the key molecular events in the immune system of mice that contribute to inflammation-related disease, including the involvement of a specific molecule found on the surface of immune cells involved in the body's fight against infection. They have now gone one step further and revealed the mechanism by which the natural drug abscisic acid interacts with this protein, known as peroxisome proliferator-activated receptor-gamma, to block inflammation and the subsequent onset of disease.

"In previous work, our research group demonstrated that abscisic acid has beneficial effects on several conditions and diseases including obesity-related inflammation, diabetes, atherosclerosis, and inflammatory bowel disease," said Josep Bassaganya-Riera, associate professor of immunology at the Virginia Bioinformatics Institute, leader of the Nutritional Immunology and Molecular Medicine Group in the institute's CyberInfrastructure Division, and principal investigator of the study. "One idea for how abscisic acid reduces inflammation in these instances is that it binds to a special region of peroxisome proliferator-

activated receptor-gamma, a binding site known as the ligand-binding domain where the drug would be expected to latch on to and exert its effect. Our results show that this is not the case and, for the first time, we have demonstrated that abscisic acid works independently of this ligand-binding domain of the receptor."

"This information is significant because it suggests the existence of new therapeutic targets or alternative modes of action that account for the effects of abscisic acid in the immune system," added Bassaganya-Riera. "Drugs that bind to the ligand-binding domain of peroxisome proliferator-activated receptor-gamma such as Avandia are associated with severe cardiovascular side effects. In contrast, the newly discovered alternative mechanism of peroxisome proliferator-activated receptor-gamma activation by abscisic acid does not appear to be linked to any known adverse side effects, thereby representing a promising new therapeutic avenue."

"The outcomes of this research illustrate the synergism that can result from combining computational and experimental approaches to characterize therapeutic targets", said David Bevan, associate professor of biochemistry at Virginia Tech. "By using molecular modeling approaches we were able to identify a potential binding site for abscisic acid on the lanthionine synthetase C-like 2 protein, a protein required for the beneficial health effects of abscisic acid. We were also able, again using docking studies, to reveal reasons for the lack of direct association of abscisic acid with peroxisome proliferator-activated receptor-gamma, which was experimentally validated by ligand-binding assays."

"Lanthionine synthetase C-like 2 represents the first step in a pathway leading to activation of peroxisome proliferator-activated receptor-gamma in immune cells by abscisic acid," said Raquel Hontecillas, assistant professor of immunology at the Virginia Bioinformatics Institute and one of the lead investigators of the study. "We have also

shown that abscisic acid affects the expression of several genes involved in inflammation, metabolism and cell signaling, which provides further clues for possible intervention points in the treatment of inflammatory and immune-mediated diseases."

The researchers hope to more closely pinpoint some of the new drug targets in the molecular network of the immune response as they continue to dissect the way that the naturally occurring drug abscisic acid reduces damage due to inflammation. In addition, the novel understanding on how abscisic acid works will be used to develop new classes of drugs that target the same alternative pathway of peroxisome proliferator-activated receptor-gamma activation, a potentially safer approach than the use of drugs that target direct binding to the receptor.

Provided by Virginia Tech