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Scientists solve longtime mystery in innate immunity

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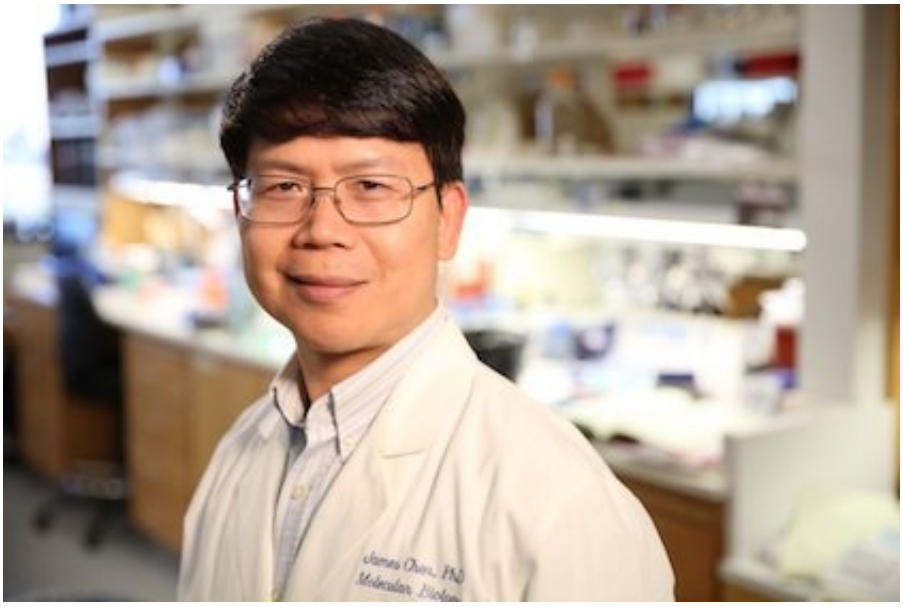

Dr. Zhijian 'James' Chen. Credit: UT Southwestern

UT Southwestern biochemist and Breakthrough Prize winner Dr. Zhijian "James" Chen's newest study answers a long-standing question in the field of innate immunity.

Scientists have long wondered how one protein, NLRP3, can promote inflammation in response to a wide range of seemingly unrelated stimuli.

Dr. Chen, Professor of Molecular Biology and Director of UT

Southwestern's Center for Inflammation Research, this month received the 2019 Breakthrough Prize in Life Sciences for identifying the DNA sensing enzyme cGAS (cyclic GMP-AMP synthase), which sounds the alarm to set off an innate immune response inside cells.

In the current study, published today in *Nature*, Dr. Chen investigated another immune system pathway that involves the NLRP3 protein, which is instrumental in the cell's assembly of the multiprotein complex called the inflammasome. In response to a plethora of noxious agents that range from toxins to cholesterol crystals, the inflammasome triggers the pathway for inflammatory cell death, or pyroptosis from the Greek word pyro, meaning fire. The inflammasome also increases the body's production of immune system substances, such as interleukins, that aid in the body's immune response.

In addition, the NLRP3 protein underlies inflammation in a group of autoinflammatory diseases called cryopyrin-associated periodic syndromes (CAPS), which includes familial cold autoinflammatory syndrome (FCAS), gout, and a form of brain-cell inflammation associated with Alzheimer's disease.

"A long-standing question in this field is how NLRP3 can be activated by many diverse agents that don't appear to share any chemical or structural similarities," said Dr. Chen, a Howard Hughes Medical Institute Investigator who holds the George L. MacGregor Distinguished Chair in Biomedical Science as well as a professorship in the Center for the Genetics of Host Defense at UT Southwestern. "These findings provide a new avenue for developing therapeutics that target the NLRP3 pathway for the treatment of inflammatory diseases."

Through a combination of biochemical, imaging, and genetic approaches, Dr. Chen and postdoctoral researcher Dr. Jueqi Chen, the study's lead author and no relation, discovered a previously unknown

structural change within the cells.

They found that diverse stimuli all cause the cellular organelle called the trans-Golgi network (TGN) to break apart into giant vesicles, or fluid-filled sacs. These vesicles contain a special lipid component (PI4P) that binds to a specific region of NLRP3. This binding triggers a series of events leading to activation of the inflammasome.

"The NLRP3 inflammasome is unique in that it can be triggered by a large array of stimuli," Dr. Chen said. "This study finds that rather than directly recognizing the noxious agents, the NLRP3 inflammasome detects a structural change caused by a range of different agents that cause cellular damage. In fact, NLRP3 activation is reminiscent of the 'guard model' that plants use to combat diverse threats by monitoring host targets that have been altered, the so-called pathogen-induced-altered-self approach.

"By binding to the disassembled trans-Golgi network vesicles as the 'altered self,' NLRP3 indirectly senses a large variety of pathogen- and danger-associated molecules," he added.

More information: Jueqi Chen et al. PtdIns4P on dispersed trans-Golgi network mediates NLRP3 inflammasome activation, *Nature* (2018). DOI: 10.1038/s41586-018-0761-3

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