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Understanding the structure of the TAL effector may be key for targeted gene correction

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Researchers at Fred Hutchinson Cancer Research Center have solved the three-dimensional structure of a newly discovered type of gene-targeting protein that has shown to be useful as a DNA-targeting molecule for gene correction, gene therapy and gene modification. The findings are published online in *Science Express* on Jan. 5.

Using a unique form of computational and X-ray crystallographic analyses, a team of researchers led by Barry L. Stoddard, Ph.D., a member of the Basic Sciences Division at the Hutchinson Center, has determined the structure of a protein called a "TAL effector," which stands for "transcription-activator-like effector."

"These proteins have a LEGO-like, modular architecture that allows them to easily be reshuffled and engineered for DNA targeting," Stoddard said. "The upcoming years will see an explosion in the development and use of TAL effectors – and more complicated molecules that are built around TAL structures – for targeted gene modification, genetic engineering and corrective gene therapy."

TAL proteins exist only in Xanthomonas, a type of gram-negative bacteria that can infect soybeans, tomatoes, peppers, rice and citrus plants, among other species. Although in nature bacteria use these proteins to target specific sites in plant DNA, they have the potential to be used in a clinical setting to help humans, Stoddard said.

"In biotechnology and medicine TAL effectors can be used by scientists to seek out and bind to DNA targets in any organism of choice, including genes in humans that contain disease-causing mutations that we might want to correct," Stoddard said, referring to a field known as "targeted gene correction," which requires the development of molecules that can be delivered directly to a single DNA site. "TAL effectors have this unique capability and can be harnessed for such uses," he said.

Since their discovery, TAL effectors have been intensely studied for gene modification applications and have been commercialized by several companies around the world. "However, until now, the lack of structure has greatly impeded the further development and improvement of TAL effectors for genetic engineering and correction," Stoddard said.

Solving the structure of the TAL effector protein allows scientists to see exactly how the protein binds to its DNA target and exactly what types of contacts it makes to the DNA in order to recognize and "read" each base in the DNA sequence. "By determining the structure, it is now possible to engineer the protein to work more effectively in a variety of biotech or medical applications, either by changing its DNA-targeting specificity, making the protein more stable or longer lived in cells, or by understanding how to attach additional protein modules to it that can drive desired changes in the DNA target," Stoddard said.

The research was conducted in collaboration with computational biologist Philip Bradley, Ph.D., an assistant member of the Hutchinson Center's Public Health Sciences Division, who specializes in the computer modeling of proteins; Amanda Nga-Sze Mak, Ph.D., a postdoctoral fellow in Stoddard's lab; Adam Bogdanove, Ph.D., a professor of plant pathology and microbiology at Iowa State University, who discovered many of the properties of the TAL proteins; and Raul Cernadas, Ph.D., a postdoctoral research associate in Bogdanove's lab.

More information: "The Crystal Structure of TAL Effector PthXo1 Bound to its DNA Target", *Science Express*, AOP (2012).

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