Keeping harmful bacteria from progressing

July 8 2009

(PhysOrg.com) -- Researchers from the University of Wyoming and an institute in Germany have completed a project that, for the first time, has identified how sunlight changes activity of a particular class of proteins called BLUF domain photoreceptors. BLUF is short for Blue Light Using Flavin adenine dinucleotide.

The research could lead to developments that could help keep harmful bacteria from progressing to a state in which they can become 10,000 times more resistant to antibiotics.

The team published a paper in the June 18 edition of *Nature* journal.

Associate Professor Mark Gomelsky led the UW College of Agriculture's Department of Molecular Biology team. Two of the department's Ph.D. graduates, Natasha Kirienko and Dmitri Ryjenkov, both of Russia, are co-authors.

"My group asks very basic questions about how bacteria interact with their environment," Gomelsky said. "We believe applications of this knowledge for human health can be profound."

While traditional treatment of infectious diseases has been to kill the bacteria, Gomelsky believes researchers need to learn how to control bacterial behavior to modify the progression of infectious diseases.

Seven scientists from the Max Planck Institute for Medical Research (MPIMR) in Heidelberg, Germany, collaborated in the research and co-

wrote the paper. The MPIMR team was headed by the institute's director, Ilme Schlichting, who was the lead author with Gomelsky.

Gomelsky, who recruited Kirienko and Ryjenkov to UW from Russia, said publishing a paper in Nature is very prestigious, and he noted this is the first time in more than five years UW students have been co-authors of an article in the journal.

Kirienko earned her doctorate degree in 2008 and is a post-doctoral researcher in the laboratory of UW molecular biology department Associate Professor David Fay.

Ryjenkov earned his Ph.D. in 2006 and is a research scientist at a ChemDiv Inc. facility in Moscow. ChemDiv is a U.S.-Russia biotechnology company with headquarters in San Diego.

"These were outstanding students whose contributions were critical for this study," Gomelsky said.

He added, "The Nature paper is a result of a long-term and very fruitful collaboration. Our two groups share similar interests and have complementary expertise. Without the constant exchange of ideas and expertise, neither of our groups would have been able to accomplish as much."

Gomelsky said the paper describes an X-ray structure and mechanism of one protein, BlrP1, whose activity is regulated by light. BlrP1, which belongs to the BLUF class of light-sensing proteins, is short for blue light regulated protein 1.

"Until this study, it has been unknown how light changes activities of BLUF proteins," said Gomelsky, who coined the term BLUF in 2002 for a protein module he first found in another protein.

"The current study has elucidated how absorption of a single photon by the light-sending BLUF domain results in the changes in positions of various structural elements of the BlrP1 protein that ultimately change its phosphodiesterase activity," said Gomelsky, who explained that phosphodiesterase is a class of enzymes.

He added, "This is a significant advance that greatly increases our understanding of how light changes protein confirmation. Someday we will learn enough to start using this knowledge for design of light-regulated proteins of our choice."

The technology, he said, could greatly improve the understanding of protein function under normal conditions and in diseases.

"Light-regulated proteins could revolutionize biomedical research," he said. "The possibility of using protein light switches to engineer photoreceptors has already been realized using other, much more extensively studied, photoreceptor types. Our paper brings protein engineering based on the BLUF domain photoreceptors closer to reality."

Gomelsky said there is a second important advance reported in the paper, and it concerns the output phosphodiesterase activity of the protein BlrP1.

"Our research shows, for the first time, how a phosphodiesterase of this particular class, called EAL domain phosphodiesterase, functions at the atomic level," he said. EAL is an amino acid sequence that defines this class of phosphodiesterases.

BlrP1 breaks a particular phosphorous-oxygen bond in a molecule called c-di-GMP, or cyclic dimeric guanosine monophosphate.

"C-di-GMP has emerged as a key messenger utilized by various bacteria for making a critical, life-changing decision, i.e. whether to stay a single cell that moves spontaneously or to settle down on a surface and start a colony," Gomelsky said.

"If we could effectively manipulate c-di-GMP level in bacteria, we would be able to make that decision for them. We could 'command' them to either stay single or to form a colony, dependent on which way is useful for us in a particular setting," he said.

"For example, most infectious bacteria colonize surfaces of internal organs and tissues and form biofilms (bacterial cells growing in extracellular matrices that they make). Once a biofilm is formed, it is hard to completely eradicate it with antibiotics because biofilm-grown cells can be 10,000 times more resistant to antibiotics than single cells," Gomelsky said.

"If one can prevent bacteria from forming a biofilm in the first place by administering certain drugs that would lower their c-di-GMP levels, then we can trick them to stay single, and the infection would not progress to the biofilm stage."

For more information about the research, see the paper at www.nature.com/nature/journal/ … abs/nature07966.html .

Provided by University of Wyoming