Flemish researchers provide the first experimental evidence of dynamic allostery in protein regulation

July 9 2010

The brand-new Jean Jeener Bio-NMR Center at the VIB Department of Molecular and Cellular Interactions, Vrije Universiteit Brussel, has already played a role in a scientific breakthrough that made it into the leading science journal *Cell*. Thanks to NMR technology, it is possible to determine the dynamic structure of proteins. So Flemish scientists put it to use to find out how the activity of certain proteins involved in the stress physiology of bacteria is regulated. This is a first in every way.

Proteins play a major role in the billions of processes that occur in the body, including the development of muscle and skin, the digestion of food, the growth of cells and the generation of human emotions. Our cells continuously produce proteins, but how these complex molecules exactly function is by and large not well understood.

Not only the chemical composition but also the spatial structure of proteins is important for the performance of their functions. The ways in which they fold and unfold in three-dimensional space help determine the function of the molecules. So, without detailed knowledge about their structure, our understanding of their function usually remains partial. However, studying the spatial structure of proteins is anything but easy.

NMR is a promising technique for determining the structure of proteins in solution. Unlike X-ray diffraction - long the standard for determining

the structure of proteins - NMR equipment can provide dynamic structure information. Even vibrations and rotations of molecules on an atomic scale can be visualized. The Bio-NMR center at the VIB Department of Molecular and Cellular Interactions, Vrije Universiteit Brussel, only opened May 7, 2010, but its 600-MHz and 800-MHz spectrometers have already helped produce a first article in a top journal.

Regulation of gene transcription is a mechanism that allows cells to adapt to rapidly changing environmental conditions. In prokaryotes, genes are typically clustered in operons with each operon being regulated as an entity. The toxin-antitoxin (TA) system, which plays a role in stress, is one instance of this process.

Abel Garcia-Pino and his colleagues study the Phd-Doc toxin-antitoxin operon of P1 bacteriophages (small viruses) under the leadership of Remy Loris. Until now, no one has been able to explain the regulatory mechanism of this system at the molecular level. Hence, these VIB researchers are the first to demonstrate that, when Doc binds to the intrinsically unfolded C-terminus of Phd, it structures the DNA-binding domain of Phd. This type of communication process between two protein domains is called allostery. Already in the sixties allostery was generally assumed to be an important regulation mechanism in enzymes and Monod even called it the second secret of life (the first one being the genetic code). Several years ago, allostery between intrinsically unfolded protein domains became accepted, based on theoretical models, but now it has been experimentally demonstrated for the first time. The regulation mechanism presented here is new and probably also applies to other genes.

The NMR technology is the only technology that can detect and quantify folding and conformational changes in proteins while simultaneously providing detailed structural information. Besides its applications in fundamental biology, NMR is also a promising technology for the

identification of therapeutic drugs.

Provided by Flanders Institute for Biotechnology