Scientists crack mystery of protein's dual function

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Researchers at The Scripps Research Institute have solved a 10-year-old mystery of how a single protein from an ancient family of enzymes can have two completely distinct roles in the body. In addition to providing guidance for understanding other molecules in the family, the research supplies a theoretical underpinning for the protein's possible use for combating diseases including cancer and macular degeneration.

The research was published in the December 13, 2009 advance, online issue of the high-impact journal Nature Structural and Molecular Biology.

The scientists, led by Scripps Research Associate Professor Xiang-Lei Yang, focused on a molecule called human tryptophanyl-tRNA synthetase (TrpRS), finding that it contains a "functional switch" that enables it to perform two different functions. In one of its forms, the molecule acts to facilitate protein synthesis. In the second form, the same molecule works to inhibit the formation of new blood vessels—an effect that, if successfully harnessed, could be medically useful.

"I'm very excited about these findings," said Yang. "This piece of work provides a very deep mechanistic understanding. It has really shown that the activity of this tRNA synthetase is of biological significance and that it's a good example of the many, many different functions that have been found with the tRNA synthetase family."

One Enzyme, Two Functions

For some time, scientists have known that the aminoacyl tRNA synthetase family is composed of 20 ancient enzymes that attach the correct amino acid to a tRNA as the first step in the synthesis of proteins.

The mystery of the protein family's dual functionality, however, was born about a decade ago, with the publication of a 1999 paper in the journal Science by Paul Schimmel, who is Ernest and Jean Hahn Professor of Molecular Biology and Chemistry and a member of The Skaggs Institute for Chemical Biology at Scripps Research, in collaboration with a member of his lab at that time, Keisuke Wakasugi.

In the 1999 paper, Wakasugi and Schimmel showed that a member of the human aminoacyl-tRNA synthetase family, tyrosyl-tRNA synthetase (TyrRS), did more than adding the amino acid tyrosine to a protein chain during protein synthesis. In addition, a fragment of the protein could function to attract immune cells and to stimulate the growth of blood vessels.

The findings were met with astonishment and some skepticism in the scientific community.

Soon afterward, however, the Schimmel lab showed that another member of the family, TrpRS, also had a dual function. In addition to its role adding the amino acid tryptophan to a protein chain during protein synthesis, a fragment of TrpRS could inhibit new blood vessel formation.

Since that time, there has been considerable therapeutic interest in TyrRS, TrpRS, and other members of the aminoacyl-tRNA synthetase family. As a pro-angiogenic factor, the TyrRS fragment could be useful in diseases where growth of blood vessels is desirable, such as in some forms of heart disease or peripheral artery disease. Likewise, the TrpRS fragment's anti-angiogenic effects could help patients reduce undesirable blood vessel growth in diseases such as cancer and a great many eye diseases that lead to catastrophic vision loss.

In fact, fragments of TrpRS were used as part of a study led by Scripps Research Professor Martin Friedlander that successfully halted the progression in animal models of highly vascular brain tumor and neovascular eye disease (*PNAS* 2007 104:967-972).

Despite the interest in tRNA synthetases, however, no one has been able to figure out exactly how they perform their different roles—until now.

Mystery Mechanism Revealed

In the current study, the research team used a combination of techniques including structural modeling analysis, mutagenesis, and cell-based functional studies to unravel the secrets of TrpRS.

The scientists identified the specific molecular changes that enabled TrpRS to perform one function or another.

In the study, the scientists show that, for its role in protein synthesis, TrpRS is typically in its full-length form. This form of the molecule contains a tryptophan-binding pocket that enables it to bind with the amino acid and shepherd it to where it is needed in protein synthesis.

In the second active form, however, the protein must first be broken into fragments by the body, creating a piece called T2-TrpRS. With the removal of the end of the full-length protein (the N-domain), new grooves in the T2-TrpRS protein fragment are revealed. Containing the now-exposed tryptophan-binding pocket, the grooves fit together with side chains of another molecule, VE-cadherin—known to be indispensable for proper vascular development.

Interestingly, the new study found that tryptophan acts to inhibit of the vasculature function of TrpRS, locking the protein into its protein-synthesis form.

Therapeutic Potential

Yang notes that the therapeutic potential of TrpRS and other tRNA synthetases are particularly good because they normally exist in abundant amounts in the body.

"Naturally, you'd imagine the body's tolerance for such a protein is pretty good," she said, "and we could use the activated form of the molecule."

In addition, Yang points out that TrpRS is intriguing because it does not effect existing blood vessel growth, only new blood vessel formation, reducing the odds of negative side effects from its use.

More information: "Orthogonal use of a human tRNA synthetase active site to achieve multifunctionality," Quansheng Zhou et at., *Nature Structural and Molecular Biology*

Source: The Scripps Research Institute (news : web)