Press release

14. Juli 2011

How the protein U2AF builds mRNA for protein production:

New mechanism in the regulation of human genes

In order to create proteins, the protein-coding gene must be transcribed into RNA and in the so-called splicing* process shortened to the correct template. Scientists at the Technische Universitaet Muenchen (TUM) and the Helmholtz Zentrum Muenchen have now discovered how the U2AF protein enables this process. The results have been published in the current edition of the renowned scientific journal *Nature.*

Scientists at the Technical University of Munich and the Helmholtz Zentrum Muenchen and along with their colleagues from the European Molecular Biology Laboratory (EMBL) in Heidelberg and the Centre for Genomic Regulation in Barcelona have discovered how the U2AF protein enables the pre-mRNA* to be spliced to form the mRNA*, which serves as a template for protein synthesis in the body.

Splicing requires the cooperation of different proteins, i.e. splicing factors. One such splicing factor, U2AF, was examined by the Munich scientists. It consists of two structural modules and binds to the RNA near the intron*-exon* boundary. Professor Michael Sattler, Director of the Institute for Structural Biology at the Helmholtz Zentrum Muenchen and Professor of Biomolecular NMR Spectroscopy at the Technische Universitaet Muenchen, summarizes how the U2AF protein contributes towards splicing: “The spatial structure of the U2AF protein alternates between a closed and an open conformation. A matching RNA sequence in the intron causes the U2AF to assume an open conformation, which activates splicing and eventually leads to the removal of the intron.”

The intron’s RNA sequence determines how effectively this conformational change can be triggered. This shift of balance between the closed and the open form of the U2AF protein occurs through a process of conformational selection, i.e. the RNA binds to a small fraction of the open conformation that already exists even in the absence of RNA. The scientists presume that similar mechanisms – balanced between a closed, inactive and an open, active conformation – play an important role in the regulation of many other signal pathways in the cell.

Background

The genes in the human genome have a specific structure. Sections with relevant exons alternate with regions known as introns, which contain irrelevant information that does not encode the corresponding protein. In order for a protein to be produced, pre-messenger RNA

Technische Universitaet Muenchen Corporate Communications Center 80290 Munich, Germany www.tum.de
Dr. Ulrich Marsch Head of Corporate Communications +49 89 289 22778 marsch@zv.tum.de
Dr. Andreas Battenberg PR Campus Garching +49 89 289 10510 battenberg@zv.tum.de

(pre-mRNA) first has to be transcribed from the DNA. The pre-mRNA copy is then spliced and the introns are removed, leaving the mRNA; which consists solely of exons. Splicing requires that the introns recognized and accurately excised. Splicing is thus an essential process in the central dogma of molecular biology: genetic information flows in one direction: from the DNA to RNA to proteins.

* Genome / gene / DNA / mRNA: Genes are the basis for the synthesis of proteins. In the first step, desoxyribonucleic acid (DNA) is transcribed to form a messenger ribonucleic acid (messenger RNA or mRNA), which in turn provides a template for protein synthesis. An organism's complete set of DNA is known as a genome.
* Splicing / exons / introns / (pre-) mRNA: Exons are the DNA sections that encode the amino acid sequence of a given protein. The introns, which lie between the exons, are removed in the splicing process. The pre-mRNA thus is processed to a more mature mRNA.

This work has been supported by funds from the European Union (3D Repertoire, Functional and Structural Genomics of Viral *RNA,* Alternative Splicing Network of Excellence, NIM3*),* the European Molecular Biology Organization (EMBO), the Institut de Chimie des Substances Naturelles (ICSN) and the Conseil régional d'Aquitaine (France), the Austrian Science Fund (FWF), the American Institute for Cancer Research (AICR) and the Spanish Fundación Marcelino Botín. The EU NMR LSF in Frankfurt and the Bavarian NMR Centre (BNMRZ) in Munich provided NMR measurement time. Prof. Michael Sattler is member of the Cluster of Excellence Center for Integrated Protein Science Munich (CIPSM).

Original publication:

Cameron D. Mackereth, Tobias Madl, Sophie Bonnal, Bernd Simon, Katia Zanier, Alexander Gasch, Vladimir Rybin, Juan Valcárcel, Michael Sattler
Multi-domain conformational selection underlies pre-mRNA splicing regulation by U2AF, Nature, Advanced online publication 13. Juli 2011 – DOI: 10.1038/nature10171
Link: http://www.nature.com/nature/journal/vaop/ncurrent/full/nature10171.html

Technische Universitaet Muenchen Corporate Communications Center 80290 Munich, Germany www.tum.de

Dr. Ulrich Marsch	Head of Corporate Communications	+49 89 289 22778	marsch@zv.tum.de
Dr. Andreas Battenberg	PR Campus Garching	+49 89 289 10510	battenberg@zv.tum.de

The Entrepreneurial University.

Technische Universität München

Contact:

Prof. Dr. Michael Sattler
Technische Universitaet Muenchen
Chair of Biomolecular NMR Spectroscopy
Lichtenbergstr. 4, 85748 Garching, Germany
Tel.: +49 89 289 13418 – Fax: +49 89 289 13869
E-mail: michael.sattler@ch.tum.de

The **Helmholtz Zentrum Muenchen** is the German Research Centre for Environmental Health. The leading research facility in this field, it conducts research into chronic and complex diseases caused by the interaction of environmental factors and an individual's genetic disposition. The Helmholtz Zentrum Muenchen has about 1,700 staff members and is headquartered in Neuherberg in the north of Munich on a 50-hectare research campus. The Helmholtz Zentrum Muenchen is a member of the Helmholtz Association, Germany's largest scientific organisation, a community of 17 scientific-technical and medical-biological research centres with a total of 30,000 staff members. www.helmholtz-muenchen.de

With around 460 professors, 7,500 staff (including Klinikum rechts der Isar) and 26,000 students, **Technische Universitaet Muenchen (TUM)** is one of Europe's leading technical universities. Its main focus areas are the engineering sciences, natural sciences, life sciences medicine and economics. It has received numerous awards and was voted University of Excellence by the Science Council of the German Research Foundation in 2006. The worldwide TUM network includes a branch in Singapore. The TUM is committed to pursuing the role model of an entrepreneurial university. http://www.tum.de

Technische Universitaet Muenchen Corporate Communications Center 80290 Munich, Germany www.tum.de

Dr. Ulrich Marsch	Head of Corporate Communications	+49 89 289 22778	marsch@zv.tum.de
Dr. Andreas Battenberg	PR Campus Garching	+49 89 289 10510	battenberg@zv.tum.de