'Decoding' gene regulation

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A recent discovery in alternative splicing provides fundamental insights into gene regulation and alternative splicing evolution

Researchers at the Max F. Perutz Laboratories of the University of Vienna and the Medical University of Vienna as well as at the University of Natural Resources and Life Sciences (BOKU) in Vienna have discovered an entirely new aspect of gene regulation they call exitron splicing. Their findings, recently published in the renowned scientific journal *Genome Research*, will help to explore the adaptive evolution of gene regulation. Furthermore, the discovery sets a basis for the development of cancer biomarkers and therapeutic targets.

Alternative splicing is a key step in controlling gene expression and is a

major source of diversity in the proteome of higher organisms. In many genes, information for proteins encoded by exons is interrupted by regions called introns. During alternative splicing, introns are removed and exons are joined in different combinations. Through this mechanism, the information stored in the genes can be processed in a variety of ways, making it possible for a single gene to produce two or more distinct proteins. About 95% of human and 61% of Arabidopsis (thale cress) genes are alternatively spliced.

This process not only explains the compact nature of the genetic information, but it is also linked to numerous human diseases including cancer. Therefore, alternative splicing events are promising targets for clinical diagnosis and therapeutic intervention. No wonder that understanding the functional impact of alternative splicing and its evolution has become one of the most challenging tasks for biological and medical research.

The group of Andrea Barta at the Max F. Perutz Laboratories (MFPL) of the Medical University of Vienna and Maria Kalyna at the BOKU in Vienna now report a novel type of alternative splicing event they call exitron splicing.

"Exitrons are internal parts of protein-coding exons that are hidden in the exonic sequence and that are alternatively spliced. They combine features of both exons and introns," explains Yamile Marquez, a postdoc in the group of Andrea Barta at the MFPL and first author of the paper. "By analyzing data sets of the model plant Arabidopsis and different human organs and cancer samples, we could demonstrate that exitron splicing is a conserved mechanism among eukaryotes," says Maria Kalyna, the corresponding author, who has been working in the group of Andrea Barta and is now a principal investigator at the BOKU. "We could also show that exitron splicing in humans occurs in many important genes, including those involved in the development of breast

cancer," adds Maria Kalyna.

Taken together, the study is of fundamental importance for understanding the mechanisms of alternative splicing and adaptive evolution of gene regulation. It also opens new avenues in combating diseases through the development of novel therapeutic targets and diagnostic tools.

More information: "Unmasking Alternative Splicing Inside Protein-Coding Exons Defines Exitrons and their Role in Proteome Plasticity." In: *Genome Research* (Mai 2015).
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