Extensive protein interaction network controls gene regulation

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The genes of a cell are like the 88 keys of a piano. To play chords and music, however, the keys must be activated in exact combinations by a pianist's hands. Those hands represent the coregulators of a cell that simultaneously and precisely activate genes to produce all of the cell's functions.

More than half of your DNA is devoted to regulating how the genes that make proteins – the workhorses of the cells – carry out their tasks, said Dr. Bert O'Malley, who, with Dr. Jun Qin, co-led a team of scientists at Baylor College of Medicine that over eight years identified and classified virtually all the transcriptional coregulators in a human cells. These coregulators – coactivators and corepressors – control how and to what degree genes are turned on or off as well as when they are active and for how long. The more than 11,000 coregulators identified – the focus of O'Malley's work for more than 15 years – form and act in approximately 3,000 multi-protein complexes that function in the human cell. A report on their work appears in the current issue of the journal *Cell*.

"Genes are how we inherit our capacities," said O'Malley, chair of molecular and cellular biology at BCM and a National Medal of Science recipient. "The DNA functions by first coding for the synthesis of RNAs (another form of genetic material), which in turn, directs the synthesis of proteins in the cells. Proteins are the final functional units emanating from the genes. They carry out all the biochemical reactions needed for a cell to live, grow and function. Coregulators are the helper proteins that

actually decode the information in our genes."

"Surprisingly, we found that over half of our total DNA is used simply to create the immense number of coregulators that, in turn, regulate the expression of our genes. This indicates that 'precise regulation' in decoding genes is an absolutely mandatory rule in human cells, and that this occurs via the coregulator proteins," he said.

Dr. Ronald Margolis, senior advisor for molecular endocrinology at the National Institute of Diabetes and Digestive and Kidney Diseases — the division within the National Institutes of Health that supported the research—said the findings provide an important new tool for further research into endocrine and metabolic diseases such as diabetes and osteoporosis.

"Ultimately this work gives us new and important insights that are key to understanding how and why all types of hormones work the way they do," he said. "It's just this kind of basic research that provides the foundation for new diagnostics, therapies and devices."

Qin, professor in the departments of biochemistry and molecular biology and molecular and cellular biology at BCM, is a world expert in mass spectrometry, the backbone technique that enabled the scientists to identify and analyze the proteins and protein complexes.

Qin said the vision of Drs. O'Malley and Adam Kuspa, chair of biochemistry and molecular biology at BCM, enabled him to take the bold step of analyzing these proteins and determining how they work together – a massive project that provides a blueprint of knowledge on which to build new understanding of how proteins work and how their malfunctions result in disease.

"A curious journey sometimes can land on the right place," said Qin.

He credits Dr. Anna Malovannaya, who came to his laboratory as a graduate student, with developing the techniques that made it possible not only to identify the proteins but to figure out which ones work together and how.

"Determining the composition of the proteome – the entire set of proteins produced by a genome – does not tell you how it all works," said Malovannaya.

"Proteins work in groups. This study does not just profile them. It also tells how they interact with one another," Qin said.

"The way we looked at it was new," said Malovannaya. "We had to build new tools for grouping proteins into functional complexes and figure out which ones were important."

Achieving that took thousands of experiments. When they had done about 1,000 experiments, the answers became clearer, said Qin.

The Nuclear Receptor Signaling Atlas (NURSA) was the catalyst for the work, said Qin. O'Malley and Dr. Ronald Evans of the Salk Institute are co-directors of the project that is funded by the National Institute of Diabetes and Digestive and Kidney Diseases.

O'Malley and his colleagues were surprised by the fact that more than half of all human DNA goes into producing the coregulators that decode genes, but in retrospect, it makes sense. They expected to find about 500 genes for directing the synthesis of coregulators and, instead, identified more than 11,000.

"The regulation of gene expression is complex," O'Malley said. "It is critical that genes turn on at the right time, in the exact right amount and under the right condition. If a gene makes 10 percent too much or too

little of a protein, then the person develops a disease or functions poorly."

"It's all about accurate regulation and combinatorial regulation," he said. "Many hundreds of genes must be regulated together at precisely the same time. The cell is a master at that. Every gene has to function perfectly for a cell to work correctly – and the coregulators make it happen. It is one of the most amazing events biologists have discovered – beautifully complex and fine-tuned."

The eight-year project is of a magnitude similar to that of sequencing the genome, but "now we have determined the composition of the coregulator proteome," said O'Malley. Synthesis of the proteome is directed by the genome. Which proteins are produced and at what time depend on the type of cell and the functions of its coregulators. Malovannaya and Dr. Rainer B. Lanz, assistant professor, both in the department of molecular and cellular biology, were first authors of the *Cell* paper and contributed equally to the research.

More information: www.cell.com

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