Researchers discover key aspect of process that activates breast cancer genes

November 15 2011

Researchers at the Keck School of Medicine of the University of Southern California (USC) have discovered key processes by which estrogen, the female sex hormone, activates genes in breast-cancer cells. Greater understanding of how this occurs is expected to eventually lead to new treatments for the disease.

Michael R. Stallcup, Ph.D., professor and chair of the Keck School's Department of Biochemistry and Molecular Biology, was the senior author, and Kwang Won Jeong, Ph.D., a postdoctoral student in Stallcup's lab, was the first author of the paper, "Recognition of enhancer element-specific histone methylation by TIP60 in transcriptional activation." It was published online in the research journal *Nature Structural & Molecular Biology* on Nov. 13.

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The researchers found that a protein, TIP60, recognizes when a common chemical process called methylation occurs in chromatin, the material that enfolds all genes. Methylation controls how genes are folded in the complex structure of chromatin, which determines whether the genes are active or inactive. The researchers discovered that after recognizing the methylation signal, TIP60 then binds to the signal, connecting TIP60 to

the chromatin and then changing the chromatin's structure, which helps to activate the gene. The methylation that TIP60 recognizes is generated by another protein, MLL1.

"It's like when you're in your car and come to a red light," said Stallcup. "The light doesn't make you stop, but it is a signal that you have to interpret and then decide to stop. In this case, the methylation modification that TIP60 recognizes is one of those signals, and then TIP60 acts on that signal."

The findings build upon previous work of Stallcup's lab. Earlier published research revealed that the methylation of chromatin and other proteins plays many important roles in controlling the activities of genes.

While the recent findings are significant, Stallcup stressed that there is much more to be discovered.

"We want to understand more about other steps in the process of gene activation," Stallcup said. "In particular, we're interested in the function of the MLL1 protein because we think it plays a key role in controlling chromatin structure and folding, which we think is critical for activation of genes by estrogen."

Stallcup also noted that estrogen regulates just a few hundred of the tens of thousands of genes in every human cell, but that the research has broader implications.

"While the process we're studying is the regulation of gene activity by estrogen, the findings have potentially global significance,,because the methylation modification of chromatin that TIP60 recognizes is found in all active and potentially active genes in human cells," Stallcup said.

Provided by University of Southern California