Opening and closing the genome

February 22 2007

At any given time, most of the roughly 30,000 genes that constitute the human genome are inactive, or repressed, closed to the cellular machinery that transcribes genes into the proteins of the body. In an average cell, only about one in ten genes is active, or expressed, at any given moment, with its DNA open to the cell' transcriptional machinery.

A dynamic cast of gatekeeper enzymes controls this access to the DNA, adding and removing particular molecules to open or close the genome to transcription as needed. Fully explicating the complex interplay among these enzymes and the molecules they manage has been a primary goal for scientists seeking to understand the mechanisms governing gene control. These mechanisms are vital for health-- when they go wrong, diseases like cancer can result.

In study published online February 22 in *Cell*, researchers at The Wistar Institute identify an important new player in this gene-control system, an enzyme responsible for removing certain molecules, or marks, involved in opening or closing chromatin, the material that makes up chromosomes. The activity of this enzyme is thought to be widespread in the genome, likely affecting many genes.

"This enzyme removes methyl groups from a specific location where they facilitate opening of the chromatin for gene expression, and therefore this enzyme maintains a repressed state of gene expression," says Ramin Shiekhattar, Ph.D., a professor at The Wistar Institute and senior author on the Cell study. Currently, Shiekhattar is also a professor at the Center de Regulacio Genomica in Barcelona. "When the enzyme

is not present, however, the marks are not removed, and the chromatin remains open for transcription."

The enzyme, called JARID1d, is the first identified member of a new family of enzymes that removes trimethylation from histone H3 at the lysine 4 location. Histones are critical components of chromatin. In mammalian genomes, trimethyl groups at the lysine 4 location of this histone have been known to be associated with gene activation. Shiekhattar and his team hypothesized the existence of an enzyme that would remove these trimethyl groups.

"We and others had wondered whether there might not be an enzyme able to remove these trimethyl marks," says Shiekhattar. "Such an enzyme would have the effect of setting the genes back to their original repressed state."

An important aspect of the work by Shiekhattar and his colleagues is their demonstration of an intimate connection between the histone demethylase enzyme JARID1d and Ring6a, a polycomb-like protein. Polycomb proteins are also known to play an important role in gene repression. Indeed, the findings show that Ring6a has the ability to regulate the enzymatic activity of the histone demethylase in vitro as well as in vivo. These results extend the role of transcriptional inhibitory polycomb complexes through their physical and functional link with histone demethylase enzymes.

Source: The Wistar Institute