Modifications to chromosomal proteins help ensure that brain-specific sugars are produced only in appropriate tissues

December 16 2011

Credit: AI-generated image (disclaimer)

Many proteins are adorned with carbohydrate chains called glycans that can dramatically alter their stability, localization or function. These diverse sugars are assembled and modified by a variety of glycosylating enzymes, with some glycans exclusively manufactured within specific

organs or tissues.

The β1,6-branched O-mannosyl glycan appears only in the mammalian brain. Naoyuki Taniguchi's team at the RIKEN Advanced Science Institute in Wako recently characterized the enzyme, N-acetylglucosaminyltransferase IX (GnT-IX, also called GnT-Vb) that produces this particular glycan variant1 (Fig. 1). "We knew that some glycan-synthesizing enzymes are expressed in restricted tissues, but did not know how they are expressed," says Yasuhiko Kizuka, a researcher in Taniguchi's laboratory. "This led us to investigate how GnT-IX is specifically expressed in the brain."

Many genes are regulated by so-called 'epigenetic mechanisms', in which gene expression is modulated via modification of the histone protein scaffold that supports chromosomal DNA, and the researchers began by examining this possibility. When histone proteins undergo a modification known as acetylation, nearby genes are typically activated; conversely, removal of this acetylation has an inhibitory effect.

Taniguchi and colleagues determined that the gene encoding GnT-IX is typically maintained in an inactive, non-acetylated state in 3T3-L1, a cell line derived from the fibroblasts that form connective tissue. However, when the researchers treated these cells with a drug that promotes histone acetylation, they strongly expressed GnT-IX. The brain tumor-derived Neuro2A cell line, however, naturally expresses high levels of GnT-IX. The researchers found that these cells normally maintain the chromatin near this gene in a state that stimulates activation.

In subsequent experiments, Kizuka and Taniguchi not only identified specific DNA sequences that directly regulate GnT-IX activity, but also two proteins that bind to these sites to drive expression. They found one of these factors, CTCF, in both 3T3-L1 and Neuro2A cells, but its recruitment to the GnT-IX gene was far stronger under the favorable

histone modification conditions found in the latter cells.

Intriguingly, a preliminary screen of four other glycosylation enzymes suggested that similar mechanisms govern their tissue-specificity. “Our work suggests that expression of many other glyco-genes could be regulated epigenetically,” says Kizuka.

In future studies, the researchers intend to explore how this regulatory mechanism plays into the bigger picture of glycan function. “Our group has been trying to elucidate the ‘glycan cycle’—how glycans are dynamically synthesized, play diverse roles and are degraded—using a systems biology approach,” says Kizuka. “This work tells us that epigenetic regulation is a part of this cycle.”

More information: Kizuka, Y., et al. Brain-specific expression of N-acetylglucosaminyltransferase IX (GnT-IX) is regulated by epigenetic histone modifications. The Journal of Biological Chemistry published online, 19 July 2011. doi: 10.1074/jbc/M111.251173

Provided by RIKEN