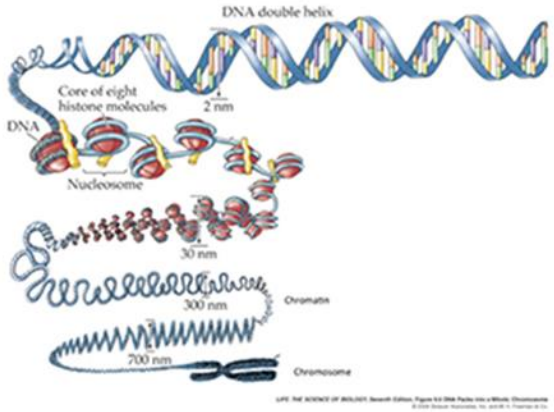
Specific histone gene may be a key player in brain development
By Allison Wagner

The devastating diagnosis of childhood gliomas accounts for 20% of childhood cancers and affects 100,000 families every year in the United States ("Survival rates for selected childhood brain and spinal cord tumors," 2014). Gliomas are tumors found in the central nervous system that often cause swelling and pressure on the brain. Although aggressive treatment involving surgery, radiation, and chemotherapy is used, the five year survival rate of patients with treatment is only 15-35% (Miller, 2013). Our research is dedicated to finding the causes of gliomas in order to facilitate development of more effective treatments.

A remarkable new discovery in 2012 provided clues as to how these pediatric cancers may develop. When examining 48 glioma samples from patients, scientists noticed a recurring mutation in a gene called *H3f3a* (Schwartzentruber et al.). Genes are segments of DNA that contain instructions for making specific proteins needed by the cell. The *H3f3a* gene encodes a protein that is critical for the structure of chromatin. When *H3f3a* is mutated, it alters the chromatin structure and often leads to cancer development. So what is chromatin?



Chromosomes are inherited structures composed of DNA. Chromosomal DNA within our cells is packaged by being tightly coiled around proteins called histones (figure 1). The combination of DNA and histone proteins is referred to as chromatin.

Chromatin is similar to a string of holiday lights - the DNA being the electrical wire and the histones being the brightly colored lights. Just as there are different colored bulbs on holiday lights, there are also different kinds of histones. There are four main types of histone proteins that come together in different combinations to form an octamer histone “core.” DNA wraps around these histone cores; an individual histone octamer plus its wrapped DNA is called a nucleosome.

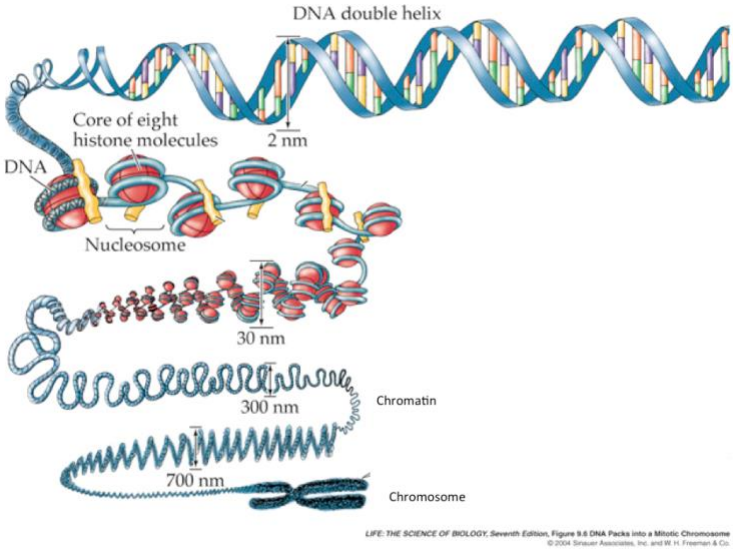


Figure 1. Structure of how DNA is condensed in cells.

The histone proteins influence the physical state of the DNA leading to activation or inactivation of genes. For example, a modification could remove the "stickiness" of a histone protein for the DNA, thereby causing the DNA to become unwound. This exposes the DNA in a way that allows other factors to bind the DNA and potentially turn on genes. The different types of histones can cause different genes to either be turned off or on.

How histones bind DNA is critical; when genes are incorrectly turned on or off it can lead to cancer (depending on the gene).

One histone variant in particular has caught the eye of scientists for its special properties and its connection with pediatric gliomas. H3.3 present in normal brain cells and mutated H3.3 is found in childhood brain cancers, We know that H3.3 is required for brain cells to function normally, but when it is mutated H3.3 can cause drastic, life-threatening changes in the cells.

The H3.3 histone protein can be created from two different genes, *H3f3a* or *H3f3b*. Mutations in the DNA sequence of the *H3f3a* gene are known to cause to pediatric gliomas, while less is known about the *H3f3b* gene. Both genes are currently being studied in the laboratory of Dr. Paul Knoepfler at the UC Davis Medical Center in partnership with Shriner's Hospital.

We have genetically altered mice by inactivating either the *H3f3a* or *H3f3b* gene . Subsequent analysis of mutant mice has indicated that histone H3.3 is necessary for normal development, but the functions of *H3f3a* and *H3f3b* are somewhat separate. The differences could be due to epigenetic distinctions in the two genes. Epigenetics refers to heritable changes in genes that do not alter DNA sequences, but can change how genes function. We are currently investigating this hypothesis and are hopeful that it will shed light on the mechanism of H3.3-based glioma formation. Discovery of the exact functions of the two genes may lead to a better understanding of normal brain development.

Our studies of histone H3.3 are bringing us closer to uncovering how gliomas develop, which is a significant step in the right direction toward finding a cure for this devastating pediatric cancer.

Literature Cited

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