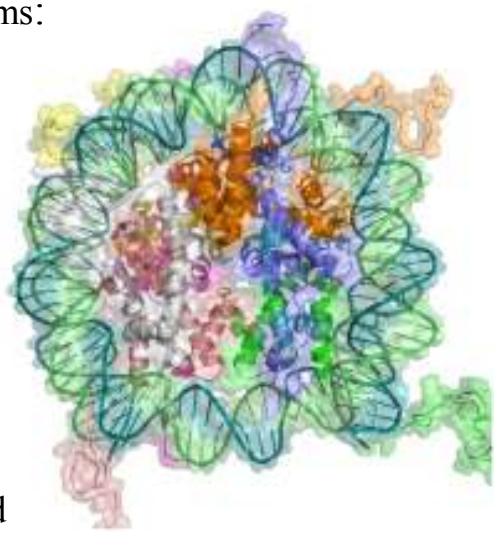
Mechanistic Understanding of Chromatin Assembly

Chromatin is actively assembled and dissembled according to nuclear processes including DNA replication, DNA repair, and transcription. Many chromatin assembly factors and chaperons are involved in the chromatin assembly process[3]. Histones translated in cytoplasm form complexes with Hsp90, small Nuclear Antigen Specific Protein (sNASP).Once Histones are translocated in nucleus, Chromatin Assembly Factor -1 (CAF-1) is the major chaperon complex and responsible for assembling nucleosome during DNA replication. Despite of many biochemi cal study of chromatin assembly, there is little mechanistic understanding how these protein machineries assemble chromatin. Therefore, we have been investigating the structural and molecular mechanism of chromatin assembly proteins and chaperons. Several types of epigenetic inheritance systems may play a role in what has become known as cell memory.

DNA methylation and chromatin remodeling

Because the phenotype of a cell or individual is affected by which of epigenetic effects. There are several layers of regulation of gene expression. One way that genes are regulated is through the remodeling

of chromatin. Chromatin is the complex of DNA and the histone proteins with which it associates. Histone proteins are little spheres that DNA wraps around. If the way that DNA is wrapped around the histones changes, gene expression can change as well. Chromatin remodeling is accomplished through two main mechanisms:



1. The first way is post translational modification of the amino acids that make up histone proteins. Histone proteins are made up of long chains of amino acids. If the amino acids that are in the chain are changed, the shape of the histone sphere might be modified. , that the modified histones may be carried into each new copy of the DNA. Once there, these histones may act as templates, initiating the surrounding new histones to be shaped in the new manner. By altering the shape of the histones around it, these modified histones would ensure that a differentiated cell would stay differentiated, and not convert back into being a stem cell.

2. The second way is the addition of methyl groups to the DNA, mostly at CpG sites, to convert cytosine to 5-methylcytosine. 5-Methylcytosine performs much like a regular cytosine, pairing up with a guanine. However, some areas of the genome are methylated more heavily than others, and highly methylated areas tend to be less transcriptionally active, through a mechanism not fully

understood. Methylation of cytosines can also persist from the germ line of one of the parents into the zygote , marking the chromosome as being inherited from this parent (genetic imprinting The way that the cells stay differentiated in the case of DNA methylation is clearer to us than it is in the case of histone shape. Basically, certain enzymes (such as DNMT1) have a higher affinity for the methylated cytosine. If this enzyme reaches a "hemimethylated" portion of DNA (where methylcytosine is in only one of the two DNA strands) the enzyme will methylate the other half. Although histone modifications occur throughout the entire sequence, the unstructured N-termini of histones (called histone tails) are particularly highly modified. These modifications include acetylation, methylation, ubiquitylation, phosphorylation and sumoylation. Acetylation is the most highly studied of these modifications. For example, acetylation of the K14 and K9 lysines of the tail of histone H3 by histone acetyltransferase enzymes (HATs) One mode of thinking is that this tendency of acetylation to be associated with "active" transcription is biophysical in nature. Because it normally has a positively charged nitrogen at its end, lysine can bind the negatively charged phosphates of the DNA backbone. The acetylation event converts the positively charged amine group on the side chain into a neutral amide linkage. This removes the positive charge, thus loosening the DNA from the histone.When this occurs, complexes like transcriptional factors can bind

to the DNA and allow transcription to occur. This is the "cis" model of epigenetic function. In other words, changes to the histone tails Have a direct effect on the DNA itself.