EPIGENETICS

Epigenetics is the study, in the field of genetics, are caused by external or environmental factors that switch genes on and off and affect how cells read genes. Also epigenetics can be defined as the study of genome function that is contained outside of DNA itself. Epigenetics is a well-established phenomenon that plays a major role in a diversity of biological processes such as embryonic development, cancer biology, and immune system response, among many others. The two most widely studied epigenetic changes are DNA methylation and histone acetylation;

Epigenetics refers to heritable changes in gene expression that occur without alteration in DNA sequence. These changes may be induced spontaneously, induced by environmental factors or as a consequence of specific mutations. There are two primary and interconnected epigenetic mechanisms: DNA methylation and covalent modification of histones. Epigenetic modifications are central to many cellular processes and essential to many organism functions, such as imprinting, X chromosome inactivation, cellular reprogramming and senescence. But if these modifications occur improperly, they can lead to major adverse health effects such as cancer or congenital diseases. Because of their role in cancer development, epigenetic

modifications offer promise as potential novel biomarkers for early cancer detection and prognosis.

Chromatin

Chromatin is comprised of histones and DNA: a 147bp of DNA chain wrapped around the 8 core histone forms the basic chromatin unit, the nucleosome. The primary functions of chromatin are

1- to package DNA into a smaller volume to fit in the cell,

2- to strengthen the DNA to allow mitosis and meiosis and prevent chromosome breakage,

3-to control gene expression and DNA replication.

In mammals, chromatin is mainly found as a condensed transcriptionally silent form called heterochromatin, which constitutes telomeres, pericentric regions and areas rich in repetitive sequences. Euchromatin is instead less condensed, and it contains most actively transcribed genes. these in turn couple to become the chromatin fiber.

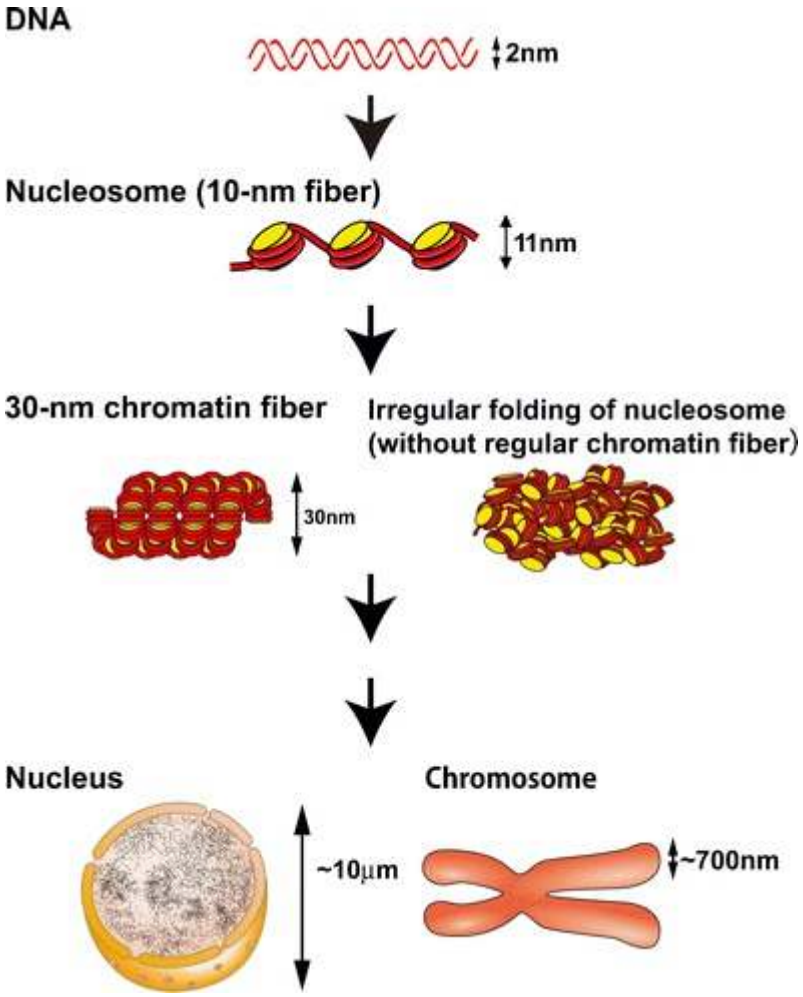


FIGURE (1) CHROMATEN AND CHROMOSOME STRUCTURE

Histone

Histones pack and order the DNA into nucleosomes, the building blocks of chromatin. Each nucleosome contains two subunits each of histones H2A, H2B, H3 and H4, known as the core histones. The linker histone H1 does not form part of the nucleosome itself but seems to act as stabilizer of the internucleosomal DNA. Histones are characterized by a “active” regions or euchromatin where DNA is accessible for

transcription, and "inactive" regions or heterochromatin where DNA is more compact and therefore less accessible for transcription. At least nine different types of histone modifications have been described, each catalyzed by a specific set of enzymes. The best understood modifications are lysine acetylation, lysine and arginine methylation, serine/threonine/tyrosine phosphorylation, and serine/threonine ubiquitylation. Other modifications include GlcNAcylation, citrullination, krotonilation and proline isomerization.

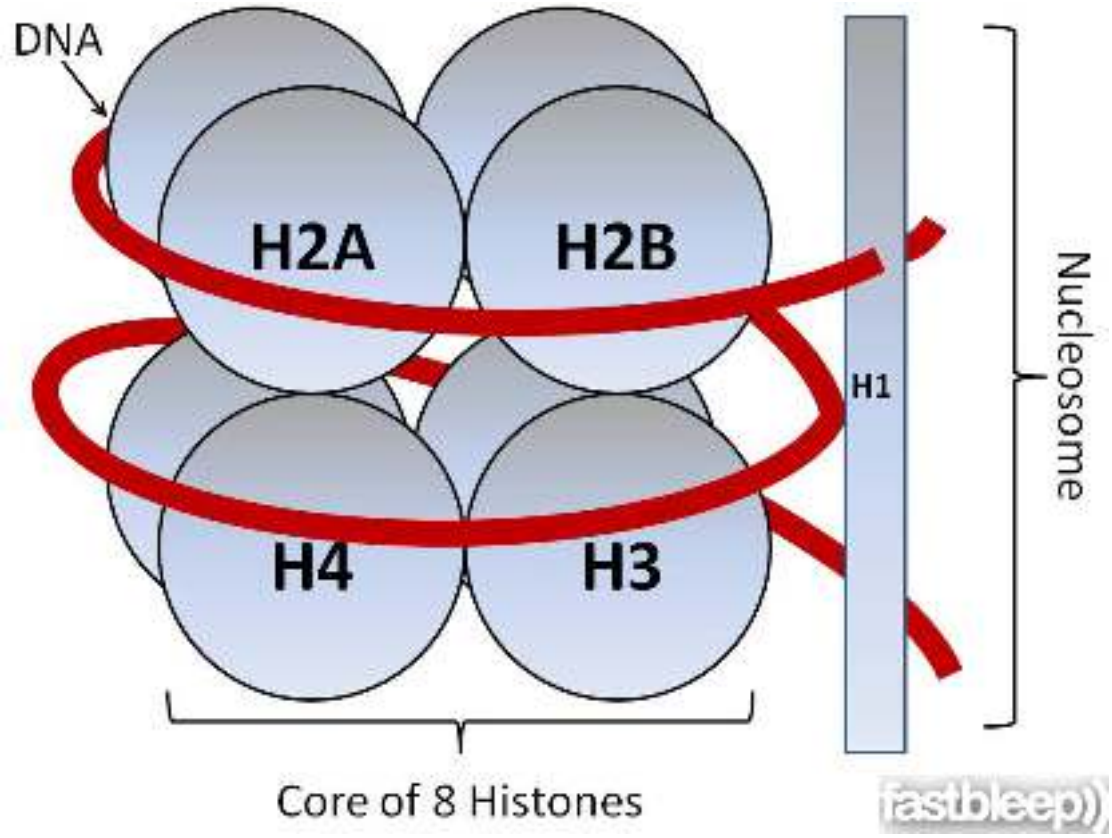


FIGURE (2) NUCLOSOME STRUCTURE

	Chromatin	Chromosome
Definition	In the nucleus, the DNA double helix is packaged by special proteins (histones) to form a complex called chromatin.	A compact structure of nucleic acids and protein found in the nucleus of most living cells, carrying genetic information in the form of genes.
Structure	Composed of nucleosomes-a complex of DNA and proteins (called histones)..	Chromosomes are condensed Chromatin Fibers.
Appearance	Chromatin Fibers are Long and thin. They are uncoiled structures found inside the nucleus.	Chromosomes are compact, thick. These are coiled structures seen prominently during cell division.
Pairs	Chromatin is unpaired.	Chromosome is paired.
Metabolic activity	Permissive to DNA replication, RNA synthesis (transcription) and recombination events.	Refractory to these processes.
Presence	Found throughout the cell cycle.	Distinctly visible during cell division (metaphase, anaphase).
Conformation	May have open (euchromatin) or compact (heterochromatin)	Predominantly heterochromatic state with a predetermined position in the nucleus

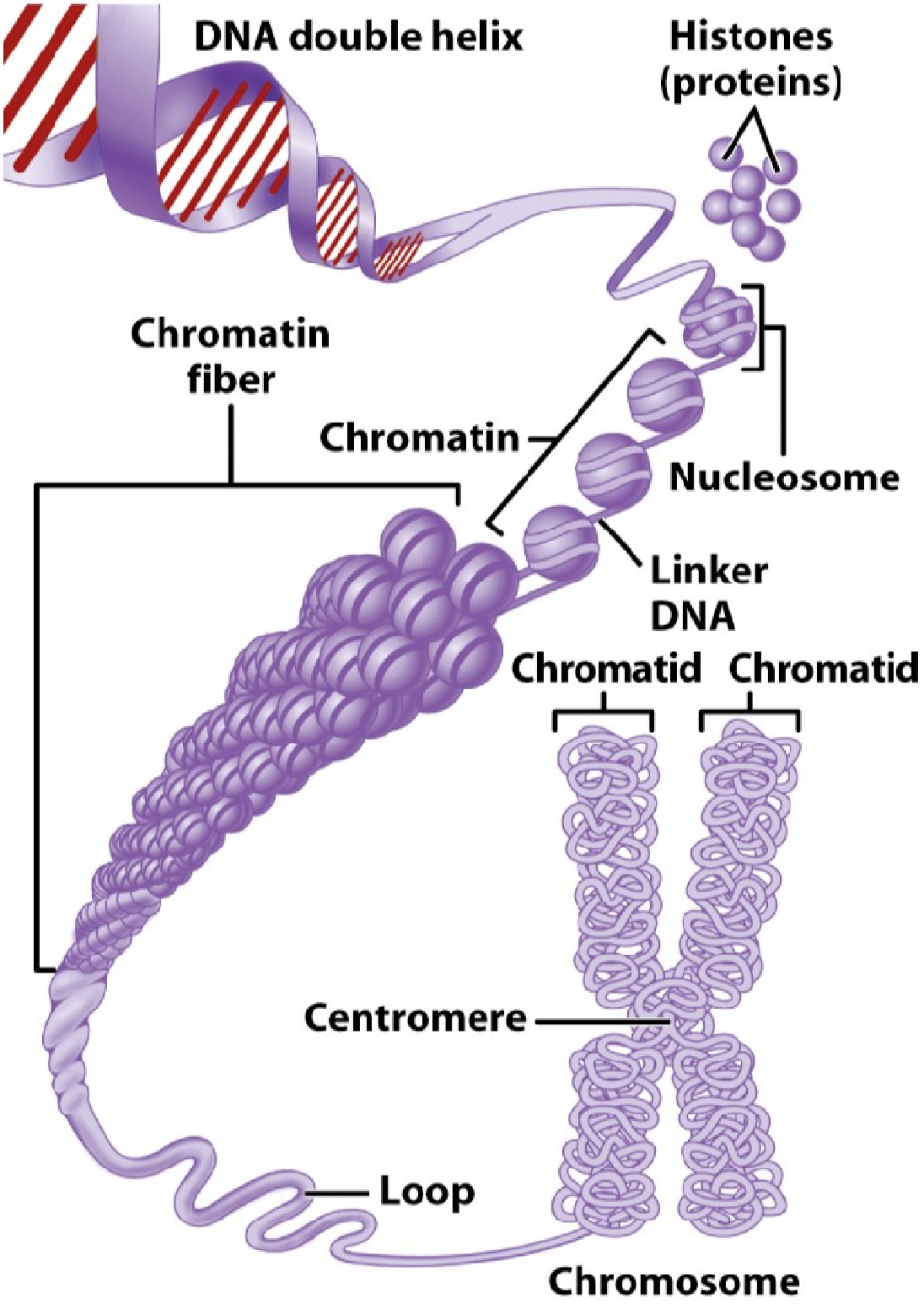
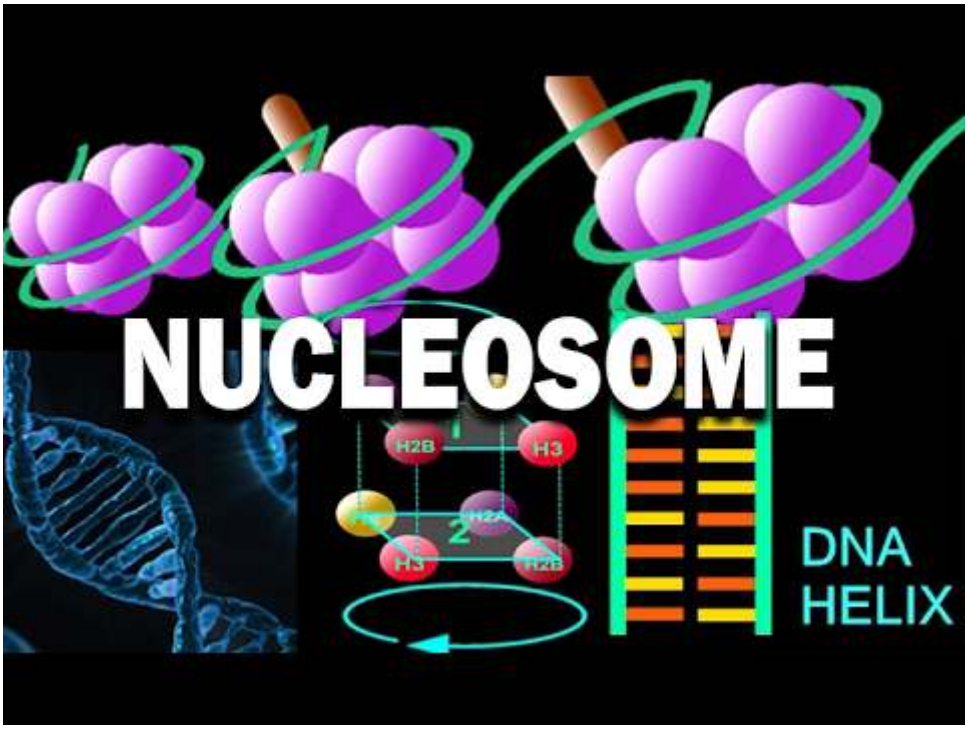


Figure 3-23 Principles of Anatomy and Physiology, 11/e


NUCLEOSOME
H2B
H3
H2A
2
H3
H2B
DNA
HELIX

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), Histone acetyltransferase complex in stepwise. Importin4 then takes over Histone complexed with Asf1 chaperon for nuclear translocation.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. CAF-1 is composed of p150, p60, and RbAp48. 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.