Medical Laboratory Techniques Department
Title of the lecture: Human Genetic
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The chromosomes
History-structure number karyotyping

History:-

- In a series of experiments beginning in the mid-1880s, Theodor Boveri gave the definitive demonstration that chromosomes are the vectors of heredity; his two principles or postulates were the ***continuity*** of chromosomes and the ***individuality*** of chromosomes.
- Wilhelm Roux suggested that each chromosome carries a different genetic configuration , and Boveri was able to test and confirm this hypothesis.
- The number of human chromosomes was published in 1923 by Theophilus Painter.
- By inspection through the microscope, he counted 24 pairs, which would mean 48 chromosomes.
- His error was copied by others and it was not until 1956 that the true number, 46, was determined by Indonesia-born cytogeneticist Joe Hin Tjio.

Chromosome structure

In M-phase the long eukaryotic DNA molecules have to be packed in small chromosomes to be able to accurately halve without breaks. Meanwhile, the original length of the DNA (several cm) is reduced by ten thousands fold (few µm). The molecular mechanism of this packaging is still not known in detail. The major points of a widely accepted model are described below (Figure 2.1).

Chromosomes also contain DNA-bound proteins, which serve in packaging the DNA and control its functions. Chromosomes vary both in number and structure among organisms and the number of chromosomes is characteristic of every species.

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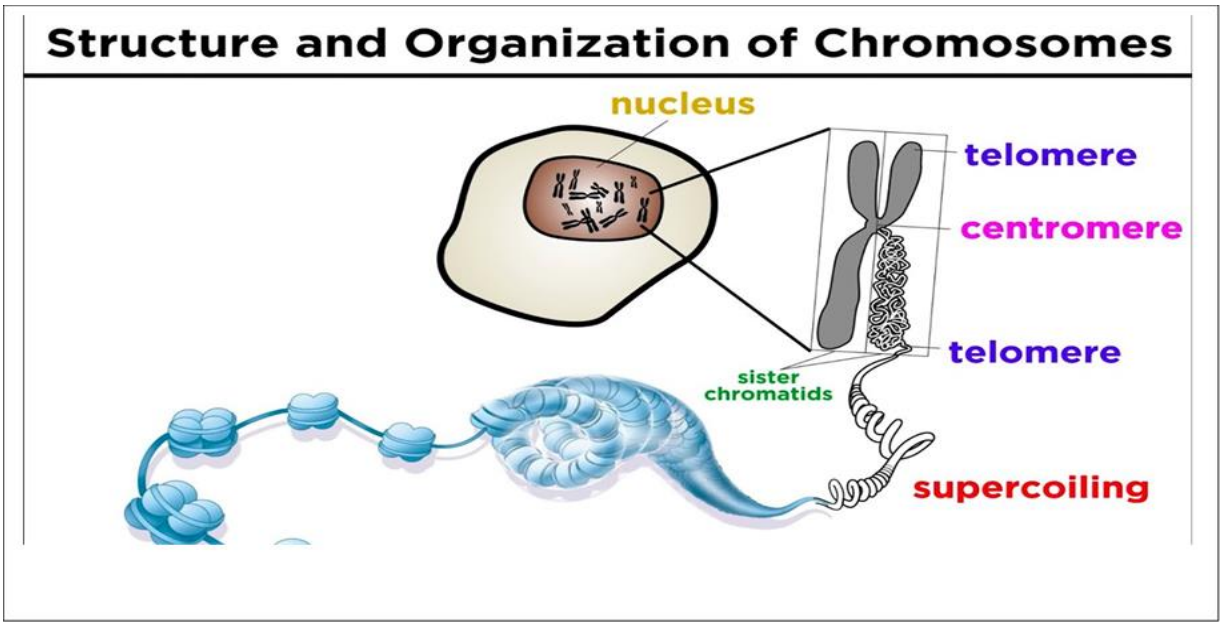

Figure 2.1 Chromosome structure

Two nm wide DNA double helix wraps the octamers of histones (2 of each H2A, H2B, H3 and H4 histone molecules) forming nucleosomes, disc-like structures connected by the continuous DNA molecule (figure 2.2). It is called nucleosomal structure having a diameter of 11 nm. H1 histone folds six nucleosomes in one plane to give a diameter of 30 nm fiber called chromatin or solenoid.

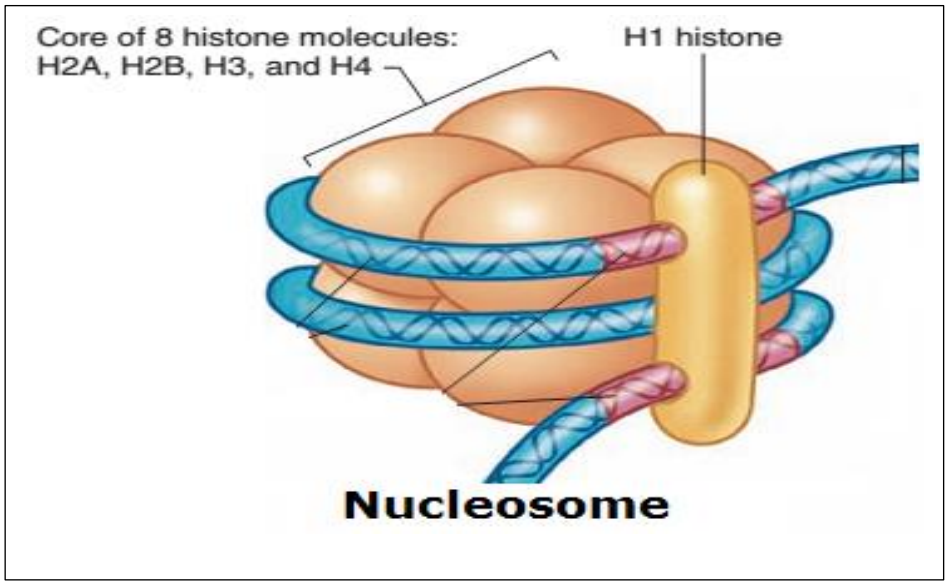

Figure: 2.2 Nucleosome structure

The chromatin fiber is attached to a protein scaffold and forms loops. These loops are the basic unit of replication and transcription, and this structure is 300 nm wide. Finally, it is further compressed and folded to produce the chromatids of 1400 nm wide metaphase chromosome (figure 2.3).

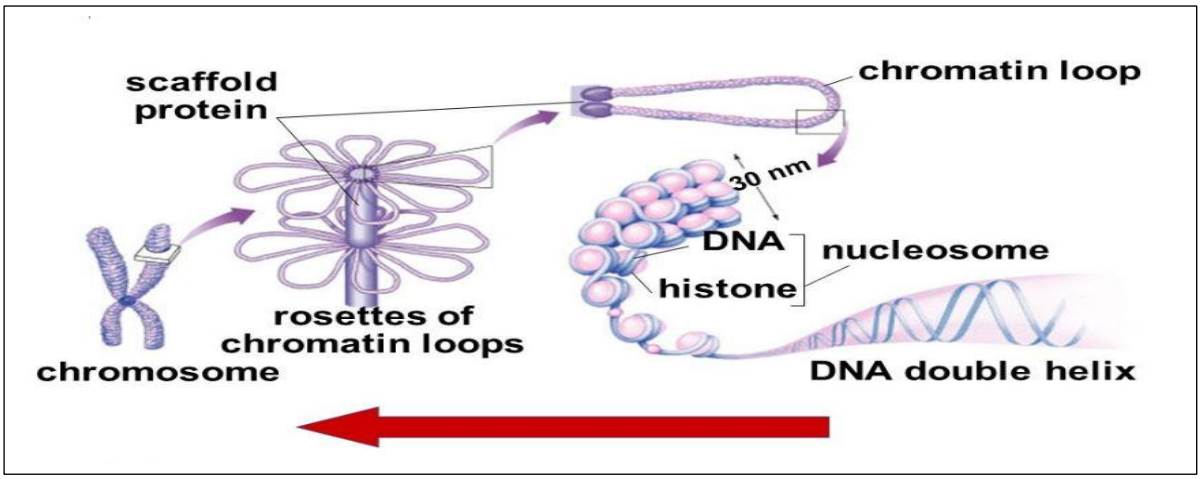

Figure: 2.3 The chromatin structure

The final step of chromosome condensation induced by the MPF (mitosis-promoting factor) activated condensins. There are two protein complexes of similar structure influencing different DNA functions: the condensins and the cohesins. They are composed of different SMC (structural maintenance of chromosomes) proteins having ATPase activity and regulatory functions, all associate in a ring- like structure (Figure 2.4).

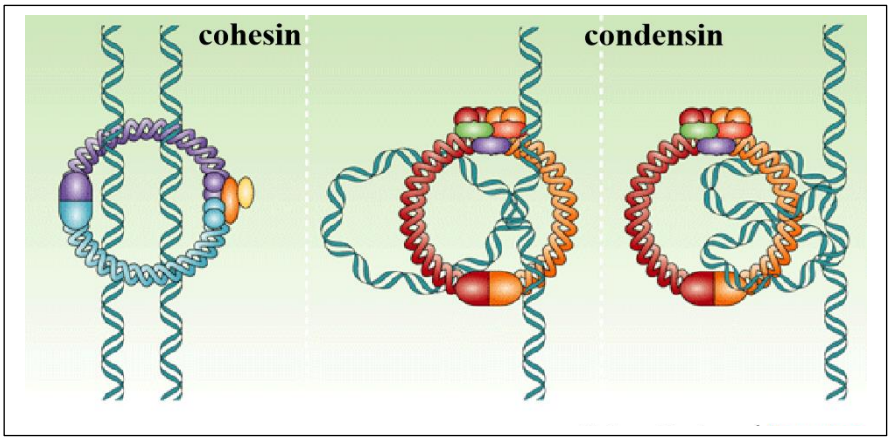

Figure 2.4 Structure of cohesin and condensing

Metaphase chromosome has very characteristic morphological structure. As the DNA is doubled in the S phase, chromosome comprises two sister chromatids. After DNA synthesis, the DNA molecules are held together by the ring-like cohesin complexes. Much of this cohesins detaches during the prophase, and at the end of metaphase it is found only at the primary constriction of chromosomes specified as centromere region. This pericentromeric cohesin is cleaved in early anaphase allowing the separation of chromatids. Chromosomes are usually classified according to the location of the centromere region. During prophase and prometaphase a special three-layer plate of protein structure called kinetochore associates to the centromeres of chromosomes. Beside many other proteins kinetochore contains both dynein and kinesintype motor proteins, and the role of it is to bind kinetochore microtubules (about 30– 40/sister chromatids). In scleroderma which is an autoimmune disease, patients produce antibodies against some of the kinetochore proteins. The centromere divides the sister chromatids into two arms, the ends of the arms are called telomeres. Loss of telomeres makes the chromosomes instable (Figure 2.4).

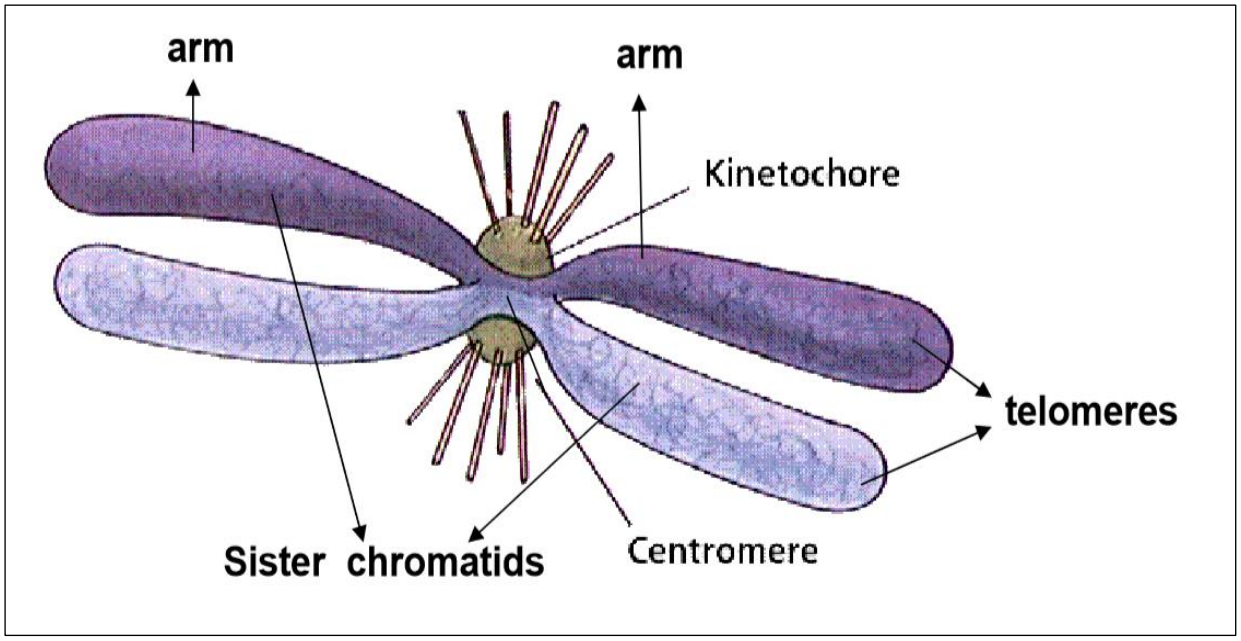

Figure 2.4 Eukaryotic chromosome

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Telomeres

Telomeres are the region of DNA at the end of the linear eukaryotic chromosome that are required for the replication and stability of the chromosome. McClintock recognized their special features when she noticed, that if two chromosomes were broken in a cell, the ends were sticky and end of one could attach to the other and vice versa. However she never observed the attachment of the broken end to the end of an unbroken chromosome suggesting that the end of chromosomes have unique features. Telomere sequences remain conserved throughout vertebrates and they form caps that protect the chromosomes from nucleases and other destabilizing influences; and they prevent the ends of chromosomes from fusing with one another.The telomeric DNA contains direct tandemly repeated sequences. Human telomeres contain the sequence TTAGGG repeated from about 500 to 5000 times (Figure 2.5).

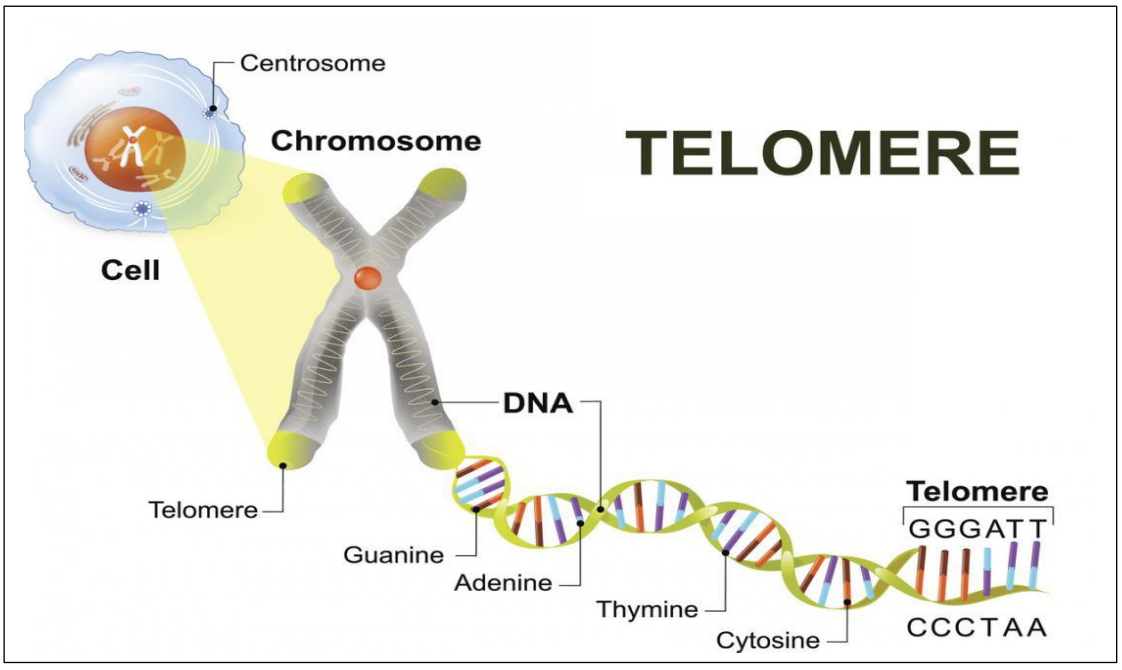

Figure 2.5 Telomere structure