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Mechanisms of Gene Regulation

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Mechanisms of Gene Regulation in Eukaryotic Cells

Most multicellular organisms develop from a single-celled zygote into a number of different cell types by the process of differentiation, the acquisition of cell-specific differences. An animal nerve cell looks very different from a muscle cell, and a muscle cell has little structurally in common with a lymphocyte in the blood. What do all these cells of a particular organism have in common? They all have a nucleus with identical DNA sequences, cytoplasm, and cytoplasmic organelles like the Golgi apparatus and mitochondria. Thinking back to the zygote, what drives the differentiation process? If all the cells have the same DNA, the same "genetic blueprint," why do they become so different?

Regulation of gene expression involves many different mechanisms.

In prokaryotes, regulatory mechanisms are generally simpler than those found in eukaryotes. Prokaryotic regulation is often dependent on the type and quantity of nutrients that surround the cell as well as a few others. A combination of activators, repressors and occasionally enhancers control transcription. Prokaryotic gene expression also happens in the same space as translation, reducing the opportunities for compartmentalization of regulation.

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Multicellular organisms have more complex genomes and the presence of a nucleus and separate cytoplasm provide a more compartmentalized structure. There are a number of different stages at which gene expression may be regulated in eukaryotes (Figure 1).In the nucleus, the process of chromatin remodelling regulates the availability of a gene for transcription. Once transcribed, the primary transcript of mRNA, or pre-mRNA, undergoes RNA processing, which involves splicing and the addition of a 5′ cap and a 3′ poly(A) tail to produce a mature mRNA in the nucleus.

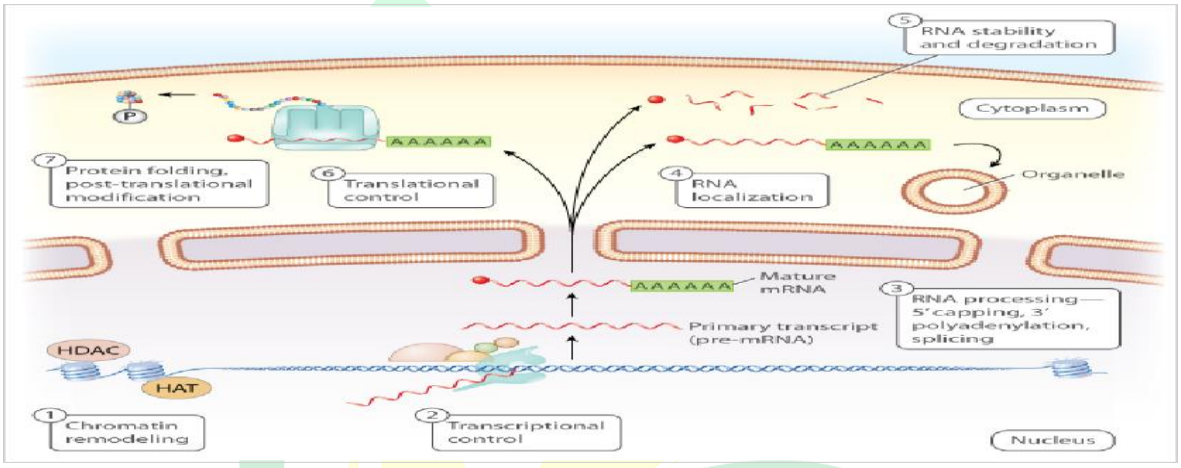

Figure 1: Regulation of gene expression in eukaryotes may take place at several different stages.

The mature mRNA is then exported from the nucleus to the cytoplasm, where its life span varies. Once outside the nucleus, localization factors may target mature mRNAs to specific regions of the cytoplasm where they are translated into polypeptides. The resulting polypeptides can undergo post-translational modifications, which can regulate protein folding, glycosylation, intracellular transport, protein activation, and protein degradation.

Several gene expression mechanisms involve chromatin structure.

When eukaryotic cells aren't dividing, chromosomes exist in an uncondensed state called chromatin. Chromatin consists of DNA wrapped around a histone protein core. The wrapped DNA isn't as available for transcription as the DNA of prokaryotes, and as we'll discuss, mechanisms exist to relieve this repression. Also in eukaryotes, the RNA polymerase doesn't bind directly to the DNA, but instead binds via a set of proteins: the transcription initiation complex.

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Two different types of chromatin can be seen during interphase: euchromatin and heterochromatin. Euchromatin, which is a lightly packed form, contains areas of DNA that are undergoing active gene transcription. Not all of the chromatin is undergoing gene transcription, however. Heterochromatin, in contrast, is mostly inactive DNA that is being actively inhibited or repressed in a region-specific manner. The chromatin state can change in response to cellular signals and gene activity. This is facilitated by enzymes that modify histones by adding methyl and acetyl groups to their N-terminal tails.

Acetylation reduces the net positive charge of the histones, loosening their affinity for DNA, and increasing transcription factor binding. Methylation, in contrast, leadsto increased binding of histones to DNA, and decreases the availability of DNA for transcription. Figure 2 shows anexample of how acetylation and methylation of histones may affect transcriptional activity in a normal cell compared to a cancer cell with inappropriate gene expression.

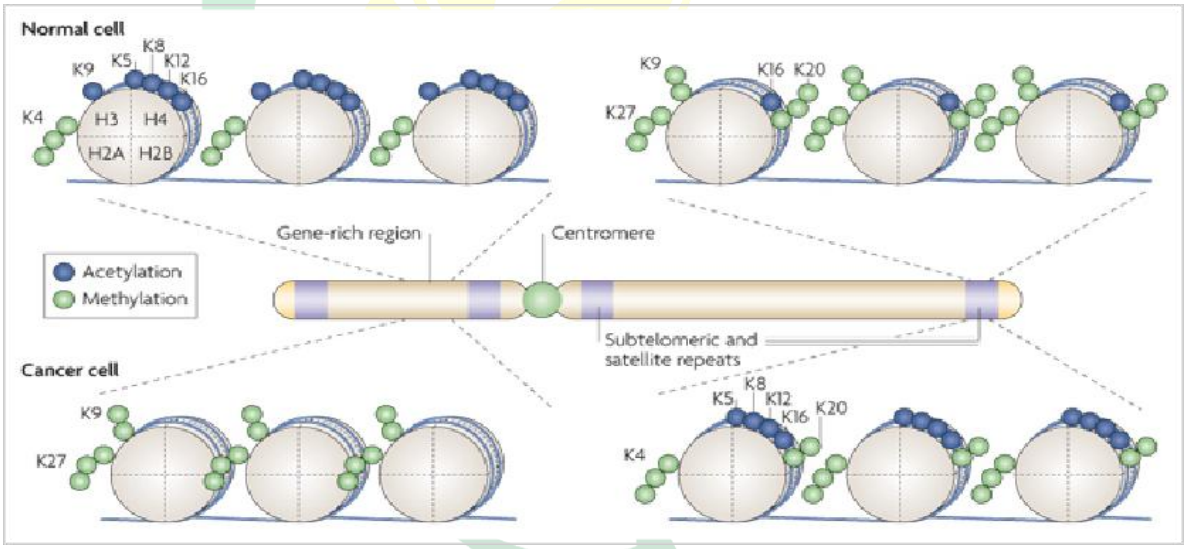

Figure 2: Modifications of methyl and acetyl groups in histones affect transcriptional activity.

The grey cylinders represent histone octamers. Acetylation (blue circles) and methylation (green circles) of histone subunits are shown. In normal cells, the promoters of tumor-suppressor genes show acetylation of histone subunits, associated with active transcription. In contrast, in cancer cells, the promoter soft umor-suppressor genes are not acetylated, and the genes are not actively transcribed. In normal cells, the

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heterochromatic regions at the ends of the chromosomes do not show acetylation,and the genes are not actively transcribed. In cancer cells, the heterochromatic regions at chromosome ends are acetylated and transcription ally active.

Others bind to proteins such as RNA polymerase II. These general transcription factors don't usually produce high rates of transcription, and for that reason, gene-specific transcription factors called activators or repressors are also required. These factors bind to proximal or distal control elements, which are specific DNA sequences that are usually four to eight base pairs long. The rate of gene expression may be greatly affected by binding of specific transcription factors to control elements.

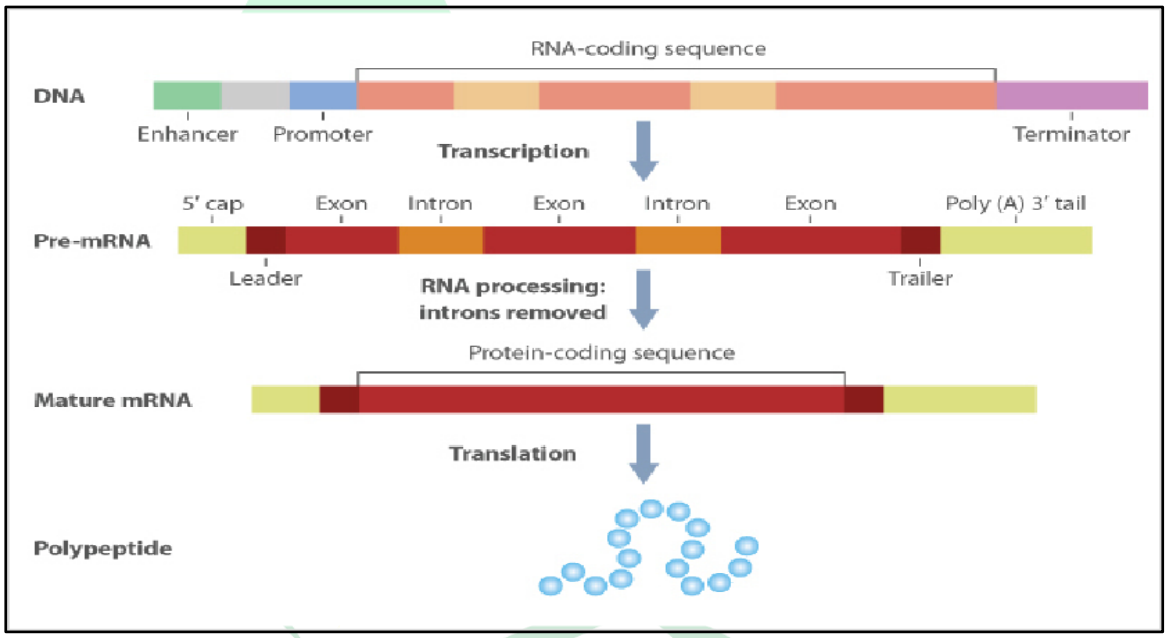

Figure 3: The structure of a eukaryotic gene and its transcript.

Proximal control elements are close to the promoter. Distal control elements may be grouped as enhancers, and may be thousands of nucleotides removed from the gene. Although one gene may have more than one enhancer, a given enhancer is usually associated with only one gene.

Each gene has a promoter, the DNA sequence where RNA polymerase, along with transcription factors, binds and begins transcription. RNA processing removes introns and splices the exons together using structures called spliceo somes, and a 5′ cap and poly(A) 3′ tail are added to the mRNA transcript. The mRNA is then translated into a polypeptide.

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How does the binding of transcription factors to control elements regulate transcription? There seem to be two structural components in transcription factors: a region that binds to DNA and an activation domain that attaches to other proteins or components of the transcription apparatus itself. There are only a few different kinds of binding regions in control elements: these are called DNA sequence motifs. The binding of transcription factors that function as activators to control elements in an enhancer may cause the DNA to bend. This bending brings the enhancer complex into contact with the protein complex at the proximal promoter, creating a large complex that promotes RNA polymerase binding. RNA polymerase II is then recruited and transcription can begin (Figure 4). Some transcription factors function as repressors that bind to control elements, effectively blocking the binding of activators.

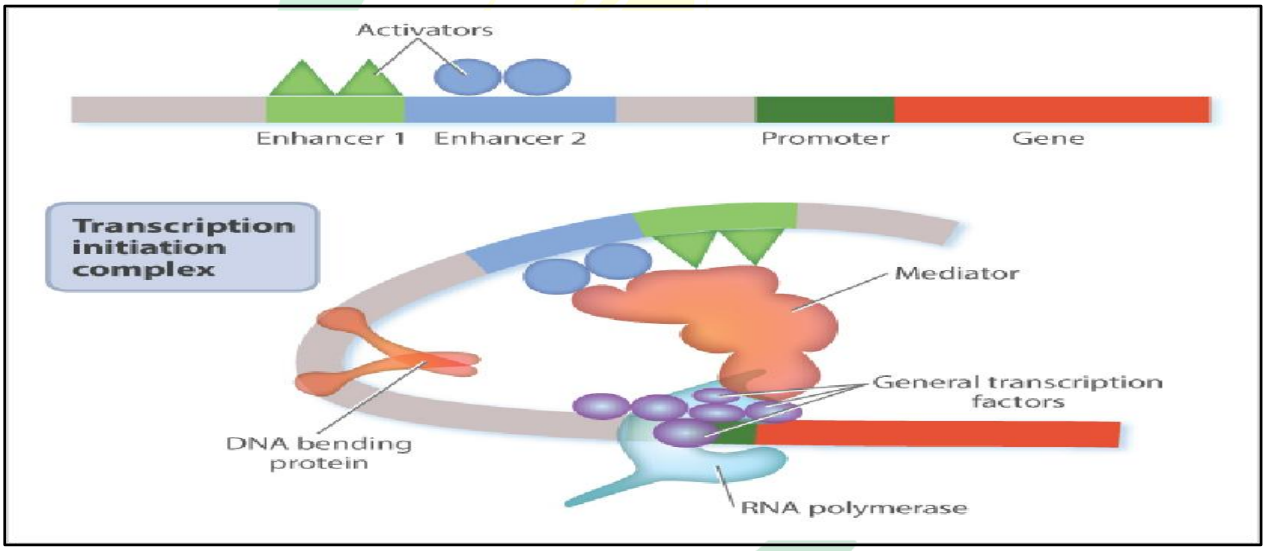

Figure 4: The eukaryotic transcription initiation complex.

When activator proteins bind to distal control elements called enhancers, the bound activators are brought closer to the promoter by a DNA-bending protein. The activators bind to the Mediator protein complex, which forms an active transcription initiation complex on the promoter together with RNA polymerase and the general transcription factors.

The number of different DNA sequence motifs found in control elements is quite small and is thought to be around ten. It is believed that the combination of control elements in an enhancer provides the specificity for gene regulation. The availability of ten different sequences gives a very large set of available combinations — much like the

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lock on a bicycle, only the correct combination will "unlock" and allow activation of an enhancer.

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