

Chapter 18

Regulation of Gene Expression

18.1. Gene Regulation Is Necessary

By switching genes off when they are not needed, cells can prevent resources from being wasted. There should be natural selection favouring the ability to switch genes on and off. A typical human cell normally expresses about 3% to 5% of its genes at any given time. Cancer results from genes that do not turn off properly. Cancer cells have lost their ability to regulate mitosis, resulting in uncontrolled cell division.

18.2. Prokaryotes

Much of our understanding of gene control comes from studies of prokaryotes. Prokaryotes have two levels of gene control. Transcriptional mechanisms control the synthesis of mRNA and translational mechanisms control the synthesis of protein after mRNA has been produced.

(a) Operons

Operons are groups of genes that function to produce proteins needed by the cell. There are two different kinds of genes in **operons**:

1. **Structural genes** code for proteins needed for the normal operation of the cell. For example, they may be proteins needed for the breakdown of sugars. The structural genes are grouped together and a single mRNA molecule is produced during their transcription.
2. **Regulator genes** code for proteins that regulate other genes.

Operons have not been found in eukaryotes

(b) The lac operon

Lactose is a sugar found in milk. If lactose is present, *E. coli* (the common intestinal bacterium) needs to produce the necessary enzymes to digest it. Three different enzymes are needed. In the diagrams below, genes A, B, and C represent the genes whose products are necessary to digest lactose. In the normal condition, the genes do not function because a **repressor protein** is active and bound to the DNA preventing transcription. When the repressor protein is bound to the DNA, RNA polymerase cannot bind to the DNA. The protein must be removed before the genes can be transcribed.

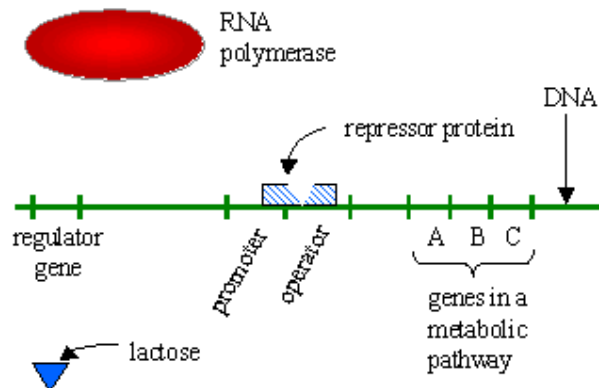


Fig.18.1a. The lac operon

Below: Lactose binds with the repressor protein inactivating it.

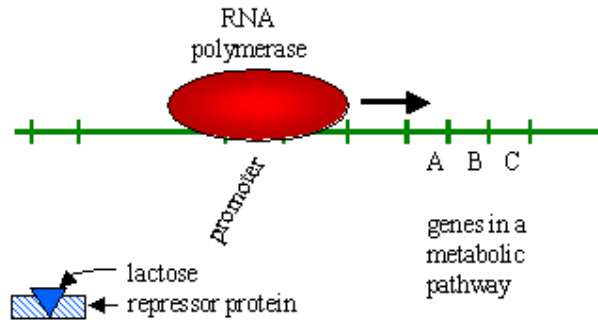


Fig.18.1b. The lac operon

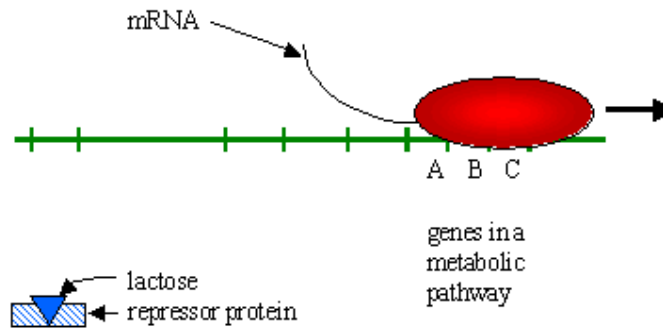


Fig.18.1c. The lac operon

The repressor protein is produced by a **regulator gene**. The region of DNA where the repressor protein binds is the **operator site**. The **promoter site** is a region of DNA where RNA polymerase can bind. The entire unit (promoter, operator, and genes) is an **operon**. The lac operon is an example of an inducible operon because the structural genes are normally inactive. They are activated when lactose is present.

(c) The trp Operon

Repressible operons are the opposite of inducible operons. Transcription occurs continuously and the repressor protein must be activated to stop transcription. Tryptophan is an amino acid needed by *E. coli* and the genes that code for proteins that produce tryptophan are continuously transcribed as shown below.

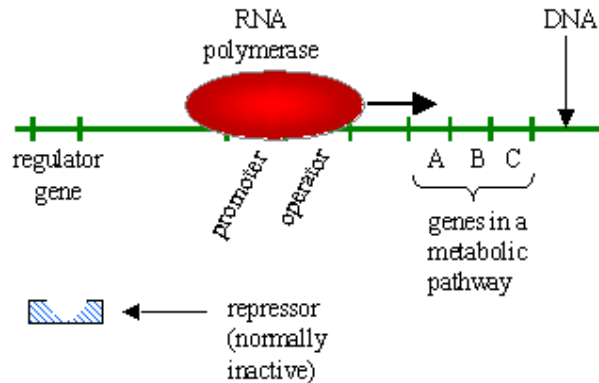


Fig.18.2a. The trp Operon

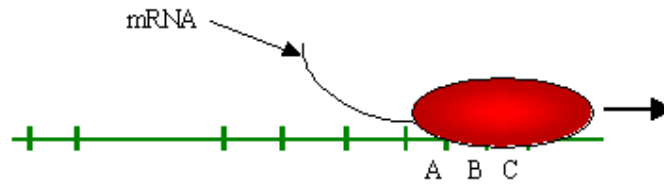


Fig.18.2b. The *trp* Operon

If tryptophan is present in the environment, however, *E. coli* does not need to synthesize it and the tryptophan-synthesizing genes should be turned off. This occurs when tryptophan binds with the repressor protein, activating it. Unlike the repressor discussed with the lac operon, this repressor will not bind to the DNA unless it is activated by binding with tryptophan. Tryptophan is therefore a corepressor.

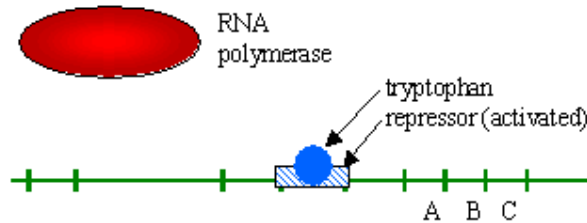
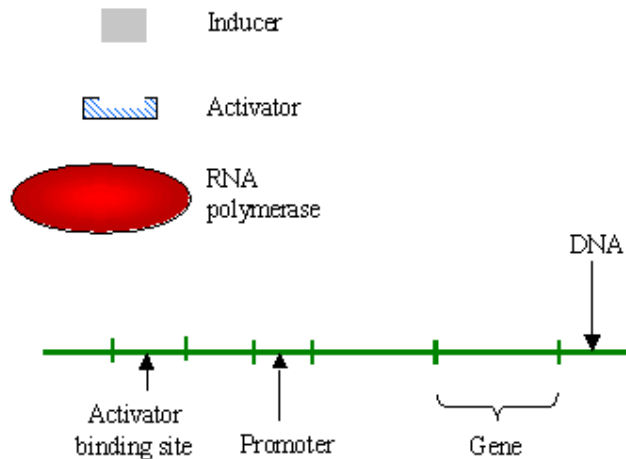


Fig.18.2c. The *trp* Operon

The *trp* operon is an example of a repressible operon because the structural genes are active and are inactivated when tryptophan is present.

(d) Negative and Positive Control

The *trp* and *lac* operons discussed above are examples of negative control because a repressor blocks transcription. In one case (*lac* operon) the repressor is active and prevents transcription. In the other case (*trp*) the repressor is inactive and must be activated to prevent transcription. Positive control mechanisms require the presence of an activator protein before RNA polymerase will attach. The activator protein itself must be bound to an inducer molecule before it attaches to mRNA.



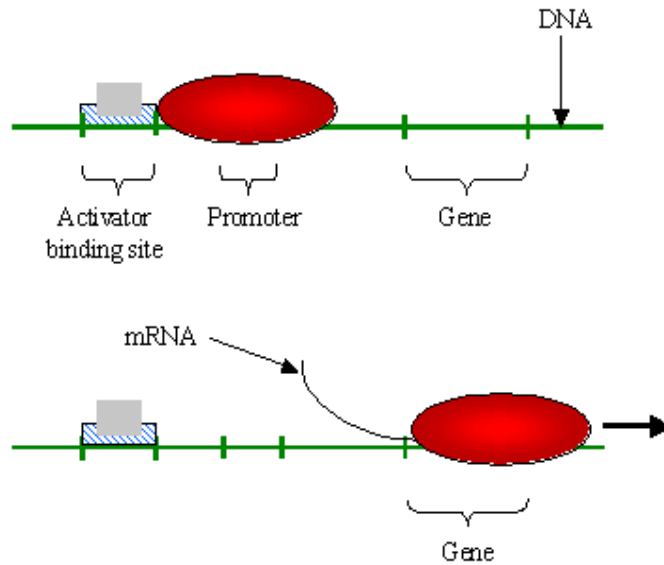
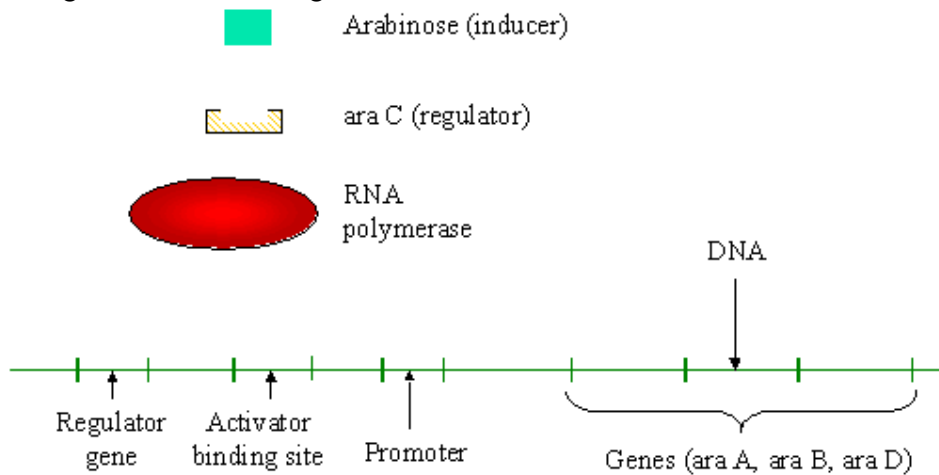


Fig.18.3. Negative and Positive Control

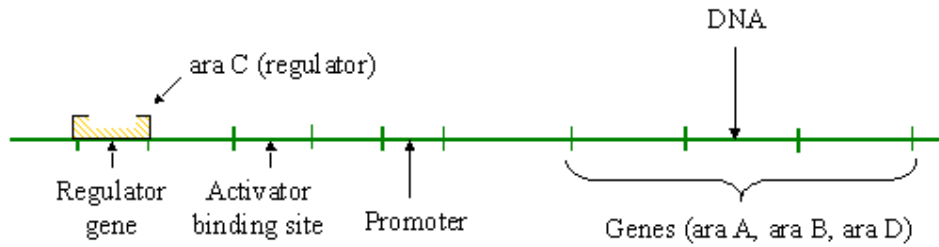
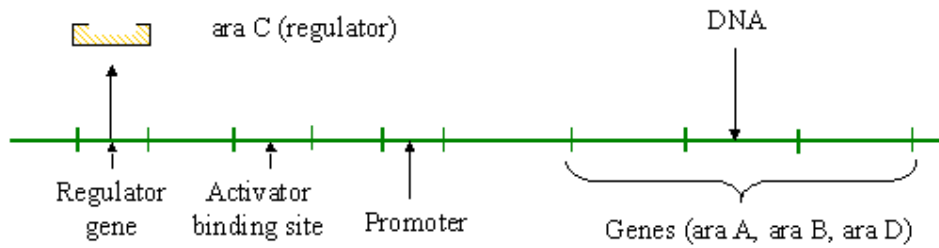
Genes which code for enzymes necessary for the digestion of maltose are regulated by this mechanism. Maltose acts as the inducer, binding to an activator and then to mRNA. The activator bound to mRNA stimulates the binding of RNA polymerase.

(e) The Arabinose Operon

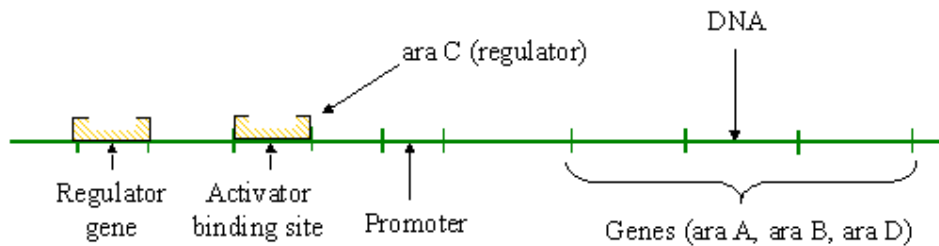
The arabinose operon uses both positive and negative control. The operon contains three different genes (ara A, ara B, and ara D) that code for three enzymes needed to convert arabinose to a usable form. A fourth gene codes for a protein (ara C) that acts to regulate the structural genes.



The regulator protein (ara C) is needed for transcription of the three structural genes (ara A, ara B, and ara D). It binds to its own structural gene preventing its own transcription, thus autoregulating its own level. When the level of ara C is low, transcription occurs and more ara C is synthesized.



Ara C also binds to other sites within the operon, inhibiting transcription of the three structural genes. The genes therefore are normally not active.



When arabinose is present, it binds to ara C causing it to change shape. The new shape promotes the attachment of RNA polymerase to the DNA, thus allowing transcription to occur.

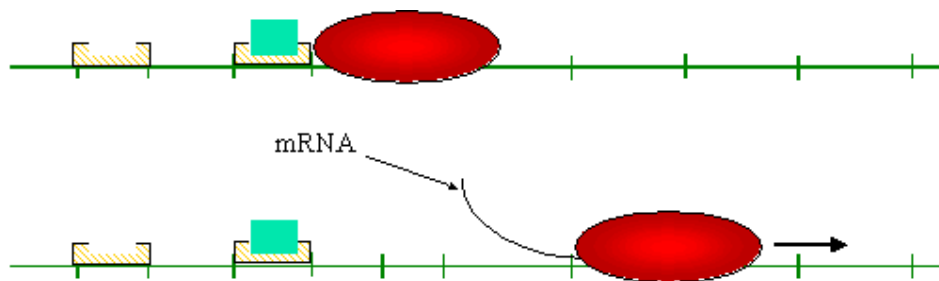
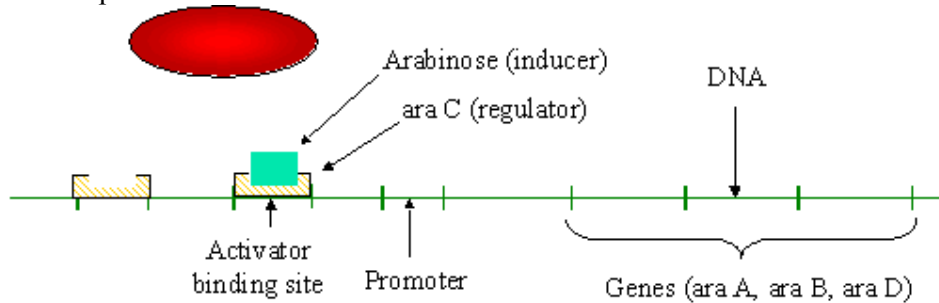


Fig.18.4. The Arabinose Operon

18.3. Promoters and Sigma Factors

The nucleotide sequence of promoters is similar but not identical. The more similar the sequence is to a consensus sequence, the more likely that RNA polymerase will attach and produce mRNA from the associated genes. Part of the RNA polymerase enzyme that recognizes the promoter is called the sigma factor. After transcription begins, this unit dissociates from the enzyme.

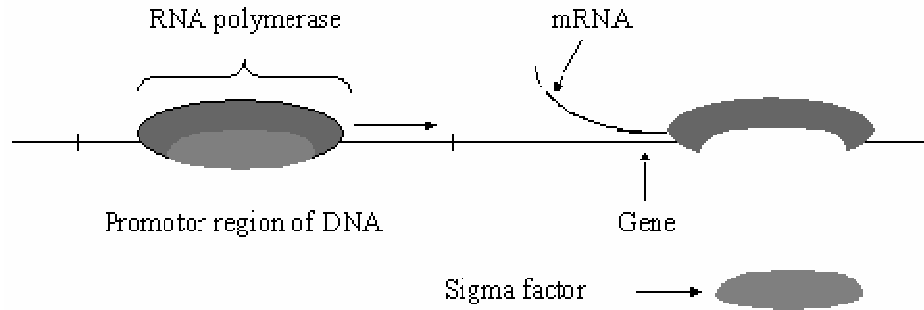


Fig.18.4a. Promoters and Sigma Factors

Different sigma factors recognize different promoters and thus, the availability of sigma factors can regulate the transcription of genes associated with these promoters.

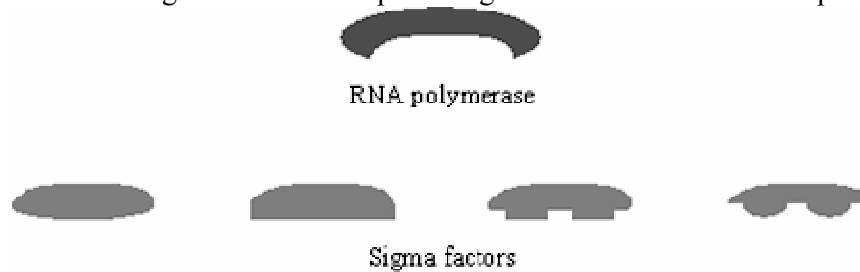


Fig.18.4b. Promoters and Sigma Factors

The availability of sigma factors can be used to regulate sets of genes. For example, a group of genes whose product is rarely needed might have a different promoter sequence than other genes and thus require different sigma factors. These genes would only be transcribed when the correct sigma factor became available.

18.4. Types of control in Eukaryotes

Gene expression in eukaryotes is controlled by a variety of mechanisms that range from those that prevent transcription to those that prevent expression after the protein has been produced. The various mechanisms can be placed into one of these four categories: transcriptional, posttranscriptional, translational, and posttranslational.

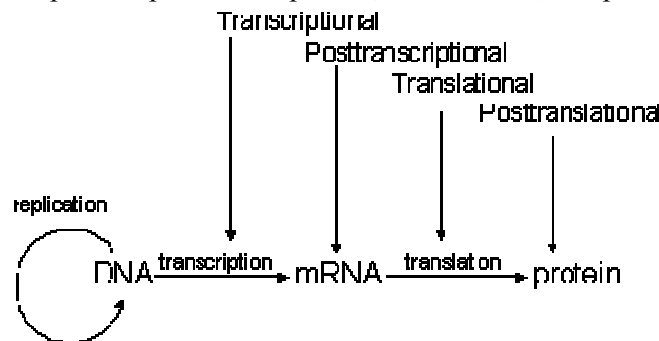


Fig.18.5.Types of control in Eukaryotes

Transcriptional - These mechanisms prevent transcription.

Posttranscriptional - These mechanisms control or regulate mRNA after it has been produced.

Translational - These mechanisms prevent translation. They often involve protein factors needed for translation.

Posttranslational - These mechanisms act after the protein has been produced.

18.5. Transcriptional

These mechanisms prevent mRNA from being synthesized.

(a) Heterochromatin and Euchromatin

Heterochromatin is tightly wound DNA and visible during interphase. It is inactive because DNA cannot be transcribed while it is tightly wound. Euchromatin is not tightly wound. It is active. E.g. One X chromosome is inactivated in females by producing a tightly-wound structure called a Barr body. The meiotic cells (oocytes) of some amphibians (frogs, toads, salamanders) have chromosomes that appear bristled. The bristles are loops of unwound DNA with many RNA polymerase and mRNA molecules. They are called lampbrush chromosomes because they resemble the brushes used to clean oil lamps.

(b) Regulatory Proteins and Transcription

Proteins called *transcription factors* function by binding to the *promoter* and to another region called the *enhancer*. The enhancer region may be located at a distance from the gene. These transcription factors are necessary for RNA polymerase to attach. Transcription begins when the factors at the promoter region bind with the factors at the enhancer region creating a loop in the DNA. In the diagram below, transcription factors are represented by the green rectangle and the red oval.

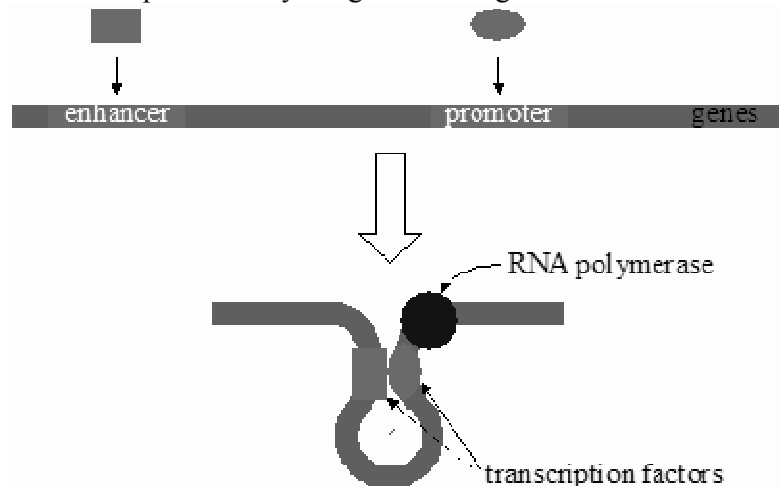


Fig.18.5. Regulatory Proteins and Transcription

Hundreds of different transcription factors have been discovered; each recognizes and binds with a specific nucleotide sequence in the DNA. A specific combination of transcription factors is necessary to activate a gene. Transcription factors are regulated by signals produced from other molecules. For example, hormones activate transcription factors and thus enable transcription. Hormones therefore activate certain genes.

18.6. Post-Transcriptional Control

These mechanisms control or regulate mRNA after it has been produced.

(a) Differential Removal of Introns

This can produce variations in the mRNA produced. Different mRNA may have different introns removed. Differential removal of introns enables a gene to code for more than one different protein. An average human gene is thought to code for 3 different proteins. For example, experiments using radioactive labelling show that calcitonin produced by the hypothalamus is different from that produced by the thyroid. In each case, the same gene produces the protein.

(b) Speed of Transport of mRNA Through the Nuclear Pores

Evidence suggests that this time may vary.

(c) Longevity of mRNA

Messenger RNA can last a long time. For example, mammalian red blood cells eject their nucleus but continue to synthesize haemoglobin for several months. This indicates that mRNA is available to produce the protein even though the DNA is gone.

(d) Ribonucleases

Ribonucleases are enzymes that destroy mRNA. Messenger RNA has noncoding nucleotides at either end of the molecule. These segments contain information about the number of times mRNA is transcribed before being destroyed by ribonucleases. Hormones stabilize certain mRNA transcripts. E.g. Prolactin is a hormone that promotes milk production because it affects the length of time the mRNA for casein (a major milk protein) is available.

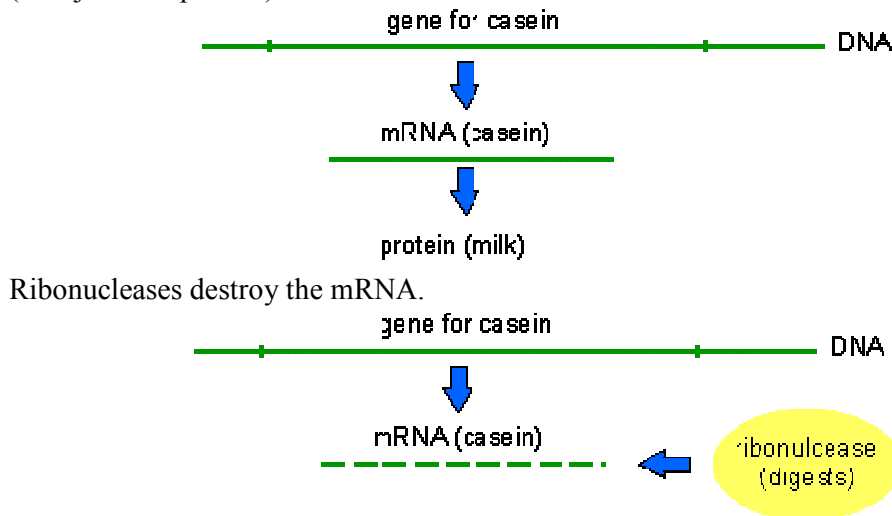


Fig.18.6a. Ribonucleases

Prolactin is a hormone that prevents destruction of the mRNA.

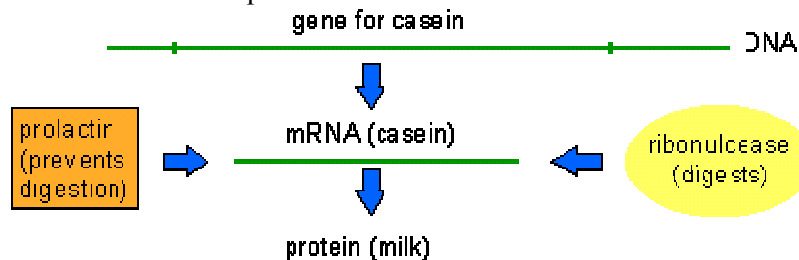


Fig.18.6b. Ribonucleases

18.7. Translational Control

These mechanisms prevent the synthesis of protein. They often involve protein factors needed for translation.

(a) Preventing Ribosomes from Attaching

Proteins that bind to specific sequences in the mRNA and prevent ribosomes from attaching can prevent translation of certain mRNA molecules.

(b) Initiation Factors

Initiation factors are proteins that enable ribosomes to attach to mRNA. These factors can be produced when certain proteins are needed. For example, the eggs of many organisms contain mRNA that is not needed until after fertilization. At this time, an initiation factor is activated.

18.8. Post-Translational Control

These mechanisms act after the protein has been produced.

(a) Protein Activation

Some proteins are not active when they are first formed. They must undergo modification such as folding, enzymatic cleavage, or bond formation. E.g: Bovine proinsulin is a precursor to the hormone insulin. It must be cleaved into 2 polypeptide chains and about 30 amino acids must be removed to form insulin.

(b) Feedback Control

Some enzymes in a metabolic pathway may be negatively inhibited by products of the pathway.

18.9. Modification of DNA

(a) Gene Amplification

In *Drosophila* (fruit flies), the chorion (eggshell) gene is copied many times in certain cells of the oviduct. These cells make large quantities of the protein needed to surround the egg. In other cells of the body, there is only one copy of this gene.

(b) The Immunoglobulin Genes

Immunoglobins (antibodies) are proteins that are used to defend the body against foreign invaders. They are able to do this because they have a shape that matches a shape found on the invader, allowing it to become attached. Particles that have antibodies attached are quickly destroyed by other cells in the immune system. Our bodies contain millions of different antibodies, each produced by a type of white blood cell called a lymphocyte. A single lymphocyte can produce only one specific kind of antibody, thus, there are millions of different kinds of lymphocytes. The genes that code for these antibodies differ from one lymphocyte to the next because when the lymphocytes are produced, different regions of the DNA are deleted so that each lymphocyte has a somewhat different version of the genes involved.

(c) Transposons

Transposons are segments of DNA that are capable of moving to another location, either on the same chromosome or on a different one. If a transposon inserts itself within another gene, it can prevent the gene from expressing itself. Sometimes the transposon carries a gene which can become activated if it becomes inserted downstream from an active promoter.