REGULATION OF GENE EXPRESSION

Each cell of a living organism contains thousands of genes. But all genes do not function at a time. Genes function according to requirements of the cell. Genes control the phenotypic expression of various characters through the production of specific enzymes. Enzymes are special proteins which catalyse chemical reactions. The production or synthesis of a particular enzyme is not constant. It varies as per the requirement of the cell in other words, the synthesis of a particular enzyme is sometimes high and sometimes low depending upon the requirement of the cell. Thus, there exists an on-off system which regulates protein synthesis in all living cells. The precise study of this on-off mechanism is called regulation of gene action or regulation of gene expression or regulation of protein synthesis.

Synthesis of enzyme depends mainly on two factors. In a degradative process, the synthesis of enzyme depends on the availability of the molecule to be degraded. If the molecule is in more quantity, the enzyme synthesis will be more and vice versa. In a biosynthetic pathway, the synthesis of an enzyme is governed by the end product. If the end product is more, the enzyme synthesis will be less and vice versa. There are two types of gene regulation, viz, (1) negative regulation, and (2) positive regulation.

In negative regulation, this system and inhibitor is present in the cell, which prevents transcription by inactivating the promoter. This inhibitor is known as repressor. For initiation of transcription, an inducer in required. Inducer acts as antagonist of the repressor. In the negative regulation, absence of product increases the enzyme synthesis and presence of the product decreases the synthesis.

Positive Control

In positive regulation, this system, an effectors molecule (which may be a protein or a molecular complex) activates the promoter for transcription. In a degradative system, either negative or positive mechanism may operate. In a biosynthetic pathway negative mechanism usually operates.

Important Terms

It is essential to define various terms which are commonly used in connection with regulation of gene expression. A brief description of important terms is presented below:

Brief description of important terms related to regulation of gene expression

Terms	**Brief description**
Repressor	In operon, protein molecules which prevents transcription. The process of inhibition of transcription is called repression.
Inducer	The substance which allows initiation of transcription (i.e., lactose in lac operon). Such process is known as induction.
Corepressor	A combination of repressor and metabolite which prevents protein synthesis. Such process is termed as corepression.
Inducible enzyme	An enzyme whose production is enhanced by adding the substrate in the culture medium. Such system is called inducible system.
Repressible enzyme	An enzyme whose production can be inhibited by adding an end product. Such system is known as repressible system.
Constitutive enzyme	An enzyme whose production is constant irrespective of metabolic state of the cell.
Negative control	Inhibition of transcription by repressor through inactivation of promoter e.g in lac operon.
Positive control	Enhancement of transcription by an effector molecule through activation of promoter.
Effector	The molecule which acts as an inducer or corepressor in the operon model of *E.coli*

The Operon Model

The operon refers to a group of closely linked genes which act together and code for various enzymes of a particular biochemical pathway. In other words, operon is a model which explains about the one-off mechanism of protein synthesis in a systematic manner. The operon model of gene regulation was proposed by Jacob and Monod in 1961. They were awarded Nobel prize for this discovery in 1965. The operon model was developed working with lactose region (lac region) of the human intestine bacteria ***E.coli.*** The gene regulation was studied for degradation of the sugar lactose. The operon model consists of seven main components, viz, (1) structural genes, (2) operator gene, (3) promotor gene, (4) regulator gene, (5) repressor, (6) corepressor, and (7) inducer. A brief description of these components is presented below:

Structural Genes

The lac operon of ***E.coli*** consists of three structural genes, viz, z, y and a. The z gene is located near to the operator gene, y is located between z and a, and a is located on right end of the operon segment. These structural genes transcribe a single polycistronic mRNA molecule. This mRNA molecule controls the synthesis of three different enzymes, viz., β- galacto-sidase, galactosidase permease and galactosidase transacetylase. The enzyme galactosidase consists of 4 units and catalyses the breakdown of lactose into glucose and galactose as given below:

The enzyme galactosidase permease is made up of one unit and permits entry of lactose from the medium into the bacterial cell. Galactosidase acetylase consists of two units. Its main function is to transfer an acetyl group from acetyl co-enzyme A to β- galactosidase. The function of all the structural genes is controlled by operator gene. Thus, the main function function of structural genes is to control synthesis of protein through messenger RNA. In an operon, number of structural genes is always equal to the number of polypeptide chains synthesized under common control. If three types of proteins are synthesized from one operon, there should be three structural genes. In prokaryotes, all the structural genes form single polycistronic m RNA molecule, whereas in eukaryotes, each structural gene forms separate (monocistronic) mRNA molecule.

Operator Gene

In lac operon of E. coli, the operator gene is located just near the structural gene z. It consists of 35 nucleotide base pairs. It is the binding site for the repressor. The main function of operator gene is to control the function of structural genes. However, its own function depends on the repressor molecule. Binding of repressor with operator makes it non-functional and thus prevents transcription. Repressor prevents transcription by inactivating the promoter gene. Mutation of operator makes it unfit for binding with repressor. In such situations, operator is free from binding with repressor and transcription can start. When the repressor is bound to the operator, initiation of transcription of lac mRNA by RNA polymerase is prevented. When operator is free, the promoter is available for initiation of mRNA synthesis.

Promoter Gene

In lac operon of **E. coli**, the promotor gene is located next to operator. This is located between operator gene and regulator gene. The promotor segment is a place where mRNA polymerase enzyme binds with DNA. The recent investigations (Pribnow, 19715) suggested that promotor segment has three sub regions, viz, (1) a recognition site, (2) a binding site, and (3) an m RNA initiation site. The main function of promotor gene is to initiate mRNA transcription. The m RNA transcription moves from promotor region to the structural genes through operator region. The promotor starts mRNA transcription only when operator is free or when repressor is not bound to the operator gene. The binding of repressor with operator inactivates the promotor gene and prevents transcription.

Regulator Gene

The regulator gene is located on one end of operon segment in *E. coil*. The function of the regulator gene is to direct the synthesis of a repressor which is a protein molecule. The repressor may be either active or inactive (a prorepressor). Active repressor has a tendency to bind with operator gene in the inducible system. The repressor binds to the operator in the absence of an inducer and prevents mRNA transcription by inactivating the promoter gene. When an inducer (i.e., lactose) is present, the repressor binds to the inducer and forms an inducer – repressor complex. This complex cannot bind to operator gene and, therefore, protein synthesis can take place. In the repressible system, the repressor molecule is inactive and, therefore, cannot bind with the operator gene. In such condition, protein synthesis by structural genes can take place. The repressor can become active on combining with co-repressor. This repressor corepressor complex blocks the operator gene and prevents protein synthesis.

Repressor

Repressor is a protein molecule. Its synthesis is directed by regulator gene. It may be either in the active form or inactive form as described above. It has affinity with operator gene. In the active form, it binds with operator gene and prevents transcription and protein synthesis by inactivating promoter gene. When it is in inactive form, the transcription and protein synthesis can take place. This can be inactivated by an inducer.

Corepressor

Corepressor is perhaps a product of one of the enzymes synthesized by structural genes. The corepressor makes the inactive repressor active in a repressible system after combining with the same. The repressor – corepressor complex can block the operator gene and stop protein synthesis by structural genes.

Inducer

Inducer is a substrate (i.e. lactose in lac operon) which promotes transcription. It binds with repressor molecule and makes the same inactive. The repressor then cannot bind with operator gene. Hence, the transcription and protein synthesis can take place.

Mechanism of Gene Regulation

The mechanism of gene regulation is of two types, viz, (1) negative regulation, (2) positive regulation. These are briefly described below:

Negative Control

In the negative regulation, absence of a product enhances the synthesis of enzyme and presence of the product decreases the synthesis of enzyme. In the lac operon of *E. coli*. The synthesis of protein depends whether the operator gene is blocked or free. When the operator gene is free, protein synthesis by structural genes will take place. On the other hand, when the operator gene is blocked, the protein synthesis is prevented. Thus, the on-off of protein synthesis is governed by the free and occupied position of the operator gene. In negative control, regulator protein acts as a inhibitor and prevents protein synthesis. In lac operon of **E.coli**, there is negative control of gene regulation. In the negative control, the regulator protein is the repressor which inhibits protein synthesis. In the inducible system, the effector molecule is the inducer. The inducer binds with repressor and inactivates it so that it cannot bind with operator. Thus, inducer permits protein synthesis by inactivating the repressor. In the repressible system, the effector molecule is the corepressor. The corepressor on binding with in-active repressor makes it active and inhibits protein synthesis, because when repressor becomes active it will bind with operator and stop transcription.

Positive Control

In positive regulation, presence of a product will enhance the synthesis of enzyme. In other words, in positive control the regulator protein acts as an activator and enhances the protein synthesis. The arabinose operon of **E.Coli** is an example of positive gene regulation.

Mutation of the Operon

The mechanism of gene regulation is affected by the mutation of genes in the operon segment of *E. Coli.* The mutation of regulator gene will lead to production of inactive or non-functional repressor. Such repressor is unable to bind with promotor and, therefore, cannot inhibit transcription. In other words, defective repressor cannot control the function of operator gene. In such situations, there is constant synthesis of enzymes by the structural genes. This type of mutants is known as constitutive mutants and the enzymes which are produced as a result of constitutive mutations are referred to as constitutive enzymes.

Similarly, a mutation in the promotor region also alters the mechanism of gene regulation. It may lead to three different situations depending upon the type of mutation which takes place in the promotor gene.

1. Total inactivation of promotor gene, as a result of mutation, will prevent binding of RNA polymerase to the DNA at the promotor site.
2. An up-promotor mutation will permit rapid binding of RNA polymerase to the promotor site and lead to enhanced transcription and enzyme sythensis.
3. A down – promotor mutant will decrease the rate of RNA polymerase binding to promotor site and lead to reduction in enzyme synthesis.

Thus, mutation of genes in the operon especially of regulator and promotor genes alters the mechanism of gene regulation in a definite manner.