Molecular Basis of Inheritance

REGULATION OF GENE EXPRESSION

Regulation of gene expression refers to a very broad term that may occur at various levels. Considering that gene expression results in the formation of a polypeptide, it can be regulated at several levels. In eukaryotes, the regulation of gene expression could be exerted at four levels.

(i) Transcriptional level : Formation of primary transcript.
(ii) Processing level : Regulation of splicing.
(iii) Transport of mRNA from nucleus to the cytoplasm.
(iv) Translational level.

The genes in a cell are expressed to perform a particular function or a set of functions. In eukaryotes, functionally related genes do not represent an operon but are present on different sites, chromosomes. Here structural gene is called split gene which is a mosaic of exons and introns, i.e., the base triplet - amino acid matching is not continuous. The entire split gene is transcribed to form a continuous strip of mRNA. The removal of non-coding intronic part and fusion of exonic coding parts of RNA is called RNA splicing. About 50-90% of primary transcribed RNA is discarded during processing. The development and differentiation of embryo into adult organisms are also a result of the coordinated regulation of expression of several sets of genes.

It is metabolic, physiological or environmental condition that regulates the expression of gene.

Britten-Davidson gene battery model: It is most popular for eukaryotic genes expression. It proposes the occurrence of 5 types of genes - producer, receptor, integrator, sensor and enhancer silencer.

In prokaryotes, control of the rate of transcriptional initiation is the predominant site for control of gene expression. In a transcription unit, the activity of RNA polymerase at a given promoter is regulated by interaction with accessory proteins, which affects its ability to recognise start sites. These regulatory proteins can act both activators (positively) and repressor (negatively). The functioning of operator depends upon the protein products.

Operon Concept

Francois Jacob (a geneticist) and Jacques Monod (a biochemist) proposed a model of gene regulation, known as operon model in bacteria. Operon is a co-ordinated group of genes such as structural gene, operator gene, promoter gene, regulator gene which function together and-regulate a metabolic pathway as a unit, e.g., lac operon, trp operon, ara operon, his operon, val operon etc.

(i) Regulator gene: It synthesises a biochemical or regulator protein which can act positively as activator and negatively as repressor. It control, the activity of operator gene.
(ii) Operator gene: It is a gene which receives the product of regulator gene. It allows the functioning of the operon when it is not covered by the biochemical produced by regulator gene.
(iii) Promoter gene: Provides attachment site for RNA polymerase.
(iv) Structural gene: Transcribes mRNA for polypeptide synthesis.

The Lac Operon

The lac operon (lac refers to lactose) consists of one **regulatory gene** or **inhibitor gene** (i), one **promoter gene**, one **operator gene** and three **structural genes**. A polycistronic structural gene is regulated by a common promoter and regulatory gene.

In E. coli, breakdown of lactose requires three enzymes. These enzymes are synthesised together in a co-ordinated manner by functional unit of DNA i.e., lac operon. Since the addition of lactose itself stimulates the production of required enzymes, thus it is called **inducible system**.

Lac Operon Genes

1. **Structural genes:** Three structural genes are:
   - **(i) lac z:** The z gene codes for β-galactosidase which is primarily responsible for the hydrolysis of the disaccharide, lactose into its monomeric units galactose and glucose.
   - **(ii) lac y:** The y gene codes for permease, which increases permeability of the cell to β-galactosides.
   - **(iii) lac a:** The a gene codes for transacetylase which can transfer acetyl group to β-galactoside.
2. **Operator gene:** It interacts with a protein molecule or regulator molecule, which prevents the transcription of structural genes.
3. **Promoter gene:** The gene possess site for RNA polymerase attachment.
4. **Regulator gene (i):** The gene codes for a protein known as **repressor protein**, it is synthesised all the time from the i-gene, that why it is constitutive gene which is functional always.

The operon is switched off when repressor protein produced by regulatory or inhibitor gene binds to operator gene. RNA polymerase gets blocked, so there would be no transcription.

Repressor protein + Operator gene → 3 Switched off

Regulation of lac operon by repressor is referred to as **negative control or regulation**.

If lactose is provided in the growth medium of the bacteria, the lactose is transported into the cells through the action of permease. A very low level of expression of lac operon has to be present in the cell all the time, otherwise lactose cannot enter the cells. In the presence of an inducer, such as lactose or allolactose, the repressor is inactivated by interaction with inducer. This allows RNA polymerase access to the promoter and transcription proceeds.

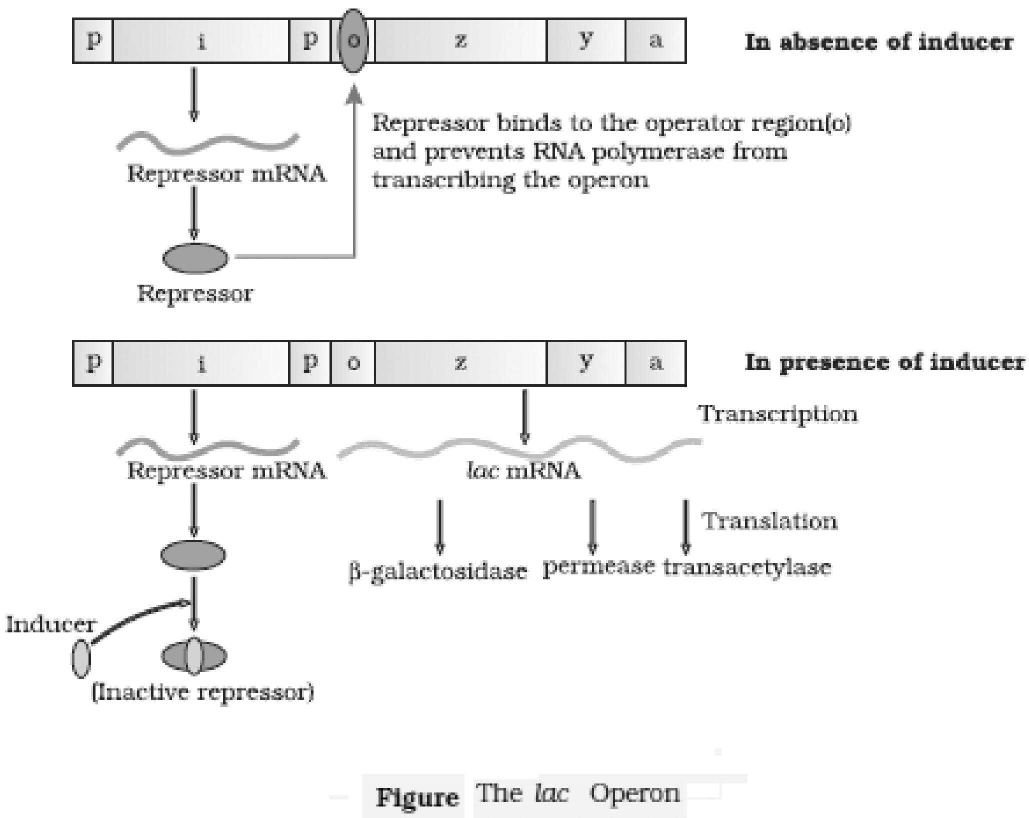

Figure The *lac* Operon

Tryptophan Operon - Repressible Operon System

Operon model can also be explained using feed-back repression. In tryptophan (trp) operon, three enzymes are necessary for the synthesis of amino acid tryptophan. These enzymes are synthesized by the activity of five different genes in a co-ordinated manner. The addition of tryptophan, however, stops the production of these enzymes. Thus, the system is known as **repressible system**.

In this system, there are five structural genes, trp A, trp B, trp C, trp D and trp E, coding for three enzyme needed for the synthesis of tryptophan, an amino acid. Regulatory gene (R) produces repressor protein which is known as **apo-repressor** because it does not get bound to the operator directly. Hence, the operator gene remains in '**switched on**' position.

Tryptophan when added, binds to the apo-repressor and is called co-repressor. This apo-repressor and co-repressor complex (activated repressor) now binds to operator gene and blocks the function of RNA polymerase. Thus, transcription would not occur and tryptophan operon would be in **switched off** position. Feed-back repression is functional when there is no further need of the end product and, hence, there is no requirement of continuation of this anabolic pathway. This operon stops the process.

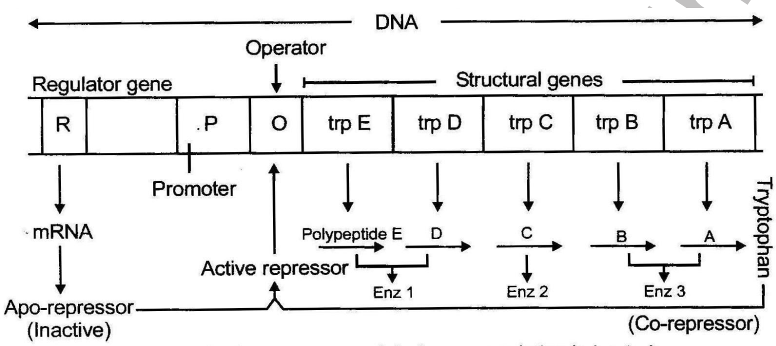

Fig. : Tryptophan operon model of gene regulation in bacteria

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