doi:10.1016/j.jmb.2011.03.041 J. Mol. Biol. (2011) 409, 1–6

Contents lists available at www.sciencedirect.com

Journal of Molecular Biology

journal homepage: http://ees.elsevier.com.jmb

# The 50th Anniversary of the Publication of the Operon Theory in the Journal of Molecular Biology: Past, Present and Future

**Moshe Yaniv**

*Department of Developmental Biology, URA 2578 CNRS, Institut Pasteur, 28 rue du Docteur Roux, 75724 Paris cedex 15, France*

Available online
22 March 2011

***Keywords:***
operon;
repressor;
transcription regulation

A series of eight review articles that appear in the present issue of the Journal of Molecular Biology celebrates the 50th anniversary for the landmark publication of François Jacob and Jacques Monod entitled "Genetic Regulatory Mechanisms in the Synthesis of Proteins". In this publication, the authors presented a model for the regulation of gene expression deduced from genetic and biochemical studies. They proposed that a new class of genes, regulatory genes, would code for repressors that bind to operator sequences upstream of operons consisting of a group of catabolic or biosynthetic genes with related functions. Binding is controlled by small metabolites, substrates or end products. The repressors control the transmission of information from genes to mRNA that is translated into proteins. The present review articles demonstrate how this publication influenced our thinking and how it stimulated the studies on the regulation of gene expression all the way to present day epigenetics and systems biology.


The review article entitled "Genetic Regulatory Mechanisms in the Synthesis of Proteins", or in brief, the "Operon Model", published by the Journal of Molecular Biology in June 1961 can be considered as a major breakthrough and one of the cornerstones in the emergence of Molecular Biology in the second half of the 20th century.[1] The double-helical model for the structure of DNA proposed by Watson and Crick in 1953 predicted how chromosomes or DNA could be replicated but did not explain how genes are expressed in cells to give rise to their respective products. The studies of François Jacob and Jacques Monod and their collaborators that culminated with the 1961 publication proposed a plausible model to explain how genes are regulated. This model was based on biochemical and genetic investigations of two systems: the regulation of the synthesis of a bacterial enzyme, β galactosidase, on the one hand and the control of bacteriophage λ lysogeny on the other hand. In both systems, they proposed that a group of structural genes with related functions is subject to coordinated control by the product of a regulator gene, the repressor. The group of coordinated genes constitutes an **Operon**, and the site on the DNA that responds to the regulator gene product was defined as **operator**. The **repressor** was capable of acting in *trans*, while the operator is functioning in *cis* to the operon. In the absence of inducer, the repressor binds to the operator and shuts off expression of the genes in the operon (Fig. 1, reprinted from the original paper). Once induced, the repressor dissociates from the operator, and the genes are expressed. In the case of the lac operon, these involve the β galactosidase that hydrolyses lactose, a specific permease gene discovered by Rickenberg, Cohen, Buttin and Monod that permits the accumulation of lactose in the cell[2] and a transacetylase of unclear function. In their paper, Jacob and Monod introduced for the first time the concept of a new class of genes, **regulatory genes**, that do not have a defined structural or metabolic

E-mail address: yaniv@pasteur.fr

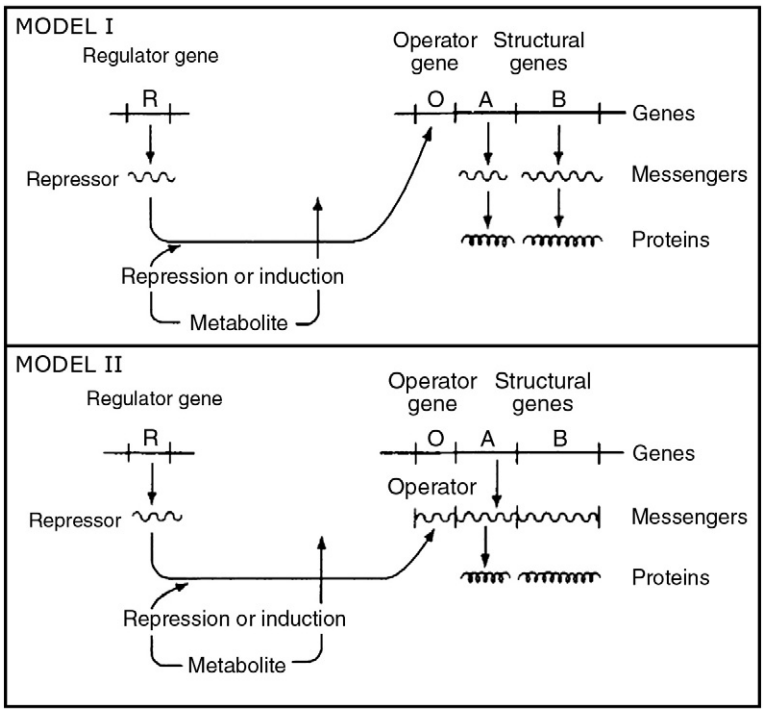


**Fig. 1.** Models of the regulation of protein synthesis or two alternative operon models. Reproduction of the original Fig. 6 from Jacob and Monod.[1]

function. These genes exist to control the expression of metabolic or biosynthetic functions.

They postulated that, for biosynthetic pathways, for example, those for amino acids tryptophan,[3] arginine[4] or histidine,[5] repressors function in an analogous but opposite way. Repressor binding to the operator(s) depends on its association with the end product of the biosynthetic pathway. Repressor dissociates when the end product is limiting, and repression generates a feedback loop in these cases. Again, a series of genes that participate in the same biosynthetic pathway is clustered in one or more operons and is co-regulated.

The operon model introduced the idea that the synthesis of bacterial proteins is subject to intricate regulatory circuits. Such circuits resemble complex control mechanisms in machines or electric circuits or even programs in computers. Indeed, Jacob and Monod can be considered as promoters of the concept of cybernetics in biology.

The Operon paper also integrated the concept of messenger RNA (mRNA). After much uncertainty as to the mechanism of protein synthesis, it became apparent that the ribosome, the site of protein synthesis, cannot contain the genetic information to code for many different proteins. Its RNA was stable, and its base composition far too well conserved to generate diversity among proteins. The experiments on β galactosidase induction and repression and on λ induction clearly demonstrated that both induction and repression are rapid and that the information encoding the enzyme or phage proteins should be unstable. Experiments on T phage infections also indicated that an RNA intermediate should be present after infection. These hints led Gros *et al*.[6] in parallel with Brenner *et al*.[7] to search for and discover the presence of a short-lived RNA in bacteria, or after phage infection, baptized mRNA, which carries the information from the genes to the ribosomes, the site of protein synthesis. The repressors block the synthesis of specific mRNA from their target operons. This was later proven once techniques of RNA–DNA hybridizations were developed. Shortly after, the genetic code that allows conversion of information encoded in mRNA into a protein sequence on the basis of three ribonucleotides to one amino acid was cracked.

Few months after the publication of the operon theory for the regulation of gene expression in bacteria, Monod and Jacob postulated how this model can be extended to explain cell differentiation in higher eukaryotes.[8]

In the 1961 publication, Jacob and Monod postulated that the repressor could be either RNA or a protein and discussed two possible modes of action: (i) direct action on the DNA or (ii) control of mRNA translation. They preferred the first option and hesitated between protein and RNA being repressors. Since they observed that inhibitors of protein synthesis such as chloramphenicol or 5-methyltryptophan did not prevent the establishment of repression after conjugation, they choose RNA. They thought that base complementarity between an RNA repressor and the operator may be an easier solution; the inducer would somehow affect the structure or