Gene regulation

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Down memory lane — unravelling the puzzle of gene regulation

In modern genetics and molecular biology, the fact that gene expression varies between different environmental states and between cell types is uncontested and taught to students early on. Many make their first approach to learning about gene regulation by discussing the first such example, the *Lac* operon of *Escherichia coli*. However, few take the time to read the seminal article by François Jacob and Jacques Monod 'Genetic regulatory mechanism in the synthesis of proteins'. I encourage every student to do so at least once.

This detailed review is an excellent showcase of how careful inductive reasoning and informed extrapolation of limited observations can provide meaningful insights into the mechanistics of a complex system, generating testable hypotheses that can expand the knowledge of a particular field. From the seemingly simple observation that there might be genes other than structural genes, that is, genes that encode structural proteins, Jacob and Monod build on a throve of genetic and biochemical observations that lead them to infer, from very few examples, the general framework of gene regulation as we know it today.

First, they identified that constitutive alleles in several systems result in an effect on all genes controlled by the proposed regulator region, meaning the mutation is in genes other than structural genes. They call these regions regulator genes and propose their product is a cytoplasmic substance that inhibits the transfer of information from a structural gene to a protein. Furthermore, they found that mutations in regulator genes disrupt the production of several proteins that participate in the same metabolic pathway and that metabolites that inhibit enzyme synthesis in repressible systems do so through the stereospecific interaction with a repressor synthesized under the control of a regulator gene — which leads to the activation of the controlled repression system.

They also found that mutations in the structural genes did not complement loss mutations in the regulator gene, which directly conflicted with the 'one gene, one enzyme' hypothesis held at the time. This conflict is resolved if structural genes are to work as an operon controlled by a single operator and if pleiotropic mutations are mutations of the operator locus. Additionally, they proposed that the operator works by specific base sequence, a reversible interaction with a repressor, which blocks the initiation of transcription and the formation of all structural genes in the operon; the repressor loses its affinity for the operator when it interacts with the metabolites targeted by the biochemical pathway under control of the operator, resulting in the activation of the operon. Finally, they also acknowledged that, even though most of the observations in bacteria suggest that the majority of systems are under repression control, alternative inducible or 'activator' systems may exist.

Their inferences are particularly remarkable in light of the limited molecular biology knowledge at the time. For example, ribosomal RNA (rRNA) was the preferred candidate template for protein synthesis. However, Jacob and Monod identified that a relatively novel RNA fraction, which they referred to as messenger RNA (mRNA), had characteristics to make it a better candidate as the template of protein synthesis, including that its base composition shifts from that of the cell to that of the phage in infected bacterial cells.

Finally, they wrapped their model together by formulating the hypothesis that the synthesis of the mRNA fraction is controlled at the genetic level by the repressor–operator interaction. They went as far as to propose that their regulator model may help illuminate problems in developmental biology, as it would explain why all cells do not express "all the potentialities inherent in their genome" concurrently, as well as areas where control is lost, such as malignancy.

In their own words: "The discovery of regulator and operator genes, and of repressive regulation of the activity of structural genes, reveals that the genome contains not only a series of blue-prints, but a co-ordinated programme of protein synthesis and the means of controlling its execution."

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We have now discovered several regulator systems that work as envisioned by Jacob and Monod, and even some that are regulated by RNA instead of proteins, as they originally proposed.

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Competing interests
The author declares no competing interests.