Control of gene expression and proteosynthesis in eukaryotes

Regulation of gene expression in eukaryotic cells is much more difficult to access experimentally and therefore more difficult to study than regulation in bacteria (https://www.wikilectures.eu/w/Bacteria) . Eukaryotic mechanisms are more complex. Despite these difficulties, research in recent years has elucidated several regulatory principles at different levels of gene expression. They turned out to be analogous to prokaryotes (https://www.wikilectures.eu/w/Prokaryote) , only somewhat more combined. Additional levels of regulation are available in eukaryotes.

Regulation at the level of gene arrangement

Genes for rRNA are represented multiple times in the genome (https://www.wikilectures.eu/w/Genome) , in some species even in many hundreds of copies. During early embryogenesis, a large number of ribosomes need to be created in a short time in the oocyte, so the genes (https://www.wikilectures.eu/w/Genetic_Code) for rRNA in the genome even multiply - **amplify** (in frogs, under these circumstances, they take up three quarters of the cellular DNA (https://www.wikilectures.eu/w/DNA)). This amplification at the level of the gene is desirable in the synthesis of rRNA, because in this case there is no longer another level of amplification, which is represented by translation (https://www.wikilectures.eu/w/Translation) in the expression of genes for proteins . Most of the genes coding for protein synthesis are found in a single copy in the genome. However, there are frequent exceptions, e.g. in tumor cells. This is known for myc and c-ras oncogenes . *In vitro* succeeded in amplifying the tetrahydrofolic acid reductase gene in tumor cells after administration of its inhibitor methotrexate. The cells thus became more resistant to the effect of the said cancerostatic agent. Another mechanism of regulation of proteosynthesis at the DNA level is rearrangement of genes (**rearrangement**) during cell differentiation. This is the case in cells synthesizing immunoglobulins . Thus, the cell can "switch" the synthesis of one type of Ig to another type during the response to an antigen.

Regulation at the level of transcription

Induction of protein synthesis is possible in eukaryotic cells as well as in bacteria. **In this sense , exogenous inducers** act mainly on cells exposed to fluctuations in the composition of the environment (hepatocytes, enterocytes). With a diet rich in proteins, the liver cell responds by inducing the synthesis of arginase, after the administration of certain drugs, the synthesis of enzymes of the microsomal oxygenase system is induced in the hepatocytes. In animal cells, it is not a question of regulation of operon systems, the arrangement of genes and the resulting mRNA are different in this case; in eukaryotic cells, genes are interrupted by introns, not polygenic, but monogenic mRNA (https://www.wikilectures.eu/w/MRNA) is formed. Positive regulation predominates in eukaryotes. Currently, **transcription enhancers are (https://www.wikilectures.eu/w/Transcription) intensively studied**, which are probably more common in nuclear cells than in bacteria. They are DNA sequences thousands of pb away from the promoter.

They were also detected in the DNA of viruses and retroviruses (part of the U3 region in the LTR section). Regulatory proteins bind to these sequences and thereby increase the activity of the "weak" promoter. Unlike the promoter, the enhancer acts in the direction, but also against the direction of transcription (if it is located after the promoter). The binding of the regulatory protein to the promoter helps to create a DNA loop, while the enhancer protein binds to the promoter region. DNA sequences are also described, the function of which is to suppress transcription (**silencers**) .

Enhancer-binding regulatory proteins include **steroid hormone receptors** and **thyroid hormone receptors**. These lipophilic substances easily penetrate the plasma membrane into the cytosol, where they bind to protein receptors, the complex is then transferred to the nucleus, where it is bound to the relevant enhancer. These hormones are therefore endogenous inducers of the synthesis of certain mRNAs and proteins. Although there are a number of differences between prokaryotic and eukaryotic transcriptional regulation, **the principles by which regulatory proteins control transcription initiation** are analogous. They can be summarized as follows:

1. The regulatory protein binds to its binding site on the promoter (DNA) and is in direct contact with the RNA polymerase (eg lac operon inducer).
2. The protein binds to a section of DNA farther from the promoter and from there interacts with RNA polymerase (e.g. regulatory protein of bacterial glutamine synthetase).
3. The regulatory protein binds directly to the RNA polymerase (e.g. σ-factor in bacteria).
4. The regulatory protein binds to DNA further from the promoter and simultaneously to another regulatory protein bound to the promoter (steroid hormone receptor in eukaryotes or prokaryotic arabinose operon regulation).

Mechanisms controlling transcription initiation

It should be noted that regulatory proteins can have a positive or negative effect on the initiation of transcription (slow it down) and that several factors (even positive and negative) can combine at the same time on the same promoter (and enhancer) and that both positive and negative effects regulatory protein can be modified (by adding another protein subunit, by covalent modification, for example by phosphorylation, by binding certain ligands, etc.).

The combination of all these factors on one promoter at a given time then gives the resulting intensity in the initiation of RNA synthesis. As in bacteria, controlled interruption and termination of transcription is also known in eukaryotes.

Regulation of pre-mRNA post-transcriptional modifications

In some systems , alternative splicing is applied . The primary transcript (pre-mRNA) is spliced in several ways. The calcitonin gene overlaps with the calcitonin-related neuropeptide (CGRP) gene. It has exons 1, 2, 3, 4, 5. After splicing in thyroid cells, exons 1, 2, 3 remain in the mRNA, whereas in ganglion cells exons 1, 2, 4, 5 are preserved. The same mechanism decides whether the IgM-producing cell will form the membrane (receptor) type and or secretory type of this immunoglobulin.

Regulation at the level of translation

An example of these mechanisms is the control of hemoglobin synthesis (https://www.wikilectures.eu/w/Hemoglobin_and_its_derivatives) units. Synthesis is regulated by heme availability. One of the protein kinases inactivates the eukaryotic initiation factor eIF-2 by phosphorylating its α-subunit. Phosphorylated eIF-2 cannot exchange GDP for GTP and recruit new Met-tRNAi to the initiation complex. In addition, the GEF (guanyl nucleotide exchange factor, or eIF-2B) protein irreversibly binds to the factor, which catalyzes the exchange of GTP – GDP on non-phosphorylated eIF-2. There is much less GEF in the cell than eIF-2, so that 30% of eIF-2 is phosphorylated to completely stop translation. The described blockade of translation is removed by heme, which inhibits elf-2 phosphorylating kinase. Globin chains are synthesized only in the presence of heme, which is energetically desirable and advantageous. The mentioned translation regulation mechanism is also used in other cells and controlled by effectors other than heme.

Controlling the rate of mRNA degradation

Some regulatory proteins bind to mRNA and slow its degradation by nucleases. An example is a protein that slows down the synthesis of the transferrin receptor by binding to the 3'-end of the respective mRNA. Iron releases this regulatory protein from binding to nucleic acid, the mRNA degrades more quickly and thus the receptors that would allow the unwanted excess of iron to be taken into the cell decrease.

Regulation of protein function by co-translational and post-translational modifications

Already during translation, the unfinished peptide chain is modified. These **co-translational modifications** include cleavage of the signal peptide (deformylation of methionine in bacteria), formation of disulfide bridges, chain conformation, formation of tertiary structure and attachment of oligosaccharide residues. After the synthesis of the protein chain is completed, its chemical modifications (**covalent modifications**) continue, which enable its function, as they ensure the correct location of the protein in the membrane, the formation of its quaternary structure, the formation and modification of the active center of the enzyme , etc. These post-translational modifications include **glycosylation proteins**, which, among other things, ensure the orientation of the molecule, solubility, location of the molecule in the cell (targeting) and the necessary kinetics of its degradation. **A peptide is cleaved** from some peptide chains , and only the resulting chains can assume a functional conformation (proinsulin – insulin). Some proteases are also activated in this way (pepsinogen – pepsin, trypsinogen – trypsin). A characteristic phenomenon of eukaryotic proteosynthesis is the possibility of the formation of **a polyprotein precursor**, a long chain, which is cleaved post-translationally by proteases into functional proteins and peptides (e.g. pro-opiomelanocortin (POMC)) is cleaved into several functional hormones (ACTH, lipotropins, endorphins, melanocyte-stimulating hormones, etc.). Some viral proteins also arise from polyproteins. The activity of other proteins, including enzymes, changes after **phosphorylation** of their serine, threonine or tyrosine residues (catalyzed by protein kinases). Proteins are also **acetylated** (histones), **ADP-ribosylated** (regulatory proteins).

The post-translational events that complete the formation of proteins and higher systems include **the assembly of subunits** into proteins with a defined quaternary structure (hemoglobin, aspartate-carbamylase). They often proceed according to a certain program, according to which the unit components are **gradually** synthesized and, **by gradually** connecting to such a supramolecular structure, create binding sites for other components. This is how viral particles (virions) and cell organelles (e.g. ribosomes) are created. Individual components are usually connected **by non-covalent bonds** during this assembly .

Links

Related Articles

- Regulation of gene expression and proteosynthesis
- Regulation of gene expression in prokaryotes
- Genome (https://www.wikilectures.eu/w/Genome)
- Transcription
- Translation

Resources

- ŠTÍPEK, Stanislav. *Stručná biochemie : Uchování a exprese genetické informace.* 1. edition. Medprint, 1998. 92 pp. pp. 62–67. ISBN 80-902036-2-0.