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REVIEW ARTICLE

A Review on Regulation of Gene in Eukaryotes

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Abstract: Gene expression in eukaryotes can be induced by environmental factors like heat and light and by chemical molecules such as hormones and growth factors. Hormone- induced gene expression is mediated by proteins that interact with the hormones. Some of these hormone receptors act directly as transcription factors by binding to DNA sequences in the vicinity of a gene; others control transcription indirectly through a signal transduction path way that targets transcription factors to a gene.

Key words: Gene; Light; heat; hormone; transcription; transduction; protein; environment; eukaryote.

Introduction

The genes that are present in the genomes of multicellular eukaryotes are normally expressed in a controlled fashion. One dimension of this control is spatial. Not every gene product is needed in every tissue. Some genes are expressed in nerve cells, other in blood cells and still others in reproductive cells. In fact, the complexity of multicellular eukaryotes is partly due to the tissue specific expression of many different genes. A second dimension of eukaryotic gene regulation is temporal. Different genes are expressed at different times, some in response to biological signals such as hormones and others in response to environmental stimuli. Temporal specificity is most dramatically seen during development, when a fertilized egg grows into a multicellular organism. As this organism forms, batteries of genes are expressed in an orderly sequence to direct the formation of tissues and organs. The temporal and spatial regulation of genes is therefore an important aspect of eukaryotic biology Snustad *et al.,* (1997).

Spatial Regulation of Tubulin Genes in Plants

The genes for tubulin polypeptide provide a dramatic example of expression that is spatially regulated. These polypeptides are the building blocks of microtubules. There are two general types of tubulin polypeptides, α and β and one molecule of each type aggregates to form a dimer. These dimers then assemble in parallel rows to form hollow, cylindrical microtubules about 24 nm in diameter. Several microtubules may aggregate with each other to create more complex structures such as cilia and flagella. Within cells microtubules are found in many places- in the cytoplasm just below the plasma membrane, around the nuclear membrane and in a special region called the microtubule-organizing center. Microtubules play an important role in cell movement.

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In cilia and flagella, their wavelike bending helps to move a cell from one position to another and inside cells, they are responsible for moving chromosomes during mitosis Baker, (1989); Karp, and Broder (1995).

Temporal Regulation of Globin Genes in animals

One of the most dramatic examples of temporally regulated gene expression comes from the study of haemoglobin, the protein that is responsible for transporting oxygen in the blood of vertebrate animals. In higher vertebrates this protein is a tetramer of polypeptides called globins, in tetramer there are two α and two β globin chains. Molecules of an iron-containing compound called haeme are loosely joined to each of these polypeptides, forming pockets that can bind molecular oxygen. In human beings, multiple genes for the α and β globins are located in two separate sites in the genome. The α globin genes occupy a 28-kb region on chromosome 16, and the β globin genes occupy a 45-kb region on chromosome 11. Because the genes within each cluster are duplicates of an ancestral globin gene, they form a small multigene family. Over evolutionary time, the members of these families have diverged from each other by random mutation so that today, each one encodes a slightly different polypeptide. In some of these duplicate genes, a frame shifting or chain-terminating mutation has abolished the ability to make a polypeptide, such non-coding genes are called pseudogenes and are denoted by the Greek letter psi (Ψ) Cavenee, and White (1995).

A remarkable feature of both the α and β gene clusters is that their members are expressed at different times during development. The genes on one side in the clusters are expressed only in the embryo, those in the middle are expressed only in the developing fetus and those on the other side

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are expressed only after birth. This sequential activation of genes from one side to the other in a cluster is apparently related to the need to produce slightly different kinds of hemoglobin during the course of human development. Embryo, fetus and infant have different oxygen requirements, different circulatory systems and different physical environments. The temporal switching in globin gene expression is apparently an adaptation to this changing array of conditions.

In eukaryotes, gene expression is spatially and temporally regulated. Some genes, such as those encoding the α and β tubulins in Arabidopsis, are expressed in a tissue-specific manner. Other genes, such as those encoding the α and β globins in vertebrates, are expressed in a specific temporal pattern during development.

Regulation of Eukaryotic Gene Expression

As in prokaryotes, the expression of genes in eukaryotes involves the transcription of DNA into RNA and the subsequent translation of that RNA into polypeptides. However, prior to translation, most eukaryotic RNA is "processed". During processing, the RNA is capped at its 5' end, polyadenylated at its 3' end, and altered internally by losing its noncoding intron sequences. Prokaryotic RNAs typically do not undergo these terminal and internal modifications. Gene expression is therefore more complicated in eukaryotes than it is in prokaryotes.

There is greater complexity of gene expression in eukaryotes because eukaryotic cells are compartmentalized by an elaborate system of membranes. This compartmentalization subdivides the cells into separate organelles, the most conspicuous one being the nucleus, eukaryotic cells also possess mitochondria, chloroplasts (if they are plant cells), and an endoplasmic reticulum. Each of these organelles performs a different function. The nucleus stores the genetic material, the mitochondria and chloroplasts recruit energy, and the endoplasmic reticulum transports materials within the cell.

The subdivision of eukaryotic cells into organelles physically separates the events of gene expression. The primary event, transcription of DNA into RNA, occurs in the nucleus. RNA transcripts are also modified in the nucleus by capping, polyadenylation and the removal of introns. The resulting messenger RNAs are then exported to the cytoplasm where they become associated with ribosomes, many of which are located on the membranes of the endoplasmic reticulum. Once associated with ribosomes, these mRNAs are translated into polypeptides. This physical separation of the events of gene expression makes it possible for regulation to occur in different places. Regulation can occur in the nucleus at either the DNA or RNA level or in the cytoplasm at either the RNA or polypeptide level.

Controlled Transcription of DNA

The control of transcription is more complex in eukaryotes than it is in prokaryotes. One reason is that genes are sequestered in the nucleus. Before they can have any effect on the level of transcription, environmental signals must be transmitted from the cell surface, where they are usually received, through the cytoplasm and the nuclear membrane and onto the chromosomes. Eukaryotic cells therefore need internal signaling systems to control the transcription of DNA. Another complicating factor is that many eukaryotes are multicellular. Environmental cues may have to pass through layers of cells in order to have an impact on the transcription of genes in a particular tissue. Intercellular communication is therefore an important aspect of eukaryotic transcription regulation Darnell *et al.,* (1990).

As in prokaryotes, eukaryotic transcriptional regulation is mediated by protein-DNA interactions. Positive and negative regulator proteins bind to specific regions of the DNA and stimulate or inhibit transcription. As a group, these proteins are called transcription factors. Many different types have been identified and most seem to have a characteristic domain that allows them to interact with DNA Snustad, *et al.,* (1997).

Cytoplasmic Control of Messenger RNA Stability

Messenger RNAs are exported from the nucleus to the cytoplasm where they serve as templates for polypeptide synthesis. Once, in the cytoplasm, a particular mRNA can be translated by several ribosomes that move along it in sequential fashion. This translational assembly line continues until the mRNA is degraded. Messenger RNA degradation is therefore another control point in the overall process of gene expression. Long lived mRNAs can support multiple rounds of polypeptide synthesis, whereas short-lived mRNAs cannot.

An mRNA that is rapidly degraded must be replenished by additional transcription, otherwise, the polypeptide it encodes will cease to be synthesized. This cessation of polypeptide synthesis may, of course, be part of a developmental program. Once the polypeptide has had its effect, it may no longer be needed, in fact, its continued synthesis may be harmful. In such cases, rapid degradation of the mRNA would be a reasonable way of preventing undesired polypeptide synthesis.

Although the longevity of mRNA has been difficult to study, a few insights have been obtained by monitoring radioactivity labeled RNAs over time. The results of these labeling

experiments indicate that mRNA longevity can be influenced by several factors, including the length of the poly-A tail, the structure of the 3' untranslated region preceding the tail, and are extremely short-lived. The sequence of the 3' untranslated region (3'UTR) also seems to affect mRNA stability. Several short-lived mRNAs have the sequence AUUUA repeated several times in their 3' untranslated regions. When this sequence is artificially transferred to the 3' untranslated region of more stable mRNAs, they too become unstable. Other studies have suggested that the stability of mRNAs can be influenced by chemical factors such as hormones. In the toad *Xenopus laevis*, the vitellogenin gene is transcriptionally activated by the steroid hormone estrogen. However, in addition to inducing transcription of this gene, estrogen also increases the longevity of its mRNA. All these findings demonstrate that by controlling the rate of mRNA degradation, cells have additional ways of modulating the overall process of gene expression Baker, (1989); Gorman and Baker (1994); Snustad, *et al.,* (1997).

Induction of Transcriptional Activity by Environmental and Biological Factors

Jacob and Monod discovered that the genes for lactose metabolism were specifically transcribed when lactose was given to the cells. It was demonstrated that lactose was an inducer of gene transcription. Even though efforts have been made to identify specific inducers of eukaryotic gene transcription, the overall extent to which eukaryotic genes are induced by environmental and nutritional factors are scarce than in prokaryotes. It is intended to describe inducible gene expression by environmental factors like temperature and light and induction by a special group of signaling molecules called hormones. The present review is aimed at describing genes that respond to hormones Darnell, *et al.,* (1990).

Genes That Respond to Hormones

Hormones circulate through the body, make contact with their target cells, and then initiate a series of events that regulate the expression of particular genes. In animals, there are two general classes of hormones. The first class, the steroid hormones, are small, lipid-soluble molecules derived from cholesterol. Because of their lipid nature, they have little or no trouble passing through cell membranes. Examples are estrogen and progesterone, which play important roles in female reproductive cycles, testosterone, a hormone of male differentiation, the glucocorticoids, which are involved in regulating blood sugar levels, and ecdysones, a hormone that controls developmental events in insects. Once these types of hormones have entered a cell, they interact with cytoplasmic proteins called hormone receptors. The receptor-hormone complex that is formed then enters the nucleus where it acts as a transcription factor to regulate the expression of certain genes Cavenee, and White (1995); Karp and Broder (1995).

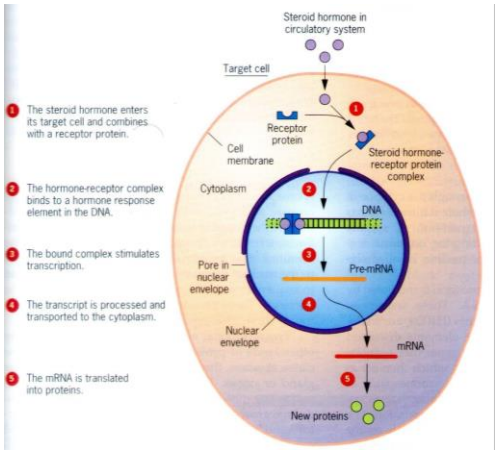

Fig. 1: Regulation of gene expression by steroid hormone

The second class of hormones, the peptide hormones, are linear chains of amino acids. Like all other polypeptides, these molecules are encoded by genes. Examples are insulin, which regulates blood sugar levels, somatotrophin, which is a growth hormone and prolactin which targets tissues in the breasts of female mammals. Because peptide hormones are typically too large to pass freely through cell membranes, the signals they convey, must be transmitted to the interior of cells by membrane-bound-receptor-proteins Evans, (1998)

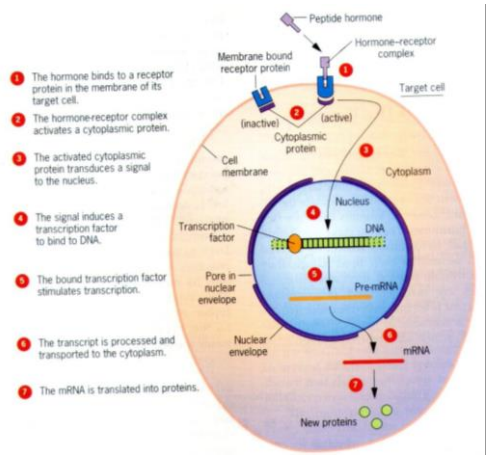

Fig. 2: Regulation of gene expression by peptide hormone

When a peptide hormone interacts with its receptor, it causes a conformational change in the receptor that eventually leads to change in other proteins inside the cell. Through a cascade of such changes, the hormonal signal is transmitted through the cytoplasm of the cell and into the nucleus, where it ultimately has the effect of regulating the expression of specific genes. This process of transmitting the hormonal signal

through the cell and into the nucleus is called signal transduction Brown, *et al.,* (1992).

Hormone-induced gene expression is mediated by specific sequences in the DNA. These sequences, called hormone response elements (HREs), are analogous to the heat-shock response. They are situated near the genes they regulate and serve to bind specific proteins, which then act as transcription factors. With steroid hormones such as estrogen, the HREs are bound by the hormone-receptor complex, which then stimulates transcription. The vigor of this transcriptional response depends on the number of HREs present. When there are multiple response elements, hormone-receptor complexes bind cooperatively with each other, significantly increasing the rate of transcription; that is, a gene with two response elements is transcribed more than twice as vigorously as a gene with only one. With peptide hormones, the receptor usually remains in the cell membrane, even after it has formed a complex with the hormone. The hormonal signal is therefore conveyed to the nucleus by other proteins, some of which bind to sequences near the genes that are regulated by the hormone. These proteins then act as transcription factors to control the expression of the genes.

Transcriptional activity can be induced by many other kinds of proteins that are not hormones in the classical sense, that is, not produced by a particular gland or organ. These include a variety of secreted, circulating molecules such as nerve growth factor, epidermal growth factor and platelet-derived growth factor, and other non-circulating molecules associated with cell surfaces or with the matrix between cells. Although each of these proteins has its own peculiarities, the general mechanism whereby they induce transcription resembles that of the peptide hormones. An interaction between the signaling protein and a membrane-bound receptor initiates a chain of events inside the cell that ultimately results in specific transcription factors binding to particular genes, which are then transcribed Parkhurst, and Meneely, (1994); Snustad, *et al.,* (1997).

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