Regulation of gene expression in eukaryotes

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Abstract

The regulation of gene expression has been the focus of research for many scientists over the past years. As scientists gained more knowledge about the prokaryotic gene regulation mechanisms, they then centered their attention in eukaryotic regulation. Every day there are more evidence showing that histone modifications, transcription and post-transcriptional modifications, RNAi and translation, are interacting and collaborating contributing towards cell differentiation and specific-gene regulation.

Introduction

Although human genome is about 95% similar with chimpanzee’s and about 50% similar with banana’s genome, what makes a human look and act like human is not (absolutely) the remaining 5% or 50% (1). The most crucial factor that differentiates species and even deeper cells from different tissues are the mechanisms that regulate gene expression. In contrast to prokaryotic gene regulation, eukaryotic cells have many levels that can be categorized in five or sometimes more stages. In this review we are going to analyze the following stages: 1) Chromatin Domains 2) Transcription 3) Post-transcriptional modification and RNA transport 4) RNAi. However there is a great harmony between the whole regulatory mechanisms, as each level interacts with the others and contributes equally to the expression of specific genes at particular environments. Moreover, many of the proteins that contribute to gene regulation processes also have roles at other pathways. Two of the most know processes that are linked are nucleotide excision repair (NER) and transcription (2).

Chromatin Domains

Histone modification

Before a gene begins the journey of expression, it must first be accessible by Transcription Factors (TF) and RNA polymerase II. DNA is normally tightly wound into a complex called chromatin. Eukaryotes utilize four proteins called histones- H2a, H2b, H3 and H4 to create a complex known as nucleosome. Nucleosomes wrap about 146 bases of DNA (3). Each of the four different histones of the nucleosomes has N-terminal tail that directly interacts with the DNA of the nucleosome. Some amino acids of the N-terminal tails are targets for enzymes like histone methyltransferases, acetyltransferases, phosphotransferases and others. Some of these enzymes are responsible for the modification or reconfiguration of chromatin, while others influence the subnuclear organization of transcription factors. For example Histone acetyltransferases (HATs) are enzymes that acetylate Lysine amino acids histone tails, leading to neutralization of the positive charge. Acetyllysine can no longer bind to DNA, leading to a more relaxed DNA-nucleosome complex (4). Another histone modification that has been well characterized is histone methylation. Enzymes called Histone methyltransferases catalyze the transfer of one, two, or three methyl groups to lysine and arginine residues. However methylation can have various effects on gene expression according to the specific amino acid that is being modified (5). Moreover histone modifications can recruit other nucleosome-remodeling or histone-modification complexes that can either enhance or repress expression. Another fact about histone modifications is that there is no certain outcome from a modification, and even more, histone modifications operate collaboratively (6).

DNA methylation

Last but not least, DNA methylation (not to be confused with histone methylation) is a very crucial step for gene regulation. DNA methylation is associated with repression of gene expression and is carried out by DNA methyltransferases which transfer a methyl group from S-adenosyl methionine (SAM) to the C5 position of cytosine in a CpG dinucleotide context. CpG islands- stretches of DNA with high frequency of CpG dinucleotides, are often associated with the 5’ ends close to the promoters of housekeeping genes and many tissue-specific genes, and sometimes with the 3’ ends of some tissues-specific genes. There are two possible mechanisms that DNA methylation could repress gene expression. The methyl groups could change the physical properties of DNA, and so affect the structure of nucleosomes leading to the formation of repressive chromatin. Otherwise the methyl groups could interact with methyl-binding proteins, such as transcriptional repressors that recruit histone deacetylases and keep histones deacetylated. However these two mechanisms
are not mutually exclusive and could both take place (7).

Transcription

The main steps for eukaryotic gene regulation are held at the stage of transcription: initiation; elongation; and termination. However initiation is the level that primarily controls gene expression. Genes are located by RNA polIII due to a DNA sequence, generally found upstream of the gene transcription start site (TSS), called promoter. However RNA polIII is not able to identify and bind to the promoter on its own with high efficiency. The TATA box is the most well known core promoter element that serves as specific binding site for general TFs (TFIIA, TFIID, TFIIF and others). Moreover there are many other cis-acting regulatory sequences that interact with trans-proteins known as activators or repressors. Most of these sequences can be found upstream of the TATA box (sometimes more than 10 kilobases away) and act as Enhancers or Repressors (8). It is important to notice that regulation of a gene by transcription factors is combinatorial, as it requires the coordinated interaction of multiple proteins. Also enhancers’ sequences may be found upstream, downstream, or within introns, and they continue to work whether in the normal orientation or turned backward in the genome (9). Finally enhancers can even act in trans. In transvection an enhancer on one copy of the gene can act upon the promoter of the other allele on the homologous chromosome (10, 11, 12). TFs -activators are able to recognize and bind to enhancer (or promoter) regions and interact with co-activators ultimately leading to the recruitment of RNA polIII. Some activators attract nucleosomes remodeling factors that alter the nucleosome structure, allowing other TFs to bind to the DNA. Repressors can bind to TFs and disable them, or they can induce the formation of heterochromatin. In general it appears that activators must interact with multiple target proteins to effect maximal transcriptional activation; whereas the majority of repressors might only require contact with a single target in order to block transcription. Finally there are some DNA sequences, known as insulators, which establish domains that separate enhancers from promoters in order to block their interaction, whereas a second type creates a barrier against the spread of heterochromatin (13).

Transcription of Immunoglobulin

The enhancer that controls the transcription of immunoglobulin genes in B lymphocytes is one of the most extensively studied. It has been proposed that the immunoglobulin enhancer is active only in lymphocytes and inactive in every other type of cell.
complex targets mRNA for cleavage, miRNA-protein complex prevents translation. In both cases mRNA is eventually destroyed and protein synthesis is prevented (19). Both noncoding RNAs form a ribonucleoprotein complex called RISC. Proteins of the RISC complex help to cut the mRNA. Moreover RNAi can at least in part; mediate gene silencing by heterochromatin. This is mainly accomplished by RNAi complexes that target homologous DNA sequences and recruit factors that modify chromatin (20, 21, 22, 23, 24).

RNAi in X-inactivation and imprinting

Although X-inactivation and genetic imprinting are both mechanisms for gene silencing, they are utilized by distinct pathways (25). However it has been reported that in both cases RNAi plays an important role. In X-inactivation –used by mammalian females for dosage compensation, the noncoding Xist gene initiates silencing of a randomly chosen X chromosome, while its antisense partner Tsix blocks silencing (26, 27, 28). In genetic imprinting, proteins like insulators, activators and repressors, as well as noncoding RNAs have been reported to be utilized.

Conclusions

As discussed in this review, regulation of gene expression in eukaryotic cells is a particular complex mechanism that is composed by many different, but interrelated levels. Proteins involved at chromatin modification may also contribute at pathways others that gene regulation. Transcription may be regulated by proximal sequences or even by sequences in the allelic gene. Furthermore proteins that take part at transcription or mRNA splicing may also interact with the RNAi pathway. To conclude, eukaryotic gene regulation is an extraordinary production of evolution that took million years to perfect.

References and Notes

1. Natural History Museum (NHM), DNA, http://www.nhm.ac.uk/nature-online/evolution/what-is-the-evidence/morphology/dna-molecules/


