Differential Gene Expression

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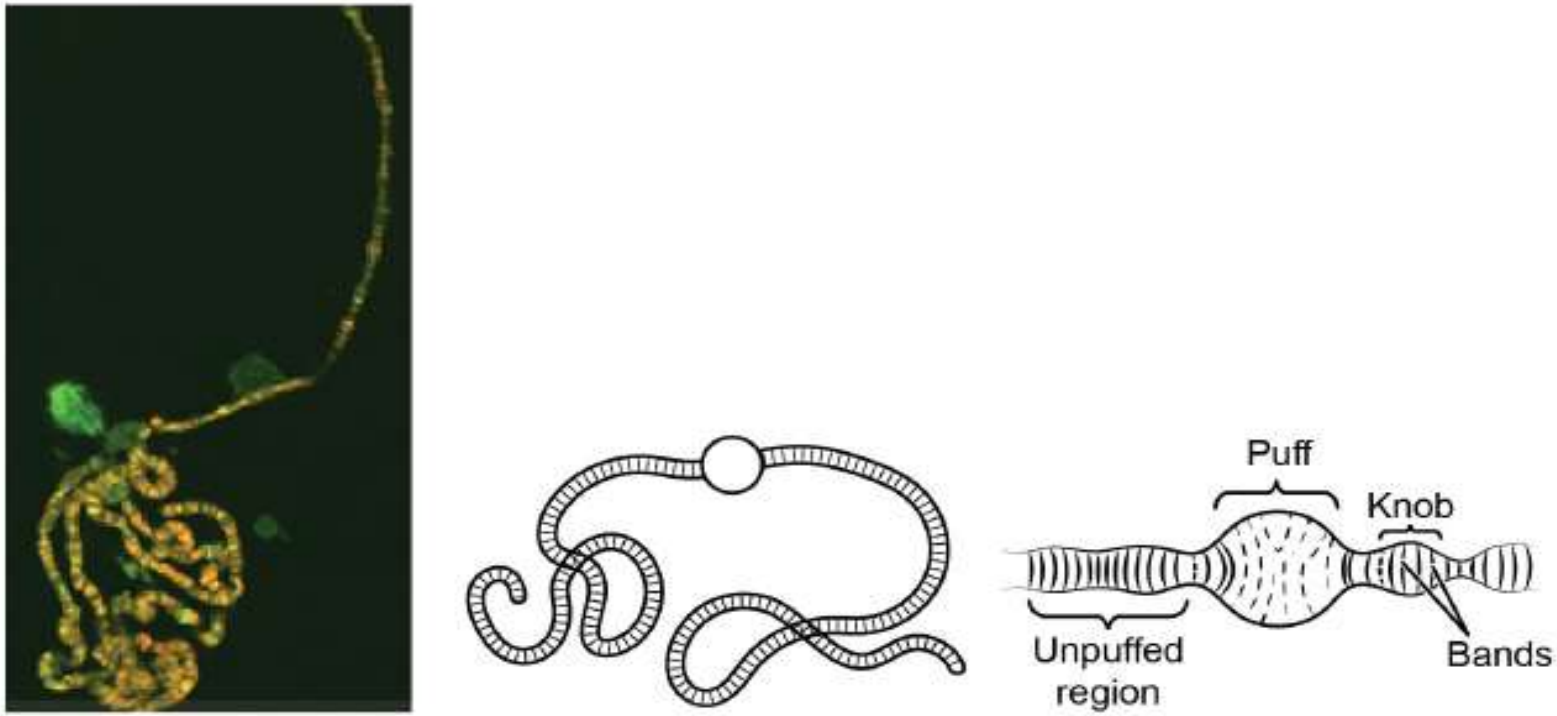
10.6.3 Differential Gene Expression

Genomic equivalence established the general principle that somatic cell nucleus of an organism contains the complete genome established at the time of fertilization and there is no change in the genetic content after differentiation of cells. If all cells in the developing embryo have the same genetic content, differences between cells must be due to **different gene activity in each cell type.** This means that only a small portion of the genome is expressed or "turned on" in each cell. As a result only those RNAs are synthesized in the cell that will translate (make) only those proteins that will provide structural information to these cells to help them differentiate and ultimately develop into very different cell types. It is important to understand how various signals cause cells to express different portions of their genetic information. Nuclear transplantation and cell fusion experiments reveal that gene activity is controlled by the **cytoplasmic environment**. New cytoplasmic signals can activate previously silent genes and silence previously active genes. Such genetic control continues throughout embryonic development and results in the generation of a variety of cell types with different gene activities. As the zygote cleaves, its cytoplasmic contents contributed by the egg do not pass uniformly into different blastomeres. The descendent cells at cleavage, therefore, have different cytoplasmic environments. This initiates a pattern of embryonic cells with a distinct programme for gene expression. Later in embryonic development, interactions between blastomeres release new signals, which then determine additional group of cells to activate new sets of genes.

Gene expression is the process by which the genetic code - the nucleotide sequence - of a gene is used to direct protein synthesis and produce the structures of the cell. Genes that code for amino acid sequences are known as 'structural genes'.

The first evidence for **differential gene expression** came from the study of polytene chromosomes of *Drosophila* larvae (Fig.10.21 a). In polytene chromosomes DNA duplication occurs in many rounds without any division and separation of the cell. The cell size increases and so as a result, the many stranded DNA is easy to observe. It was seen that the banding pattern of the chromosomes was identical throughout the various cells of the larva. No loss or addition of any chromosome portion was seen in different cell types in the larva. However, different parts of the chromosome were 'puffed up' in different cell types suggesting that different RNA was being synthesized in different cells and while one part was puffed up in one cell type the other genes were silent and so not puffed up in that cell (Fig.10.21 b).



(a) Ploytene chromosome (b) Entire chromosome (c) Enlarged view of a part

Fig 10.21: Polytene chromosome from salivary gland of *Drosophila malanogaster.* http://www.biologydiscussion.com/chromosomes/useful-notes-on-

By the late 1980s it was understood that gene expression could be regulated basically at 4 steps and this could explain the mechanism of differential gene expression.

i) At the stage of **gene transcription** so that only those genes that are required for that particular cell type are expressed in the form of nuclear RNA. Transcription is the first step of gene expression and its control involves general and tissue specific transcriptional regulators.

ii) At the nuclear RNA **processing** stage, by regulating which part of the RNA or which of the transcribed RNAs are allowed to leave the nucleus.

iii) At the RNA **translation** stage**s by regulating** which of the mRNAs are to be translated into proteins.

iv) At the **protein modification** stage, so that only those proteins are modified that can provide the structure and function to the specific cell type.

In order to understand the way genes are expressed it would help if you were to read Box 10.2 so that you can quickly recapitulate the principles of the **central dogma of biology.** Before proceeding further let us look at the structure of a gene. You know that a gene is a distinct sequence of the DNA molecule that has the information to make a polypeptide or a nucleotide. Figure 10.22 shows the gene responsible for making the β-globin in the haemoglobin molecule. The β-globin is made up of different components. Only the parts labelled exons will provide the information for the appropriate amino acid sequences for translating the appropriate protein and not the parts labelled intron. On this portion of DNA the transcription will start at the **transcription initiation site** and end at transcription termination site. This

segment will form the HnRNA (hetrogenous n RNA) and will undergo processing in which the transcribed introns will be spliced or removed. This would the result in putting together the consecutive exons and forming the mRNA. In further modification, 7-methylguanosine (G) cap and a poly (A) tail will be added to the 5-prime end and 3- prime end of this mRNA respectively. This modified mRNA will then leave the nucleus to move into the cytoplasm where it will be translated into a protein of interest. Look at the gene again in the figure 10.22. You will see that the DNA has a portion marked promoter which is not transcribed. The promoter is very important as it is at this location where the proteins and factors bind which can thus regulate or enable the process of transcription. Furthermore in the upstream (anterior end) region or in some cases even in downstream (posterior end) region and also in the introns, there will be sequences that will be able to influence the promoter to initiate transcription. These sequences are regulatory factors also known as enhancers (that stimulate), repressors or silencers (that inhibit transcription).

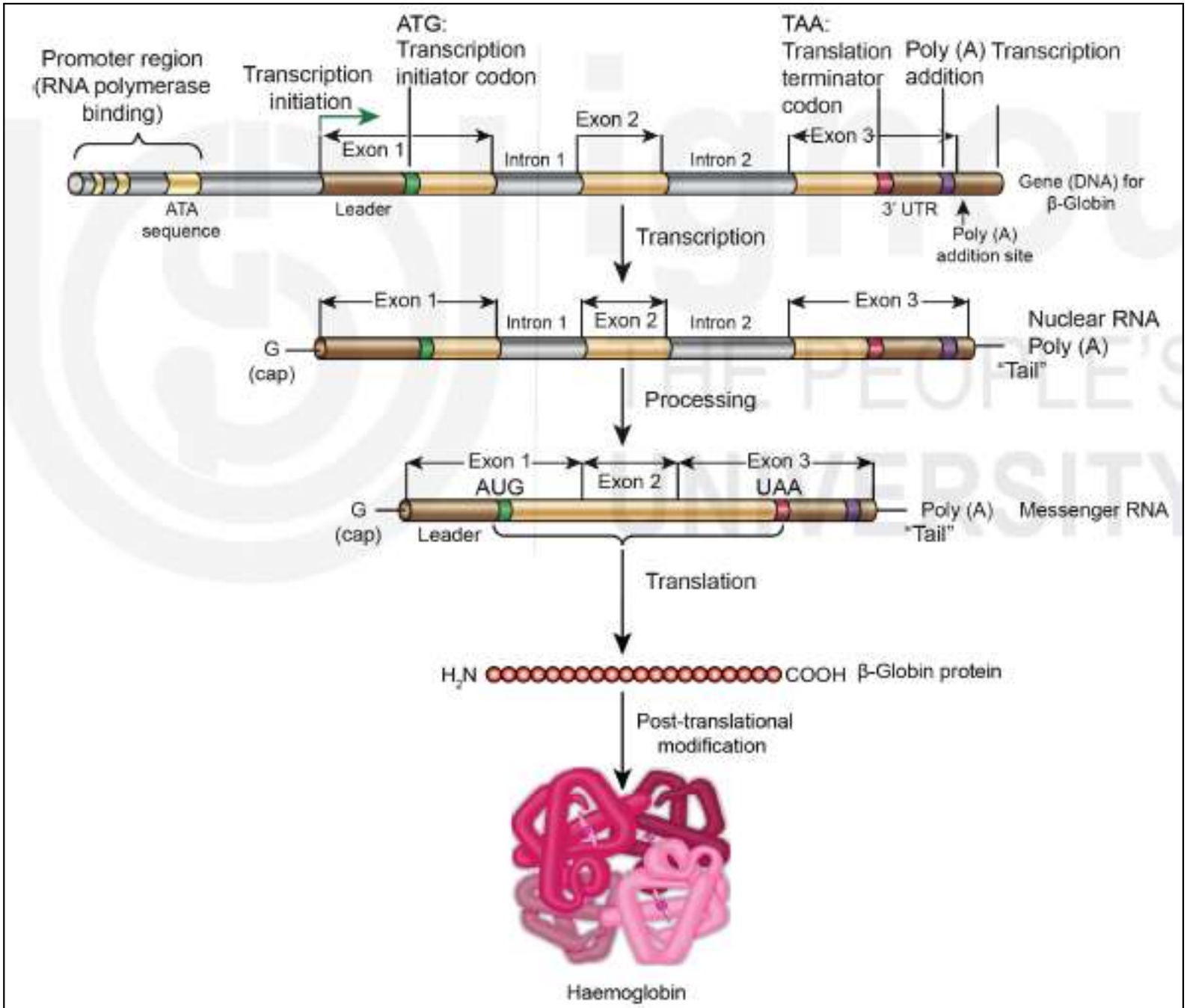


Fig.10.22: The making of beta-globin for the haemoglobin molecule. Beta-globin is inactive unless it is modified and combined with alpha globin to make the complete haemoglobin molecule.

Let us now see how regulation of gene expression can occur. Earlier in the section we had said that gene expression can be regulated at all stages from transcription to the final making of the gene product, namely protein. We will discuss the regulation at the transcription level in a little more detail so that you can understand this important mechanism. If a gene is to be regulated then first it should be accessible to a variety of factors that can bind to the DNA and regulate its expression.

1) The first step would be the loosening of the chromosome so that it can change from hetrochromatin state (when the DNA is packaged and coiled around the histones) to the euchromantin state (when the uncoiling of the DNA occurs) so that the gene becomes accessible to a variety of factors. Therefore, regulating the chromatin to uncoil or coil will influence where and when in the genome certain genes can be expressed. For this process small organic molecules can be added or removed from the histones around which the DNA remains coiled. DNA remains coiled if the histones have methyl groups attached to their tails and uncoiling occurs when the methyl groups are replaced by acetyl groups on the histone tails. It is a general rule that acetylation will give access to the promoter region and initiate active transcription, while methylation will repress transcription. Experiments have shown that this is one way of regulating gene expression.

2) Another way of regulation is by transcription factors that bind to the promoter region and can turn genes on or off. If even one transcription factor is changed in the embryo it can have dramatic effects. For example, the loss of a gene ultrabiothorax can have drastic effects in insects. This gene is a homeobox gene which contains a transcription factor, whose absence changes the segmentation pattern in the fly. As a result the fly forms two pairs of wings instead of the usual one pair due to loss of a gene ultrabiothorax. There are different transcription factors which bind to their affiliated DNA binding domains and these are very specific. Let us take the example of an enhancer region on a gene. A transcription factor specific to that enhancer forms a complex with it and can change the shape of DNA so that the promoter and transcription factor- enhancer complex come near the promoter. This causes a very important enzyme DNA polymerase to bind to the promoter which causes the transcription of a particular RNA. If transcription factor binds to the repressor region it will stop or slow down the gene from expressing. For example, the human foetal embryo liver cells synthesize serum albumin but only after a certain stage of development. Till then the gene that encodes for serum albumin is silent or repressed as a transcription factor is bound to the repressor domain. Thus, again it is the specific combination of the transcription factor with the enhancer or repressor that will regulate the rate of transcription in specific cells and cause differential gene expression. Often there is a cascade of reactions in which the gene for making a transcription factor is regulated by another transcription factor.

Therefore, it is important for you to understand that there are a variety of ways to regulate the gene and the protein it forms, which in turn

influence the differentiation of the incredible varieties of cells seen. Scientists have still a lot to learn and discover about these mechanisms.

BOX 10.2: Central Dogma of Biology

Central dogma is the sequence of events that enable the information stored in the DNA of the nucleus to be copied and transcribed into instructions for translating proteins in the cytoplasm of the cell. These proteins decide the ultimate structure and function of the differentiated cell. The sequence is given below in the chart.

DNA

Transcription ⇩ (double stranded opens up and is copied)

HnRNA (single stranded transcript containing exons and introns)

Processing ⇩ (noncoding regions or introns removed to form consecutive coding region or exons)

Transport ⇩ (leaves the nucleus and enters the cytoplasm)

Ribosome –mRNA complex

⇩ (amino acid polymerisation via tRNA)

Polypeptide Assembly

Modification ⇩ (includes folding, addition of functional moieties such as carbohydrates,phosphates or cholesterol groups)

Functional Protein

(supports structure and functional properties of the cell)

CYTOPLASMIC DETERMINANTS

- A cell can divide to produce 2 daughter cells committed to different fates. This can be achieved through the asymmetric distribution of cytoplasmic factors (e.g. proteins and RNAs) that can influence the fate of the daughter cells.
- Cytoplasmic determinants are found in many developmental systems: this strategy is used frequently in early development, when maternal gene products, localized to particular egg regions, are asymmetrically distributed to different blastomeres during cleavage.
- **Cytoplasmic determinants** are special molecules which play a very **important** role during oocyte maturation, in the female's ovary.
- During this period of time, some regions of the **cytoplasm** accumulate some of these **Cytoplasmic determinants**, whose distribution is thus very heterogenic.

Role of Cytoplasmic determinants

- They play a major role in the development of the embryo's organs. Each type of cell is determined by a particular determinant or group of determinants.
- Thus, all the organs of the future embryo are distributed and operating well thanks to the right position of the cytoplasmic determinants.
- The action of the determinants on the blastomeres is one of the most important ones. During the segmentation, cytoplasmic determinants are distributed among the blastomeres, at different times depending on the species and on the type of determinant. Therefore, the daughter cells resulting from the first divisions are totipotent :

- They can, independently, lead to a complete individual. That is not possible after the cytoplasmic determinants have been distributed in the differentiated blastomeres.

Cytoplasmic determinants and Cell divitions

- During the mosaic development, the future embryo contains all the distinct cytoplasmic determinants that are distributed in distinct cells.
- Regions of the organism differentiate very quickly if each cell contains specific cytoplasmic determinants since the first divisions : then the cell divides to give all the other cell of its type, and the same process happens in all types of cells in the organism.
- As a result, in the case of the mosaic development, cell totipotence disappears very quickly during segmentation. Indeed, each new created cell determines a new region of the future organism, and it is independent from the other ones : thus development is independent from interaction between cells.
- It is most of all known in certain animals as nematodes C. elegans, or ascidians (marine animals).