D2.2 Gene expression

Continuity and change—Cells

Additional higher level: 3 hours

Guiding questions

• How is gene expression changed in a cell?

• How can patterns of gene expression be conserved through inheritance?

Additional higher level

Note: There is no SL in D2.2.

D2.2.1—Gene expression as the mechanism by which information in genes has effects on the phenotype
Students should appreciate that the most common stages in this process are transcription, translation and the function of a protein product, such as an enzyme.
Gene expression is the mechanism by which genetic information is turned into a cellular function that affects a cell's phenotype (shape, size, metabolic activity, and overall function). This is a highly complex process that involves the regulation of transcription and translation, so malfunctions are detrimental. In prokaryotes, transcription and translation occur almost simultaneously due to the absence of a nucleus. Thus, the control of gene expression primarily occurs at the transcriptional level. In eukaryotes, regulation of gene expression is much more complex and occurs at five main levels: 1. **epigenetic** level (how tightly coiled the DNA is) 2. **transcriptional** level (rate of transcription) 3. **post-transcriptional** level (pre-mRNA processing) 4. **translational** level (production of polypeptides from mRNA) 5. **post-translational** level (alterations to polypeptide after formation) Gene expression not only involves turning genes 'on' or 'off' but also modulating levels of expression 'up' or 'down' (i.e. rate of transcribing a specific gene may be lowered to reduce expression instead of completely stopping it/turning it 'off').

D2.2.5—Differences between the genome, transcriptome and proteome of individual cells
No cell expresses all of its genes. The pattern of gene expression in a cell determines how it differentiates.
The **genome** is the totality of all coding and non-coding genes in an organism. The **transcriptome** is the whole set of mRNA molecules transcribed by a cell. The **proteome** is the entire set of all proteins produced by a cell. The **metabolome** is the collection of all molecules involved in metabolic reactions within a cell. No cell expresses all of its genes simply because it is (a) too metabolically expensive (b) would require unfolding all the DNA, which is physically infeasible. Regulating which genes are expressed (transcribed and translated) determines the function of a cell, thus how it differentiates.

D2.2.2—Regulation of transcription by proteins that bind to specific base sequences in DNA

Include the role of promoters, enhancers and transcription factors.

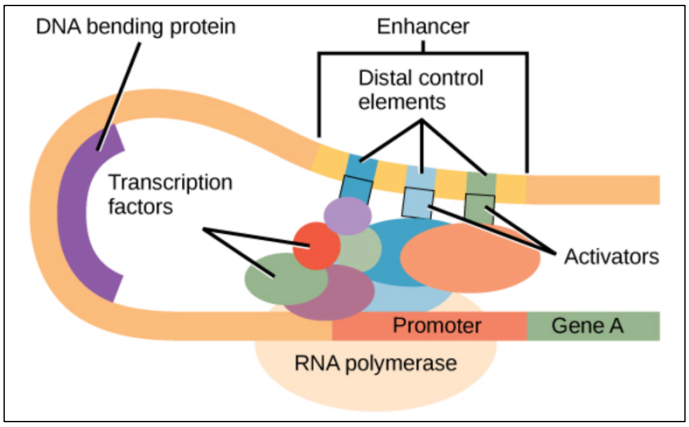

Figure 1: transcription level regulation of gene expression (Ann Clark).

In eukaryotes, regulation of gene expression at the transcriptional level involves the following:

1. **Promoter**: located towards the 5' end (upstream) of the gene, this sequence of DNA is responsible for initiating and regulating transcription by binding with transcriptional factors (proteins), since RNA polymerase by itself is unable to initiate transcription. The promotor region can be short or long; the longer it is the more transcription factors it can hold and hence the more it can be controlled. The length of the promotor is gene-specific, so the level of gene expression control can differ dramatically between genes. The promoter is composed of two main parts:
    a) **Core promoter**: this is the closest region of the promoter to the target gene and ~25-30 base pairs in length. It contains the **TATA box**, which is a sequence (5' – TATAA – 3') of repeated T and A bases found in most eukaryotes that binds to **basal transcription factors** and recruits RNA polymerase to initiate transcription.
    b) **Proximal promoter elements**: located a few hundred base pairs upstream, these regions bind to **specific transcription factors** and help in *regulating* transcription.
2. **Enhancers**: located upstream, downstream, within the coding region, or thousands of base pairs away, enhancers are made up of multiple shorter DNA sequences (**distal control elements**) and bind to specific transcription factors to regulate transcription rate. When a specific transcription factor binds to the enhancer, it undergoes a conformational change that enables it to interact with transcription factors at the core promoter to regulate transcription. Since these DNA sequences are far away from the promoter, a **DNA bending protein** attaches to DNA and causes it to bend (or loop) in order to bring the distal control elements and core promoter closer to each other, enabling their transcription factors to interact. Although two different genes can have the same promoter, they each have different distal control elements to enable differential gene expression.
3. **Transcription factors**: are proteins that bind to regulatory DNA sequences and can be of two types:
    a) **Basal transcription factors**: bind exclusively to the core promoter to recruit RNA polymerase and initiate transcription.
    b) **Specific transcription factors**: bind to proximal promoter elements and enhancers to regulate transcription rate (they cannot initiate transcription). Thus, they can either be **activators** (which increase transcription rate) or **repressors** (which reduce transcription rate).

D2.2.3—Control of the degradation of mRNA as a means of regulating translation

In human cells, mRNA may persist for time periods from minutes up to days, before being broken down by nucleases.

At the post-transcriptional level, pre-mRNA is processed before turning into mature mRNA. This includes the addition of a **poly-A tail** at the 3' end, which is just a sequence of ~100-200 repeated adenine bases that prevents the mRNA from being immediately digested by nucleases. Each mRNA has a specific stability and rate of decay, which is influenced by the length of the poly-A tail (the longer the tail, the slower the rate of decay, the more stable the mRNA). This helps to regulate translation by ensuring that proteins needed for longer periods of time have stable mRNAs whereas those needed only for a shorter time period have instable mRNAs.

D2.2.4—Epigenesis as the development of patterns of differentiation in the cells of a multicellular organism

Emphasize that DNA base sequences are not altered by epigenetic changes, so phenotype but not genotype is altered.

Epigenesis is the process by which a multicellular organism develops from undifferentiated (stem) cells.

Epigenetics are the inheritable changes in gene expression that control the transcriptional access of DNA without altering its base sequences. Epigenetic changes occur via the action of **epigenetic tags**, which are chemicals (methyl, acetyl, etc.) that alter the accessibility of a gene to being transcribed.

D2.2.6—Methylation of the promoter and histones in nucleosomes as examples of epigenetic tags

Methylation of cytosine in the DNA of a promoter represses transcription and therefore expression of the gene downstream.
Methylation of amino acids in histones can cause transcription to be repressed or activated.
Students are not required to know details of how this is achieved.

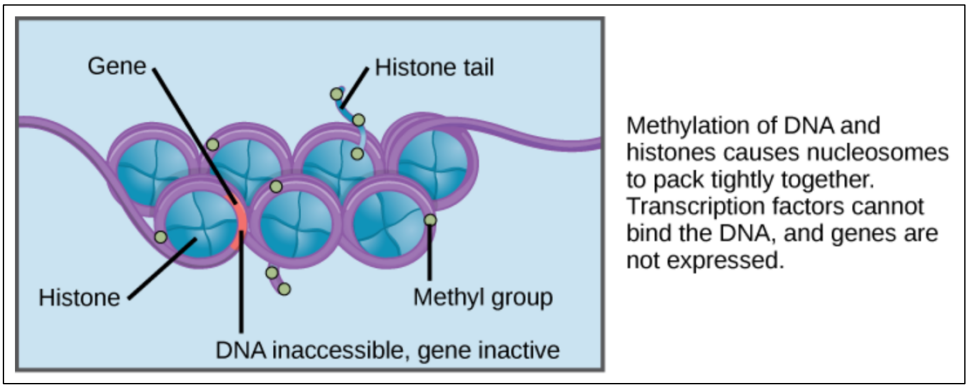

Figure 2: histone methylation (Ann Clark).

Methylation is the substitution of a hydrogen atom in a molecule with a methyl (CH_3) group, an epigenetic tag.

Since DNA is negatively charged and histone proteins are positively charged, methylation of amino acids in histones causes the nucleosomes to pack even more tightly together, causing the gene to be inaccessible to transcription factors hence 'deactivating' it.

Methyl is also added to cytosine bases within the promoter region of a gene in a stretch of highly repeated C and G base pairs (5' – CG – 3') called **CpG sites** (CpG = **C**ytosine **P**aired with **G**uanine). This represses transcription and silences the gene.

Methylation levels are affected by the environment, such as stress levels, diet, toxins, etc.

D2.2.8—Examples of environmental effects on gene expression in cells and organisms

Include alteration of methyl tags on DNA in response to air pollution as an example.

Air pollutants are environmental factors that change patterns of gene expressions in cells and organisms. Second-hand smoking, traffic-related air pollution, and cigarette smoke have been shown to alter DNA methylation patterns in human cells, leading to a variety of cardiovascular and pulmonary diseases, in addition to multiple types of cancer (lung, breast, etc.).

D2.2.7—Epigenetic inheritance through heritable changes to gene expression

Limit to the possibility of phenotypic changes in a cell or organism being passed on to daughter cells or offspring without changes in the nucleotide sequence of DNA. This can happen if epigenetic tags, such as DNA methylation or histone modification, remain in place during mitosis or meiosis.

Although most epigenetic tags are reset (reprogrammed) during meiosis, some are passed down to the offspring when fertilization occurs. However, during mitosis epigenetic tags are preserved and passed onto daughter cells within the eukaryote.

D2.2.9—Consequences of removal of most but not all epigenetic tags from the ovum and sperm

Students can show this by outlining the epigenetic origins of phenotypic differences in tigons and ligers (lion–tiger hybrids).

Genomic imprinting is a type of non-Mendelian inheritance in which some genes retain their epigenetic tags after meiosis in the sperm/ovum, even after epigenetic reprogramming. Instead of the offspring receiving two functioning alleles, one from each parent, one allele remains methylated (thus silenced) and the other is unmethylated (thus active). This occurs only in mammals and can lead to diseases, especially if a dominant healthy allele is silenced as it will result in the expression of the disease-causing recessive allele.

An example of genome imprinting is a hybrid cross between a tiger and lion.

- Male and female lions have different goals for their offspring: while males want large offspring to outcompete other males for breeding, females want quality and survival, so maternal genes increase offspring survival by inhibiting fetal growth/size (i.e. silencing growth genes through heritable epigenetic tags).
- Tigers are more solitary animals and males do not have to compete for breeding, so inhibiting fetal growth has not evolved in female tigers.
- Thus, if a male lion mates with a female tiger, the offspring (liger) grows to be larger than its parents. If a male tiger mates with a female lion, the offspring (tigon) grows to be smaller than its parents.

D2.2.10—Monozygotic twin studies

Limit to investigating the effects of the environment on gene expression.

Studies have been done on monozygotic (identical) twins which showed that differences in their **epigenome** (totality of all epigenetic tags and their patterns) accumulated with age due to environmental effects. This phenomenon is termed **epigenetic drift**, which describes how epigenetic tags change with age. This is possible due to cell and organ **phenotypic plasticity**, which describes how the phenotype expressed by a genotype is influenced by the exogenous (external) or endogenous (internal) environments.

D2.2.11—External factors impacting the pattern of gene expression
Limit to one example of a hormone and one example of a biochemical such as lactose or tryptophan in bacteria.
In humans, steroid hormones, like estradiol, testosterone, and progesterone bind to intracellular receptors and act as transcription factors to directly alter gene expression. In prokaryotes like bacteria, genes coding for proteins involved in the same biochemical pathway are clustered next to each other to form an **operon**. When glucose levels are low, bacteria can use other sugars to generate energy, like lactose. The ***lac* operon** encodes the genes required for acquiring and processing lactose. When lactose is absent, a repressor protein binds to the **operator**, which is a region of DNA sequences present in prokaryotes only to regulate transcription. Binding of the repressor to the operator prevents transcription. When lactose is present, it prevents the repressor from binding to the operator, thus allowing the expression of the genes necessary for lactose breakdown.

Linking questions

• What mechanisms are there for inhibition in biological systems?

• In what ways does the environment stimulate diversification?

Review questions

- Define gene expression. [1]
- Distinguish between the transcriptome and proteome. [2]
- A mutation in the transcription factor p53 can disrupt its role in regulating the cell cycle. Outline the potential consequences of this disruption on cellular growth. [2]
- Outline how air pollution can lead to diseases and cancers in humans. [2]
- Explain why a pancreatic cell does not have to undergo differentiation again after being formed mitotically from a parent cell. [2]
- Outline the significance of gene expression for all living organisms. [2]
- Distinguish between basal and specific transcription factors. [2]
- A mutation in an enhancer region can alter its interaction with transcription factors. Outline the consequences of this mutation on the expression of the target gene. [2]
- Outline what is meant by gene expression. [3]
- Explain the action of the *lac* operon. [3]
- Explain the significance of mitotic and meiotic genetic imprinting. [3]
- Outline the effects of genomic imprinting on offspring, using an example. [4]
- Outline the ways in which the environment stimulates diversification. [4]
- Compare and contrast the regulation of gene expression in prokaryotes and eukaryotes. [4]
- Discuss the roles of non-coding DNA sequences in transcriptional and post-transcriptional regulation of gene expression. [7]
- Discuss the various mechanisms of regulating gene expression. [8]

References

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