

Part I of the lecture:

30 minutes: a quick assessing exam

30 minutes:

- Importance of studying gene expression and regulation.
- A quick revision for Gene expression including video.

1h:

- An introduction for gene regulation including video and definitions and terminology of the main processes which will be discussed in more details in the following lectures.

Importance of studying gene expression and regulation

- 1- First, from a basic perspective, an appreciation of transcriptional mechanisms is central to our understanding of virtually all complex biologic processes, including those involving growth, differentiation, and adult homeostasis.
- 2- Aberrant gene regulation underscores a wide variety of diseases **such** as alzahymer, cancer and other diseases.
- 3- Understanding the mechanisms of these diseases will give the opportunity to develop novel therapeutics.

Gene Expression

In [genetics](#) gene expression is the most fundamental level at which genotype gives rise to the phenotype. The genetic code is "interpreted" by gene expression, and the properties of the expression products give rise to the organism's phenotype.

Steps of Gene expression:

Transcription:

Transcription is the production of RNA copies of the DNA which is performed by RNA polymerase.

Worth mentioning note: This [RNA](#) is complementary to the DNA nucleotide being transcribed; i.e. a T on the DNA means an A is added to the RNA. However, in RNA the nitrogen-containing base Uracil is inserted instead of [Thymine](#) wherever there is an Adenine on the DNA strand. Therefore, the mRNA complement of a [DNA](#) strand reading "TAC" would be transcribed as "AUG".

RNA processing:

The most common RNA processing is splicing to remove introns. Introns are [RNA](#) segments which are not found in the mature RNA, although they can function as precursors, e.g. for snoRNAs, which are RNAs that direct modification of nucleotides in other RNAs. Introns are common in eukaryotic genes but rare in prokaryotes.

RNA export

In eukaryotes most mature RNA must be exported to the cytoplasm from the nucleus. While some RNAs function in the nucleus, many RNAs are transported through the nuclear pores and into the cytosol. Notably this includes all RNA types involved in protein synthesis.

Translation

For some RNA (non-coding [RNA](#)) the mature RNA is the finished gene product. In the case of messenger RNA (mRNA) the RNA is an information carrier coding for the synthesis of one or more proteins. mRNA carrying a single protein sequence (common in eukaryotes) is monocistronic whilst mRNA carrying multiple protein sequences (common in prokaryotes) is known as polycistronic.

Each triplet of nucleotides of the coding regions of a messenger RNA corresponds to a binding site for a transfer [RNA](#). Transfer RNAs carry amino acids, and these are chained together by the ribosome. The ribosome helps transfer RNA to bind to messenger RNA and takes the amino acid from each transfer RNA and makes a structure-less protein out of it.

In prokaryotes translation generally occurs at the point of transcription, often using a messenger RNA which is still in the process of being created. In eukaryotes translation can occur in a variety of regions of the cell depending on where the protein being written is supposed to be. Major locations are the cytoplasm for soluble cytoplasmic proteins and the endoplasmic reticulum for proteins which are for export from the cell or insertion into a cell membrane. Proteins which are supposed to be expressed at the endoplasmic reticulum are recognised part-way through the translation process. This is governed by the signal recognition particle - a protein which binds to the ribosome and directs it to the endoplasmic reticulum when it finds a signal sequence on the growing (nascent) amino acid chain

Enzymes called chaperones assist the newly formed protein to attain (fold into) the 3-dimensional structure it needs to function. Similarly, [RNA](#) chaperones help RNAs attain their functional shapes. Assisting protein folding is one of the main roles of the endoplasmic reticulum in eukaryotes.

Protein transport

Many proteins are destined for other parts of the cell than the cytosol and a wide range of **signalling sequences** are used to direct proteins to where they are supposed to be. In prokaryotes this is normally a simple process due to limited compartmentalisation of the cell. However in eukaryotes there is a great variety of different targeting processes to ensure the protein arrives at the correct organelle.

Not all proteins remain within the cell and many are exported, for example digestive enzymes, [hormones](#) and extracellular matrix proteins. In eukaryotes the export pathway is well developed and the main mechanism for the export of these proteins is translocation to the endoplasmic reticulum, followed by transport via the Golgi apparatus.

Gene regulation

Several steps in the gene expression process may be modulated, including the transcription, RNA splicing, translation, and post-translational modification of a protein. Gene regulation gives the cell control over structure and function, and is the basis for cellular differentiation, morphogenesis and the versatility and adaptability of any organism.

Definition and importance:

Regulation of [gene expression](#) refers to the control of the amount and timing of appearance of the functional product of a [gene](#). Control of expression is vital to allow a cell to produce the gene products it needs when it needs them.

- Examples: Control of [Insulin](#) expression so it gives a signal for blood glucose regulation
- Cyclin expression levels control progression through the eukaryotic cell cycle

Any step of gene expression may be modulated, from the [DNA-RNA](#) transcription step to post-translational modification of a protein. The stability of the final [gene](#) product, whether it is RNA or protein, also contributes to the expression level of the gene - an unstable product results in a low expression level. In general gene expression is regulated through changes in the number and type of interactions between molecules that collectively influence transcription of DNA and translation of RNA.

Transcriptional regulation

Regulation of transcription can be broken down into three main routes of influence; genetic (direct interaction of a control factor with the gene), modulation (interaction of a control factor with the transcription machinery) and epigenetic (non-sequence changes in DNA structure which influence transcription).

Direct interaction with DNA is the simplest and most direct method a protein can change transcription levels and genes often have several protein binding sites around the coding region with the specific function of regulating transcription. There are many classes of regulatory DNA binding sites known as **enhancers, insulators, repressors and silencers**. The mechanisms for regulating transcription are very varied, from blocking key binding sites on the [DNA](#) for RNA polymerase to acting as an activator and promoting transcription by assisting RNA polymerase binding.

The activity of transcription factors is further modulated by intracellular signals causing protein post-translational modification including phosphorylated, acetylated, or glycosylated. These changes influence a transcription factor's ability to bind, directly or indirectly, to promoter DNA, to recruit [RNA](#) polymerase, or to favor elongation of a newly synthesized RNA molecule.

More recently it has become apparent that there is a huge influence of non-DNA-sequence specific effects on translation. These effects are referred to as epigenetic and involve the higher order structure of DNA, non-sequence specific DNA binding proteins and chemical modification of [DNA](#). In general epigenetic effects alter the accessibility of DNA to proteins and so modulate transcription.

DNA methylation:

Methylation of DNA (not to be confused with histone methylation) is a common [epigenetic signaling tool](#) that cells use to lock genes in the "off" position. [DNA methylation](#) is a widespread mechanism for epigenetic influence on [gene expression](#) and is seen in bacteria and eukaryotes and has roles in heritable transcription silencing and transcription regulation. In eukaryotes the structure of chromatin, controlled by the histone code, regulates access to DNA with significant impacts on the expression of genes in euchromatin and heterochromatin areas.

Post-Transcriptional regulation

In eukaryotes, where export of RNA is required before translation is possible, nuclear export is thought to provide additional control over [gene](#) expression. All transport in and out of the nucleus is via the nuclear pore and transport is controlled by a wide range of importin and exportin proteins.

RNA stability

Expression of a gene coding for a protein is only possible if the messenger RNA carrying the code survives long enough to be translated. In a typical cell an RNA molecule is only stable if specifically protected from degradation. [RNA](#) degradation has particular importance in regulation of expression in eukaryotic cells where mRNA has to travel significant distances before being translated. In eukaryotes RNA is stabilised by certain post-transcriptional modifications, particularly the 5' cap and poly-adenylated tail.

Intentional degradation of mRNA is used not just as a defence mechanism from foreign RNA (normally from [viruses](#)) but also as a route of mRNA "destabilisation". If an mRNA molecule has a complementary sequence to a small interfering RNA then it is targeted for destruction via the RNA interference pathway.

Translational regulation

Direct regulation of translation is less prevalent than control of transcription or mRNA stability but is occasionally used. Inhibition of protein translation is a major target for toxins and antibiotics in order to kill a cell by overriding its normal gene expression control. Protein synthesis inhibitors include the antibiotic neomycin and the toxin ricin.

Protein degradation and turnover

Once protein synthesis is complete the level of expression of that protein can be reduced by protein degradation. There are major protein degradation pathways in all prokaryotes and eukaryotes of which the proteasome is a common component. An unneeded or damaged protein is often labelled for degradation by addition of [ubiquitin](#).