Control of Gene Expression

Why?

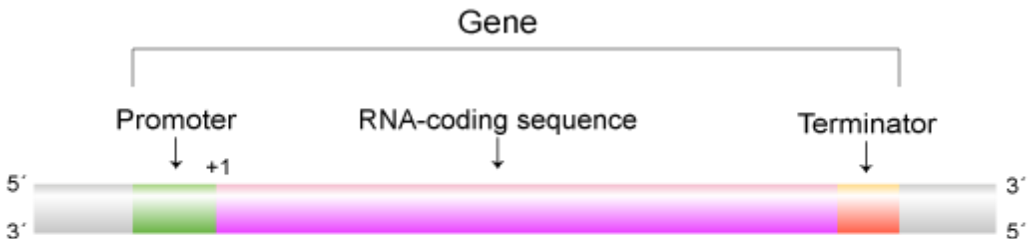
- as cells specialise into different tissues, some genes need to be switched off and others turned on
- cells need to adapt and produce different levels of protein, depending on the external environment

Control of gene expression at occur at several levels

- ➢Control of DNA transcription
- ➢Control of translation
- ➢Post-translational modifications
- ➢Epigenetic control of gene expression

Control of DNA Transcription

- Transcription is initiated at the promoter region
- Transcription is controlled by RNA Polymerase



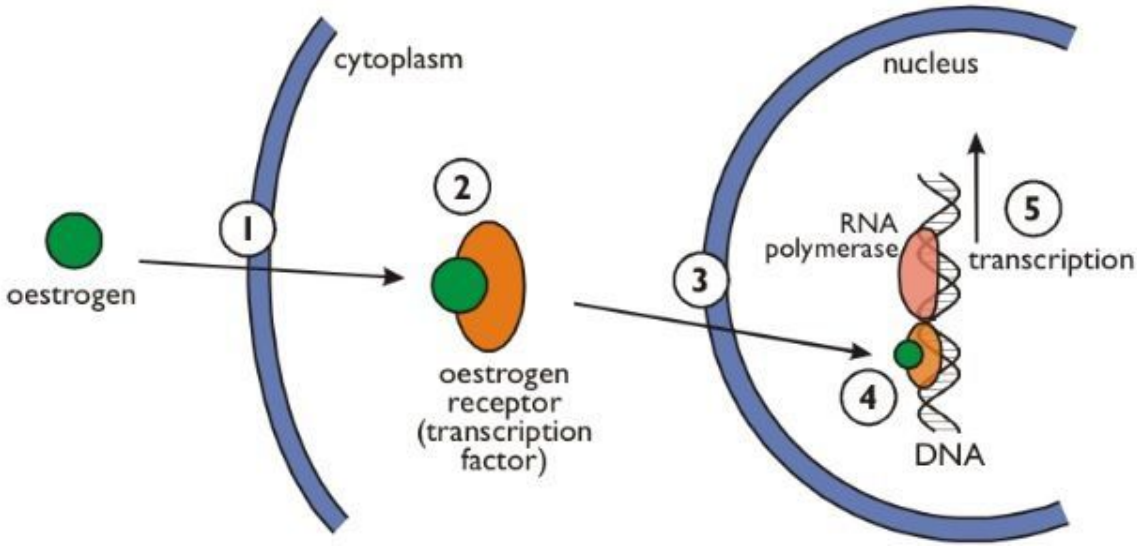
Transcription can be controlled by

- Keeping the promoter in an OFF state, and only allowing it to switch on in the presence of a molecule called a transcription factor

- Keeping the promoter in an ON state and switching it off when needed

Switching the promoter from OFF to ON

e.g the hormone oestrogen (secreted by the ovaries) can turn on the production of the hormone FSH in the pituitary gland (page 511 in textbook)

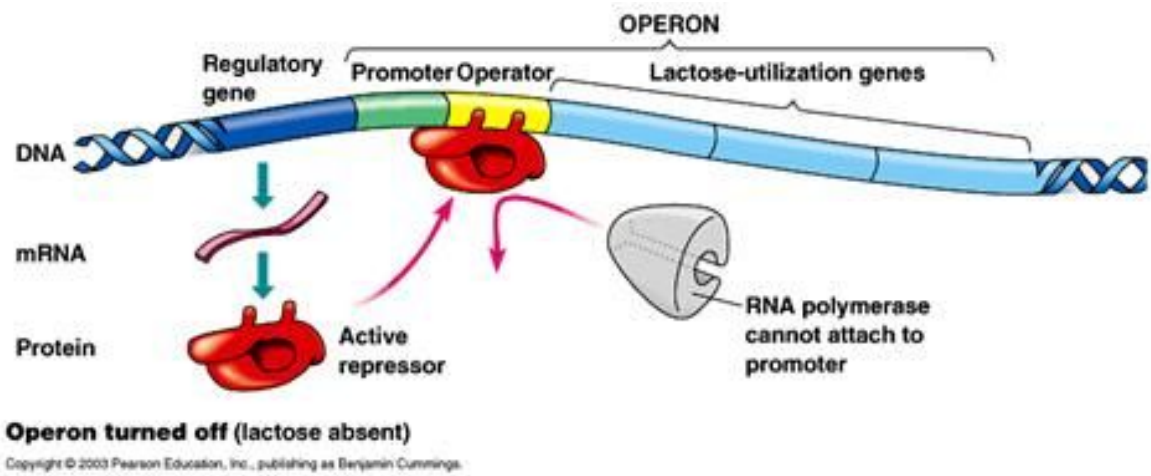


e.g the hormone oestrogen (secreted by the ovaries) can turn on the production of the hormone FSH in the pituitary gland

1. Oestrogen diffuses into the blood stream and reaches the pituitary gland
2. Oestrogen is a lipid-soluble hormone, and can diffuse across the cell membrane and enter the cells of the pituitary gland
3. Oestrogen binds to a complementary transcription factor (TF), activating the TF
4. TF diffuses from the cytoplasm into the nucleus
5. TF binds to promoter
6. Promoter is turned ON
7. RNA Polymerase can initiate transcription

Switching the promoter from ON to OFF

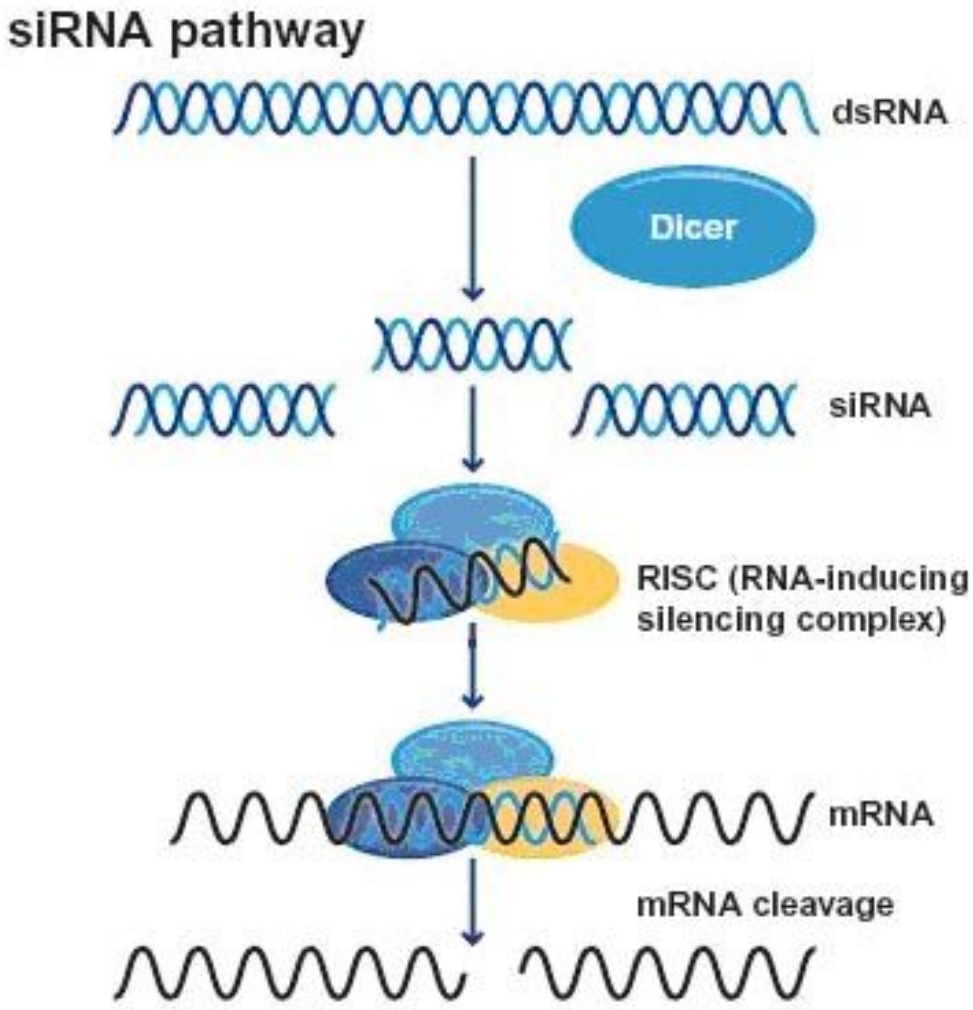
Enzymes to digest lactose (beta-galactosidase) are only made when lactose is present in the diet - at other times the gene is switched off (Details not required)



- In the absence of lactose, the regulatory gene produces a repressor protein
- Repressor proteins binds to the Operator region
- Binding of repressor to Operator changes the shape of the promoter
- Preventing RNA Polymerase from binding to it

Control of Translation using silencing RNA (siRNA)
(page 517, Fig 3)

e.g. to silence gene A, cell produces an mRNA from gene B - the two mRNAs are complementary and form an double-stranded RNA duplex



e.g. to silence gene A, cell produces an mRNA from gene B - the two mRNAs are complementary and form an double-stranded RNA duplex

1. The enzyme Dicer recognizes the duplex as ‘foreign’ and cleaves it into smaller fragments - siRNA

2. One of the strands (from gene A) is degraded and the other (from gene B) attaches to a set of enzymes, called the RNA-Induced Silencing Complex (RISC)

3. The RNA in the RISC is complementary to mRNA from gene A

4. This complex now seeks out any full length intact mRNA of gene A, and binds to it

5. mRNA is cut into two halves, and cannot be translated

Post-Translation Modification

e.g. Liver and Muscle cells contain enzymes to break down glycogen to glucose, however, these enzymes are kept in the inactive state.

Binding of adrenaline during the fight or flight response activates these enzymes.

See video:
https://www.youtube.com/watch?v=ejq99wLEMTw

Liver and Muscle cells contain enzymes to break down glycogen to glucose, however, these enzymes are kept in the inactive state.

Binding of adrenaline during the fight or flight response activates these enzymes.

1. Adrenaline (first messenger) is a water-soluble hormone, it cannot pass through the plasma membrane

2. It binds to (adrenergic) receptors on the surface of the cell

3. Binding of adrenaline activates the enzyme Adenylate Cyclase on the inside of the cell

4. Adenylate Cyclase converts ATP into cAMP (second messenger)

5. Cyclic AMP binds to, and activates the enzyme protein kinase which breaks down glycogen into glucose

6. Glucose is released into the bloodstream/muscle tissue

Epigenetic Control of gene expression

Epigenome - DNA with associated chemical tags

Epigenetics: (page 513)

- a type of nongenetic cellular memory - environment, lifestyle, diet

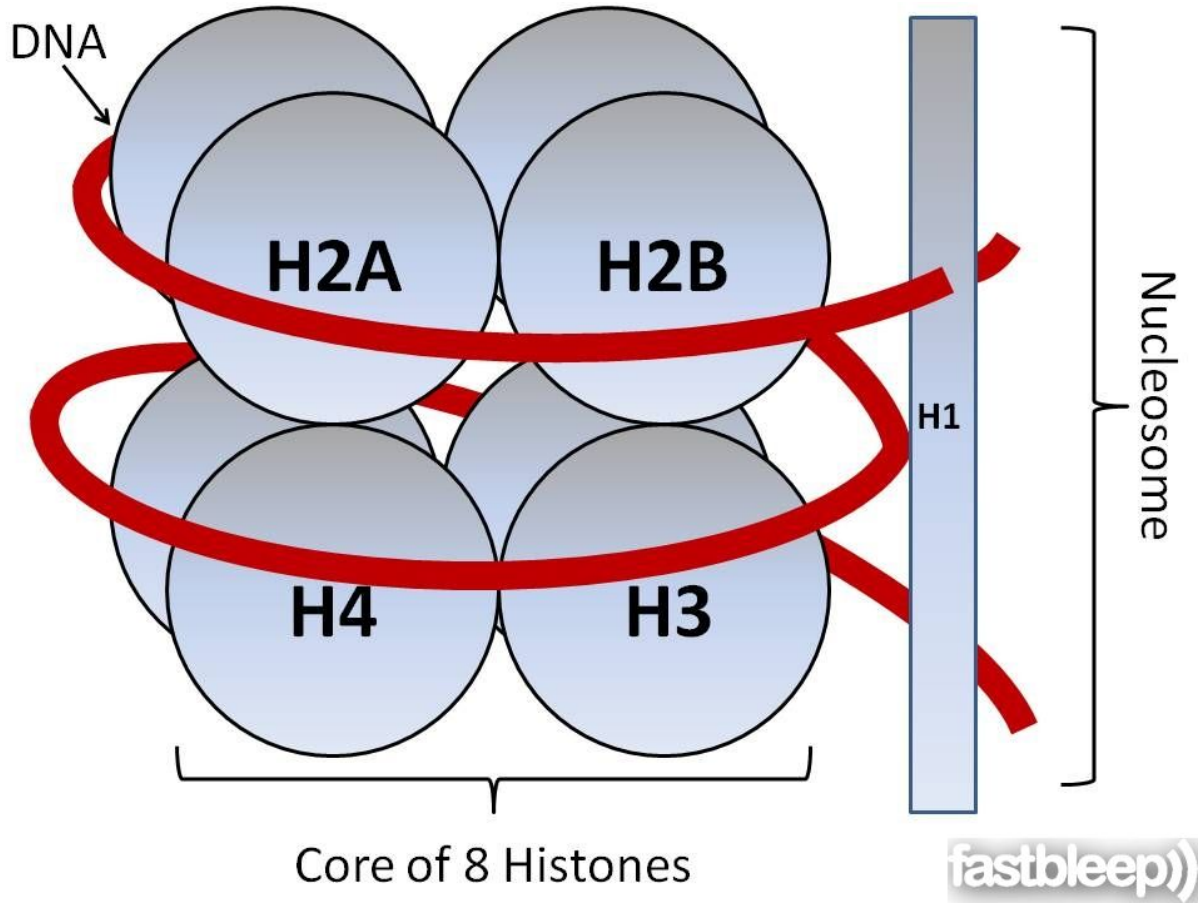
- Involves chemical modification: methylation, acetylation

- change in phenotype, without affecting genotype

- heritable - epigenetic tags can be passed on to offspring

- reversible

In the nucleus, DNA is associated with positively charged proteins called histones



Binding to histones can result in 3 structures: (pg 514)

- Euchromatin

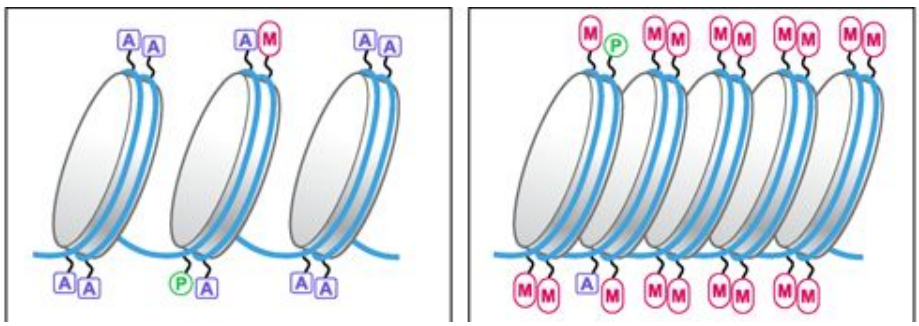
  DNA is loosely coiled around histones - easy to unzip DNA and transcribe genes

- Heterochromatin

  DNA is tightly coiled around histones - no transcription

- Chromosomes

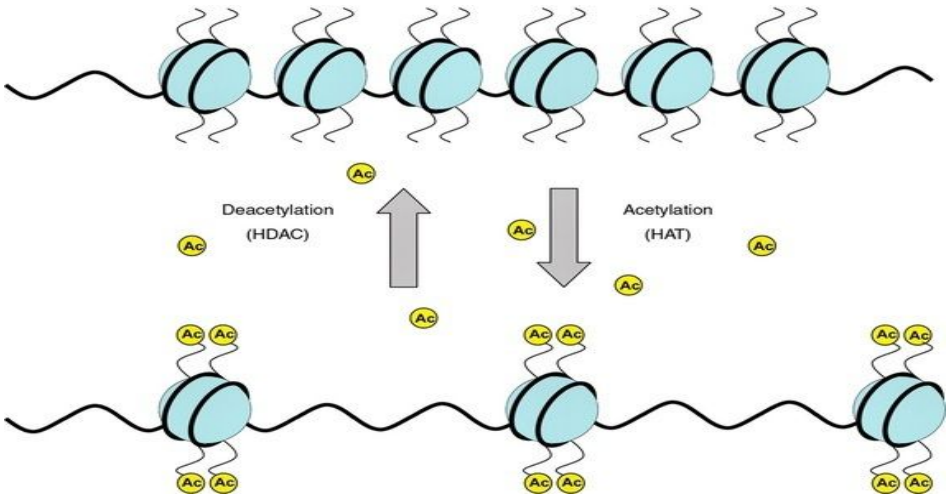
  DNA is super-coiled around histones, forming dense compact structures - no transcription



It is possible to switch from euchromatin to heterochromatin structure by modifying chemical groups on the histones

Effect of adding acetate groups to histones

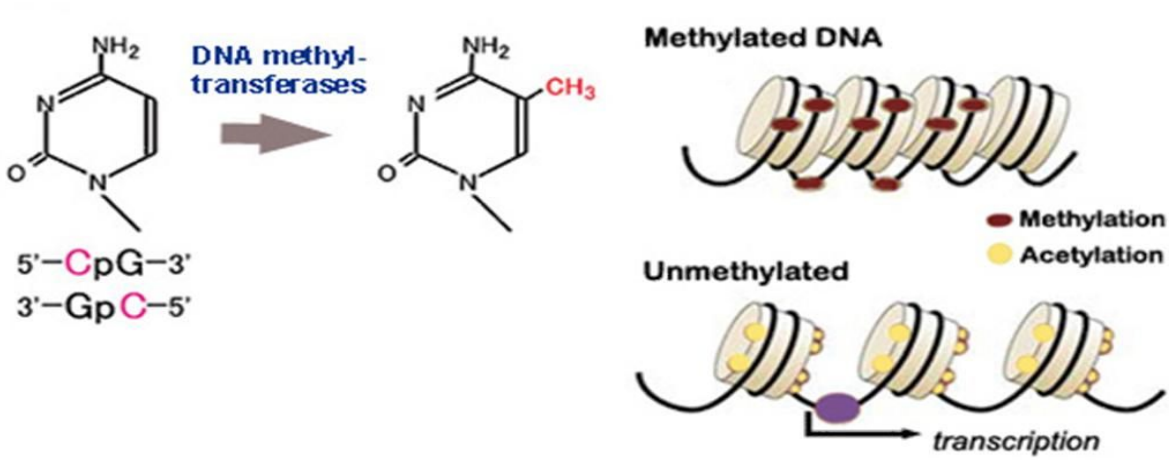
- Acetylcoenzyme A donates an acetate group to the histones
- Adding an acetate group reduces the positive charge on histones
- Reduced attraction to DNA
- DNA switches from heterochromatin to euchromatin form
- Genes in this section can now be transcribed into mRNA



Effect of adding methyl groups to DNA

- Methyl groups are added to the base cytosine
- Induces deactetylation of DNA - therefore histones now more attracted to DNA - gene turned OFF
- Prevents binding of transcription factors to the promoter region - gene turned OFF

(Methylation patterns are also used to distinguish between self and non-self DNA)



Epigenetics in the early embryo - inheritance (pg 515)

During fertilisation, most of the epigenetic tags on DNA are removed and the fertilised embryo is reprogrammed to make a fresh start = genetic "blank slate"

However, some tags remain, because some genes must remain 'ON' to direct the development of the embryo - these tags are passed on to the offspring

Other tags are added depending on the environment and nutrition provided by the mother during foetal development

i.e. if the mother has gestational diabetes, epigenetic changes in the foetus can mean that the child has a higher chance of developing diabetes in later life

Epigenetics and cancer (pg 521, pg 515)

In certain cancers, like breast and colon cancer,

- The promoter region of tumour-suppressor genes is modified by adding methyl groups (**hypermethylation**)
- DNA switches to heterochromatin form
- This prevents RNA polymerase from binding to the promoter
- The gene is turned **OFF** (silenced) = cancer

Hypomethylation (removal of methyl groups) can turn ON oncogenes

Hypermethylation of DNA repair genes turns these genes OFF - therefore they are unable to repair DNA after mutation

Epigenetics and disease (pg 515)

Duchenne muscular dystrophy in females

- X-linked condition

- Failure to make the protein dystrophin, which results is progressive muscle weakness and wastage

- Dystrophin helps stabilise skeletal muscles by acting as a shock absorber

- Females are usually carriers but not affected by the disease

- In all females, one of the X-chromosomes is switched off to prevent overexpression of proteins

- In rare cases, the X with the healthy copy of dystrophin is switched off, resulting in female with DMD

Prader-Willi Syndrome

- Each person has two copies of chromosome 15

- The copy from the mother is always switched off via DNA methylation

- A random mutation can result in the deletion of key genes on paternal chromosome 15

- The child has one epigenetically-silenced copy of chromosome 15 and one non-working copy

Understanding how epigenetics controls DNA expression can help with: (pg 516)

- develop diagnostics tests that can detect cancer at an early stage, giving a better chance of a cure

- developing drugs that can reverse the effects of epigenetic modifications - eg. histone deactetylase inhibitors