6.1 Cellular Control

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6.1.1 GENE MUTATIONS

Gene Mutations & Their Effect on Polypeptides

- A **gene mutation** is a **change** in the **sequence of base pairs** in a DNA molecule that may result in an **altered polypeptide**
- Mutations occur **continuously**
- These mutations usually have no effect on us:
  - As most mutations **do not alter the polypeptide** or only alter it **slightly** so that its **structure** or **function** is **not changed** (as the genetic code is **degenerate** i.e. several different triplets often code for the same amino acid)
  - Many mutations occur in non-coding sections of DNA and so have no effect on the amino acid sequence at all
- However, a mutation in a gene can **sometimes** lead to a **change in the polypeptide** that the gene codes for (as the DNA base sequence determines the sequence of amino acids that make up a protein)
- There are three main ways that a mutation in the DNA base sequence can occur:
  - **Insertion** of one or more nucleotides
  - **Deletion** of one or more nucleotides
  - **Substitution** of one or more nucleotides

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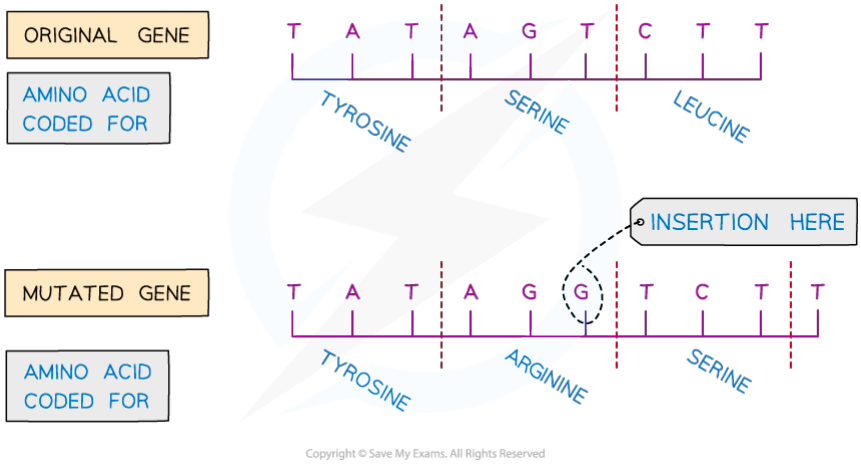
Insertion of nucleotides

- A mutation that occurs when **a nucleotide (with a new base) is randomly inserted** into the DNA sequence is known as an **insertion** mutation
- An insertion mutation **changes the amino acid that would have been coded for by the original base triplet**, as it creates a **new, different** triplet of bases
    - Remember – every group of three bases in a DNA sequence codes for an amino acid
- An insertion mutation also has a **knock-on effect** by **changing the triplets** (groups of three bases) **further on in the DNA sequence**
- This is sometimes known as a **frameshift** mutation
- This **may dramatically change the amino acid sequence produced** from this gene and therefore the **ability of the polypeptide to function**



An example of an insertion mutation

Deletion of nucleotides

- A mutation that occurs when **a nucleotide (and therefore its base) is randomly deleted** from the DNA sequence
- Like an insertion mutation, a deletion mutation **changes the amino acid that would have been coded for**
- Like an insertion mutation, a deletion mutation also has a **knock-on effect** by **changing the groups of three bases further on in the DNA sequence**
- Like an insertion mutation, this is sometimes known as a **frameshift** mutation
- This **may dramatically change the amino acid sequence produced** from this gene and therefore the **ability of the polypeptide to function**

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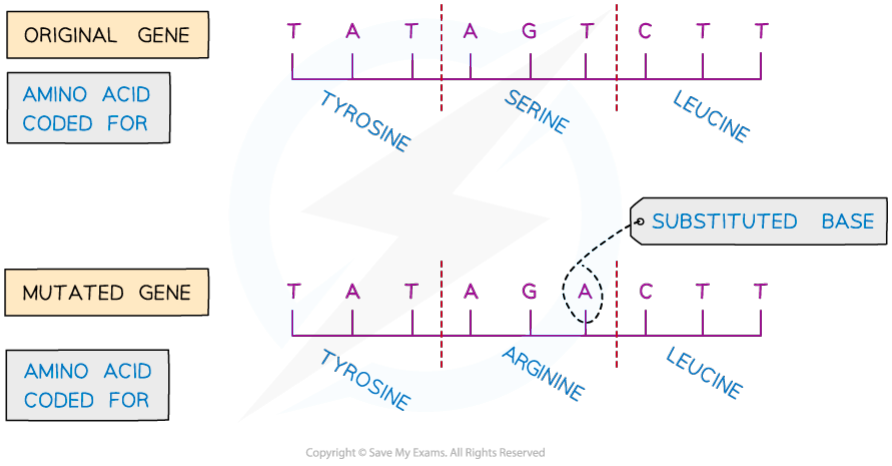
Substitution of nucleotides

- A mutation that occurs when **a base in the DNA sequence is randomly swapped for a different base**
- **Unlike** an insertion or deletion mutation, a substitution mutation will **only change the amino acid for the triplet** (a group of three bases) **in which the mutation occurs**; it will **not have a knock-on effect**
- Substitution mutations can take three forms:
  - **Silent mutations** – the **mutation does not alter the amino acid sequence** of the polypeptide (this is because certain codons may code for the same amino acid as the genetic code is degenerate)
  - **Missense mutations** – the **mutation alters a single amino acid** in the polypeptide chain (sickle cell anaemia is an example of a disease caused by a single substitution mutation changing a single amino acid in the sequence)
  - **Nonsense mutations** – the **mutation creates a premature stop codon** (signal for the cell to stop translation of the mRNA molecule into an amino acid sequence), causing the polypeptide chain produced to be incomplete and therefore affecting the final protein structure and function (cystic fibrosis is an example of a disease caused by a nonsense mutation, although this is not always the only cause)



An example of a substitution mutation

The effect of gene mutations on polypeptides

- Based on the effect they have on an organism, gene mutations can be placed into one of three categories:
  - **Beneficial** mutations
  - **Harmful** mutations
  - **Neutral** mutations

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Beneficial mutations

- A small number of mutations result in a significantly altered polypeptide with a different shape
- This may alter the ability of the protein to perform its function. For example:
  - If the shape of the active site on an enzyme changes, the substrate may no longer be able to bind to the active site
  - A structural protein (like collagen) may lose its strength if its shape changes
- In some cases, this alteration to a polypeptide may actually result in an **altered characteristic** in an organism that causes **beneficial effects for the organism**
  - In these cases, the original mutation is referred to as a **beneficial mutation**
- An example of a beneficial mutation that occurred in humans involves the production of the pigment **melanin**:
  - Early humans living in Africa had **dark skin** as they produced **high concentrations** of the pigment melanin
  - This provided **protection from harmful UV radiation** from the Sun, whilst **still allowing vitamin D to be synthesised** (due to the high sunlight intensity)
  - However, at **lower sunlight intensities**, pale skin synthesises vitamin D **more easily** than dark skin
  - As humans moved into cooler temperate climates, certain mutations occurred that led to a **decrease in the production of melanin**
  - These paler-skinned individuals would have had a **selective advantage**, as they could synthesis **more vitamin D** (a lack of vitamin D causes a range of health problems, including rickets and reduced protection against heart disease and cancers)
  - The mutations that led to a decrease in the production of melanin are therefore referred to as **beneficial mutations**

Harmful mutations

- By altering a polypeptide, some mutations can lead to an **altered characteristic** in an organism that causes **harmful effects for the organism**
  - In these cases, the original mutation is referred to as a **harmful mutation**
- Many **genetic diseases** are caused by these harmful mutations (e.g. **haemophilia** and **sickle cell anaemia**)
- An example of a harmful mutation that occurs in humans is that which causes **cystic fibrosis**:
  - In around 70% of cystic fibrosis sufferers, the mutation that causes this disease is a **deletion mutation** of three nucleotides in the **gene coding for the protein CFTR**
  - The **loss of function** of the CFTR protein caused by this deletion mutation results in a number of symptoms, including **lung and pancreatic problems** as a result of **extremely thickened mucus**

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Neutral mutations

- Neutral mutations offer **no selective advantage or disadvantage** to the individual organism
- This can occur either because:
  - A mutation **does not alter** the polypeptide
  - A mutation only alters the polypeptide **slightly** so that its structure or function is **not changed**
  - A mutation **alters** the structure or function of the polypeptide but the resulting difference in the characteristic of the organism **provides no particular advantage or disadvantage** to the organism
- An example of a neutral mutation that occurs in humans involves **the ability to taste a bitter-tasting chemical** that is found in **Brussel sprouts**:
  - This chemical is not toxic so it is **not advantageous** for us to be able to taste it
  - The ability to taste this chemical is caused by a **mutated allele of the *TAS2R38* gene**
  - The *TAS2R38* gene allows us to taste bitter things by coding for **receptor proteins** that can detect bitter-tasting chemicals
  - However, the mutated allele of this gene causes an **increased perception of bitterness**, meaning that people with this mutation can taste the bitter-tasting chemical in Brussel sprouts (whereas people without the mutation cannot)
  - Although this is now seen as a **neutral** mutation, it may have been **advantageous** in the **past** for humans to be able to detect these bitter-tasting chemicals, as large quantities of bitter substances can be harmful and many poisons have a bitter taste

Exam Tip

You may also have read about silent mutations, which is a type of neutral mutation. A silent mutation is a change in the nucleotide sequence that results in the same amino acid sequence.

This is possible because some amino acids can be coded for by up to four different triplet codon sequences.

Silent mutations are often a change in the 2nd or 3rd base in the codon, rather than the first.

For example, the amino acid valine is coded for by four different triplet codon sequences (GUU, GUC, GUA and GUG) – therefore, as long as the first two nucleotides in the codon are guanine and uracil, the amino acid valine will be inserted into the polypeptide.

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6.1.2 GENE CONTROL

Gene Control

- The nucleus of every cell in the human body contains the **same genes**
  - However, **not every gene is expressed** in every cell
  - In addition, not all of these genes are expressed **all the time**
- There are several mechanisms that exist within cells to make sure the **correct genes are expressed in the correct cell** at the correct time
  - These mechanisms are known as **regulatory mechanisms**
  - They control which genes are expressed at different points in time (e.g. during development)
- There are **three main types** of regulatory mechanisms, including:
  - Regulation at the **transcriptional level** (i.e. regulatory mechanisms that occur **during transcription**)
  - Regulation at the **post-transcriptional level** (i.e. regulatory mechanisms that occur **after transcription**)
  - Regulation at the **post-translational level** (i.e. regulatory mechanisms that occur **after translation**)
- These regulatory mechanisms are controlled by many different **regulatory genes**

Structural and regulatory genes

- A **structural gene** codes for a protein that has a **function** within a cell (e.g. enzymes, membrane carriers, hormones etc.)
  - For example, the *F8* gene codes for the protein Factor VIII involved in blood clotting
- **Regulatory genes** code for proteins (or various forms of RNA) that **control the expression of structural genes**

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6.1.3 GENE CONTROL: LAC OPERON

Gene Control: Lac Operon

- Regulatory genes control structural genes and their levels of protein production
- Regulatory genes sometimes have control over **several structural genes at once**
  - If the structural genes being controlled are in any way involved in the process of transcription, then gene control is occurring at the **transcriptional level**
- The *lac* operon provides an example of a regulatory mechanism at the **transcriptional level** (i.e. a regulatory mechanism that occurs **during transcription**)

The *lac* operon

- Structural genes in **prokaryotes** can form an **operon**: a group or a cluster of genes that are **controlled by the same promoter**
- The ***lac* operon** found in some bacteria is one of the most well-known of these
- The *lac* operon controls the production of the enzyme **lactase** (also called β-galactosidase) and two other structural proteins
- Lactase breaks down the substrate lactose so that it can be used as an energy source in the bacterial cell
- It is known as an **inducible** enzyme (this means it is **only synthesized when lactose is present**)
- This helps prevent the bacteria from wasting energy and materials

Structure of the *lac* operon

- The components of the *lac* operon are found in the following order:
  - Promoter for structural genes
  - Operator
  - Structural gene ***lacZ*** that codes for **lactase**
  - Structural gene *lacY* that codes for permease (allows lactose into the cell)
  - Structural gene *lacA* that codes for transacetylase
- Located to the left (upstream) of the lac operon on the bacterium's DNA there is also the:
  - Promoter for regulatory gene
  - Regulatory gene ***lacI*** that codes for the ***lac* repressor protein**
- The lac repressor protein has **two binding sites** that allow it to bind to the **operator** in the lac operon and also to **lactose** (the **effector** molecule)
  - When it binds to the operator it **prevents the transcription** of the structural genes as RNA polymerase cannot attach to the promoter
  - When it binds to lactase the shape of the repressor protein distorts and it can **no longer bind to the operator**

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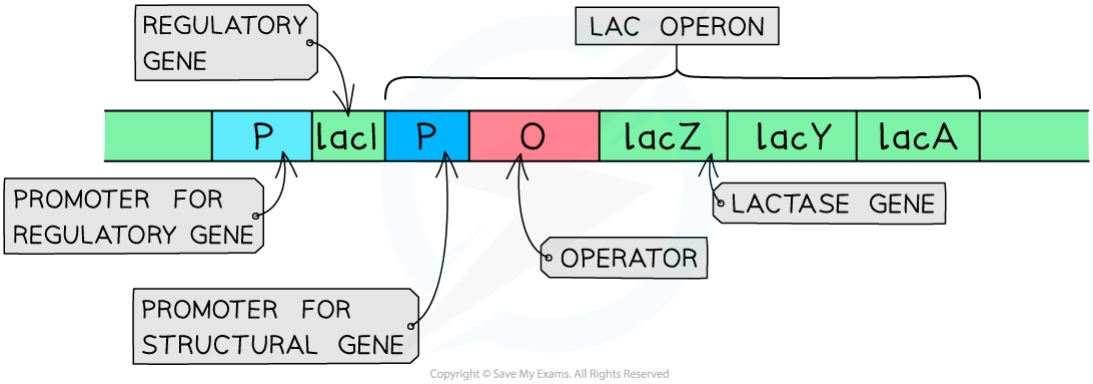
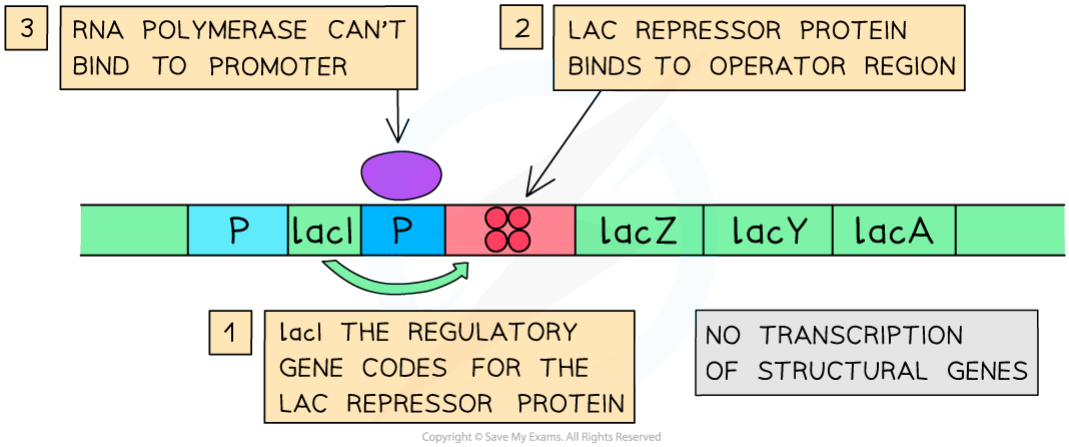


The components of the lac operon along with the upstream regulatory gene and its associated promoter

When lactose is absent

- The following processes take place when lactose is **absent** in the medium that the bacterium is growing in:
  - The regulatory gene is transcribed and translated to produce *lac* repressor protein
  - The *lac* **repressor protein binds to the operator** region upstream of *lacZ*
  - Due to the presence of the repressor protein **RNA polymerase is unable to bind to the promoter region**
  - Transcription of the structural genes does not take place
  - **No lactase enzyme is synthesized**



The repressor protein binding to the operator region of the lac operon and preventing transcription of the structural gene

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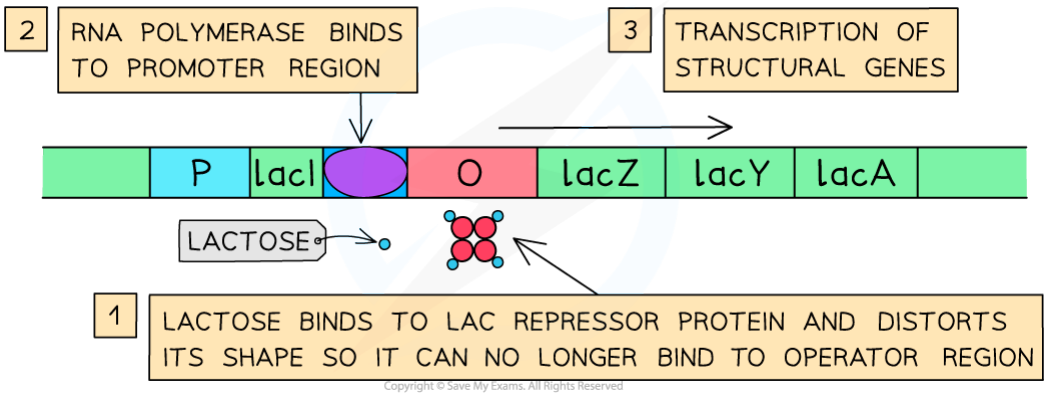
When lactose is present

- The following processes take place when lactose is present in the medium that the bacterium is growing in:
  - There is an uptake of lactose by the bacterium
  - The **lactose binds to the second binding site on the repressor** protein, distorting its shape so that it cannot bind to the operator site
  - **RNA polymerase is then able to bind to the promoter region** and transcription takes place
  - The mRNA from all three structural genes is translated
  - **Enzyme lactase is produced** and lactose can be broken down and used for energy by the bacterium



The binding of lactose to the repressor protein frees up the operator region of the lac operon so RNA polymerase can bind and begin transcription of the structural genes

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Exam Tip

The example above explains how the genetic control of an inducible enzyme works. However, you could get some questions on the genetic control of **repressible enzymes**. In this mechanism, an effector molecule also binds to a repressor protein produced by a regulatory gene. However this binding actually **helps the repressor bind to the operator region** and prevent transcription of the structural genes. So it's the opposite of the lac operon: when there is **less of the effector** molecule, the repressor protein cannot bind to the operator region and **transcription of the structural genes goes ahead,** meaning the enzyme is produced.

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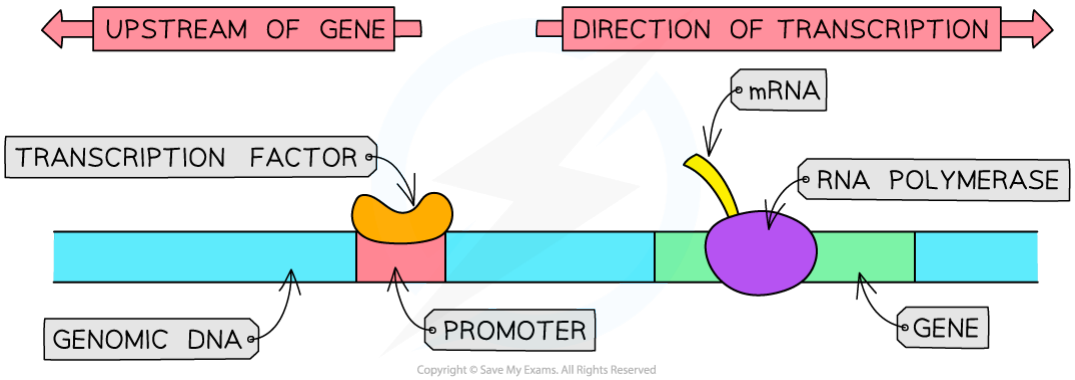
6.1.4 GENE CONTROL: TRANSCRIPTION FACTORS

Gene Control: Transcription Factors

- Prokaryotes use **operons** to control the expression of genes in cells
- Eukaryotes also use **transcription factors** to control gene expression
  - Transcription factors are proteins that bind to specific regions of DNA to **control the transcription of genes**
- It is estimated that ~10% of human genes code for transcription factors
  - There are several types of transcription factors that have varying effects on gene expression
  - This is still a relatively young area of research and scientists are working hard to understand how all the different transcription factors function
  - Transcription factors allow organisms to respond to their environment
  - Some hormones achieve their effect via transcription factors

How transcription factors work

- Some transcription factors **bind to the promoter region** of a gene (i.e. the region of DNA 'upstream' of the gene that controls the expression of the gene)
  - This binding can either **allow or prevent the transcription** of the gene from taking place
- The presence of a transcription factor will either **increase** or **decrease** the **rate of transcription** of a gene
  - For example, **PIF** is a transcription factor found in plants that **activates** the transcription of the **amylase gene**



A transcription factor binding to the promoter region of a gene which allows RNA polymerase to bind and for transcription to occur

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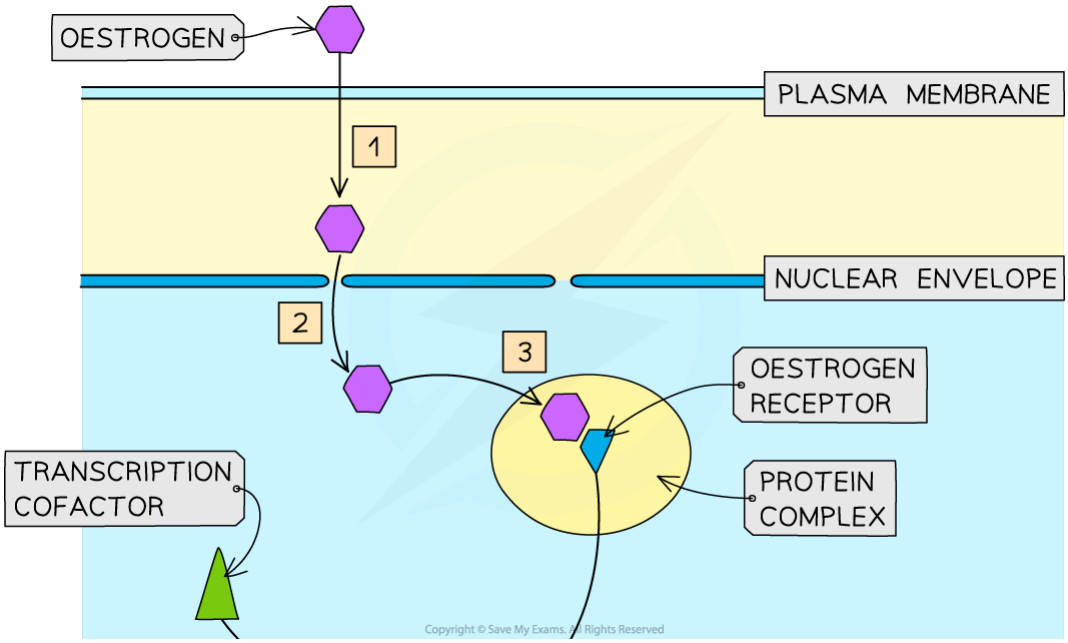
Gene control: oestrogen

- In mammals, the hormone oestrogen is involved in controlling the oestrus cycle and also in sperm production
- Oestrogen is a **lipid-soluble molecule** and can therefore **diffuse through the plasma membrane** of cells
- It then moves to the **nucleus** and **binds to an oestrogen receptor**
- These receptors are actually **transcription factors** that are able to **initiate transcription for many different genes** by binding to their **promoter regions**
- Once bound, oestrogen causes a **change in the shape of the receptor**
- As a result, the receptor **moves away from the protein complex it is normally attached to** and binds to the promoter region of one of its **target genes**
- This allows **RNA polymerase to bind** and to begin **transcribing** that gene



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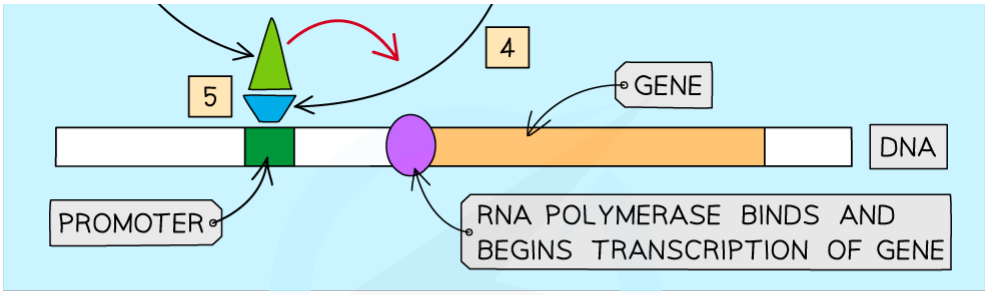

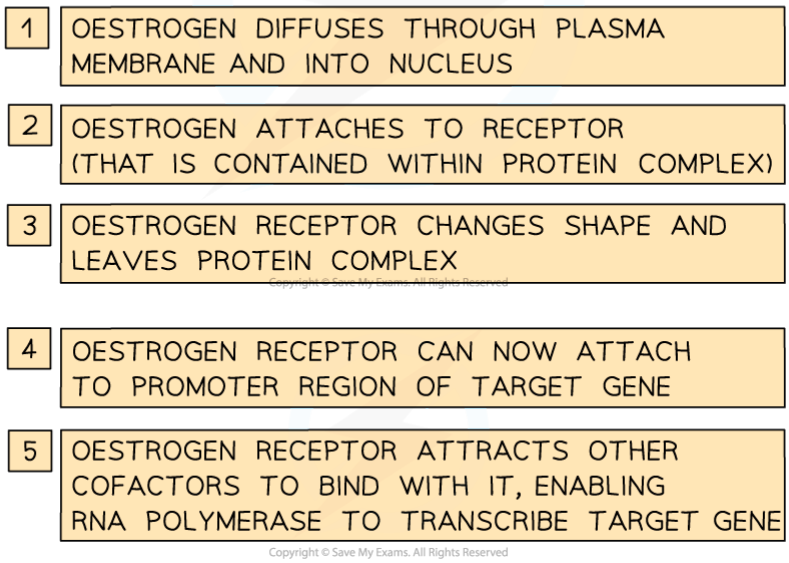

A summary of how oestrogen can stimulate the transcription of a gene

Gene control: gibberellin

- Plant cells use transcription factors in a similar way to animal cells
- Gibberellin is a **hormone** found in plants (e.g. wheat and barley) that **controls seed germination** by stimulating the synthesis of the enzyme amylase
- It does this by influencing **transcription of the amylase gene**
  - When gibberellin is applied to a germinating seed there is an increased amount of the mRNA for amylase present

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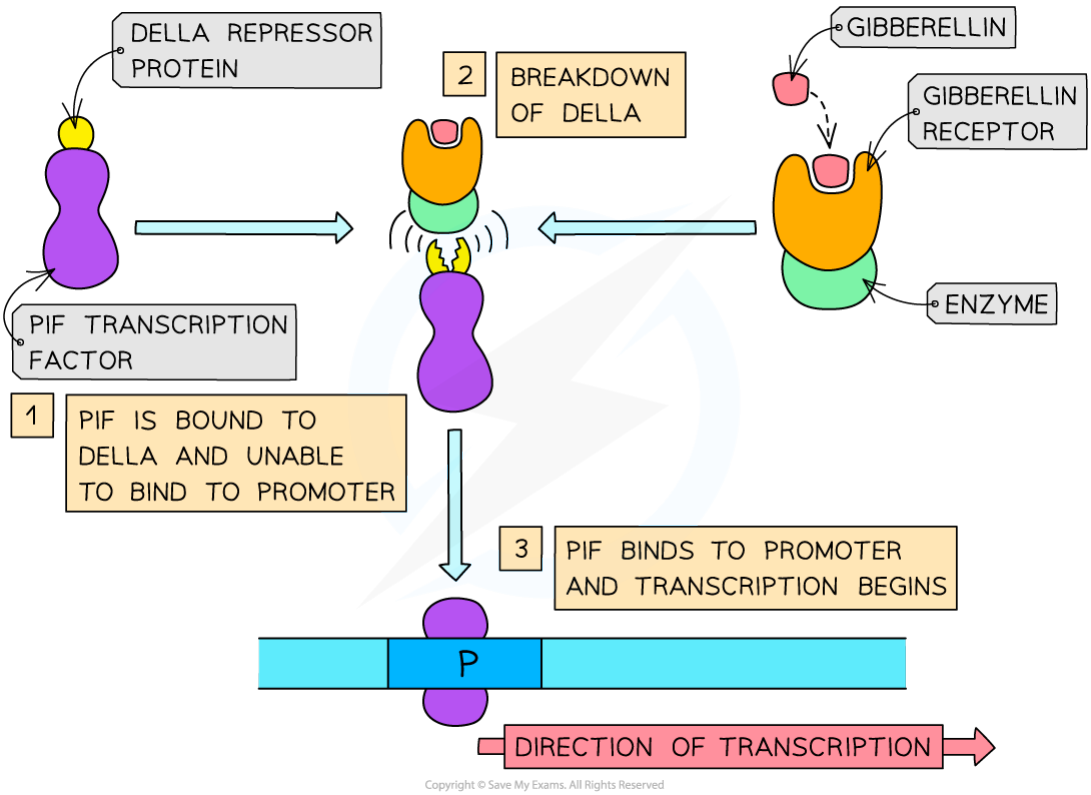
Mechanism

- The **breakdown of DELLA protein by gibberellin** is necessary for the synthesis of amylase
- The following components are involved:
  - Repressor protein **DELLA**
  - Transcription factor **PIF**
  - **Promoter** of amylase gene
  - Amylase **gene**
  - **Gibberellin**
  - Gibberellin **receptor and enzyme**
- The process occurs as follows:
- DELLA protein is bound to PIF, **preventing it from binding to the promoter** of the amylase gene so no transcription can occur
- Gibberellin binds to a gibberellin receptor and enzyme which starts the **breakdown of DELLA**
- **PIF** is no longer bound to DELLA protein and so it **binds to the promoter** of the amylase gene
- Transcription of amylase gene begins
- Amylase is produced



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The breakdown of DELLA protein by gibberellin allows the transcription factor PIF to bind to the promoter for the amylase gene and for transcription to initiate

Exam Tip

In your exam you may be asked to explain why RNA analysis is important with regards to gene expression. From the outside most cells look almost identical with the same DNA in their nucleus. However we know that they are most likely expressing different genes. When a cell expresses a gene, RNA is produced by transcription. This RNA present in a cell can be analysed. Scientists can match the RNA present in a cell to specific genes and work out which genes are being expressed in that specific cell.

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6.1.5 GENE CONTROL: POST-TRANSCRIPTIONAL MODIFICATION

Post-Transcriptional Modification

- Within eukaryotic genes, there are both **coding** and **non-coding sequences** of DNA
  - The **coding sequences** are called **exons** and these are the sequences that will eventually be **translated** into the amino acids that will form the final polypeptide
  - The **non-coding sequences** are called **introns** and are **not translated** (they do not code for any amino acids)
- **When transcription of a gene occurs, both the exons and introns are transcribed**
- This means the messenger RNA (mRNA) molecule formed also **contains exons and introns**
  - This RNA molecule is often referred to as primary mRNA or pre-mRNA
- As the **introns** are not to be translated, they must be **removed** from the pre-mRNA molecule
- The **exons** are then all **fused together** to form a continuous mRNA molecule called **mature mRNA** that is ready to be **translated**
- This process is sometimes called '**splicing**' and is part of the process of **post-transcriptional modification** (referring to the modification of the RNA molecule **after transcription** but **before translation** occurs)
- Splicing ensures that **only the coding sections** of mRNA are used to form proteins by translation (if any introns were included in the mature mRNA, the resulting protein would not be formed properly and may not function as it should)

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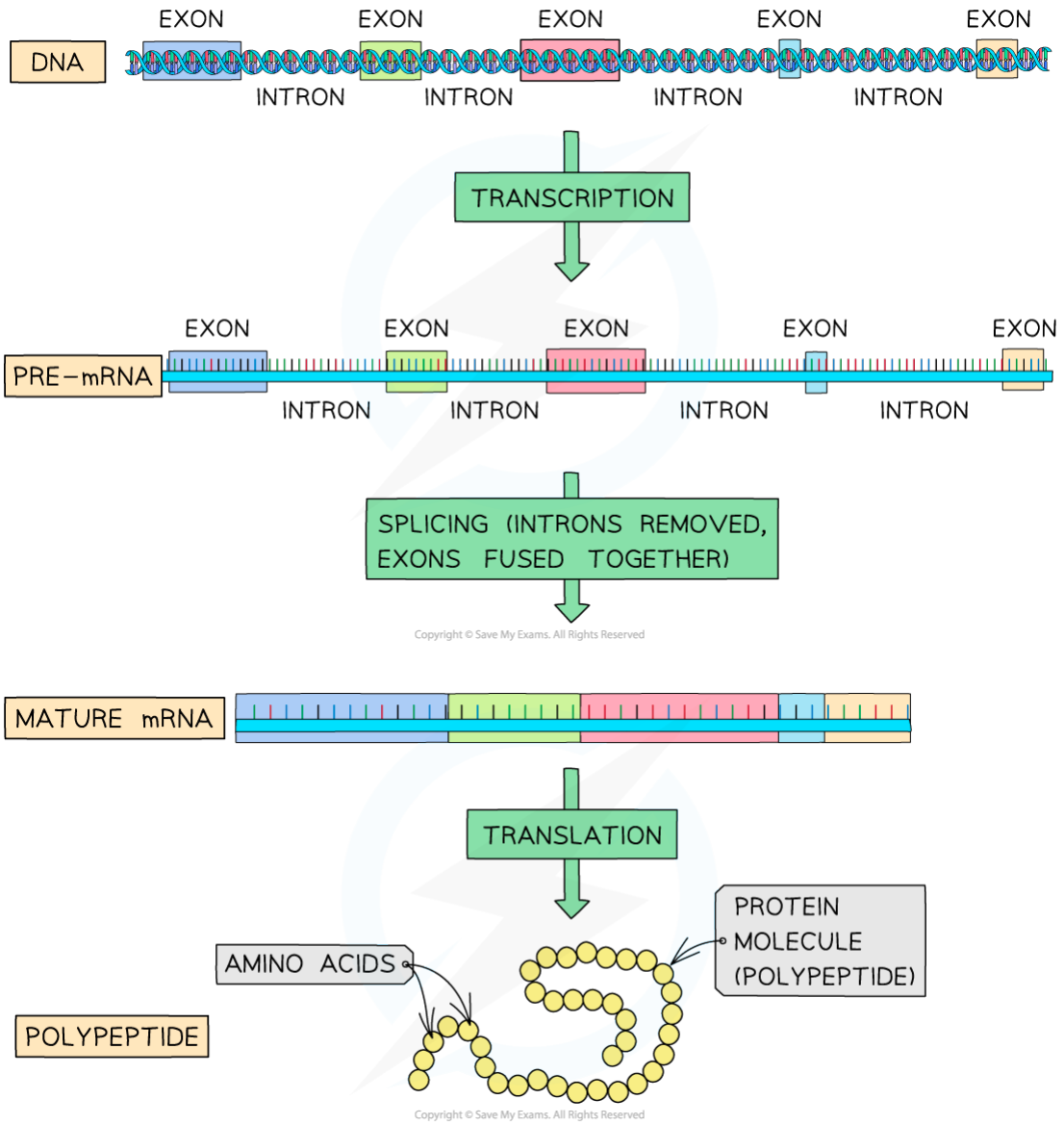

The RNA molecule (known as pre-mRNA) produced from the transcription of a gene contains introns that must be removed (to form mature mRNA) before translation can occur

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Control at the post-translational level

- After polypeptides are formed by translation, they undergo modifications in the Golgi apparatus or in the cytosol
- Some polypeptides may then require **activation** by **cyclic AMP** (also known as **cAMP**)
  - cAMP is derived from ATP and is formed by the action of the enzyme adenyl cyclase
- One important role carried out by cAMP is the activation of protein kinases
  - In eukaryotic cells, cAMP activates protein kinase A (also known as PKA)
  - PKA is an inactive precursor enzyme
  - Once it is activated, it can activate other proteins (e.g. other enzymes)
- For example, **when muscle cells require energy**, an enzyme called **glycogen phosphorylase** releases glucose from glycogen
- This enzyme is **activated by cAMP**, which changes the shape of the enzyme to **expose its active site**

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6.1.6 GENE CONTROL: BODY PLANS

Body Plans & Hox Genes

- Cells in **developing organisms** need to be able to **differentiate** and **specialise** for different **roles**
  - In order to do this, they must be able to **control which genes are functioning at a particular time**
  - This is achieved by 'switching **on**' and 'switching **off**' genes
  - This must occur in a **specific, tightly controlled sequence**
  - This sequence is determined by **transcription factors** (proteins that bind to specific DNA sequences in order to control the rate at which particular genes are transcribed into mRNA)

Homeobox genes

- A **homeobox** is a **DNA sequence** that codes for a **protein transcription factor**
  - The transcription factors (that homeobox sequences code for) attach to DNA at **specific locations** and **regulate the transcription of genes** (e.g. genes that control the early development of eukaryotic organisms) by turning various different genes on and off in the **correct order**
- A **homeobox gene** is any gene that contains a homeobox sequence
- Homeobox gene sequences in plants, animals and fungi are **similar** and **highly conserved** (meaning they have been **maintained by natural selection** i.e. they remain relatively **unchanged** when travelling back in evolutionary time)
  - The sequences are all similar as they all code for amino acid sequences that will form transcription factors, the **DNA-binding regions** of which must all have the **same shape**
  - Mutations that cause changes in these homeobox sequences can lead to organisms that are **not viable** (not properly developed) so they are **not favoured by natural selection**. This strong negative selection pressure explains why the sequences are highly conserved
- Homeobox genes are responsible for the **genetic control of the development of body plans in different organisms**
  - This means they help to form the **basic pattern of the body**
  - For example, they control the **polarity** of the organism (which end will develop into the **head** and which end will develop into the **tail**)
  - They also control the **segmentation** of organisms such as insects and mammals into **distinct body parts** and they control the development of body parts such as wings and limbs, as well as what **organs** are present in each section of the body
- In this way, homeobox genes can be seen as '**master genes**' that control which genes function at different stages of development

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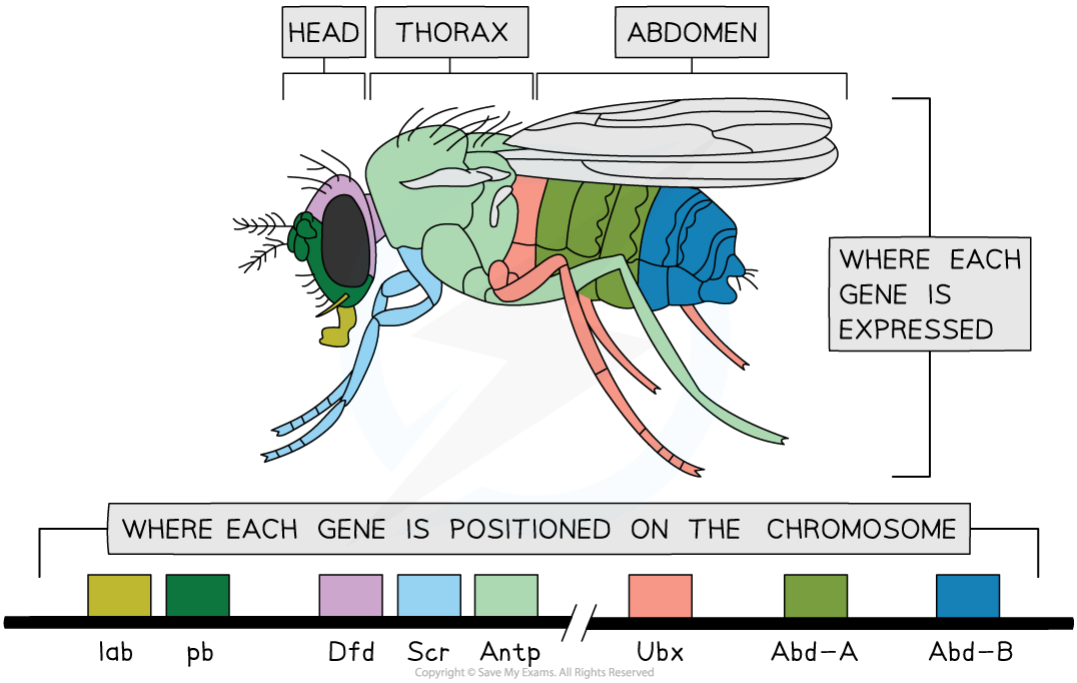

Eight homeobox genes (specifically, Hox genes) of the fruit fly, Drosophila melanogaster, that control the development of the body plan into specific regions e.g. the head, thorax, and abdomen. The break mark (//) in the chromosome shows that these are two clusters of genes that are separated by a long intervening region of the chromosome that is not shown here

Hox genes

- Hox genes are **a very important subset of homeobox genes**
- They determine the identity of **embryonic body regions** along the anterior-posterior axis (i.e. the **head-tail axis**)
- These Hox genes are organised into **groups** known as **Hox clusters**
- Vertebrates have **four Hox clusters** (each containing 9-11 Hox genes), which are found on **different chromosomes**
- There is a **linear order** to the Hox genes in each Hox cluster and **this order is directly related to the order of the regions of the body that they affect**

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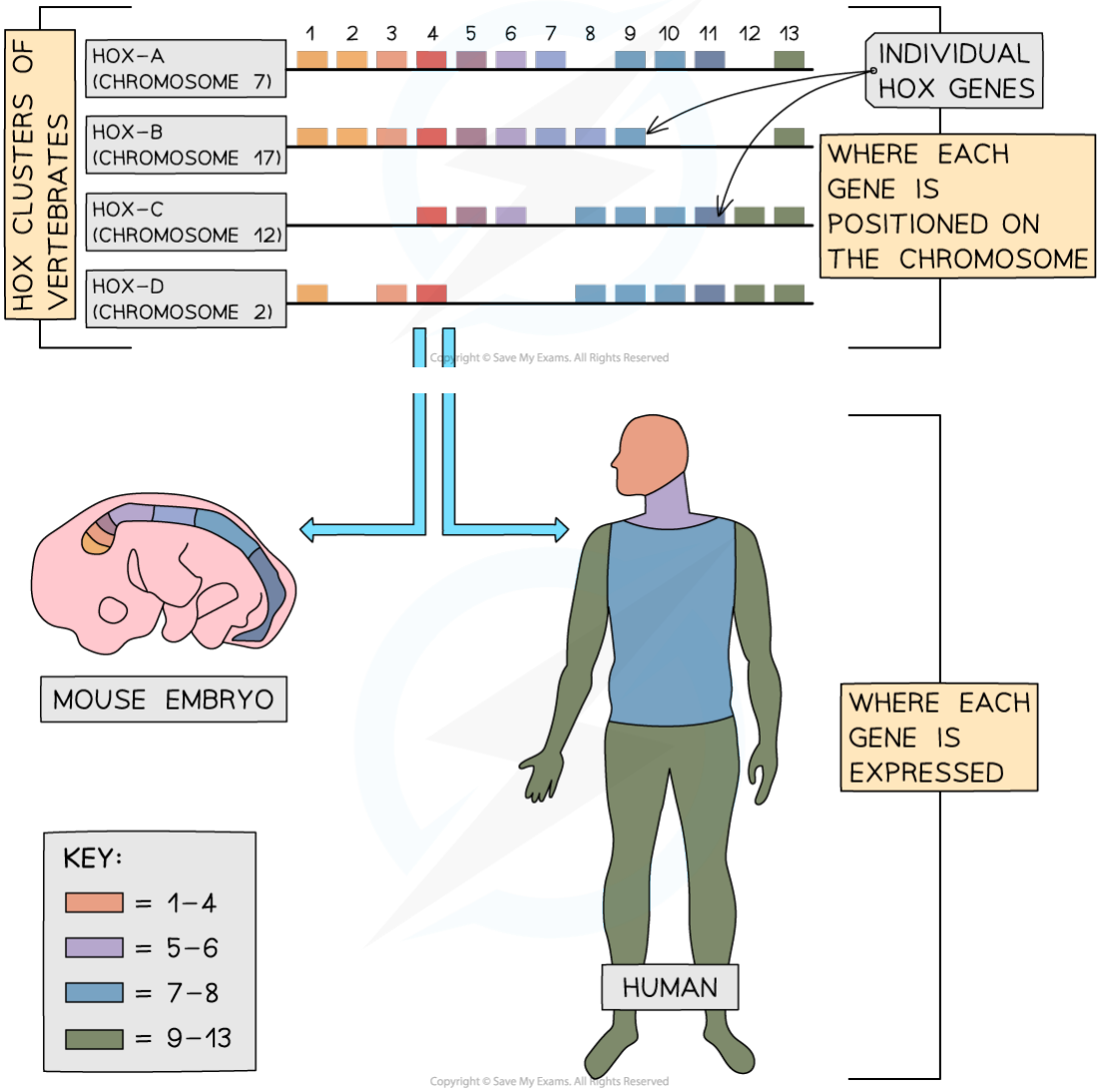

The four Hox clusters containing the Hox genes that control the development of the body plan of vertebrates into specific regions

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6.1.7 THE IMPORTANCE OF MITOSIS & APOPTOSIS

The Importance of Mitosis & Apoptosis

- **Mitosis** is the type of cell division that produces **identical new cells** for processes such as **growth**, **cell replacement** and **tissue repair**
- **Apoptosis** is **programmed cell death** (sometimes referred to as natural cell death)
- In apoptosis, **old cells** that have already undergone a large number of **mitotic cell divisions** (approximately 50 divisions, although this depends on the cell type) are systematically taken through various processes leading to **cell death**
- These processes include:
  - The **DNA** of the cell becoming **denser** and **more tightly packed**
  - The **nuclear envelope** of the cell's nucleus **breaking down** and **chromatin condensing**
  - **Vesicles** forming that contain **hydrolytic enzymes**
  - Phagocytes engulfing and digesting the cell via **phagocytosis**

The importance of mitosis and apoptosis in controlling body plan development

- By constantly **replacing and destroying cells** throughout the **early development** of an organism, mitosis and apoptosis are both **key mechanisms** controlling the development of **body form**
- Apoptosis is important in development as, in some cases, **some cells that are produced** (by mitosis) earlier on in development **may no longer be needed**
- As a result, these cells are **destroyed** (by apoptosis) as part of the development of the organism
- For example, structures like **fingers and toes** first develop as a **single combined unit** and are then **separated later** via programmed cell death (apoptosis) of the cells in between the digits

6.1 Cellular Control

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The control of mitosis and apoptosis

- Mitosis is **controlled** by various different genes that are categorised into **two distinct groups**:
  - **Proto-oncogenes** are genes that **stimulate** cell division
  - **Tumour-suppressor genes** are genes that **reduce** cell division
- Tumour-suppressor genes can also **stimulate apoptosis** in cells with damaged DNA that cannot be repaired
  - This protects the body as it ensures that any cells that are **genetically damaged** (and that could, therefore, lead to **cancer**) are **destroyed**
- During the cell cycle (in cells due to undergo mitosis) there are various '**checkpoints**' that need to be passed to ensure that damaged cells are not produced
- These controls ensure that the cell is prepared for the **mitosis phase** of its cell cycle and that any DNA damage is repaired
- These controls are regulated by **two groups of proteins**, known as **cyclins** and **cyclin-dependent kinases** (CDKs), that regulate the progress of the cell through the cell cycle
  - Cyclins act as **regulators**
  - CDKs act as **catalysts** (once **activated by cyclins**)
  - For example, CDKs that have been activated by cyclins will catalyse the phosphorylation of particular target proteins, which can either **activate** or **inactivate** them
  - **This ensures the cell cycle progresses from one stage to the next**
  - Different cyclins are produced at different stages of the cell cycle in response to internal molecular signals
- The genes that control the cell cycle and apoptosis are able to respond to:
  - **Internal** cell stimuli
  - **External** cell stimuli

Examples of internal cell stimuli

- Internal factors that affect apoptosis and the cell cycle include:
  - Irreparable genetic damage
  - RNA decay
  - Internal biochemical changes that lead to cell changes or cellular injury (e.g. oxidative reactions)
  - Production of cyclin D
- These factors can all **initiate apoptosis** in cells that are undergoing **cell stress**

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Examples of external cell stimuli

- External factors that affect apoptosis and the cell cycle include:
  - The presence of cell signalling molecules such as **cytokines** from the immune system, **hormones** and **growth factors**
  - Viruses and bacteria, harmful pollutants or ultraviolet light can affect the delicate balance of mitosis and apoptosis by **damaging or destroying cells faster than they can be repaired or replaced**
- Cells often respond to such stressful stimuli by activating **pathways** to **increase their chance of survival**, or by **initiating apoptosis**
  - For example, a cell will often begin by defending itself and trying to recover from the stressful stimulus by counteracting any damage caused to it
  - However, if the stressful stimuli remain, cell death pathways are activated (i.e. apoptosis is initiated)