HN

SEASON 2

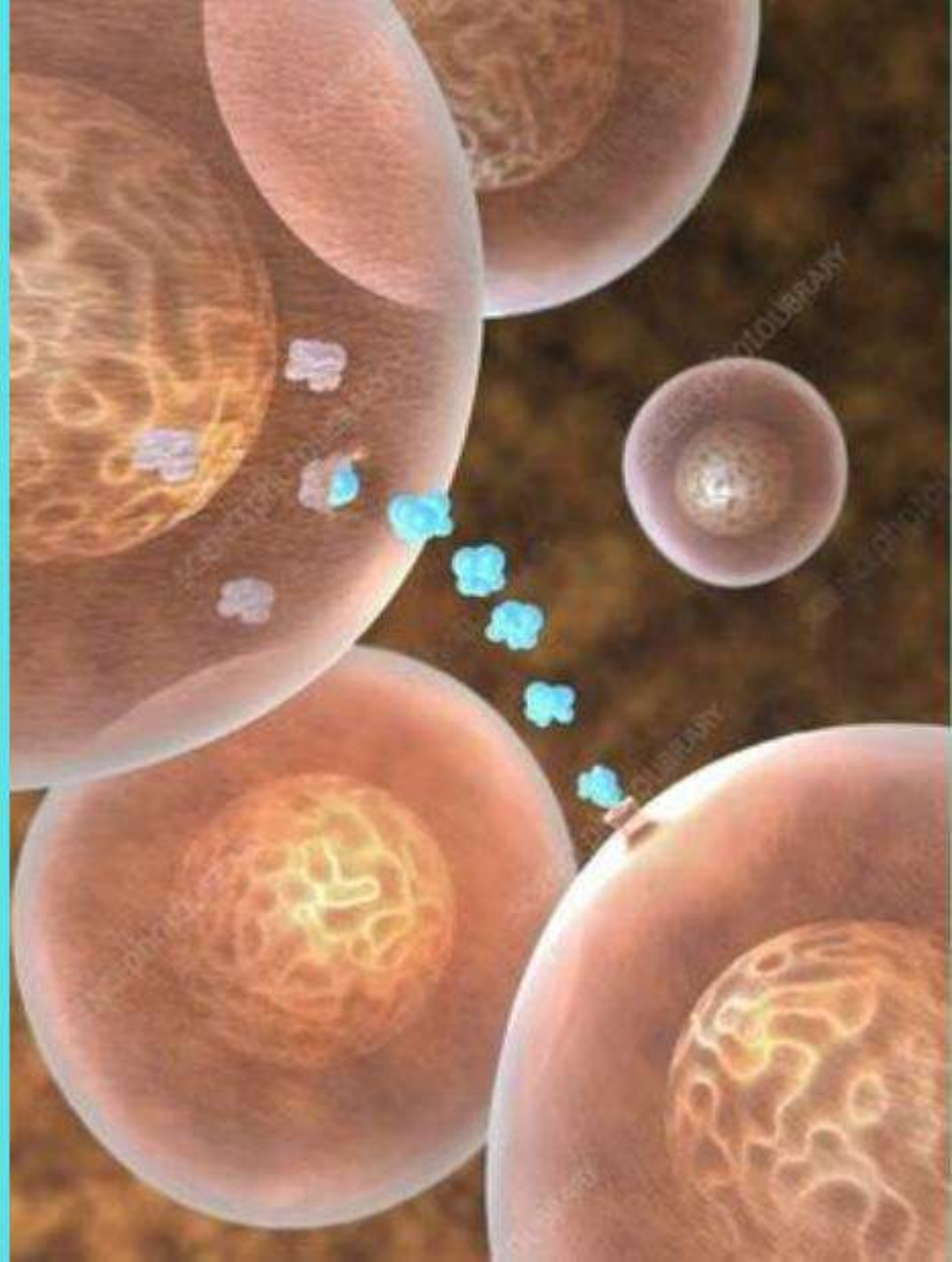
Farah Saeed FS Farah Saeed

Understanding Cancer

Lecture 2
Hallmarks of cancer

DR HAFSA WASEELA ABBAS

www.hafsaabbas.com



RECAP:

What you hopefully should understand so far from Lecture 1

- **Cancer** is a disease caused by **random changes in the genes** called **mutations**. This leads to **uncontrolled cellular growth at the primary site that** can **spread to other parts of the body to form secondary tumours** that are **malignant.**
- **A number of scientists and archaeologists have helped shape our understanding of cancer.**
- **Cell communication** is important to understand on how **cells sense, respond to signals, and coordinate activities.**
- **Largest to smallest: Cell → Nucleus → Chromosome →DNA →gene.**
- **Genes encode proteins**, and the instructions for making proteins require **transcription and translation**.
- Genes can become faulty based on **mutations passed from parents (spontaneous) or environment (induced).**
- **Proto-oncogenes** stimulate cell division. **Tumour suppressor genes** inhibit cell division**. DNA repair genes repair** errors that occurs during cell division in the cell cycle**.**

What will we learn today?

- What are the hallmarks of cancer? *Who developed them?*
- A brief overview of Hall mark cancer 1: *Sustained proliferative signalling*.
- A brief overview of Hall mark cancer 2: *Evading growth suppressors*
- A brief overview of Hall mark cancer 3: *Resisting apoptosis (programmed cell death)*
- A brief overview of Hall mark cancer 4: *Enable replicative immortality*
- A brief overview of Hall mark cancer 5: *Invasion and metastasis*
- A brief overview of Hall mark cancer 6: *Stimulate angiogenesis*
- Other hallmarks of cancer and contributors

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Don’t worry about the big and complex words, we will explain ☺

GENTLE REMINDER
An ideal way of learning:

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday

Mini-lectures.

Approximate total time: 1 hour

Divide over 7 days at your **own pace**.

Challenge yourself with a quiz!

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RECAP: How to support your learning?

- **Key facts with diagrams by HN designs presented in a simplified way.**
- **Glossary to help understand what key words mean.**
- **Summary doodle revision posters by HN designs.**
- **Quizzes to test your knowledge and reflect.**
- **Reference list for further reading.**

Acknowledgements: Special thanks to my parents, family, friends and colleagues for their support and the respected teachers and health professions who taught me and installed the passion of cancer/oncology.

What are the hallmarks of cancer?
Who developed them?

Key facts:

Douglas Hanahan and Robert Weinberg

In 2000, they developed the hallmarks of cancer.

Douglas Hanahan

An American biophysicist, Professor and Director emeritus of the Swiss Institute for Experimental Cancer Research at EPFL (École Polytechnique Fédérale de Lausanne) in Switzerland.

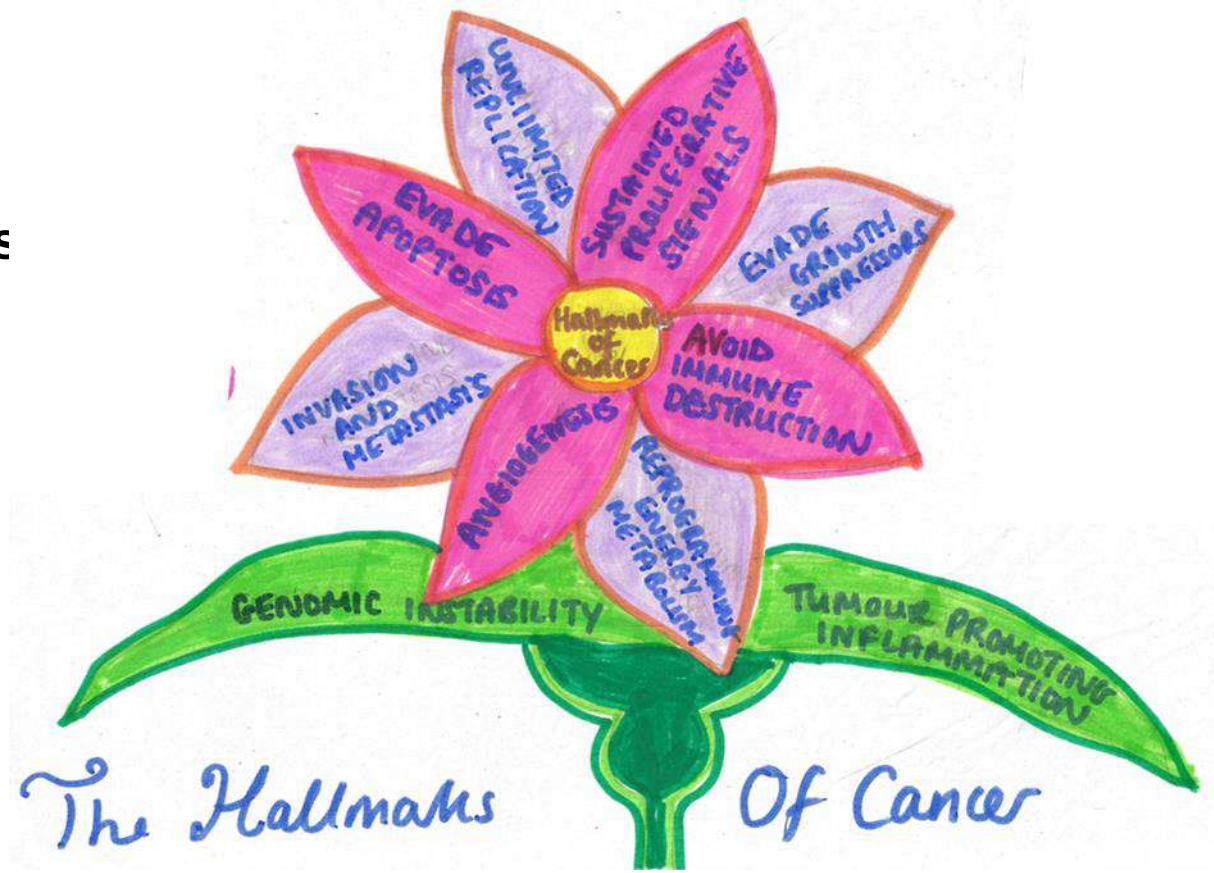
Robert Weinberg

An American biologist, Daniel K. Ludwig Professor for Cancer Research at Massachusetts Institute of Technology (MIT), Director of the Ludwig Center of the MIT, and American Cancer Society Research Professor.

Key facts: What are the hallmarks of cancer?

- They are **characteristics and features of cancer needed for malignant behaviour.**
- A framework that **helps inform key differences** between **normal cells and cancer cells.**
- The **dysregulated** pathways **in how cells normally communicate** underlies most hallmarks.
- **SOME CANCERS** produce **MORE THAN ONE FEATURE**.

Example: A cancer cell can avoid apoptosis and growth suppressors.



Key facts: What are the hallmarks of cancer?

❑ **SOME FEATURES CONTRIBUTE OR HELP**

towards **CANCER DEVELOPMENT:**

Example:

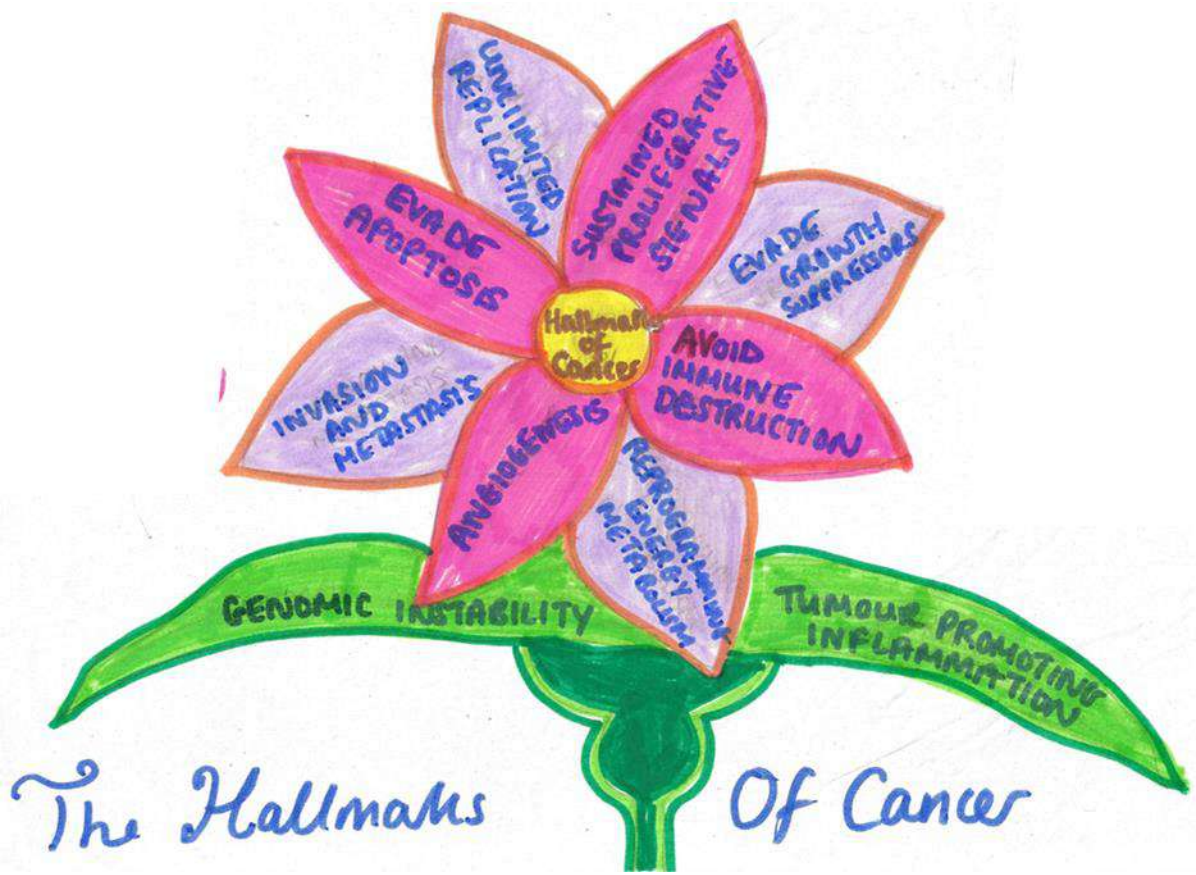
Genomic instability is where there is an

imbalance in the **genes** caused by:

a) **loss-of-function DNA repair genes**

b) **mutations**

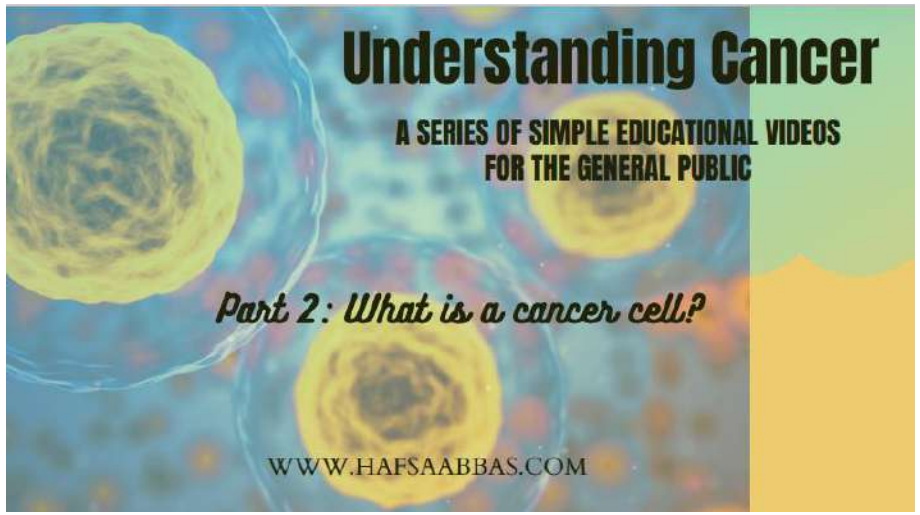
c) Loss of **cell cycle arrest** due to **damage to DNA.**

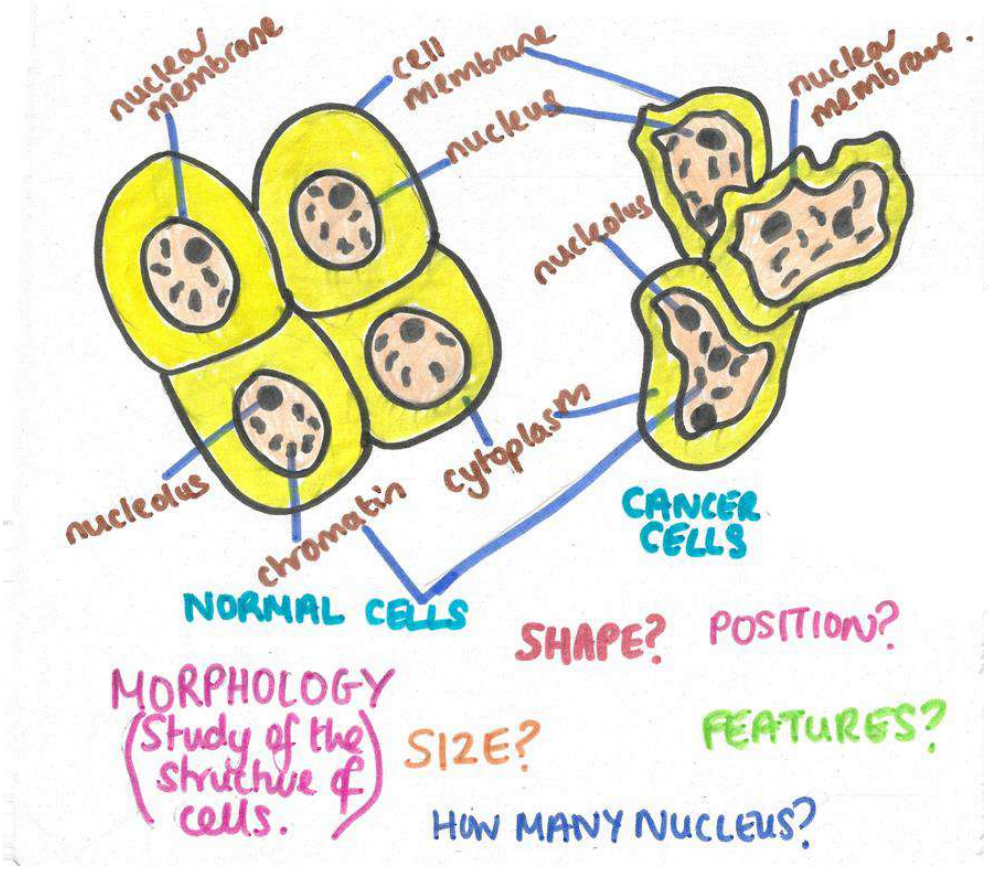


RECAP: What are differences between normal and cancer cells?

Season 1 Part 2: What is a cancer cell?

- The characteristic traits
- The hallmarks of cancer





DOUGLAS HANAHAN

ROBERT WEINBERG

The Hallmarks Of Cancer

A brief overview of Hall mark cancer 1: *Sustained proliferative signaling.*

Key Facts: What is proliferation?

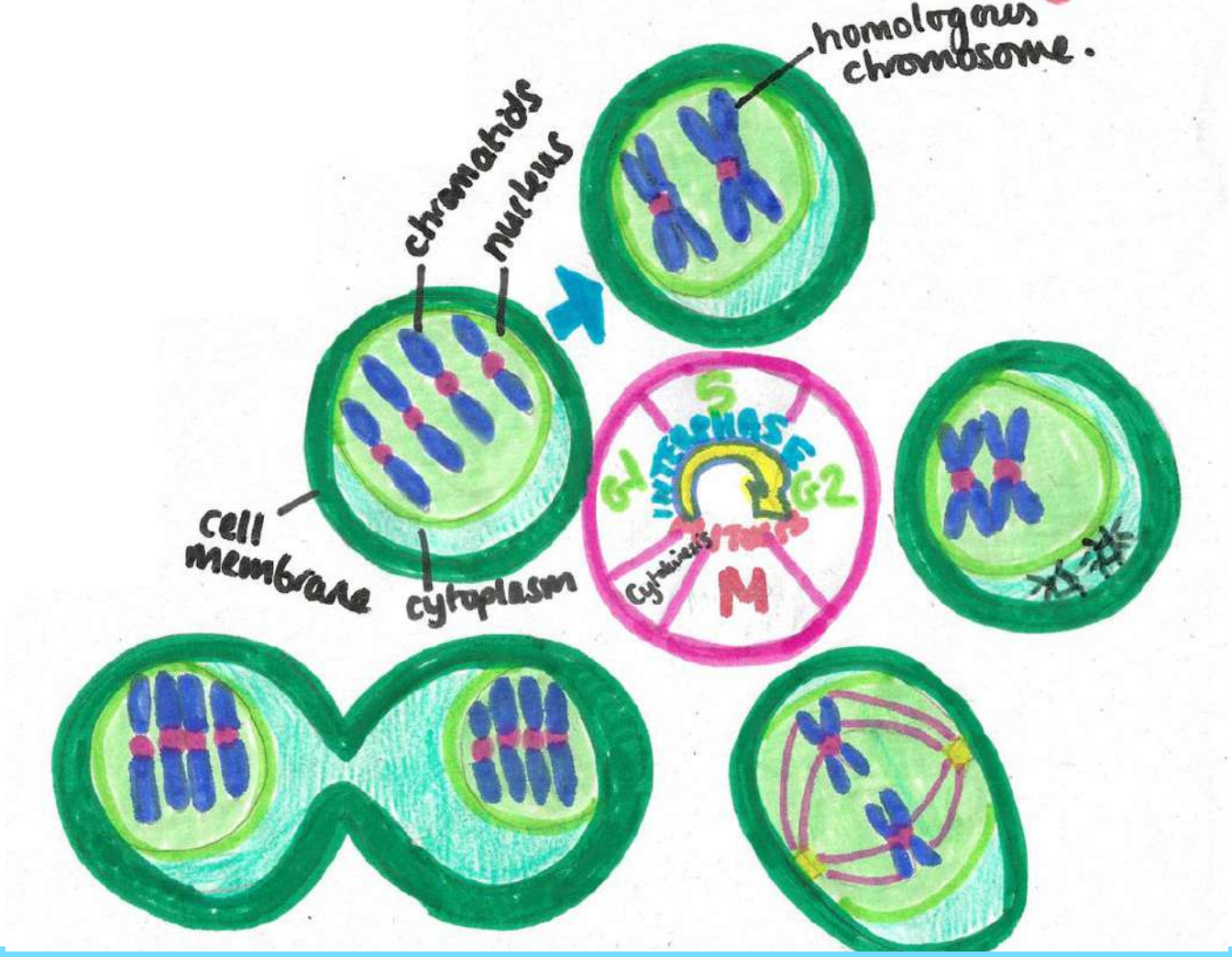
Cell proliferation is when **a single cell divides** by a process called **mitosis** to **produce two cells** known as **daughter cells.**

Mitosis is a type of **cell division** for **growth and repair.**

However, each cell has a **limited number of cell divisions**.

This is known as the **Hayflick limit.**

Mitosis and The Cell Cycle.

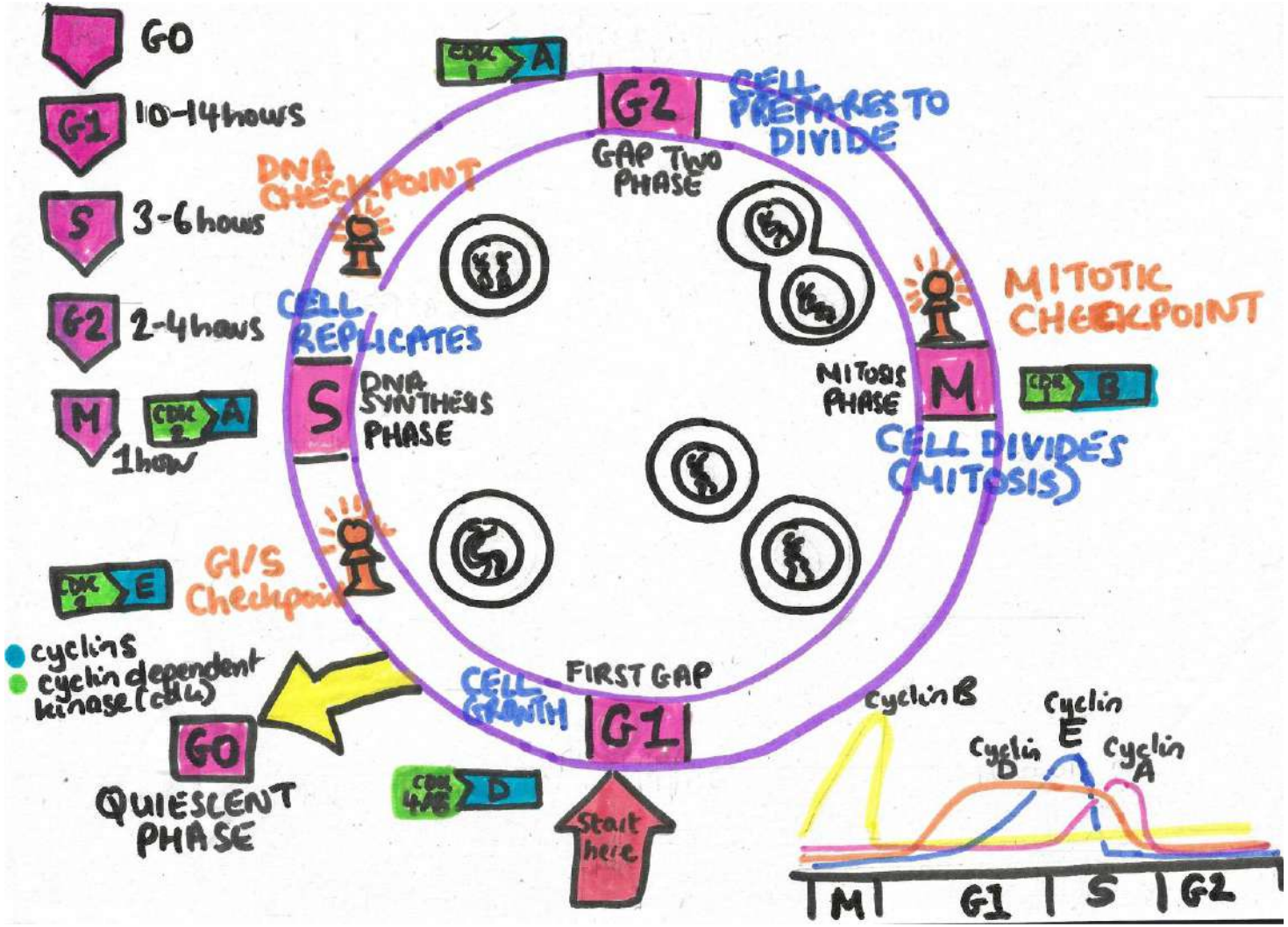


Key Facts: The cell cycle

Normal cells have a cell cycle that presents the stages/phases in how **normal cells divide and grow.**

This ensures the following:

- ❑ Each cell has **normal, functional genes**
- ❑ Healthy **organelles**
- ❑ **No errors in DNA**
- ❑ **Normal cell growth**



Key Facts: The stages in the cell cycle

Average length of time for the cell cycle: 16 hours

Two sections:

1. **Interphase: *G1, S and G2 phases (15 hours)***
2. **Mitosis: *M phase and cytokinesis (1 hour)***

Quiescent: G0 phase Inactive period outside the cell cycle.

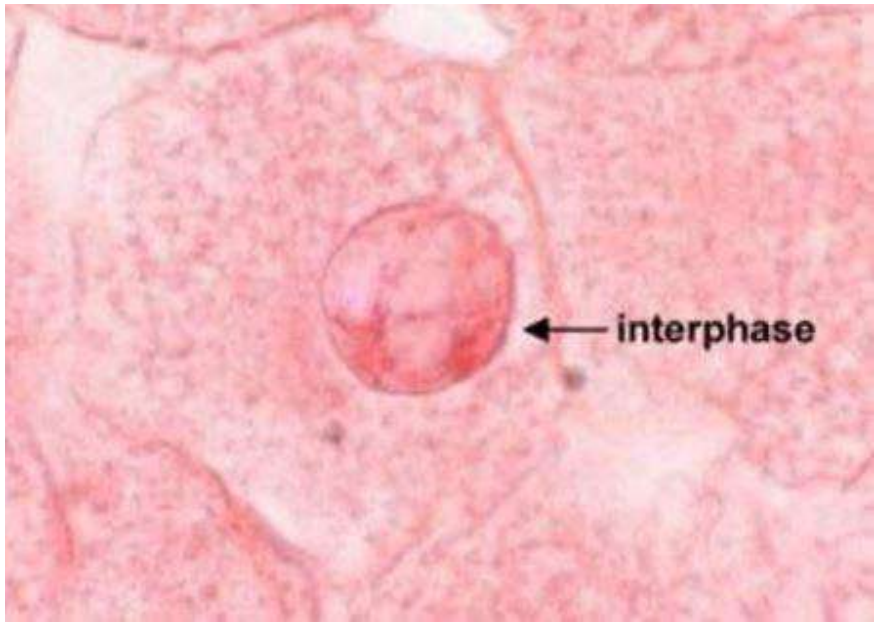
Stage	Name of phase	What occurs at the stage	Length of time (hours)
1	Gap 1 (G1)	Growth of cell and organelles Production of proteins needed for DNA synthesis	10-14
2	S	The synthesis and replication of DNA	3-6
3	Gap 2 (G2)	Growth and preparation for mitosis	2-4
4	Mitosis (M)	The division of the cell to produce two daughter cells. Cytokinesis is the division of the cytoplasm to fully produce the two daughter cells	1

Did you know?

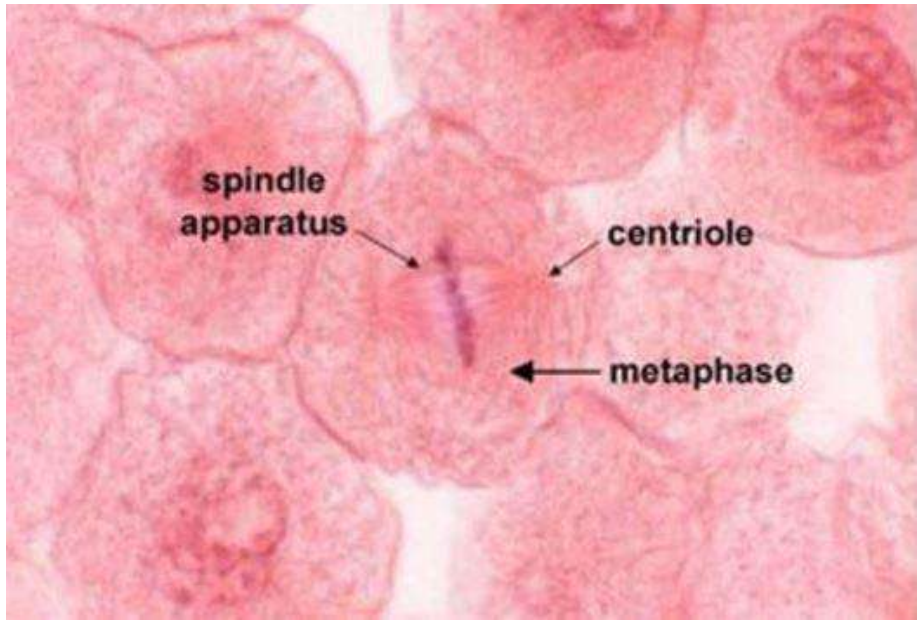
You cannot see chromosomes at the interphase, only in M phase using a device called a microscope.

Chromosomes are produced in the M phase from chromatin.

Chromatin contains DNA and proteins and helps form chromosomes.



Microscope Slide of Animal Cell During Interphase
Source: ScientistCindy.com, n.d.



Microscope Slide of Animal Cell During Metaphase
A phase during mitosis were chromosomes line the middle
Source: ScientistCindy.com, n.d.

Key Facts: Friends of the cell cycle

Genes

Example 1: **p53**

Type of gene: **Tumour suppressor**

***Role*:**

- ❑ **It helps regulate the cell cycle.**
- ❑ **Maintains the genome**
- ❑ **It can slow or stop the G1 phase before S phase.**

Key Facts: Friends of the cell cycle

Genes

Example 2: **Rb (retinoblastoma)**

Type of gene: **Tumour suppressor**

***Role*:**

- **Alters the activity of transcription factors and therefore controls cell division.**
- **Inhibiting the G1 to S phase transition.**
- **Cellular differentiation**

Key Facts: Friends of the cell cycle

Example 3

Type of gene: **DNA repair genes**

***Role*:**

- **It helps correct errors when cells duplicate or double their DNA before cell division.**
- **This occurs particularly during G2 phase after the S phase.**

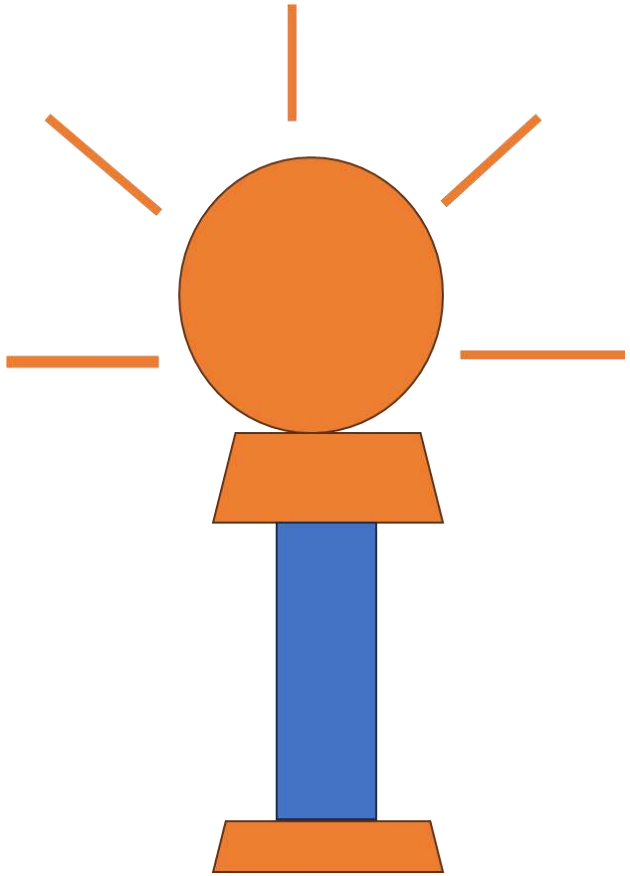
Key Facts: Friends of the cell cycle

Cell cycle checkpoints

They are **proteins that sense, alert and start a cellular response** to **DNA damage.**

The normal response to DNA damage are **cell cycle arrests/pause.**

This helps **maintain the integrity of the genome.**



Key Facts: Friends of the cell cycle

Types of Cell cycle checkpoints

Name of checkpoint	Description of role
G1/S	To ensure DNA damage is not replicated during S phase.
S/G2 phase	To ensure all DNA is replicated in S phase. DNA damage or unreplicated DNA cause cell cycle arrest.
M	To check the alignment of the chromosomes on the spindle is appropriate.

Key Facts: Friends of the cell cycle

Growth Factors.

Growth factors otherwise known as **mitogens** can help cells in the **G0 phase to re-enter the cell cycle a**nd pass through the **G1 checkpoint.**

EGF

This is a **temporary process** to ensure that **cells can confidently pass through the G1 control point** and then **independently move without growth factors** through the **remainder of the cell cycle.**

Key example:

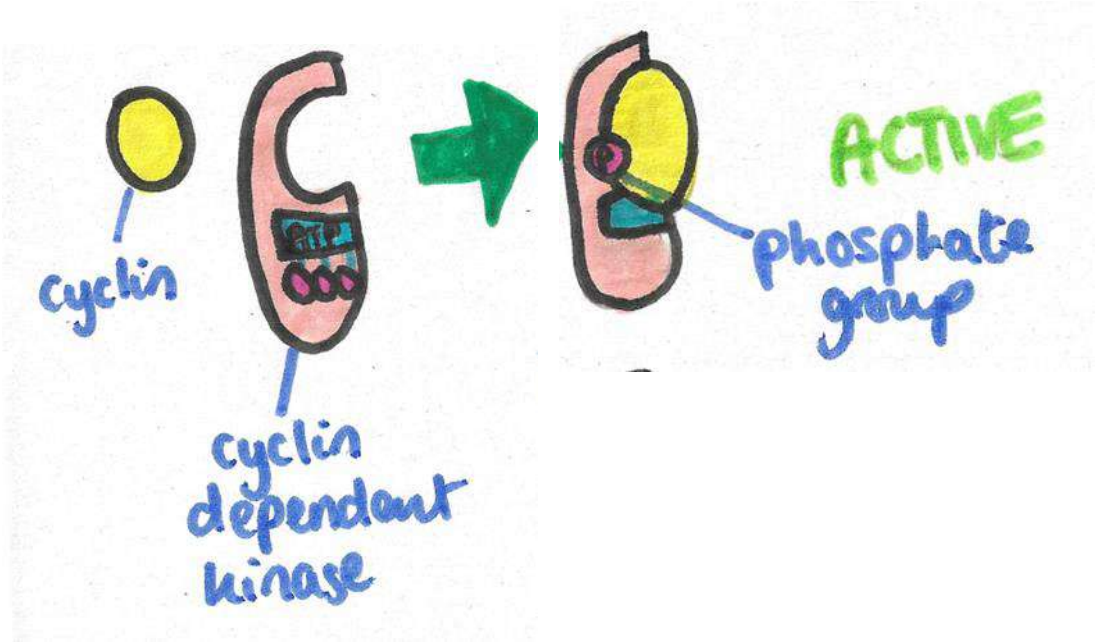
Epidermal growth factor.

Key Facts: Friends of the cell cycle

Cyclins Part 1

They are **proteins that monitor and coordinate the cell cycle.**

They **work with specific enzymes called cyclin-dependent kinases (cdk).**

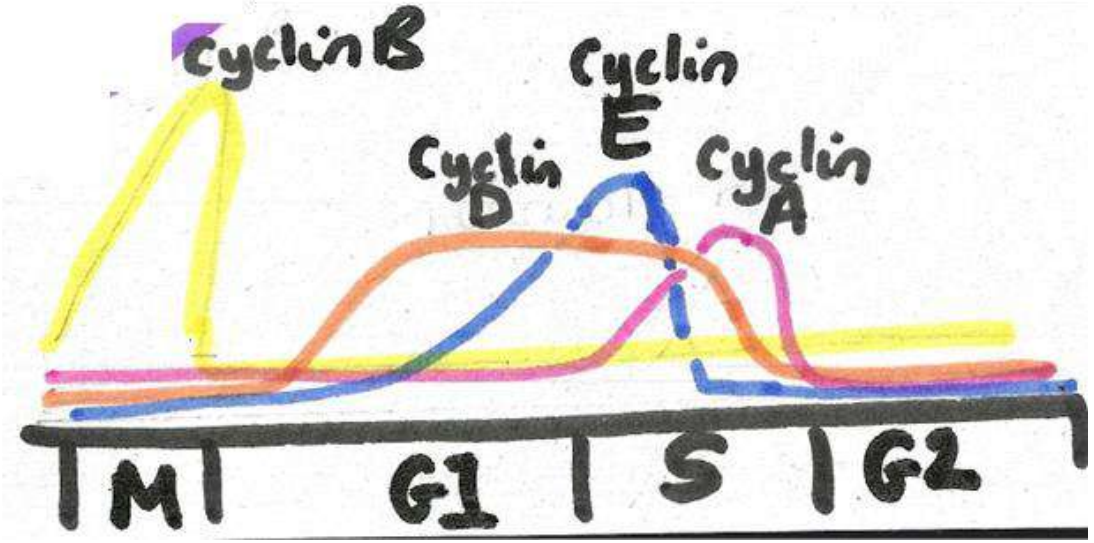


Just like with base pairs, **cyclins have complementary binding with cdks like a lock and key model.**

Key Facts: Friends of the cell cycle

Cyclins Part 2

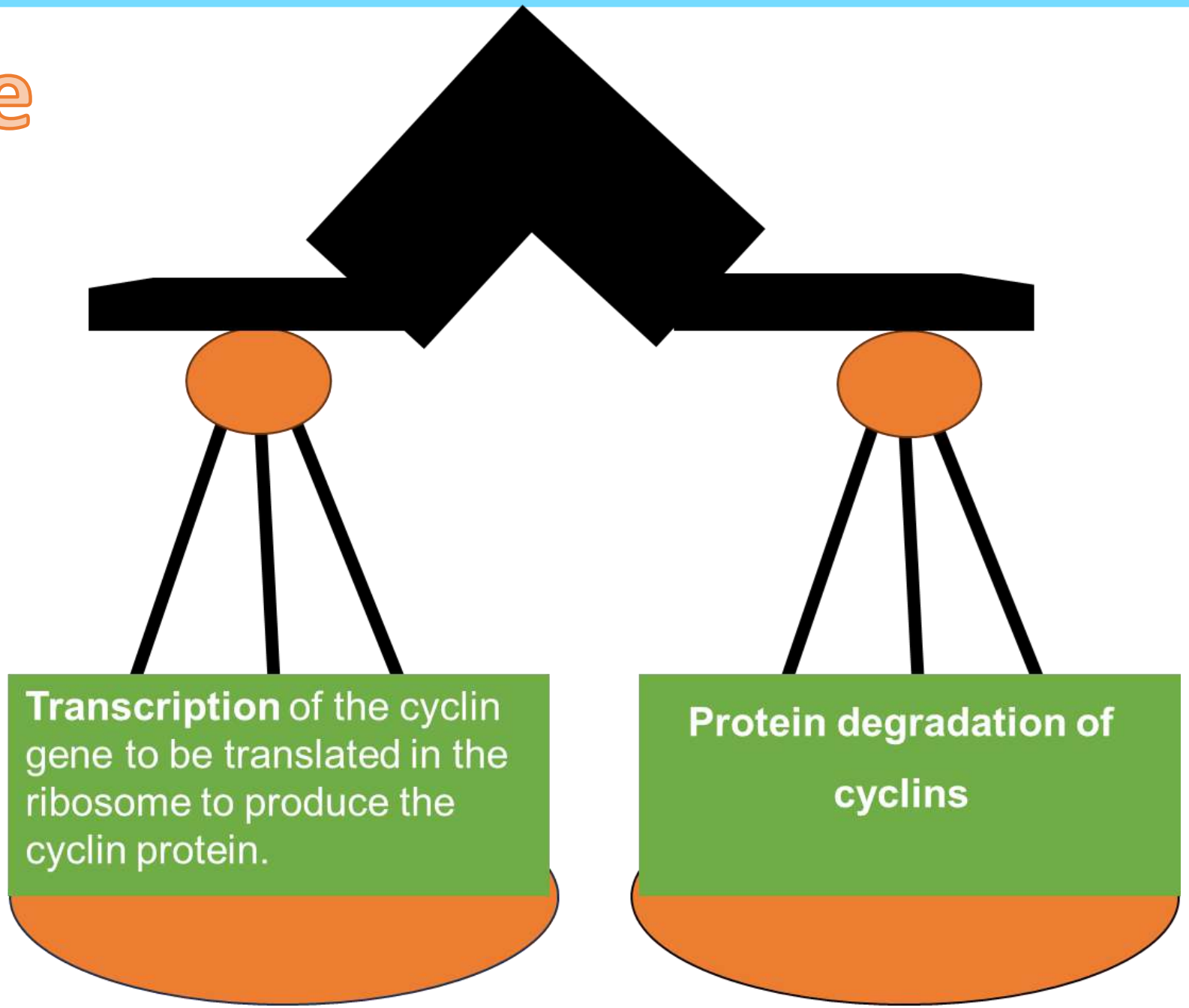
The word **‘cyclin’** was derived because of the **changes in their levels or concentrations during cell division.**



The level of cyclin depends on the **balance between production and degradation of cyclins.**

The levels of cdk **DOES NOT** change.

Balance


Transcription of the cyclin gene to be translated in the ribosome to produce the cyclin protein.
Protein degradation of cyclins

Key Facts: Friends of the cell cycle

Cyclin binds to the catalytic subunit of cdk and induces conformational change.

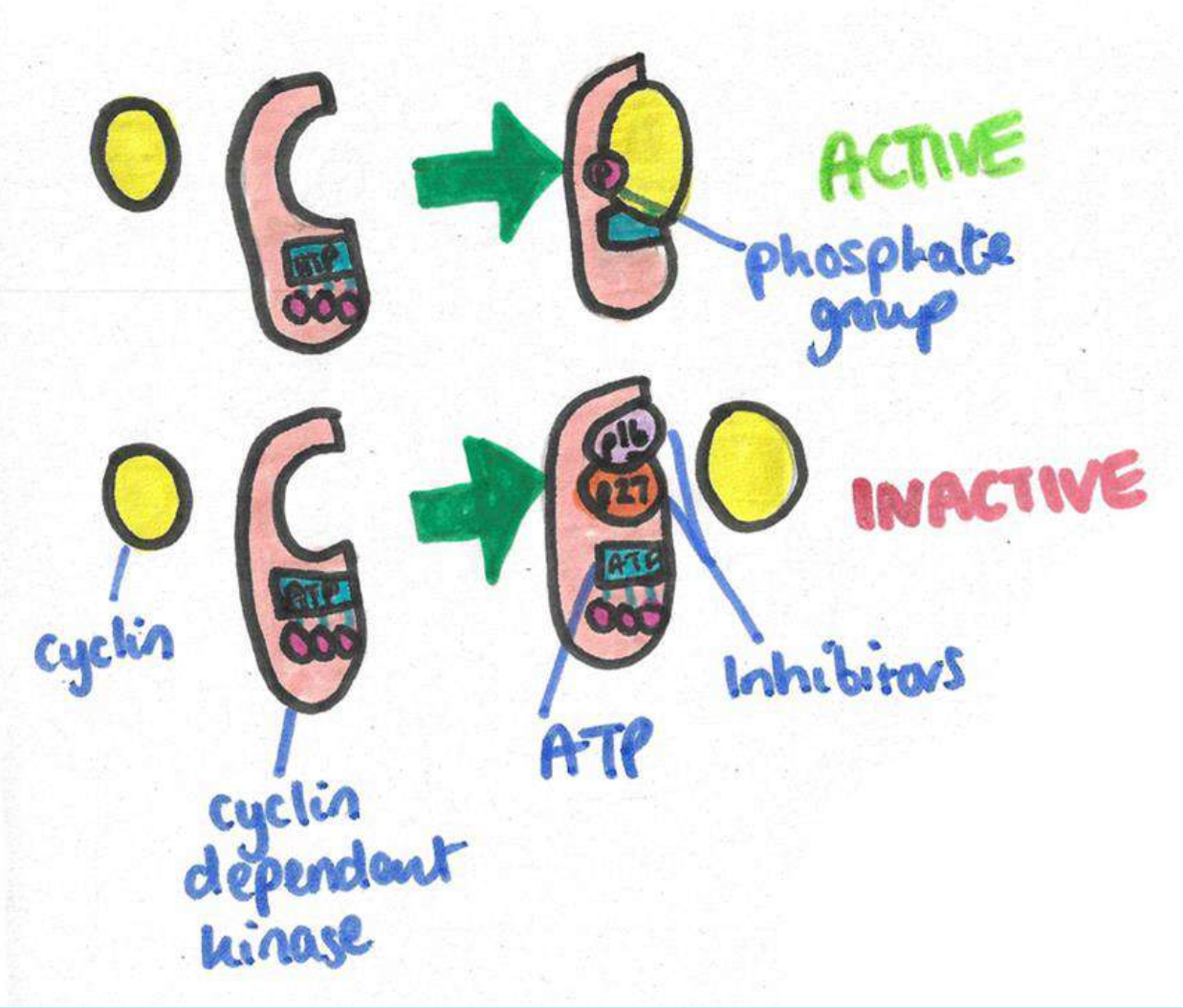
The active site of cdk is revealed where chemical reaction takes place between the cyclin and cdk.

The cyclin-cdk complex adds a phosphate to target proteins. This is known as phosphorylation.

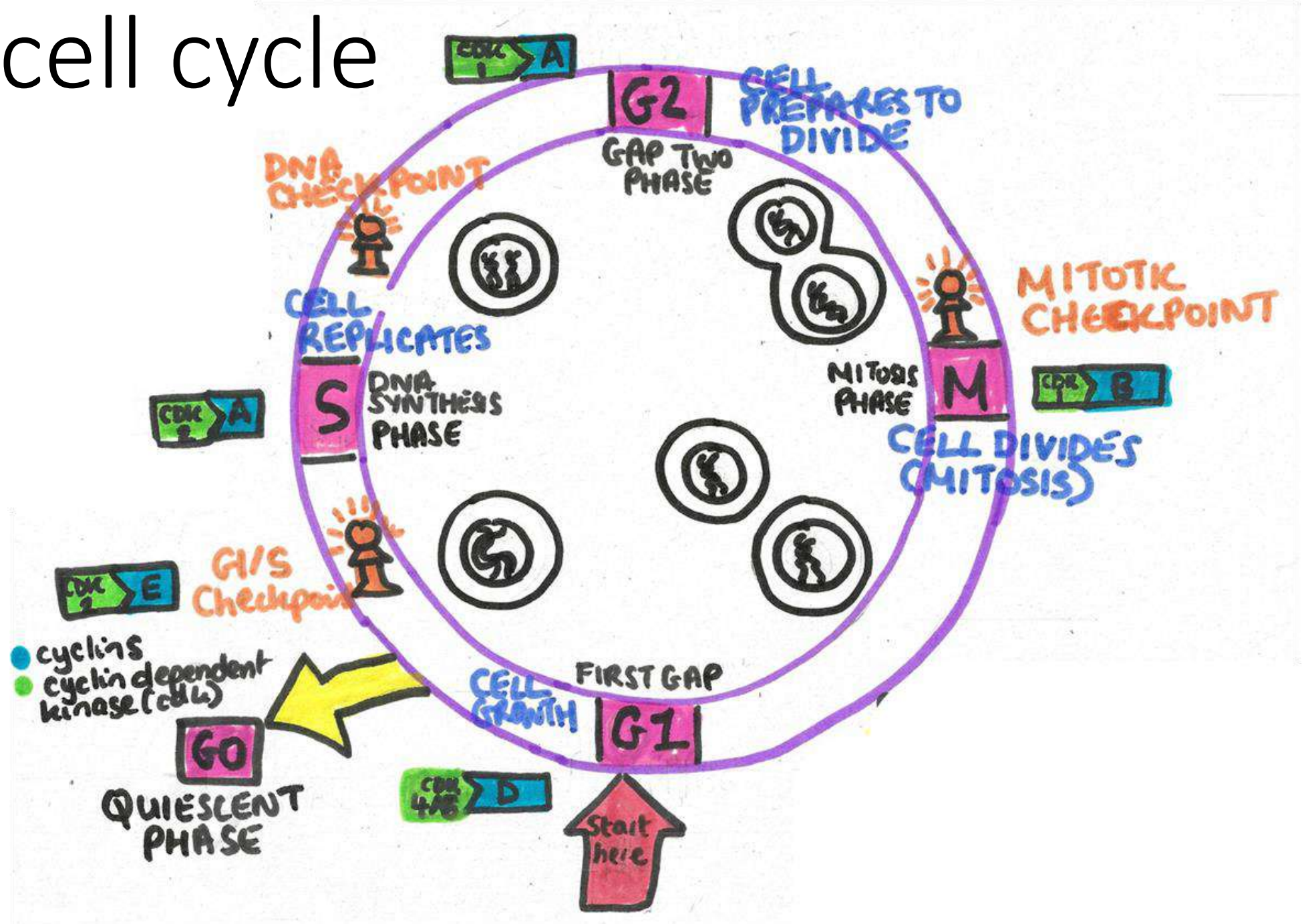
Some cyclins persuade by increasing affinity of cdk with substrates.

P16 and p21 are inhibitors of cell cycle.

Cyclins Part 3



The cell cycle



Key Facts: How do cancer cells continue to proliferate?

Cancer cells are able to respond to their own growth factors to continue to grow.

Overproduction of growth factors:

e.g. **glioblastoma,** a type of brain cancer has **loss-of-function** of PDGF **Platelet-derived growth factor** which helps regulating **cell proliferation, differentiation and development.**

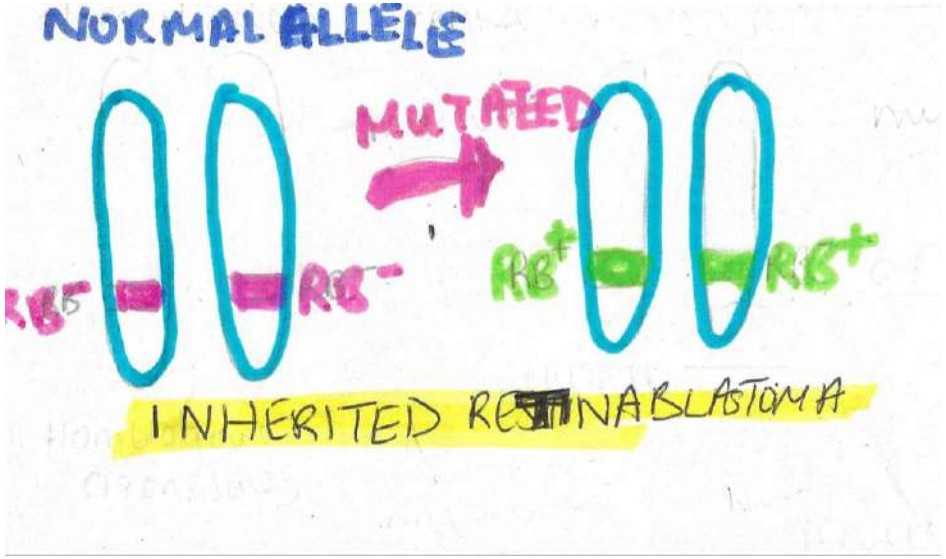
EGFR (EGF receptor) in breast cancers.

Disruption of checkpoints This causes **genomic and chromosomal instability** This increases **number of mutations and cause cancer.**

Key Facts: How do cancer cells continue to proliferate?

Mutations in Rb are **hereditary.**

An **allele is a different form of the same gene.**



<u>60% sporadic</u>

Somatic mitotic recombination occurs when normal gene replaced by an immortal method.

Key Facts: How do cancer cells continue to proliferate?

Mutation in germ cell/sex cell/reproductive cell is passed onto child from parent.

This increases **risk of a second mutation.**

A second mutation is needed to **inactivate the two copies of the Rb allele** and **prevent the expression of the Rb protein** to cause the **tumour in the retina of the eye to develop.**

40% familial Both alleles mutated = **RETINOBLASTOMA**

KNUDSON TWO-HIT HYPOTHESIS

NORMAL ALLELE

RB⁻ RB⁻

MUTATED

SPORADIC

RB⁺ RB⁻ 1ST HIT

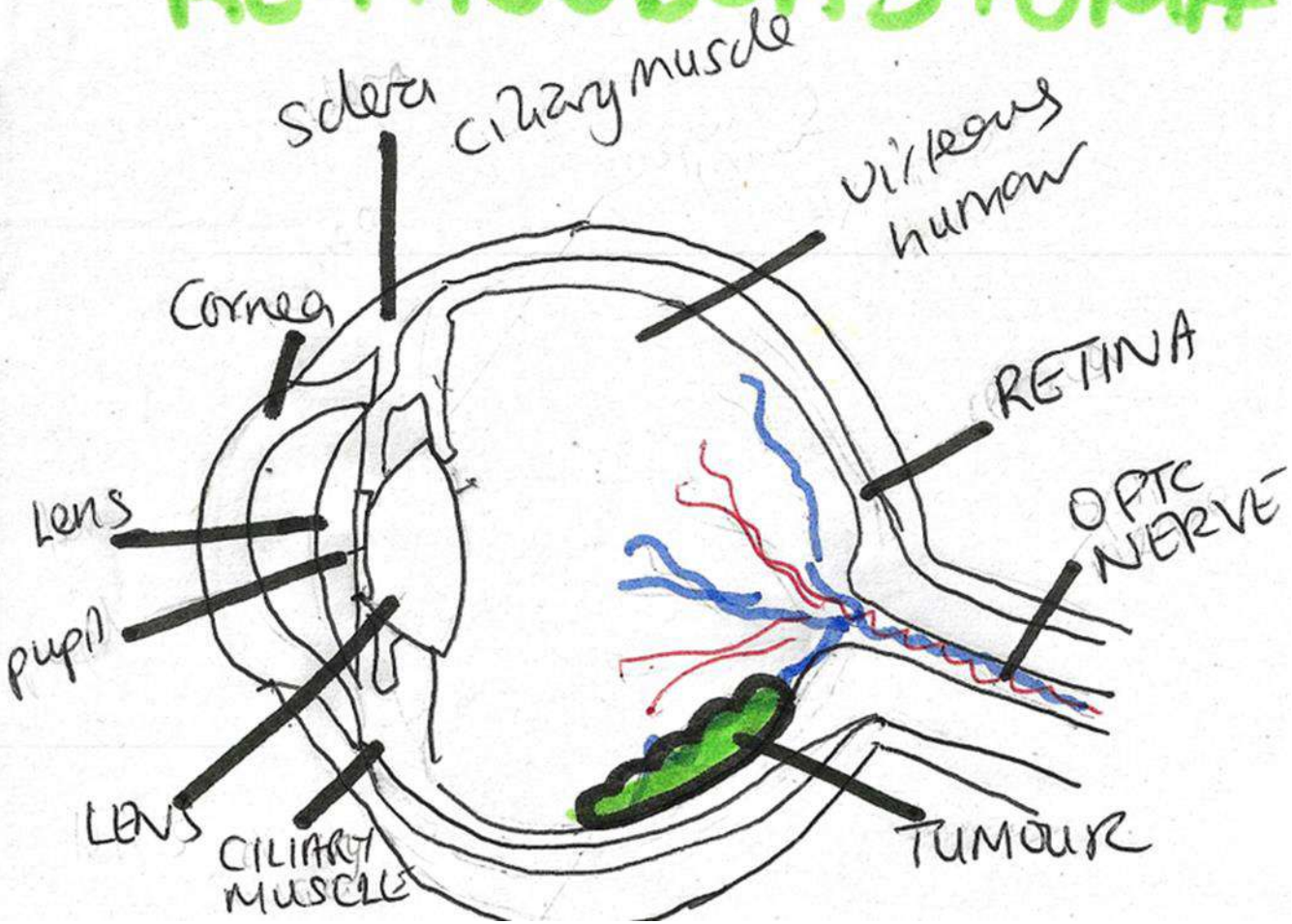
SPORADIC MUTATED

RB⁺ RB⁻ 2ND HIT

mutated allele (Rb)

normal allele

RETINOBLASTOMA



A brief overview of Hall mark cancer 2: Evading growth suppressors

Key Facts: What does evading growth suppressors mean?

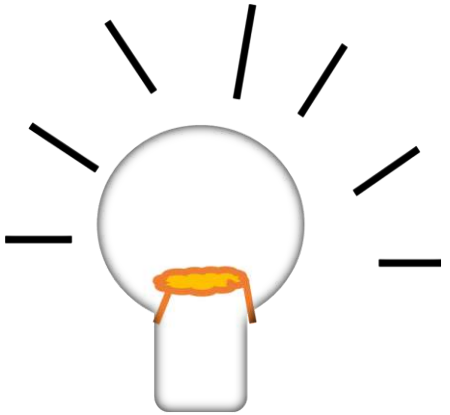
Cancer cells are able to **continue to grow by avoiding signals that informs them to stop growing or die**.

To **increase growth:**

1) Cancer cells **AVOID apoptosis and tumour suppressor proteins.**

2) Cancer cells **increase the rate of autophagy** to **maintain the nutrient state.**

3) **Autophagy** can help **facilitate other hallmarks of cancer** by **promoting angiogenesis and inflammation**.



Apoptosis discussed more soon.

Key Facts: Autophagy

It means '**eating of one's self'.**

Role:

- ❑ **It helps protect cells from stress.**
- ❑ **Removes proteins** that are **abnormal and non-functional.**

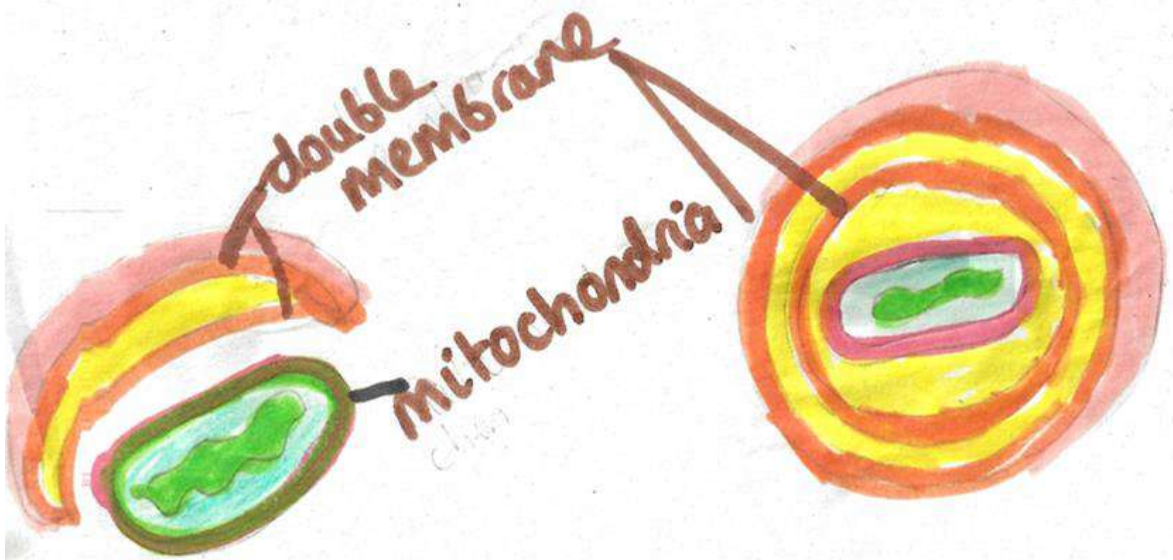
An **old organelle** gets **enclosed by a double membrane** to form an **autophagosome.**

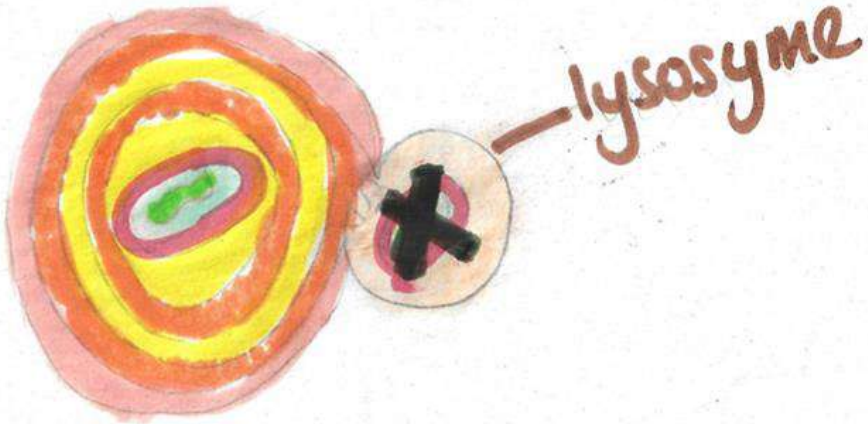
→

The autophagosome binds to an organelle called lysozyme to help digest intracellular materials.

→

Small molecules released and recycled back to the **cytosol/cytoplasm.**





PHAGOPHORE

membrane begins to endose an organelle. In this case, mitochondria

AUTOPHAGOSOME

Double membrane enclases an organelle to form autophagosome.

AUTOPHAGOLYSOSYME

Autophagosome joins with lysosyme and fuse. The mitochondria is degraded and recycled back to the cytosol.

Autophagy

Key Facts: Apoptosis

Apoptosis is a **programmed cell death** in which cancer cells are able **to resist in order to grow.**

DNA mutations helps cancer cells to:

- ❑ Bypass the **DNA damage checkpoint (S phase)**.
- ❑ **Dysregulate the signalling pathways** involved in **apoptosis.**

Apoptosis is **not autoimmune**. They can **lower activation of inflammation and immune response.**

A brief overview of Hall mark cancer 3: Resisting apoptosis (programmed cell death)

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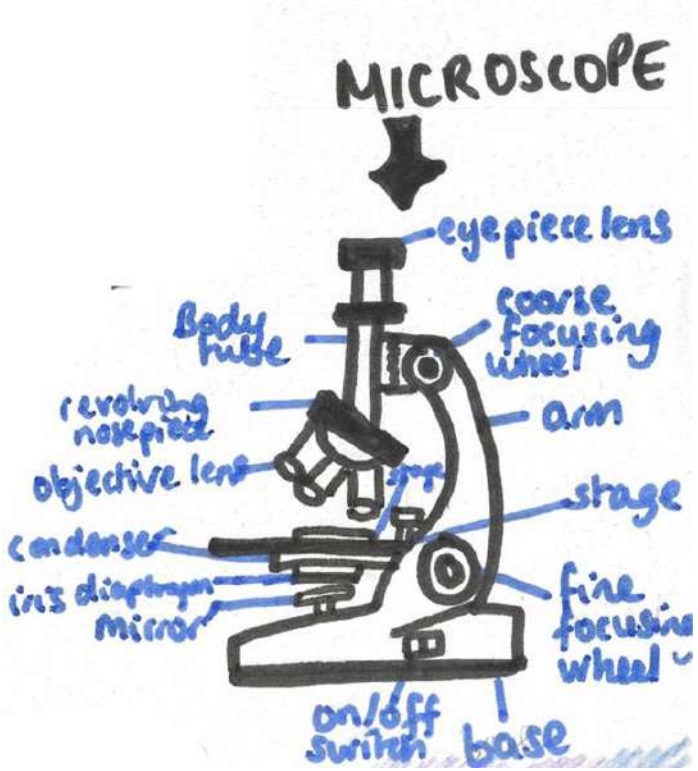
Key Facts: Features of apoptosis

Morphology:

The study of **the shape, size and form of an object.**



Characteristics of Apoptosis

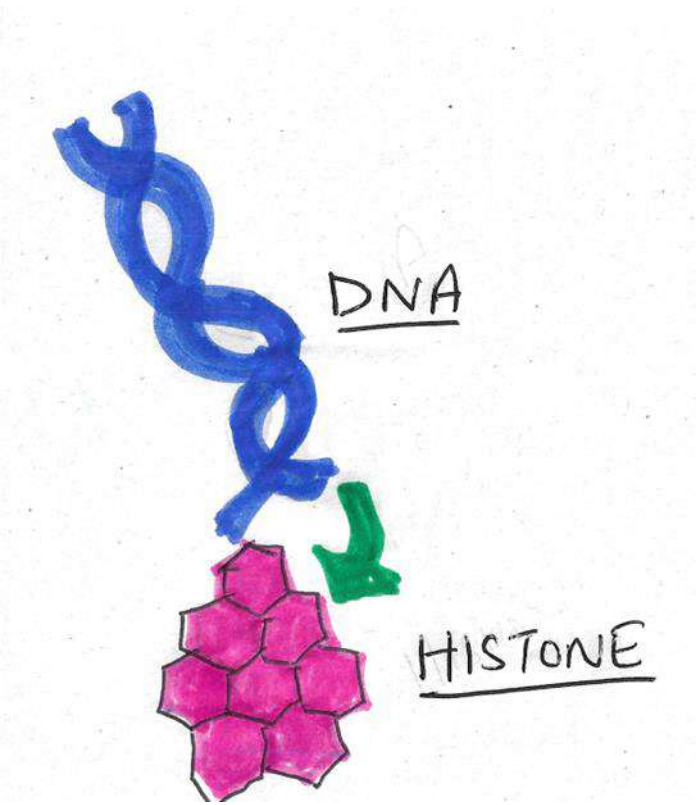
1) <u>Shrinking of cells, organelles and swelling.</u>

2) <u>Membrane blebbing</u>

The **cytoskeleton is the network of protein filaments (actin and intermediate) and tubules to break.**

The membrane **bulges outward taking some cytosol with them.**

Key Facts: Features of apoptosis



Characteristics of Apoptosis

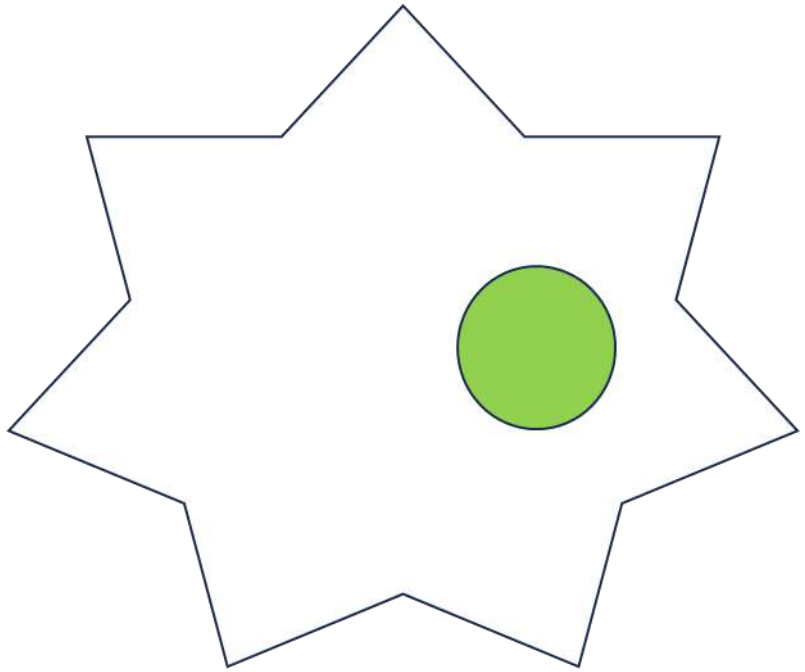
3) Pyknosis (condensing chromosomes and shrinking of nucleus).

4) **DNA laddering**

DNA degraded/cleaved by caspase-activated DNase (CAD) between nucleosome to form DNA fragments 180–185 base-pairs.

This occurs at **internucleosomal linker regions** which are sites that have **no histones** – a **type of proteins wrapped around DNA.**

Key Facts: Features of apoptosis



macrophages

Characteristics of Apoptosis

5) **Karyorrhexis**

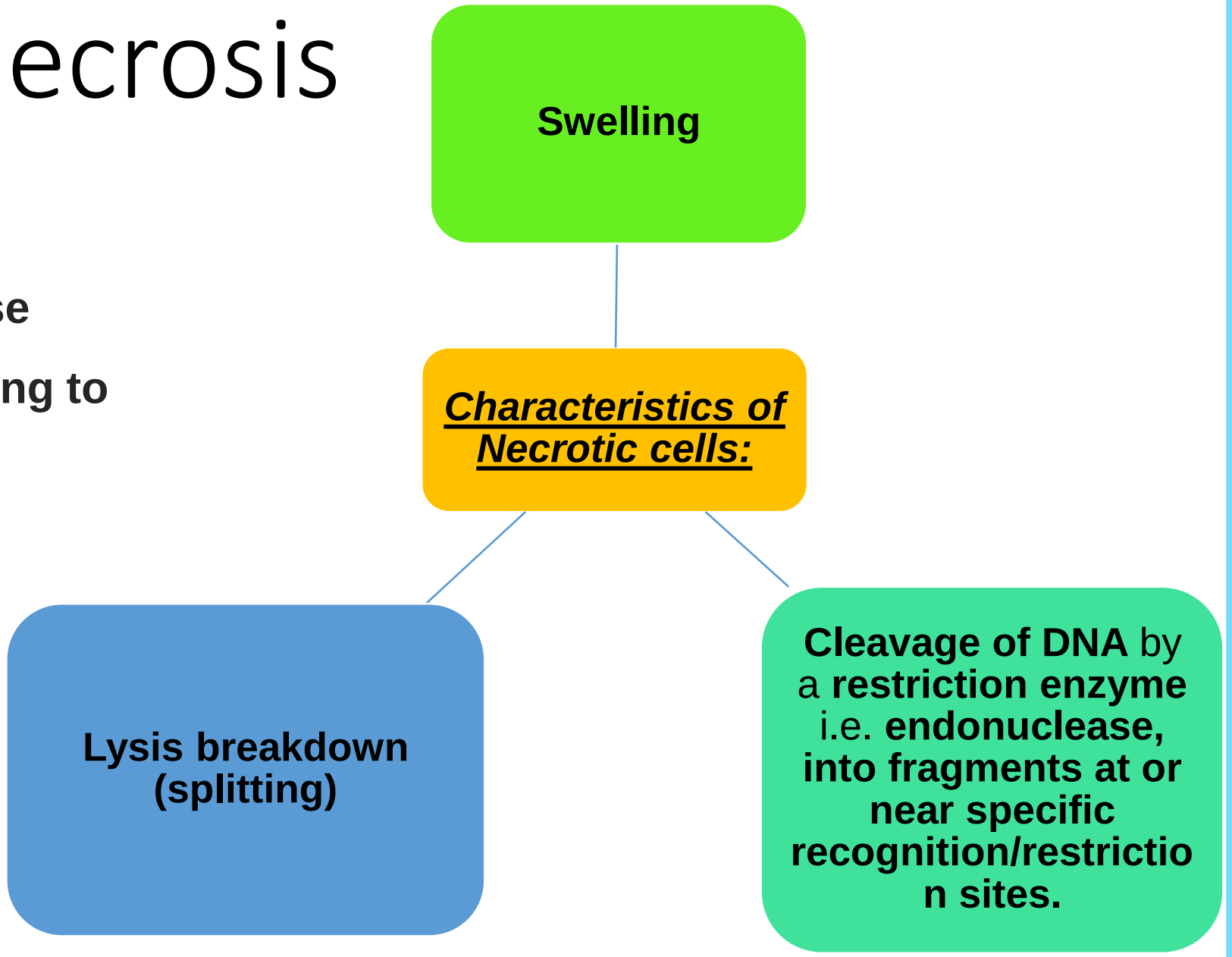
Fragments of the **nucleus**

6) **Engulfment of the cell by phagosomes**

Phagosomes structures in a type of **white blood cell called phagocytes/macrophages)**

Key Facts: Necrosis

Necrosis is when **cells are destructed quickly** to **release contents into the surrounding to induce inflammation**.

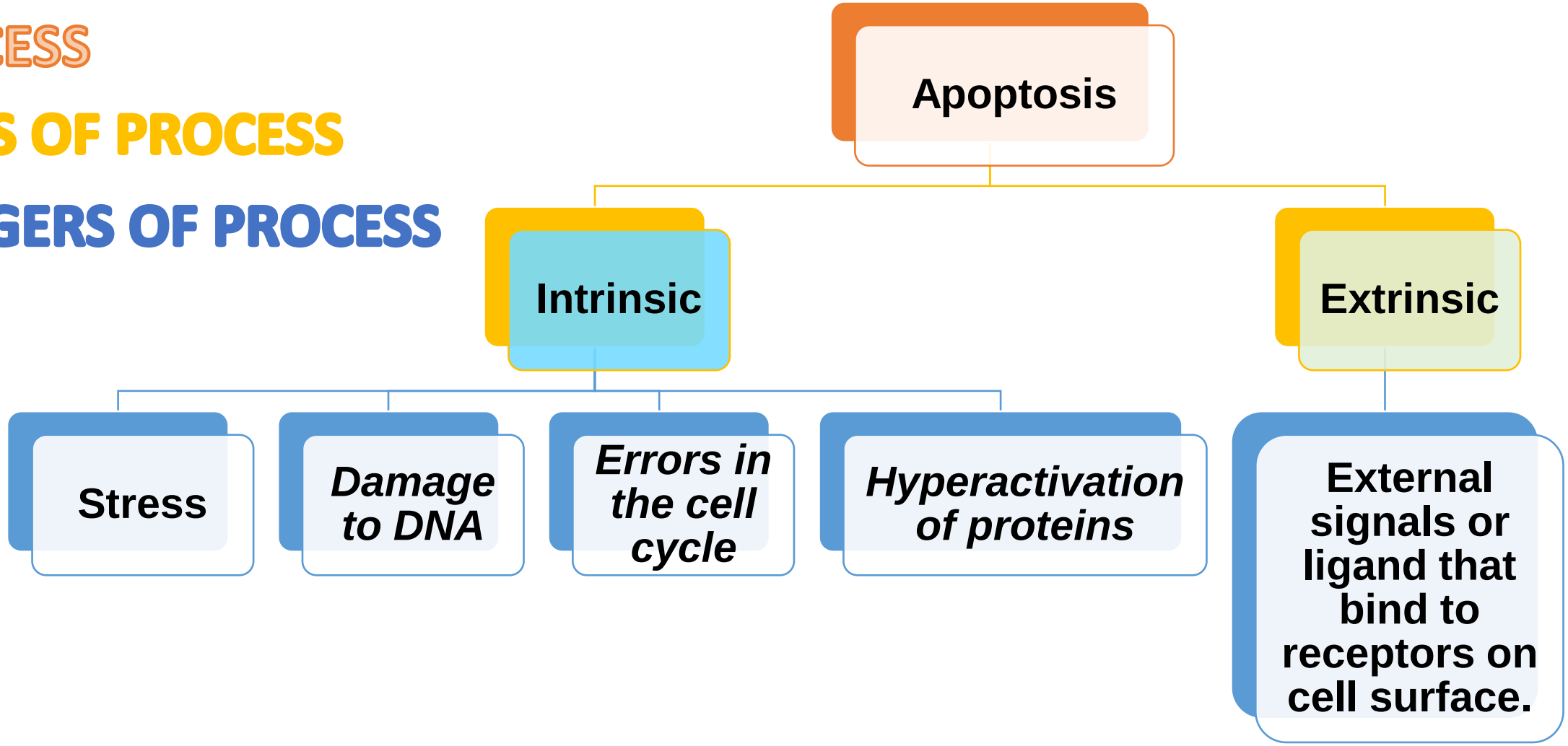


Key Facts: Types of apoptotic pathways

PROCESS

TYPES OF PROCESS

TRIGGERS OF PROCESS



Key Facts: Friends of apoptosis

Caspases – enzymes required by intrinsic and extrinsic pathways

They belong to a family of enzymes known as proteases that cleave intracellular proteins.

Cleave is the division or splitting into particular parts.

They act like molecular scissors that are highly concentrated with cysteine.

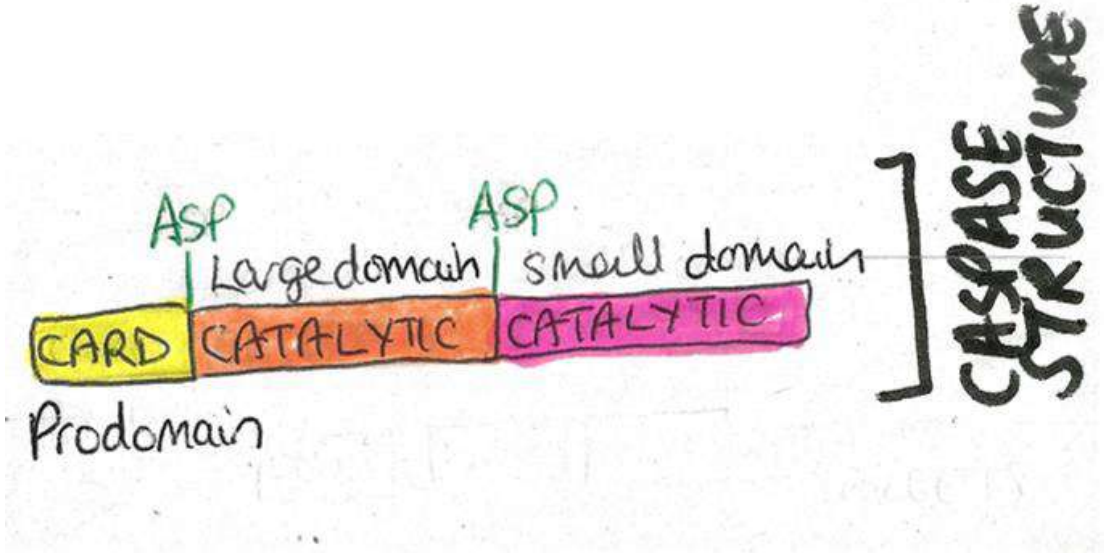
They specifically cleave at aspartate.

Aspartate is a type of amino acids.

Amino acid is the monomer and building blocks that make protein

Inactive form: **pro**caspase

Active form: caspase



Key Facts: Friends of apoptosis

Types of caspases

Initiator caspases	Effector caspases	Inflammation
• Caspase-2 • Caspase-8 • Caspase 9 • Caspase-10	• Caspase-3 • Caspase-6 • Caspase-7 • Caspase-14	• Caspase-1 • Caspase-4 • Caspase-5 • Caspase-13

Key Facts: Friends of apoptosis

Bcl2 protein family required by intrinsic pathways to regulate apoptosis

There are **25 members in the family.**

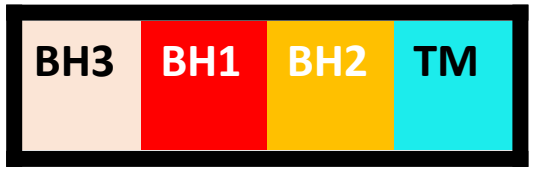
They act on the **outer membrane of the mitochondria**.

They **contain at least one Bcl-2 homology (BH) domain** that **mediates protein–protein interactions.**

A **domain** are **functional or structural unit in a protein**.

Most family members share **three or four BH domains**.

The **intermembrane space between the two mitochondrial membranes** are a stock cabinet for **pro-apoptosis.**



Pro-apoptotic

Anti-apoptotic

BH3 only

Blocking the **BH3 domains** of pro-apoptotic proteins to inhibit apoptosis.

C-terminal hydrophobic domain (TM) helps binding with the mitochondrial membrane.

Bcl-2 with no TMs: A1 and many BH3-only proteins (Bid, Bad, Bmf, Noxa and Puma).

Key Facts: Friends of apoptosis

Apoptosis is necessary for normal cells to ensure there is **a balance with signals.**

The Bcl-2 proteins is subdivided into that:

A) Promote apoptosis (proapoptotic)

B) Evade apoptosis (anti-apoptotic)

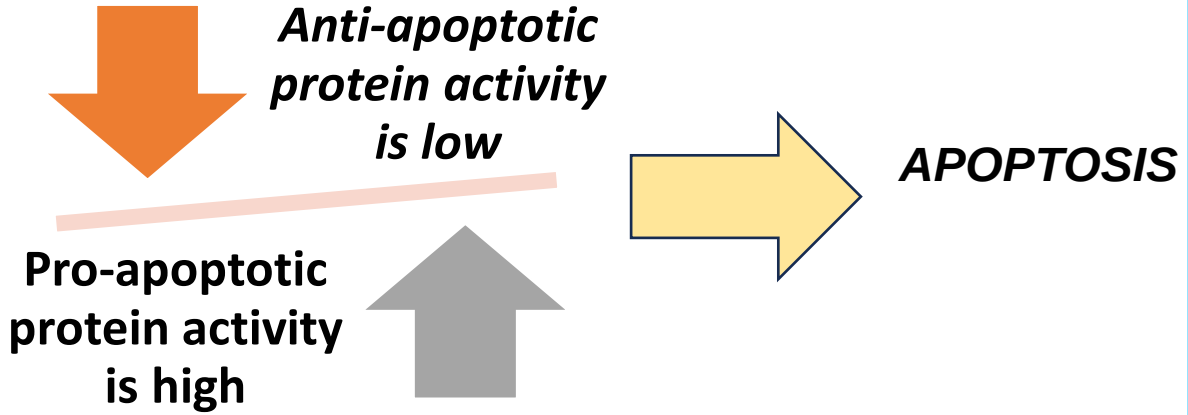
This help **cells grow healthily as they divide.**

Pro-apoptotic proteins	Anti-apoptotic proteins	BH3 only (pro-apoptotic proteins
Bax	A1	Bim/Bod
Bak	Mcl-1	Bik/Nbk/Blk
Bok/Mtd	Boo	Hrk/DPS
Bcl-GL	Bcl-xL	Puma/Bbc3, BNIP3, BNIP1
Bcl-G5	Bcl-w	Bad
	Bcl-2	Bid
		Bim
		Noxa

BH3-only proteins have one BH domain, BH3.

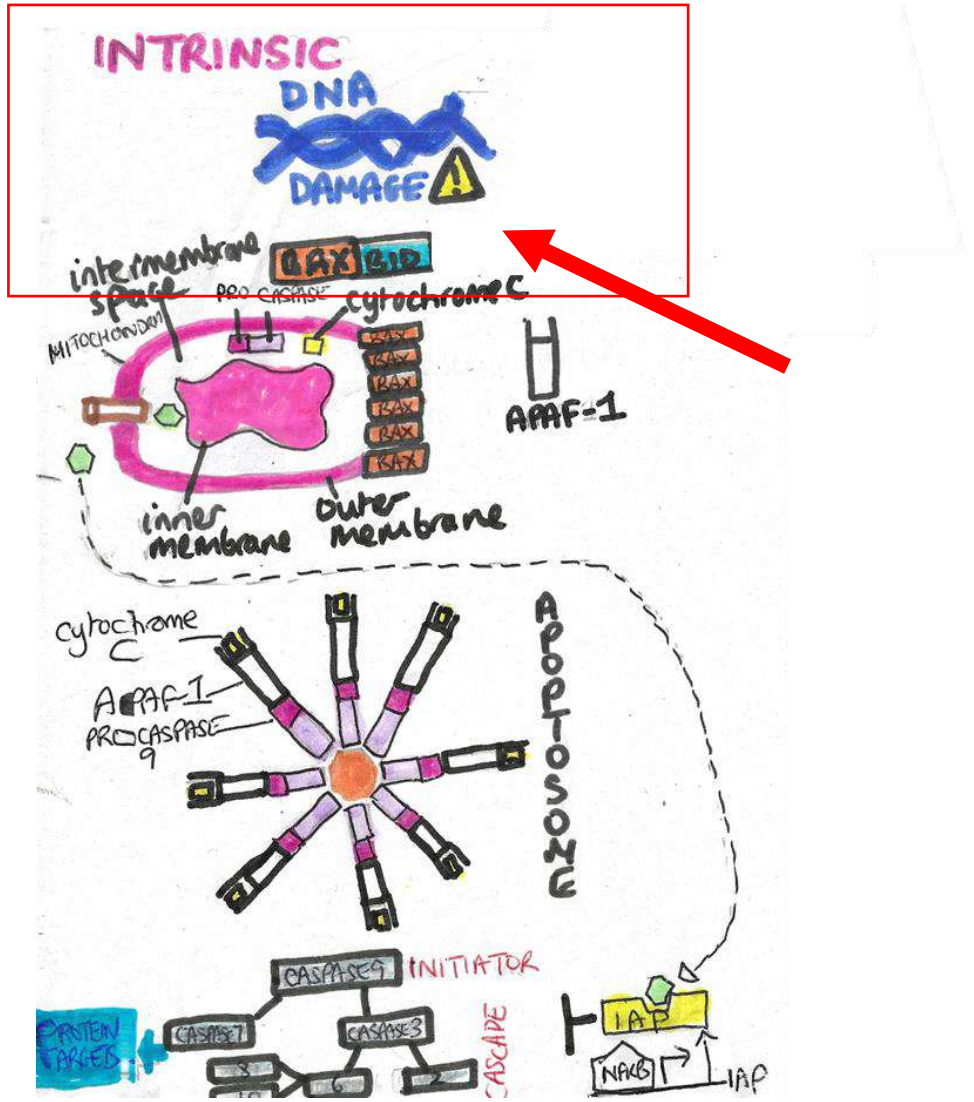
The role of BH3-only proteins is to help regulate activity.

It **increase the activity of the pro-apoptotic molecules (BH3-only activators)** or by **binding and inhibiting the anti-apoptotic molecules.**



Key Facts: Intrinsic apoptotic pathway

1) Cell stress triggers **BH3-only protein Bid** to bind and activate **prop-apoptotic protein Bax**



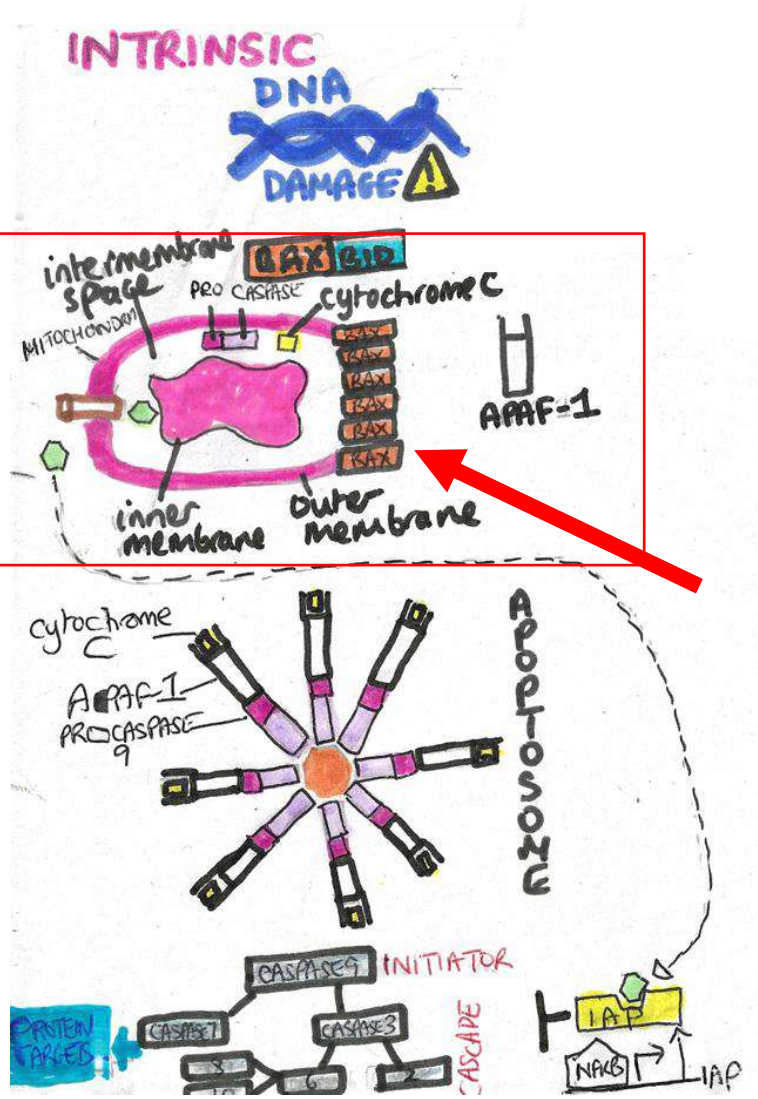
The BH3 domain of Bax is required for its killing activity and interactions with anti-apoptotic proteins.

Key Facts: Intrinsic apoptotic pathway

1) **Cell stress** triggers **BH3-only protein Bid** to bind and activate **prop-apoptotic protein Bax.**

2) **Bax undergoes a conformational change**, it **translocate from the cytoplasm to the mitochondria**, binds and enters the **outer membrane of the mitochondria.**

It produces a **larger protein and oligomerizes where 6–8 molecules come together.**



Key Facts: Intrinsic apoptotic pathway

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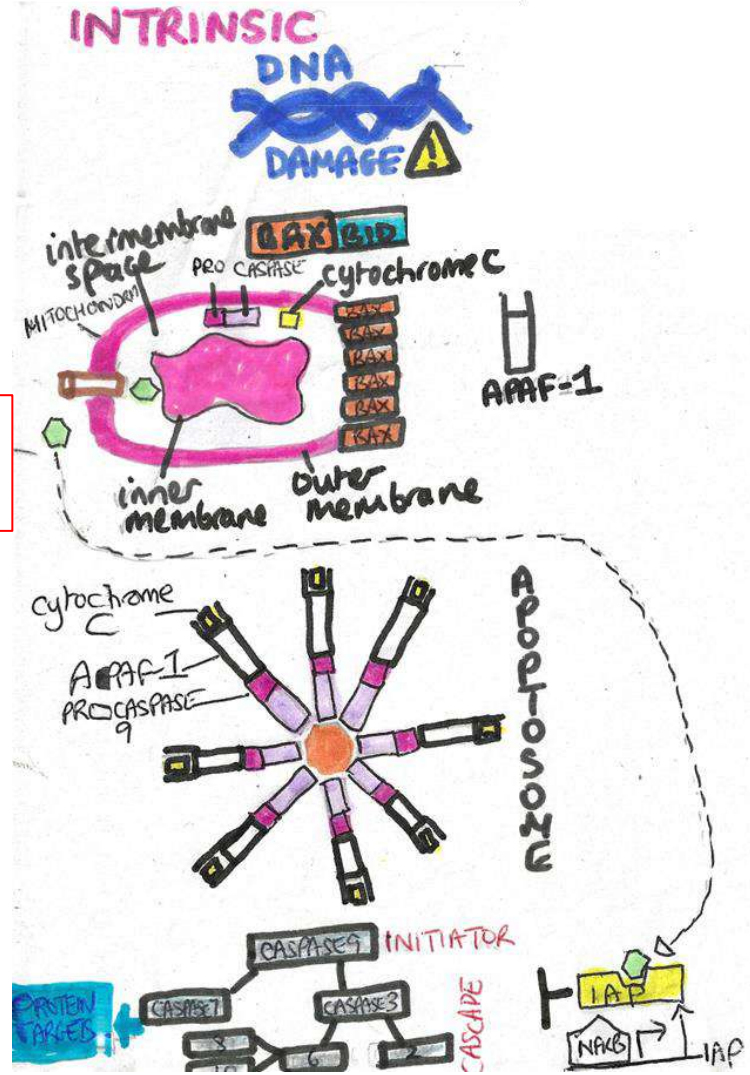
3) **Important regulators** are **released** from the **intermembrane space**

Smac/ Diablo

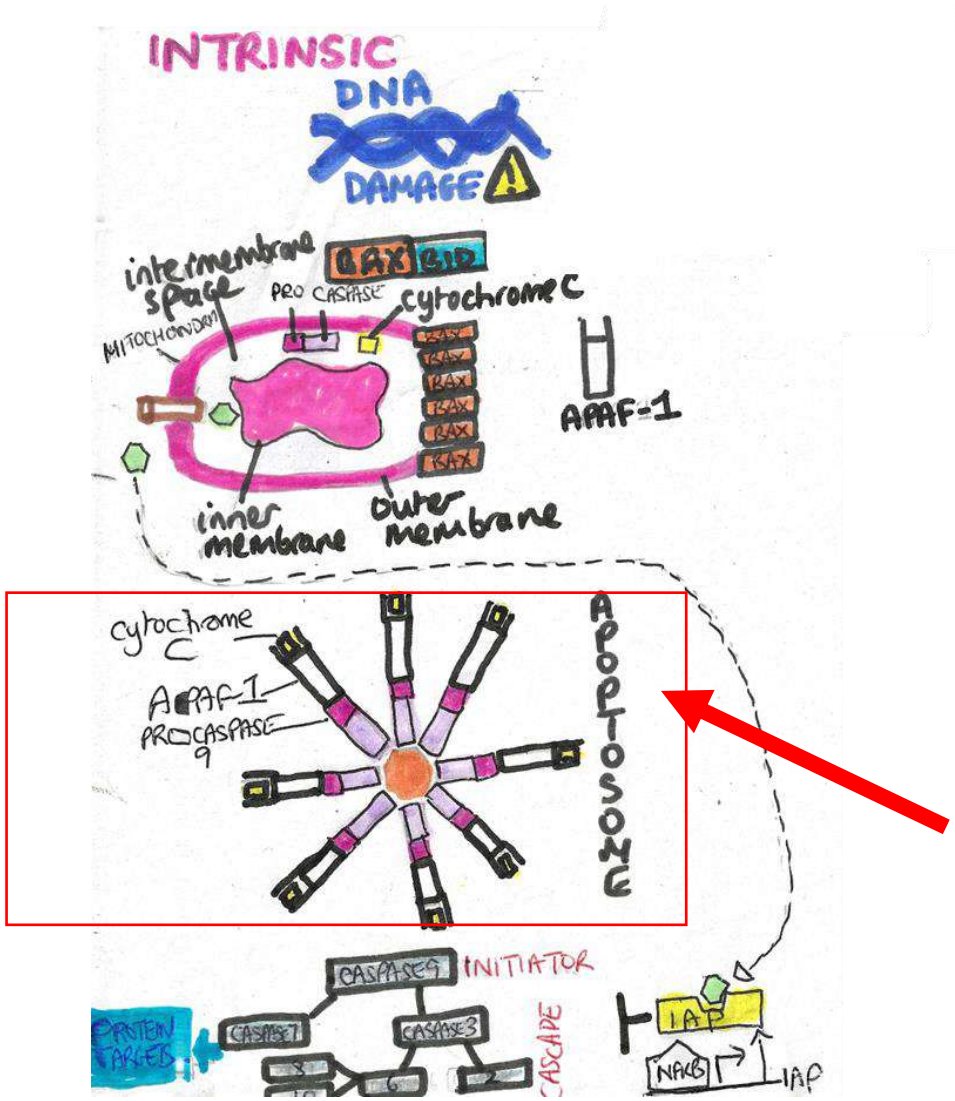


Key Facts: Intrinsic apoptotic pathway

4) The **small, water-soluble (hydrophilic) heme protein, cytochrome c** is associated with the **inner membrane of the mitochondrion.**

It functions in the electron transport chain of ***aerobic respiration to produce energy.***

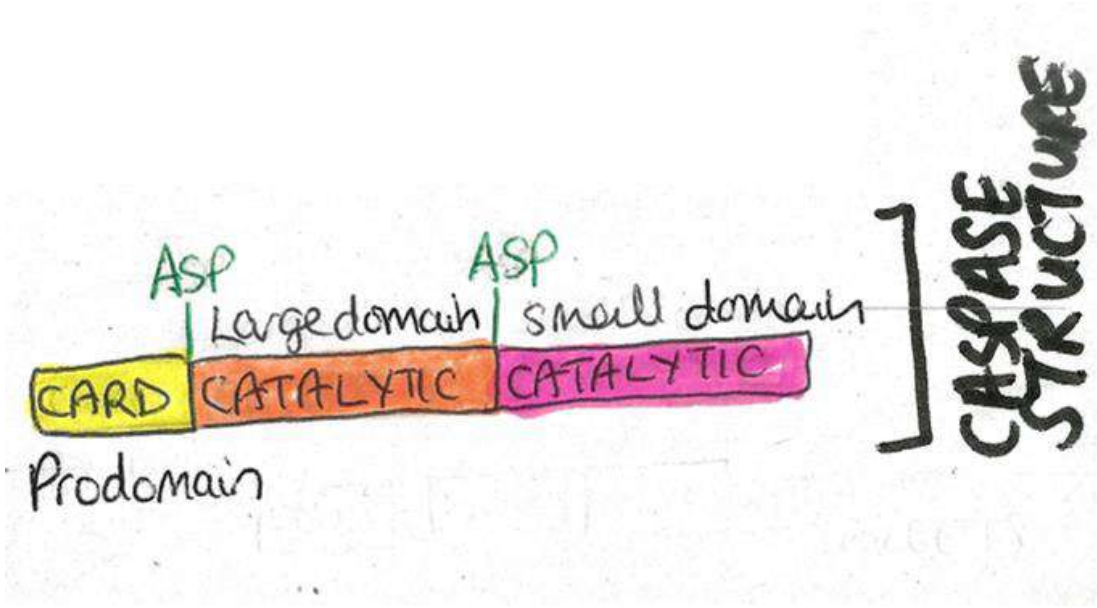
Cytochrome c joins the **inactive enzyme procaspase 9** and a **key cytosol molecule Apoptotic protease activating factor-1 (Apaf-1)** to form the **apoptosome**. The apoptosome is a **7-subunit (heptameric) protein complex.**



Key Facts: Intrinsic apoptotic pathway, a closer look

Recruitment of **procaspase-9** are via protein domains, called **CARD domains.**

They are present on both **Apaf-1 and procaspase-9**.



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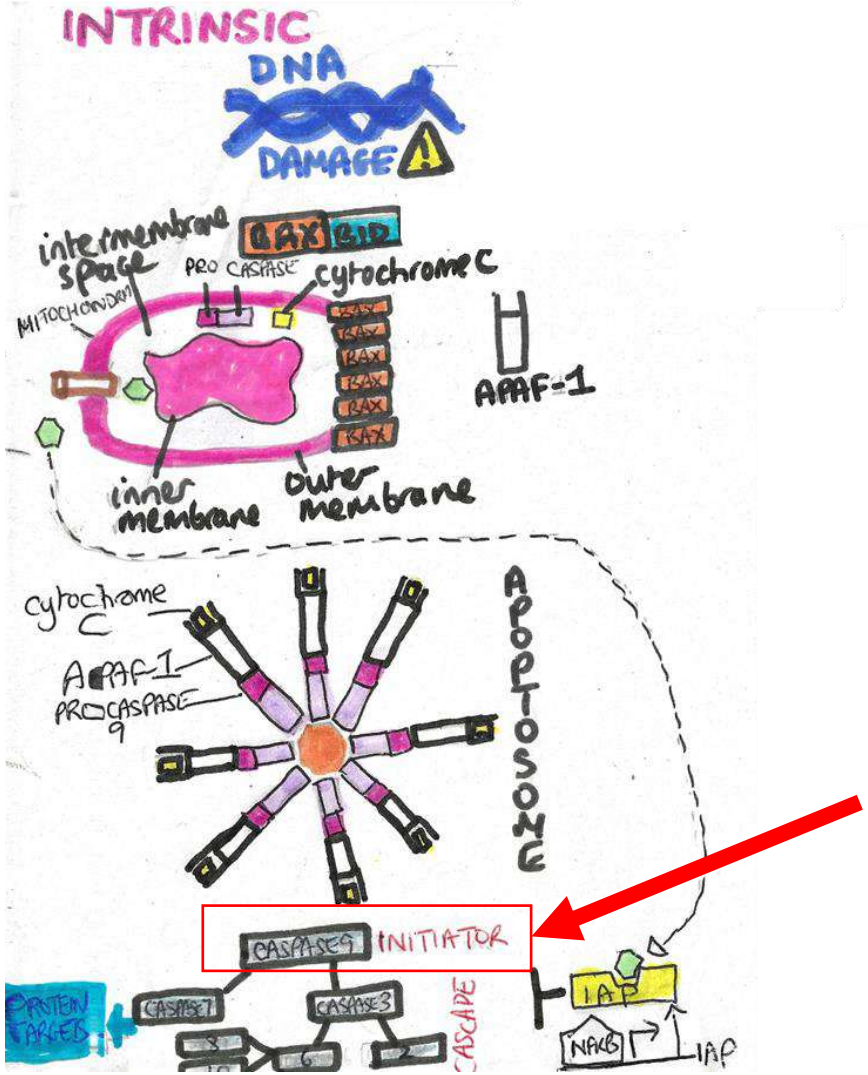
5) Apaf-1 is a protein co-factor that is needed to activate procaspase 9 to form caspase 9.



Key Facts: Intrinsic apoptotic pathway

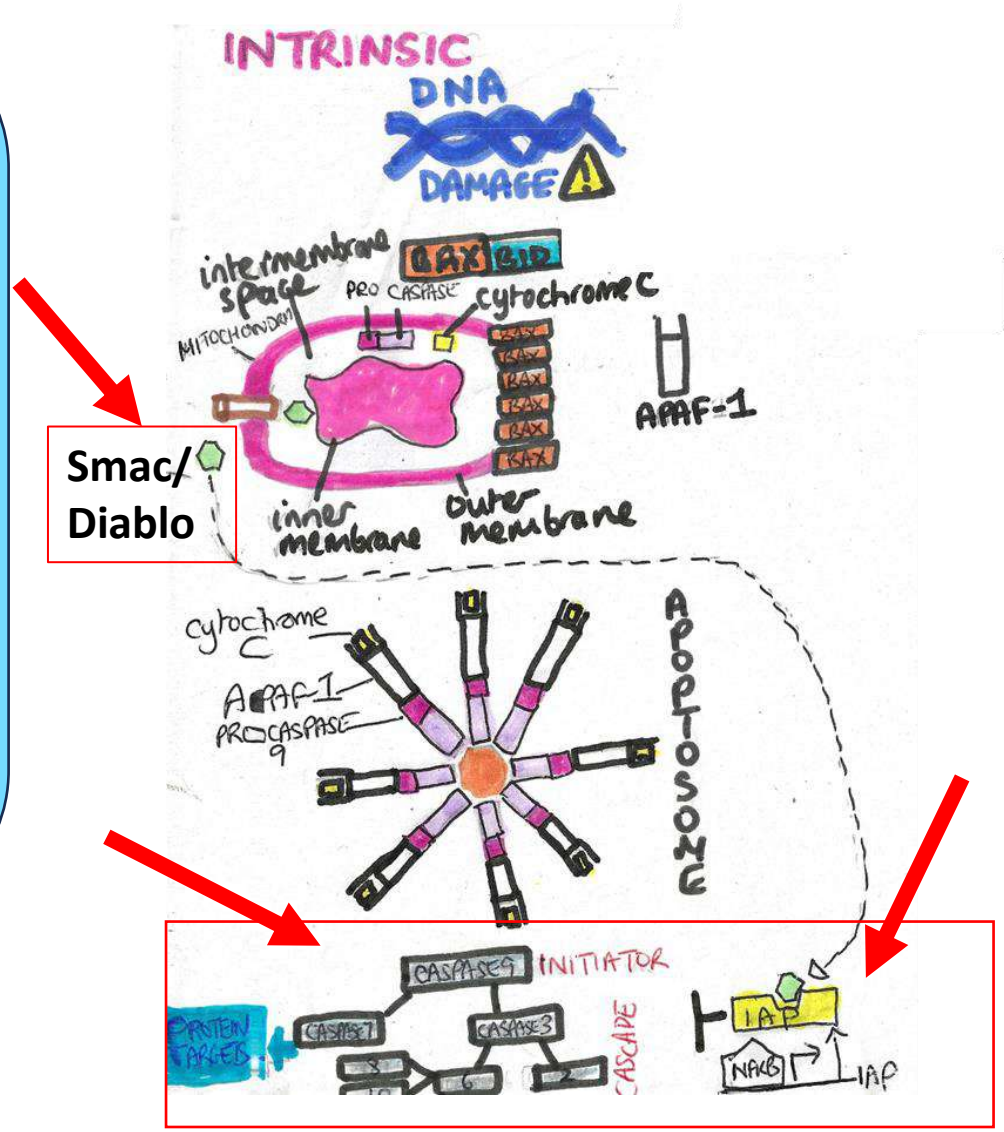
6) Caspase cascade.

Initiator caspase
Caspase 9

Effector/executioner caspase
Caspase 3/6/7

To **maintain caspase activity**, the **Smac/DIABLO is released from the mitochondria to stop inhibitors of apoptotic proteins (IAPs)** that **normally block caspases.**

eight mammalian IAPs have been identified



Key Facts: Intrinsic apoptotic pathway

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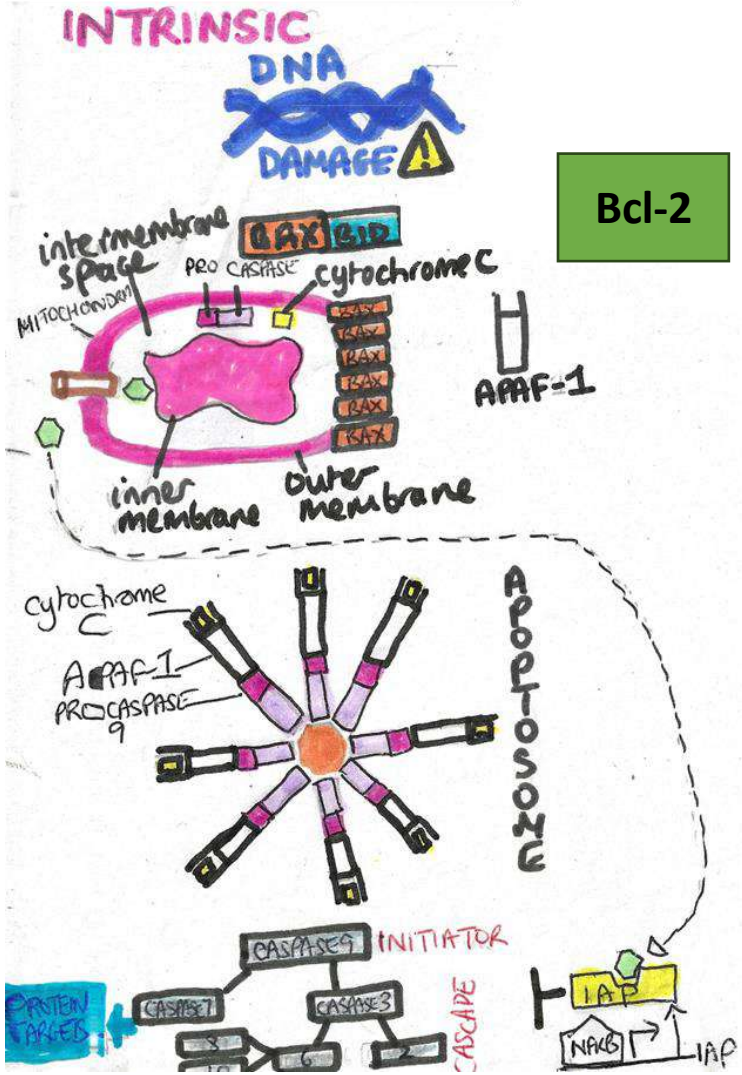
↓

7) Bcl-2 pro-apoptotic proteins regulate the release of pro-apoptotic activity from the mitochondria. This is known as mitochondrial outer membrane permeabilization (MOMP)



Key Facts: Intrinsic pathway process

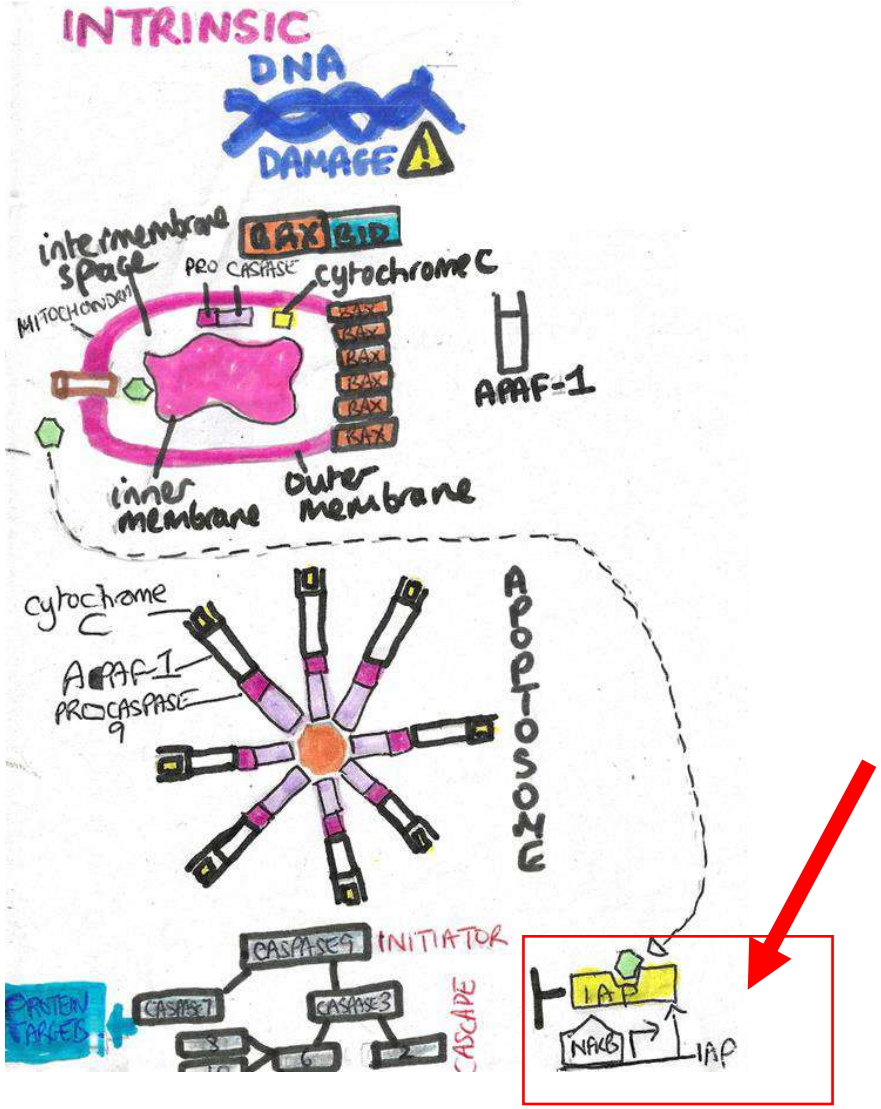
8) X-chromosome linked member XIAP is a member of **IAP family.**

Smac/Diablo and caspase 9 can bind with XIAP via their tetrapeptide IAP-binding domain.

Recap: Smac/Diablo binds with IAPs to allow caspase activity to continue.

IAP stops the caspase cascade where it can inhibit caspase activity of 3, 7 and 9 vis their active sites.

- **NFκB is a transcription factor** where it induces **transcription of IAPs** and plays a major role in **inflammation.**

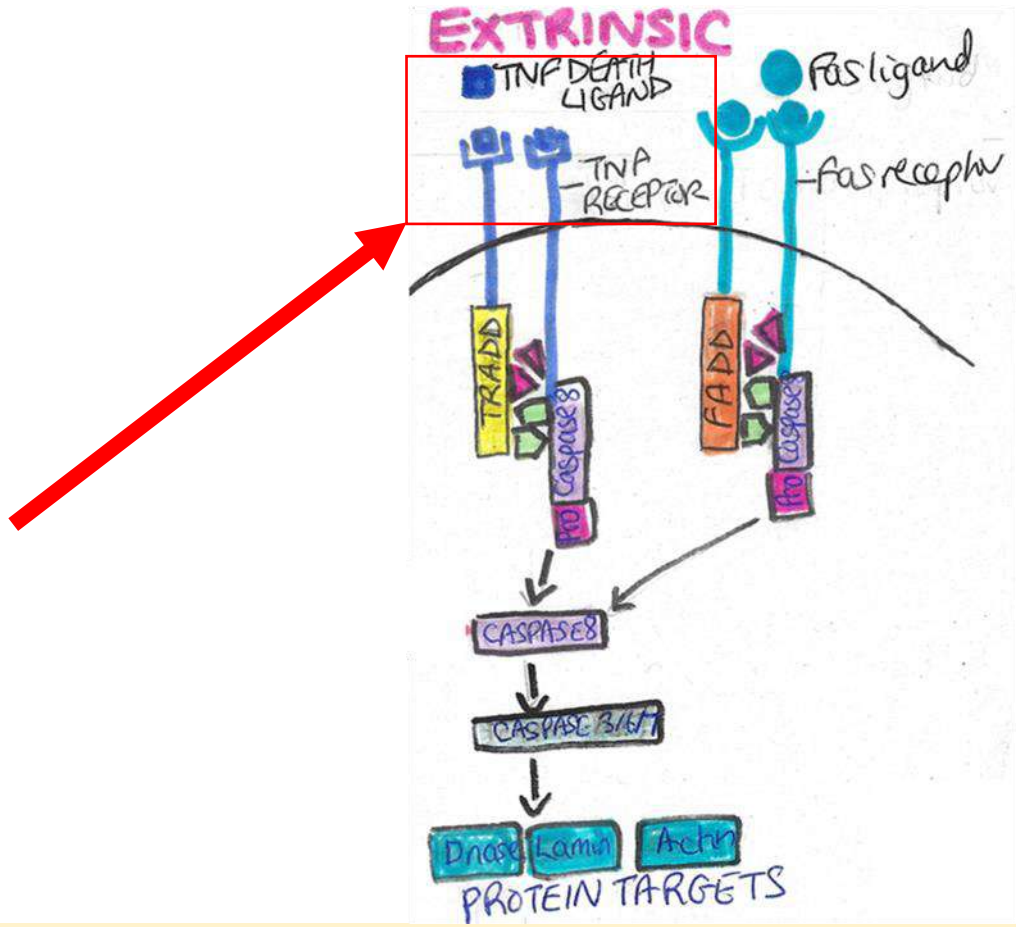


Key Facts: Extrinsic pathway process

1) Death signals or ligands bind to their **specific transmembrane receptor** via the **extracellular death receptor domain** to **activate the receptor.**

This is similar to a **lock and key manner**.

TNF and FasL ligands are soluble **type 2 membrane-bound proteins.**



tumour necrosis factor (TNF) ligand + TNF receptor ---> TNF receptor-ligand complex.

Fas ligand (FasL) + Fas receptor ---> Fas receptor-ligand complex.

Key Facts: Extrinsic pathway process

1) Death signals or ligands bind to their **specific transmembrane receptor** via the **extracellular death receptor domain** to **activate the receptor.**

This is similar to a **lock and key manner**.

TNF and FasL ligands are soluble **type 2 membrane-bound proteins.**

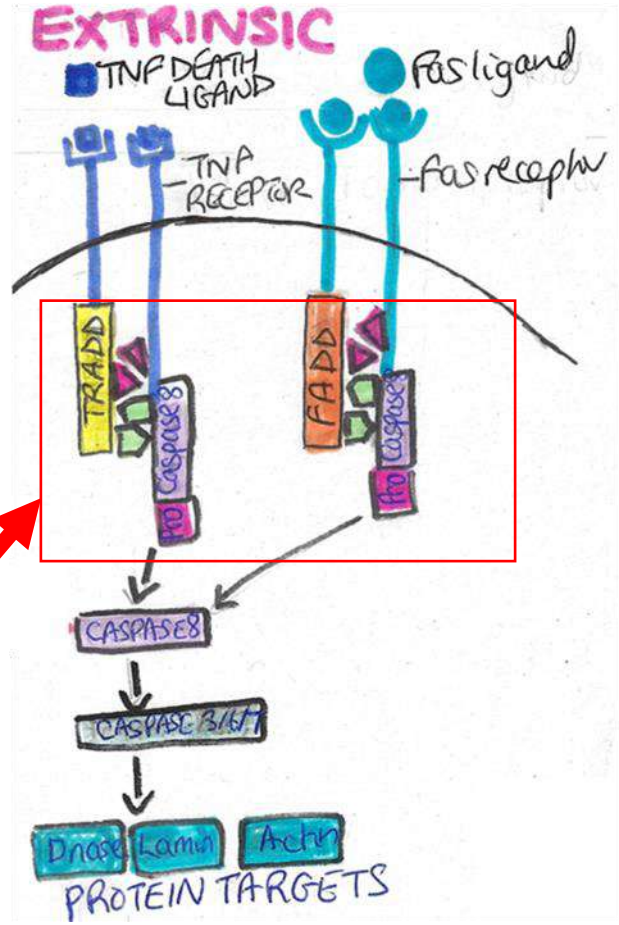
2) The activated receptors undergo a conformational change which exposes the **death domains (DD) or cytoplasmic motif [pink triangles].**

This binds with the DD of specific proteins called **intracellular adaptor proteins.**

The function of adaptor proteins is to **transduce the death signal from the receptor to caspases.**

Activated TNF receptor bind to TRADD (TNF receptor-associated death domain protein) via DD.

Activated Fas receptor bind to FADD (Fas-associated death domain protein) bind to via DD.



Key Facts: Extrinsic pathway process

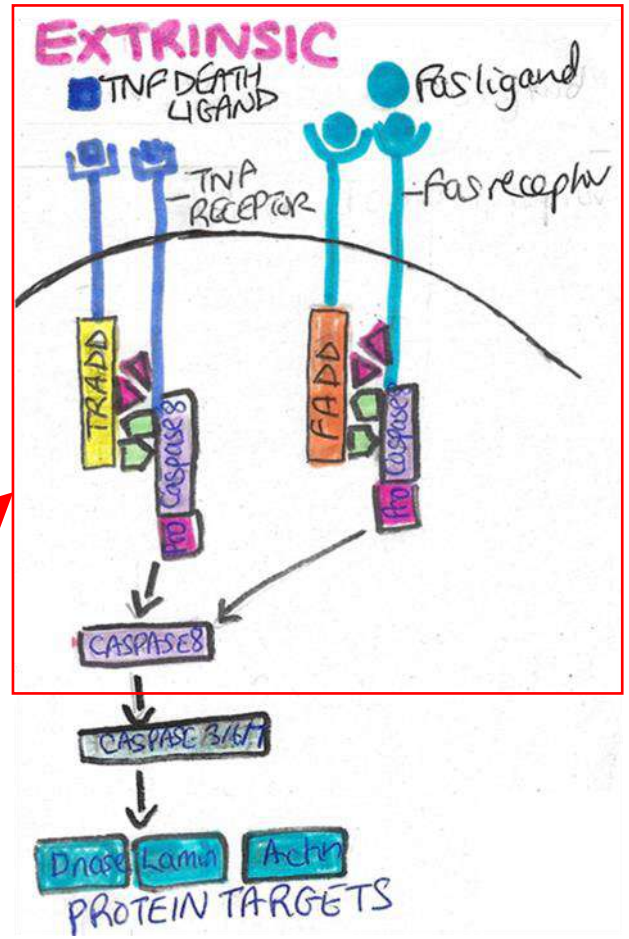
3) **FADD interacts with caspases** through another domain called **death effector domain (DED) [green pentagons]**

It recruits a **few molecules of procaspase-8** that become **close and self-cleave** because **procaspases have slow enzymatic activity**.

Caspase 8 is the initiator caspase.

A complex called **death inducing signalling complex (DISC)** is formed between the **death ligands, receptors, adaptor proteins, and initiator caspase**.

FasL, FAS receptor, FADD, procaspase 8/10.



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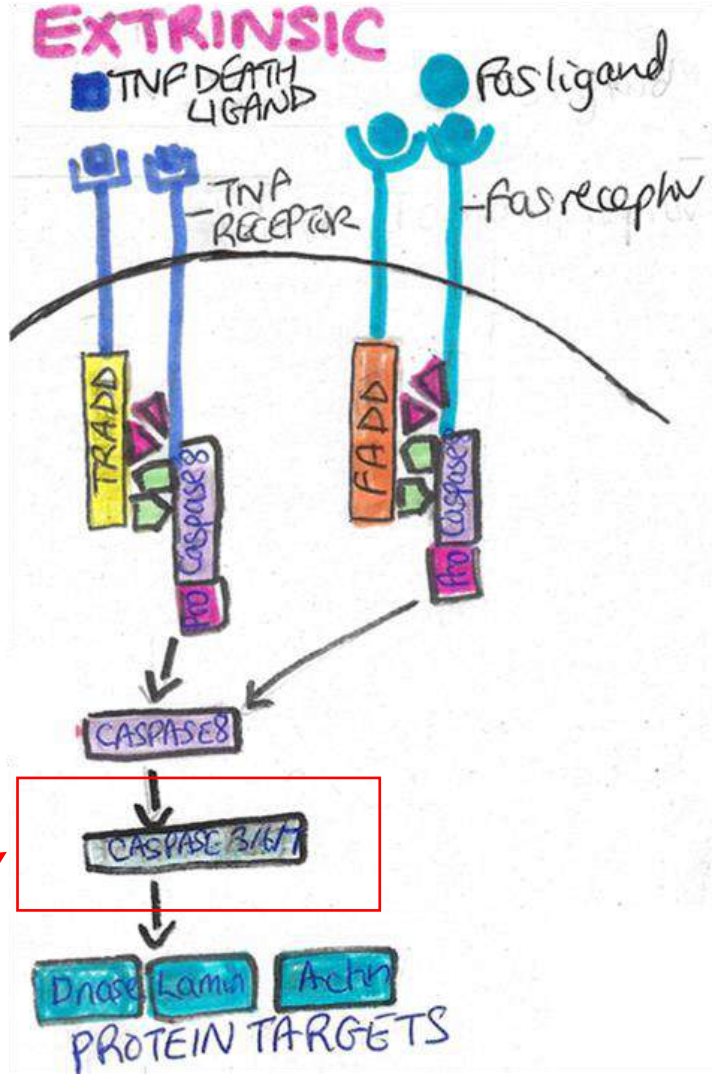
FasL, FAS receptor, FADD, procaspase 8/10.

4) The **activated caspase 8 cleaves other effector/executioner caspases (3, 5 and 7)** in a cascade.



Key Facts: Extrinsic pathway process

5) This **extrinsic process can be inhibited by c-Flip.**

c-Flip can bind to adaptor FADD via a DED

c-Flip can inhibit caspase-8 recruitment and activation.

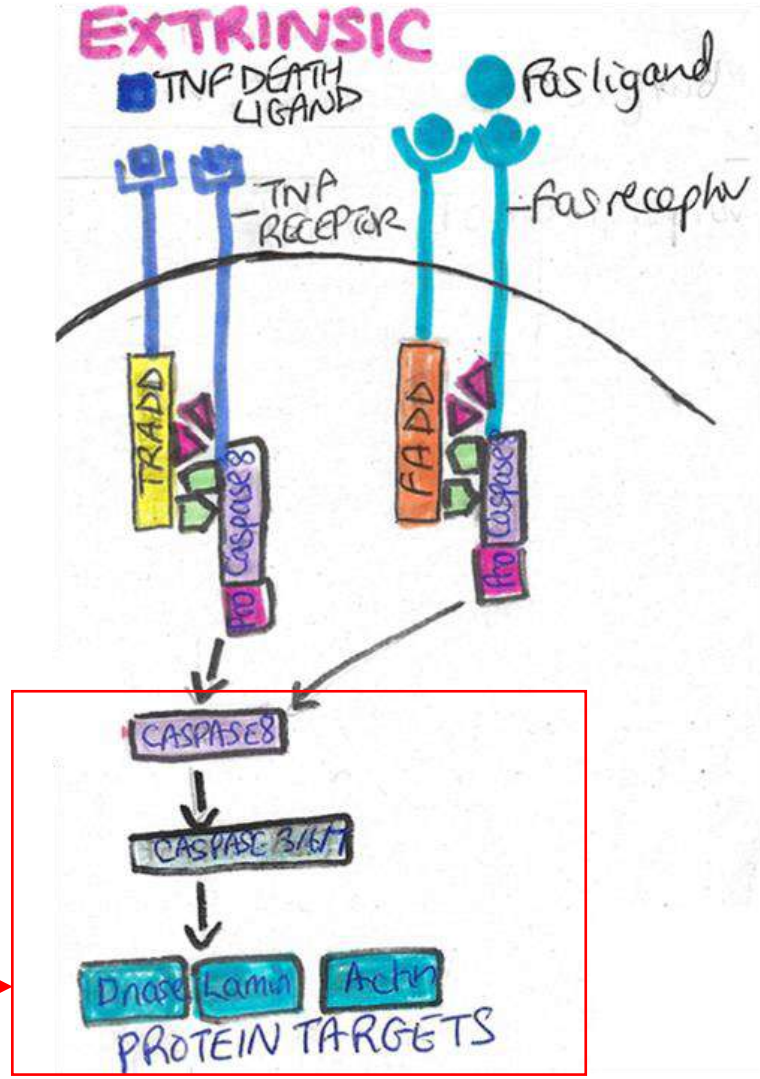
6) The **cascade** ultimately causes the **cleavage/proteolysis of specific target proteins** and results in **apoptosis.**

For example:

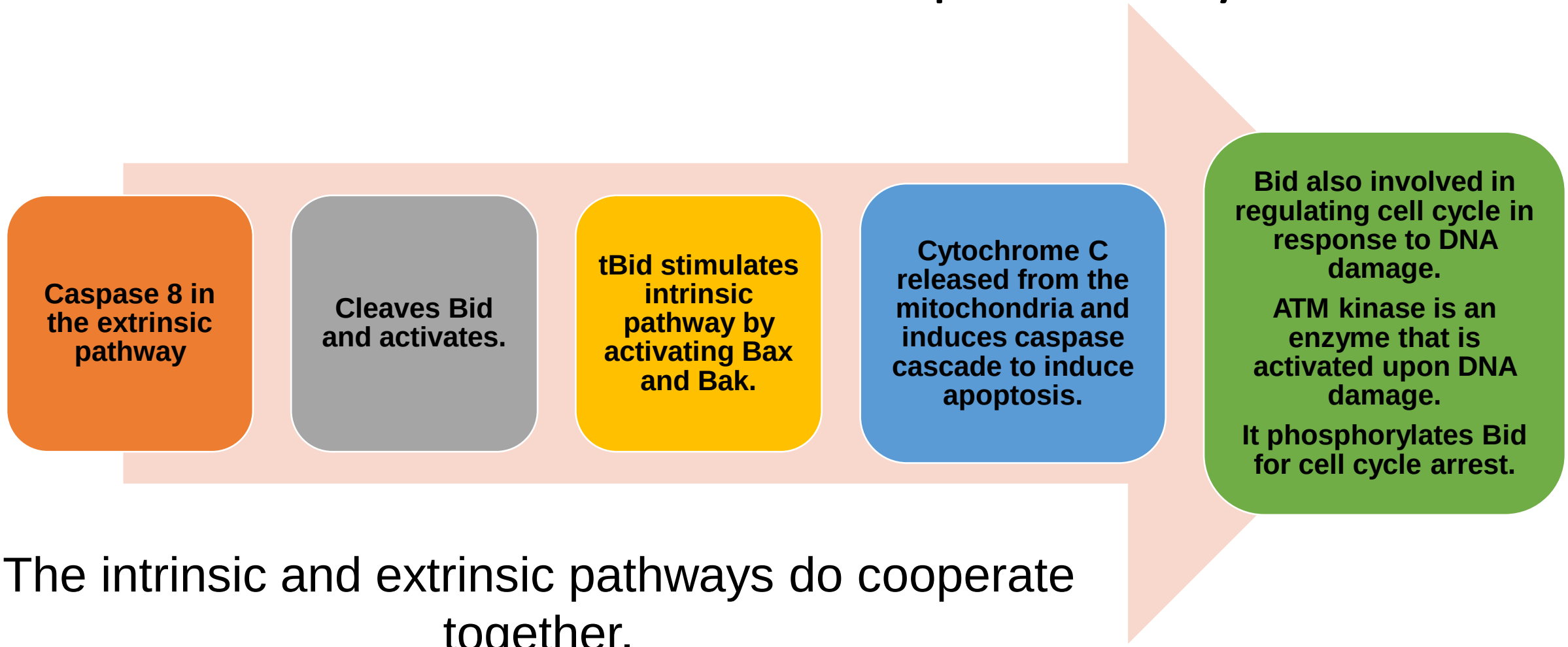
*Shrinkage of nucleus – breakdown of **nuclear lamins.***

*Cytoskeleton – breakdown of **actin and intermediate filaments** for rearranging cell structure.*

*Cell signalling – **protein kinases.***

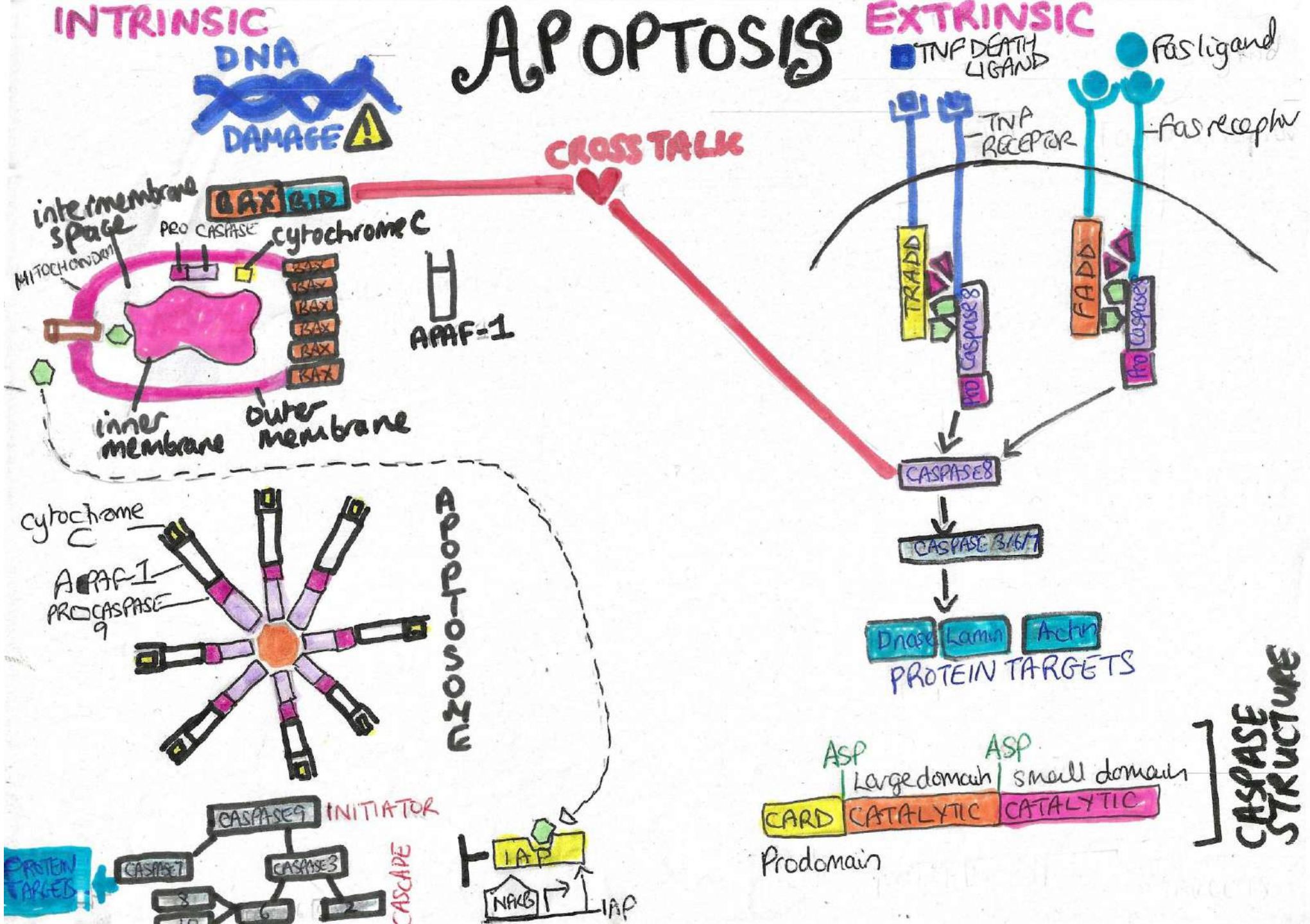


Key Facts: Cross-talk between extrinsic and intrinsic pathways.



The intrinsic and extrinsic pathways do cooperate together.

Cross-talk between extrinsic and intrinsic pathways.



Key Facts: More on cross-talk

The activated Bid (tBid) stimulates: **Bax and Bak to promote MOMP (mitochondrial outer membrane permeabilization (MOMP).**

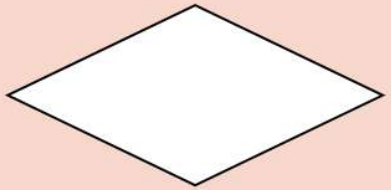
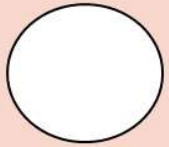
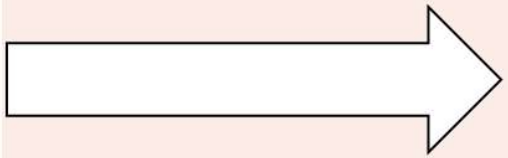
This causes membrane channels to release:

- ❑ **Cytochrome C**
- ❑ **Smac/Diablo**
- ❑ **HtrA2/Omi**

This helps and contributes to apoptosis.

- ❑ **tBid inhibited the following antiapoptotic protein:** *Bcl-2 and Bcl-xL*

You could use these shapes to create a flow chart that represents how the cell undergoes apoptosis.

Name	Symbol	Description
Start/Stop		Start and end of a flowchart
Process		To carry out a task
Decision		To make a decision. More than one arrow can be used
Input/Output		Input/output
Direction of flow		Join flow charts that cannot fit on one page.
Connector		Direction of travel

Example

Name	Symbol	Description
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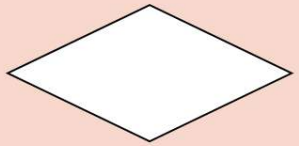
Decision		To make a decision. More than one arrow can be used
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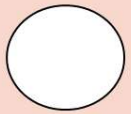
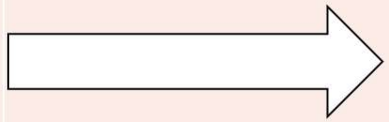
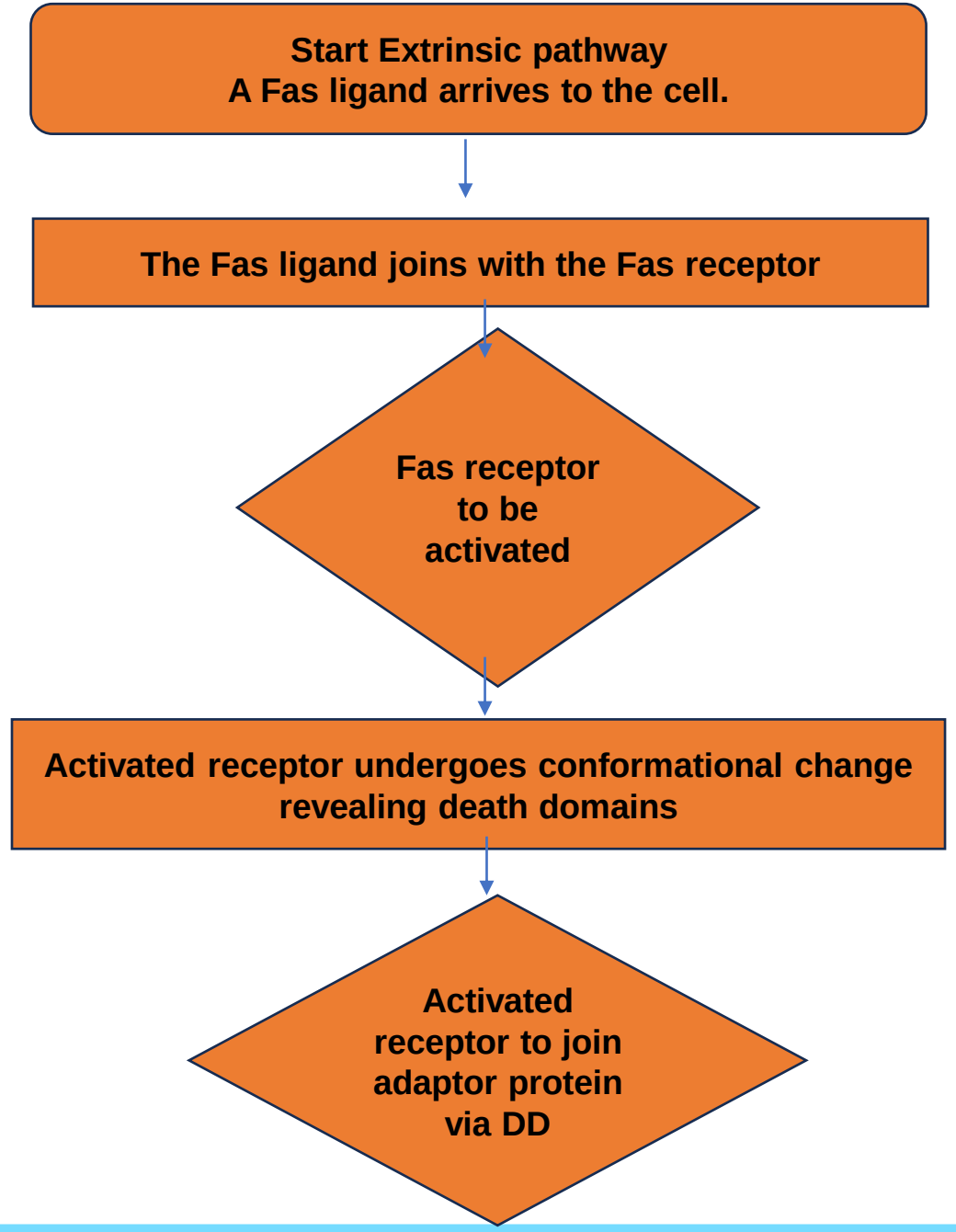
Direction of flow		Join flow charts that cannot fit on one page.
Connector		Direction of travel



A brief overview of Hall mark cancer 4: Enable replicative immortality

Key facts: DNA replication

DNA replication is when **copies of DNA are performed.**

Each normal cell has a finite number of replications.

DNA replication takes place in the **S phase (cell cycle).**

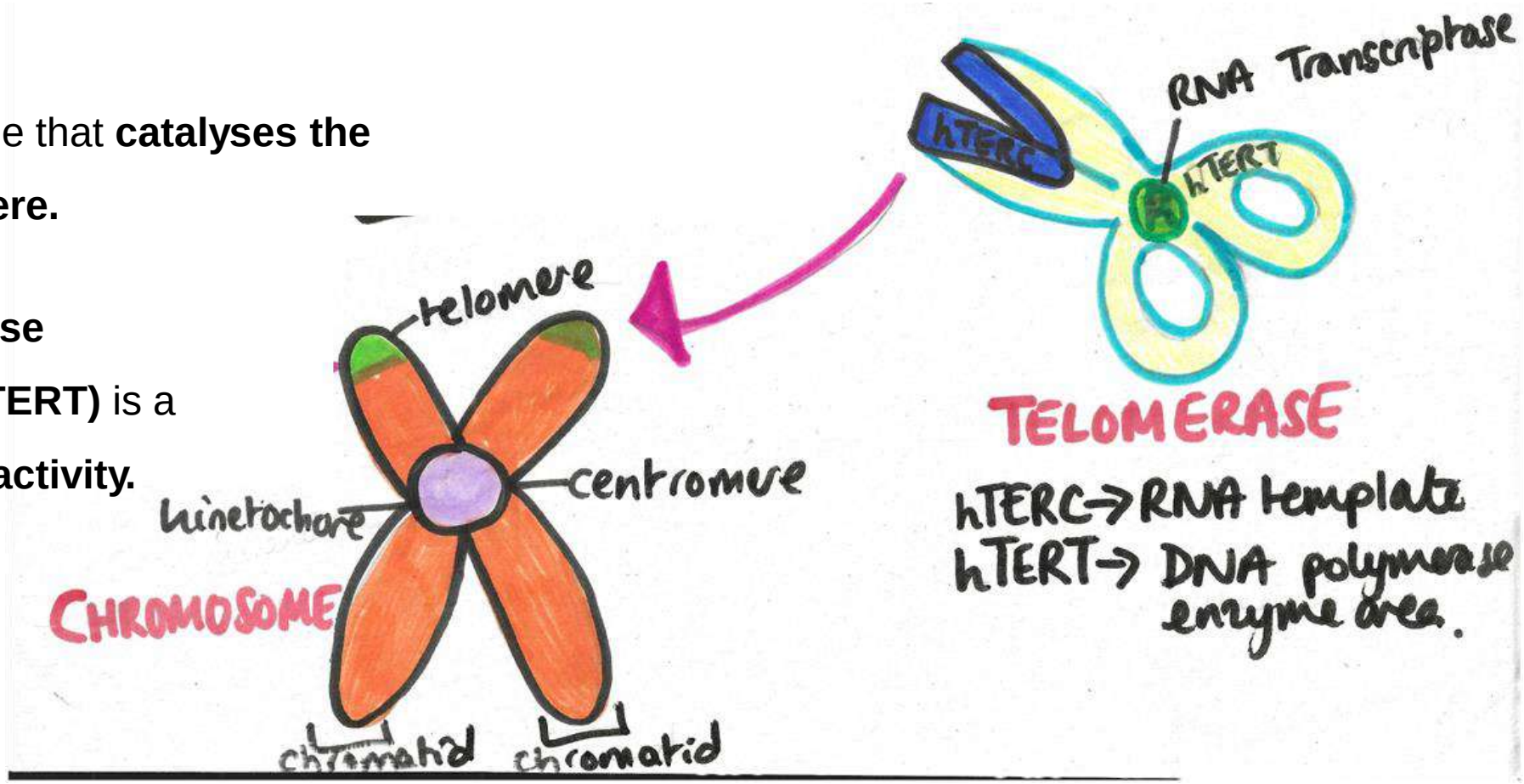
Telomeres are found at the **end of chromosomes** and they **protect the chromosomes from nuclear enzymes that digest them.**

Key facts: DNA replication

For **every cell division**, **normal replication** involves the **shortening of telomeres**. This is about **100-200 bases.**

Telomerase is the enzyme that **catalyses the replication of the telomere.**

Human telomerase reverse transcriptase activity (hTERT) is a major part of **telomerase activity.**

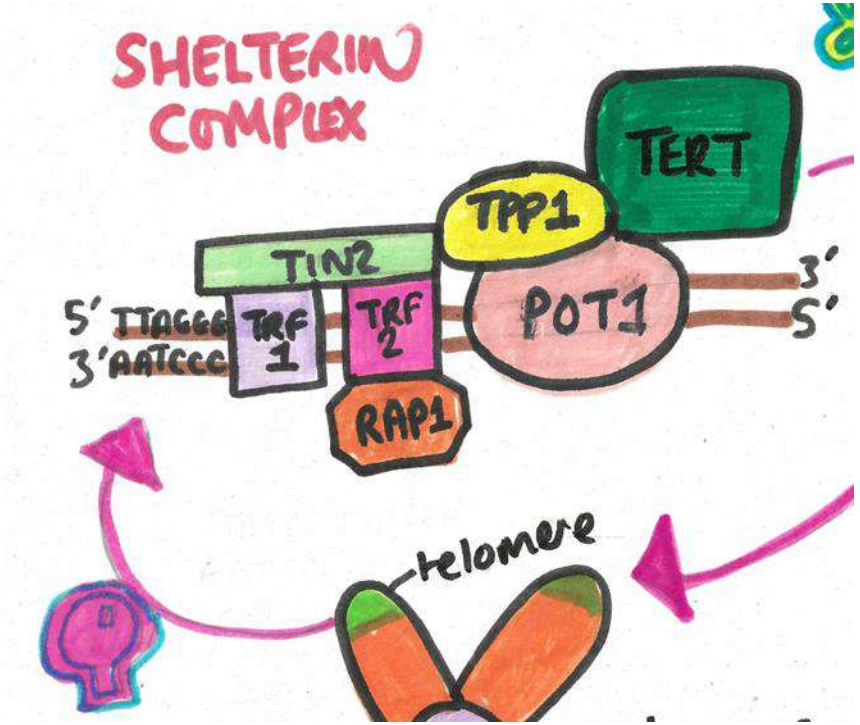


Key facts: A closer look

Telomeres are found at the **end of chromosomes** and **consist of repetitive DNA sequences (TTAGGG) and six associated proteins called the shelterin complex.**

The shelterin complex controls the **telomere length** and **protect the chromosomal ends.**

DNA polymerases proceed only in the **5′–3′ direction** to start **DNA synthesis.**



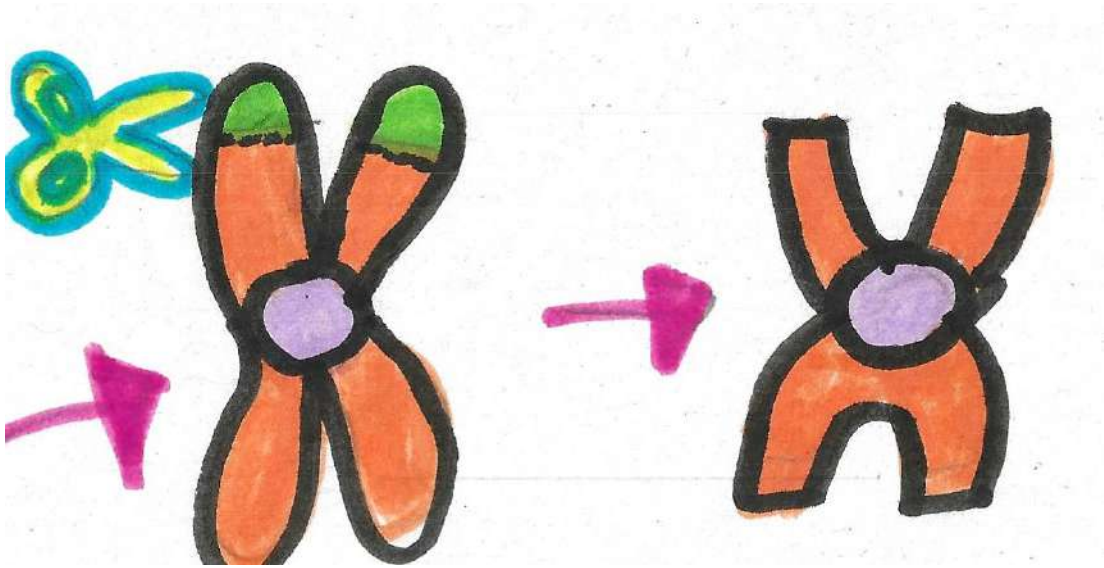
Shelterin complex.

- TRF1 and TRF2 directly bind to double strand telomere DNA.
- Pot1 bind to single strand G-strand DNA (G-tail).
- TPP1, Rap1 and POT1 are recruited to telomeres by protein–protein interactions.

Key facts: What happens next?

When chromosomes reach their limit, cells undergo a permanent growth arrest called **senescence**.

If cells are able to pass the senescence stage, this is because of **mutations** and results in **unstable chromosomes with short telomeres** and **apoptosis.**



Key facts: DNA replication and cancer cells.

Cancer cells are able **to continue to replicate to grow without limit**.

This is achieved by two methods:

1. Increase levels of **telomerase enzyme**
2. **Recombination:** DNA has been changed and is from two or more **sources.**

Cancer cells have **short telomeres.**

This generates a bad signal and leads to **ARREST OF THE CELL CYCLE,**

SENESCENCE AND APOPTOSIS.

A brief overview of Hall mark cancer 5: Invasion and metastasis

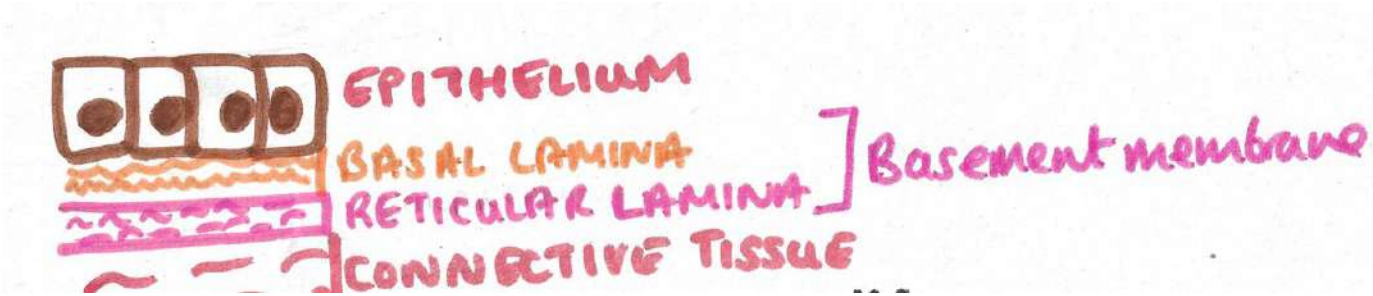
www.hafsaabbas.com

Key facts: Invasion

Invasion is the process that allows **cancer cells to expand** around the **surrounding tissue** which help **colonise distant sites.**

This involves **breaking the binding that keep epithelial cells together.**

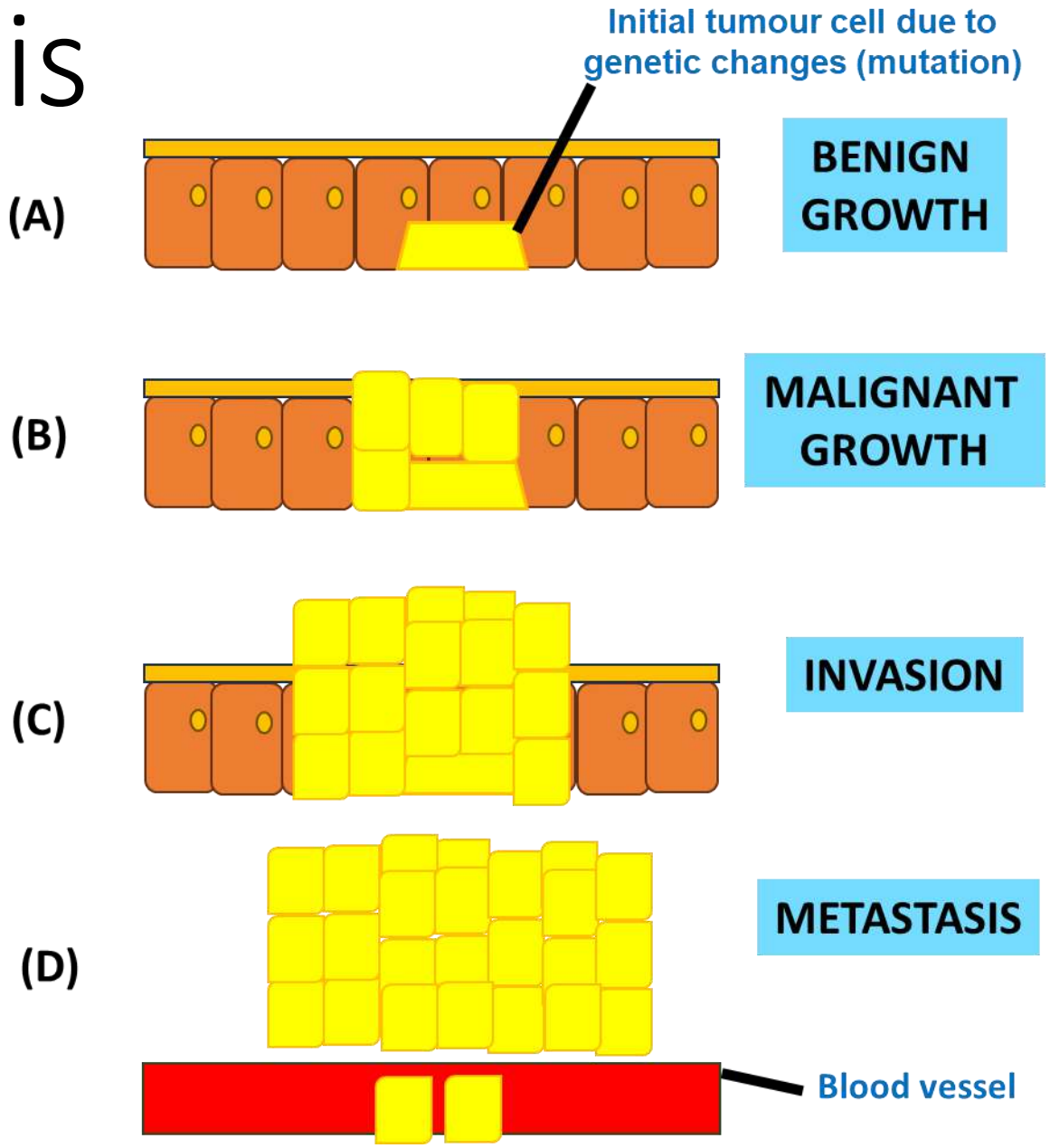
E-cadherin protein is a **tumour suppressor** that is involved in **cell-to-cell adhesion.**



Key facts: Metastasis

Metastasis is the process that helps tumour cells migrate from the **primary site via basal lamina** of the **parent epithelium** to colonise other areas to form **secondary tumours**.

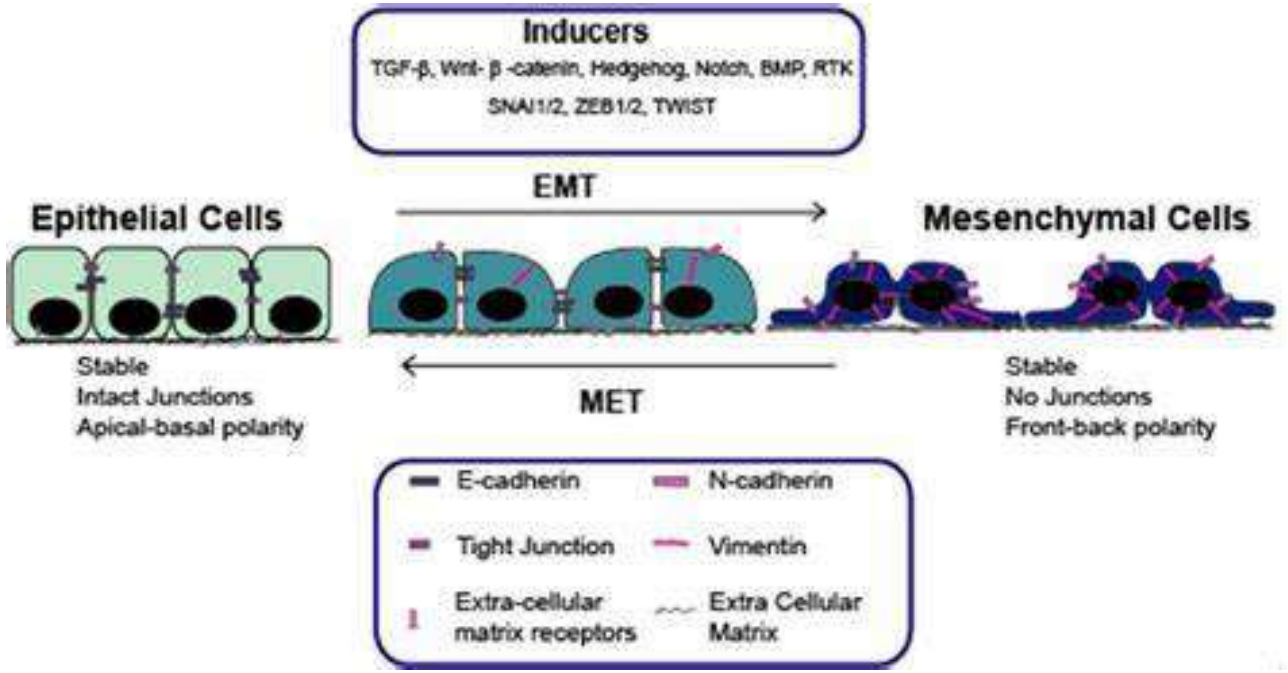
This is achieved via the **blood or lymph vessels**



Key facts: epithelial-to-mesenchymal transition (EMT)

Cancer cells are part of a tissue environment known as **epithelial-to-mesenchymal transition (EMT)** whose role is help **alter cell to cell interactions** and **increase survival of cancer cells to invade and metastasize.**

Cancer cells compete with other cells such as **immune cells and fibroblasts.**



Hill, C., and Wang, Y. (2020)

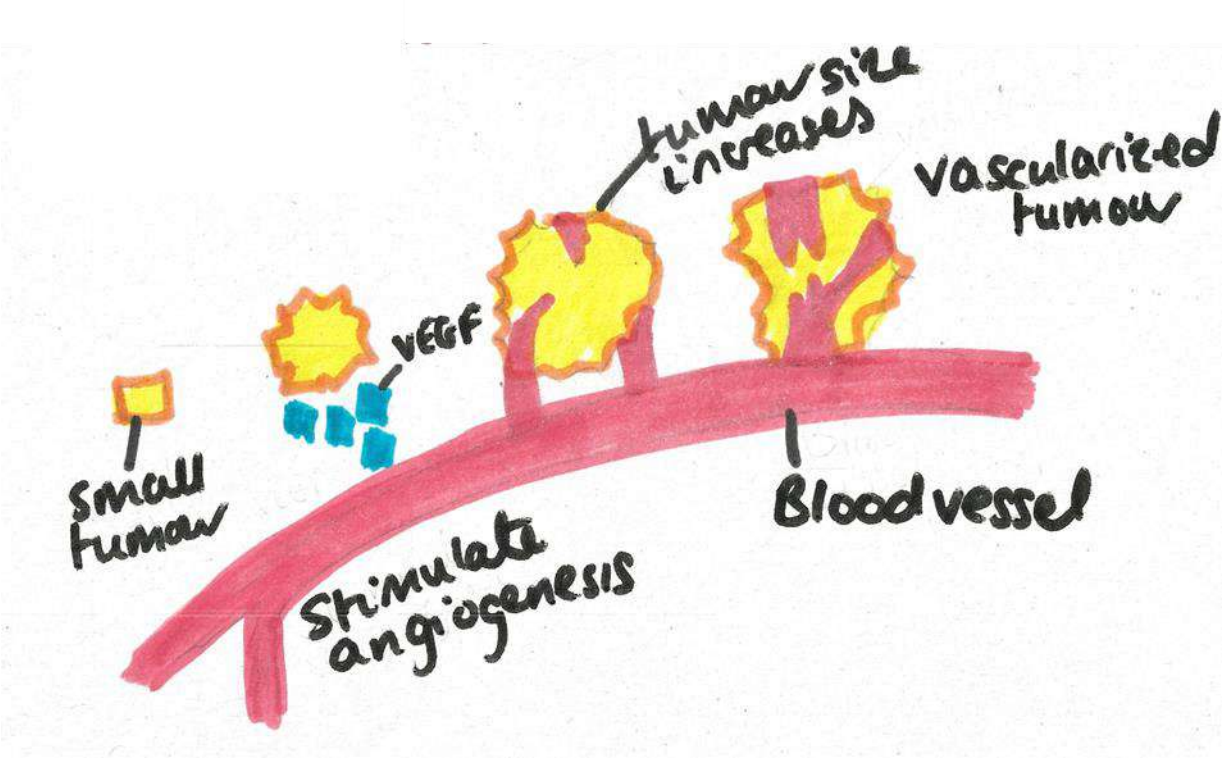
A brief overview of Hall mark cancer 6: Stimulate angiogenesis

Key facts: What is angiogenesis?

Angiogenesis is the growth of **new blood vessels** from **pre-existing vasculature.**

Vasculature is the arrangements of blood vessels in an organ.

Cancer cells receive **nutrients and oxygen to grow and metastasize and remove waste** via small blood vessels called **capillaries.**



Key facts: What is angiogenic switch?

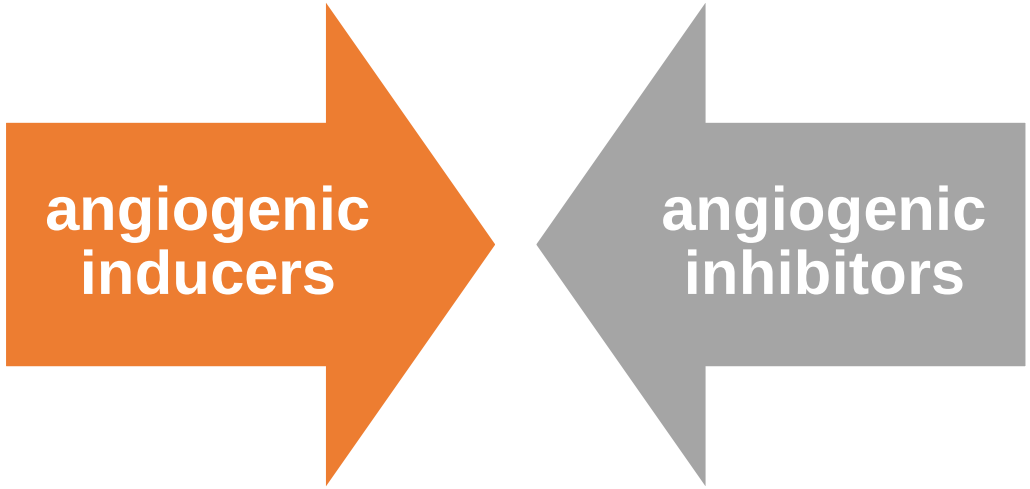
There are ***ca*. 100 micrometres** between cells in the body and blood capillary and require additional blood vessels.

For a cancer to grow larger than **0.4 nm in diameter** – a **new blood supply is needed**.

Angiogenic switch is the change in the balance between the angiogenic inducers and inhibitors.

The ability of tumours to recruit new blood vessels by producing growth factors to grow and metastasis.

Key factors such as **VEGF, fibroblast growth factor (bFGF), and platelet-derived growth factor (PDGF),** promote **angiogenesis of the tumour.**



Other hallmarks of cancer and contributors

Key facts: Other hallmarks of cancer

Avoiding immune destruction

Tumour cells are able to **evade the immune response**.

The purpose of the immune system is to **remove pathogens specifically and non-specifically** to **protect the body from disease and maintain healthy cells.**

Reprogramming of energy metabolism

Cancer cells require a lot of energy and nutrients to maintain growth and proliferation.

They change the normal pathways that provide energy to survive environmental stress i.e. low oxygen levels (hypoxia). Transcription factors such as HIF1α/ HIF2a / HIF1β regulate hypoxic levels and promote tumour growth. This is known as Warburg effect.

Contributors of hallmarks of cancer

Tumour-promoting inflammation

- **Inflammatory cells** can provide **growth factors and enzymes** to **promote angiogenesis**, **invasion and metastasis** instead of destroying tumour cells.
- The **transcription factor *NF-κB*** normally regulates **cytokines** and **dysregulation is linked to cancer**.

Genomic instability

- **Genome** was invented in 1920s to describe the **entire genetic material of an organism**.
- **Changes to the genome affects the production of proteins** and therefore, the role of **enzymes involved in invasion and adhesion of cells**.

By the end of this lecture, you should understand

- There are **8 hall marks of cancer developed by Hanahan and Weinberg: sustained proliferative signalling, evading growth suppressors, resisting apoptosis, enable replicative immortality, invasion and metastasis, angiogenesis, reprogramming energy metabolism and avoiding immune destruction**.
- There are **two contributing factors**: **genomic instability and tumour-promoting inflammation that underlies most of the hallmarks of cancer.**
- **The cell cycle** presents the phases in how **normal cells divide and grow. There are four phases: Gap 1 (G1), S phase, Gap 2 (G2) and Mitosis (M).**
- **There are two types of apoptotic pathways and depend on molecular scissors called caspases: intrinsic and extrinsic.**
- **Cancer cells interact with other cells in the EMT in order to invade and metastasise.**

Reference list for further reading

Abcam (2023) '*Studying Hallmarks of Cancer'* https://www.abcam.com/cancer/studying-hallmarks-of-cancer?msclkid=6fe15060d12911ecbfa3533e76ab88c6

Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K. and Walter, P. (2002) *Molecular Biology of the Cell*. 4th edn. New York: Garland Science; 2002. The Molecular Basis of Cancer-Cell Behavior. [online] Available from: https://www.ncbi.nlm.nih.gov/books/NBK26902/

Bower, M. and Waxman, J, (2010). *'Lecture Notes: Oncology'*. 2nd edn. West Sussex: Wiley–Blackwell.

Brooker, R., Widmaier, E., Graham, L., Stiling, P. (2008) '*Biology: Chemistry, Cell Biology and Genetics'*. United States of America: McGraw Hill.

Cassidy, J., Bissett, D., Spence, R., Payne, M., (2010) '*Oxford Handbook of Oncology'*. New York: Oxford University Press.

EPFL (2023) '*Prof. Douglas Hanahan*' [online] https://www.epfl.ch/labs/hanahan-lab/prof-douglas-hanahan/

Gale, R. (2022) '*Cellular and Molecular Basis of Cancer*' [online] Available from: https://www.msdmanuals.com/en-gb/professional/hematology-and-oncology/overview-of-cancer/cellular-and-molecular-basis-of-cancer

Hanahan, D. (2022) '*Hallmarks of Cancer: New Dimensions*.' Cancer Discovery 12(1):31-46.

Reference list for further reading

Hanahan, D., and Weinberg, R.A. (2011) ‘Hallmarks of cancer: the next generation.’ *Cell*. 144(5):646-74.

Hill, C., and Wang, Y. (2020) "The importance of epithelial-mesenchymal transition and autophagy in cancer drug resistance" *Cancer Drug Resistance*. 3, 1: 38-47.

Ishikawa, F. (2013) ‘Portrait of replication stress viewed from telomeres’, *Cancer Science*, 104(7), pp. 790–794. doi:10.1111/cas.12165.

Nussenblatt, R.B. (2010) ‘Elements of the immune system and concepts of intraocular inflammatory disease pathogenesis’, *Uveitis*, pp. 1–36..

Parsons, M.J. and Green, D.R. (2010) ‘Mitochondria in cell death’, *Essays in Biochemistry*, 47, pp. 99–114. doi:10.1042/bse0470099.

Pecorino, L. (2012) ‘*Molecular Biology of Cancer Mechanisms, Targets, and Therapeutics’* UK: Oxford University Press.

*Schätzlein, A. and Kozielski, F. (2021) ‘*Fundamentals of Cancer: Understanding Cancer - Treating Cancer’ [online] Available from: *http://cancermedicines.org/hallmarks.html?msclkid=6fe0d0d7d12911ec9d11f6487a7f8e99*

scientistcindy.com (n.d.) ‘Laboratory 6 – Reproduction’ [online] Available from: https://www.scientistcindy.com/lab-7---reproduction---bio-111l.html

Zhang, Y. (2013) ‘Caspases in Alzheimer's disease’, *Neurodegenerative Diseases* [Preprint]. doi:10.5772/54627.

SEASON 2

Understanding Cancer

Lecture 3
Types of cell signalling

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