9) **Apoptosis (Programmed cell death)**

Cells of a multicellular organism are members of a highly organized community. Therefore the number of cells in this community is tightly regulated. It is done by :-

(i) controlling the rate of cell division and (ii) Controlling the rate of cell death.

If cells are no more needed, they undergo an intracellular death programme, which is called as Apoptosis (Programmed cell death).

The programmed cell death is a normal physiological form of cell death in contrast to accidental cell death due to injury (called as Necrosis). The programmed cell death plays a key role in maintenance of adult tissues and in embryonic development. The abnormal or, virus-infected cells also undergo programmed cell death to limit the spread of viral infection or elimination of altered cells.

Events in Apoptosis :- The programmed cell death also called as Apoptosis, is an active process. During apoptosis, a cell shrinks & condenses, cytoskeleton collapse.

nuclear envelope disassembles, nuclear DNA breaks up into fragments and most importantly cell surface altered by displaying properties that causes the dying cell to be rapidly phagocytosed by neighbouring cells or, phagocytes, before any leakage of it's contents.

The intracellular machinery of apoptosis depends upon a family of proteases, called as "Caspases". These caspases have a cysteine in their active site, and they cleave their target proteins at specific aspartic acid residues.

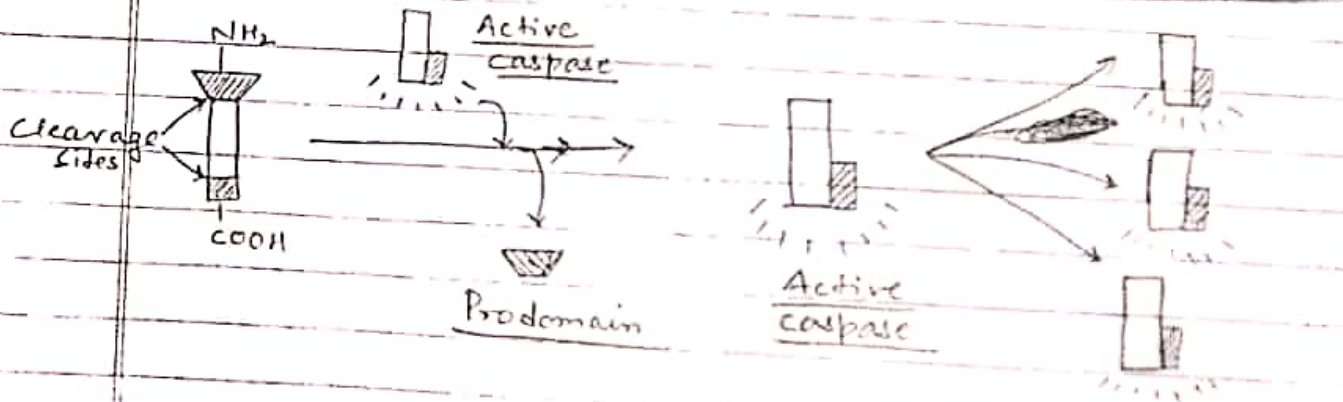
Mechanism of Apoptosis :-

The proteolytic enzymes "Caspases" play a key role in apoptosis. They are synthesized within the cell and remain in inactive form as 'Procaspases'. When a stimulus or signal for starting the process of apoptosis, is generated, then the Procaspases get activated by cleaving at their aspartic acid residues. The activated caspases then cleave other caspases by cleaving them at their specific aspartic acid residue. Thus the caspases get amplified within the

Some of the caspases then cleave other key proteins like nuclear lamins, other caspases cleave the protein which holds DNAase (DNA degrading enzymes) in inactive state, as result of which DNAase get activated, which in turn, degrade the DNA. Thus, a cell disintegrates finally in a short interval of time.

Activation of Procaspases :-

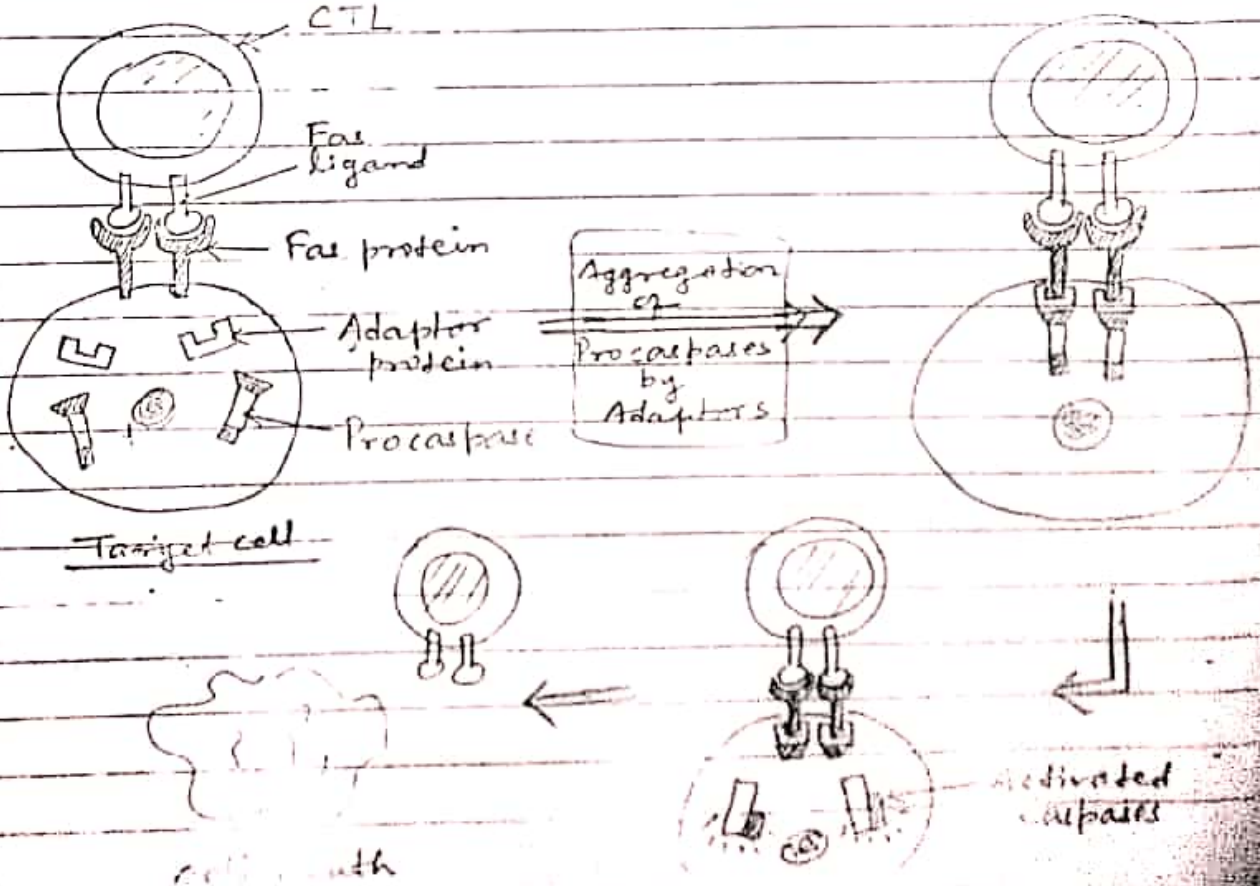
For initiation of procaspases, and thereby initiation of caspase cascade, many procaspases molecules have to bring together in a close aggregate. This job is done by specific proteins called as "Adaptor proteins"



(caspase cascade).

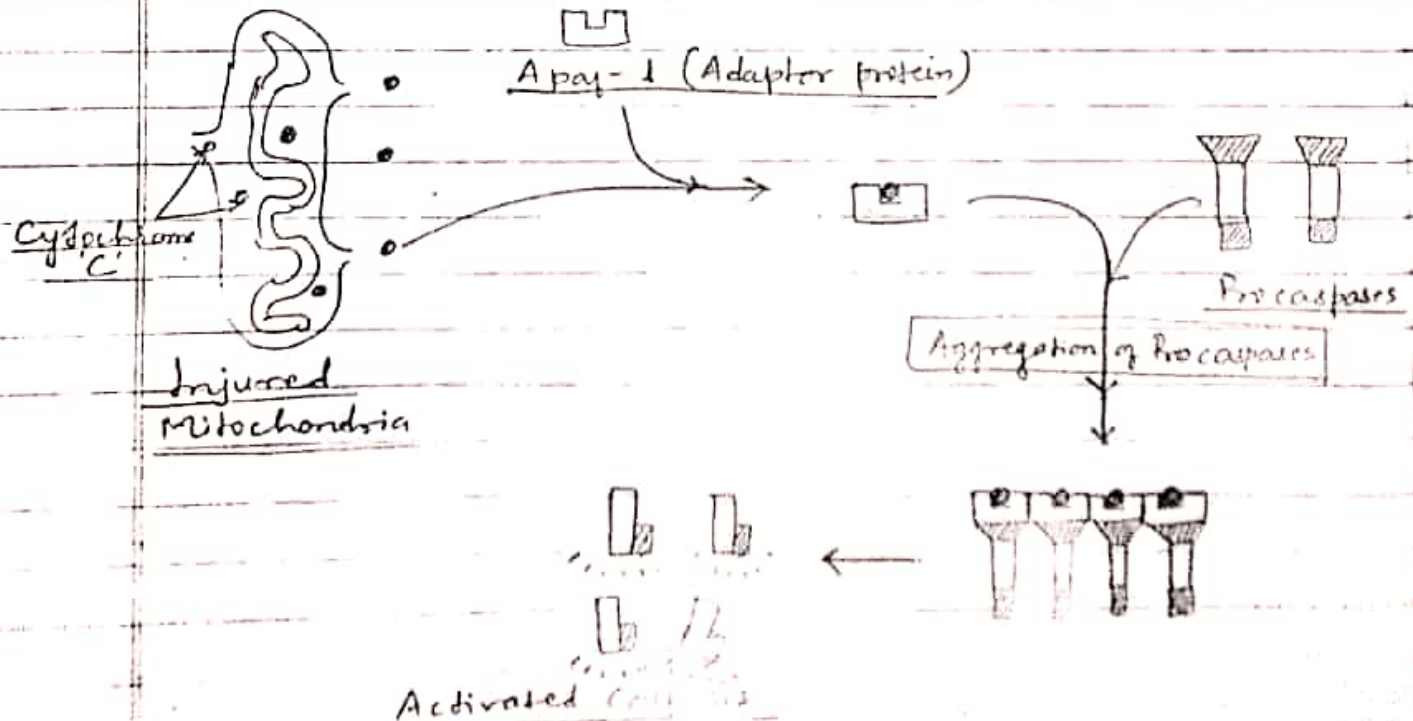
(1) Activation of apoptosis from outside the cell (Extrinsic pathway) :-

The cytotoxic T-lymphocytes (CTL) produce a protein called as Fas ligand which binds to a receptor (death receptor) called as Fas protein displayed on the membrane of the target cell. The clustered Fas protein then recruits intracellular Adaptor proteins, which in turn bind & aggregate procaspases-8 molecules. These procaspases-8 molecule then cleaved & activate one another as result the caspase cascade starts.



(II) Activation of apoptosis from inside the cell (Intrinsic pathway) :-

When cells are damaged or stressed, they can also kill themselves by procaspases aggregation & activation within the cell. In the best understood pathway, the Mitochondria are induced to release the cytochrome-C (an electron carrier protein of electron transport chain complex) into the cytosol. The cytochrome-C binds & activates the Adapter proteins Apaf-1, which in turn binds & aggregates procaspases. As result procaspases cleave and activated to initiate the caspase cascade. However, DNA damage can also trigger apoptosis.



Intracellular regulation of Apoptosis :-

There are specific families or groups of proteins within the cell which regulate the process of apoptosis. Some of them are best studied which are :-

~~(1) Bcl-2 family of intracellular proteins~~

(1) Bcl-2 family of proteins :-

This group of proteins include Bcl-2, Bcl-X_L, Bad, Bax, Bak, Bid etc.

Bcl-2 and Bcl-X_L :- Inhibit apoptosis by blocking the release of cytochrome-c from mitochondria.

Bad :- Binds and inactivates the apoptosis inhibiting proteins of it's family, thereby promote apoptosis.

Bax and Bak :- Promote apoptosis by stimulating the release of cytochrome-C from mitochondria.

Bid :- Promotes apoptosis by activating B and E.

(ii) IAP (Inhibitors of Apoptosis) family :-
These proteins are thought to inhibit apoptosis probably in two ways :-

(a) They bind to some procaspases to prevent their activation.

(b) They bind to caspases to inhibit their activity.

When mitochondria releases cytochrome - c to activate Apaf-1, they also release a protein which inhibits IAPs, thereby greatly increasing the efficiency of apoptosis.

Extracellular regulation of Apoptosis :-

(i) Extracellular signals that inhibit apoptosis :-

Animal cells need signals from other cells, not only to grow & proliferate, but also to survive. The chemicals, secreted by some specific cells, which maintains the survival of other cells are called as Survival factors. In absence of such survival factors many cells activate their intracellular death program & die by apoptosis.

In Mammals, ~~survival fac~~ specific survival factors binds to cell-surface receptors of their target cells.

and activates Protein kinase B (PKB). The activated PKB phosphorylates and inactivates Bad protein, thereby inhibits apoptosis.

The activated PKB also phosphorylates & inactivates gene regulatory protein (belong to Forkhead family of proteins). These gene regulate proteins actually stimulates the gene expression of those genes whose products actually promote apoptosis. Thus, as the PKB inactivates these gene regulate proteins, the synthesis of apoptosis promoting proteins inhibited, thereby apoptosis is inhibited.

In Drosophila, the survival factors stimulates the phosphorylation ~~of "Hid proteins"~~ & thereby inactivation of "Hid proteins". The Hid proteins, when not phosphorylated, inhibits the IAPs, thereby promote apoptosis. Thus inactivation of Hid proteins result in activation of IAPs & thereby apoptosis is inhibited.

(ii) Extracellular signals that promote apoptosis :-

There are some extracellular signal proteins like TGF-, and it's relative proteins which promotes the

* Myostatin is a TGF-β family member, which inhibits the proliferation of Myoblasts (cells that tissues develop to form the skeletal muscles). In absence of Myostatin, muscles grow abnormally.

apoptosis in some cases, thereby inhibiting cell proliferation.

One example of an apoptosis-inducing extracellular signal is BMP (Bone morphogenetic protein), a TGF-β family member. These proteins also help to promote the apoptosis, that removes the tissues developing between the developing digits in mouse paw. These proteins actually change the activity of specific gene regulatory proteins, thereby regulating the gene expression, whose products regulate apoptosis.

Another example of extracellular signal protein which promotes apoptosis is *Myostatin, which inhibits the proliferation of myoblasts by inducing apoptosis in them.

Significance of Apoptosis :-

Apoptosis is a normal physiological form of cell death which play a key role in maintainance of adult tissues & development. Apoptosis is significant for :-

= In adults, apoptosis is responsible for balancing cell proliferation,

and maintaining constant cell numbers in tissues.

= As an example; about 5×10^{11} blood cells are eliminated by apoptosis daily in humans, balancing their continuous production in the bone marrow.

= Apoptosis provides a defense mechanism by removal of damaged or infected or potentially dangerous cells can be eliminated from the body. For example in virus-infected cells frequently undergo apoptosis thereby preventing production of new virus particles and limiting the spread of viral infection.

= DNA damage can also induce apoptosis. In case of DNA damage, apoptosis may eliminate cells carrying harmful mutations (including mutations that may cause cancer).

= During development, apoptosis plays a key role in sculpting

unwanted cells from a variety of tissues. For example, apoptosis is responsible for removal of unwanted larval tissues during development of amphibian (removal of tail of tadpole larva) and insect larvae.

= Elimination of tissues between fingers and toes is also done through apoptosis, during embryonic or larval development.

= During development of mammalian nervous system, neurons are produced in excess, and upto 50% of developing neurons are eliminated by apoptosis.

= During development or, in general, the survival of many types of cells is dependent upon survival factors or, contacts with neighbouring cells or, extracellular matrix, in absence of which cells may undergo apoptosis. So, apoptosis is play an important role in regulating association between different cells or tissues.

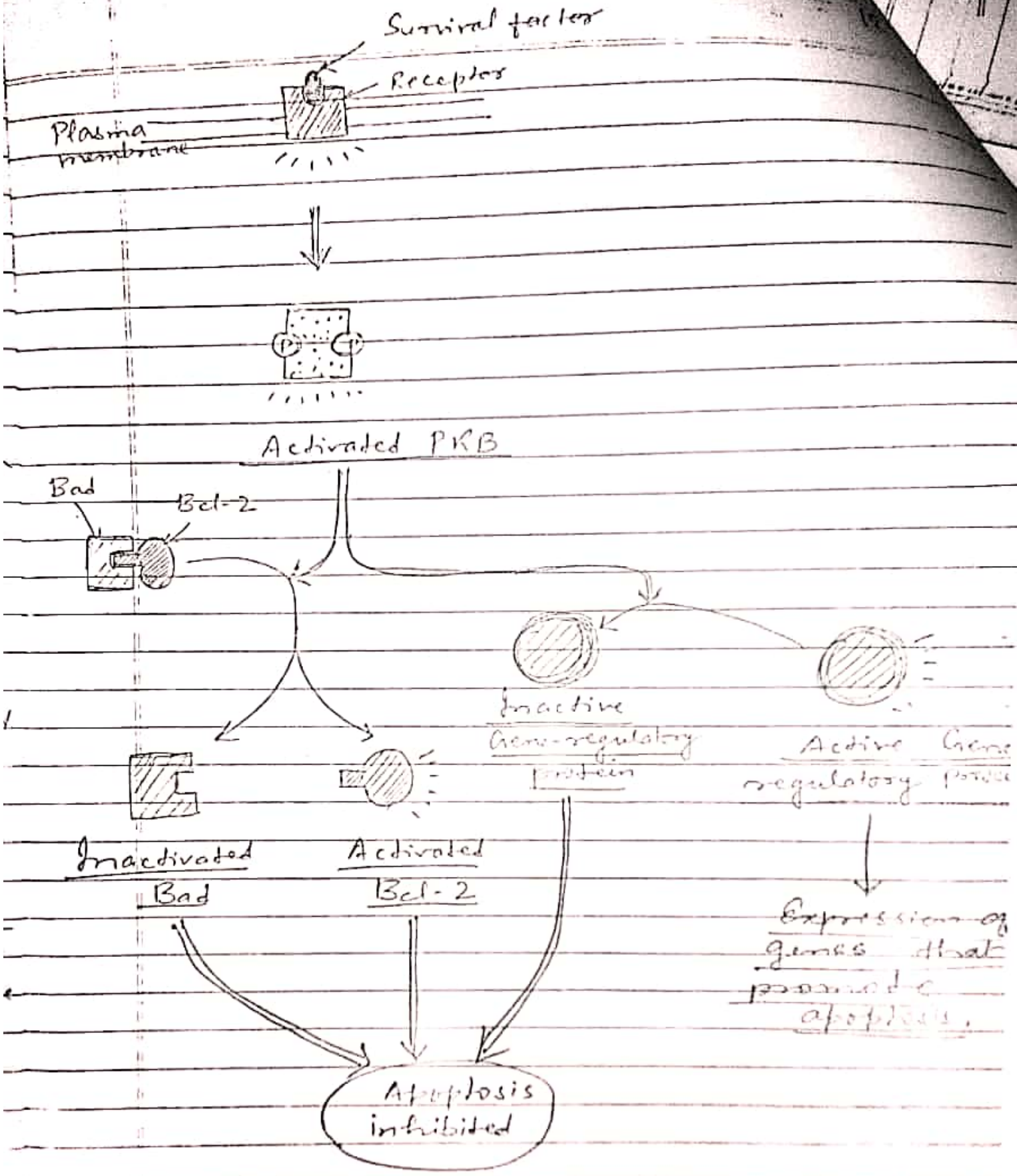


Fig: Inhibition of apoptosis by survival factors in Mam[illegible].