

STEP 3-CELLULAR DYSFUNCTION AND RESULTANT TOXICITIES

- ✓ The reaction of toxicants with a target molecule may result in im-paired cellular function as the third step in the development of toxicity .
- ✓ Each cell in a multicellular organism carries out defined programs. Certain programs determine the destiny of cells-that is, whether they undergo division, differentiation (i.e., express proteins for specialized functions), or apoptosis.
- ✓ Other programs control the ongoing activity of differentiated cells, determining whether they secrete more or less of a sub- stance, whether they contract or relax, and whether they transport and metabolize nutrients at higher or lower rates.
- ✓ For regulations of these cellular programs, cells possess signaling networks that can be activated and inactivated by external signaling molecules.
- ✓ To execute the programs, cells are equipped with synthetic, metabolic, kinetic, transport, and energy-producing systems as well as structural elements, organized into macromolecular complexes, cell membranes, and organelles, by which they maintain their own integrity (internal functions) and support the maintenance of other cells (external functions).

- ✓ the nature of the primary cellular dysfunction caused by toxicants, but not necessarily the ultimate outcome, depends on the role of the target molecule affected.
- ✓ If the target molecule is involved in cellular regulation (signaling), dysregulation of gene expression, and/or dysregulation of momentary cellular function occurs primarily.
- ✓ However, if the target molecule is involved predominantly in the cell's internal maintenance, the resultant dysfunction can ultimately compromise the survival of the cell.
- ✓ The reaction of a toxicant with targets serving external functions can influence the operation of other cells and integrated organ systems.

Toxicant-Induced Cellular Dysregulation

- ✓ Cells are regulated by signaling molecules that activate specific cellular receptors linked to signal transducing networks that transmit the signals to the regulatory regions of genes and/or to functional proteins.
- ✓ Receptor activation may ultimately lead to
- ✓ (1) altered gene expression that increases or decreases the quantity of specific proteins and/or
- ✓ (2) a chemical modification of specific proteins,

typically by phosphorylation, which activates or inhibits proteins.

- ✓ Programs controlling the destiny of cells primarily affect gene expression, whereas those regulating the ongoing activities primarily influence the activity of functional proteins; however, one signal often evokes both responses because of branching and interconnection of signaling networks.

Dysregulation of Gene Expression

- Dysregulation of gene expression may occur at elements that are directly responsible for transcription, at components of the intracellular signal transduction pathway, and at the synthesis, storage, or release of the extracellular signaling molecules.

Neoplasia;

- Is an abnormal growth of tissues when forming a mass is commonly known as tumor.

Apoptosis;

- Is a process of programmed cell death that occur in multicellular organisms
- Biochemical events leads to characteristic cell changes(morphology) and death.

- These changes includes bleeding, cell shrinkage, nuclear fragmentation, chromatin condensation, chromosomal DNA fragmentation and mRNA decay.
- Apoptosis is highly regulated and controlled process that is important during organisms life.
- For example; the separation of fingers and toes in developing embryo occurs because cells between the digits undergo apoptosis
- Apoptotic cells have the ability to engulf damaged cells in the body before they cause any damage
- Between 50-70 billion cells die each day due to apoptosis in an average human adult.
- For an average child between the age of 8-14 approx. 20 billion to 30 billion cells die a day.
- Apoptosis become unhealthy or abnormal when cellular processes that keep the body in balance either cause too few or too many cell deaths.
- For example; in many Autoimmune diseases like muscular dystrophy and Alzheimers are thought to be due to excessive apoptosis causing muscle or nerve cells to die before their time

Necrosis;

- Is a form of cell injury that results in premature death of cells in living tissues by autolysis.(self digestion)
- It is caused by external factors to the cell or tissue such as infection, toxins, or trauma that results in unregulated digestion of cell components.
- Necrosis is a form of traumatic cell death that results from acute cellular injury,
- Necrosis is always detrimental and can be fatal.

Hemostasis / haemostasis;

- Is a process that causes bleeding to stop i.e. to keep the blood in the damaged blood vessels.
- It is the first stage of wound healing .
- It involves the changes of liquid blood into gel.
- Hemostasis involves 3 major steps;
 1. Vasoconstriction
 2. Temporary blockage by a platelet plug
 3. Blood coagulation

STEP 4; INAPPROPRATE REPAIR AND ADAPTATION

1. MOLECULAR

- PROTEIN
- LIPID
- DNA

2. CELLULAR

3. TISSUE

- Apoptosis
- Proliferation
 - ✓ Cells
 - ✓ Extracellular matrix

Mechanism of repair;

- ✓ Damaged molecules may be repaired in different ways.
- ✓ Some chemical alterations such as oxidation of protein thiols and methylation of DNA are simply reversed.
- ✓ In some cases the Damaged molecules are totally degraded and resynthesized

✓ This process is time consuming such as in case of regeneration of cholinesterase after organophosphate intoxication.

Cellular repair;

In most tissues injured cells die and are replaced by new cells

Nervous cells do not have the ability to regenerate