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Cell Damage and Death

Overview

Cells respond to stress in several ways – they can **adapt** to a new steady state, they can become **injured** (reversibly or irreversibly), and they can **die.**

- Sometimes, when some of the metabolic functions are deranged, they can also accumulate intracellular materials which are visible on light microscopy.
- Causes of stress range from **physiologic** to **pathologic**.
  - **Physiologic** or **mild pathologic** stimuli → more likely to result in adaptation
  - **Severe stress** may → lead to **injury and cell death.**

Learning objectives

- **Definitions** of specific important terms
- **Causes of cell damage** (eg. hypoxia, chemical agents)
- **Mechanisms of cell damage** (i.e. ATP depletion)
- **Morphological changes in cell damage and death**

Mindmap 1 - Cellular response to stress:
https://medicine.nus.edu.sg/pathweb/pathology-demystified/cell-damage-and-death/

Cell Adaptation

Definition: Reversible ***functional and structural responses*** to physiological stresses or pathologic stimuli during which ***new steady states*** are achieved. This allows cells to survive and function.

FOUR main types of cellular adaption. These have specific mechanisms, and produce morphologic changes in cells which in turn result in morphologic changes in organs (e.g. organ enlargement or shrinkage):

1. Hypertrophy
2. Hyperplasia
3. Atrophy
4. Metaplasia

Mindmap 2 - Cell adaptation:
https://medicine.nus.edu.sg/pathweb/pathology-demystified/cell-damage-and-death/i-cell-adaptation/

Table 1: Types of Adaptive Responses

Adaptive response	Definition	Mechanism	Example (Physiologic)	Example (Pathologic)
Hypertrophy	Increase in size of cells, resulting in an increase in organ size. *Note: This can occur together with hyperplasia.*	Increased functional demand; simulation by hormones or growth factors → increased synthesis of structural components of cells	Eg. "Pumping iron" → increased work demand in skeletal muscle → muscle size increase due to hypertrophy Eg. Pregnancy – Hormone-induced uterine smooth muscle hypertrophy	Eg. Hypertension → increased workload in left ventricular myocardium → left ventricular hypertrophy
Hyperplasia	Increase in the number of cells in an organ/tissue, usually resulting in increased mass of the organ/tissue. *Note; This may occur together with hypertrophy.*	Only possible in cells capable of dividing. 1. Mature cells - Growth factor driven cell proliferation 2. Increased cell output from stem cells	Eg Compensatory hyperplasia – Liver cell proliferation after partial hepatectomy	Eg. Hormone-driven – Increased oestrogen levels gives rise to endometrial hyperplasia in the uterus
Atrophy	Reduced size of an organ or tissue resulting from a decrease in cell size and number.	Reduced metabolic activity → decreased protein synthesis. Nutrient deficiency, disuse → increased protein degradation in cells.	Normal embryonic development – thyroglossal duct atrophy during fetal development	Atrophy of disuse – Immobility (eg. limb in cast after fracture) leads to skeletal muscle atrophy due to decreased workload
Metaplasia	Reversible change from one mature (differentiated) cell type to another. This may be because certain cell types withstand adverse environment better than others.	Cytokines, growth factors, extracellular matrix components → reprogramme genetic expression in stem cells present in normal tissues → differentiate along a different pathway		Eg. Cigarette smoking → chronic irritation in respiratory tract → columnar epithelium changes to squamous epithelium (squamous metaplasia)

Cell Injury and Death

Definitions

Cell injury: Sequence of events that occurs when stresses exceed the ability of cells to adapt. Responses are initially reversible, but may progress to irreversible injury and cell death.

Cell death: Results when continuing injury becomes irreversible, at which time the cell cannot recover.

There are **TWO** principle types of cell death: **1. Necrosis** and **2. Apoptosis**

1. Necrosis – Death of cells in living tissues characterised by the breakdown of cell membranes. These changes occur because of digestion and denaturation of cellular proteins, largely by release of hydrolytic enzymes from damaged lysosomes.
There are many subtypes/morphological patterns of necrosis: Coagulative; Liquefactive; Caseous; Suppurative; Haemorrhagic; Gangrenous; Fat; Fibrinoid.

Table 2: Common Patterns of Necrosis

Pattern of necrosis	Definition / Causes	Morphology (Gross + Micro)	Example
Coagulative necrosis	Often secondary to hypoxia or loss of blood supply (ischaemia).	Gross: Pale area Micro: Ghost outlines (cell structure present but with **loss of nuclei**)	Myocardial infarction Kidney infarction
Liquefactive	Characterised by digestion of dead cells.	Gross: Cystic "liquefied" appearance. Micro: depends on cause	Cerebral infarction Suppurative bacterial infections (enzymatic digestion from leukocytes).
Caseous	Secondary to Mycobacterial tuberculous infection.	Gross: "Cheesy" necrosis (friable/crumbly appearance). Micro: Amorphous granular debris, surrounded by granulomatous inflammation.	Tuberculosis (eg. lung, lymph nodes)

2. Apoptosis – Programmed cell death characterized by nuclear dissolution, fragmentation of the cell without complete loss of membrane integrity, and rapid removal of the cellular debris. Apoptosis can be *physiological* or *pathological.*

Other Processes in Cellular Stress

Intracellular accumulations – Accumulations of substances within cells, which are due to metabolic derangements. Substances can be endogenous (eg. lipids, proteins) or exogenous (eg. mineral dust, microbial products).
(Examples are included in Mindmap 5: Morphology)

Autophagy – Process in which a cell eats its own organelles, usually during stress (eg. nutrient deprivation). This may result in the formation of residual bodies which may accumulate as lipofuscin (wear and tear pigments).
Significance **–** Autophagy may be a means of cell loss in some diseases (eg. Degenerative disease of the CNS), but the exact mechanism is unclear.

More Mindmaps:
- 3. Cell injury and death
- 4. Causes and mechanisms
- 5. Morphology
https://medicine.nus.edu.sg/pathweb/pathology-demystified/cell-damage-and-death/ii-cell-injury-and-death/
Talking POTs and Slides
https://medicine.nus.edu.sg/pathweb/pathology-demystified/cell-damage-and-death/ii-cell-injury-and-death/
Exercises
https://medicine.nus.edu.sg/pathweb/pathology-demystified/cell-damage-and-death/cell-damage-and-death-exercises/