Tissue repair, metaplasia, dysplasia, squamous cell carcinoma

Tissue repair

Polyp
1 – Myocardial hypertrophy
2 – Granulation
3 – Intestinal metaplasia of gastric mucosa
4 – Dysplasia of squamous epithelium
5 – Preinvasive carcinoma
6 – Squamous cell carcinoma

Polyp

• Def: A mass, that projects above the mucosal surface to form a macroscopically visible structure
• This term says us nothing about its histological structure
• The most common within the gut – the mass that protrudes into the lumen

Ma: Polyp

• May be pedunculated or sessile
• May be formed as the result of hyperplasia or abnormal mucosal maturation, inflammation or architecture – these polyps are non-neoplastic
• These polyps that arise as the result of epithelial proliferation and dysplasia are true neoplastic lesions
• Some polyps may be caused by submucosal or mural tumours

Ma: Polyp

Pedunculated adenoma showing a fibrovascular stalk lined by normal colonic mucosa and a head that contains abundant dysplastic epithelial glands, hence the blue color with the H & E stain
1 - Myocardial hypertrophy

- Hypertrophy – increase in the size of cells resulting in increase in the size of the organ. No new cells, just bigger, enlarged cells
- Hyperplasia – increase in cell number
- Can be physiologic or pathologic and is caused either by increased functional demand or by specific hormonal stimulation

1 – Myocardial hypertrophy

- The striated muscle cells in both the skeletal muscle and the heart can undergo only hypertrophy because in the adult they have limited or no capacity to divide

Two mechanisms:
- Mechanical triggers such as stretch
- Trophic triggers such as activation of alfa-adrenergic receptors

1 – Myocardial hypertrophy

- These stimuli turn on signal transduction pathways – induction of a number of genes – synthesis of numerous proteins (growth factors and structural proteins)
- The limit is reached when the enlargement of muscle mass can no longer compensate for the increased demand – several degenerative changes (fragmentation, loss of myofibrillar contractile elements) occur in the myocardial fibres. Some cells die being replaced by minute scar. Myocytes gradually become less effective and residual blood distend the chamber – decompensated concentric hypertrophy

1 – Myocardial hypertrophy

- In the heart increased work resulting from pressure or volume overload or from trophic signals induced myocardial hypertrophy (catecholamines, angiotensin II)
- Pressure-overloaded ventricles (in hypertension or aortic valve stenosis) develop concentric hypertrophy (with increased wall thickness and reduced the cavity diameter)
- Volume overload (in aortic valve insufficiency) – hypertrophy with ventricular dilation – eccentric hypertrophy

Schematic representation of the sequence of events in cardiac hypertrophy and its progression to heart failure, emphasizing cellular and extracellular changes.

Altered cardiac configuration in left ventricular hypertrophy without and with dilation, viewed in transverse heart sections. Compared with a normal heart (center), the pressure-hypertrophied heart (left) have increased mass and a thick left ventricular wall, but the hypertrophied and dilated heart (right) has increased mass but a normal wall thickness.
1 – Myocardial hypertrophy

Concentric hypertrophy
• Ma: ventricular wall is thick, the heart weight is increased (normal weight ranges from 300-350g)
• Mi: myocyte diameter increases (thickening and elongation), typically associated with prominent, irregular nuclear enlargement and hyperchromasia. No mitoses. There is increased interstitial fibrosis

2 - Granulation

• Tissues can be repaired by regeneration with completely restoration of form and function or by replacement with connective tissue and scar formation
• Repair by connective tissue starts with the formation of granulation tissue and culminates in the laying down of fibrous tissue
• Multiple growth factors stimulate the proliferation of the cell types involved in repair

Wound healing

Three main phases:
• Inflammation
• Formation of granulation tissue
• ECM deposition and remodeling

Inflammation - cell migration

1. Neutrophils – ingest and kill bacteria, release enzymes destroying damaged tissue
2. Macrophages – phagocytose debris, when filled with indigestible material, lose motility and turn into epithelioid histiocytes, release chemoattractants for:
3. Fibroblasts, myofibroblasts
4. T lymphocytes – secrete lymphokines
5. Endothelial cells – form new capillaries

Epithelioid histiocytes

Neutrophils
Granulation

- The term derives from the pink, soft, granular gross appearance
- Mi: proliferation of fibroblasts and new, thin-walled, delicate capillaries in a loose extracellular matrix (ECM)
- Granulation tissue than progressively accumulates connective tissue matrix, eventually resulting in the formation of a scar, which may remodel over time

Granulation tissue

Young, new tissue:
- Oedematous
- Highly vascular
- Rich in fibroblasts
- Minimal mature collagen

Granulation tissue showing numerous blood vessels, edema, and a loose ECM containing occasional inflammatory cells. This is a trichrome stain that stains collagen blue; minimal mature collagen can be seen at this point. B, Trichrome stain of mature scar, showing dense collagen, with only scattered vascular channels.

Wound healing

Three main phases:
- Inflammation
- Formation of granulation tissue
- ECM deposition and remodeling

Extracellular matrix organisation

EMCs includes:
- Collagen (the major protein)
- Elastin (allows tissue to stretch and recoil) [skin, artery walls, lung]
- Glycoproteins (mediators between cells and matrix)
  - Laminin-constituent of basement membranes
  - Fibronectin-with domains that bind to integrins
- Remodeling by digestive enzymes (metalloproteinases MMPs)
Repair – late stage

A lot of scattered, elongated fibroblasts; collagen fibres

Repair

Wound healing

- Wound with closely opposed edges → small scar “healing by primary intention”
- Wound with tissue loss → large scar “healing by secondary intention”

“healing by primary intention”

Healing by second intention

Repair

The sequence of wound healing
1. Early stage: plasma fibrins → blood clot next: neutrophils, macrophages
2. Mid-stages: fibroblasts, formation of granulation tissue
3. Late stage: contraction of the wound site, type I collagen [bones, skin] replaces type III collagen

Steps in wound healing by first intention (left) and second intention (right). Note large amounts of granulation tissue and wound contraction in healing by second intention.
3 – Intestinal metaplasia of gastric mucosa

- Metaplasia: the reversible change of differentiation of maternal cells in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type (transformation of a mature tissue into another, also mature one)
- Often a response to chronic irritation that makes cells better able to withstand the stress
- Induced by altered differentiation pathway of tissue stem cells
- May result in reduced function or increased propensity for malignant transformation

3 – Intestinal metaplasia of gastric mucosa

- In the course of chronic gastritis gastric glands may become transformed into those mimicking the crypts of small or large intestine (with the formation of goblet and Paneth cells)
- Precancerous condition – because gastrointestinal type of gastric carcinoma seems to arise from dysplasia of this metaplastic epithelium.

4 – Dysplasia of squamous epithelium

**Intraepithelial squamous cell neoplasia**

**Definition:**
 Loss in the uniformity of the individual cells and a loss in their architectural orientation
 Changes in cellular differentiation/maturation
 Differentiation: the ability of maternal cells to develop in a determined direction only
 Maturation means that differentiated cells go through the chain of transformations with the formation of cells characteristic for particular tissue
 Nowadays both terms are replaced one by the other

4 – Dysplasia of squamous epithelium

Concern epithelial tissue, both the protective and the glandular one
Dysplasia of squamous epithelium can affect:
- Vaginal portion of uterine cervix
- Oral cavity
- Larynx
- Oesophagus
4 – Dysplasia of squamous epithelium

**Intraepithelial neoplasia**

- Abnormal cells (cellular atypia)
  - ↑ nuclear size and hyperchromasia
  - ↓ cytoplasm
  - ↑ pleomorphism (cell size and shape)
  - ↑ mitotic figures (in abnormal locations within the epithelium)
  - ↑ abnormal mitotic figures
- Architectural anarchy

**Normal squamous epithelium**

**Cellular atypia**

**Viruses and human cancer**

- Viral infections are responsible for about 15% of all human cancers
- Human Papilloma viruses induce lesions that progress to squamous cell carcinoma
- HPV16 and 18 viruses are associated with cancer of the uterine cervix
  - The oncogenic ability of HPV is related to the expression of two viral oncoproteins E6 and E7. They bind to RB and p53 respectively, neutralizing their function; they also activate cyclins
- Koilocytes – epithelial cells that demonstrate perinuclear halos due to accumulation of viral particles within the cytoplasm, are localized in the upper layers of the epithelium

**Koilocytes**: cells with nuclear hyperchromasia and angulation with perinuclear vacuolization produced by cytopathic effect of HPV

**Squamous cell neoplasia of uterine cervix**

**Cervical Intraepithelial Neoplasia CIN**

- within epithelium, not below the basement membrane!
- **CIN 1** – mild dysplasia and koilocytes mostly in the superficial layers of the epithelium
- **CIN 2** – moderate dysplasia, involvement more than 2/3 of the epithelium
- **CIN 3** – severe dysplasia – all layers of the epithelium with loss of maturation
Normal squamous epithelium

CIN I with koilocytic atypia

CIN II with progressive atypia in almost all layers of epithelium

CIN III/ preinvasive carcinoma with atypia in all layers of epithelium and loss of maturation

5: Preinvasive carcinoma

carcinoma in situ

- Almost the same as CIN III
- Dysplastic changes are more atypical
- In all layers of the epithelium

Dysplasia

Dysplastic lesions:

- Can regress with removal of the underlying cause
- Can be preneoplastic and progress to invasive carcinoma
6: Squamous cell carcinoma
Invasive carcinoma

- Invasion of dysplastic (atypical cells) below the basement membrane

Invasive squamous cell carcinoma

- Nests of neoplastic cells in subepithelial tissue.
- Keratinizing type.
- Whorls of keratin — “keratin pearls”