Inflammation and Neoplasia

1. Inflammation
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1. Inflammation

- **Inflammation** is a *localised, protective vascular* response to tissue injury or destruction
  - The inflammatory process aims to *isolate* both the *offending stimulus* and *injured tissue*
    - Local *macrophages* detect tissue injury via *Toll-like receptors* and release *cytokines*
    - *Vasodilatation* increases local blood flow and pressure producing a *fluid transudate*
    - *Increased vascular permeability* produces a protein-rich *cellular exudate*
    - *Leucocyte extravasation* recruits phagocytic *neutrophils* and monocytes to the site of injury
  - **Acute inflammation** is characterised by the presence of *neutrophils* within hours following the insult
    - Classic symptoms are *rubor* (redness), *calor* (heat), *tumor* (swelling) and *dolor* (pain)
    - These are generally accompanied by a *systemic malaise and fever* and localised *loss of function*
  - There are various possible outcomes following acute inflammation the ideal being *resolution*
    - *Resolution* occurs with *minimal damage* and rapid removal of the offending stimulus
    - *Repair* generally occurs otherwise and involves *collagenous scar tissue formation*
    - If the antigenic stimulus persists then it may give rise to *chronic inflammation*
  - **Chronic inflammation** is a process of ongoing *repair and fibrosis* characterised by *macrophages*
    - A *granuloma* may form with *TNF-α* mediation and persist which may be *painful and swollen*
    - Clinically this can be identified through a raised serum *CRP* and *ESR* with *weight loss*

- **The various inflammatory mediators** involved tend to be *potent and rapidly inactivated*
  - **Eicosanoids** are *cell-membrane derived* fatty acids involved in most inflammatory processes
  - The **prostanoids** are eicosanoids derived using the enzyme *cyclo-oxygenase (COX)*
    - *Prostacyclin (PGI₂)* is stored in *mast cells* and inhibits platelet aggregation
    - *Thromboxane A₂ (TXA₂)* is produced by *platelets* and conversely *promotes* platelet aggregation
    - *Prostaglandins (PGD₂-F₂)* induce *vasodilatation* and *increased vascular permeability*
    - Though they do not cause pain directly the prostanoids *sensitise* afferent *C-fibre* endings
  - The **leukotrienes** are eicosanoids derived using the enzyme *lipoxygenase*
    - All *increase vascular permeability* and are *chemotactic* to leucocytes
  - **Histamine** is stored in *mast cells* and *basophils* and acts on *endothelial cells* and *smooth muscle*
    - Acts on *H₁* receptors to induce *vasodilatation* and *increased vascular permeability*
  - **Bradykinin** is released following activation of *factor XII* in the *intrinsic clotting cascade*
    - *Increases vascular permeability* and mediates pain sensation
  - The **anaphylatoxins** (C₃a, C₄a, C₅a) are generated in the common pathway of the complement system
    - All act on *mast cells* and *basophils* to induce *degranulation*
    - C₃a and C₅a are *chemotactic* to *neutrophils*

- **NSAIDs** are the first-line *broad spectrum* drugs to combat *non-severe* inflammation
  - The **NSAIDs** all act by inhibiting *cyclo-oxygenase (COX)* to limit *prostanoid* production
    - *COX1* is *ubiquitous* across tissues and involved in various *cell-signalling processes*
    - *COX2* is specifically involved in *inflammation* and the target of NSAIDs
  - Most NSAIDs are *non-specific* and inhibit generalised *PGE₂* and *prostacyclin* production acting on *COX1*
    - These prostanoids are *cytoprotective* to the gastric mucosa – may lead to *nausea* and *ulceration*
    - They also facilitate *renal vasodilatation* – may lead chronically to *renal damage* or renal failure
  - Most NSAIDs act as *anti-inflammatory*, *anti-pyretics* and mild *analgesics*
    - *Inflammation* is reduced through inhibiting the inflammatory effects of prostanoids (see above)
    - *Fever* is reduced through inhibiting hypothalamic prostaglandin production
    - *Pain* is reduced through diminished C-fibre sensitisation and CNS prostaglandin production
2. Cellular division and adaptation

- The normal cellular processes of growth, division and death are tightly regulated
  - Cells remain in a default non-proliferative state (G₀) until growth factors activate replication genes
    - Retinoblastoma (pRb) inhibits regulatory proteins required for replication gene transcription
    - Erythropoietin specifically stimulates proliferation of erythrocytes – produced by the kidneys
    - Other growth factors (PDGF, EGF etc.) have broader stimulatory effects across cell types
  - Once cellular division has been activated the full mitotic cycle (4 phases) takes 18-24 hours to complete
    - The first 3 phases (G₁, S, G₂) do not involve mitosis and together form interphase
    - The final phase (M) involves mitosis and cytokinesis (splitting into 2 progeny cells)
    - Each phase is regulated by short-lived cyclins interacting with cyclin-dependent kinase (CDK)
  - G₁ phase – after latent period of variable duration reaches checkpoint
    - Only proceeds if the cell is of sufficient size with adequate nutrition and intact DNA
    - Cyclin-CDK complex required for activation of DNA replication machinery and S phase entry
    - The complex is also responsible for phosphorylation and consequent deactivation of pRb
    - DNA damage activates the tumour suppressor p53 which acts via p21 to inhibit CDK
  - S phase – DNA is replicated such that each of the 46 chromosomes comprise 2 identical DNA chains
    - Telomeres contain specialised proteins that terminate the DNA sequences at each end
    - Normally each DNA replication cleaves up to 200 base pairs at the telomere 3’ terminal
    - This ensures that the number of replications is limited – cells thus remain ‘mortal’
    - Replication can be delimited by a reverse transcriptase adding a repeat DNA sequence
  - G₂ phase – final checkpoint before mitotic division
    - Only proceeds if all DNA has been satisfactorily replicated and the cell is of sufficient size
    - Another cyclin-CDK complex required for entry into M phase
  - M phase – nuclear and cytoplasmic division produces two identical independent progeny cells
    - Following division pRb is dephosphorylated to arrest further out-of-phase proliferation

- Cells adapt their morphology and behaviours in response to environmental stressors
  - Atrophy (wasting) is a process of diminishing cell size and may result in tissue or organ wasting
    - Triggered by reduced workload, blood supply, nutrition or innervation
    - Occasionally a normal physiological phenomenon but generally pathological
  - Hypertrophy is conversely a process of increasing cell size and may result in tissue or organ overgrowth
    - Triggered by increased workload or excessive hormonal stimulation
    - Not in itself a risk factor for cancer as the actual number of cells does not increase
  - Hyperplasia is an abnormal increase in cell number which may also result in tissue or organ overgrowth
    - Triggered by increased workload on division-capable cells – often accompanies hypertrophy
    - Although slightly increasing the risk of cancer this is not a specifically neoplastic process
  - Metaplasia is a reversible alteration of a sensitive adult cell type e.g. from squamous to columnar
    - Triggered by a change in environmental stressors – sometimes part of normal physiology
    - Although slightly increasing the risk of cancer this is not a specifically neoplastic process
  - Dysplasia is an abnormal alteration in cell size, morphology or number and can be pre-malignant
    - Often classified as either mild, moderate or severe – may initially be reversible
    - Severe dysplasia with uncontrolled cell proliferation may develop into a malignant neoplasm
3. Neoplasms and chemotherapy

- **Neoplasms** are abnormal, uncontrolled persistent cell proliferations independent of stimuli
  - **Benign neoplasms** are non-metastatic, non-invasive and generally curable with treatment or surgery
    - Tend to develop gradually over long periods with few mitotic divisions at any one time
    - Often well-differentiated with normal nuclei and a defined border (well circumscribed)
  - **Malignant neoplasms** (cancers) are characteristically invasive, often metastatic and eventually fatal
    - Tend to develop rapidly with numerous abnormal mitotic divisions
    - Often variably differentiated with pleomorphic, hyperchromatic nuclei and no clear border
    - Defined by degree of differentiation (grade) and extent of metastasis (stage)
  - Neoplasms are classified by cell of origin and behaviour as either benign or malignant
    - **Benign epithelial neoplasms** are either papillomas (non-glandular) or adenomas (glandular)
    - **Malignant epithelial neoplasms** are carcinomas (e.g. adenocarcinoma, squamous carcinoma)
    - **Benign non-epithelial neoplasms** have tissue-specific names with an -oma suffix e.g. lipoma
    - **Malignant non-epithelial neoplasms** instead mostly have a -sarcoma suffix e.g. osteosarcoma
  - Neoplasms of more than 1mm diameter generate direct vascularisation for growth and metastasis
  - **Paraneoplasia** is defined as physiological disturbances indirectly associated with malignant neoplasms
    - Not directly related to invasion of the tumour e.g. from ectopic hormone production
    - May be diverse hormonal, neurological or haematological effects
  - Most neoplasms are found to be monclonal from clonal expansion of a single genetically-damaged cell
    - **Non-lethal** cell damage causes genetic damage (e.g. carcinogens) resulting in DNA repair errors
    - **Oncogenes** (growth-promoting genes) may be over-expressed or tumour suppressors inhibited
  - Some viruses have been associated with cancers in conjunction with various other factors
    - Viruses may directly stimulate cell division, trigger immune responses or cause cellular damage
    - **Human T cell lymphotrophic virus** (hTLV) is a rare RNA virus that causes T cell leukaemia
    - Other retroviruses possess viral oncogenes which can be triggered in infection

- **Chemotherapy** is the use of drugs to selectively destroy malignant neoplastic tissue
  - **Alkylating agents** were the first chemical treatments developed for cancers – based on mustard gas
    - Examples include chlorambucil (oral), melphalan (IV) and busulphan (for chronic leukaemias)
    - **Cyclophosphamide** requires enzymatic bioactivation and may cause bone marrow depression
    - Still used in treatment of lymphomas and breast cancer in combination with other agents
  - **Cisplatin** is a widely-used platinum-based compound that cures 90% of metastatic testicular teratomas
    - Relatively severe side-effects including vomiting, renal impairment, peripheral neuropathy
    - **Carboplatin** is a more stable analogue with fewer side-effects and comparable activity levels
  - Numerous other drugs are used in chemotherapy and are mostly effective against one cancer type
    - **Methotrexate** inhibits folate metabolism inducing remissions in childhood leukaemia
    - **Fluorouracil** also inhibits folate metabolism and is used in treating colon cancer
    - **Gemcitabine** induces DNA chain termination and is used in pancreatic and lung cancers