Cancer: Genetic disease caused by the progressive accumulation of mutations.

Loss of function mutation on tumour-suppression genes

Gain of function mutation on proto-oncogenes

Cell cycle regulation: cyclin and cyclin-dependent kinases.

- G1 checkpoint: before cell proceed into S-phase and replicate DNA
  - Cyclin D bind to Cdk4/6
  - Cdk phosphorylate retinoblastoma(Rb) protein, which dissociates from E2F transcription factor allow transcription of Cyclin E/A.
  - Cyclin E/A binds to Cdk2, promote expression of S-phase promoting genes.

Retinoblastoma (Lof of tumour-suppression gene), no inhibition in expression of cyclin A/E

- Inherited retinoblastoma
  - Heterozygous cell (Rb+/Rb-), accumulation of mutation lead to cancer forming
- Sporadic retinoblastoma
  - Non-inheritory, accumulation of mutation causes loss of function in both Rb alleles.

- G0 stage: terminal stage for differentiated cells, non-proliferative functional stage. Cancer can lead to inappropriate exiting from G0 stage.
- G1 stage: Check for cell size and nutrient availability,
- S phase checkpoint: Check for complete replication of the gene before advancing into G2 phase. S-checkpoint mutation lead to cancer cells with many DNA aberrations.
- G2 phase checkpoint: Check for genome integrity before mitosis, cell size check.
- M-phase checkpoint: Check for proper attachment of microtubule spindles to kinetochores before separating sister chromatids.

Apoptosis: programmed cell death

- Chromatin compaction, cytoplasm condensation, fragmented nuclear envolope, intact cell membrane, no inflammation

Necrosis: Injury/stress induced cell death

- Leakage of cell content, induce inflammation

Apoptotic pathway:

- Instrinsic
  - Trophic factor binding activates PI3K pathway, activates PKB, phosphorylates bad
  - Bad phosphorylation allow 14-3-3 binding sequestrate bad, does not inhibit Bcl2
  - Bcl2 protein normally binds with bax, prevent oligomer formation
  - If Bax form oligomer, allow exiting of cytochrome C
  - Cytochrome C exit, bind with apaf 1 in cytosol, activates apaf1
  - Apaf-1 induce cleavage of procaspase 9 into caspase 9
  - Caspase 9 induce cleavage of procaspase 3 into caspase 3
  - Caspase 3 induce downstream degradation of organelles —> apoptosis
- Extrinsic
  - Tumour Necrosis Factor α (TNF-α): extrinsic signal that induce cell death.
  - TNFα bind with TNF-α receptor on cell surface, promote TNF complex assembly (FADD and TRADD)

- TNF complex assembly induce cleavage of procaspase 8 and activation of caspase 8
- Caspase 8 induce cleavage of various downstream procaspases, activating caspase (inc. caspase 3)
- Caspase 8 also induce inhibition of Bcl2, allow bax to form oligomer, activating intrinsic pathway

- Senescence
  - Telomere is a length of repetitive guanine rich sequence
  - Length shortens over time, maintained by ribonucleoprotein telomerase in stem cells
  - Replicative senescence: telomere shortens over the cycles, functional DNA shortened causes mutations
  - Senescent cells show phenotypic changes, produce inflammatory cytokines, DNA damage induce apoptosis (p21)
  - Senescence mechanism reduce proliferative capacity, reduce chance of cancer formation.

Cell cycle checkpoints

G1 detail

Rb

Apoptosis/necrosis

2 apoptotic pathways

Senescence