Tumour cells characteristic

- Uncontrolled division
- Undifferentiated
- No quiescence
- Dedifferentiation

Mechanisms of oncogenesis:

- LoF tumour suppression genes (e.g. cell cycle checkpoints, cell death signalling pathway)
- GoF Proto-oncogenes (e.g. metabolic and growth pathways)

Three most common pathways of oncogenesis:

- Cell cycle entry (Rb)
- Cell proliferation (Ras)
- Cell survival genes (p53, PI3K(PTEN))

Mechanism of oncogenic activation: where mutation could occur & consequences

- Point mutation: change in primary structure, change in protein structure
- Regulatory region: change in expression levels
- Chromosomal translocation: recombined gene - hybrid protein produce novel effects
- Insertion: inserted nucleotide into the gene - non-functional gene,
- Duplication of genes: amplification of expression

E.g. EGFR truncation leads to constitutive activation

P53: DNA damage monitor.

- Structure:
    - transactivation domain (interact with polymerase, transcription factors)
    - DNA binding domain (bind to p53 response element)
    - Tetramerisation domain (function as a tetramer)
    - Regulatory domain
- P53 signalling pathway (Promote cell death when activated)
    - Regulator of P53 MDM2 downregulates P53 activation by ubiquitination tagging for degradation and nuclear export
    - Upon DNA damage (e.g. dsb), ATM is activated, which activated downstream CHK2, which phosphorylate and activates P53, phosphorylation prevents ubiquitination
    - Upon cellular stress, ATR activated, which activates Casein Kinase 2, phosphorylate and activates P53.

    - P53 upregulate thrombospondin, inhibitors of angiogenesis
    - P53 downregulates bcl expression, upregulate bax expression, induce apoptosis
    - P53 upregulate P21 expression, which inhibit cyclin-Cdk complex action arresting cell cycle
    - P21 expression also inhibit PCNA (clamp loader in eukaryotes), prevent DNA replication and promote repair
- P53 mutation:
    - Loss of function: lack of apoptosis, no DNA repair, no quiescence, overproliferation

PTEN: regulator for cell growth (tumour suppressor gene)

- PTEN signalling pathway:

- Growth factor activates PI3 kinase
- PI3K induce phosphorylation of PI3 to PIP2 to PIP3, adding a phosphate group
- Phosphorylation of PIP3 lead to activation of AKT then mTOR pathway, upregulating protein synthesis, inhibiting apoptosis
- PTEN dephosphorylation of PIP3, counteract growth signal

- PTEN mutation
  - LoF mutation lead to uncontrolled cell growth, lack of apoptosis

Ras: promotor of cell growth (proto-oncogene)

- Growth factor binding with receptor tyrosine kinase cause dimerisation, autophosphorylation and activate Ras, which is a GTPase able to activate other proteins
- Ras-GDP <— —> Ras-GTP, phosphorylation by GEF, dephosphorylation by GAP
- The ras pathway converges onto the mTOR pro-proliferation pathway by Ras activating PI3K, and ERK in another signalling pathway
- Gain of function mutation (constitutive activation) of ras leads to increased cell proliferation and metabolism, no response to external signals

Tumour characteristic

Types of mutation

P53, PTEN, Ras

Structure, pathway