PHSI3012/3912: Physiology of Disease

Topics:

Module 1: Cancer

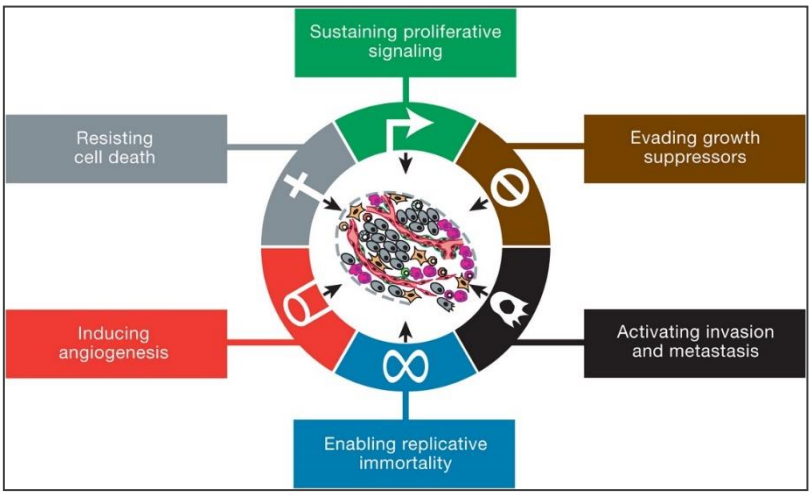
Module 2: Cardiovascular disorders

Module 3: Metabolic disorders

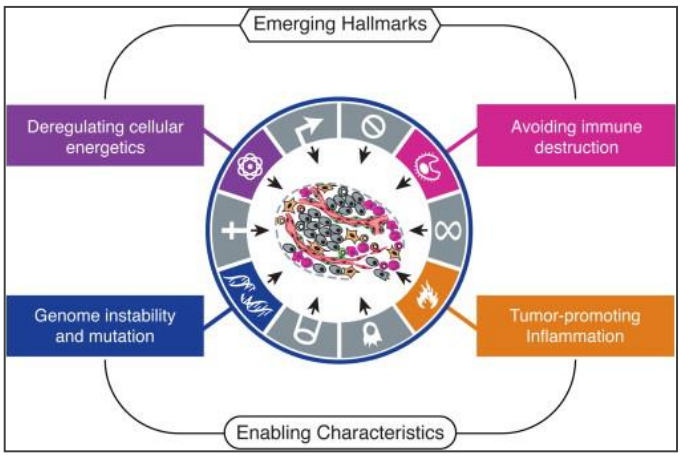
Cancer: uncontrolled proliferation of abnormal cells, which can grow into and invade surrounding healthy tissues and organs. Carcinogenesis is the initiation of cancer formation.

Hallmarks of cancer

- Cells can incur nuclear damage and alter their normal physiology to allow them to become cancerous.
- These changes are known as the hallmarks of cancer and are self-sufficient growth allowing for proliferation, evading tumour suppression, evading apoptosis, inducing angiogenesis (blood vessel formation), limitless replicative potential and the ability to invade and metastasise.
- These changes assist in cancer initiation (carcinogenesis) and spread to distant organs (metastasis).



4 more emerging cancer hallmarks:

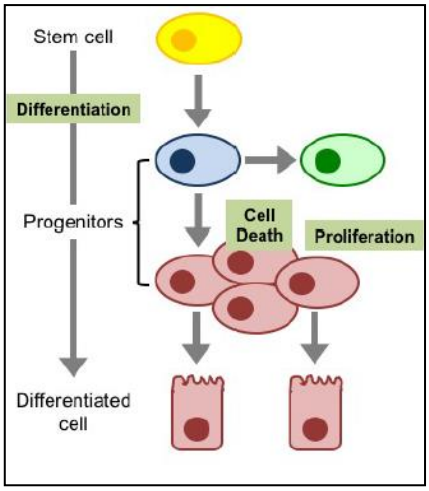


- Defects in DNA repair - leading to genomic instability
- Altered cellular metabolism - ex: switch to aerobic glycolysis (Warburg effect)
- Avoiding immune destruction: number of mechanisms of immune escape – can produce proteins that are not able to be recognised by the immune system
- Tumour-promoting inflammation - ex: release of cytokines promoting proliferation

Each hallmark is driven by complex signalling networks and current research is attempting to identify and target these pathways therapeutically to treat cancer.

Carcinogenesis

Cancer initiation is complex and involves different levels of regulation. Stem cell development into differentiated cells relies on growth factor signals, hormones and other environmental factors and these pathways can become dysregulated and lead to cancer formation.



Transcription factors

Transcription factors are proteins that contribute to gene expression by promoting gene transcription. Ex: RUNX transcription factors are a family of transcription factors that bind to CBF-β and either promote or inhibit gene transcription.

RUNX2

- Expressed in mammary epithelial cells and HC11 cells
- The master regulator of bone development
- RUNX2 knockout = organism death because no skeleton develops
- Breast cancer metastasises to bone and RUNX2 is expressed by both breast and bone – signifies that it could be involved in the vicious cycle of metastasis

RUNX2 in the breast

- Normal expression is decreased when the mammary gland is undergoing differentiation
- Regulates lobuloalveolar development
- Critical for specifying the luminal and alveolar progenitor cell fate
- RUNX2 knockout leads to impaired lobuloalveolar differentiation and impairs the expression of milk proteins
- Suppressed by prolactin
- Induces epithelial-to-mesenchymal transition (EMT) and enhances cell migration – assists with cancer metastatic ability
- Regulates Notch activation – RUNX2 acts on progenitors to cause a more aggressive phenotype, drives proliferation and then it is suppressed to allow differentiation

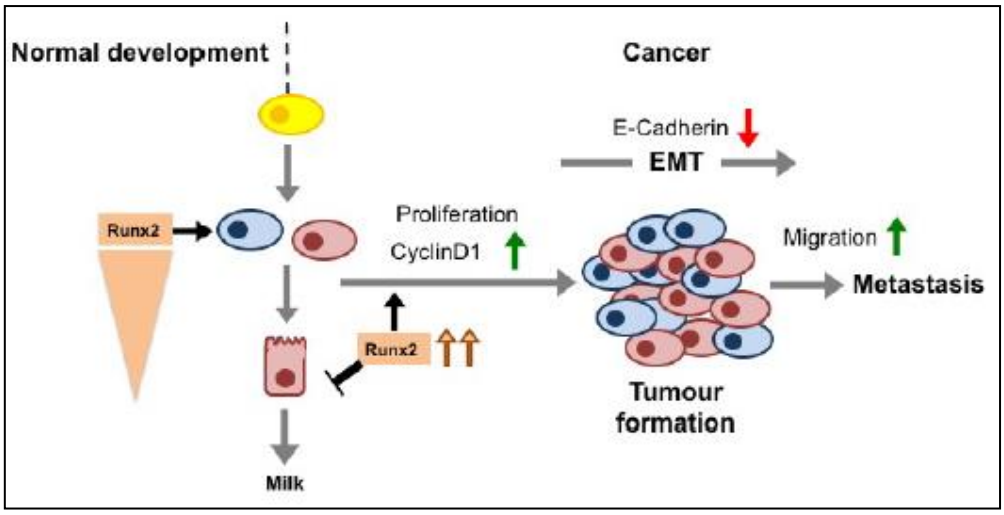
Breast cancer and RUNX2

- Best breast cancer prognosis is the type luminal A and the worst prognosis is basal cancer
- RUNX2 levels higher in basal cancer – RUNX2 contributes to poor breast cancer prognosis by promoting tumour **formation** and **metastasis**
- Knocking out RUNX2 slows down breast cancer development
- RUNX2 may be a novel target for therapeutic intervention in breast cancer

SatB1 and RUNX2

- SatB1 is a transcription factor and the master regulator of breast cancer growth and metastasis

- Higher SatB1 levels = poor prognosis
- RUNX2 expression correlates with SatB1 in human breast tumours



CBF-β

- Binding factor that increases cell proliferation
- Regulates normal mammary gland development and required for early expansion of the ducts by acting only on the stem cells and progenitors
- Increased expression correlates with aggressive breast cancer subtypes
- Knocking out CBF-β slows down breast cancer cell migration, impairs progression and metastasis
- Low levels of CBF- β in luminal A, which has a better prognosis than other breast cancer types
- Basal breast cancers have a high expression of CBF-β = poor prognosis
- CBF-β nuclear localisation correlates with poor patient prognosis in estrogen receptor negative breast cancer
- Estrogen receptor positive tumours with high CBF-β still has a good prognosis

Prostate cancer

- CBF-β is also expressed in the prostate
- Knockout slows down the ability of prostate cancer cells to migrate and proliferate
- RUNX2 drives prostate cancer cell migration