5.2 Cancer Genetics

▼ What is cancer?

cells that **grow and reproduce uncontrollably** with some invading and destroying surrounding healthy tissues including organs (metastasis)

Benign	Malignant
Grows more slowly	Grows faster
Well-differentiated	Poorly differentiated
Capsulated	Not capsulated
Does NOT invade neighbouring tissue	Invades neighbouring tissue
Does NOT metastasize	Invades basement membrane and metastasizes

▼ What are cancer genes?

key genes that cause the abnormal behaviour of cancer cells due to changes in their DNA sequence

▼ What are proto-oncogenes?

- normal gene that produces protein that promotes cell growth and proliferation e.g. KRAS
- proto-oncogene with driver mutation is called **oncogene**
- this can lead to cancer as permanently switched on → continues proliferation → cancer

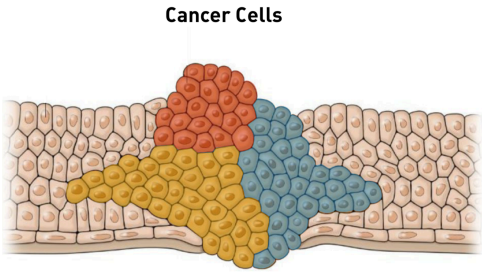
▼ What are tumour suppressor genes?

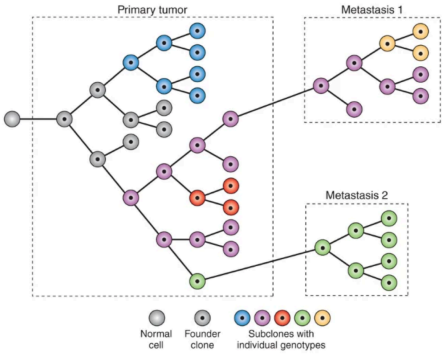
- normal gene produces protein that limits cell growth and proliferation e.g. P53
- driver mutations in tumour suppressor genes could lead to cancer as mutation means it can no longer do this → uncontrolled cell growth → cancer

▼ What is tumour heterogeneity

The observation that different tumour cells can show distinct **morphological** and **phenotypic profiles**, including cellular morphology, gene expression, metabolism, motility, proliferation, and metastatic potential

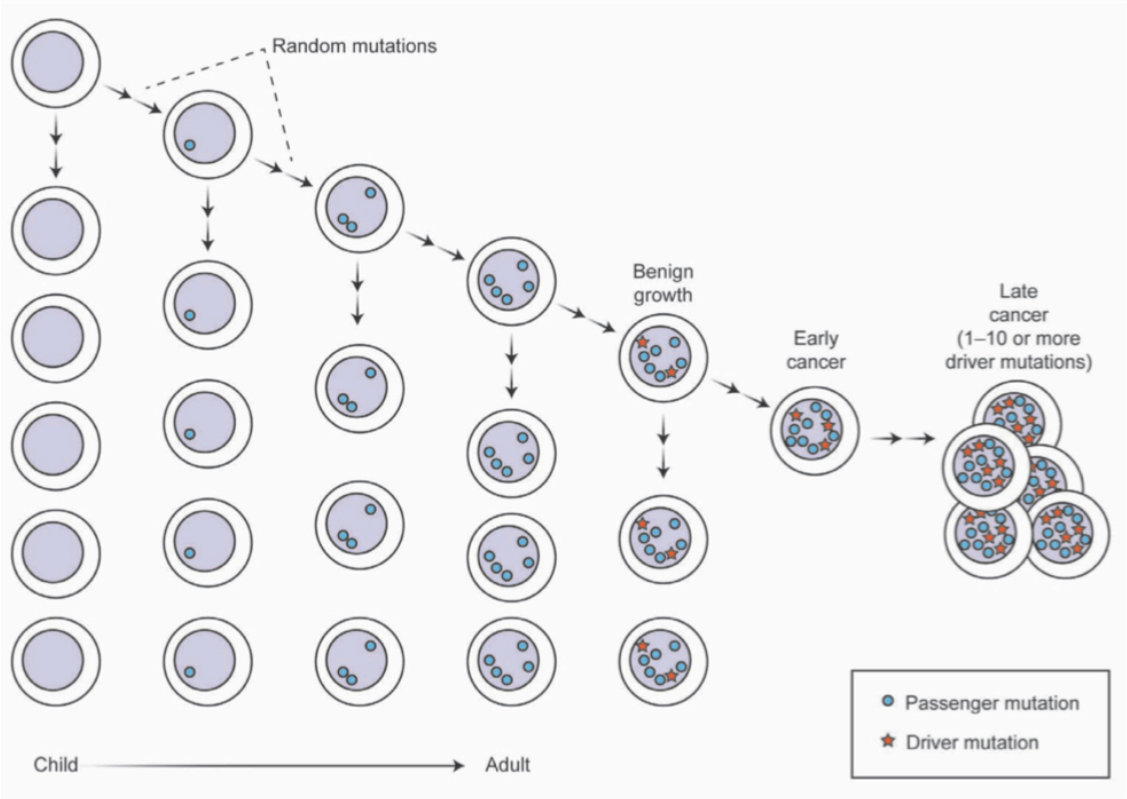
- occurs between tumours (**inter-tumour heterogeneity**)
- within tumours (**intra-tumour heterogeneity**) e.g. one lung cancer not same as another lung cancer





▼ What are passenger and driver mutations?

- passenger mutations: changes in DNA sequence but don't cause problems: occur randomly and no selective growth advantage → don't drive cancer initiation
  - Occur during cancer growth (**do not drive cancer initiation and progression**) normally fixed by cell mechanisms
- driver mutations give tumour cells a specific growth advantage and contribute to the development of cancer
  - Contribute to cancer growth (**drive cancer initiation and progression**)



▼ What are cancer risk genes

genes in which drive mutations can occur, about 37 identified according to census so far (cancer gene census)

these genes are normally protective of cancer and correct any DNA damage in cell divisions, mutations here or inheriting variants (faulty versions) can increase risk of cancer e.g BRCA1 or BRCA2

▼ Give 2 examples of driver mutations and describe their effects.

1. proto-oncogene mutations e.g kRas
    a. kRas normally promotes cell growth, mutation means it is permanently switched on → uncontrolled cell proliferation
    b. oncogenes are dominant (only need one mutated allele), one mutation enough to cause tumour growth - haploinsufficiency
2. Tumour Supressor Gene mutations e.g p53
    a. p53 usually binds to the promoter region to stop cell growth, mutation means it acquires oncogenic functions

▼ What is the **Knudson hypothesis**?

also known as the **two-hit hypothesis**, is the hypothesis that most tumour suppressor genes require both alleles to be inactivated to cause a phenotypic change.

Topic Summary:

- Tumour suppressor genes (TSGs) are recessive
- Therefore, it requires a mutation in **both TSGs** to lead to a tumour growth
  - This is called the **two-hit hypothesis**
- However, sometimes one mutation is sufficient to cause tumour growth
  - This is called **haploinsufficiency**
- Oncogenes are dominant – a tumour growth can be caused by only one mutated allele

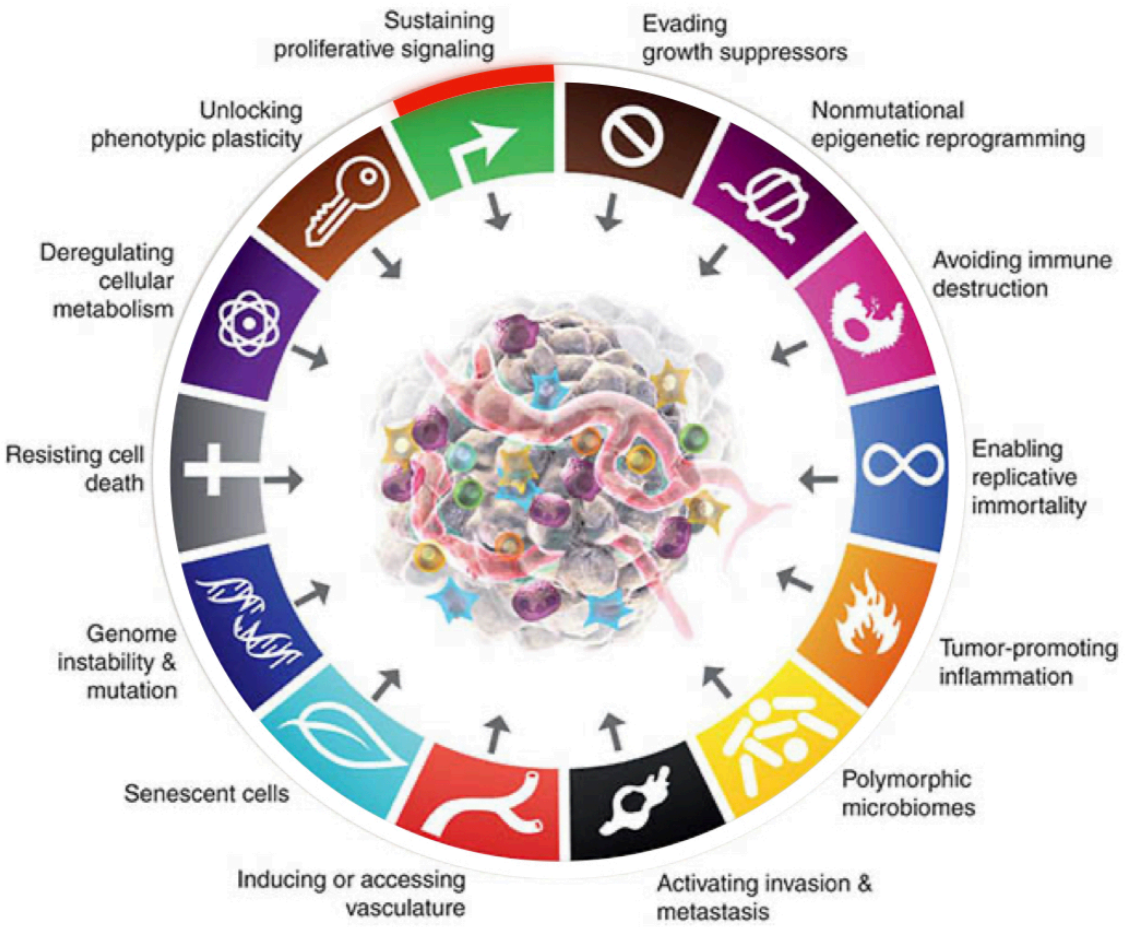
▼ Whats the definition of the hallmarks of cancer?

set of functional capabilities acquired by human cells to grow from normalcy to cancer, driver mutations in cancer risk genes can result in 1 or more of these hallmarks

▼ What are the 14 hallmarks of cancer?

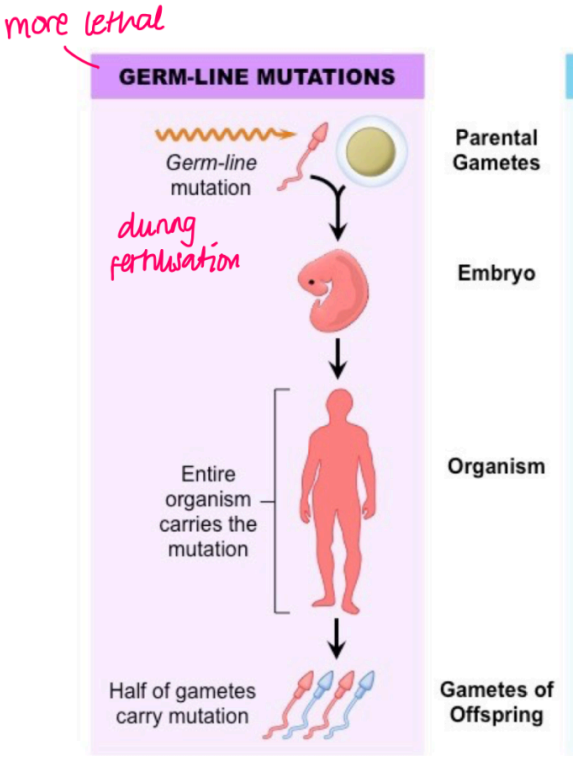
1. **evading growth suppressors** e.g p53
2. **non-mutational epigenetic reprogramming** - tags on DNA that can be switched on or off
3. **avoiding immune destruction** -they evade immune system
4. **enabling replicative immortality** - continue to divide and accumulate additional mutations → more aggressive over time
5. **tumour-promoting inflammation** - chronic inflammation → development of cancer (as cytokines contribute to cancer growth)
6. **polymorphic microbiomes** - pathogens can release things that contribute to cancer (diverse microbiome)
7. **activating invasion & metastasis** - invade surrounding tissues
8. **inducing or accessing vasculature** - release factors that cause angiogenesis to provide nutrients and oxygen for survival

9. **senescent cells** - cessation of cell division, they can recruit these and make them start dividing again
10. **genome instability & mutation** - cancer cells have high mutation rate and genetic instability so more likely to promote tumour growth
11. **resisting cell death** (apoptosis)
12. **deregulating cellular metabolism** - cancer cells change their metabolism to support survival (faster or better for them)
13. **unlocking phenotypic plasticity** - switch between different cellular states depending on their environment
14. **sustaining proliferative signalling** - defects in signalling pathways that normally regulate cell growth e.g. KRAS



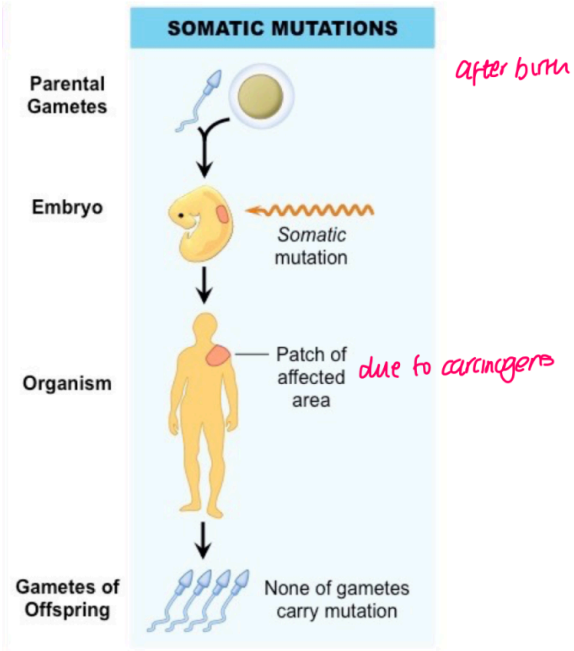
▼ What are germline mutations?

- mutations present in the gametes → passed onto offspring → all cells in the offspring carry the mutation
- contributes to 10% of cancers
- half of the gametes offspring carry this mutation



▼ What are somatic mutations?

- mutations that occur in the body cells (not in the gametes)
- not passed on from parents to offspring
- contribute to 90% of cancers



after burn

due to carcinogens

▼ What is cancer gene census

An ongoing effort to catalogue those genes which contain mutations that have been causally implicated in cancer (cancer risk genes)
There are 736 cancer genes in the most recent version of the cancer gene census. Each of these genes have the potential to have driver mutations, resulting in the acquisition of 1 or more of the hallmarks of cancer.

▼ How may cancer be treated? (5)

1. surgery - directly remove tumour
2. chemotherapy - chemicals to kill rapidly dividing cells
3. radiotherapy - radiation targeted at cancer cells
4. targeted therapy - identify the gene
5. immunotherapy - antibodies attached to anti-cancer drugs

💡 it's easy to kill tumour cells but it's hard to not kill healthy cells with them

**number of mutations in coding genes vary between cancer types, number of driving genes vary between cancer types*

*large scale studies help provide meaning to cancer genetic profiles and DNA sequencing/whole genome sequencing helps us see this **