Cancer

- failure of mechanisms that usually control cell growth and proliferation
- cell birth and death rates determine adult body size and the rate of growth in reaching that size
- cancer causing mutations occur mostly in somatic cells, not in the germ-line cells, and hence mutations are not passed onto the next generation
- oncogenesis/tumorigenesis — interplay between genetics & environment

- **Metastasis** – malignant tumors give rise to metastases, making the cancer hard to eradicate

Cancers are determined by two heritable properties:
- uncontrolled cell division
- metastasis

A **tumor** is defined as an abnormal cell that grows and proliferates out of control creating a growing mass of tissue

- tumor is said to be benign as long as neoplastic cells do not become invasive
- Malignancy is defined by an ability to invade surrounding tissue
  - ↳ invasiveness is an essential characteristic of cancer cells — forming secondary tumors called metastases at other sites in the body

- Tissues under attack are more vulnerable if they produce growth factors & readily grow new vasculature - more resistant if they produce anti-proliferative growth factors, inhibitors of proteolytic enzymes & anti-angiogenesis factors

Classification of cancers

① **Carcinomas** – cancers arising for epithelial cells, most common cancers in humans

② **Sarcomas** – arising from connective tissue or muscle cells

③ **Leukemias & lymphomas** – derived from WBCs & their precursors as well as the nervous system

④ Adenoma – benign epithelial tumor with glandular organisation, corresponding malignant tumor is adenocarcinoma

⑤ About 80% of all cancers are carcinomas as cell proliferation in adults occurs in epithelia and epithelial tissues are most frequently exposed to various forms of physical and chemical change

A benign glandular tumor remains inside the basal lamina that marks the boundary of the normal structure whereas a malignant glandular tumor destroys duct integrity

If a single abnormal cell is to give rise to a tumor – the mutation/aberration has to be heritable
If heritable aberration is due to a genetic change that is, an alteration in the cell's DNA sequence – or to an epigenetic change, that is, a persistent change in the pattern of gene expression without a change in the DNA sequence

Carcinogenesis – generation of cancer — linked to mutagenesis - production of change in the DNA sequence

Two classes of agents responsible :

- chemical carcinogens — causes simple local changes in the nucleotide sequence
- radiation – such as X-rays which typically cause chromosome breaks & translocations
- UV light — cause DNA base alterations

Rarely does a mutation in a single gene lead to onset of cancer
↳ a series of mutations in multiple genes progresses more rapidly (sporadic cancer)

Are cancers hereditary?

No. Cancer is not really hereditary in the true sense of the word
↳ but people who inherit faulty genes have a higher chance of developing that particular cancer

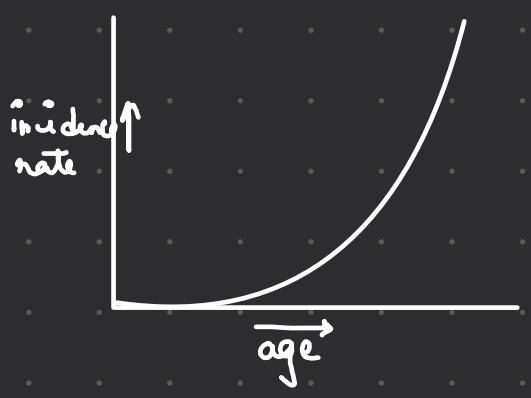
A single mutation is not enough to cause cancer

Development of cancer requires mutations in many genes – a substantial

number of independent, rare genetic accidents occur in the lineage of a cell

At each stage, one cell acquires an additional mutation or epigenetic change that gives it a selective advantage over its neighbours → this enables the cell to thrive in its environment → the environment inside the tumor maybe harsh, with low levels of O_2, scarce nutrients, and the natural barriers to growth presented by the surrounding normal tissues → offspring of the best adapted cell continue to divide, eventually taking over the tumor & becoming the dominant clone in the developing lesion

Cancer incidence increases with age:



If a single mutation was required to trigger cancer, and this mutation had an equal chance of occurring at any time, the incidence would be independent of age

Cervical cancers are prevented by early detection:

- the epithelium covering the cervix is initially organised as a stratified multilayered squamous epithelium
- cell proliferation normally occurs only in the basal layer, generating cells that stop dividing and then move out toward the surface, differentiating as they move to form flattened squamous cells.
- when specimens of cervical epithelium are examined → often, patches are found in which this organisation is disturbed in a way that suggests the beginnings of a cancerous transformation – intraepithelial neoplasia → low-grade
  → high-grade

Epigenetic changes associated with cancer progression

- cancer cells contain an unusually large amount of heterochromatin and maintenance involve specific covalent modifications of histones; in this way, genes can be turned off in a cell-to-cell inherited manner without change in the DNA sequence

- it is possible to associate new heterochromatin formation with epigenetic silencing of specific genes that would otherwise block tumor progression
- many cancerous mutations alter proteins that determine chromatin structure

A mutation results from an irreversible change in DNA seq.
Epigenetic changes on the other hand can be reversed by ① site-specific changes in histone mod.
② site-specific DNA demethylation

Epigenetic changes are not inherited b/w generations

Human cancer cells are genetically unstable

- cells can fail to repair certain kinds of DNA damage or correct replication error of various kinds
- other cancer cells fail to maintain either nr. or integrity of their chromosomes
- some of the DNA changes alter epigenetic control mechanisms in ways that produce extra heterochromatin and DNA methylation.

Causes of cell cancer - increased cell division and decreased apoptosis

- cancer cells often fail to undergo apoptosis
- cause – accumulation of mutations and epigenetic changes that lead to defects in normal control of cell division, apoptosis and differentiation

Tumors induce angiogenesis

- angiogenesis – formation of new blood vessels, reqd for the growth of tumors beyond a certain size
- these signals are produced in response to hypoxia – which begins to affect as the tumors grows in size
- hypoxia → activation of angiogenesis switch → ↑ in level of Hypoxia Inducible Factor 1-a (HIF 1-a) → activation of genes that code for pro-angiogenic factors (VEGF)
- vessels provide escape route for cells to metastasize
- e.g. bFGF, TGF, VEGF

Benign tumors → Malignancy

- benign tumors are localised and of small size
- cell adhesion molecules that hold tissues together keep benign tumor cells localised to tissues
- benign tumors are problematic only if → their bulk interferes with normal functioning
  → excessive secretion of biologically active sub. like hormones

Cancers spread through invasion & metastasis

Invasion - direct migration & penetration by cancer cells into neighbouring tissues

Metastasis - ability of cancer cells to penetrate into lymphatic & blood vessels, circulate through the bloodstream & invade normal tissues elsewhere in the body

Barriers to metastasis include → escape from parent tissue (difficult)
→ travel through circulation (easy)
→ colonisation of remote site (difficult)

Hallmarks of Cancer

① self-sufficient growth ② Ignore anti-proliferative signals ③ evade apoptosis ④ uncontrolled cell division ⑤ induce help from normal stromal cells ⑥ trigger angiogenesis ⑦ metastasis ⑧ genome instability

⑨ Telomerase / maintaining telomeres

Cancer Stem Cells

① Origin

- From normal stem cells (that acquired mutational / epigenetic changes)
- From differentiated cells (reverting to a stem cell state due to ↻)

② Key properties

- Self-renewal
- Differentiation
- Tumorigenicity

③ Identification & Isolation

- CD44
- CD24
- CD29
- CD90
- CD133
- ESA
- ALDH1

④ Therapy (2)

- involved in the regulation of CSCs properties - miRNA

- resistant to conventional treatment (chemo & radiation therapy)
- important roles in cancer and metastasis

Viruses and other infections associated with cancer

- Infection associated cancers —
  1. 15% of cancers are linked to pathogenic infections
  2. Main culprits – DNA viruses

- Viruses associated cancer —

① Human Papillomaviruses (HPV)

- some cause benign warts, some cause cervical cancer
- viral genes subvert cell division, leading to uncontrolled proliferation

② Hepatitis B and C virus

- associated with liver cancer
- chronic inflammation (hepatitis) → cell div ↑
- viruses directly promote cell division

③ Human Immunodeficiency Virus (HIV)

- associated with Kaposi's sarcoma
- HIV supresses the immune system
- enables secondary infection by Human Herpes Virus (HHV-8) which is carcinogenic

- Bacteria and Parasites in Cancer

① Helicobacter pylori

- associated with cancer
- chronic infection causes ulcers & inflammation
- promotes mutations through long term tissue damage

② Parasites

- chronic infection → inflammation induced cancers

Key mechanisms

① Chronic inflammation ② Direct viral action ③ Immune suppression

DNA tumor viruses

- disrupt cell cycle and apoptosis
- hijack host DNA replication machinery
- Replication strategies
  - Lytic cycle – rapid replication → killing host to release progeny
  - Latent phase – integrated into host chromosome

persist as an extrachromosomal plasmid without causing damage for a long time

- Cancer formation mechanisms
  - Accidental activation
    - during latent phase, random events → ↑ viral proteins
    - activation → uncontrolled cell division
  - Persistent Proliferation
    - viral genes turn on cell cycle machinery → host cell division ↑
    - apoptosis blocked → accumulation of additional mutations

- Viruses are not interested in killing the cell
- in latent phase, accident can occur that prematurely activates some of the viral proteins, switching on persistent proliferation of host cell → cancer

- DNA tumor viruses → can promote the development of cancer by encoding proteins that inhibit the products of some tumor suppressor genes
- Papillomaviruses use 2 proteins E6 & E7 to sequester the host cell's p53 & Rb respectively

Rb – binds to & inhibits E2F proteins, limiting entry into S phase

p53 – does not allow abnormal cell to survive / divide

Cancer critical genes

① Proto-oncogenes :
- promote cell proliferation
- gain-of-func mutation for cancer (dominant)
- mutant, overactive & overexpressed forms → oncogenes
- encode growth factors & receptors, anti-apoptotic proteins, transcription factors

② Tumor suppressor gene :
- loss-of-func mutation → cancer (recessive)

③ DNA maintenance gene : mutations result in genomic instability

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