NEOPLASIA

This pdf was prepared
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Note on References

See box to the right for reference notations.

PubMed references usually link to abstracts, which provide useful information. But most abstracts link to a free, full-text article for in-depth reading.

Image references usually link to a whole page of images. The images themselves may be useful, but care must be taken to ensure that they relate to the topic of the text. Images are most valuable as a gateway to publications related to the topic. Clicking on the image will take you to the publication. However, to get the full publication it sometimes may be necessary to copy the url and transfer it to your browser.

- **Reference notations: when references are listed, the following suffixes indicate:**
- **pm = PubMed**
- **w = Wikipedia**
- **i = Images (usually Google images)**
- **rg = ResearchGate**
- **yt = YouTube**
- **sd = Science direct**
- **ow = Other website**
- **Selected text = PubMed, Wikipedia, or images**

What is neoplasia? (1ow, 2i, 3i, 4sd)

- New, abnormal growth of tissue
- Uncontrolled growth of cells not under physiological regulation
- Abnormal growth of tissue forming a mass
  - Early neoplasia may not form a mass
- Abnormal proliferation of cells

What are the central causes of neoplasia?

- DNA damage
  - Genetic mutations
  - Acquired mutations
  - Chromosomal aberrations and aneuploidy
- Deficient DNA repair

  - Mutations in one or more of 34 DNA repair genes (e.g. p53 mutations)

What are pre-metastatic cellular changes preceding cancer?

- Metaplasia (1w; 2a-i, 2b-i, 2c-i, 2d-i, 3e-i, 3sd, 4rg): change of cells to a less to a less specialized form and may be a prelude to cancer.
- Dysplasia (1w, 2a-i, 2b-i, 2c-I, 2d-i, 3rg) cell changes including cells of unequal size, abnormally shaped cells, excessive pigmentation, and mitotic figures.
- Anaplasia (1i): cell changes including nuclear pleomorphism, altered cytoplasmic ratio, presence of nucleoli, and high proliferation index suggestive of possible malignant transformation.

Hallmarks of Cancer

- "The Hallmarks of Cancer“ was an article published in *Cell* in January 2000
- The authors were Douglas Hanahan and Robert Weinberg.
- They contend that the complexity of cancer can be reduced to a small number of principles called ***hallmarks***.
- The authors more recently revisited their 2000 article.

What are the hallmarks of cancer? (1sd)

(1) Self-sufficiency in growth signals.
(2) insensitivity to anti-growth signals
(3) evading apoptosis
(4) limitless replicative potential
(5) sustained angiogenesis
(6) tissue invasion and metastasis.
(7) Deregulated metabolism
(8) Evading the immune system
(9) Genome instability
(10) Inflammation

Hallmarks of Cancer: Self-Sufficiency in Growth Signals (1ow)

- Cells require growth factors to survive and multiply; otherwise they enter a dormant state and eventually undergo apoptosis.
- Growth factors include platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and epithelial growth factor (EGF).
- These can be produced to excess by the tumour cells themselves, or the tumour cells can produce excessive numbers of receptors, allowing them to respond to a lower concentration of these factors.
- Mutant genes for downstream parts of the intracellular pathway, such as the Ras family of oncogenes (activated in 25% of all human tumours), may have a similar effect.

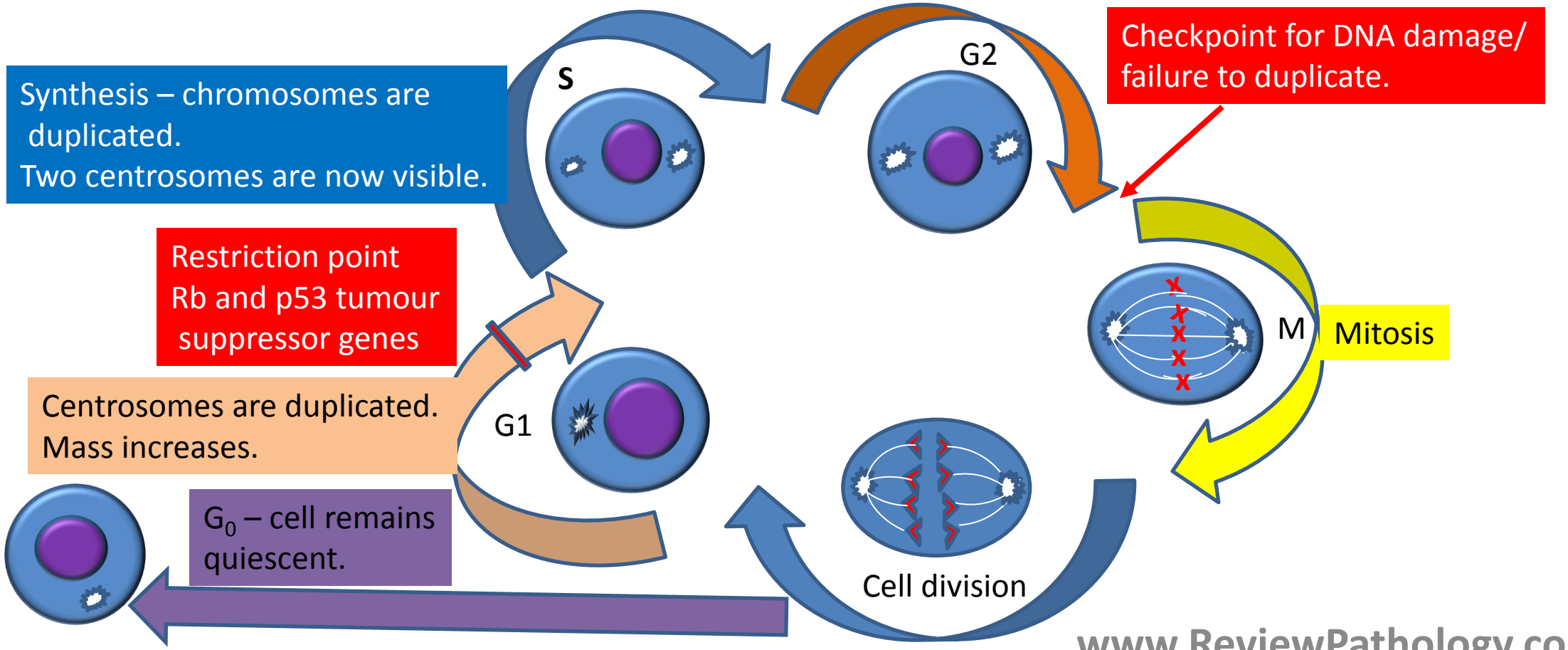
Hallmarks of Cancer: Insensitivity to anti-growth signals (1ow)

- The stages of the cell cycle where inhibition occurs are the two "checkpoints" between G1/S and G2/M (see next two slides).
- The Rb protein, a tumour suppressor gene, must be inactivated in order for the cell cycle to progress from growth to synthesis of a new set of DNA.
- Transforming growth factor beta (TGF-β) prevents the inactivating phosphorylation of the Rb protein, allowing the cell cycle to progress to synthesis without culling of damaged DNA. Mutations which allow potential cancer cells to evade the effect of TGF-β include diminished or non-responsive TGF-β receptors and the loss of downstream proteins which form a crucial part of the TGF-β pathway.

What are the cell cycle checkpoints?

- Cell cycle checkpoints (1i, 2i, 3i) act to block progression of the cell cycle that help to prevent development of neoplasia.
- The G1 (G1/S) checkpoint (1i, 2i, 3i) prevents cell cycle progression in the presence of DNA damage or other cellular inadequacies. If damage is present, the cell will not be allowed to continue to the S phase of interphase.
- The G2 (G2/M) damage checkpoint (1i, 2i, 3i) ensures all of the chromosomes have been replicated appropriately before the cell enters mitosis

Where are the checkpoints in the cell cycle that prevent neoplasia (1i, 2i, 3i, 4i)?



Hallmarks of Cancer: Apoptosis Evasion (1ow)

- Apoptosis is the natural process through which senescent, unneeded, and stressed cells (including the stress of damaged DNA) die.
- All cancers are characterized by the ability to evade apoptosis (1i, 2i).
- This may be done by altering the stress signals which initiate the apoptosis pathway (as seen with dysfunction of p53); downregulating the production of pro-apoptotic proteins; or downregulating the production of downstream effector molecules to block the apoptotic "executioner" caspase cascade (1i).

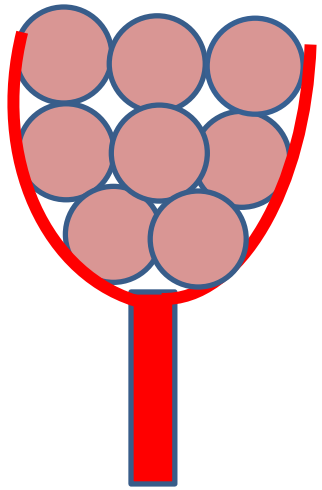
Hallmarks of Cancer: Limitless Replicative Potential (1ow)

- Normal cells cease dividing after 40 to 60 replications (the "Hayflick limit", determined by the shortening of telomeres.
- Telomeres are a repetitive sequence of nucleotides (TTAGGG in vertebrates) capping the ends of chromosomes to protect them from damage, fusion with other chromosomes, etc. Because replication of strands is never complete, telomeres are lost with each successive replication.
- Ca. 90% of human cancers manifest telomerase, a reverse transcriptase enzyme which allows the addition of new telomeres to the strand. Therefore, they can continue to replicate indefinitely.

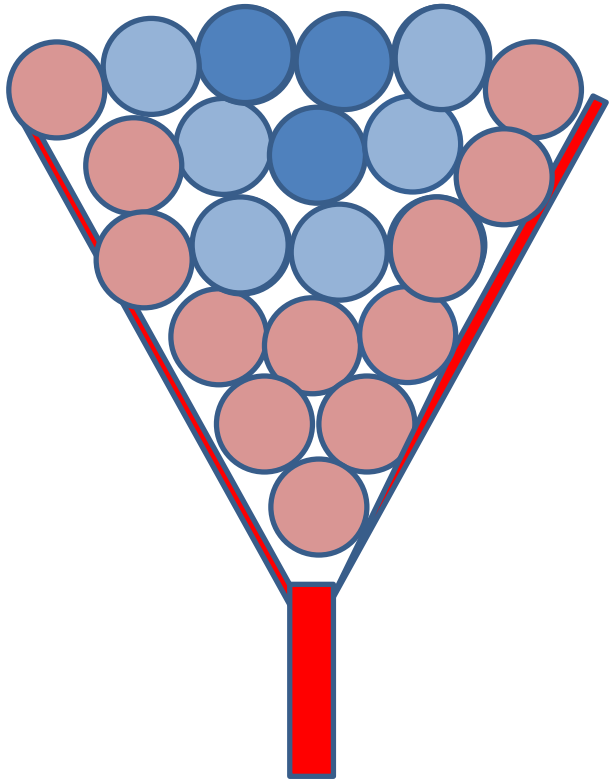
Hallmarks of Cancer: Sustained Angiogenesis (1ow)

- Like all tissues, tumour tissues require oxygenation and nutrients, which require circulation. To ensure tumour growth, angiogenesis must be sustained.
- At a distance of 1 mm. or greater from capillaries, cells begin to become hypoxic and will eventually become necrotic if circulation is not provided. The irregular nature of angiogenesis often leads to necrotic pockets, particularly central necrosis, within thriving tumours.
- Hypoxia in cells leads to build up of hypoxia-inducible factor (HIF), which in turn initiates the pathway leading to expression of vascular endothelial growth factor (VEGF) (and other angiogenic genes) and suppresses angiogenesis suppressors.
- Activated endothelial cells produce platelet derived growth factor (PDGF), stimulating pericytes (which support new blood vessel structure and guide developments) to produce more VEGF, promoting an ongoing cycle.

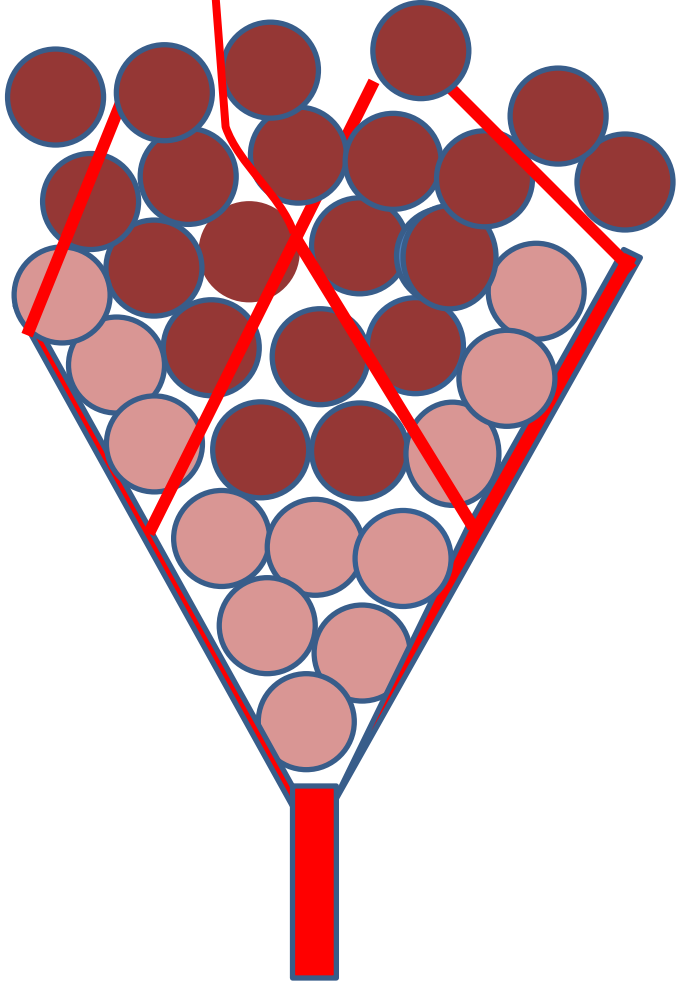
Normal



Tumour cells proliferate;
Hypoxia becomes apparent



HIF stimulates VEGF. Activated endothelial cells produce PDGF, which activates and stimulates pericytes.



Angiogenesis provides O_2, nutrition, waste disposal. Tumour cell proliferation expands.

Hallmarks of Cancer: Tissue Invasion and Metastasis (1ow, 2pm)

Tumour cells detach from one another because of reduced adhesiveness

Tumour cells secrete proteolytic enzymes, degrading the basement membranes

Cells bind to proteolytically generated binding site

Tumour cells migrate through basement membranes and invade neighboring tissues or enter the bloodstream and/or lymphatic system.

By what mechanisms do tumours invade locally?

- Two patterns: collective cell migration and individual cell migration (1pm, 2i).
- Types of migrating tumour cells: mesenchymal (fibroblast-like) and amoeboid (1pm, 2pm, 3pm)
- Motile cells pass through the basement membrane and extracellular matrix (1pm, 2ow)

What proteins play a role in aiding or preventing tumour cell migration through the ECM? (1pm, 2pm, 3pm)

- Integrins (1i)– link cells to the ECM.
- Immunoglobulins (1i)– involved in cell/cell adhesion.
- Cadherins (1i) – involved in cell/cell adhesion; phosphorylated by the proto-oncogenic src-kinase pathway.
- E-cadherin (1i)– transfers anti-growth signals between cells (contact inhibition), an important control on proliferation. Generally lost in migrating cancer cells.
- N-cadherin (1i) – increased in migrating cancer cells; aids in passage through the ECM.

What role does the extracellular matrix (ECM) play in tumour invasion?

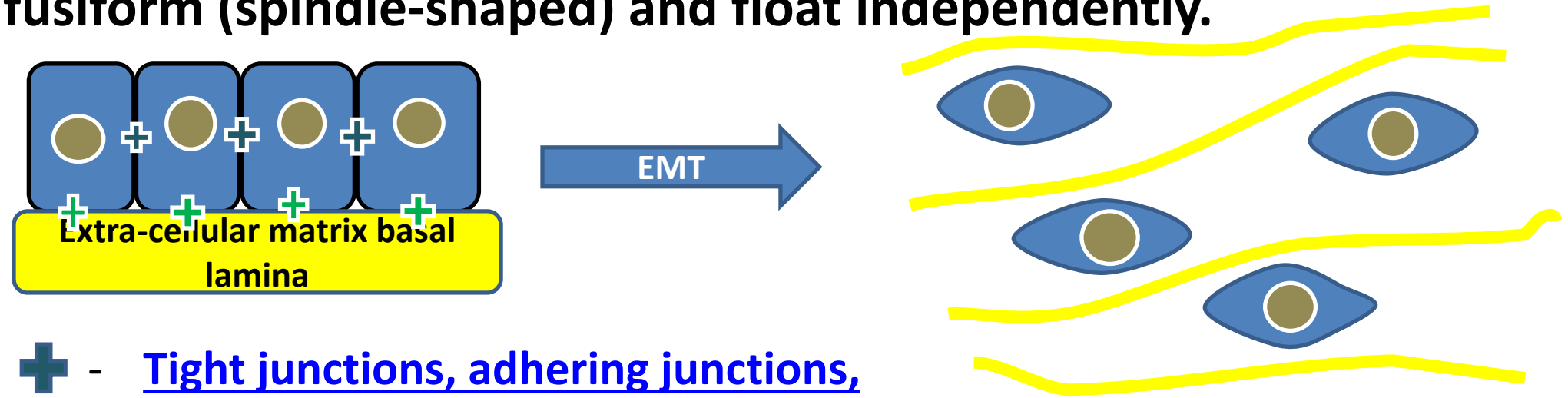
- The extracellular matrix (1i) is a complex composite of collagens, elastin, glycoproteins, proteoglycans, and glycosaminoglycans.
- It plays a critical role in tissue invasion of malignant cells (1pm).
- This matrix supports tissue homeostasis, and its dysregulation contributes to neoplastic progression (1OW).
- For example, malignant cells can invade the extracellular matrix leads through tracks that are remodeled by cancer-associated fibroblasts (1pm, 2pm).

What is the epithelial to mesenchymal transition (EMT)?

- A recently-identified pathway through which epithelial cells (vertically oriented, tightly packed, attached firmly to ECM and each other) become similar to mesenchymal cells (no vertical orientation, loosely packed, unattached to ECM and each other) (1pm)
- Extracellular matrix (ECM) and *both* cell-cell junctions and cell-ECM junctions are degraded; E-cadherin is dissolved; cells lose polarity and are able to migrate freely or be recruited to distant sites, where they revert to an epithelial character. This pathway is crucial to embryological development, and provides one of the chief dangers of aggressive cancer.

What histological changes do cells undergo in the epithelial to mesenchymal transition (EMT)?

- From well-ordered rows of epithelial “cobblestones”, cells become fusiform (spindle-shaped) and float independently.



- Tight junctions, adhering junctions, and desmosomes

- Integrins bound to laminin and fibronectin, hemidesmosomes

ECM filaments with mesenchymal cells floating freely.

Hallmarks of Cancer: Deregulated Metabolism (1pm, 2ow)

Cancer cells generally demonstrate abnormalities of metabolism. These are currently classified as:

- **Deregulated glucose and amino acid uptake**
- **Opportunistic means of acquiring nutrition**
- **Glycolysis/TCA intermediates used for biosynthesis and NADPH production**
- **Increased demand for nitrogen**
- **Alteration of metabolite-driven gene regulation**
- **Metabolic interaction with the microenvironment**

What is the Warburg effect?

- In tumour cells, anaerobic glycolysis predominates over aerobic oxidation (the Warburg effect) (1i).
- The Warburg hypothesis postulates that defects in aerobic oxidation drives tumourigenesis.
- Otto Warburg received the Nobel Prize in 1931 for his research on oxidative respiration.
- Lactic acid is the predominant in product of anaerobic metabolism.
- Malignant transformation apparently results from mutations that favor predominant anaerobic glycolysis.

What is the significance of deregulated metabolism in cancer cells?

- **Sources rapid reproduction and activity.**
- **Useful in diagnosis and staging:**

  - Positron-emission tomography (PET) shows increased uptake of a radioactive glucose analog.
- **In thyroid cancer, radioactive iodine is used both diagnostically in scans to identify the presence of cancer, and therapeutically, as the increased iodine uptake self-targets cancer cells for radioactive treatment.**
- ***The entire concept of chemotherapy is based on taking advantage of the differences between cancer cells and normal cells in order to destroy the former while doing as little harm as possible to the latter.***

Hallmarks of Cancer: (Evasion of the Immune System 1pm, 2pm, 3sd)

- The immune system plays a considerable role in combatting cancer cells, often treating them as foreign pathogens. To survive and metastasize, the cancer cell must evade this natural defense.

- Genetic instability produces cancer cells displaying reduced tumour antigens. These cells survive to proliferate their kind.

How do tumour cells evade the immune system?

- Tumour cells can produce transforming growth factor (TGF)-β, converting CD4+ T-cells into immunosuppressive T-regulatory cells.

- Production of other cytokines and factors such as TNF-α, IL-1, IL-6 VEGF, and colony-stimulating factor (CSF) hijack the immune response and contribute to increased tumour proliferation.

- Lack of costimulatory molecule expression induces tolerance in T-cells by engaging the receptors without actually co-stimulating.

What are tumour antigens?

- Tumour antigens (1i, 2rg) are fragments of intracellular molecules presented on the cell's surface.
- Tumour-associated antigens (TAA) are generally seen on the membranes of tumour cells; tumour-specific antigens (TSA) are only seen on the membranes of tumour cells.
- They represent a range of the changes which may take place within tumour cells, from genetic changes made by oncogenic viruses to abnormal protein levels.
- The immune system response to tumour antigens must be evaded in some manner if a tumour is to thrive and spread.

Evolving Hallmark of Cancer: Genomic Instability (1pm)

- The genomic instability of fast-proliferating cancer cells benefits them in the same manner as fast-mutating pathogens are benefitted by their adaptive ability.
- A successful mutation such as lack of tumour antigen expression allows the cell displaying it to survive and reproduce.
- Each successful mutation survives to evade the immune system or methods of therapy and create a more resistant version of the cancer; to thrive and proliferate more effectively; and to outcompete the normal cells surrounding it.

Hallmark of Cancer: Inflammation (1ow)

- Inflammation and chronic irritation were first linked to cancer by Virchow in 1863, and are generally accepted to be important, if not crucial, elements of tumourigenesis.
- Some of the most obvious examples of this include the relationship of increased risk between gastro-oesophageal reflux disease (GORD) and oesophageal cancer; hepatitis C and liver cancer; inflammatory bowel disease and intestinal cancer.

GORD

Repeated irritation of the oesophageal lining by stomach acid increases likelihood of:

Barrett's Oesophagus
(intestinal metaplasia of oesophageal lining)

Which in turn, increases the likelihood of:

Oesophageal adenocarcinoma

Genetics of Cancer

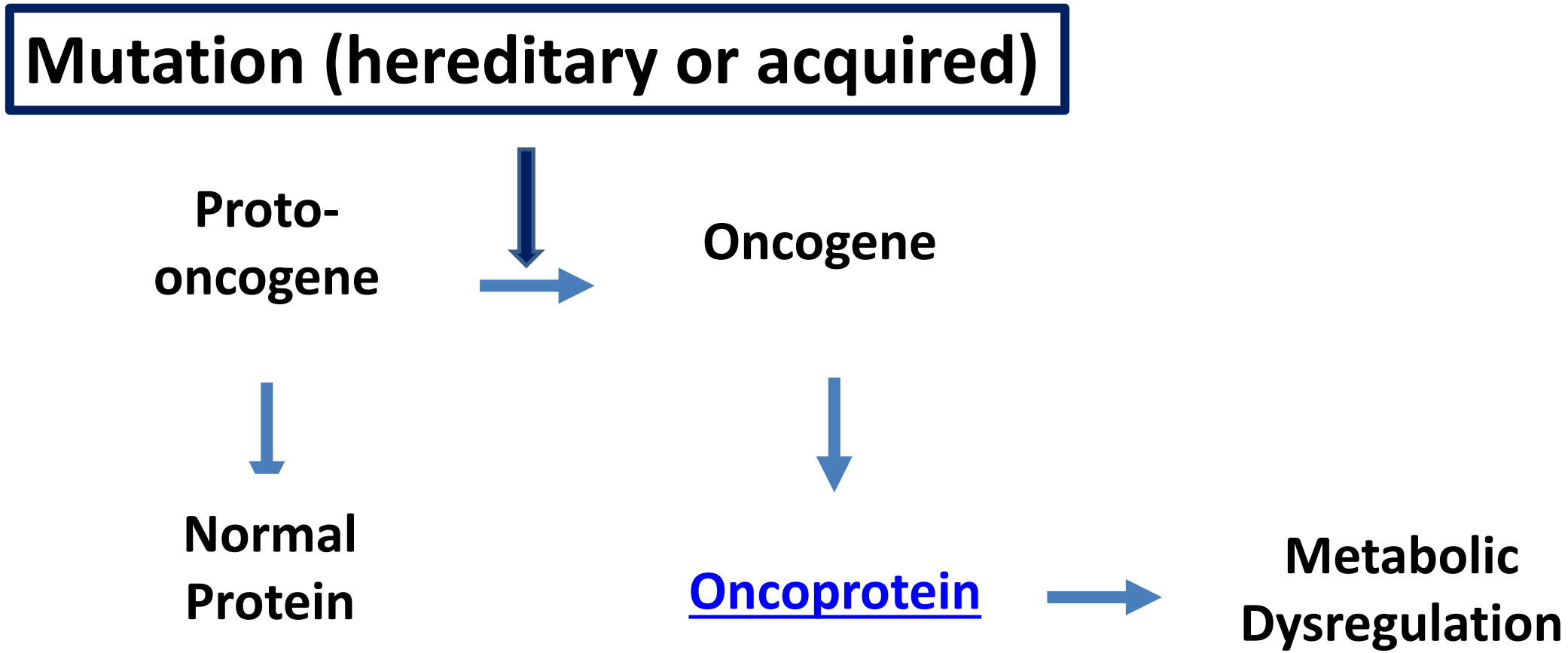
What genes are involved in carcinogenesis (1i, 2ow, 3ow, 4ow)?

- Proto-oncogene/oncogenes
- Tumour suppressor genes
- DNA repair genes

What is an oncogene? (1ow, 2ow, 3sd, 4ow, 5i, 6i, 7i)

- An oncogene is a gene that contributes to cancer.
- It is a gene that in certain circumstances can transform a cell into a tumour cell.
- Activated oncogenes can cause cells designated for apoptosis to survive and proliferate instead.
- Oncogenes not only induce cell proliferation but may reprogram the epigenome.

How do oncogenes lead to cancer?



How are proto-oncogenes activated? (1i, 2pm, 3pm, 4sd)?

- Viral insertion
- Chromosomal rearrangements
  - Altered regulation
  - Fusion genes
- Gene amplification
- Point mutations
- Loss of degradation signals

What are different types of oncogenes? (1i, 2i)

- Growth Factors/mitogens: e.g., c-Sis – over-expression of platelet-derived growth factor (PDGF) (1pm)
- Genes for tyrosine kinase receptors: e.g., EGFR, PDGFR, VEGFR – common in many malignancies (1ow, 2pm, 3ow)
- Genes for cytoplasmic tyrosine kinase: e.g., Src (1ow, 2i)
- Genes for cytoplasm serine/threonine kinase: e.g., Raf (1pm, 2i)
- Genes for regulatory GTPases: e.g., Ras gene family (1sd, 2ow).
- Transcription factors: e.g., myc genes (overexpression leads to increased cell proliferation and hence increased tumourgenicity) (1, 2)

What is an oncoprotein?

- An oncoprotein is encoded by an oncogene which can cause the transformation of a cell into a tumour cell.
- This protein is coded for by an oncogene which has been integrated into the genome of a eukaryotic cell and is involved in the regulation or synthesis of proteins linked to tumourigenic cell growth.

What is the prevailing theory of oncogenesis?

The somatic mutation theory: (1pm, 2ow, 3pm, 4pm)

-- Mutations in DNA or epimutations upset the normal balance between proliferation and cell death, leading to uncontrolled cell division and formation of tumours.

What is the stem cell theory of cancer?

- The stem cell theory of malignancy (1pm, 2pm, 3pm, 4pm) hypothesizes that a few cancer cells can act as stem cells that reproduce themselves.
- Cancer stem cells are few in number but may be responsible for tumour recurrence and tumour resistance (1pm).

What is the embryonal rest theory of cancer?

- The embryonal rest theory holds that cancers develop from tissue stem cells in adults (1pm, 2ow, 3pm).
- Wilm's tumours (nephroblastomas) and neuroblastomas are presented as possible tumours of embryonic rests in children (1pm, 2pm).
- Teratocarcinomas (1i, 2rg) may evolve from totipotent cancer stem cells.

What are some of the best-known DNA repair gene abnormalities?

- Nucleotide excision repair (NER group – XP gene in xeroderma pigmentosum, possibly bladder cancer).
- Mismatch repair genes (MMR – hereditary colorectal cancer).
- DNA crosslink repair (1ow) (Fanconi anaemia).
- Homologous recombination genes (BRCA1 – breast, ovarian, uterine, gastric, bladder non-small cell lung cancer).
- A fuller list is available in the linked article.

What is a tumour suppressor gene?

- Tumour suppressor genes (1pm, 2pm, 3i) protect a cell from one step on the path to cancer.
- p53 protein (1i) is one of the best known tumour suppressor proteins
- Tumour suppressor genes are normal genes that slow down cell division, repair DNA mistakes, or promote programmed cell death (apoptosis).
- Mutations in tumour suppressor genes allows cell division to occur abnormally.

What is the most common cancer-related gene?

- In people with cancer, the most common mutated gene is TP53, which produces the p53 protein.
- TP53 is located on the short arm of Chromosome 17 (17p13/1)
- TP53 is a tumour suppressor gene.
- It encodes for proteins that can either repair damaged cells or cause damaged cells to die (apoptosis)
- The p53 protein is known as "the guardian of the genome".

How does p53 act as “guardian of the genome”?

- Activates DNA repair proteins.
- Halts the cell cycle at the G1/S restriction point.
- Identifies irreparable genetic damage and stimulates cell apoptosis.
- Aids in normal cell senescence response to shortened telomeres after a given number of cell divisions.

What are some of the actions of tumour suppressor genes?

Actions of tumour suppressive genes include:

(1 pm, 2ow, 3ow)

- **Inhibition of cell division.**
- **Repairing DNA damage.**
- **Promoting apoptosis in damaged cells.**
- **Blocking loss of cell contact, thereby suppressing metastasis.**

How many oncogenes and tumour suppressor genes are there?

- UniProtKB has a keyword 'Proto-oncogene' associated with 560 genes and a keyword 'tumour Suppressor' associated with 631 genes.

(The UniProt Knowledgebase (UniProtKB) is the central hub for the collection of functional information on proteins, with accurate, consistent and rich annotation)

What is cancer epigenetics?

- Cancer epigenetics (1pm, 2pm, 3sd, 4i) consist of modifications in the actions of DNA that do not involve changes in nucleotide sequence but may contribute to carcinogenesis.

How do epigenetic changes work in DNA repair genes?

- DNA repair gene promoters are frequently silenced by methylation.
- This inactivates the repair genes, contributing to failure of effective repair and transmission of defective DNA to daughter cell lines.
- Paradoxically, overexpression of some DNA repair genes can also lead to increased aggression and metastasis of tumours.

What modifications in DNA action play a role in epigenetic carcinogenesis?

- DNA methylation
- Silencing of tumour suppressor genes
- Activation of oncogenes
- Histone modifications
- Dysregulation of nucleic acid binding proteins
- Nucleosome positioning
- Changes in non-coding RNA profiles

What are driver and passenger mutations

- Driver mutations are those that directly drive neoplasia; e.g., activating proto-oncogenes or deactivating tumour suppressor genes.
- Passenger mutations are random mutations, which may nonetheless be carried throughout the process of tumour development.
- Previously thought to be harmless/irrelevant to cancer development, there is now reason to think that passenger mutations may play a role in tumour evolution and phenotype (1ow).

Tumour Categorization and Differentiation

What are the two major types of tumours?

- **Benign**
  - **Incapable of distant spread; usually slowly invasive or non-invasive; less often life threatening**

- **Malignant**
  - **Capable of distant spread; always invasive, usually swiftly; more often life threatening**

How do benign and malignant tumours usually differ in gross appearance?

- **Benign tumours are often encapsulated or only locally invasive.**
- **Malignant tumours are usually ragged-edged, aggressively locally invasive, and often metastasize to distant sites.**

What are the features of local tumour invasion?

- Progressive infiltration
- Destruction
- Compression
- Penetration of adjacent structures (malignant tumours)

  > blood vessels, lymphatics, body cavities

What are the chief dangers of benign and malignant tumours?

BENIGN:

Mass effect (pressure disrupting a surrounding area; e.g., the homonymous hemianopsia of a pituitary adenoma pressing on the optic chiasm).

Disruption of organ's normal function.

Loss or overproduction of organ's normal products and benign-tumor associated paraneoplastic syndromes (1pm).

MALIGNANT:

Destruction of surrounding tissues and structures.

Mass effect compromising surrounding tissues, structures, and functions.

Stricture formation (e.g., the characteristic radiological "apple-core" sign most often associated with colon cancer).

Erosion and bleeding.

Paraneoplastic syndromes.

What are the common histological characteristics of benign tumours?

Histological Features of Benign Tumours (1i, 2i)

- Usually well-differentiated (cells resemble those of parent tissues and can normally be identified as the same type as the tissue of origin.
- Structure is normally well-organized and resembles that of the parent tissue.
- Likely to carry out normal function, although often to either a reduced or excessive degree.
- Relatively few and normally shaped mitotic figures (doubling nuclei seen during cellular reproduction) indicating a lower rate of proliferation.

What are the common histological characteristics of malignant tissue?

Histological Characteristics of Malignant Tissue (1ow, 2i)

- May be anywhere from well differentiated to totally anaplastic, but are generally more likely to be poorly differentiated.
- Structure is often disorganized and may not resemble that of the parent tissue in any manner.
- Significant variation between cells in size, shape, and appearance.
- Some abnormal cell types are specifically diagnostic of cancer: e.g., the signet ring cell seen (1i, 2i, 3i) most often in gastric carcinoma and its metastases.
- Unlikely to carry out normal function.
- Increased numbers of mitotic figures, often of abnormal appearance.

In what other ways can tumours be categorized?

- Tumours may be categorized by tissue of origin, subdivided into benign and malignant variations. They may further be categorized by structure or other specific characteristics.
- Epithelial: malignant = carcinoma, benign = papilloma or adenoma (glandular).
- Cartilage: malignant = chondrosarcoma, benign = chondroma
- Adipose tissue: malignant = liposarcoma, benign = lipoma
- Muscle: malignant = myosarcoma*, benign = leiomyoma (smooth muscle)
- Lymphoid tissues: malignant = lymphoma, benign = benign lymphoid hyperplasia

*Leiomyosarcoma = sarcoma of smooth muscle; rhabdomyosarcoma = sarcoma of striated muscle.

What are the benign epithelial tumours?

- Papilloma – characterized by increasingly complex folds of squamous epithelial tissue. The common human wart (verruca vulgaris) is a typical papilloma.
- Adenoma – derived from glandular ducts and acini. Proliferates into complex tubules which usually separate from the source tissue.

- most common source of endocrinological dysfunction: e.g., insulinomas from pancreatic β-cells causing hypoglycaemia; various conditions including acromegaly (excess growth hormone), galactorrhea (excess prolactin), and Cushing's disease (excess ACTH) from different types of pituitary adenoma.

How are adenomas subdivided by form and type?

- Cystic adenoma – adenoma retaining secretions to form a cystic structure, sometimes massive.
- Fibroadenoma – includes a high proportion of fibrous tissue. The classic benign "breast mouse" presenting as a small, firm, but highly mobile lump in the breast tissue.
- Adenomatous polyp – an adenoma which has extended into a hollow viscus, forming a complex structure resembling that of a papilloma. Most often seen in the colon; may be a precursor of colorectal cancer (hence the high risk level in familial adenomatous polyposis, given the vast number of these polyps), but normally benign.

What are the malignant epithelial tumours?

- ***Carcinoma*** **is the generic term for a malignant epithelial tumour.**

- **The word derives from the Greek for "crab", due to both the ragged spreading appearance and the frequent appearance of ulcerations resembling the depredations of this animal. "Cancer" is from the Latin for "crab", for the same reasons.**

How are carcinomas subdivided?

- By cells of origin: e.g., basal cell carcinoma and squamous cell carcinoma.
- By cellular morphology: e.g., small-cell carcinoma (a.k.a. “oat cell” carcinoma) of the lung, clear-cell carcinoma of the kidney.
- By structure: e.g., the gland-like structures seen in adenocarcinomas.
- By other characteristics: e.g., carcinomas which secrete and retain large amounts of mucus are described as mucinous carcinomas.

What are the benign connective tissue tumours?

- Osteoma – arising from bone. Most often small and located in the skull. Other forms include osteoid osteoma, osteoblastoma, and osteochondroma.
- Lipoma – arising from adipose tisssue.
- Chondroma – usually found in the tubular bones of extremities.
- Leiomyoma – smooth muscle tumour. More commonly known as “fibroid”, and generally found in the uterus; may be extensive.
- Rhabdomyoma – striated muscle tumour. Often found in cardiac muscle, but may be present elsewhere.

What are the malignant connective tissue tumours?

- The generic term for malignant connective tissue tumours is “sarcoma”. Sarcomas are divided by tissues of origin, and often contain spindle cells. Types include:
- Myosarcoma (rhabdomyosarcoma = striated muscle; leiomyosarcoma = smooth muscle)
- Liposarcoma – adipose tissue.
- Chondrosarcoma – cartilage.
- Synovial sarcoma – unknown origin; stem cells are suspected. Called “synovial” because it is often found near joints and the cells resemble primitive synovial cells.

What is the most important other type of malignant tumour?

- Malignant melanoma is common and devastating, particularly among light-skinned people. It arises from mutated melanocytes.
- The primary aetiological factor is exposure to UV radiation (sunlight); BRAF oncogene mutations are found in about 50%. The most common sites for malignant melanoma are sunlight-exposed areas of skin, but it can be found anywhere, including the retina, meninges, and nail beds.
- It is distinguished by site and character. Lentigo maligna – facial area, especially the elderly; superficial spreading – usually male trunk or female legs; acral lentiginous – palms, soles, mucous membranes; nodular – usually on trunk.

What are some other types of tumour?

- Benign pigmented naevus (1i) – the common mole, arising from melanogenic neuroectodermal cell migration in the foetal period.
- Hamartoma – mixed tissues characteristic of the site, but growing in a disorganized manner and resembling a neoplastic growth.
- Teratoma (1ow) – arising from totipotent stem cells. Mainly ectodermal, but may contain various types of well-developed tissue. Teeth and hair are not uncommon. Usually seen in ovary (generally benign) or testis (more often malignant), but may occur anywhere along the midline. An occasional inspiration for horror writers and sometimes called “evil twin tumour”.
- Haemangioma (1i) – divided into capillary haemangioma (the common red or purple “birthmark”, though may occur in internal organs) and cavernous haemangioma (typically found in the liver).

What is the difference between solid tumours and non-solid tumours?

- Solid tumours are those which have a clear physical structure. Examples of solid tumors are sarcomas, carcinomas, and lymphomas.
- Non-solid tumours (not a standard definition) comprise the haematological malignancies: leukaemias, multiple myeloma, polycythaemia vera, etc. Often these are not called “tumours” at all, since there is no actual “tumour” mass or swelling present.
- Solid tumours may be treated with surgery. This may be curative, part of a broader regimen involving other modalities as well, or palliative (removing an immediately problematic mass).
- Non-solid tumours cannot be treated with surgery: they require a broader targeted approach such as chemotherapy, radiation, immune system stimulation, or stem cell transplantation

Clinical Aspects of Cancer: Diagnosis and Evaluation

How is neoplasia detected?

- **Depending on the type and location, there may be an obvious lesion or lump apparent on visual examination by patient and/or clinician.**
- **Otherwise, by evaluation of secondary symptoms (warning signs), which may vary widely by tumour type, including but not limited to:**

Pain of unclear cause, especially if variable or worsening

A lesion that does not heal

Unexplained bleeding (such as painless haematuria) or discharge

Skin changes or progressive alteration in a mole

Symptoms of metabolic disturbances (a wide range of electrolyte or hormonal imbalances; the flushing and diarrhea of carcinoid syndrome)

General symptoms such as night sweats, recurrent fevers, pruritis, fatigue, nausea/vomiting, etc.

What are paraneoplastic syndromes?

- Paraneoplastic syndromes (1pm, 2pm, 3pm, 4pm, 5i) are signs and/or symptoms occurring distant to the site of tumours or their metastases.
- They cover an extremely wide range of organs and presentations, demonstrating the multiple possibilities for metabolic disturbances of virtually every sort in cancer.
- Often the symptoms of the paraneoplastic syndrome will be the first presenting complaints of the cancer. For instance, a parathyroid adenoma or adenocarcinoma is likely to manifest initially via the symptoms of hypercalcaemia; a carcinoid tumour may first become noticeable with the onset of carcinoid syndrome.

What are the major categories of paraneoplastic syndromes?

- General symptoms – fever, night sweats, cachexia, anorexia.
- Carcinoid syndrome – flushing, abdominal cramps, diarrhea
- Cutaneous manifestations of internal diseases
- Paraneoplastic endocrine syndromes
- Gastrointestinal
- Haematological – see subsection in general review of syndromes
- Neurological – various (1i, 2i
- Renal – several paraneoplastic syndromes are directly or indirectly related to the kidney. (1i,
- Rheumatological manifestations

What is carcinoid syndrome and what causes it?

- Carcinoid syndrome, characterized by flushing, abdominal cramps, and diarrhea, is produced specifically by neuroendocrine tumours (carcinoid tumours) (most commonly in the ileum, but can occur anywhere in the small intestine, pancreas, bronchi, or gonads. The syndrome is accentuated when the tumor metastasizes to the liver. Some extremely aggressive tumours (small cell/oat cell carcinoma of the lungs, medullary thyroid cancers) may also produce it.
- Carcinoid syndrome is the result of vasoactive amine secretion by the tumour: serotonin and kallikrein/bradykinin, histamine and other vasoactive molecules.

What are the symptoms of the carcinoid syndrome?

- Flushing head and the upper part of thorax.
- Diarrhea
- Abdominal pain
- Bronchoconstriction
- Secondary restrictive cardiomyopathy
- Tricuspid insufficiency
- Pulmonary stenosis
- Nausea and vomiting

How is neoplasia evaluated?

- **Triple Multi-Disciplinary Team (MDT)**
- **1) Clinician – evaluates suspicious clinical findings (mass, visible lesion, symptoms suggestive of neoplasia).**
- **2) Imaging – evaluates some characteristics (e.g., cystic vs. solid mass) and responsible for *staging* (spread and potential metastases).**
- **3) Pathology – responsible for *grading* the tumour and identifying its source (original growth or metastasized from elsewhere).**

Staging Tumours: TNM (from the National Cancer Institute)

- TNM: Tumour, Nodes, Metastasis.
- Tumour – size and local invasion.
- T_0 – primary tumour cannot be found.
- T_X – primary tumour cannot be measured.
- $T_{1, 2, 3, 4}$ – 1 is smallest and least invasive, 4 is largest/most invasive.
- Nodes – spread of tumour to lymph nodes.
- $N_{0,}$ - cancer cannot be found in lymph nodes.
- N_X – cancer cannot be measured in lymph nodes.
- $N_{1,2,3,}$ etc. – number of lymph nodes containing cancer
- Metastasis – spread of tumour to elsewhere in the body.
- M_0 - no metastasis
- M_X - metastasis elsewhere cannot be measured
- M_1 – cancer has spread beyond primary tumour.

5-Stage Staging systems (from the National Cancer Institute)

- **Stage 0 – Carcinoma in situ: abnormal cells are found, but have not invaded surrounding tissue or formed distant metastases.**
- **Stages 1-3 – Tumour is present with some degree of local invasion; stage 3 is the most serious.**
- **Stage 4 – Distant spread.**

A cancer may also be staged as: “in situ” (no invasion); “localized” (local tissue invasion); “regional” (spread to nearby organs or tissues); “distant” (spread to distant organs/tissues); or “unknown”.

Grading Tumours

- Tumours are graded according to cellular differentiation.
- Differentiation means the similarity between the tumour tissue and the tissue of origin.
- Both cellular appearance and tissue structure are taken into account in grading a tumour. A good comparative example and short description can be found at the Pathology Student website (here).
- Tumours are normally graded by means of biopsy.

What is immunocytochemical staining?

- Immunocytochemical staining is used to reveal the presence or absence of specific cell markers.
- These serve multiple purposes in tumour evaluation, including:

1) Identification of the origin of a metastastic or suspected metastatic tumour's primary.

2) Targeting for chemotherapy or biological drug treatment according to the pattern revealed.

3) Evaluating response to therapy.

See (1), (2) for lists of tumour markers.

What is the difference between immunocytochemistry and immunohistochemistry?

- **“Immunocytochemistry” (ICC) and “immunohistochemistry” (IHC) are often used interchangeably.**
- **The same enzyme reactions are used, but the nature of the sample is different:**

Immunohistochemistry uses processed slices of sample tissue, whereas immunocytochemistry uses either a deposition of cells in suspension or a cultured monolayer of cells.

Metastasis

What is a metastasis?

- The development of secondary malignant growths at a distance from a primary site of cancer.
- Metastases are estimated to be the actual cause of death in ca. 90% of malignant cancer deaths.
- Metastatic cancers are likely to require systemic treatment (radiation, chemotherapy, targeted biological drugs) as adjuncts to or in place of surgery, as simple excision does not guarantee destruction of all tumour seeds.

What are routes of metastases?

- Transcoelomic: through body cavities
- Lymphatic: through lymph nodes and ducts
- Haematogenous: through blood vessels
- Canalicular: along anatomical canaliculi

What are the main theories regarding preferred metastatic sites for tumour types beyond the obvious routes?

- "Homing theory": distant organs attract cancer cells via adhesion receptors or soluble chemotactic factors.
- "Seed and soil theory" (Stephen Paget, 1889): the environments provided by different organs are more or less supportive to cancer cells of various types.
- Genetic host factors: polymorphisms such as Sipa1 and in specific metastatic suppressor genes such as BRMS1 affect the likelihood and processes of metastasis.

What is bone-homing of tumour cells?

- Bone is a common site of metastasis from several solid tumours, such as breast, prostate and lung (bone-homing malignancy).
- Bone-homing is driven by recruitment of bone marrow derived cells, which seemingly promote creation of a “pre-metastatic niche”.
- This mechanism is characterized by remodeling the extracellular matrix, suppressing immune function and enhancing vascular permeability.
- The vascular microenvironment of bone is particularly suited towards tumour cell recruitment, due to high levels of chemokines, growth factors, and ECM matrix proteins.

What are the routes and sites of metastasis favoured by various cancers?

- Gastric – haematogenous, transcoelomic, lymphatic. To liver, peritoneum, lung, bone, ovaries.
- Liver – haematogenous, transcoelomic, lymphatic. To portal vein, lymph nodes, lungs, bones, brain, adrenal glands.
- Lung – haematogenous, lymphatic. To nervous system, liver, bone, respiratory system, adrenal glands.
- Kidney – haematogenous, lymphatic. To lung, bone, lymph node, liver, adrenal, brain, and miscellaneous other sites (including renal vein and inferior vena cava – clear cell renal cancer).

Routes and sites of metastasis (continued)

- Uterine – all routes, notably in endometrial carcinoma. To abdominal cavity (via Fallopian tubes), pelvic and para-aortic lymph nodes, lungs, liver, adrenal glands, bone, and many others
- Ovarian – all routes. To Fallopian tube, contralateral ovary, omentum, peritoneum.
- Breast – haematogenous, lymphatic. To bone, lung, liver, brain, lymph nodes, and others.
- Testicular – haematogenous, lymphatic. To lymph nodes, bone, lung, liver, brain, kidneys, and many others

Routes and sites of metastasis (continued)

- **Pancreatic – lymphatic, haematogenous. Chiefly to liver, peritoneum, lungs, pleura, bones, adrenal glands; but may rarely metastasize to any organ system.**
- **Colo-rectal – lymphatic, haematogenous. To liver, peritoneum, lung, lymph nodes, bone, other sites.**
- **Sarcomas – lymphatic, haematogenous. To lungs, liver, lymph nodes**
- **Brain – lymphatic, haematogenous, canalicular. Extraneural spread occurs, but is extraordinarily rare (Constantine Kanaklidis in https://www.researchgate.net/post/Why_are_brain_tumour_cells_unable_to_show_metastasis). The term "metastatic brain tumour" almost universally refers to metastases into the brain from a distant primary tumour.**

Cancer Epidemiology

What is th relative frequency of the major forms of cancer? (World Cancer Research Fund, 2012)

- Lung – 13.0%
- Breast – 11.9%
- Colorectal – 9.7%
- Prostate – 7.9%
- Stomach – 6.8%
- Liver – 5.6%
- Cervix uteri – 3.7%
- Oesophagus – 3.2%
- Bladder – 3.1%
- Non-Hodgkin lymphoma – 2.7%
- Leukaemia – 2.5%
- Pancreas – 2.4%
- Kidney – 2.4%
- Corpus uteri – 2.3%
- Lip, oral cavity – 2.1%
- Thyroid – 2.1%

These percentages exclude non-melanoma skin cancer.

What external factors underlie cancer?

- Tobacco 30%
- Diet 30%
- Obesity 15%
- Infection 7%
- Physical Inactivity 5%
- Alcohol 4%
- Radiation 3%
- Occupational 3%
- Other 3%

Cancer incidence and mortality

In the United States, the odds of developing an invasive cancer of some sort (birth to death) are 39.7 for men and 37.6 for women. The odds increase rapidly with age, from 3.4/5.5% (men/women) at ages 0-49 to 32.2/26.0% (men/women) =/> 70.

WHO estimates that nearly 1 in 6 deaths worldwide are due to cancer, and that approximately 70% of those deaths are seen in low and middle-income countries. In 2015, this accounted for 8.8 million deaths worldwide (1).

What environmental factors contribute to cancer?

Substance-related include:

- Tobacco
- Asbestos
- Aflatoxins
- Aromatic amines
- Benzene
- Benzidine
- Cadmium
- Silica
- Ethylene oxide
- Soot
- Nickel
- Vinyl chloride
- Wood dust
- Sex steroids

Environmental include:

- UV radiation (sun)
- X-ray exposure
- Radon exposure
- Dioxins
- Diesel exhaust
- Insecticides
- Smoke

Pathogens include an increasing list of:

- Viruses
- Bacteria
- Fungi
- Parasites

What are direct-acting, indirect-acting, and epigenetic chemical carcinogens?

- **Direct-acting carcinogens** are immediately carcinogenic in their natural state/on contact. These include: alkyl or aryl epoxides, nitrosoureas, nitrosamines. They directly damage host DNA.
- **Indirect-acting carcinogens** require metabolic processing to become carcinogenic. These include: polycyclic aromatic hydrocarbons, aromatic amines, alkyl nitrosamines, aflatoxin B_1. Their metabolites damage host DNA.
- **Epigenetic carcinogens** are carcinogens that, rather than damaging DNA directly, contribute to tumour formation by other means: inducing the procarcinogen > carcinogen metabolic enzymes, inhibiting detoxifying enzymes, interfering with DNA repair, or acting inappropriately as promoters, among other possibilities.

What are the mechanisms of radiation as a cause of carcinogenesis?

Radiation can act either by directly damaging a cell's DNA (usually characterized by large portions of gene destruction) or by predisposing it to genetic instability (characterized by point mutations and/or small deletions).
Dose and frequency rate of radiation exposure must overwhelm the host's natural ability to carry out DNA repair/identify damaged cells for apoptosis in order for radiation to cause carcinogenic transformations.

What viruses have been shown to be associated with cancer?

- Epstein-Barr (nasopharyngeal, Burkitt's lymphoma, and possibly other lymphomas)
- Human papilloma virus, especially strains 16 and 18 (cervical cancer)
- Hepatitis B (hepatocellular carcinoma)
- Hepatitis C (hepatocellular carcinoma)
- HIV (increased likelihood of various cancers)
- Human Herpesvirus VIII (Kaposi's sarcoma)
- HTLV-1 (Adult T-cell Leukaemia/Lymphoma)
- Merkel Cell Polyomavirus (Merkel Cell carcinoma)

What are the mechanisms of virus-related carcinogenesis?

- Transforming retroviruses may transduce oncogenes.
- Non-transforming retroviruses may activate proto-oncogenes
- DNA viruses may bind to and inactivate cell proteins, including tumour suppressor proteins such as Rb and p53.
- The chronic inflammation associated with Hepatitis B and C increases the risk of carcinogenesis.
- The damaged immune system of a patient with HIV is less well able to protect against tumour cells.
- All the known tumourigenic viruses are chronic, increasing the likelihood of genetic alterations.

What bacteria have been shown or suspected to be associated with cancer?

Helicobacter pylori – strong link with gastric cancer

Suspected links:

Salmonella typhi (gall bladder cancer)
E. coli (gall bladder cancer)
Streptococcus bovis (colorectal cancer)
Chlamydia pneumonia (lung cancer)
Mycoplasma (leukaemia, lung cancer)
Chlamydia trachomatis (interaction with HPV to promote cervical cancer)

What are the mechanisms of bacterium-related carcinogenesis?

Multiple mechanisms have been proposed(1, 2, 3).
Chronic irritation and inflammation.
Constitutive activation of proliferation/survival regulator NF-κB.
Suppression of p53.
Protein activation of the MAP kinase cascade (affects growth, motility, morphology).
Attack mitochondria.
Production of carcinogenic metabolites.

What fungi have been shown or suspected to be associated with cancer?

Aspergillium flavus
Aspergillium parasiticus

- **Both produce aflatoxins, which are strongly linked to liver cancer. It is also suspected that there may be a link between aspergillosis and lung cancer.**

Candida albicans - oropharyngeal cancer

What are the mechanisms of fungus-related carcinogenesis?

Aflatoxins:
Induce mutations in the TP53 gene, producer of p53.

Candida albicans:
Produces carcinogenic byproducts (nitrosamines) and affects procarcinogen metabolism.
Contributes to inflammation.
Induces Th17 response.
Cross-reaction of antibodies against C. albicans CR3RP and complement receptor 3 (CR3 – responsible for leucocyte adhesion and extravasation).

What parasites have been shown or suspected to be associated with cancer?

Schistasoma haematobium (blood fluke) – bladder cancer
Opisthorchis viverrini (liver fluke) – bile duct cancer
Chlonorchis sinensis (liver fluke) – bile duct cancer
Plasmodium spp. (malaria) – interacts with Epstein-Barr virus
Strongyloides stercoralis (roundworm) – interacts with HTLV-1 virus
Trypanosoma cruzi – GI cancer and uterine leiomyoma

What are the mechanisms of parasite-related carcinogenesis?

Chronic inflammation
Sustaining proliferation
Moderating the host's immune system
Reprogramming of glucose metabolism and redox signaling
Inducing genomic instability
Stimulating angiogenesis
Resisting cell death
Activating invasion and metastasis

What other diseases are associated with cancer?

- Inflammatory bowel disease
- Pancreatitis
- Chronic cholecystitis
- Barrett's esophagus
- Sjogren's syndrome
- Gastritis/ulcers
- Hepatitis
- Cirrhosis of the liver
- Osteomyelitis
- Chronic cervicitis
- Chronic cystitis
- Chronic skin inflammation
- Sialadenitis

Chronic inflammation generally presents an increased risk of cancer!

How do genetic abberations affect carcinogenesis?

A Few of Many Examples

- Through master-regulator proteins that are hyperconnected and autoregulated modules (termed tumour checkpoints).
- Through oncogenic viruses that effect messenger RNA (mRNA) splicing, transcriptional enhancers, oncogenes and tumor suppressors, signal transduction, immune regulation, and cell cycle control.
- Through DNA mutations resulting from ionizing radiation

How do genes and environment work in carcinogenesis?

- Genetic polymorphisms have been demonstrated to varyingly increase risk or offer protection in regards to the body's response to environmental factors.
- These include not only the more obvious proto-oncogenes and tumour suppressor genes, but other factors such as genes controlling the metabolism and clearance of toxins.

What are examples of gene-environmental interactions in cancer development?

Heritability quotient in identical twins:

- Stomach 28%
- Colorectum 35%
- Lung 26%
- Breast 27%
- Cervix uteri 20%
- Ovary 22%
- Prostate 42%
- Bladder 31%

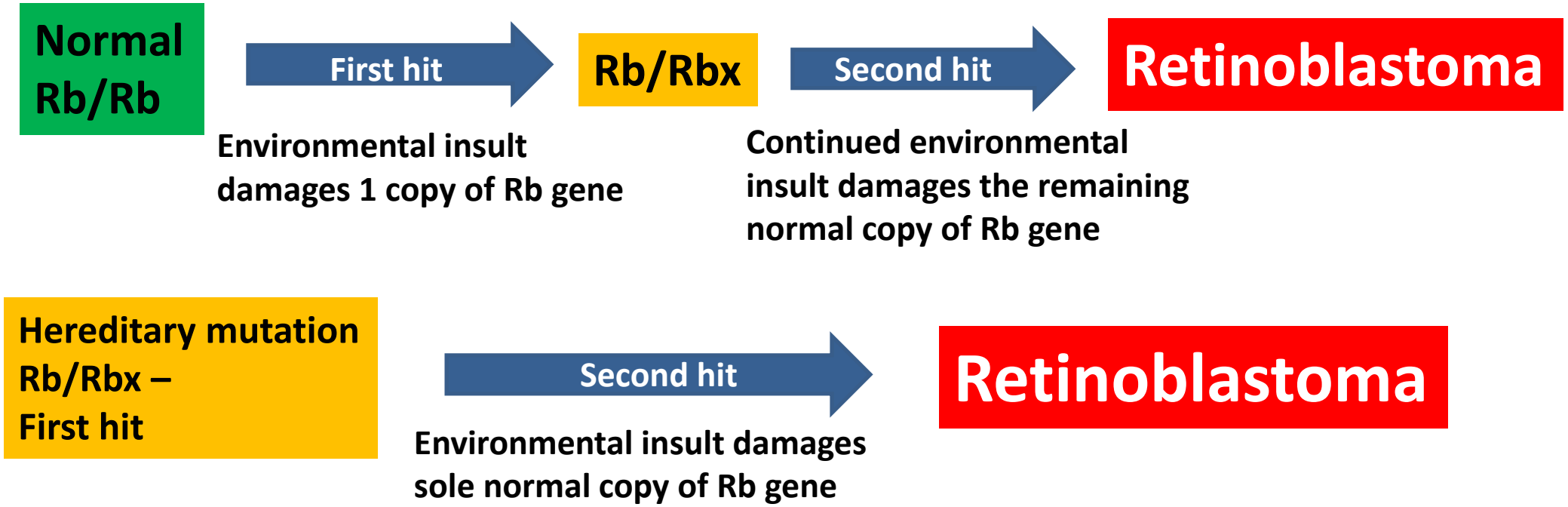
(Lichtenstein et al., N Engl J Med. 2000 343:78-85

What are common environmental/genetic interactions in cancer?

- Factors both genetic and epigenetic have been shown to affect the development and progression of lung cancer in tobacco smokers (in regards to both risk and protection).
- In breast cancer, the presence of mutated BRCA1 and 2 genes presents an increased risk factor, but it is suspected that both endogenous and exogenous estradiol play a role in determining which patients with this gene will develop cancer (1).
- Males with these mutations are at a significantly increased risk (1.2% for BRCA1, 6.8% for BRCA2) compared to the general population (.01%), but much lower than that of women with the same mutations (72% and 69% respectively).

What is the “Two-Hit (Knudson) Hypothesis?”

The theory that cancer requires two (or more) mutations to arise.



What is the relationship between increasing age and cancer?

- Between the ages of 50 and 70, the likelihood of cancer increases roughly tenfold in men and four and a half-fold in women.
- There are several possible reasons, not mutually contradictory:

1) Increasing time to accumulate mutations (the Knudson hypothesis).
2) Decreased ability of the immune system to fight cancer.
3) Weakened immune system increasing the risk and severity of carcinogenic disease.
4) Increased period of exposure to carcinogenic environmental factors.