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Cancer as a complex disease

Pathophysiology of oncologic emergencies

General medicine
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„Read and Write genome“ concept

- Genomes are DNA databases containing coding and formatting sequences that permit heritable transmission of the capacity to synthesize biologically adaptive RNA and protein molecules. In the course of evolution, the coding sequences and formatting signals change to encode novel adaptations. Traditionally, these genome changes have been attributed to accidental causes. But research on the mechanisms of DNA mutability has led to a different picture of active biologically mediated genome restructuring ([Shapiro, 2011](#) and [Shapiro, 2013](#)).
- The fluid read–write (RW) genome replaces the constant read-only memory (ROM) genome.

„Read and Write (RW) genome“ concept

- The basic idea of the RW genome is that cells use DNA as a modifiable data storage medium to encode the RNA and protein molecules they need to deal with changing circumstances.
- Change is continual for living organisms. Alterations occur as cells progress through the **cell cycle**, as **environmental conditions vary**, as **cells experience damage**, as **multicellular morphogenesis proceeds**, and as they **interact with other cells and organisms**.

„Read and Write (RW) genome“ concept

- To manage recurring **short-term variations**, cells primarily deploy transient nucleoprotein complexes to regulate expression of genome data and carry out the necessary tasks of **cell growth and replication**.
- For **longer-term changes**, such as **cellular differentiation and multicellular morphogenesis**, heritable **epigenetic modifications of the genome** come into play over a number of cell generations.
- For the **longest-term changes** that create **new biological functions in evolution**, cells engage their **natural genetic engineering (NGE)** capabilities to acquire and alter DNA sequences and reconfigure genome organization. Sometimes, NGE functions also alter DNA structure to meet shorter-term needs, such as rapid generation of diversity among adaptive immune system receptors and countervailing variation of surface antigens on microbial invaders.

„Natural genetic engineering systems“

- The phrase “natural genetic engineering” (NGE) reflects the reality that living cells possess all the biochemical tools necessary for cutting, splicing, polymerizing and modifying DNA (*i.e.*, writing on their genomes).
- NGE functions are analogous to the tools we use in artificial genetic engineering. In addition, there are certain complexes of biochemical activities and DNA sequences that constitute **specialized genome change cassettes**, summarized under the title **“mobile DNA”** ([Craig et al., 2015](#)).

NGE

Endo- and exo-nucleases

Ligases

Error-free and mutator DNA polymerases

Site-specific recombinases

Homologous recombination complexes

Non-homologous end-joining (NHEJ) complexes

Reverse transcriptases (RTs)

Transposons and transposases

Retroviruses / retrotransposons and cDNA integrases

RNA chaperones / endonucleases and RTs for target-primed reverse transcription (TPRT) and genome insertion of cDNA copies of retroelement or cellular RNAs

DNA secretion and uptake systems

RNA secretion and uptake systems

Viruses

RW concept and cancer

- Cancer occurs when cells decouple from an organism's normal regulatory apparatus and proliferate uncontrollably to form a neoplasm, which may spread around the body to colonize remote organs (metastasis).
- Cancer remains deeply mysterious.

RW concept and cancer

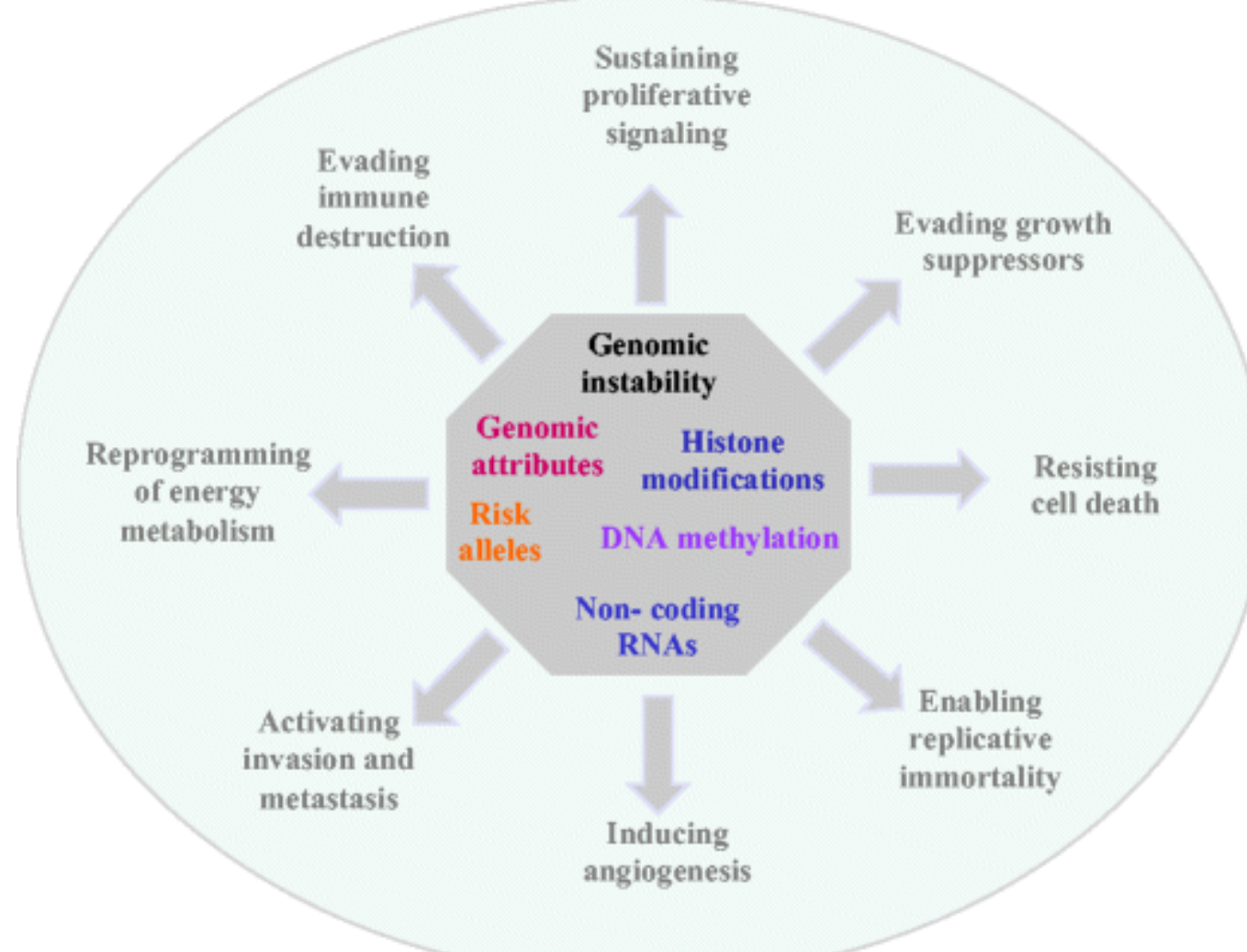
- Cancer comes in many varieties (it is, for example, specific to the organ of origin), but **its progression generally follows a pattern.**
- Clinicians have identified a dozen or so “hallmarks” of cancer, such as **genome instability and heterogeneity**, a **shift in metabolism from oxidation–phosphorylation to fermentation (glycolysis)**, **disabling of apoptotic pathways**, **transition to a motile state**, **evasion of the immune system**, and a **degree of cell–cell cooperation** including the recruitment of normal cells in the vicinity of the primary tumor and in metastatic niches.

RW concept and cancer

- In spite of the focus on cancer as a human disorder, it is found to be widespread in biology, occurring among mammals, fish, reptiles and even plants. This suggests **ancient evolutionary roots**.
- Multicellular organisms outsource their heritability to specialized germ cells, and in return somatic cells are subject to strict controls over their proliferation, such as apoptosis and tumor suppressor mechanisms.
- **Cancer represents a breakdown in these controls**, and thus an abrogation of an ancient covenant that dates back to the dawn of multicellularity over 1 billion years ago. Even “primitive” organisms such as sponges, with lineages hundreds of millions of years old, possess tumor suppressor genes.

Cancer

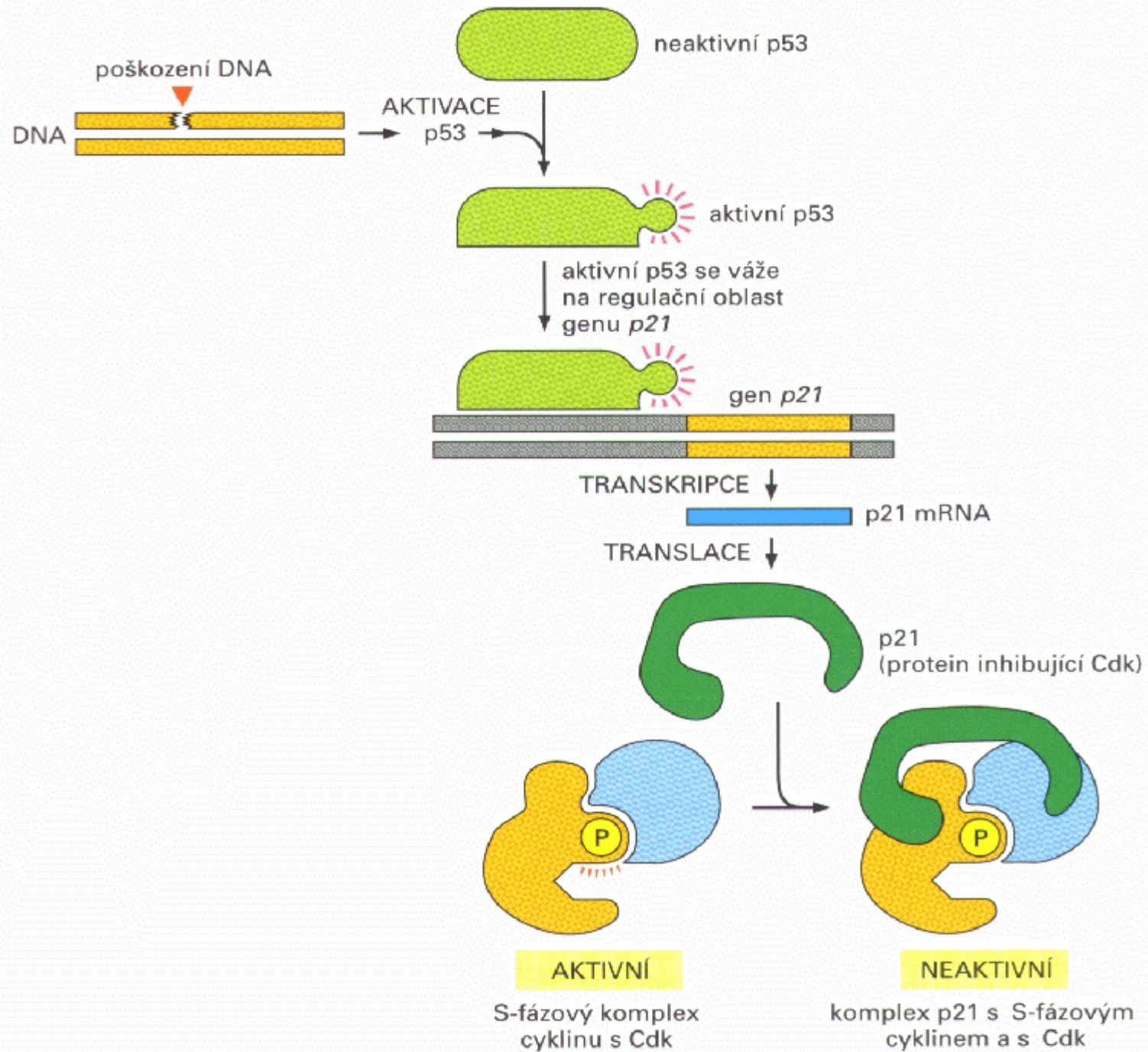
- Cancer does not seem to be a series of genetic accidents, but **a deeply pre-programmed, ancient, systematic response to an insult or stress!**
- The “cancer subroutine” is unlikely to be as simple as a cassette of genes activated in an orderly sequence but a **gene regulatory network with a pre-defined dynamical trajectory.**



Tumorigenesis is a multistep evolutionary process involving myriad, genetic, and epigenetics alterations. Epigenetic alterations during cancer initiation and progression provide an abundant source of variability that not only promotes rapid tumor adaptation but also provides a rich source of labile biomarkers to complement genetic analysis.

Genome stability

- Since our genomes are constantly exposed to **exogenously-derived** (e.g. UV radiation) and **endogenously-derived** (e.g. metabolically generated reactive oxygen species) **DNA damaging agents**, an impaired ability to detect and/or respond appropriately to these effects can impact on the **maintenance of genetic stability**.



Tumor-supresor protein p53 (TP53)

- Is a nuclear protein with key role between G0 and G1 phase of the cell cycle.
- Mutant variants of the p53 gene can be found in many cancer types.
- Somatic mutations-usually
- Germ mutations (*syndrome Li-Fraumeni*).

p53-germ cell mutation

- Li-Fraumeni syndrome (LFS) is a hereditary cancer predisposition syndrome that is commonly associated with a germline mutation in the tumor suppressor gene p53.
- Loss of p53 results in increased expression of CD44, a cancer stem cell (CSC) marker, which is involved in the scavenging of reactive oxygen species (ROS).

Genome stability

- There are many examples of human Mendelian disorders defective in the repair of or response to DNA damage.
- The importance of these pathways is demonstrated by the increase in **cancer predisposition** and **developmental abnormalities** associated with these conditions.

Copy number variants

- The changes in gene copy number are associated with different phenotypes in humans. Perhaps, the most well known example of this is the *trisomy 21 causative of Down syndrome*.
- An increased expression of the genes on chromosome 21 results directly or indirectly in a clinically heterogeneous disorder incorporating *cognitive impairment, facial dysmorphism, growth retardation, cancer predisposition, microcephaly, heart and skeletal abnormalities*

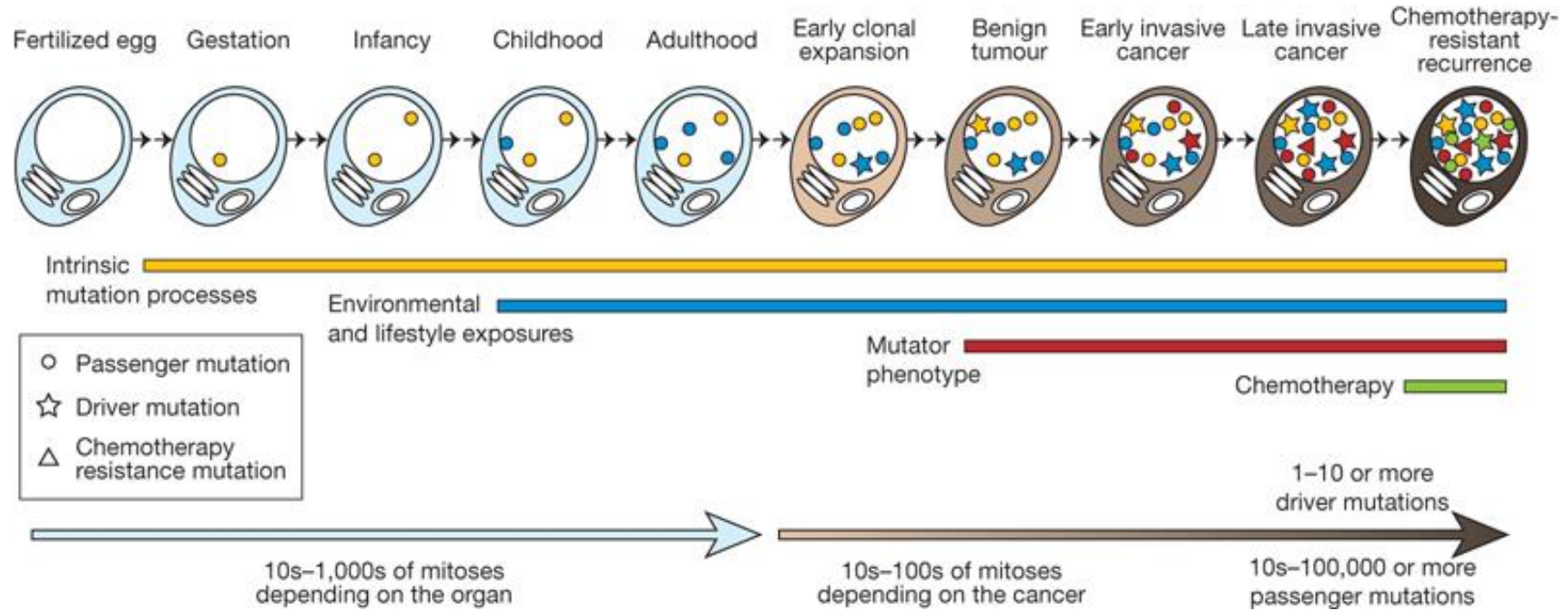
Gene mutations as a cause of variability in genes

- **Rare alleles** - prevalence less than 1% in population as a result of selection pressure and/or „recent“ mutation. These mutations represent „great genetic factors“ causing *monogenic diseases*
- **Polymorphisms** - prevalence more than 1% in population, smaller genetic factors in interactions with environmental factors conditioning *complex diseases (including most of sporadic cancers)*.

Gene mutations as a cause of variability in genes

- *Mutations in somatic cells*
 - ✓ are generating in somatic cells during the lifetime
 - ✓ are cell and/or tissue specific, without transfer to offspring
- *Mutations in germ cells*
 - ✓ they become components of genetic predisposition
 - ✓ they are present in all cells of the individual
 - ✓ they are transferred to offspring

Somatic cell mutations: an example Sporadic colorectal cancer

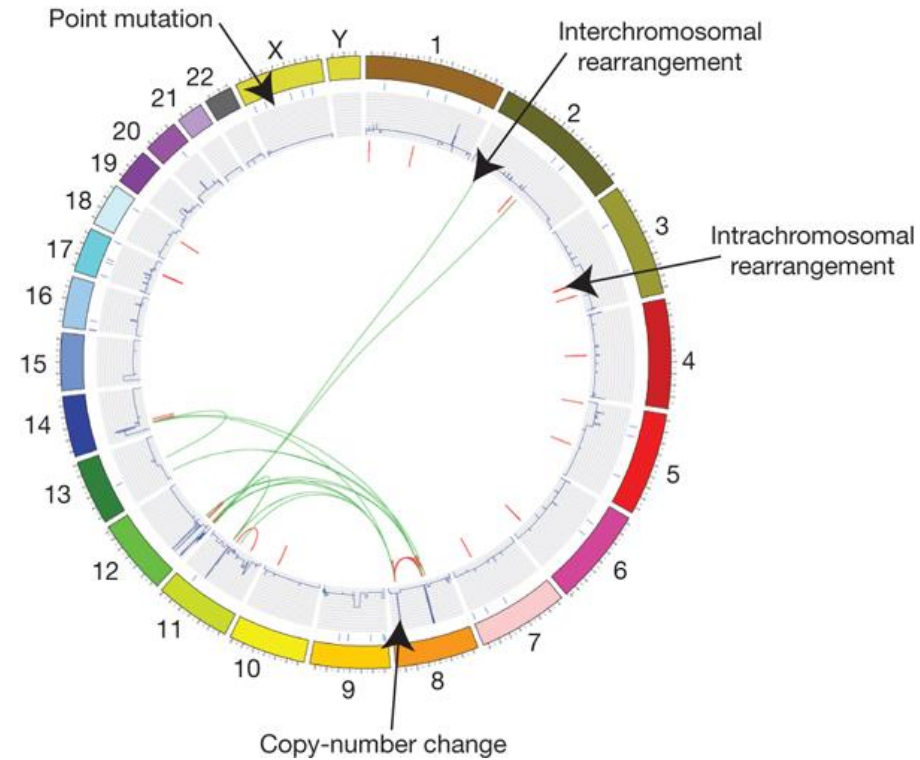


MR Stratton *et al. Nature* **458**, 719-724 (2009)

The lineage of mitotic cell divisions from the fertilized egg to a single cell within a cancer showing the timing of the somatic mutations acquired by the cancer cell and the processes that contribute to them.

nature

Figurative depiction of the landscape of somatic mutations present in a single cancer genome.



MR Stratton *et al.* *Nature* **458**, 719-724 (2009)

Tumor epigenetics

- It is now generally accepted that human cancer cells harbor global epigenetic abnormalities and that epigenetic alterations may be the key to initiating tumorigenesis ([Baylin and Jones, 2011](#); [Sandoval and Esteller, 2012](#); [Sharma et al., 2010](#)).
- The cancer epigenome is characterized by substantial changes in various epigenetic regulatory layers.
- Differences in DNA and histone methylation and acetylation state of histones in cancer DNA have been found.

DNA methylation

- Human malignant tumors are characterized by pervasive changes in the patterns of DNA methylation. These changes include a globally hypomethylated tumor cell genome and the focal hypermethylation of numerous 5'-cytosine-phosphate-guanine-3' (CpG) islands, many of them associated with gene promoters.
- Specific DNA methylation changes were linked with tumorigenesis in a cause-and-effect relationship.
- **Cancer-associated DNA hypomethylation** may increase genomic instability.
- **Promoter hypermethylation** events can lead to silencing of genes functioning in pathways reflecting hallmarks of cancer, including **DNA repair, cell cycle regulation, promotion of apoptosis or control of key tumor-relevant signaling networks.**
- Many of the most commonly **hypermethylated genes encode developmental transcription factors**, the methylation of which may lead to permanent gene silencing. Inactivation of such genes will deprive the cells in which the tumor may initiate from the option of undergoing or maintaining lineage differentiation and will lock them into a perpetuated stem cell-like state thus providing an additional window for cell transformation.

Tumor phenotype

Is characterised by the process of malignant transformation of the cell with

- *loss of control of cell division* (alterations in cell cycle, antiapoptotic state, „immortality „ of tumor cell, alteration in signal transduction),
- *loss of cell-cell contact inhibition,*
- *invasivity,*
- *changes in metabolism*
- *proangiogenic activation*

Malignant transformed cells

- Continue their division.
- Needs for presence of hormones and growth factors decreased.
- Production of own growth factors (*autocrinnal stimulation*).
- Decrement of ability to stop the growth.
- Decreased ability to stop the growth in worse nutrition conditions

Tumors and immortality of cells

- Increased activity of telomerase.
- Telomeres are key stabilisation factors of terminal part of the chromosome.
- Telomeres have repetitive sequence TAGGG.
- The length of telomeres is decreased after multiple divisions of the cell (1 cell cycle is shortening of 1 telomere).
- Their renewal is catalysed by telomerase.
Two mechanisms during tumorigenesis:
mechanisms **TERT** („telomerase reverse transcriptase“)
„alternative lengthening of telomere (**ALT**) pathway“),

Metastatic phenotype

- Increased *motility, invasion* and ability to form *metastases*.
- Increased production of receptors (adhesive molecules)
- Increased production of hydrolytic enzymes
- Function of chemokines
- *Loss of dependence* to adhere to substrates (tumor cells are able to divide even in tissue culture)
- *Loss of gap junctions*.
- *Changes in cell membrane* (glycolipids and glycoproteins modifications).

Phenomenon of tumor support

- Chemical cancerogenes:
- *Initiators:* compounds with cancerogenic potential after their metabolism (P450).
- *Promoters:* effects possible after initiators (*phorbol ester*).

Inflammation and tumorigenesis

- Epigenetic switches play an important role in cancer development.
- Most of the currently discovered switches are induced by inflammation or involve inflammatory signaling.
- **Chronic infections and inflammation** contribute to about 25 % of all cancers.
- In many examples, the same inflammatory trigger (e.g., IL-6) that induced the switch is constitutively activated in cancer cells to maintain the new (tumor) phenotype.

Apoptosis and tumorigenesis

- *Overexpression of Bcl2* (B-cell lymphoma 2) gene was found to be related to inhibition of apoptosis during tumorigenesis.

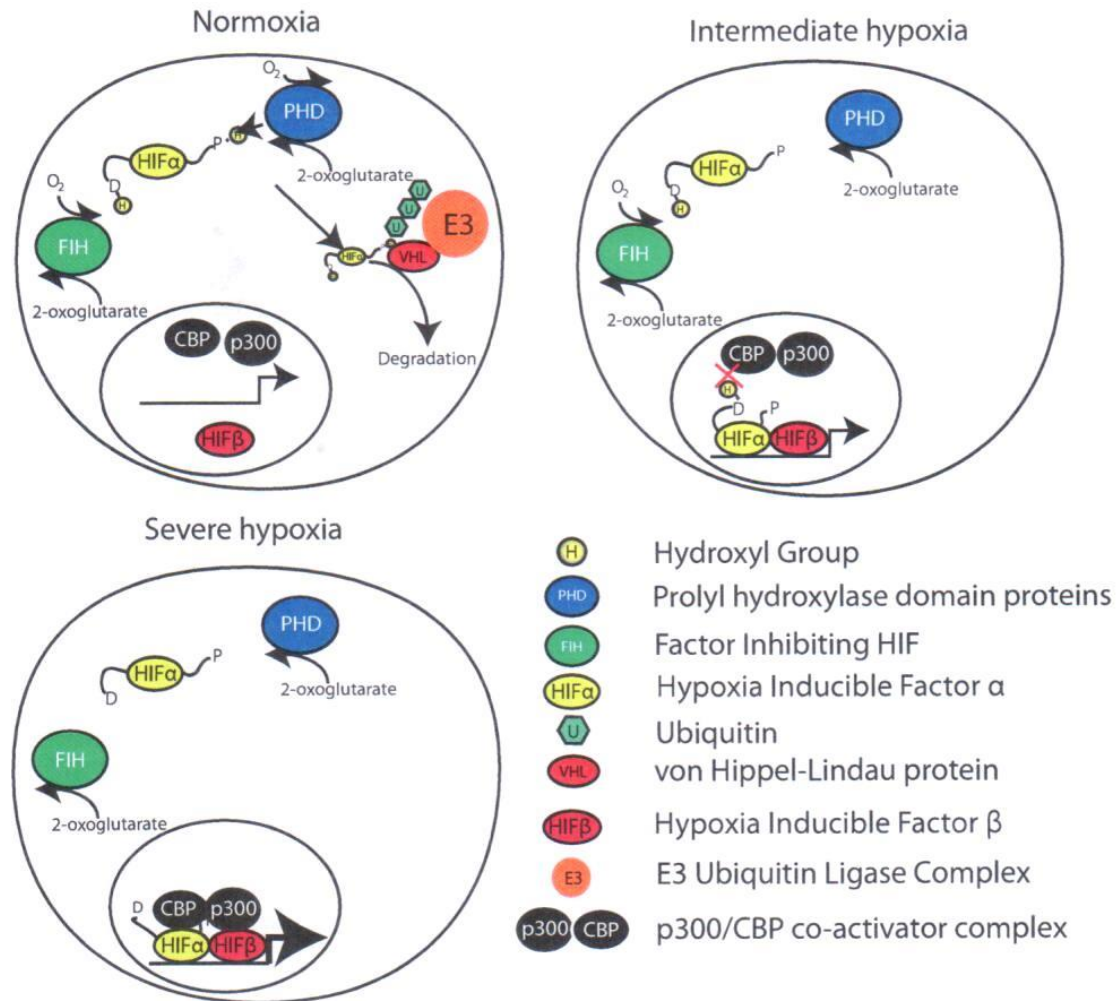


Figure 1. Mechanism of HIF activity. Under normoxic conditions, HIF α subunits are hydroxylated on proline residues. Hydroxylated prolines are recognised by the von Hippel-Lindau protein, ubiquitinated by the E3 ubiquitin ligase, and targeted for proteosomal degradation. As oxygen levels fall, HIF α is stabilised and enters the nucleus to form a transcriptional complex with HIF β subunits. FIH activity is maintained at lower oxygen levels than PHDs and remains active, hydroxylating asparagines. Hydroxylation of asparagines by FIH prevents association of the CBP/p300 coactivator complex with the HIF α /HIF β transcriptional dimer. Under very low oxygen conditions, FIH becomes inactive and maximal HIF transcriptional activity is promoted.

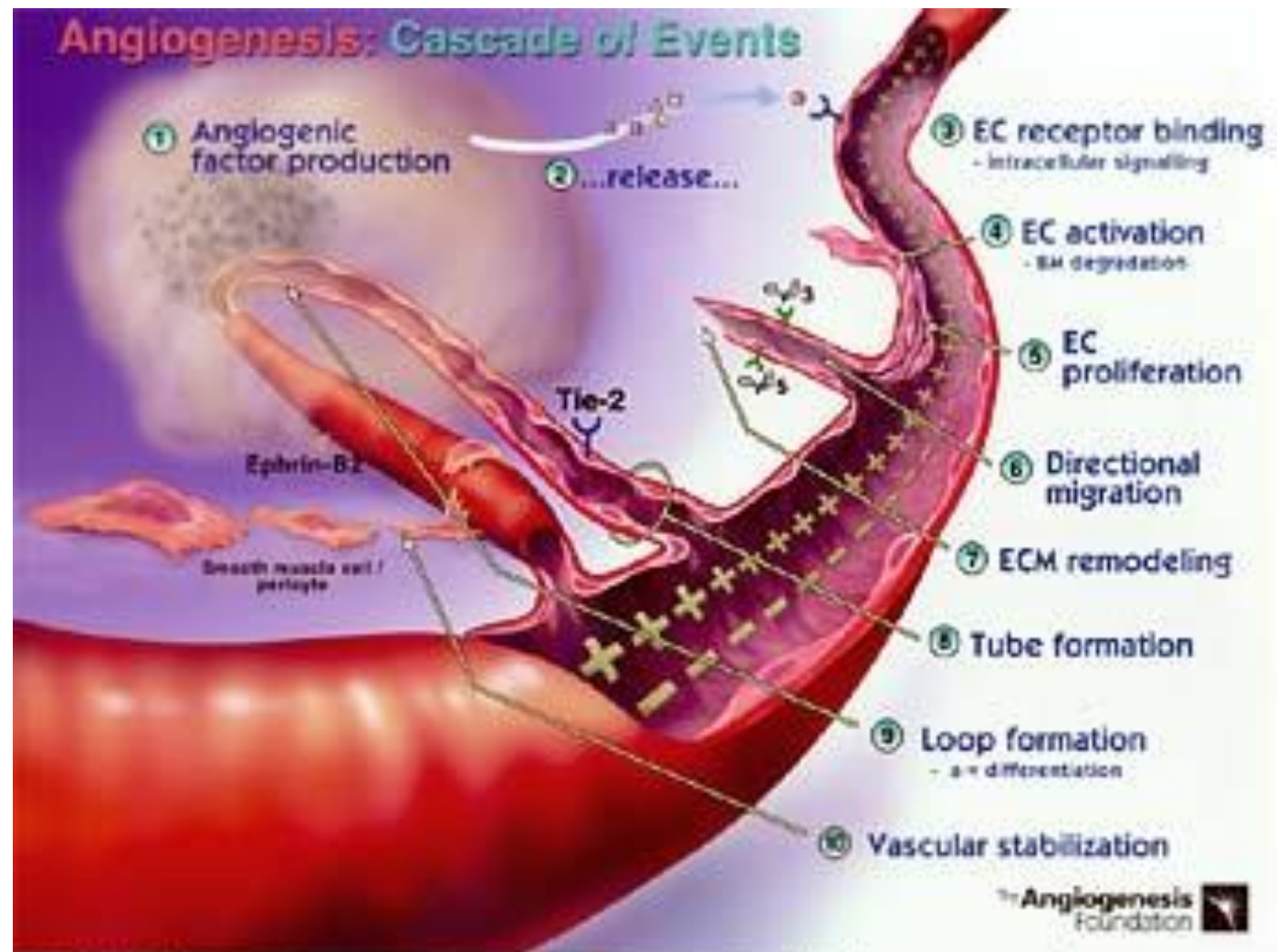
doi:10.1371/journal.pbio.1001116.g001

Tumor neoangiogenesis

- Dysequilibrium between antiangiogenetic and proangiogenetic factors („angiogenetic switch“).
- Without neoangiogenetic switch, the tumor growth is possible only to 1 – 2 mm³, when O₂ and nutrients support is possible by diffusion from surrounding tissue.
- Hypoxia of tumor cells
- HIF- alpha induced transcription angiogenetic factors

Hypoxia and tumor angiogenesis

- Hypoxia occurs in chronic and acute vascular diseases and tumor formation.
- Human tumors grew like cords around blood vessels, and tumor cells located $> 180 \mu\text{m}$ from the blood vessels were observed to become necrotic.
- Hypoxia induces angiogenesis during tumor growth; when tumor growth progresses, HIF-1 program is switched on in the tissue. As a result, also angiogenesis occurs and the tumor develops its own vasculature.



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Oncologic emergencies

- can occur at any time during the course of a malignancy, from the presenting symptom to end-stage disease.
- Although some of these conditions are related to cancer therapy, they are by no means confined to the period of initial diagnosis and active treatment.
- Prompt identification of and intervention in these emergencies can prolong survival and improve quality of life, even in the setting of terminal illness.

Hypercalcemia

- Hypercalcemia will be experienced by up to one-third of cancer patients at some point in their disease course. Among patients hospitalized for hypercalcemia, malignancy is the most common cause
- Breast, lung, and renal cell carcinomas; multiple myeloma; and adult T-cell leukemia/lymphoma are the prevailing causes of hypercalcemia.

Hypercalcemia

- **Bone metastases** may cause a local paracrine effect by producing several factors that stimulate osteoclasts, leading to bone resorption with resultant hypercalcemia and bone destruction. This is most commonly seen in metastatic breast cancer and multiple myeloma. Prostate cancer, despite the frequency with which it metastasizes to bone, only rarely causes hypercalcemia, underscoring that it is not just osseous involvement but the specific tumor-bone interaction that determines calcium liberation from bone.
- Very rarely, a tumor will manufacture **PTH** itself.
- Tumor production of **vitamin D analogues** is a less common etiology of malignant hypercalcemia.

Hypercalcemia

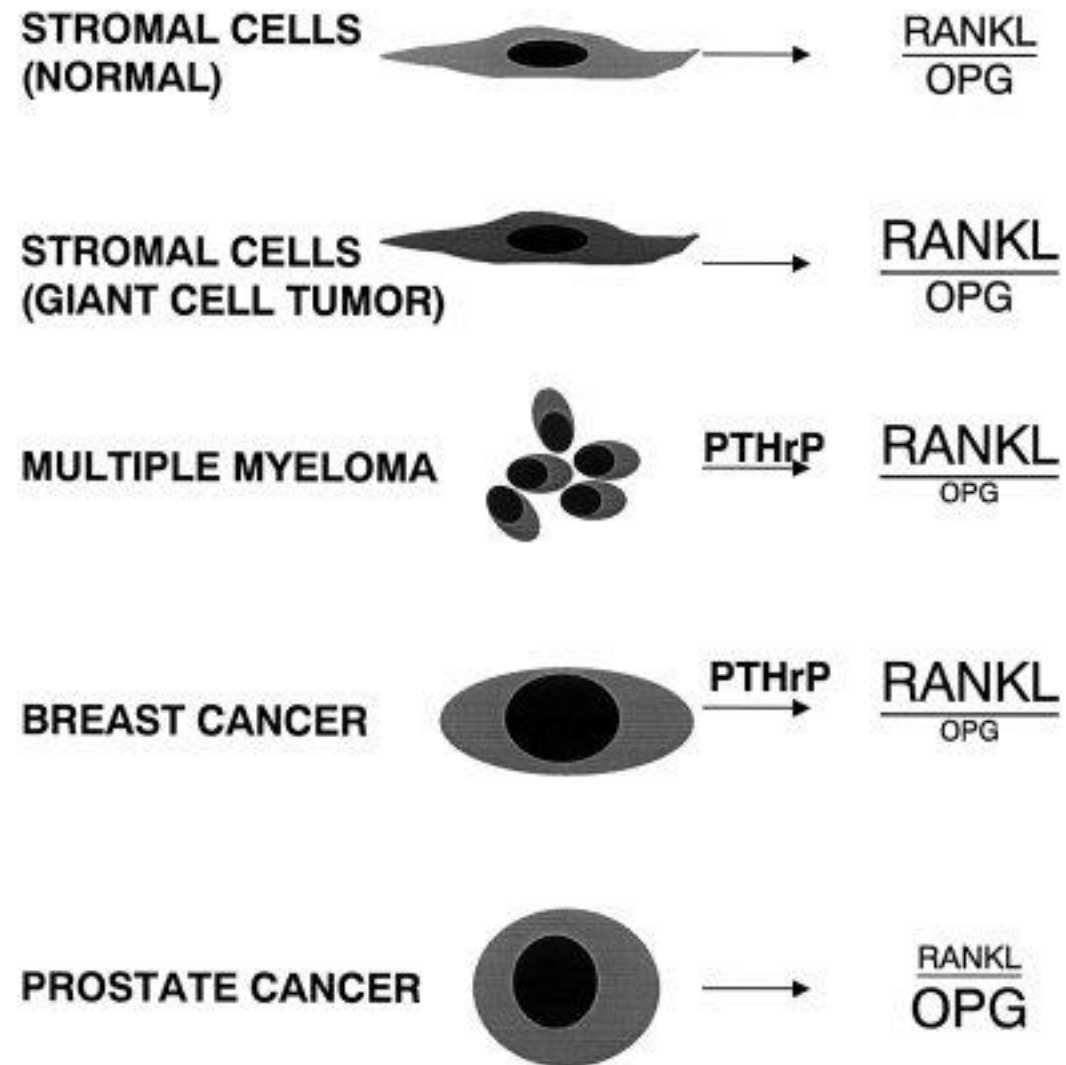
- Up to 80% of malignant hypercalcemia is caused by PTHrP released by the tumor into the systemic circulation. Given its homology to parathyroid hormone (PTH), PTHrP can mimic the action of PTH on the bones and kidneys but, unlike PTH, PTHrP does not influence intestinal absorption of calcium.
- The effects of PTHrP represent a true **paraneoplastic syndrome** (ie, systemic signs and symptoms caused by a tumor), with circulating PTHrP causing bone resorption and renal retention of calcium. Squamous cell carcinomas from the aerodigestive and genitourinary tracts commonly cause this type of “humoral” hypercalcemia but this can also be seen in breast, kidney, cervical, endometrial, and ovarian cancer.

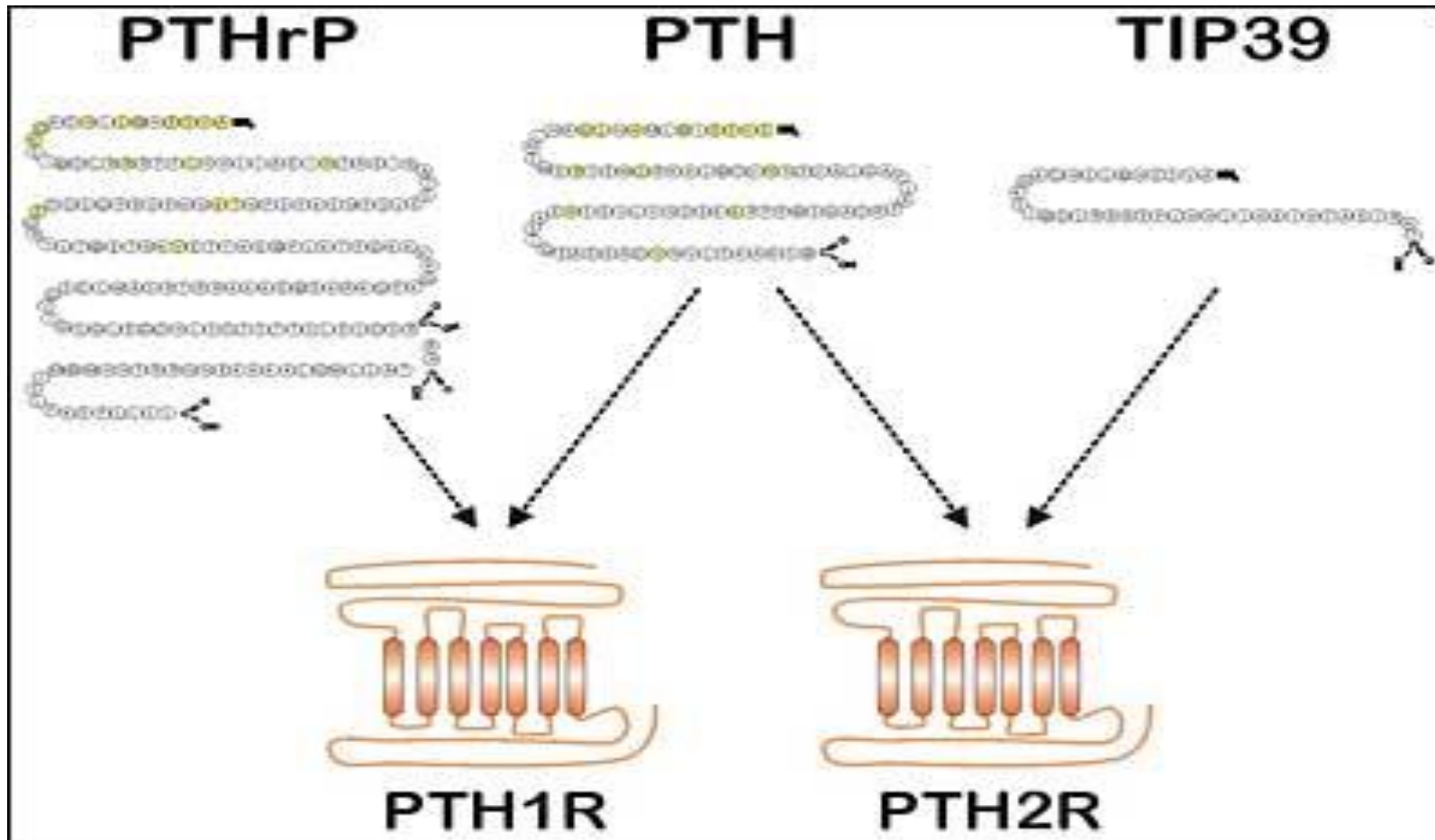
Parathyroid Hormone Relation Peptide (PTHrP)

- PTHrP was discovered as mediator of syndrome "**humoral hypercalcemia of malignancy**" (HHM).
- During the syndrome in different type of cancer (in absence of metastases) similar compounds to PTH are produced which is related to:
 - **Hypercalcemia**
 - **Hypophosphatemia**
 - **Increased cAMP excretion by urine**
- The effects are similar to those caused by PTH; no PTH levels are detected.

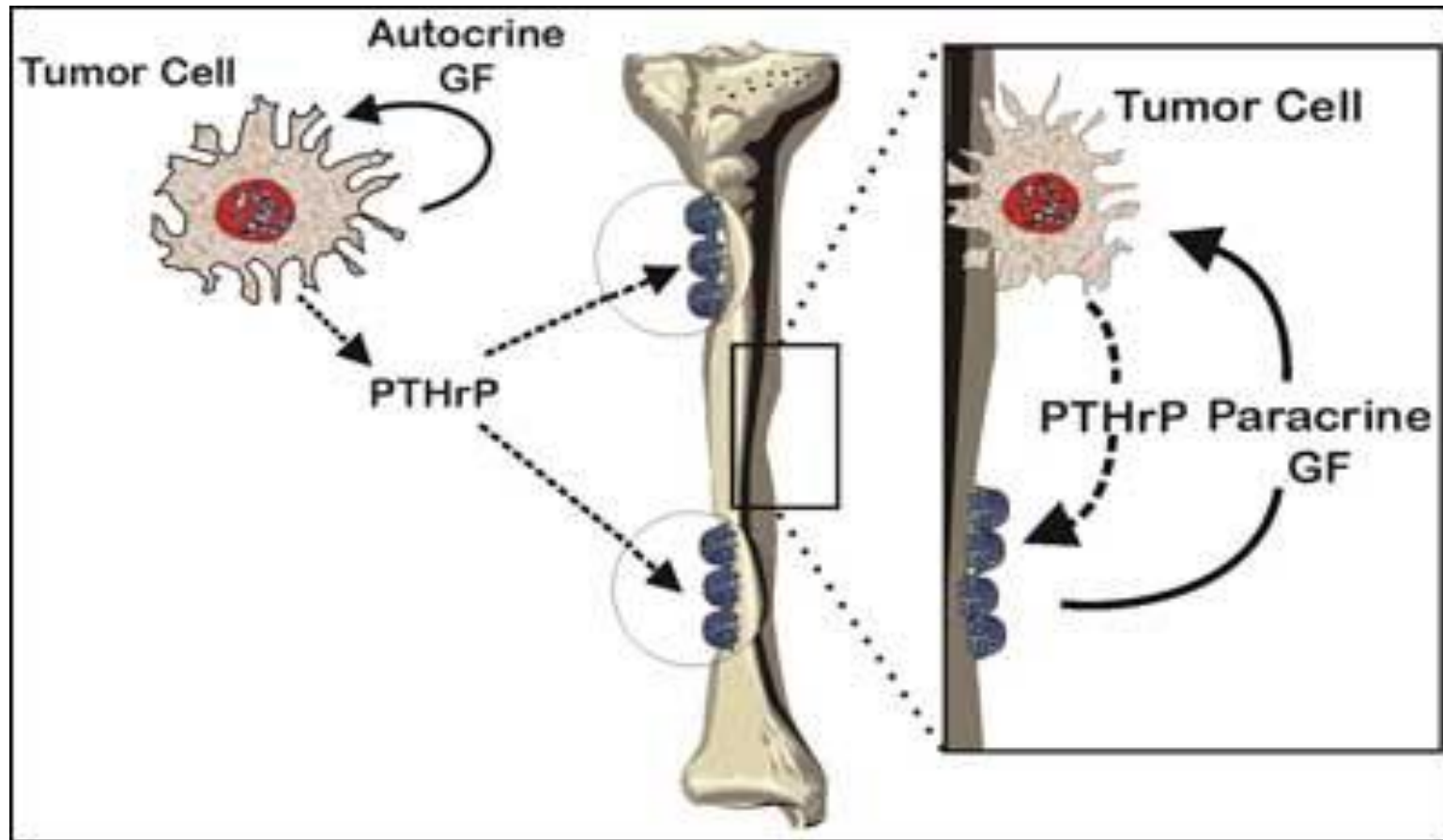
OPG/RANK/RANKL as a common effector in bone immune system and a vascular system

- OPG, RANK and RANKL are selectively produced by many cell types in different tissue: lymphocytes, osteoblasts and endothelial cells.
- RANKL is functioning as a survival factor for dendritic cells and as an osteoclastogenic factor after RANK ligation.
- OPG inhibits activation of osteoclasts by blocking RANKL/RANK interaction.
- OPG/RANKL/RANK triad is considered an **osteimmunomodulating complex**.





Genetic families of PTH and PTHrP: PTHrP, PTH and TIP39 are probably members of the same genetic family. Their receptors PTH1R and PTH2R are 7 transmembrane G protein-coupled receptors.



Production of PTHrP regulated by growth factor (GF) in tumor states. Tumor cells are able to be stimulated at a distance (outside the bone) by autocrine growth factors to an increased production of PTHrP. It reaches via circulation the bone tissue and supports bone resorption. Metastatic tumor cells in the bone are able to secrete PTHrP supporting bone resorption and paracrine growth factors which further support PTHrP production.

Oncogenic osteomalacia

- **Oncogenic osteomalacia** is a paraneoplastic syndrome in which a bone or soft tissue tumor or tumor-like lesion induces **hypophosphatemia** and **low vitamin D** levels that reverse when the inciting lesion is resected.
- In the past 15 or so years, a humoral factor, **phosphatonin**, has been identified in clinical and experimental studies as being responsible for the serum biochemical changes.
- Phosphatonin causes hyperphosphaturia by inhibiting the reabsorption of phosphate by the proximal renal tubules.
- **Fibroblast growth factor 23**, phosphate-regulating gene with homologies to endopeptides located on the 'x' chromosome (**PHEX**) and matrix extracellular phosphoglycoprotein (**MEPE**) are candidates proposed for the production of phosphatonin and the altered pathophysiology in oncogenic osteomalacia.

Symptoms of hypercalcemia

- The symptoms of hypercalcemia are nonspecific, and delayed recognition of this metabolic derangement can worsen morbidity and mortality. The mnemonic “bones, stones, moans, and groans” is used to emphasize
 - skeletal pain,
 - nephrolithiasis,
 - abdominal discomfort, and
 - altered mentation

Symptoms of hypercalcemia

- **Bone pain** is usually related to discrete metastases
- Even in the setting of profound hypercalciuria, not all patients will form **kidney stones**, which may be due to differences in the urine mineral concentration needed to precipitate calculi.
- **Abdominal pain** can arise from dysregulated intestinal motility, pancreatitis, or severe constipation.
- Changes in sensorium can occur along a spectrum from **lethargy to coma**.
- In addition, hypercalcemia **shortens the QT interval** and can produce **arrhythmias**.

Hyponatremia

- The assessment of hyponatremia in cancer patients, as in all patients, requires a critical determination of volume status.
- The sodium concentration is the largest contributor to plasma osmolarity and reflects how much water is present in the blood relative to the cells, in which the majority of the body's water is stored. Laboratory measurement of the sodium concentration thus reveals the distribution of water among the body's fluid compartments, and **hyponatremia means that intravascular water is present in excess relative to sodium, either through water retention and/or sodium loss.**

Hyponatremia

- The **amount of sodium in the body**, not the plasma sodium concentration, determines the volume of fluid outside the cells, and this volume can be readily measured by physical examination.
- If the total body sodium is high, then the extracellular fluid volume is large and the patient will appear edematous.
- If the total body sodium is low, then the extracellular space (including the circulatory volume) will contract and the patient will progressively develop **hypotension and tachycardia**.
- A low plasma sodium concentration can thereby be associated with **clinical hypervolemia, hypovolemia, or euvoemia, depending upon total sodium content**. The physician must correctly evaluate the hyponatremic patient's volume to understand both their sodium and water balance and then select the appropriate treatment.

SIADH

- Euvolemic hyponatremic patients with cancer have normal extracellular fluid volume, reflecting appropriate total sodium content, but excessive water in the intravascular space can be observed, most commonly mediated through the **syndrome of inappropriate antidiuretic hormone (SIADH)**.
- Antidiuretic hormone promotes free water uptake in the distal tubules by binding to the vasopressin 2 (V2) receptor. Compounding the problem is **continued free water** intake because the thirst mechanism is not sufficiently inhibited.

SIADH

- SIADH should be suspected based upon the location of primary and metastatic tumors because SIADH is more commonly encountered in diseases originating in or involving the **lungs, pleura, thymus, and brain**. Between 10% to 45% of patients with small cell lung cancer will show evidence of SIADH.
- Iatrogenic causes of hyponatremia include **cisplatin, cyclophosphamide, ifosfamide, the vinca alkaloids, and imatinib**. Each of these drugs can cause SIADH, but all can also produce hyponatremia through a variety of other mechanisms (eg, platinum-induced salt-wasting nephropathy), and therefore careful evaluation is required to determine the underlying etiology of hyponatremia in patients receiving these medications.
- Drugs with high emetogenic potential can stimulate ADH release through nausea, an appropriate physiologic response that may be confused with SIADH.

Hyponatremia

- Hyponatremia can be classified as **mild** (131-135 mmol/L), **moderate** (126-130 mmol/L), or **severe** (<125 mmol/L). Serum glucose should be measured to ensure that hyperglycemia is not creating a spurious finding of hyponatremia.
- SIADH is diagnosed when, after exclusion of adrenal insufficiency and hypothyroidism, the effective osmolality (calculated by subtracting [blood urea nitrogen (BUN)/2.8] from the measured osmolality) is less than 275 milliosmoles (mOsm)/kg of water, and the urine osmolality exceeds 100 mOsm/kg of water.
- Urine sodium greater than 40 mmol/L in the absence of excessive dietary sodium intake, hypouricemia less than 4 mg/dL, and BUN less than 10 mg/dL all support the diagnosis of SIADH.

Hypoglycemia

- **Hypoglycemia** can arise in the patient with cancer through several etiologies. Some tumors are capable of ectopic production of substances that affect glucose metabolism. **Insulin** is made in excess by insulinomas and nesidioblastosis.
- **Mesenchymal tumors** like sarcoma, including gastrointestinal stromal tumor and solitary fibrous tumor, can produce **insulin-like growth factors** (IGFs) such as IGF-2, which increases glucose utilization by tissues and blunts the secretion of growth hormone.
- Levels of a related protein, IGF-1, have been reported to be elevated in rare cases of **lung cancer**. Rapidly proliferating neoplasms can consume glucose prodigiously. Overexpression of the mitochondrial enzyme hexokinase II allows some cancer cells to maintain glycolysis even in the presence of oxygen.

Hypoglycemia

- In fact, this disproportionate uptake through the **Warburg effect** is exploited in fluorodeoxyglucose positron emission tomography imaging to visualize tumors against a background of normal tissue. Given the anabolic and biosynthetic demands of dividing cells, **tumors with high mitotic rates may consume glucose with sufficient briskness as to induce hypoglycemia**; this is most often seen in aggressive lymphomas (eg, Burkitt lymphoma) but has also been described in small cell lung cancer. The swift proliferation may be associated with **increased lactic acid**, even in the absence of hypoxemia. Tumors can infiltrate organs that play crucial roles in normal glucose metabolism, such as **hepatocellular carcinoma** replacing the liver parenchyma or **pheochromocytoma** overtaking the adrenal gland.

Signs and symptoms

- of hypoglycemia arise both from **neuroglycopenia** and **adrenergic counterregulation**.
- Neurologic manifestations range from confusion and blurred vision to seizures and coma.
- The catecholamine response to hypoglycemia can result in diaphoresis, palpitations, and dilation of the pupils.

Tumor Lysis Syndrome (TLS)

- Tumor lysis occurs when **cancer cells release their contents into the bloodstream**, either **spontaneously or following antineoplastic therapy**, leading to an influx of electrolytes and nucleic acids into the circulation.
- The sudden development of **hyperkalemia, ammonia, hyperuricemia, and hyperphosphatemia** can have life-threatening end-organ effects on the myocardium, kidneys, and central nervous system (CNS).
- **Hypocalcemia**, a consequence of hyperphosphatemia, is included in the constellation of metabolic disturbances known as tumor lysis syndrome (TLS).

TLS

- Patients are variably symptomatic from the metabolic derangements of TLS. Clinical TLS is diagnosed when **one or more of 3 conditions arise**:
 - **acute renal failure** (defined as a rise in creatinine to 1.5 times or more the upper limit of normal that is not attributable to medications),
 - **arrhythmias** (including sudden cardiac death), and
 - **seizures**
- Acute renal failure can manifest as a decrease in urine output, uremia-related altered sensorium, or crystalline obstructive uropathy.
- Arthralgias can arise from gout flare.

TLS

- TLS is more common in the rapidly proliferative **hematologic malignancies** such as acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and Burkitt lymphoma, but has been documented in **solid tumors**, notably small cell lung cancer, germ cell tumors, inflammatory breast cancer, and melanoma. **Liver metastases may increase TLS risk.**
- **Treatment-provoked TLS** can occur following chemotherapy, treatment with single-agent corticosteroids in patients with sensitive tumors, radiation, surgery, or ablation procedures.
The onset of TLS can be delayed by days to weeks in a patient with a solid malignancy.

Cardiovascular Emergencies

Pericardial Effusion and Cardiac Tamponade

- The pericardial sac is distensible up to a volume of 2 l, if stretching occurs over a slow time period.
- Rising intrapericardial pressure affects all 4 cardiac chambers, but the right ventricular wall is much thinner and more susceptible to extrinsic compression. Diastolic pressures throughout the chambers begin to equalize and adversely affect cardiac output by compromising filling.
- At this point, **tamponade pathophysiology** emerges.

Cardiovascular Emergencies

Pericardial Effusion and Cardiac Tamponade

- **Malignant pericardial effusions** develop through direct or metastatic involvement of the pericardial sac. Direct extension is most common in those tumors with sites of origin adjacent to the heart: lung cancer, breast cancer, and mediastinal lymphoma.
- Metastases to the epicardium are seen in noncontiguous breast and lung cancer, as well as in melanoma.
- Primary neoplasms of the pericardium are exceedingly rare, but include mesothelioma.
- Cancer treatment, especially **thoracic irradiation**, can cause transudative effusions. **Immunosuppression** can also allow suppurative infections to develop in the pericardial space.

Pericardial Effusion and Cardiac Tamponade

- Pericardial effusions can be asymptomatic, although their presence portends a poor prognosis, especially if larger than 350 mls.
- Pericarditis symptoms may precede the emergence of tamponade. Tamponade classically presents with the Beck triad: **hypotension, elevated jugular venous pressure, and a muffled precordium**. However, only a minority of patients actually demonstrate all 3 signs. Most patients complain of **dyspnea and chest discomfort, which may begin abruptly**.
- Tamponade pathophysiology can arise from volumes of as little as 100 ml if they accumulate rapidly. Even if the effusion forms over a longer period of time, the **“last drop” phenomenon** describes the critical point of pathophysiologic collapse at which intrapericardial pressure finally overcomes the compensatory mechanisms of the heart and causes cardiac output to drop precipitously. In this manner, a chronic effusion can cause hyperacute symptomatology.

Diagnosis

- The diagnostic utility of the physical examination should not be discounted but should be coupled with appropriate studies. **Tachycardia** is nearly universal, and pulsus paradoxus is an ominous finding, with a value greater than 10 mm Hg having been arbitrarily defined as abnormal.
- **Chest x-rays** may show cardiomegaly and the classic “water bottle” cardiac silhouette.
- **Electrocardiography** can show low voltage and electrical alternans from the shifting axis of the heart as it moves like a pendulum within the fluid-filled sac.
- **Echocardiography** is the definitive test, demonstrating right ventricular collapse during early diastole.

Superior Vena Cava Syndrome

- The thin-walled superior vena cava (SVC) returns all blood from the cranial, neck, and upper extremity vasculature to the right side of the heart.
- Primary or metastatic tumors can cause **compression**.
- Nononcologic etiologies include **syphilitic aortic aneurysms** (vanishingly rare since the advent of penicillin), **fibrosing mediastinitis** (classically associated with histoplasmosis), **substernal hypertrophy of the thyroid**, **granulomatous disease** (such as tuberculosis and sarcoidosis), and **thrombosis**, particularly that due to an underlying hypercoagulable state or endothelial damage from an indwelling vascular device.

Superior Vena Cava Syndrome

- The extent of SVC obstruction and acuity of development dictate the patient's presentation. Blockage is better tolerated when there has been time for collateral veins to develop in adjacent venous systems like the azygos and internal mammary, a process that usually takes weeks.
- The **veins** on the patient's chest wall may be visibly **distended**.
- **Edema in the arms, facial plethora (not necessarily unilateral), chemosis, and periorbital edema** may also occur. Stridor is an alarming sign that edema is narrowing the luminal diameter of the pharynx and larynx.
- **Hoarseness and dysphagia** can result from edema around the aerodigestive tracts.
- **Presyncope or syncope** is more common early on, when cardiac output declines without compensation.
- **Headaches** stem from distention of cerebral vessels against the dura, but confusion may indicate cerebral edema.
- All of these symptoms may be more noticeable when the patient is supine.

Diagnosis

- Cancers classically associated with SVC syndrome include lung cancer (particularly right-sided), breast cancer, primary mediastinal lymphoma, lymphoblastic lymphoma, thymoma, and germ cell tumors (either primary or metastatic to the mediastinum).
- Radiographic imaging is crucial to diagnosis and treatment planning, especially if radiation and endovascular stents are potential interventions.

Infectious Emergencies

Neutropenic Fever

- A patient's **absolute neutrophil count (ANC)** can decline through a cancer's direct interference with hematopoiesis, as in leukemia or metastatic replacement of the bone marrow, but neutropenia is most commonly seen as an effect of cytotoxic therapy.
- Other risk factors include the **rapidity of the ANC decline**; exposure to prior chemotherapy or current immunosuppression; pretreatment elevations in alkaline phosphatase, bilirubin, or aspartate aminotransferase levels; reduced glomerular filtration rate; and cardiovascular comorbidities.
- The classes of chemotherapy with the highest risk of inducing neutropenia are the anthracyclines, taxanes, topoisomerase inhibitors, platinum, gemcitabine, vinorelbine, and certain alkylators like cyclophosphamide and ifosfamide.

Neutropenic fever

- Infection is responsible for at least half of the cases of neutropenic fever. Fever is a single oral temperature of 38.3°C (101°F) or higher, or temperatures of 38.0°C (100.4°F) or higher measured 1 hour apart.
- A patient's reduced ability to mount an inflammatory response can limit localizing signs and symptoms, and therefore fever may be the only abnormal finding at presentation. Skin and soft tissue infections may not be associated with erythema or induration, and abscesses will not accumulate in the absence of pus-generating neutrophils. Pulmonary infections may not result in audible or radiographically visible.

Infectious Emergencies

- A minority of cases of febrile neutropenia will have an offending infectious agent identified. Of those that do have a documented infectious source, a variety of organisms can be responsible.
- **Gram-positive cocci**, which are now responsible for the majority of culture-positive cases of neutropenic fever, include *Staphylococcus aureus*, *Staphylococcus epidermidis* (especially in patients with indwelling devices), *Streptococcus pneumoniae*, *Streptococcus pyogenes*, the *Streptococci viridans*, and *Enterococcus faecalis* and *faecium*. *Corynebacterium* is the most likely gram-positive bacillus.
- **Gram-negative bacilli** include *Escherichia coli*, *Klebsiella* species, and *Pseudomonas aeruginosa*.
- **Candida** is the most common fungal infection, but *Aspergillus* and *Zygomycetes* are more feared for their angioinvasive predilection.

Neurologic Emergencies

- **Malignant spinal cord compression (MSCC)** was first described in 1925 by Spiller and remains a common oncologic emergency that requires prompt treatment to relieve pain and preserve neurological function.
- Although all tumor types have the potential to cause MSCC, breast, prostate, and lung cancer each account for approximately 15% to 20% of the cases, with non-Hodgkin lymphoma, renal cell carcinoma, and myeloma each causing 5% to 10% of cases.
- Although most cases of MSCC occur in patients with a known diagnosis of malignancy, **5% to 25% of MSCC cases occur as the initial presentation of malignancy.**

Neurologic Emergencies

- MSCC is defined as the compressive indentation, displacement, or encasement of the thecal sac that surrounds the spinal cord or cauda equina by cancer.
- **Compression** can occur by posterior extension of a vertebral body mass, by **anterior extension** of a mass arising from the dorsal elements, or by **growth of a mass invading the vertebral foramen**.
- The majority of the cases occur when metastatic tumor reaches the vertebral bodies via hematogenous spread, with secondary erosion into the epidural space.

Neurologic Emergencies

- Early detection is critical because the single most important prognostic factor for regaining ambulation after treatment of MSCC is pretreatment neurologic status.
- The clinical presentation of MSCC can vary significantly depending on severity, location, and duration of the compression.
- The most common initial symptom is **back pain**, which occurs in approximately 90% of the cases. Because back pain is a common symptom and has multiple causes, clinicians must always keep MSCC in their differential diagnosis. It is also important to remember that **MSCC can be the initial presentation of malignancy**. In a retrospective series of 337 patients with MSCC at the Mayo Clinic, compression was the first sign of malignancy in 20% of the cases, with lung cancer, multiple myeloma, and non-Hodgkin lymphoma accounting for approximately 75% of these initial presentations manifested by spinal epidural metastases.
- The back pain associated with MSCC may gradually worsen over time and usually **precedes neurologic symptoms by weeks to months**. Referred pain is common and varies according to the location of the offending lesion. Cervical compression can present as subscapular pain, thoracic compression as lumbosacral or hip pain, and lumbosacral compression as thoracic pain.6

Neurologic Emergencies

- Once symptoms other than pain are present, the progression can be quite rapid. These symptoms include **motor weakness, sensory impairment, and autonomic dysfunction**. **Cauda equina syndrome** may present as urinary retention and overflow incontinence (90% sensitivity and 95% specificity). Other symptoms include decreased sensation over the buttocks, posterior superior thighs, and perineal region.
- Physical examination findings depend on the location of the lesion(s) as well as the degree and duration of impingement.
- Most patients have tenderness to percussion over the affected spinal region.
- The Valsalva maneuver may worsen their back pain.
- Hyperreflexia, spasticity, and loss of sensation (position, temperature, pinprick, and vibratory) can occur early.
- Deep tendon reflexes may then become hypoactive or absent.
- Late signs include weakness, Babinski sign, and decreased anal sphincter tone.

Malignant spinal cord compression (MSCC)

Because there is no clinical model to rule out MSCC in cancer patients with back pain, all reports of new-onset back pain should prompt an immediate assessment. For those patients with only back pain and a normal neurologic examination, imaging of the spinal axis should be completed within the next 48 to 72 hours. Those with neurologic deficits need emergent evaluation before nerve damage becomes permanent. The gold standard for the diagnosis of MSCC is **MRI, with a sensitivity of 93%, a specificity of 97%, and an overall accuracy of 95%.**

Increased Intracranial Pressure

- Elevated intracranial pressure (ICP) secondary to malignancy in the brain can cause devastating neurologic injury. Successful management requires prompt recognition and therapy. The vast majority of all intracranial neoplasms are metastatic, with lung cancer (20%), breast cancer (5%), melanoma (7%), renal cancer (10%), and colorectal cancer (1%) being the most common tumors of origin.
- Untreated patients have a median survival of approximately 4 weeks.

Increased Intracranial Pressure

- The majority of metastases travel to the brain via hematogenous spread.
- Tumor microemboli tend to lodge in the distal arteries and small capillaries of the “watershed” areas and the gray-white matter junctions. The distribution of metastases also follows the relative blood flow volume of the brain, with most occurring in the cerebrum, then the cerebellum, followed by the brainstem.
- Increased ICP is due to both the **mass effect of the tumor as well as cerebral edema caused by neoplastic disruption of the blood-brain barrier**, which is caused in part by local production of vascular endothelial growth factor (VEGF).

The clinical presentation of brain metastases

- will vary depending on the location, size, and rate of growth of the tumor. In a series of 111 patients with brain metastases, the most common presentation was **headache**, seen in 48% of patients and most often described as tension (in 77%).
- In contrast to benign tension headaches, however, these headaches tended to worsen with bending over or with Valsalva maneuvers, and in many cases were also accompanied by **nausea or emesis**.
- **The “classic” tumor-associated headache pattern, consisting of an early morning headache that improves during the day, occurred in only 36% of the cases.**
- **Seizures** range from 10% to 20% in incidence and are almost exclusively caused by supratentorial lesions.
- **Strokes** occur if the tumor embolizes, bleeds, or compresses an artery. Melanoma, choriocarcinoma, thyroid cancer, and renal cell carcinoma are more likely to cause hemorrhagic strokes.
- **Focal neurologic dysfunction** is dependent on the location of the lesion. Clinicians must consider brain metastases in patients with cancer who report new or changing headaches, focal neurologic changes, or cognitive changes. A physical examination should be performed to evaluate for focal neurologic deficits and papilledema.
- The triad of signs referred to as the Cushing response (hypertension with wide pulse pressure, bradycardia, and an irregular respiratory rate) is a late effect and indicates impending herniation.

Diagnosis

- Once an intracranial malignancy is suspected, contrast-enhanced MRI is the preferred method of diagnosis.
- Contrast-enhanced MRI is more sensitive than either nonenhanced MRI or CT scanning in differentiating metastases from other CNS lesions.
- Noncontrast CT scan is the preferred scanning technique, however, in an acute situation when hemorrhage or hydrocephalus is suspected.

Seizures

- Seizures are the presenting symptom of intracranial metastases in 10% to 20% of patients with intracranial involvement.
- Seizures may or may not be associated with ICP.
- Status epilepticus requires emergent treatment.

Hematologic Emergencies

Hyperviscosity Syndrome

- **Hyperviscosity syndrome (HVS)** refers to the clinical sequelae caused by increased blood viscosity. Increased serum viscosity (SV) is a result of **excess proteins, usually immunoglobulins (Igs)**, most commonly arising from **Waldenström macroglobulinemia (WM) (85%) and multiple myeloma (MM)**.
- Increased blood viscosity can result from elevated cellular components seen in hyperproliferative states such as **leukemia and myeloproliferative diseases** such as **polycythemia vera (PV)**.

Hematologic Emergencies

Hyperviscosity Syndrome

- Similarly, **polycythemia vera (PV)** can cause elevated blood viscosity due to increased red blood cell mass.
- PV can cause vascular symptoms and complications secondary to thrombocytosis with platelet hyperaggregability, leukocytosis, and/or high hematocrit, causing elevated blood viscosity. A decrease in cerebral blood flow and a **high incidence of thrombotic complications** are seen in these patients.

Hyperviscosity Syndrome

- In normal healthy subjects, **hematocrit** is the main determinant of blood viscosity, with **fibrinogen** being the main determinant of plasma viscosity due to a combination of its large size, asymmetric shape, charge, and concentration, even though albumin is the most abundant protein in the blood.
- In **paraproteinemias**, such as WM and MM, excessive amounts of circulating **Igs** are produced. IgM is the largest Ig (molecular weight, 1,000,000) and is the most likely paraprotein to cause hyperviscosity, but HVS has also been documented in cases of MM or kappa light chain disease.
- As the concentration of Igs increases, they form **aggregates** and bind water via their carbohydrate content, which **causes a rise in oncotic pressure and increases the resistance to blood flow**. Igs are positively charged and therefore decrease the repellant forces between the negatively charged red blood cells. When present in excess, these proteins electrostatically bind to the red blood cells, causing rouleaux formation as well as decreasing the red blood cell malleability. Eventually, this leads to impaired transit of blood cells, microvascular congestion, decreased tissue perfusion, and subsequent tissue damage.

HVS

- The “classic triad” of HVS includes **neurologic abnormalities**, **visual changes**, and **bleeding**, although all 3 need not be present to make the diagnosis.
- Hyperviscosity causes impaired microcirculation in the brain that manifests itself in the form of headache, altered mental status, nystagmus, vertigo, ataxia, paresthesias, seizures, or even coma.
- Ophthalmologic examination can detect hyperviscosity, revealing dilated, engorged veins that resemble “sausage links,” a finding known as fundus paraproteinaemicus. If untreated, this will progress to **complete retinal vein occlusion and flame-shaped hemorrhages**.
- Mucosal bleeding and purpura are also common clinical manifestations of HVS, with proteins coating the platelets and hindering their function.
- Other clinical consequences of HVS include congestive heart failure, ischemic acute tubular necrosis, and pulmonary edema, with multiorgan system failure and death occurring if treatment is not promptly initiated.

Leukostasis

- Leukostasis is a hematologic emergency that is associated with **respiratory failure, intracranial hemorrhage, and early death**. If it is not recognized and treated promptly, the mortality rate can be as high as 40%.
- Risk for leukostasis **increases with a white blood cell count (WBC) greater than 100,000/mm³**. The incidence ranges from 5% to 13% in patients with AML and 10% to 30% in adult patients with ALL.
- Other risk factors include younger age (with presentation in infants being most common); ALL with 11q23 rearrangement or the Philadelphia chromosome; and AML subtypes M3, M4, and M5.
- Hyperleukocytosis portends a poor prognosis, with a higher risk of early mortality, especially in patients with ALL. The WBC count is the most important prognostic factor in ALL, and patients who present with a WBC greater than 50,000/mm³ have a particularly poor prognosis; very few children with hyperleukocytosis become long-term survivors

Leukostasis

- The pathophysiology of leukostasis is not completely understood. There is believed to be a component of “sludging” by the leukemic blasts in the microvasculature secondary to increased whole blood viscosity.
- On average, the leukemic myeloblasts have a mean cell volume that is almost twice that of the leukemic lymphoblasts and therefore the manifestations are more common in patients with AML than those with ALL. There is also differential expression of adhesion molecules on the lymphoblast and myeloblast cells that has been implicated in the higher incidence of leukostasis noted in patients with AML versus patients with ALL.
- Evidence also suggests that there are leukemic blast/endothelial cell interactions that lead to vascular wall disruption as well as complement-induced granulocyte aggregation.
- In general, whole blood viscosity is not dramatically increased in leukostasis because the rise in the WBC is often counterbalanced by a decrease in the erythrocyte count. This is important to recognize because packed red blood cell transfusions in patients with asymptomatic hyperleukocytosis can rapidly lead to leukostasis.

Leukostasis

- can involve any organ system, but the initial symptoms most commonly are related to the respiratory system and the CNS.
- Pulmonary symptoms can range from exertional dyspnea to severe respiratory distress, with diffuse interstitial or alveolar infiltrates often present on chest x-ray, although these are not required for the diagnosis.
- Neurologic manifestations span the spectrum from mild confusion to somnolence. Patients commonly report headache, dizziness, tinnitus, blurred vision, or visual field defects. Physical examination can reveal papilledema, retinal vein bulging, and retinal hemorrhage. Intracranial hemorrhage can present with focal neurologic deficits.
- Other symptoms include myocardial infarction, limb ischemia, renal vein thrombosis, and disseminated intravascular coagulation.
- Fever is almost always seen and can be greater than 39°C. Although infection is found in only a few cases, it does need to be ruled out because this syndrome can mimic sepsis.
- Thrombocytopenia is also usually present and underestimated because WBC fragments can be counted as platelets in some automated cell counters.
- Disseminated intravascular coagulation is often seen in association with this syndrome, most commonly in the M3 subtype of AML, although it can occur in all types of leukemia.

Respiratory Emergencies

– Malignant Airway Obstruction

- Airway obstruction can be caused by virtually any malignancy, but the most common culprits include **tumors of the tongue, oropharynx, thyroid, trachea, bronchi, and lungs.**
- Mediastinal tumors such as lymphomas and germ cell tumors can also cause airway obstruction, more commonly in the pediatric population.
- Primary bronchogenic carcinomas are the most common cause of malignant airway obstructions, and up to 30% of patients with primary lung tumors will develop airway obstruction. Airway obstruction does not appear to adversely affect overall survival, with a median survival of 8.2 months versus 8.4 months when comparing patients with airway obstruction with those without.
- Prompt recognition and treatment can lead to a markedly improved quality of life, with up to 95% of patients reporting a decrease in dyspnea and a significant increase in quality of life after treatment.

Malignant Airway Obstruction

- Airway obstruction may result from external compression of the trachea or bronchi by the tumor, or by an involved lymph node.
- The obstruction can also occur by infiltration of the tumor within the oropharynx, trachea, and bronchi, causing severe narrowing.
- The clinical manifestations of malignant airway obstruction depend on the severity and location of the obstruction. The symptoms are nonspecific and can be mistaken for more common conditions including chronic obstructive pulmonary disease exacerbations, asthma, or bronchitis.
- The most common presentation of malignant airway obstruction is **dyspnea**. The symptoms usually worsen at night and while lying supine.
- Patients will often have a productive cough and wheezing, and may also present with stridor, especially if the obstruction is located in the trachea or carina. In these cases, the symptoms may be quite minimal until the airway is critically narrow, but then appear rapidly and pose a life-threatening situation.

Chemotherapeutic Emergencies

Extravasation of Chemotherapy

- Extravasation, defined as the unintended leakage of the chemotherapy drug into the extravascular space, is a dreaded complication of chemotherapy administration
- **Vesicants** are chemotherapy agents that have the ability to induce tissue necrosis, resulting in functional impairment and disfigurement. Vesicants include the anthracyclines, vinca alkaloids, and mitomycin C.
- **Irritants** such as the platinum compounds, taxanes, and topoisomerase I inhibitors cause an inflammatory reaction but not tissue necrosis. This classification is not absolute because the severity of tissue injury is dependent on drug concentration and volume. For example, platinum compounds or taxanes can behave like vesicants and induce ulcerations at high concentrations or at large volumes.
- **Nonaggressive agents** are drugs that rarely cause any reaction when extravasation occurs.
- The frequency of extravasation in adults is estimated to be between 0.1% to 6% of peripheral iv infusions and somewhat less in implanted venous access port infusions.

Chemotherapeutic Emergencies

Extravasation of Chemotherapy

- Extravasations vary in their clinical presentation and severity. Symptoms may occur immediately after the incident or develop in subsequent days or weeks.
- In most cases, initial symptoms include **pain, blistering, induration, and discoloration.**
- **Ulceration** may not appear for several days and may continue to worsen for months, as the drug diffuses into the adjacent tissue. In severe cases, **necrosis of the skin and the underlying tissues** may develop, leading to infection, scars, treatment delay, functional deficits, amputation, and, rarely, death.
- In the case of **irritant extravasation, symptoms include erythema, swelling, and tenderness.** **Phlebitis, hyperpigmentation, and sclerosis** can subsequently develop along the vein. These symptoms usually resolve within weeks and long-term sequelae are extremely rare.
- Patients with small, deep veins or those with damaged veins secondary to multiple venipunctures are at higher risk, as are patients with neurologic deficits because of an inability to follow instructions or secondary to an impaired ability to detect changes in sensation. Obesity and movement during chemotherapy administration also increase the risk of extravasation.

Chemotherapeutic Emergencies

Extravasation of Chemotherapy

– Diagnosis

- Extravasation is usually diagnosed by local symptoms of **pain, erythema, and swelling**, or by **leakage of fluid around the iv site**, but a change in the rate of infusion or absence of blood return from the vascular access may be the initial sign.
- Once suspected, even if asymptomatic, the infusion needs to be discontinued and treatment initiated immediately.

Anaphylactic Reactions to Chemotherapy

- Essentially any chemotherapeutic agent has the potential to cause an infusion reaction, which can range significantly in severity. These are often called hypersensitivity reactions; however, because some do not have a hypersensitivity component, they are more properly termed **infusion reactions**.
- **Anaphylaxis** is defined as a serious allergic reaction that is rapid in onset and may cause death. It is rare with most conventional cytotoxic agents, although it is well established with platinum drugs and the taxanes. Other agents known to commonly cause infusion reactions include cyclophosphamide, ixabepilone, bleomycin, L-asparaginase, and monoclonal antibodies such as rituximab.

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