Malignant transformation of the cell - cancer

Cell cycle control
Oncogene × suppressor genes/proteins
Principle of malignant transformation
Interaction of tumor and organism
Metastases

Cancer – basic facts

- Pathological process (disease) due to impaired control of cell cycle and thus cell division
  - if genes that control the orderly cell replication become damaged it allows the cell to reproduce without restraint
    - our genome is constantly attacked by mutagens, but fortunately most of the alterations are harmless, i.e. become repaired or affects genes not critical for cell division
  - it might eventually spread into neighbouring tissues and set up secondary growths throughout the body (metastases)
  - the reason for this dys-regulation is genetic – mutations of originally just 1 somatic cell (but also germline in some cases)
    - tumor classification according to the growth rapidity
      - benign – grow only in the site of origin, not aggressive, maintain differentiation
      - malignant – rapid growth, invasive, spreading to other places, undifferentiated

- All types of cancers are due to genetic alteration of key genes controlling cell cycle
  - however, only a few are inherited (i.e. familiar) = due to the mutation in germ line cell
  - majority of cancers are due to the acquired genetic changes during the life (i.e. sporadic) = due to the mutation in somatic cell

- Key genes controlling cell cycle
  - (proto)oncogens – genes that normally potentiate cell division and growth under the physiologic stimuli, if mutated process becomes uncontrolled and spontaneous
  - suppressor genes – genes that normally inhibit cell division, initiate DNA repair or apoptosis, if mutated growth becomes uncontrolled and resistant to apoptosis
  - DNA repair genes – genes encoding enzymes that can repair reparable DNA damage occurring due to the environmental or endogenous agents (e.g. UV light, oxygen radicals), if mutated unrepaired alteration can be transmitted into daughter cells

- Genetic alteration can appear
  - (1) due to internal errors during DNA replication and cell division
  - (2) as a consequence of exposure to the external factors (carcinogens)
    - physical – e.g. UV and ionising light
    - chemical – organic substances, toxins, heavy metals
    - biologic – e.g. RNA and DNA viruses

- Tumor usually stems from a mutation in a single cell (monoclonal)
  - tumor cell transformation is a multistep process (i.e. subsequent accumulation of mutations), therefore, tumor becomes genetically heterogeneous

- Histologically – based on the original tissue – 3 groups can be distinguished
  - epithelial
    - skin, mucose membranes, ductal lining
    - papilloma, adenoma (b.), carcinoma (m.)
  - mesenchymal
    - connective tissue, endothelia, muscle, hematopoietic and lymphatic tissue, bone
    - fibroma, haemangiomia, myoma (b.), sarcoma, lymphoma, leukaemia (m.), ...
  - neuroectodermal
    - CHS and peripheral nerves, pigment nevi
    - astrocytoma, glioma, epidermoid, neurinoma, melanoma
Gradual change of cellular phenotype

Cell cycle (CC)
- most of the somatic cells grows, double the amount of cell organelles and divide = cell cycle
- CC (4 phases)
  - Interphase
    - cell growth (G1-phase)
    - DNA replication (S-phase)
    - additional growth (G2-phase)
  - mitosis (M-phase)
- duration of CC is very variable in different cell types
  - hours in enterocytes
  - months in liver cells
  - life time in neurons (in G0-phase)
- G1-phase has the most variable length
  - CC is naturally inhibited in G1 (growth arrest)
    - by contact inhibition
    - by products of suppressor genes
- CC is highly regulated by very often counteracting
  - internal factors – e.g. inhibition by suppressor proteins
  - external factors – e.g. stimulation by growth factors
- cancer = dysregulation of CC
- cell cycle carries on only if
  - all phases proceed without errors
  - 3 check points
    - energy is available
    - external stimuli (growth factors) are acting

CC phases

G0
Resting phase. Cell perform its function, maintain basal metabolism and does not divide.

G1
Interval between previous Mitosis and subsequent Synthesis (= DNA replication). Intensive synthesis of all sorts of RNAs in the nucleus. Proteosynthesis in the cytoplasm and overall cell growth. G1 duration basically determines the CC length. G1/S check point (= favourable conditions and energy supply, intact DNA)

S
DNA replication in the nucleus and histone synthesis in the cytoplasm. At the and the cell contains doubled the amount of DNA.

G2
Interval between previous Synthesis and subsequent Mitosis. Cell further grows and synthesises protein (mainly tubulin and other proteins necessary for mitotic apparatus). G2 check point (= completeness and correctness of DNA replication).

M
Mitosis (6 phases) – first 5 (prophase, prometaphase, metaphase, anaphase, telophase) represent division of nucleus, the last one (cytokinesis) division of the whole cell. M (spindle) check point (= correct formation of mitotic spindle in metaphase/anaphase transition)

CC check points and mitosis

Interphase
- All chromosomes
- Cell growth

Prometaphase
- Nuclear envelope breaks down
- Chromosomes align at midpoint of cell

Metaphase
- Chromosomes align at midpoint of cell

Anaphase
- Sister chromatids separate

Telophase
- New cells formation

Cytokinesis
- Two daughter cells formed
CC regulatory proteins

- **(A) products of (proto)oncogenes**
  - growth factors
  - receptors for growth factors
  - G-proteins (e.g. Ras)
  - membrane tyrosine kinases (e.g. abl)
  - other cytoplasmic proteins (e.g. Raf)
  - transcription factors (e.g. jun, fos, myc)
  - cyclins
  - cyclin-dependent proteinkinases (cdk)

- **(B) products of suppressor genes**
  - Rb
  - p53
  - p21
  - ...

- **(C) products of genes encoding DNA repair enzymes**
  - mismatch repair
  - excision repair
  - homologous recombination

### (A) Protooncogenes

- **(1) growth factors (GF)**
  - GF acts in extremely low concentrations in a paracrine fashion
  - e.g. TGF-β, PDGF, EGF, FGF, VEGF, erythropoietin
  - different target cells according to the expression of specific receptors

- **(2) GF receptors**
  - extracellular, transmembrane and cytoplasmatic domain
    - usually with tyrosinekinase activity

- **(3) G proteins (= GTP-ases, e.g. Ras)**

- **(4) other cytoplasmic factors**
  - Tyr-kinases (Src, Abl, …)

- **(5) transcription factors/ early-response genes**
  - e.g. fos, jun a myc (= products of protooncogenes fos, jun and myc)
  - regulate transcription of late-response genes

- **(6) late response genes (~1 hrs) = cyclins**
  - expression of cyclins and cdk under the stimulation with fos, jun, myc regulatory proteins

- **(7) cyclin-dependent kinases (cdk)**
  - 9 types – cdk1 to cdk9

  - only complex of cdk with cyclin is active
  - activate target proteins by phosphorylation of Ser and Thr
    - e.g. Rb-protein
  - normally present in the complex
  - cyclin
  - cdk
  - PCNA (Proliferating Cell Nuclear Antigen)

- **(8) anti-apoptotic factors**
  - e.g. Bcl-2, Bcl-X

- **(9) others (e.g. β-catenin)**

### (A) Protooncogenes - summary

- **(6) cyclins**
  - 8 types – A, B, C, D, E, F, G, H
  - specific for particular CC phases

- **(7) cyclin-dependent kinases (cdk)**
Cyclin / cdk interplay

Summary of the protooncogenes

(B) Suppressor genes
- encode proteins arresting CC, activating DNA repair and apoptosis
  - (1) Rb protein (ch. 13q14)
    - pocket protein family member
    - principal negative regulator of CC, controls the G1-S-phase transition, activity modulated by de-/phosphorylation (by cdk4/6 + cyclin D complex)
    - mutations in Rb (microdeletions) predispose to the retinoblastoma
  - (2) p53 protein (ch. 17p13)
    - "guardian of the genome" – active in G1 and G2 checkpoints
    - DNA damage increases expression of p53
    - act as a transcription factor for DNA repair and apoptosis genes
  - (3) Inhibitors of cyclin-dependent kinases (e.g. p21, p27, p16, ...)
    - p21 is the main target of p53, inhibitor of Cdk – CC arrest in G1 phase by inhibition of Cdk2/cyclin E complex
  - (4) pro-apoptotic genes
    - family of Bcl genes (Bax, Bak, Bad, ...)
  - (5) other, e.g. inhibitory transcription factors, M-spindle checkpoint, Wnt pathway etc.
- inherited mutations in suppressor genes can confer susceptibility to the inherited (familiar) forms of cancer
  - very often named according to the type of tumor developing due to their mutation
    - Rb (= retinoblastoma)
    - WT (= Wilm's tumor)
    - NF1 and NF2 (= neurofibromatosis)
    - APC (= Adenomatous Polyposis Coli)
    - DCC (= Deleted in Colon Cancer)
    - VHL (= von Hippel-Lindau syndrome)

Rb protein (Rb/E2F G1 checkpoint)
- Rb is a main inhibitor/regulator of CC
  - binding to the transcription factor E2F, which upon release from Rb↑ expression of S-phase genes (e.g. DNA replication enzymes, PCNA, ...)
- Rb controls the transition from G1- to S-phase
- Rb is present all the time, however, its activity is modulated by de-/phosphorylation by MAPK/cdk pathways
  - phosphorylated Rb = inactive
  - dephosphorylated Rb = active
Partial summary – CC “kick-off”

- Mitogens drive CC progression by induction of cyclin D and inactivation of the retinoblastoma (Rb) protein
  - CC is driven by the coordinated activation of CDKs (expressed throughout the CC) and their activating subunits – the cyclins (oscillating between rapid synthesis and degradation).
  - The interface between mitogens and the cell cycle is cyclin D (and to a lesser extent cyclin E), whose expression is induced by mitogens.
  - Cyclin D- and cyclin E-dependent kinases phosphorylate and thereby disable the Rb tumor suppressor protein, which is a principal checkpoint controlling the progression from G1 to S phase.
  - Inactivation of the Rb protein marks the restriction point at which cell-cycle progression becomes independent of mitogens.
  - Inactivated Rb releases E2F transcription factors, which stimulate the expression of downstream cyclins and other genes that are required for DNA synthesis.

Protein p53 (ch. 17p13)

- Nuclear protein, active as a phosphorylated tetramer, acts as a transcription factor.
- Main controller of genome stability.
- If DNA is mutated or incompletely replicated p53 becomes activated and:
  - Upregulation of CC inhibitors → temporary CC arrest in G1/S checkpoint enabling DNA repair (‘major repair’).
    - p51 (WAF1 gene) → p21 protein
  - Upregulation of GADD45 (Growth Arrest and DNA Damage) → DNA excision repair
    - Bax expression → apoptosis
- p53 mutations are the most frequent genetic abnormality found in human cancer.
  - ~50% of all cancers!!!
  - There are also some familiar forms of cancer due to inherited p53 heterozygous mutations.
    - LOH mechanism

p53 tumor suppression

- A negative regulatory feedback loop controls cellular levels of p53. In normal cells, p53-dependent transcription of MDM2 promotes p53 degradation.
- Cellular stress, such as oncogene activation, induces p14ARF, which sequesters MDM2.
- In addition, DNA damage and chemotherapeutic agents activate protein kinases, such as ATM and ATR, which, through DNA-dependent protein kinase (DNA-PK) and casein kinase II (CKII), respectively, phosphorylate the amino terminus of p53 to prevent MDM2 binding, and the carboxyl terminus of p53 to increase sequence-specific DNA binding.
- These events increase p53 levels and activate the transcription of p53 target genes.
  - p21 and 14-3-3 promote growth arrest at the G1 and G2 DNA-damage checkpoints by inhibiting cyclin-dependent protein kinase (CDK) activity.
  - FAS, BAX, and p53AIP promote apoptosis if repair is not possible.
  - And GADD45 promotes DNA repair.

Apoptosis

- Type of active (=energy requirements), programmed cell death affecting isolated cells.
- Induction of apoptosis.
  - Extrinsic (receptor) pathway:
    - Death receptors (FAS, TRAIL) and their ligands (TNFα, LTA, TRAIL) → DISC (death-inducing signaling complex)
    - Tc lymphocytes and NKbb. (granzyme)
    - Absence of growth stimuli
  - Intrinsic (non-receptor) pathway – mitochondria having the main role
    - ROS, hypoxia, DNA damage, starvation, ...
    - Permeabilisation of mitoch. membrane (Bax, …), release of cytochrome-c and Ca2+
    - Formation of apoptosome in cytoplasma - cytochrome-c + Apaf + Ca ions and activation of “upstream” caspases (pro-caspase 9)
  - Both pathways converge on the level of caspase 3, both regulated by Bcl family members.
    - Anti-apoptotic (Bcl-2, Bcl-X, …)
    - Pro-apoptotic (Bax, Bak, Bad, …)
  - Execution of apoptosis:
    - Caspases (cystein aspartases)
      - Upper caspases (receptor path c-8, non-receptor path c-9)
      - Lower caspases (3, 6, 7)
    - Substrates: cytoskeleton, membrane proteins
    - Endonucleases
      - Fragmentation of DNA
  - Morphology of apoptosis
    - Rounding of cell
    - Budding/blebbing
    - Apoptotic bodies
Apoptosis-initiating pathways

EXTRINSIC PATHWAY
- Ligands: TNF-α, LTA, TRAIL, Fas-L
- Adaptor proteins (FADD, TRADD, ...)
- Caspase activation
- Proteolysis (nuclear membrane, cytoskeleton, ...)

INTRINSIC PATHWAY - mitochondria-related
- ER-related
- Initiators (Bcl-2, Bcl-X, ...)
- Pro-apoptotic proteins (e.g., cytochrome c)
- Caspase activation
- Proteolysis (nuclear membrane, cytoskeleton, ...)

Formation of apoptosome and convergence of both pathways

(C) DNA repair (stability) genes

1. MMR genes/proteins ("Mismatch repair")
   - Enzymes can repair erroneous base pair defects in respective genes leading to the microsatellite length instability (MIN)
   - Example is HNPCC (Hereditary Non-Polyposis Colon Cancer)
2. Excision repair (single strand break)
3. Genes of homologous recombination
   - Main pathway activated on DNA damage (double strand break) involves:
     - BRCA1 and BRCA2
     - ATM and ATR (ATM-related) kinases
     - CHK2 and CHK1 checkpoint kinases
6. Inborn defects lead to several forms of familiar cancers
   - Ataxia telangiectasia
   - Bloom syndrome
   - Fanconi anemia
   - Xeroderma pigmentosum
   - Fragile X syndrome
Mitotic (spindle) checkpoint

- majority of tumor cells show aneuploidy
  - consequence of failure of M-spindle checkpoint = chromosome non-disjunction
  - aneuploidy contributes to further chromosome instability and cancerogenesis
  - higher dose of oncogene or loss of tumor suppressor, ...
- marker of poor prognosis
- higher risk of cancer in syndromes of constitutive aneuploidy (e.g. Down syndrome, ...)
- M-control is assisted by tumor supresor APC
  - mutated in familiar multiple adenomatous polyposis syndrome (FAP)

Process of cancer transformation

- mutations in critical DNA positions contributing to CC regulation as a result of:
  - exposure to mutagens / carcinogens
  - spontaneous error during replication
- mutation with carcinogenic potential leads to:
  - hyperactivity of proto-oncogene (transformation to oncogene)
    - „gain of function” = dominant effect (i.e. single mutated allele sufficient to produce pathologic phenotype)
  - inactivation of suppressor or DNA repair genes
    - „loss of function” = recessive effect (i.e. both alleles have to be mutated)
    - either sporadic mutation in somatic cell or one dysfunctional allele already in germ line cell (see familiar cancer predisposition further) and second mutated later during life (so called „loss of heterozygosity”, LOH)
  - random mutation
gene conversion (attempt to repair)
non-disjunction during mitosis

Role of APC chromosome disjunction

Types of DNA mutations

- point mutation
  - silent = no effect (alternative codon, same AA)
  - non-synonymous (missense) = different AA (change of protein function, hyper- or inactivity)
  - stop-codon (nonsense) = termination of translation (truncated protein)
  - mutation of regulatory regions of genes (promotors) = quantitative effect on transcription
- short insertions and deletions
  - “frameshift” effect
- pyrimidine dimers
  - by photochemical reaction (UV light)
  - thymine and cytosine covalent bridges = no replication
Types of DNA mutations

- **Chromosomal aberrations**
  - Deletions = loss of function (e.g., suppressor)
  - Duplication = doubling the dose (e.g., proto-oncogene)
  - Translocation = fusion gene
    - Very common in haematological malignancies
    - Part of the gene (e.g., proto-oncogene) attached to regulatory region of housekeeping gene

LOH example: retinoblastoma

- Rb mutations (ch. 13q14) – most often microdeletions lead to retinoblastoma (tumor of retina)
  - (1) Inherited (familiar) from retinoblastoma
    - Patient inherited one mutated allele, second one is mutated early during the life (= loss of heterozygosity, LOH)
  - (2) Acquired (sporadic) retinoblastoma
    - Inactivation Rb by mutation of both alleles anytime during the life

Mutagens / carcinogens

- **Physical**
  - UV light (skin carcinoma and basalioma, melanoma)
  - Ionising radiation and X-rays (leukaemia, thyroid gland, bones, ...)

- **Chemical**
  - Polycyclic aromatic and chlorinated hydrocarbons, aromatic amines, nitrosamines, heavy metals, mycotoxins, ...
    - GIT cancer as a result of dietary toxins exposure
    - Lung cancer as a result of smoking
    - Alcoholic liver cirrhosis

- **Biological**
  - Viruses
    - Incorporation of viral genome into the host one in critical regions
      - RNA viruses – retrovirus (activation of cellular or viral oncogenes)
      - E.g., B-lymphoma
    - Inactivation suppressors
      - DNA viruses (herpes, EBV, hepatitis virus, papillomavirus, adenovirus)
      - E.g., B-lymomas, hepatocellular ca, cervical ca, larynx, oral cavity
    - Indirect effect
      - Increased sensitivity to mitogens – HTLV (T hairy-cell leukaemia) – 1 expression of IL2 receptors
      - Immunodeficiency – HIV (Kaposi sarcoma)

- **Chronic inflammation = pre-cancerous**
  - Barret’s esophagus in GER, ulcerative colitis and Crohn’s disease, diverticulitis, ...

Partial summary

- Cumulated mutations in 3 groups of genes contribute to the malignant transformation
  - Protooncogenes (POG)
    - Physiologically promote cell division by stimulating transition through cell cycle phases and transmitting the mitogenic signals
    - Mutation of 1 allele is sufficient to produce uncontrolled cell division
  - Suppressor genes (TS)
    - Physiologically control cell division by arresting cell cycle or by inducing apoptosis
    - 1 functional copy is sufficient to exert the function
    - Inactivation of both alleles contributes to tumorigenesis
  - DNA stability genes (SG)
    - Not immediately involved in the tumorigenesis, but lack of their function leads to the higher mutation rate in general incl. POG and TS
Malignant transformation is a multistep process

- multistage process of subsequent changes of genome - mutations in the critical DNA region
- usually 6 – 10 necessary
- takes time
- typical incidence of cancer in advanced age
- the younger the age the more probable the role of inherited susceptibility

Tumor growth kinetics

- our body composed of $\sim 10^{14}$ cells
  - daily billions of cells made !!!
  - cell division = 6 billions of nucleotides
  - approx. 700 kg material during lifetime
  - such a number of divisions surely brings lots of errors, however cancer affects only $\sim 1/3$ people
  - removal of damaged cells by immunity, apoptosis, desquamation, ...
  - restriction of cell division by external factors
- cell divisions in the clone of tumor cells: $N=2^n$
  - 2, 4, 8, 16, 32, ...
  - 10 divisions = $\sim 1000$ cells
  - 20 divisions = $\sim 1 000 000$ cells (m=1mg)
  - 30 divisions = $\sim 1 000 000 000$ cells (m=1g)
  - 40 divisions = m=1kg
- given $\sim 12$-hr cell cycle in approx. 20 days
- in reality the growth is much more slower due to death or variable proportion of tumor cells and other factors:
  - prolongation of cell cycle duration
  - non-proliferating fraction of cells (differentiated)
  - tumor cell death (malnutrition, cytotoxic lymphocytes, NK cells)
  - mechanical loss of cells (desquamating e.g. in intestine)
- tumor grows only after formation of stroma and capillary network (= angiogenesis)
  - in that case growth overbalance the loss of cells

Tumor growth - angiogenesis

- ↑ cell proliferation/↓ cell death in tumor
  - need for energy (oxygen and substrates)
  - cell mass $\sim 1$mm$^3$ ($\sim 10^9$ of cells) can’t grow further without vascularisation (proliferation = apoptosis)
  - as a response to hypoxia hypoxia-inducible factor-1 (HIF-1) is produced
  - HIF-1 has 2 subunits - hydroxylation of HIF-1a (under the normoxia conditions leads to the rapid degradation)
  - under the hypoxia conditions HIF-1a migrates to the nucleus, binds to HIF-1b and HIF-1 complex functions as a transcription factor
  - after the translocation into nucleus HIF-1a stimulates transcription of many genes, e.g. vascular endothelial growth factor (VEGF)
- VEGF stimulate formation of new vessels (angiogenesis)
- proteolytic enzymes produced by tumor (matrix metalloproteinases) degrade extracellular matrix and enable "budding" of new vessels from the existing ones
- proliferation and migration of endothelial cells is further potentiated by angiogenic factors secreted by tumor (e.g. VEGF, basic fibroblast growth factor (bFGF), transforming growth factor-b (TGF-b), and platelet-derived growth factor (PDGF)
- new vessels enable invasion of tumor cells into circulation and distant metastases

Hypoxia-induced gene transcription

- VEGF stimulate formation of new vessels (angiogenesis)
- hypoxia-induced gene transcription
- HIF-1a regulation by proline hydroxylation
Cancer angiogenesis

Abnormalities of tumor cell growth – in vitro

Loss of contact inhibition, anchoring and intercellular communication
- integrins – with ECM
- cadherins (supressors) – cell to cell – inhibit β-catenins (oncogene)
  - act as transcription factors

Loss of E-cadherin signals proliferation

Wnt and E-cadherin pathways
Hormonal stimulation

- Growth of some tumors is significantly potentiated by hormones, typically by sex hormones
  - breast, uterus, ovary, prostate

Immune system vs. tumor

- Tumor cells have several immunological abnormalities
  - Quantitative changes in the expression of surface antigens (e.g., MHC)
  - Qualitative - expression of neo-antigens ("oncofetal")
  - Diagnostic markers (e.g., CEA, alpha-fetoprotein)
- Cytotoxic mechanisms are a major tool of anti-tumor immunity
  - CD8+ T-lymphocytes
  - NK-cells
- Although the immune system on its own is not powerful enough to seal with advanced tumors, the role of immunity in the anti-tumor surveillance is very important
  - People with immunosuppression have a high rate of cancer
    - E.g., Burkitt's lymphoma in Central Africa (malnutrition)

Metastasing

- Formation of daughter tumors distant from original site
- Several ways of spreading
  - Blood
    - Very often in the direction of flow
    - From GIT to the liver
    - By venous blood to the lungs
    - From lungs by artery blood to bones and brain
  - Lymphatic
    - First neighbouring lymph nodes, then distant

Changes in adhesion during the metastatic process

- Cancer cells lose E-cadherin-dependent intercellular adhesions, acquire a migratory phenotype, penetrate the basement membrane, and invade the interstitial matrix
  - Production of MMPs
- Tumor angiogenesis then allows cancer cells to enter the bloodstream, either directly or through the lymphatic system, by a process called intravasation
- In the circulation, tumor cells form small aggregates with platelets and leukocytes
- Finally, after stopping in the microcirculation of the target organ, tumor cells exit the bloodstream, by a process called extravasation, and undergo local expansion
Resistance to anoikis

Example – colorectal carcinoma

Interaction of tumor with the host

- local effect of tumor
  - mechanical compression (e.g. brain tumors)
  - obstruction (e.g. de. choledochus)
  - bleeding, anemia (leukaemia)
  - chronic blood losses into GIT (gastric and intestinal tumors)
  - oedema (e.g. lymphomas)
  - thromboses (DIC)
  - loss of vision (compression of optic nerve by hypophyseal adeoma)
  - voice change (laryngeal ca)
  - coughing (lung ca)
  - difficult swallowing (oesophageal ca)
  - pathological fractures (myeloma)

- systemic effects
  - increased temperature/unexplained fever
    - production of cytokines (pyrrogens) by tumor (IL-1, TNFα)
  - tumor cachexia
    - anorexic mediators (TNFα)
    - supression of bone marrow (anemia)
  - paraneoplastic syndromes
    - some tumors produce hormones (adenomas) – important diagnostically!
      - pigmentation
      - endocrinopathy
      - Cushing sy, hypercalcaemia, etc.

Tumor anorexia / cachexia

- initial anorexia might be a part of non-specific defence mechanisms (energetic deprivation of growing tumor)
  - gradually if becomes advert complication leading to progressive cachexia and further compromise on self-defence
  - i.e. tumor cachexia is an end-result of tumor anorexia and secondary effects (energy deprival, obstruction, treatment side-effects)
- initial tumor anorexia (also experimentally inducible - TNFα) is different from nausea and sickness as a side-effect of treatment
- also consequences of tumor anorexia are more serious than effect of simple starvation in otherwise healthy man
  - energetic requirements of growing tumor are increased and compromise other organs
- pathophysiology of tumor anorexia/cachexia
  - altered activation of regulatory centres in hypothalamus regulating food intake (n. arcuatus) due to cytokines produced by tumor or by the host's immune system (IL-1, IL-6, TNF-α)
    - cytokines stimulate release of serotonin and thus persistent activation of POMC/CART neurons
  - hypothalamic centres respond by a long-term decrease of concentration of NPY (orexigenic) and, conversely, over-activation of system POMC/CART (anorexigenic)
Hereditary cancer predisposition

- (1) sporadic cancers
- (2) some rare types of cancer due to inborn mutation (manifested usually in childhood):
  - retinoblastoma (retina)
  - Wilm's tumor (kidney)
  - Li-Fraumeni syndrome (various types of cancer incl. sarcomas, brain tumors and leukaemia)
  - familial adenomatous polyposis (~1% of all colon cancers)
- (3) other mutations increase susceptibility/probability of common types of cancer (+ exposure to the environmental factors):
  ~5 – 10% of all cancers
  - colon
  - ovary or breast cancer (BRCA1 gene)
  - nevertheless, because breast and colon cancer are so widespread, even a small fraction of the total equals a very large number
  - it is estimated that as many as 1 in 300 women may carry inherited mutations of breast cancer susceptibility genes, and approximately the same proportion carry mutations that make them susceptible to colon cancer
- genetic prediction possible – genetic screening and counselling

Tumor classification

- morphologic = typing = histological type
- invasivity = grading = benign × malignant
- initial extent = staging = TNM classification (T = tumor, N = node, M = metastasis)

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<th>Mode of inheritance</th>
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<td>Colon, thyroid, stomach, intestine, hepatoblastoma</td>
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<td>APC</td>
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<tr>
<td>Von Hippel-Lindau syndrome</td>
<td>Retinal and central nervous hemangioendothelioma, phaeochromocytoma, renal cell carcinoma</td>
<td>Dominant</td>
<td>TS</td>
<td>VHL</td>
</tr>
<tr>
<td>Wilms tumor syndrome</td>
<td>Wilms tumor</td>
<td>Dominant</td>
<td>TS</td>
<td>WT1</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>Retinoblastoma, osteosarcoma</td>
<td>Dominant</td>
<td>TS</td>
<td>RB1</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>Soft tissue sarcoma, osteosarcoma, breast, adenocarcinoma or glioma, leukemia, brain tumor</td>
<td>Dominant</td>
<td>TS</td>
<td>TP53</td>
</tr>
<tr>
<td>Multiple exostosis</td>
<td>Chondrosarcoma</td>
<td>Dominant</td>
<td>TS</td>
<td>EXT1/EXT2</td>
</tr>
<tr>
<td>Werner syndrome</td>
<td>Osteosarcoma, meningioma</td>
<td>Recessive</td>
<td>SG</td>
<td>WRN</td>
</tr>
<tr>
<td>MEN 1</td>
<td>Pancreatic islet cell tumor, pituitary adenoma, parathyroid adenoma</td>
<td>Dominant</td>
<td>TS</td>
<td>MEN1</td>
</tr>
<tr>
<td>MEN 2</td>
<td>Medullary thyroid carcinoma, pheochromocytoma, parathyroid hyperplasia</td>
<td>Dominant</td>
<td>OG</td>
<td>RET</td>
</tr>
</tbody>
</table>

TS - tumor suppressor gene; OG - oncogene; SG - stability gene; OMIM - online Mendelian inheritance in man