Tumor markers

Etiopatogenesis of tumors

Tumors

- Tumor is a pathological state (disease) due **to impaired control of cell division**

- genetic variation often one somatic (but germinal) cells causes impaired regulation

- cells resulting from pathological clone proliferate uncontrollably (at different rates), and then eventually spreading to secondary sites (**metastasis**)

- according to the rate of proliferation we distinguish tumors:

- **benign** - usually grow only in the point of origin, not aggressive, they retain differentiation

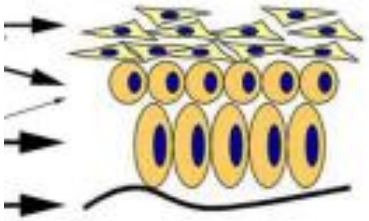
- **malignant** - they grow quickly, invasive and spread to other places, undifferentiated

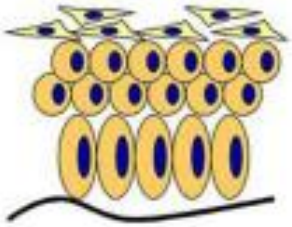
- **All tumors are due to genetic defects, namely the key genes controlling cell cycle**
- **(Proto)oncogenes** - normally promote cell growth and division, if mutated, uncontrolled division
- **suppressor genes -** normally suppress the cell division, if mutated, allowing uncontrolled division
- **DNA repair genes -** normally repair (repairable) DNA modifications, if mutated, uncorrected changes can be transferred to daughter cells

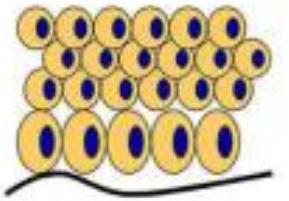
- however only some of them are also heritable (ie. Familial) = mutation in the germinal cell

- most tumors are random, ie. **sporadic** = mutations in somatic cell

Tumors

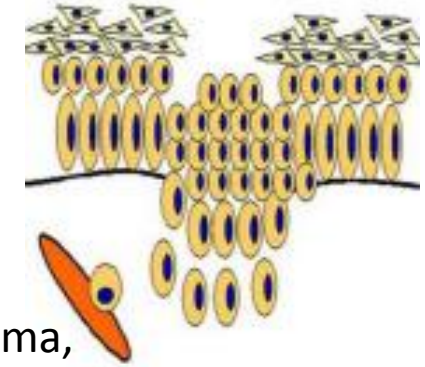






- **Genetic variation may develop**
  - by error during DNA replication and cell division
  - by action of external factors (**carcinogens**)
    - physical - eg. UV and ionizing radiation
    - chemical - organic substances, toxins, heavy metals
    - biological - some RNA and DNA viruses
- The tumor usually originally comes from mutations of 1 cell (**monoclonal**)
  - however the process of neoplastic transformation is multi-stage (the gradual accumulation of several mutations) so that gradually becomes genetically **heterogeneous**

-tumor switches from precancerous stage, via benign to malignant



- Histologically - depending on which tissues derived, we distinguish 3 groups:

- **epithelial**: skin, mucous membrane (Papilloma, adenoma, carcinoma)
- **mesenchymal**: connective tissue, endothelial, muscle tissue, lymphatic and hematopoietic tissue, bone (fibroma, hemanginom, myoma, sarcoma, lymphoma, leukemia)
- **neuroectodermal**: CNS and peripheral nerves, pigmented nevi (astrocytoma, glioma, blastoma, neuroma, melanoma)

TEST

Which genes are altered during carcinogenesis?

- The tumor is not monogenic disease
- It is estimated that for tumor development is necessary 4-7 events (hits)
- Many specific genes can be altered during carcinogenesis (tens)
- Generally, there are six basic characteristics of fully malignant tumor:

Six acquired characteristics of a malignant tumor

acquired characteristics	example
1. **self- sufficiency in growth signals**	H-ras activation
2. **insensitivity to signals stopping the cell cycle**	loss of RB
3. **damage apoptosis**	IGF production
4. **limitless replicative potential**	telomerase activation
5. **strengthening angiogenesis**	VEGF production
6. **metastasis**	E-cadherin inactivation

Instability of the genome as a condition for accumulation of necessary changes.

TEST

Classification of tumors

- Morphological diagnosis = **typing**

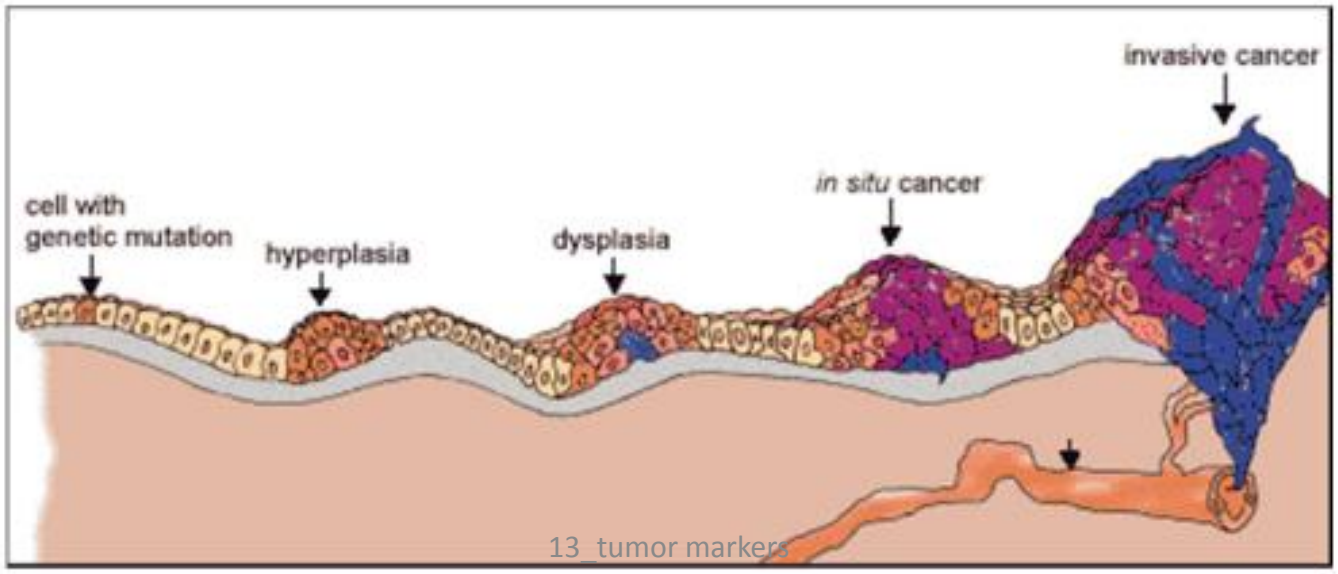
  - determining the histological type

- Rating invasiveness = **grading**

  - determining benignity x malignancy

- Determining the initial scope = **staging**

  - TNM classfication(T = tumor, N = node, M = metastasis)



The process of neoplastic transformation

Mutation in a critical spot DNA

(protooncogen, suppressor, reparation gene)

- Chromosomal aberrations (translocations, insertions, deletions, duplications
- Gene mutations (point mutations, the length (ins / del))

Mutagenes/carcinogens

-**physical:** UV (carcinoma and basalioma of skin, melanoma)

ionizing radiation and RTG radiation (leukemie, thyroid gland, bones)

- **chemical:** polycyclic aromatic hydrocarbons and chlorinated aromatic amines, nitrosamines, heavy metals, mycotoxins

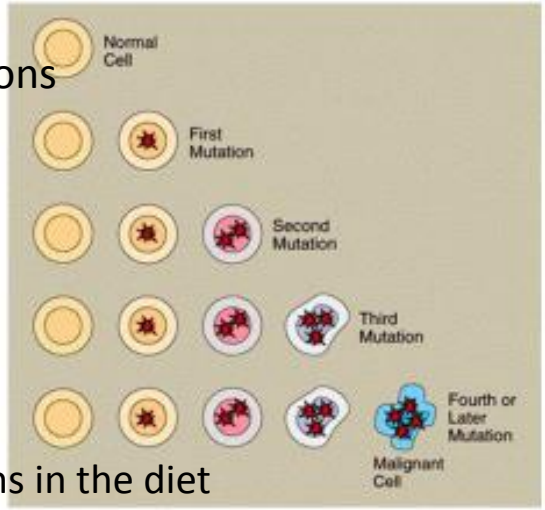
- Tumors of the gastrointestinal tract as a result of exposure to carcinogens in the diet
- Lung cancer as a result of smoking
- Alcoholcirrhosis

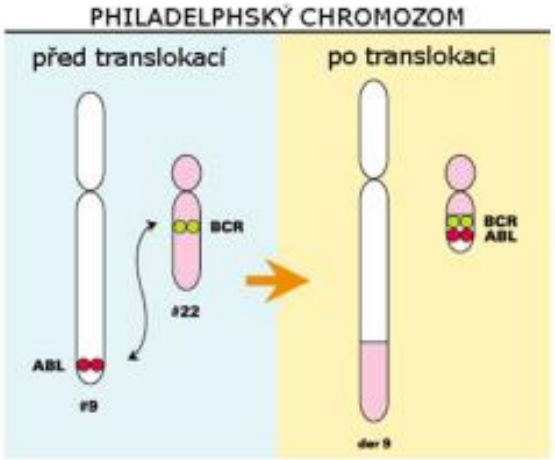
- **biological = incorporation of the viral genome into the host, again in critical places**

- DNA viruses (hepes EBV- lymfomas; hepadnaviruses HBV- hepadnacellular ca; papovaviruses - papillomaviruses, adnoviruses)
- RNA viruses – retroviruses (HIV – Kaposiho sarkoma, B- lymfoma HTLV – T-cell leukemia)

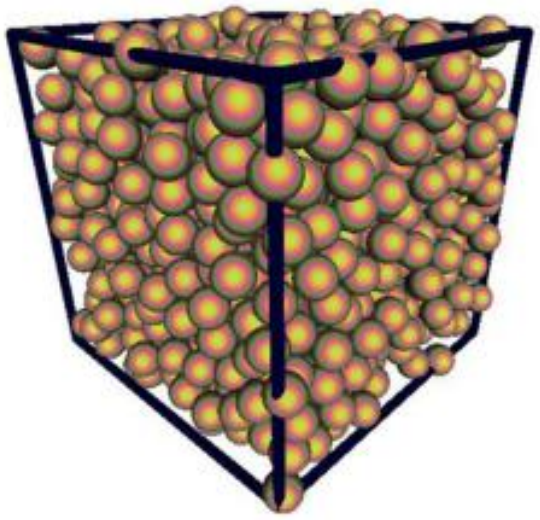
- **precancerous = chronic irritation from inflammation**

- Barrett's esophagus in GER
- ulcerative colitis and Crohn's disease
- diverticulitis





Tumor growth



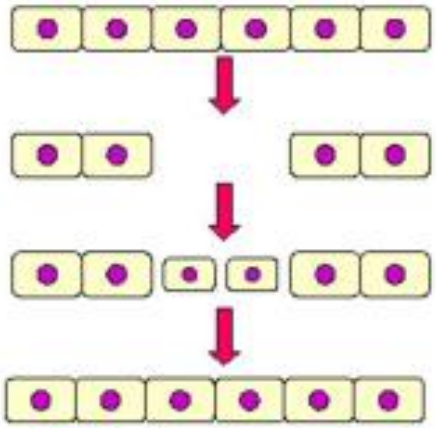
- Dividing tumor cells in clone: $N=2^n$
  - 2, 4, 8, 16, 32, …
  - 10 division= ~ 1 000 bb.
  - 20 division = ~ 1 000 000 bb.
  - 30 division = ~ 1 000 000 000 bb.
  - 40 division = m = 1kg (at 12-hour cell cycle for about 20 days)
- however in reality is the growth of tumors much slower - dividing x cell death
  - extending the duration of the cell cycle
  - Non-proliferating fraction of cells (differentiated))
  - Cell death (malnutrition, cytotoxic. Lymphocytes)
  - Mechanical losses cells (peeling e.g. in the intestine)
- Condition for growth is the creation of tumor stroma and capillary networks (angiogenesis)
  - then dominate proliferation over the of cell death

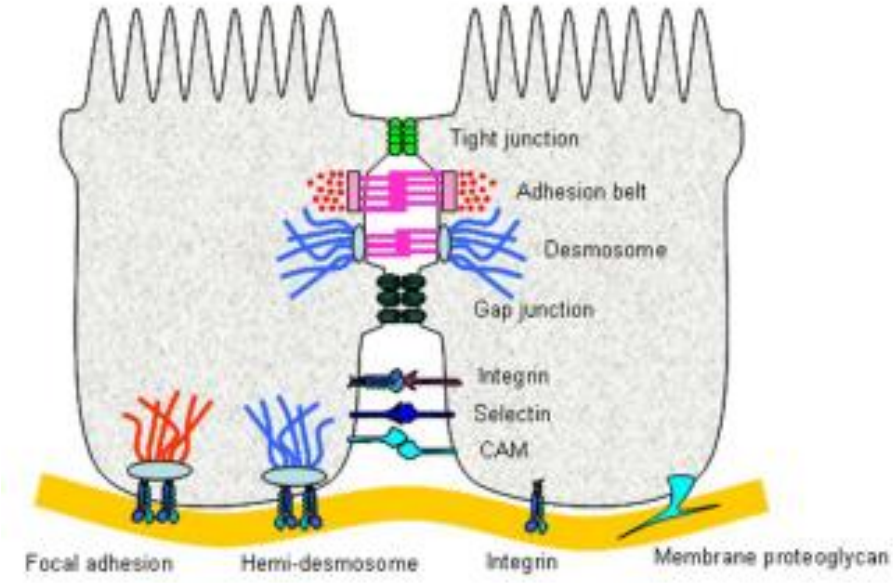
Tumor growth: other factors affecting the cell cycle

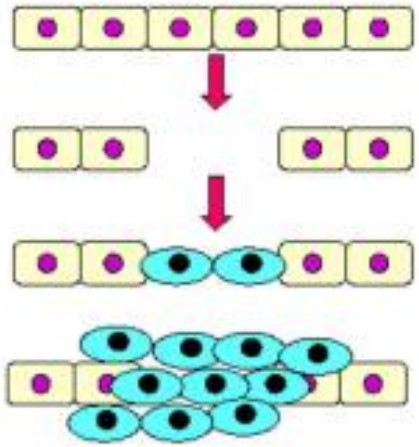
- intercellular communication

  (~ contact inhibition)

  - integrins– together with ECM
- - cadherins – the connection between each cell

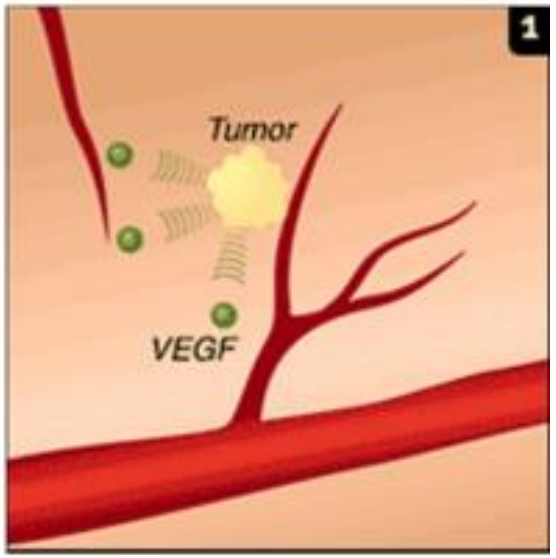






Tumor growth: other factors affecting the cell cycle

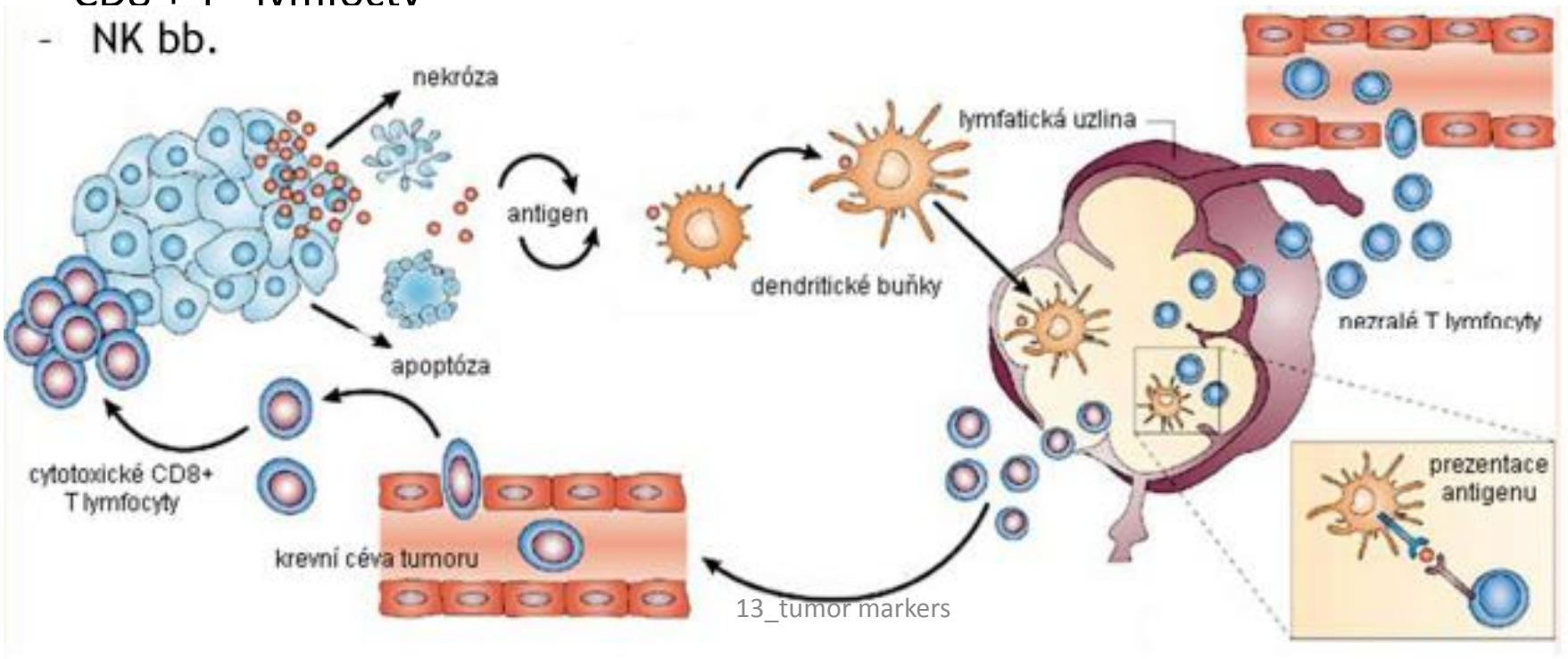
- Metabolism = **energy demand**
  (Oxygen and substrates)



- Cell mass the size of about 1 mm^3 (about $1x10^6$ cells) without vascularization isn´t capable of further growth (proliferation is in equilibrium with apoptosis)
- In response to hypoxia is regulated hypoxia-1a (HIF-1a) which, after translocation into the nucleus affects transcription of a number genes:
  - Repression of E-cadherin
  - ↑ Expression of GLUT1 and 3 = ↑ substrates
    (Also the effect of hormones and growth factors)
  - vascular endothelial growth factor (VEGF) and angiopoietin
    - This stimulates the formation of new blood vessels (**angiogenesis**) required for tumor growth
  - Chemotaxis of macrophages in tumor production and other angiogenic growth factors
  - VEGF, bFGF (basic fibroblast growth factor), TGF-b (transforming growth factor –b), PDGF (platelet-derived growth factor)

Immune system vs. tumor

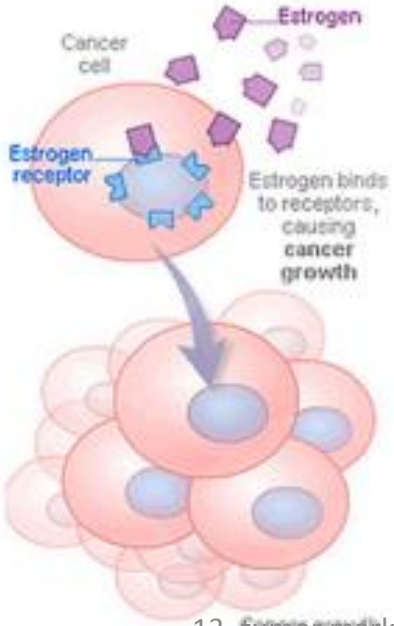
- Tumor cells have some immunological differences
  - Changes in natural surface antigens (e.g. MHC loss)
    - Escape immune recognition and destruction
  - Expression of the novel (oncofetal) antigens
    - diagnostic markers (e.g. CEA, alpha-fetoprotein etc.)
- Cytotoxic mechanisms are applied in the anti-tumor immunity
  - CD8 + T- lymfocty
  - NK bb.



Hormonal stimulation

- Growth of some tumors is significantly potentiated by hormones (usually sex hormones)

  - ca breast, uterine, ovarian, prostate



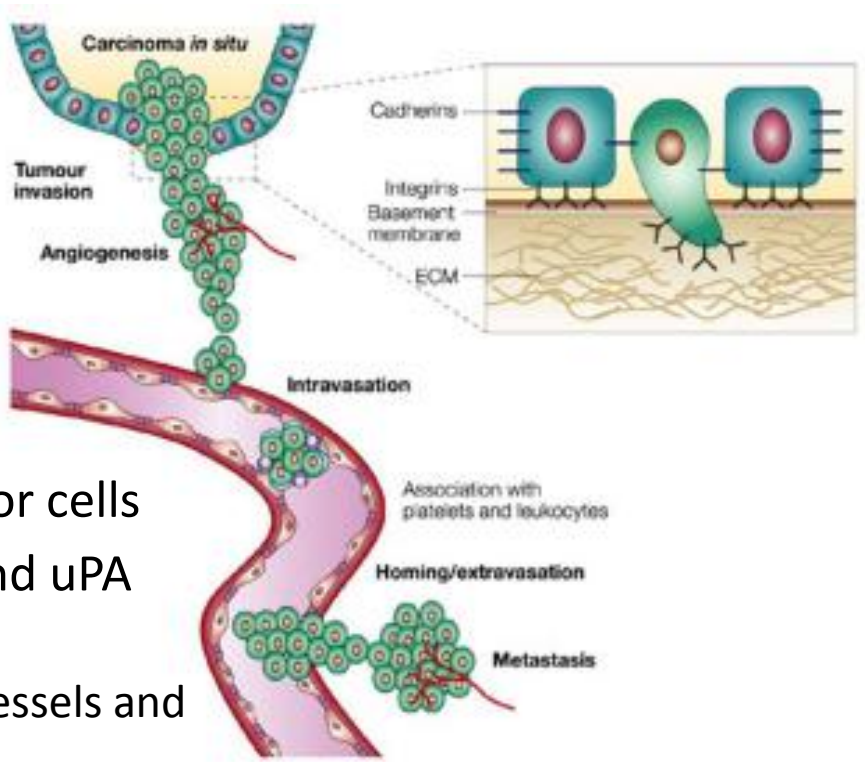
Invasiveness of tumor

- Cancer cells acquire a "motility" phenotype

by loss of adhesion proteins (E-cadherin)

(epithelial-mesenchymal transition, EMT)

- Loss of apikobazal cell polarization
  - Epithelial tumors (carcinomas) form 2/3 of all cancers
- Production of proteolytic enzymes by tumor cells
  - The matrix metalloproteinase (MMP) and uPA
    - Degrade extracellular matrix and It allows for "sprouting" of new blood vessels and extravasation of tumor cells
- Resistance to anoikis
  - A form of apoptosis initiated "Peeling away" of the epithelial cells from the ECM



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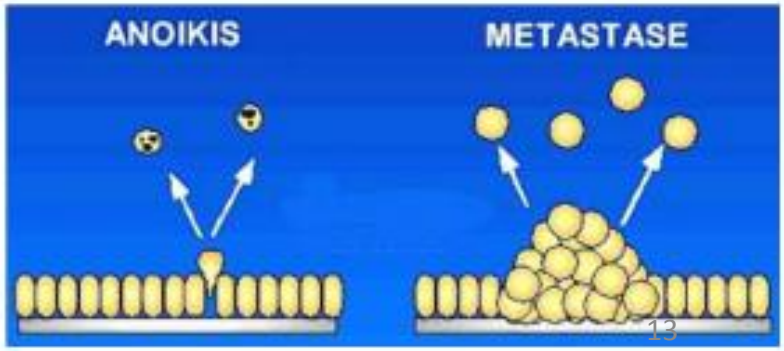
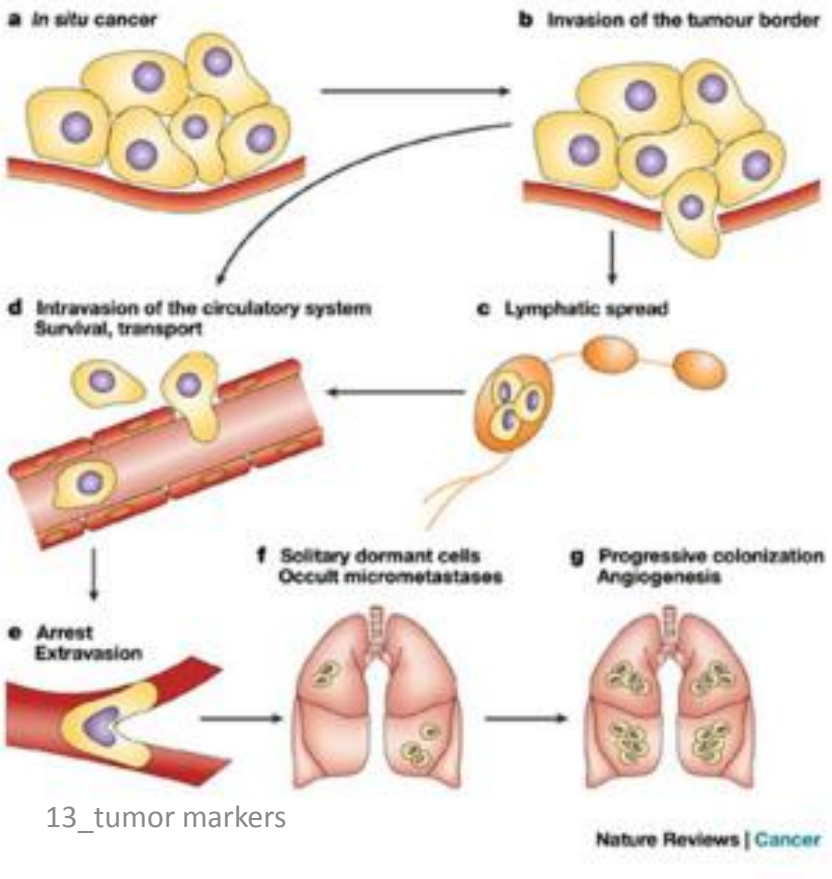


Metastasis

- Creating secondary tumors distant from the primary site
  - by blood
    - often downstream (e.g. from the gastrointestinal tract into the liver, venous blood to the lungs, of pulmonary arterial blood to the bone and brain)
  - by lymph
    - first closest lymph nodes, then farther



Some consequences of tumors

- hyperkalemia
- hypoglycemia
- Anemia
- acidosis
- hormonal disorders
- Cancer cachexia

Hyperkalemia : increased potassium levels in the blood. Normal values range from 3.8 to 5.0 mmol/l. Given that kalemia depends on the acid-base status, it must be considered in relation to pH

Cancer cachexia syndrome is a progressive loss of body mass, which causes significant morbidity and mortality of cancer patients. Metabolic changes conditioned by activity of proinflammatory cytokines, leading ultimately to the depletion of muscle and fat mass, are often present at the beginning of the disease, and therefore must be considered as early cancer cachexia phenomenon.

- Malignant neoplasms are the most common causes of death
- Growth of incidence of what types of tumors?
- There is a shift to younger ages
- The objective is the earliest possible diagnosis
- Imaging methods vs. immunochemical methods
- Methodological improvements

- Diagnosis of tumors
- Given that cancer is in our society frequent and dreaded disease there is much effort to understand and improve diagnosis and treatment.
- Treatment of cancer depends on early diagnosis and diagnose cancerous disease is not always easy.
- **Clinical diagnosis is determined mostly only in the tumor size of about 1 cm - 1 g, containing about 10^9 cells.**
- Histological examination, imaging (US, CT, NMR, PET, scintigraphy)
- Tumors often have no symptoms and can only appear after onerous and costly investigations that can not be done for each patient.
- Inevitably, the question emerged: Would it be possible to detect the presence of tumor in some conventional testing, e.g. from blood?
- It was found that in the case of many tumors to some degree we really can. It was demonstrated that the presence of a tumor in the body is associated with increased concentrations of certain substances that we can detect in the laboratory from a blood sample.
- These substances are called **tumor markers**.

TUMOR MARKERS

- Tumor markers are molecules predominantly of a protein character, which are present in the organism due to the formation and development of a malignant process.

Resolution of tumor markers allows in favorable cases to reveal tumor weighing 1 mg, about 10^6 malignant cells, determined by clinical diagnosis it is usually only in the tumor size of about 1 cm - 1 g, which contains about 10^9 cells.

TEST

Tumor markers are produced either

- tumor itself (then called tumor-associated antigens) or
- other tissues in response to a malignant process in the organism (then it is induced tumor markers, e.g. acute phase proteins).

We can distinguish tumor markers

- **cellular** (occurring in tissue cancer)
- **humoral** (occurring in body fluids).

The concentration of tumor markers in serum is usually in a direct relationship with the type and extent of disease.

TEST

The ideal tumor marker should meet the following criteria:

- It is produced only in malignant diseases
- is organ-specific
- in biological fluids are present in high concentrations (sufficient sensitivity)
- its level correlates with tumor size
  with stage of disease
  prognosis
  with a therapeutic effect
- allows the identification residual tumor tissue
- **At present, such an ideal marker not known.**

The universal tumor marker is yet to be discovered, or the specificity or sensitivity of the method is below 100%. This means that failure to raise the concentration of the tumor marker is not evidence of absence of malignant disease and, conversely, a positive result does not necessarily mean cancer.

They can be defined as a laboratory detectable marks in biological fluids, tissues or cells, by which it can be demonstrated:

- risk of formation
  presence
    prognosis
    efficiency (harmfulness) of therapy
    metastasis or residual disease.
- The main role of tumor markers (in medicine and laboratory) is
    tracking the disease
    monitor the effectiveness of therapy.

CLASSIFICATION OF TUMOR MARKERS

by chemical structure

by function

by organ-specificity

by origine

CLASSIFICATION OF TUMOR MARKERS

- humoral - detection in body fluids
- cellular – immunohistochemistry - directly in the tumor tissue

Methodology for determination of soluble markers:
Enzymatic analysis using commercial sets

Chemical structure

- glykoproteins
- glykolipids
- peptides
- imunoglobulins
- polyamines
- carbohydrates

Internal specificity

- **high:** ***calcitonin*** **-** medullary carcinoma of the thyroid
  PSA **-** prostate cancer
  NSE **-** small cell lung cancer
  hCG **-** germ-cell tumors
  AFP **-** hepatocellular and germ-cell carcinoma
- **moderate:** ***CA 19-9*** **-** pancreatic cancer
  CA 125 **-** ovarian cancer
  CA 15-3 **-** breast cancer
- **low:** ***CEA***
  TPA

TEST

Function

- oncofetal antigens
- oncoplacental antigens
- enzymes
- hormones
- serum proteins
- receptors
- others

TEST

1) Oncofetal antigens

- **substances produced during fetal life**
- present in high concentrations in the sera of fetuses, decrease to low levels or disappear after the birth
- **reappear in patients with cancer**
- Their production demonstrates that certain genes are reactivated as a result of the malignant transformation of the cell.
- substances occurring in high concentrations in the fetus (on the surface of differentiating cells) and the presence of cancer in adults
- in healthy adults is very low level
- level correlates with the size of the tumor mass
- determination is mainly used for prognosis and therapy control

- ***examples: AFP, CEA, CAs, CYFRA 21-1, SCC, MCA, MSA, TATI***

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2) Oncoplacental antigens

- **produced by the trophoblastic cells of the placenta in both pregnancy and pathological conditions and also by germinative tumors as a mark of malignant dedifferentiation**
- **↑ levels show evidence of ↑ malignancy and metastatic potency of the given tumor**

- ***examples: hCG, SP-1***

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3) Enzymes

- **present in much higher concentrations inside cells**
- **released into circulation as the result of tumor necrosis or a change in the membrane permeability of the cancer cells**
- elevated enzyme levels may signal the presence of malignancy but usually are **not specific** enough to identify a cancer type or organ involvement
- We can divide them into two groups:
- ***enzymes involved in cell division:*** their level is in excessive proliferation significantly increased, therefore, apply in determining prognosis and stage of disease.
- enzymes occurring even in healthy tissue, where they perform their biological functions are the most highly organ-specific and therefore are used to determine the primary location of the tumor.

- ***examples: NSE, TK, ALP, PSA,*** **isoenzymys of LD, ALP**

TEST

4) Hormones

- **The production of hormones in cancer involves two separate routes:**

1. the endocrine tissue that normally produces the given hormone can produce its **excess amounts**
2. **ectopic syndrome -** hormone produced by a distant nonendocrine tissue that normally does not produce this hormone

- for instance: ***ACTH*** normally produced by the **pituitary gland** ectopicaly produced by the **lung small cells**
- elevation of a hormone is not specific ← it may be produced by a variety of cancers

- ***examples: ACTH, ADH, PTH, calcitonin, STH, prolactin***

6) Serum proteins

- **produced either by tumor cells or by an organism in the presence of tumor**
- **non-specific**
- **monitoring**

- ***examples: β_2-microglobulin, ferritin, paraprotein***

7) Receptors

- **cellular markers used in hormone-producing tumors**

- ***examples:* *estrogen and progesterone receptors, Her2/neu, EGFR***

8) Other tumor markers and circulating cellular elements

- **tissues - produced substances, which we cannot class with the previously mentioned groups**
- **circulating cellular elements (circulating tumor cells, circulating endothelial cells and circulating endothelial precursors).**

- ***examples: TPA, TPS, CgA, neuropeptide Y, S-100β, 5-HIAA***

9) genetic abnormalities

Besides the usual applications of classical (soluble) tumor markers appear to be clinically useful as tumor markers, some **genetic abnormalities** and in particular to specify the abnormality determining tumor cell treatment.
It is both **a direct detection of mutations in DNA, protein products of oncogenes** (e.g. c-myc, c-fos, k-ras, src), **changes in their post-translational modifications in malignant tissue or "new" genetic changes in malignant cells** (e.g. chromosomal rearrangement of bcr-abl)
or detection of mutations in tumor suppressor genes (BRCA1, BRCA2, p53).

USE OF TUMOR MARKERS

- **Screening:** ***calcitonin*** in families with MEN syndrome, ***AFP*** in patients with liver cirrhosis, ***PSA*** in men >50 years
- **Dg and diff. dg** in symptomatic individuals
- **Clinical staging of cancer**, is aided by quantitation of the marker, i. e. the serum level of the marker reflects the number of cancer cells present in the body
- **Monitoring** of the disease and estimation of tumor value
- **Prognostic indicator** of disease progression and patient survival
- **Detection of cancer recurrence**, permits early treatment or a change in therapy
- **Monitoring of responses to therapy**

TEST

- **screening –** for majority of markers inappropriate., with limitations in high-risk groups:
  AFP in liver cirrhosis
  calcitonin , eventually.RET oncogene in families with MEN syndromes and relatives of a patient with medullary Ca thyroidea
  PSA in men over 50 years to exclude prostate Ca
- **primary diagnosis and dif. dg. –** performance of other tests

- **staging** – mostly inappropriate. High value can draw attention to a poorly laid lower-stage disease.
- **monitoring of disease and responses to therapy – main and critical application of Tu markers**

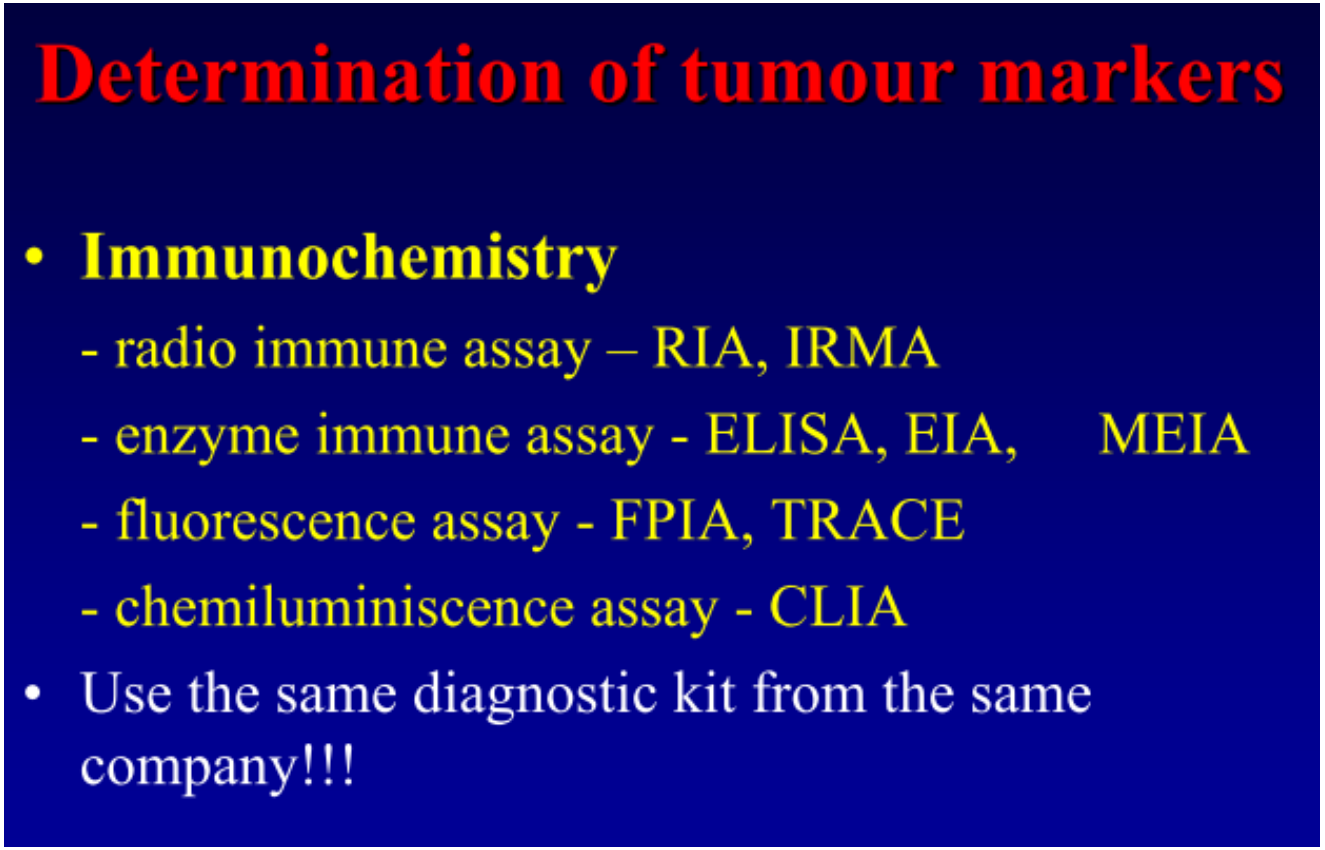
- **prognosis –většinou nevhodnémostly inappropriate. High value can show higer staging of diseases**

INDICATION FOR EXAMINATION OF TUMOR MARKERS

- **screening , presence**
- **primary diagnosis and dif. diagnosis**
- **staging (metastasis...)**
- **monitoring**
- **prognosis**
- **monitor the effectiveness of anticancer therapy**
- ***The main role of tumor markers***(in medical and laboratory) is
- **tracking the disease**
- **monitor the effectiveness of therapy**

TEST

Methods



- Molecular biology

Frequency of tumor markers examination

Recommended intervals according to WHO:

- **Before therapy initiation**
- **After therapy finalization (usually 3rd -4th week)**
- **1 month in 1st ½year after** primary therapy
- **2 months in 2nd ½ of 1st year**
- **3 months in 1st ½ of subsequent year (y. 1-1,5)**
- **6 months after 1.5 year and in subsequent years** of monitoring
- **When therapy changes**
- **When course of disease is obscure**

Minimal interval between two determinations in the same patient is **14 days.**

Tu markers kinetics

- **Doubling time** = time to double its (serum/plasma) level.
  The shorter, the more aggressive Tu growth.

- **biological half-life:**

Marker	Days	Hours	Marker	Days	Hours
ACTH		0.2	FER	2	
AFP	5		NSE	1	
B2M		0.7	P-ACP		2
CA 125	4		PRL		0.3
CA 15-3	7		PSA	2	
CA 19-9	5		SCCA		0.3
CEA	14		TG	2.5	
CT		0.2	TK	2	
CYFRA 21-1		3	TPA	7	

- **1) ENZYMES**
- **Alkaline Phosphatase (ALP)**
- Increased alkaline phosphatase activities are seen in primary or secondary **liver cancer**. Its level may be helpful in evaluating metastatic cancer with bone or liver involvement. Placental ALP, regan isoenzyme, elevates in a variety of malignancies, including ovarian, lung, gastrointestinal cancers and Hodgkin's disease.

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- **Prostatic acid phosphatase (PAP)**
- It is used for staging prostate cancer and for monitoring therapy. Increased PAP activity may be seen in osteogenic sarcoma, multiple myeloma and bone metastasis of other cancers and in some benign conditions such as osteoporosis and hyperparathyroidism.

- **Prostate Specific Antigen (PSA)**
- The clinical use of PAP has been replaced by PSA. PSA is much more specific for screening or for detection early cancer. It is found in mainly **prostatic tissue**.
- PSA exists in two major forms in blood circulation. The majority of PSA is complexed with some proteins. A minor component of PSA is free.
- PSA testing itself **is not effective in detecting early prostate cancer.** Other prostatic diseases, urinary bladder cateterization and digital rectal examination may lead an increased PSA level in serum.
- The ratio between free and total PSA is an reliable marker for differentiation of prostatic cancer from benign prostatic hyperplasia.

- **PSA** – serin protease, glycoprotein, monitoring of prostata CA

  ratio fPSA/PSA

TEST

- The use of PSA should be together with digital rectal examination and followed by transrectal ultrasonography for an accurate diagnosis of cancer.
- **Serum level of PSA** was found to be correlated with clinical stage, grade and metastasis
  - The greatest clinical use of PSA is in the **monitoring of treatment.**
  - This treatment includes radical prostatectomy, radiation therapy and antiandrogen therapy.
  - The PSA level should fall below the detection limit.
  - This may require 2-3 weeks. If it is still at a high level after 2-3 weeks, it must me assumed that residual tumor is present.

- Androgen deprivation therapy may have direct effect on the PSA level that is independent of the antitumor effect. **This subject must be considered always.**

- **2) HORMONES**
- **Calcitonin**
- Calcitonin is a hormone which decreases blood calcium concentration.
- Its elevated level is usually associated with **medullary thyroid cancer**.
- Calcitonin levels appear to **correlate with tumor volume and metastasis.**
- Calsitonin is also useful for **monitoring treatment and detecting** the recurrence of cancer.
- However calcitonin levels are also at a high levels in some patients with cancer of lung, breast, kidney, liver and in nonmalignant conditions such as pulmonary diseases, pancreatitis, Paget's disease, hyperparathyroidism, myeloproliferative disordes and pregnancy.

TEST

- **Human Chorionic Gonadotropin (hCG)**
- It is a glykoprotein appears in pregnancy. Its high levels is a useful marker for tumors of placenta and some tumors of testes.
- hCG is also at a high level in patients with primary testes insufficiency.
- hCG does not cross the blood-brain barier. Higher levels in BOS may indicate metastase to brain.

TEST

3) ONCOFETAL ANTIGENS

- Most reliable markers in this group are **α-fetoprotein and carcinoembryonic antigen (CEA)**

• Carcinoembryonic antigen (CEA)

- It is a cell-surface protein and a well defined tumor marker.
- CEA is a marker for colorectal, gastrointestinal, lung and breast carcinoma.
- CEA levels are also elevated in smokers and some patients having benign conditions such as cirrhosis, rectal polips, ulcerative colitis and benign breast disease.
- **CEA testing should not be used for screening.** Some tumors don't produce CEA. **It is useful for staging and monitoring therapy.**

TEST

- **α-Fetoprotein (AFP)**

- α-fetoprotein is a marker for hepatocellular and germ cell carcinoma.
- It is also increased in pregnancy and chronic liver diseases.
- AFP is useful for screening (AFP levels greater than 1000 µg/L are indicative for cancer except pregnancy), determining prognosis and monitoring therapy of liver cancers.
  - AFP is also a prognostic indicator of survival.
  - Serum AFP levels is less than 10 µg/L in healthy adults. Elevated AFP levels are associated with shorter survival time.
  - AFP and hCG combined are useful in classifying and staging germ cell tumors.One or both markers are increased in those tumors.

TEST

4) CARBONHYDRATE MARKERS

- These markers either are antigens on the tumor cell surface or are secreted by tumor cells.
- They are high-molecular weight mucins or blood group antigens. Monoclonal antibodies have been developed against these antigens.
- Most reliable markers in this group are CA 15-3, CA 125 and CA19-9.

TEST

- **CA 125** – monitoring of ovarian CA
- **CA 15-3** – monitoring of breast CA
- **CA 72-4** – monitoring of gastric CA
- **CA 19-9** – glycolipid, determinant of blood group Lewis a (5% of population does not produce it), for monitoring of pancreas CA (and bile ducts)

- **CA 15-3**

- CA 15-3 is a marker for breast carcinoma. Elevated CA 15-3 levels are also found in patients with pancreatic, lung, ovarian, colorectal and liver cancer and in some benign breast and liver diseases.
- **It is not useful for diagnosis.** It is most useful for monitoring therapy.

- **CA 125**

- Although CA 125 is a marker for ovarian and endometrial carcinomas, it is not specific. CA 125 elevates in pancreatic, lung, breast, colorectal and gastrointestinal cancer, and in benign conditions such as cirrhosis, hepatitis, endometriosis, pericarditis and early pregnancy.
- It is useful in detecting residual disease in cancer patients following initial therapy.

- A preoperative CA 125 level of less than 65 kU/L is associated with a greater 5 y survival rate than is a level greater 65 kU/L.
- It is also useful in differentiating benign from malignant disease in patients with ovarian masses.
- In the detection of recurrence, use of CA 125 level as an indicator is about 75 % accurate.

- **CA 19-9**

- CA 19-9 is a marker for both colorectal and pancreatic carcinoma.However elevated levels were seen in patients with hepatobiliary, gastric, hepatocellular and breast cancer and in benign conditions such as pancreatitis and benign gastrointestinal diseases.
- CA 19-9 levels correlate with pancreatic cancer staging.
- It is useful in monitoring pancreatic and colorectal cancer.

- Elevated levels of CA 19-9 can indicate recurrence before detected by radiography or clinical findings in pancreatic and colorectal cancer.

7) PROTEIN MARKERS

- Most reliable markers in this group are β_2-microglobulin, ferritin, thyroglobulin and immunoglobulin.

- **β_2-microglobulin**
- β_2-microglobulin is a marker for multiple myeloma, Hodgkin lymphoma. It also increases in chronic inflammation and viral hepatitis.

- **Ferritin**

- Ferritin is a marker for Hodgkin lymphoma, leukemia, liver, lung and breast cancer.

- **Thyroglobulin**
- It is a useful marker for detection of differentiated thyroid cancer.

- **Immunoglobulin:** Monoclonal immunoglobulin has been used as marker for multiple myeloma for more than 100 years.
- Monoclonal paraproteins appear as sharp bands in the globulin area of the serum protein electrophoresis.
- Bence-Jones protein is a free monoclonal immunoglobulin light chain in the urine and it is a reliable marker for multiple myeloma.

8) RECEPTOR MARKERS

- **Estrogen and progesterone receptors** are used in breast cancer as indicators for hormonal therapy.
- Patients with positive estrogen and progesterone receptors tend to respond to hormonal treatment.
- Those with negative receptors will be treated by other therapies.

TEST

- **Estrogen receptors** – prediction of the effect of hormonal therapy in breast cancer, **determination in the tumour tissue**
- **Progesteron receptor** – prediction of the effect of hormonal therapy in breast cancer, **determination in the tumour tissue**

- Hormone receptors also serve as a prognostic factors in breast cancer. Patients with positive receptor levels tend to survive longer.

- Cytoplasmic estrogen receptors are now routinely measured in samples of breast tissue after surgial removal of a tumor. Of patients with breast cancer, 60 % have tumors with estrogen receptor.
- Approximately two thirds of patients with estrogen receptor (+) tumors respond to the hormonal therapy. 5% of patients with estrogen receptor (-) tumors respond to the hormonal therapy.

- Progesterone receptor testing is a useful adjunt to the estrogen receptor testing. Because progesterone receptor synthesis appears to be dependent on estrogen action.
- Measurement of progesterone receptors provides a confirmation that all the steps of estrogen action are intact. Indeed breast cancer patients with both progesterone and estrogen receptor (+) tumors have a higher response rate to hormonal therapy.

C-erbB2 (HER-2 Neu)

- It is receptor for epidermal growth factor (EGF) but it doesn't contain EGF binding domain. It serves as a co-receptor in EGF action
- In the case of increased expression of C-erbB2 leads the oto-activation and increased signal transduction
- Increased expression of C-erbB2 was determined in some cancers. It was suggested as an important factor for carcinogenesis and metastasis
- Routine measurement of C-erbB2 was started in our hospital

GENETIC CHANGES

- Four classes of genes are implicated in development of cancer:
- 1) **protooncogenes** which are responsible for normal cell growth and differentiation
- 2) **tumor suppressor genes** which are involved in recognition and repair of damaged DNA.
- 3)**apoptosis-related genes** are responsible for regulation of apoptosis
- 4)**DNA repair genes**
- Alterations on these genes may lead tumor development.

TEST

- **Susceptible protooncogenes:**

- K-ras, N-ras mutations are found to be correlated acute myeloid leukemia, neuroblastoma

Susceptible DNA repair genes:

- BRCA1 and BRCA2 are specific genes in inherited predisposition for developing breast and over cancer, and mutations on these genes are newly measured in some laboratories.
- Mismatch-repair genes are mutated in some colon cancers

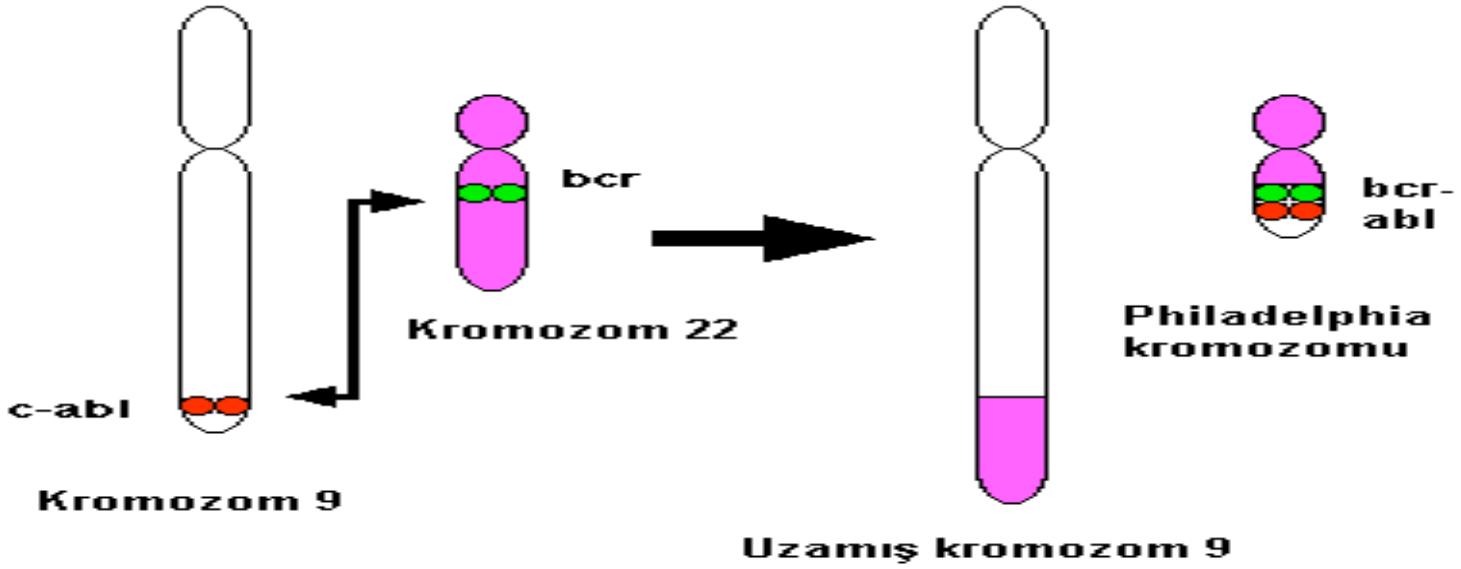
- **Susceptible tumor suppressor genes:**

- Retinoblastoma gene
- P53 gene
- P21 gene
- Those genetic markers are very new and not routinely measured in laboratories.

Chromosomal translocation

- c-myc gene has been found to be translocated from 8.chromosom to 14. chromosom and than become activated in Burkitt’s lymphoma.
- myc gene encodes a DNA-binding protein which stimulates cell dividing.

- In chronic myeloid leukemia, there is a translocation between chromosomes 9 and 22.



Summary -The biological nature of the tumor markers

As tumor marker we mean **substance presents in the tumor or produced by tumor or host** as a response to the presence of tumor.

This substance can be used to **differentiate the tumor from normal tissue**, or reflect the presence of the tumor based on the analysis of body fluids.

The substance can be measured **qualitatively or quantitatively** by chemical methods, immunological and molecular biology methods.

Among the markers produced by the tumor include:

enzymes (eg. LD, NSE, PSA, thymidine kinase, prostatic acid phosphatase),

immunoglobulins or their fragments or subunits (monoclonal immunoglobulins called "paraproteins"),

hormones (eg. hCG, PTH, ACTH, calcitonin, gastrin, prolactin, norepinephrine, epinephrine), fragments of complex glycoproteins, (eg. CA19-9, CA15-3, CA125),

fragments of of cytokeratin (TPA, TPS, CYFRA21-1), oncofetal antigens (AFP, CEA),

Molecules of the groups of receptors (estrogen and progesterone receptor, interleukin 2, HER2 / neu, and EGF) and circulating cellular elements (circulating tumor cells, circulating endothelial cells and circulating endothelial precursors).

Besides the usual applications of classical (soluble) tumor markers appear to be clinically useful as tumor markers, some genetic abnormalities and in particular to specify the abnormality determining tumor cell treatment. It is both a direct detection of mutations in DNA, protein products of oncogenes (e.g. c-myc, c-fos, k-ras, src), changes in their post-translational modifications in malignant tissue or "new" genetic changes in malignant cells (e.g. chromosomal rearrangement of bcr-abl) or the detection of mutations in tumor suppressor genes (BRCA1, BRCA2, p53).

TEST