

# **TUMOR MARKERS**

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- **substances which can be related to the presence or progress of a malignancy**
- **antigens expressed on the tumor cells surfaces -**  
*cellular tumor markers*
- **different substances (found in the blood or other body fluids) produced by the tumor cells (*Tu-associated m.*) or by an organism (*induced m.*) in the presence of tumor -**  
*humoral tumor markers*
- **The ideal marker should be both specific for a given type and localization of cancer and sensitive enough to detect small tumors for early diagnosis or during screening.**

# UTILIZATION 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**

# **CLASSIFICATION OF TUMOR MARKERS**

- **According to chemical structure**
- **According to visceral specificity**
- **According to function**

# Chemical structure

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

# Visceral 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*

# Function

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

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



# 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*

# 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**  
ectopically 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***

# 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
- *examples: **NSE, TK, ALP, PSA, LD***

# Serum proteins

- produced either by tumor cells or by an organism in the presence of tumor
- non-specific
- monitoring
- *examples:  $\beta_2$ -microglobulin, ferritin, paraprotein*

# Receptors

- **cellular markers used in hormone-producing tumors**
- *examples: **estrogen and progesterone receptors***

## Other tumor markers

- tissues - produced substances, which we cannot class with the previously mentioned groups
- *examples: TPA, TPS, CgA, S-100B*

## ***AFP ( $\alpha$ 1 – fetoprotein)***

- **glycoprotein synthesized in large quantities by the fetal yolk sac and liver**
- **one of the major proteins in the fetal circulation**
- **in adults AFP /S  $\uparrow$ : pregnancy  
liver diseases**
- **marker for hepatocellular and germ-cell carcinoma**
- **cut off value < 13.0 IU/ml**

## ***CEA (carcinoembryonic antigen)***

- family of related oncofetal cell-surface glykoproteins
- nonspecific
- ↑: liver cirrhosis, pulmonary emphysema, benign breast cysts disease, ulcerative colitis, rectal polyps lung, ovarial and breast carcinoma
- marker for colorectal, pancreatic, gastric and bile ducts Ca
- cut off value < 4,6 ng/ml



# ***Carbohydrate markers*** ***(CA - carbohydrate antigen)***

- high-molecular-weight mucins or blood group antigens on the tumor cell surface or secreted by the tumor cells
- ***CA 15-3***
- marker in **monitoring of therapy and disease progression in metastatic breast cancer**
- **cut off value  $\leq 28$  IU/ml**
- ***CA 125***
- marker for **ovarian and endometrial carcinomas**
- **cut off value  $\leq 35$  IU/ml**
- ***CA 19-9***
- marker for **pancreatic and colorectal carcinoma**
- **cut off value  $\leq 37$  IU/ml**
- ***CA 72-4***
- marker for **carcinomas of stomach, pancreas and ovary**
- **cut off value  $\leq 5$  IU/ml**

## ***SCC (squamous cell carcinoma antigen)***

- glycoprotein Ig receptor physiologically present in squamous epithelium cells
- ↑: pregnancy  
lung dis., hepatic and renal failure
- marker for **pulmonary (NSCLC), orofacial, genital, and endometrial carcinoma**
- cut off value  $\leq 1,5 \mu\text{g/l}$

## ***CYFRA 21-1 (cytokeratin fragment)***

- **cytokeratin fragment present in lung, uterine and GIT cells. Marker of degradation of malign tissues and necrosis.**
- **↑: cirrhosis, asthma, respiratory infections, renal failure**
- **marker for cervical and pulmonary (NSLC) carcinoma**
- **cut off value  $\leq 3,3 \mu\text{g/l}$**

***MCA (mucinous carcinoma antigen),  
MSA (mammar serum antigen)***

- **↑: breast Ca**

***TATI (tumor associated trypsin inhibitor)***

- **↑: GIT Ca and ovarian mucinous  
cystadenoCa**

## ***hCG (human chorionic gonadotropin)***

- glycoprotein secreted by the syncytiotrophoblastic cells of placenta
- consists of two subunits:  $\alpha$ -subunit (common to several other hormones, e. g. FSH, LH or TSH)  
 $\beta$ -subunit (unique to hCG)
- $\uparrow$ : pregnant women  
hydatidiform mole
- marker for tumors of placenta (trophoblastic tumors, particularly choriocarcinoma), and germ-cell tumors of the testis and ovary
- cut off value < 2.00 IU/l males, < 9.00 IU/l females

***SP-1 (Schwangerschaftsprotein;  
 $\beta_1$ -specific pregnancy glycoprotein)***

- **mixture of glycoproteins produced by the trophoblastic cells of placenta**
- **↑: pregnant women  
chorioCa, germinative Tu**

## ***PSA (prostate-specific antigen)***

- glykoprotein protease (237 AA, Mr = 33 000) produced exclusively by the epithelial cells of the prostate gland, secreted into seminal fluid. In serum, it occurs as free fPSA and chymotrypsin or  $\alpha_2$ -macroglobulin bonded.
- ↑: benign prostatic hyperplasia BPH, prostate inflammation, urological manipulations
- marker for **screening** (men > 50y, urinating difficulties), **dg and monitoring of course and treatment of prostate cancer**
- **cut off value < 4,0  $\mu\text{g/l}$**

## *Derived parameters*

- ***tPSAD (tPSA density)***: adjustment of BPH and PCa: **0,15**
- ***tPSA-TZ (tPSA/transition zone ratio)***
- ***PSAV (tPSA velocity)***: healthy **0,04  $\mu\text{g/l/y}$** , BPH **0,07-0,27  $\mu\text{g/l/y}$** , PCa  **$\geq 0,75 \mu\text{g/l/y}$**
- ***age specific tPSA levels***: normal  $\uparrow$  **0,04  $\mu\text{g/l/y}$** ; **cut off 40-49 y** **2,5 or 1,5  $\mu\text{g/l}$** , **50-59 y** **3,5 or 2,5  $\mu\text{g/l}$** , **60-69 y** **4,5  $\mu\text{g/l}$** , **70-79 y** **6,5 or 7,5  $\mu\text{g/l}$**
- ***index fPSA/tPSA***:  $\downarrow$  in CaP than BPH (**cut off  $< 20\%$** )
- ***tPSADT (tPSA doubling time)***: adjustment of local recurrence x metastasis (shorter time) after radical prostatectomy



## ***NSE (neuron-specific enolase)***

- **enolase - enzyme of glycolysis** (2-phosphoglycerate → phosphoenolpyruvate)
- **NSE - form of enolase found in neuronal and neuroendocrine tissues**
- **↑: lung and liver dis., renal failure**
- **marker for small-cell lung cancer (SCLC), pheochromocytoma, neuroblastoma, medullary carcinoma of the thyroid, melanoma, and pancreatic endocrine tumors**
- **cut off value < 15 µg/l**

## ***TK (thymidine kinase)***

- **enzyme of DNA synthesis** (thymidine → thymidine monophosphate)
- **↑: psoriasis, sarcoidosis, kolagenosis, rheumatic dis., pernicious and megaloblastic anemia**  
**lung, breast, prostate, testicular or colorectal Ca**
- **marker for hematologic malignancies monitoring**
- **cut off value < 5 IU/l**

## ***LD (lactate dehydrogenase)***

- **enzyme of glycolysis (lactate  $\leftrightarrow$  pyruvate)**
- **non-specific**
- **↑: heart failure, lung and liver dis. etc. (isoenzymes)  
hematological and other malignances  
↑ isoenzyme LD<sub>5</sub> in liver metastases**
- **marker for acute leukemia, non-hodgkin lymphoma,  
testikular Ca and Ewing Sa monitoring**
- **ref. values : ♂ 3,3 - 7,5  $\mu$ kat/l, ♀ 3,3 - 6,3  $\mu$ kat/l**

## ***ALP (alkaline phosphatase)***

- **Zn<sup>2+</sup> glycoprotein, in alkaline environment (pH= 8-10) it catalyses the hydrolysis of H<sub>3</sub>PO<sub>4</sub> monoesters and transphosphorylation**
- **bone isoenzyme**
- **↑: osteoSa, bone metastases  
other bone affections; growth**
- **liver isoenzyme**
- **↑: liver metastases  
other liver diseases**
- **Regan isoenzyme (placental alike)**
- **↑: GIT and lung tumors**
- **ref.values : adults 0,5-2,4 μkat/l, 1 month - 15 years  
1,0-4,8 μkat/l, newborns 0,6-5,3 μkat/l**

# *Cathepsins*

- lysosomal proteinases, participate in connective tissue and cell membranes degradation → facilitate the tumor progression and origination of metastases
- *cathepsin B* ↑ in breast, ovarian, colorectal, stomach and laryngeal Ca
- *cathepsin H* ↑ in breast, lung, head and neck Ca, mainly in tumor progression and occurrence of metastases
- *cathepsin D* ↑ in adenoCa mammae

# ***Prolactin***

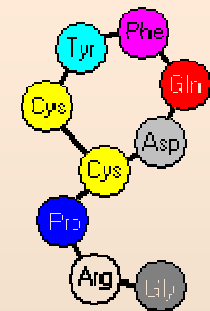
- **peptide (198 AA) anterior pituitary hormone that stimulates and maintains the secretion of milk. It`s secretion is stimulated by TRH and inhibited by dopamine.**
- **↑: prostatic and breast cancer**
- **marker for prolactinoma**
- **ref. values males 80 – 390 mIU/l  
females 70 – 520 mIU/l**

## ***ACTH (adrenocorticotrophic hormone)***

- **anterior pituitary hormone that stimulates the secretion of glucocorticoid hormones.** It's secretion is stimulated by corticotropin-releasing hormone of hypothalamus.
- **↑: ectopic formation: SCLC, Ca of pancreas, breast, GIT**
- **marker for pituitary tumors**
- **cut off value < 46.0 ng/l**

## ***ADH (antidiuretic hormone, vasopressin)***

- **peptide (9 AA) hormone** synthesized in the supraoptic nuclei of the **hypothalamus** and transported via the hypophyseal tract to the posterior pituitary. It's binding and stimulation of insertion of aquaporines into distal and collecting tubules membranes **increases the water reabsorption** → **↑ blood pressure and ↓ excretion of urine**
- **↑: pneumonia, porphyria**
- **marker for SCLC, adenocarcinoma of the lung**
- **ref. value 2 - 8 ng/l**



**Antidiuretic hormone**



## ***PTH (parathyroid hormone)***

- **peptide (84 AA) hormone of the parathyroid glands.** Its release is stimulated by  $\text{Ca}^{++} / \text{P} \downarrow$ . **PTH** activates osteoclasts,  $\uparrow \text{Ca}^{++}$  renal resorption and  $\uparrow \text{Ca}^{++}$  intestinal absorption via stimulation of calcitriol renal production  $\rightarrow \uparrow \text{Ca}^{++} / \text{P}$ .
- $\uparrow$ : **secondary and primary hyperparathyroidism**
- marker for **parathyroideal tumors**
- **ref. values 10 – 65 ng/l, 1.6 – 6.9 pmol/l**

# *Calcitonin*

- **polypeptide (32 AA) produced by the C cells of the thyroid**
- **normally secreted in response to  $\uparrow$   $\text{Ca}^{++}$  /P**
- **inhibits the release of calcium from bone (inhibition of osteoclasts)**
- **marker for **medullary carcinoma of the thyroid****
- **cut off value  $\leq 19$  ng/l**

# *Ferritin*

- **Fe<sup>3+</sup> storage protein**
- **↑: iron overload**  
**acute hepatitis and liver cells necrosis,**  
**inflammations (positive acute phase protein)**
- **marker for Hodgkin lymphoma and melanoma monitoring**
- **ref. values males 48 - 708 pmol/l, females 20 - 640 pmol/l**

## ***$\beta_2$ -microglobulin***

- **part of the class 1 HLA, physiologically produced by B-lymphocytes and plasmocytes, helps Tc function**
- **↑: inflammations, chronic renal and liver dis. after chemo- and radiotherapy**
- **marker for MM dg, CLL therapy**
- **ref. value 1 – 2.3 mg/l**

## ***$\kappa$ , $\lambda$ light chains (paraproteins, Bence Jones proteins)***

- **the first described tumor markers produced by neoplastic plasma cells in monoclonal gammopathies.** They are small enough (22 kD) to pass through the kidney into the urine → **prerenal „over-flow“ proteinuria.**
- **↑: monoclonal gammopathy of uncertain significance** (isolated finding of a Bence Jones protein without a clinical symptomatology)  
**Waldenström macroglobulinemia, lymphomas and leukemias, osteogenic sarcoma, bone metastases**
- **marker for multiple myeloma**
- **ref. values: FLC (free light chains)/S:**  $\kappa = 3.3-19.4$  mg/l,  $\lambda = 5.7-26.3$  mg/l, index  $\kappa/\lambda = 0.26-1.65$ ; **polyclonal FLC/U = 1-10 mg/24h;**  $\kappa/U = 1.25-5.5$  mg/l,  $\lambda/U = 0.51-3.2$  mg/l, index  $\kappa/\lambda = 0.82-3.0$

## ***TPA (tissue polypeptide antigen)***

- non-specific cytokeratins fragments produced by both normal and tumor cells
- **↑ levels seen in increased cell proliferation → its estimation is useful for monitoring of the disease**
- **↑: liver dis., DM, rheumatoid dis.  
breast and GIT tumors**
- **TPA/ U - marker for urinary bladder carcinoma**
- **cut off value  $\leq 85$  U/l**

## ***CgA (chromogranin A)***

- **glycoprotein of the secretory vesicles of the neuroendocrine cells. Precursor to several functional peptides including vasostatin, pancreastatin, catestatin and parastatin. Regulates the storage and/or secretion of hormones and peptides inside the cell.**
- **↑: renal and hepatal dis., corticosteroids therapy neuroendocrine tumors**
- **marker for carcinoid, pheochromocytoma, SCLC, MEN I, neuroendocrine tumors of GIT, particularly pancreas, children's neuroblastomas**
- **ref. value < 35 U/l**

## ***S-100B***

- **Ca<sup>2+</sup>- binding protein of nervous system glial cells and melanoma cells.** Participates on signal transmission, enzyme activity regulation and homeostasis → **stimulates neuronal growth and ↑ their survival.**
- ↑: **brain injury**  
**Down and Alzheimer dis.**  
**malignant melanoma**
- **marker for malignant melanoma monitoring**
- **ref. value < 0,105 µg/l**



## New bone markers in bone metastases dg and monitoring

- ***P1NP (N-terminal propeptide of type I collagen):*** monitoring of bone formation, highly specific for osteoblastic metastases formation. Is released into IC environment during collagen synthesis, than into the blood → assesment /S.
- ***b-CTX ( $\beta$ -Cross Laps):*** bone resorption marker, monitoring of antiresorption therapy
- **ref. value < 0,704  $\mu$ g/l**
- ***ICTP (c-telopeptide of type I collagen):*** marker of bone resorption mediated by MMP9 (matrix metalloproteinase 9), activated in pathological conditions (physiological bone resorption is mediated by cathepsin K). Replaced by b-CTX.

## Other perspective prognostic and predictive markers

- ***MMP-7 (matrilysin)***: metalloproteinase participating in EC matrix degradation, tumor invasion and progression, used in **breast Ca**
- ***SMR (mesomark, soluble mesothelin-related protein)***: marker for **mesothelioma** (no marker before now)
- ***Heparanase***: cleavage of heparane sulphate. ↑ metastatic potencial of tumor, ↓ surgical survival; for example in **pancreatic Ca**.
- ***RECAF (AFP receptor)***: allows transport of molecules into the fetal and malignant cells. Detectable in the tissues of **breast, ovarian, lung, stomach, prostate, and cervical Ca, lymphoma, melanoma etc.**
- ***hK (human kallikreins)***: Ser proteases of hormone-dependent tissues, used in **prostate and ovarian Ca; hK3 = PSA**