Oncogenesis, tumor progression, classical tumor therapy and targeted therapy

Tumor as effect of bypassing cellular senescence

p53
pRB

The tumor cell is not alone…

Tumor stroma
- Non-cancer cells
- ECM

Matrix metalloproteinases (MMPs) are calcium-dependent zinc-containing endopeptidases

- Collagenases MMP-1, 8, 13, 18 are capable of degrading triple-helical fibrillar of bone cartilage, dentin in particular: I, II, III, V, IX
- Gelatinases, MMP-2 i-9 collagen type IV, laminin, gelatin
- Stromelysins, MMP-3 i-10 degradation of ECM
- Matrilysin MMP-7 i-26 degradation of matrix = cleavage of: FASL, pro TNFalfa, E-cadherin
- Membrane type MMP are localized directly in the cell membrane
- Other MMP

- TIMP tissue inhibitors of metalloproteinases TIMP 1, 2, 3, 4
- Metalloproteinases are secreted by: tumor cells, fibroblasts, macrophages, mast cells, neutrophils, endothelial cells
- The enzymes regulate migration, angiogenesis, EMT

Composition of metalloproteinases

The MMPs have a common domain structure. The three common domains are the pro-peptide, the catalytic domain, and the haemopexin-like C-terminal domain, which is linked to the catalytic domain by a flexible hinge region.

Cleavage and removal of prodomain is required for activation of most metalloproteinases.

EMT
Epithelial-mesenchymal transition

MDR Multidrug Resistance

Tumor angiogenesis
Hypoxy
VEGF

Tumor metastases

Tumor stroma

Metalloproteinases

Local growth factors and Cytokines

Tumor as effect of bypassing cellular senescence

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MMP

- Only few metalloproteinases are secreted directly by the tumor cells.
- Tumor cells by paractine secretion produce interferons, interleukins, growth factors, and extracellular matrix metalloproteinase inducer (EMMPRIN) that stimulate surrounding host cells for MMP production.
- MMP secreted by non-tumor cells might be then absorbed at the surface of tumor cells.

Tumor angiogenesis

- Growth of tumor above 2-3 mm requires nutrients and oxygen via blood vessels.
- There exist three main processes of blood vessel formation:
  - Vasculogenesis: de novo formation from angioblasts
  - Angiogenesis: basing on existing blood vessels, by proliferation of endothelium
  - Vasculogenic mimicry: is the formation of microvascular channels by aggressive, metastatic and genetically deregulated tumur cells
- Part of novel blood vessels due to rapid growth of the tumor become discontinued especially in the middle of the tumor that provokes hypoxia and stimulates angiogenesis
- Due to rapid growth, tumor vessels are curled and have permeable basement membrane

Angiogenesis from existing blood vessels

Hypoxia and necrosis in the middle of the tumor stimulates angiogenesis

- MMPs
- TGFb
- VEGF
- bFGF

Sorafenib

- Sorafenib is a small molecular inhibitor of several tyrosine protein kinases that inhibit mainly tumor angiogenesis
- This drug inhibits (VEGFR and PDGFR) (tyrosine kinase inhibitor or TKI) and Raf kinases (more avidly C-Raf than B-Raf) also inhibits some intracellular serine/threonine kinases (e.g. C-Raf, wild-type B-Raf and mutant B-Raf)
- Sorafenib is approved for the treatment of primary kidney cancer (advanced renal cell carcinoma), advanced primary liver cancer (hepatocellular carcinoma), and radioactive iodine resistant advanced thyroid carcinoma.

Cell adhesion

Is indispensable for proper 3D structure of the tumor, for growth and survival signaling.

- Adhesion complexes are composed of three basic elements: 
  - receptors, adhesion proteins in extracellular matrix (lamin, fibronectin) and cell to cell adhesion molecules (desmosomes, adherens plaques etc).
- Most important adhesion molecules are:
  - integrins
  - selectins
  - immunoglobulin-like molecules
  - cadherins
Epithelial-mesenchymal transition (EMT)

- Cells of epithelial phenotype with strong cell-cell connections (cadherins), and strong cell ECM connections (integrins) become the ability for movement.
- These cells undergoing EMT loose their connections with ECM.
- EMT is accompanied with change in cell morphology form epithelial like to mesenchyme like.
- Changes in cadherin expression occurs (N-cadherin is up-regulated while E-cadherin is repressed).

Epithelial cells are closely connected to each other by tight junctions, gap junctions and adherens junctions, have an apico-basal polarity, polarization of the actin cytoskeleton and are bound by a basal lamina at their basal surface.

Mesenchymal cells, on the other hand, lack this polarization, have a spindle-shaped morphology and interact with each other only through focal points.

Epithelial cells express high levels of E-cadherin, whereas mesenchymal cells express those of N-cadherin, fibronectin and vimentin.

Several signaling pathways (TGF-beta, FGF, EGF, HGF, Wnt/beta-catenin and CSF) and hypoxia may induce EMT.

Transcription factors activated in cell undergoing EMT are: Snail (SNAI1), Slug (SNAI2), Twist

Activation of the transcription factors activates many genes (increase in cell proliferation, cell motility, induction of anti apoptotic pathways)

EMT confers resistance to oncogene-induced premature senescence.

Cells that undergo EMT gain stem cell-like properties and become positive for tumor stem cells markers (Notch and Oct-4).

Initiation of metastasis requires invasion, which is enabled by EMT. The same EMT is a crucial process in embryogenesis, cell differentiation.

Later, when these circulating tumor cells (CTCs) exit the bloodstream to form micrometastases, they undergo MET for clonal outgrowth at these metastatic sites.

For MET transition are responsible tumor stroma cells in far metastases.

It’s still a hypothesis

Such cells undergo rarely mitoses and usually are in G0 of the cell cycle

They usually are hidden from external environment (at the bottom of crypts, in the bone marrow)

Have increased expression of gp-100 and are MDR

They are usually resistant to apoptosis induction

Transcription factors in EMT

**Twist**
- TF helix-turn-helix composition
- N-cadherin, E-cadherin, metastases, angiogenesis, tumor stem cells development, chemotherapy resistance.

**Snail Slug**
- TF zinc finger composition
- Repressor of E-cadherin expression
- Snail/Slug activation increases MMP's production, angiogenesis inducers, antiapoptotic molecules (IAP)

Tumor stem cells

- It’s still a hypothesis
- Such cells undergo rarely mitoses and usually are in G0 of the cell cycle
- They usually are hidden from external environment (at the bottom of crypts, in the bone marrow)
- Have increased expression of gp-100 and are MDR
- They are usually resistant to apoptosis induction
Multidrug resistance MDR and gp-100

- Apoptosis reduction
- Cell cycle progression
- Increased drug metabolism
- Change in gene expression of therapy targets
- Reduced DNA repair
- Drug compartmentalization

Gp100 = ABCB1 = MDR1

- P-gp (ABCB1 gene chromosome 7) belongs to the ATP-Binding Cassette (ABC) transporter superfamily (ABC, z ang. ATP-binding cassette).
- ABC superfamily is composed of membrane transporters that carry molecules through cell membrane against concentration gradient, using energy from ATP hydrolysis.
- There are 48 proteins in the human genome (divided into 7 subfamilies) and at present there are 15 genetic conditions associated with defects in 20 members of this superfamily including (cystic fibrosis).
- P-gp is the first discovered protein in subfamily B, thus its official name is ABCB1 (ATP-binding cassette subfamily B member 1). The other common name for p-gp is MDR 1 (multidrug resistance protein 1).
- Substrate enters P-gp either from an opening within the inner leaflet of the membrane or from an opening at the cytoplasmic side of the protein. ATP binds at the cytoplasmic side of the protein. Following binding of each, ATP hydrolysis shifts the substrate into a position to be excreted from the cell.

ABC transporters in MDR

- ABCB1
- ABCC1
- ABCG2

Overlapping substrate specificity of ABCB1, ABCC1 and ABCG2

- ABCB1
  - Paclitaxel
  - Colchicine
  - Vinblastine
  - Calcein-AM

- ABCC1
  - Doxorubicin
  - Mitoxantrone
  - Etoposide

- ABCG2
  - Prazosin
  - Dihydropyridines
  - Fluoropiridol p53 inhibitor

Antitumor drugs

- Classical
  - Cisplatin
  - Doxorubicin
  - 5FU

- Targeted
  - Proteasome inhibitors
  - Antibodies – rituximab
  - Small molecular thyrosine kinase inhibitors Gleevec

- Thalidomid

Mechanisms of chemotherapy

- Damage the DNA of the affected cancer cells.
  - Cisplatin, doxorubicin and etoposide

- Inhibit the synthesis of new DNA strands to stop the cell from replicating, because the replication of the cell is what allows the tumor to grow.
  - e.g., methotrexate, mercaptopurine, fluorouracil hydroxyurea

- Stop the mitotic processes of a cell. Stopping mitosis stops cell division (replication) of the cancer and may ultimately halt the progression of the cancer.
  - e.g., Vinblastine, Vincristine, Paclitaxel
Classical antitumor drugs with mechanisms of action:

Alkylating drugs: Inhibition of DNA synthesis (attaches an alkyl group to the guanine base of DNA, at the number 7 nitrogen atom of the purine ring)
- EXAMPLES: cisplatin, Chlorambucil, busulfan, cyclophosphamide, ifosfamide, fotemustine, busulfan, dacarbazine

Antimetabolites: Inhibition of biosynthesis of nucleic acids
- EXAMPLES: methotrexat, capecitabine (is converted in the body to 5FU)
  5-fluorouracil (5FU), folinic acid, fludarabine, gemcitabine

Alkaloids:
- Podophyllin derivates: Inhibition of topoisomerase II → DNA synthesis inhibition → block in the cell cycle
  - EXAMPLES: etoposid, teniposid
- Vinca alkaloids: tubulin destabilisation → M-kinase block
  - EX: Vincristin, vinblastine
- Taxanes: Stabilisation of microtubules → M-kinase block
  - EX; paclitaxel, docetaxel

Anti-tumor antibiotics: Inhibition of DNA and RNA synthesis by intercalating between base pairs of the DNA/RNA strand
- Inhibition of topoisomerase II enzyme, preventing the relaxing of supercoiled DNA and thus blocking DNA transcription and replication
- Induction of free radicals, damaging protein, lipid and nucleic acid molecules
- Doxorubicin, epirubicin, bleomycin, Daunorubicin, Epirubicin, Idarubicin, Valrubicin, Mitoxantrone

- Steroids: Are active in G1 phase of the cell cycle
  - Dexamethasone – lymphoma, multiply myeloma
  - Prednisone – lymphoma, leukemia
  - Medroxyprogesterone – breast, endometrium and kidney cancer
  - Methyloprednisolone anti emetic, anti oedematous

Common combination chemotherapy regimens

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Drugs</th>
<th>Acronym</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>Cyclophosphamide, methotrexate, 5-fluorouracil</td>
<td>CMF</td>
</tr>
<tr>
<td>Hodgkin's disease</td>
<td>Mustine, vincristine, procarbazine, prednisolone</td>
<td>MOPP</td>
</tr>
<tr>
<td>Non-Hodgkin's lymphoma</td>
<td>Cyclophosphamide, doxorubicin, vincristine, prednisolone</td>
<td>CHOP</td>
</tr>
<tr>
<td>Germ cell tumor</td>
<td>Bleomycin, etoposide, cisplatin</td>
<td>BEP</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>Epirubicin, cisplatin, 5-fluorouracil</td>
<td>ECF</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>Methotrexate, vincristine, doxorubicin, cisplatin</td>
<td>MVAC</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Cyclophosphamide, doxorubicin, vincristine, 5-fluorouracil</td>
<td>CA/5F</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>5-fluorouracil, folinic acid, oxaliplatin</td>
<td>FOLFOX</td>
</tr>
</tbody>
</table>

Medicaments specific for particular phase of the cell cycle:

- **G1 phase of the cell cycle**:
  - Asparaginaza
  - Glikorkotyosterdy

- **S phase of the cell cycle**:
  - Dokorubicyna
  - Fludarabina
  - Fluorouracil

Catagories of novel anti-tumor agents

- **New anticancer drugs**
  - Monoclonal antibody -drug, -toxin, or –radionuclide conjugates
  - Biological response modifiers (e.g., interferons, interleukin-2)
  - Adoptive immunotherapy
  - Hematopoietic growth factors
  - Induction of tumor cell differentiation

- **Antisense therapy**
  - Therapy directed against tumor metastases
  - Inhibitors of angiogenesis
  - Proteasome inhibitors (bortezomib, carfilzomib)
Target drugs

- **Tyrosine kinase** inhibitors: imatinib (Gleevec)
- **B-Raf** inhibitors: verumafenib
- **mTOR** inhibitors: everolimus, tacrolimus (immunosuppressive tacrolimus)
- Pan kinase inhibitor: **angiogenesis** inhibitor sorafenib
- **HER2** inhibitor: trastuzumab (herceptin), b
- **Estrogene receptor** inhibitor: tamoxifene
- **Proteasome inhibitor** - bortezomib, carfilzomib
- VEGF-A ab - bevacizumab (avastin)

Nomenclature of biologic therapies

Suffix indicates class of biologic therapy

- **cept** = human receptor fusion protein
  - e.g. etanercept
- **ximab** = chimaeric monoclonal antibody (75% human)
  - e.g. infliximab
- **zumab** = humanized monoclonal antibody (80-95% human)
  - e.g. efalizumab
- **umab** = fully human monoclonal antibody (100% human)
  - e.g. adalimumab, ustekinumab
- **inib** = small molecular kinase inhibitor

List of the top 10 best-selling cancer drugs of 2013

<table>
<thead>
<tr>
<th>No.</th>
<th>INN</th>
<th>Trade names</th>
<th>Companies</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rituximab</td>
<td>Rituxan/Mab</td>
<td>Antibody against CD-20 on Bcells</td>
<td>Non-Hodgkin’s lymphoma, CLL</td>
</tr>
<tr>
<td>2</td>
<td>Bevacizumab</td>
<td>Avastin</td>
<td>Angiogenesis inhibitor, humanized anti-VEGF-A</td>
<td>Colorectal, lung, ovarian and brain cancer</td>
</tr>
<tr>
<td>3</td>
<td>Trastuzumab</td>
<td>Herceptin</td>
<td>Anti HER2 antibody, Breast, esophagus and stomach cancer</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Imatinib</td>
<td>Gleevec</td>
<td>Tyrosine kinase inhibitor in chromosome Philadelphia</td>
<td>Leukemia, GI cancer</td>
</tr>
<tr>
<td>5</td>
<td>Lenalidomide</td>
<td>Revlimid</td>
<td>Derivative of thalidomide E3 ligase for transcription factor KLF1 and 3</td>
<td>Multiple myeloma, mantle cell lymphoma</td>
</tr>
<tr>
<td>6</td>
<td>Pemetrexed</td>
<td>Alimta</td>
<td>Antimetabolite thiol acid antagonist</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>7</td>
<td>Bortezomib</td>
<td>Velcade</td>
<td>20S proteasome inhibitor</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>8</td>
<td>Cetuximab</td>
<td>Erbitux</td>
<td>Anti EGF antibody</td>
<td>Colon and head and neck cancer</td>
</tr>
<tr>
<td>9</td>
<td>Leuprorelin</td>
<td>Lupron, Eligard</td>
<td>Analog GnRH – in hormone-sensitive tumors</td>
<td>Prostate and ovarian cancer</td>
</tr>
<tr>
<td>10</td>
<td>Abiraterone</td>
<td>Zytiga</td>
<td>Antiandrogen</td>
<td>Prostate cancer</td>
</tr>
</tbody>
</table>

Targeted therapy

Ras/Raf/MEK/ERK

- Kinase pathway activated by most growth factors (ie. EGF)
- K-Ras (lung cancer, colon, pancreas)
- N-Ras (malignant melanoma)
- H-Ras (urinary bladder ca.)
- Ras proteins are farnesylated and anchored to plasma membrane
- Hyper-activation of Ras is observed in 20-80% of malignances
- Ras hyperactivation plays a curtail role in malignant melanomas
- MEK is the most important kinase
- ERK activates transcription factors c-myc (proliferation) and elk-1
**Ras/Raf/MEK/ERK**

B-Raf inhibitor - Vemurafenib
used in malignant melanoma therapy

**B-Raf inhibitor - Vemurafenib**
used in malignant melanoma therapy

**Inhibitors of farnesyltransferase**
- Tipifarnib
- Lonafarnib

**HMG-CoA inhibitors:** Statins

**Isoprenylation of Ras**

**WNT/Catenin**

**APC and Wnt/catenin pathway in colorectal cancer**

*Modulation of Wnt/catenin pathway by NSAID is a suggested mechanism of action of ASA in possible prevention of colorectal cancer*

**PI3K/AKT**

**Modulation of Wnt/catenin pathway by NSAID is a suggested mechanism of action of ASA in possible prevention of colorectal cancer**
mTOR

- Mammalian target of rapamycin – serine-threonine protein kinase
- Regulates cell growth and proliferation
- Regulates protein translation
- Crosstalks with insulin signaling

PI3K-AKT-mTOR

mTOR inhibitors

- everolimus i temsyrolimus
  TAKROLIMUS

- Everolimus: liver cancer, renal cell cancer
- PTCI stents – prevent occlusion of coronary artery

Growth factors receptors

HER2 is a member of the human epidermal growth factor receptor (HER/EGFR/ERBB) family

Receptor tyrosine-protein kinase erbB-2, also known as CD340 (cluster of differentiation 340), proto-oncogene Nau, Erbb2 (rodent), or EBB2 (human) is a protein that in humans is encoded by the EBB2 gene, which is also frequently called HER2 (from human epidermal growth factor receptor 2) or HER2/neu.

- Activates PI3K/Akt, and Ras/MAPK.
- HER2 inhibition promotes G1 arrest, inhibits angiogenesis and inducts ADCC

Receptor tyrosine kinase

Imatinib

is a tyrosine-kinase inhibitor used in the treatment of multiple cancers, most notably Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) and Gastrointestinal stromal tumors (c-KIT positive).
Herceptin = tastaizumab
Breast cancer

- Human monoclonal antibody IgG1 against HER2 (Human Growth Factor Receptor – HER2).
- Used in breast cancer HER2 positive.
- Side effects: heart and skin (epidermis) injury

VEGF-A inhibition and angiogenesis

Bevacizumab, trade name Avastin, is an angiogenesis inhibitor, a drug that slows the growth of new blood vessels.

Bevacizumab (AVASTIN) usage:
- Lung cancer
- Colorectal cancer
- Eye proliferative diseases

Breast cancer and Estrogen receptors - Tamoxifen (TMX)

Tamoxifen (TMX)
Selective estrogen receptor modulation
usage:
- Breast cancer - estrogen positive
- Infertility
- Gynecomastia

The Ubiquitin Proteasome System for protein degradation

Proteasome inhibitors
- Bortezomib (Velcade; Neom) is the first therapeutic proteasome inhibitor approved in humans.
- Carfilzomib (Kyprolis) selective proteasome inhibitor (analog of epoxomicin).
- Both use in myeloma multiplex (plasmocytoma)
New drugs

- **Gleevec imatinib**: TRK inhibitor
  - Philadelfia chromosome
- **Tasigna Nilotinib**: Inhibitor kinazy BCL-ABL II generation oraz kinaz SRC
  - Stosowany w leczeniu przewlekłej białaczki szpikowej z chromosomem Filadelfia
- **Sorafinib**: Inhibitor wielu kinaz ERK/MEK/RAF i angiogenezy
- **Vedace Bortezomib**: Inhibitor proteasomów w szpiczaku mnogim II generacji: Carfilzomib i Kyprolis
- **Velcade Bortezomib**: Inhibitor proteasomów
- **Nilotinib**: Inhibitor kinazy tyrozynowej zwłaszcza w białaczkach z chromosomem Filadelfia
- **Velcade**: Bortezomib
  - W szpiczaku mnogim
  - Inhibitor proteasomów
  - W leczeniu przewlekłej białaczki szpikowej
  - Wykorzystywany w leczeniu przewlekłej białaczki szpikowej

Monoclonal Antibodies

- **Rituximab**: Anti CD-20
  - Anti HER2
- **Bevacizumab**: anti VEGF-A
- **Gemtuzumab**: Anti CD33
  - Carpath®
  - Alemtuzumab Anti CD52
  - Withdrawal from market due to side effects
- **Gentuzumab and Alemtuzumab**: Withdrawal from market due to side effects

Nomenclature

- **ab** = monoclonal antibody
- **-ximab** = chimeric monoclonal antibody (75% Human) e.g. infliximab
- **-zumab** = humanized mAb (95% human) e.g. efalizumab
- **-umab** = Human Ab (100% human) e.g. adalimumab, ustekinumab
- **-cept** = FC fragment of Antibody e.g. etanercept

Targeted therapy in other diseases

- **Anti TNF alfa** – inflammatory bowel diseases, reumatoid arthritis and psoriasis
  - Infliximab, adalimumab
- **Anti CD20** - inflammatory bowel diseases, reumatoid arthritis
  - Rituximab
- **Anti IL-12 i -23** - psoriasis
  - Ustekinumab
- **Anti RANK-L** – osteoporosis
  - Demosumab (Prolia) – inhibits osteoclasts maturation

TNF-α

- Primarily expressed by activated macrophages, T and B cells
- Biological effects are numerous
  - Integral to granuloma formation and maintenance
  - Activates macrophages to ingest and kill mycobacterium and other pathogens
- Mice deficient in TNF-α/p-55 signaling pathway more susceptible
  - TB, Histoplasma, Listeria, Klebsiella, S. pneumoniae

TNF signaling

| Inflammation cell proliferation | vs | apoptosis |

NF-κB- transcription factor involved in cell survival and inflammation

TLR signaling

Imflamosome

Osteoporosis
denosumab
anti-RANKL ab

Table 1.2: Biologic Agents to Treat Rheumatoid Arthritis USA

<table>
<thead>
<tr>
<th>Agent</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept</td>
<td>T-cell costimulation modulator</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>TNF-α inhibitor</td>
</tr>
<tr>
<td>Anakinra</td>
<td>IL-1 receptor antagonist</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>TNF-α inhibitor</td>
</tr>
<tr>
<td>Etanercept</td>
<td>TNF-α inhibitor</td>
</tr>
<tr>
<td>Golimumab</td>
<td>TNF-α inhibitor</td>
</tr>
<tr>
<td>Infliximab</td>
<td>TNF-α inhibitor</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Anti-CD 20</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>IL-6 receptor antagonist</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>Janus kinase enzyme inhibitor 5 mg PO</td>
</tr>
</tbody>
</table>

IL = interleukin; IV = intravenously; PO = by mouth; SC = subcutaneously; TNF = tumor necrosis factor.