DEBRECENI EGYETEM

BIOLOGICAL THERAPY in ONCOLOGY

Ilona Benkő M.D., Ph.D.

associate professor

Dept. of Pharmacology and Pharmacotherapy

CANCER CHEMOTHERAPY

Biological therapy

Biological therapy uses living organisms to obtain large molecules which may control cancer cells. Recombinant DNA technology is used often to produce these drugs.

Some types of biological therapy exploit the immune system's natural ability to detect and eliminate of cancer cells, whereas other types target cancer cells directly.

Classification of drugs for anticancer biological therapy:

1. Monoclonal antibodies
2. Cytokines
3. Gene therapy
4. Therapeutic vaccines
5. Miscellaneous

Complex therapy of malignancies

1. Prevention – chemoprevention

2. Influencing tumor cells with combined anticancer therapy

   „personalized” therapy e.g. by biological drugs

3. Inhibition of metastases – efficient by biological therapy

4. Immunotherapy

5. Prevention and therapy of complications
   prophylaxis and therapy of infections – antimicrobial drugs
   colony stimulating factors for cytopenias

6. Improving quality of life
   therapy of side effects

7. Prevention and therapy of relapses
   follow-up for many years

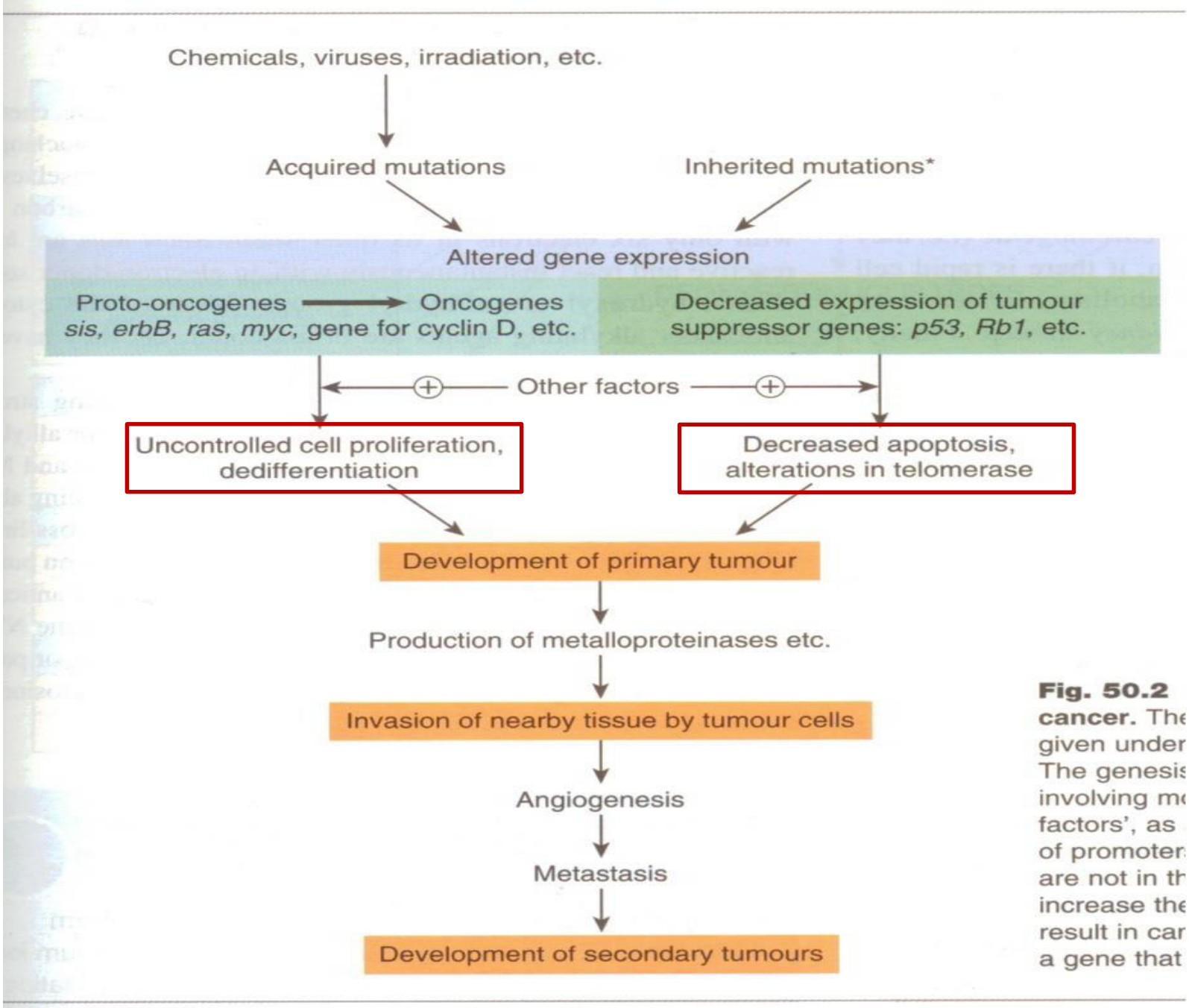


Fig. 50.2 cancer. The given under The genesis involving m factors', as of promoter are not in th increase the result in car a gene that

Rang and Dale's Pharmacology, textbook

Cancer chemotherapy

1. Antiproliferative treatment with classical cytotoxic drugs

Cytotoxic drugs kill cancer cells

2. Biological therapy

Biological therapy

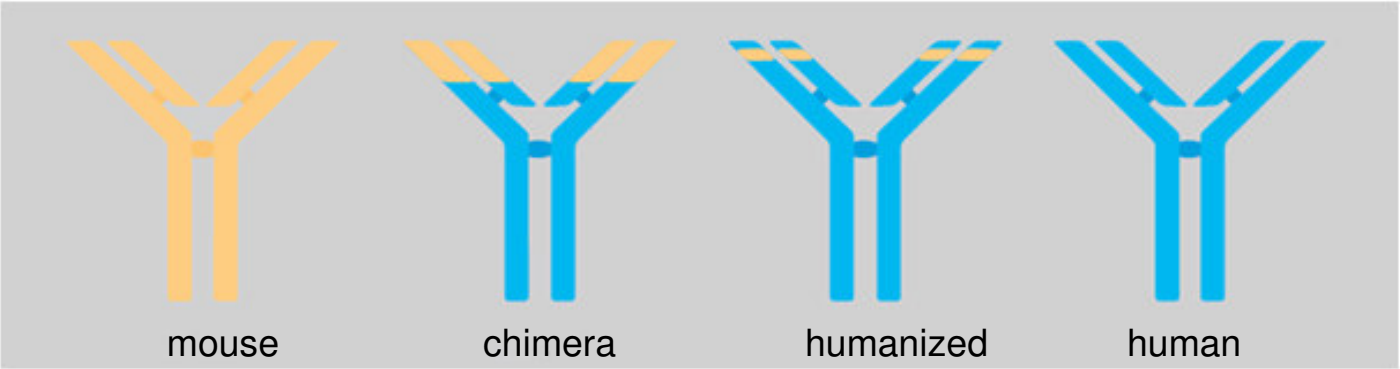
reins cancer cells, which survive.

MONOTHERAPY BY BIOLOGICAL DRUGS IS RARELY EFFECTIVE ONLY in some special cases for short periods.

e.g. in elderly may be enough

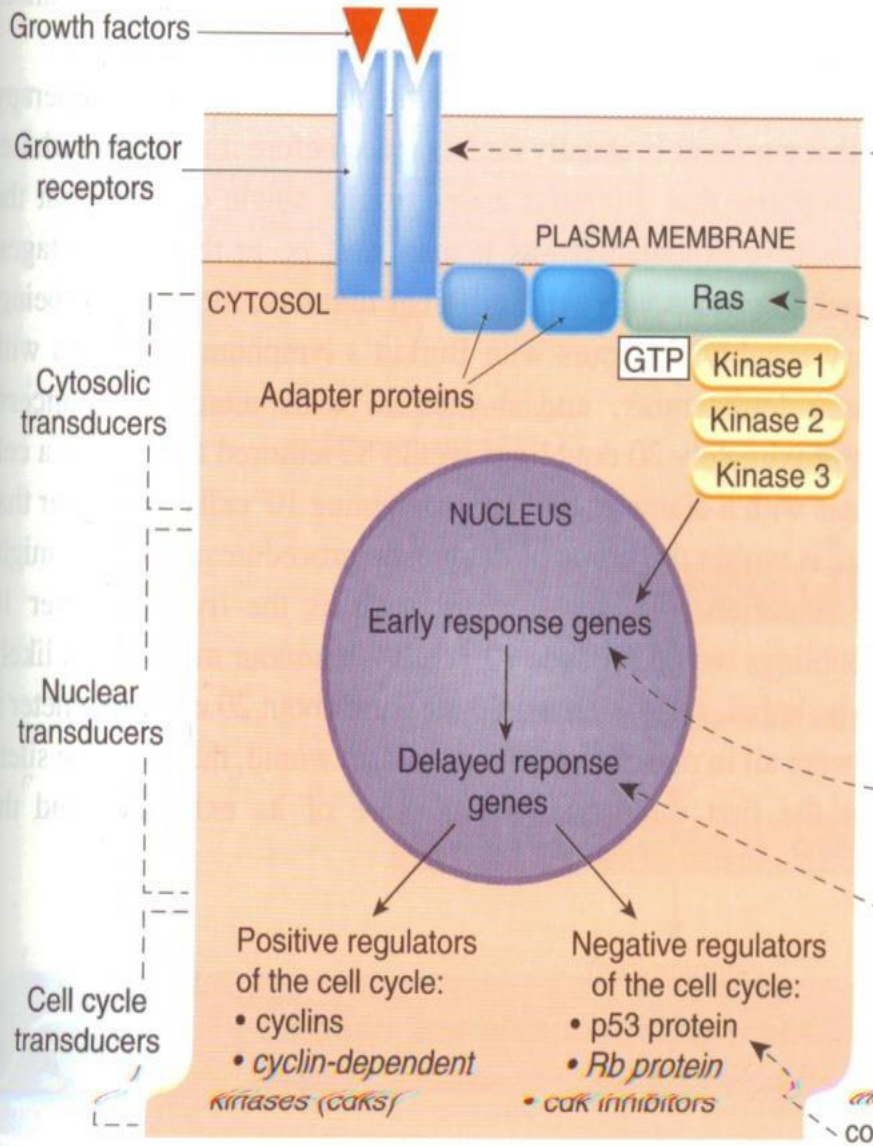
Production of monoclonal antibodies

Monoclonal antibodies are produced by mice frequently.
At the beginning mouse antibodies were used. IMMUNE responses were generated !!
Less antibody formation is seen if monoclonal antibodies bring human parts.



Transgenic mice produce human monoclonal antibodies are obtained.
First Human gene transfer into mice then the cells originated from the mouse spleen are fusioned with , e.g. myeloma cells in vitro. These cells produce desirable monoclonal antibodies permanently .

Drugs for biological therapy are in the red box



Proto-oncogene	Proto-oncogene products	Cancer	Anticancer drugs
Genes for growth factors e.g. for IGF	Growth factors e.g. IGF	Prostate, breast colorectal, etc.	Research in progress.
Gene for EGF receptors (e.g. c-*erbB*)	Her2*, (a receptor tyrosine kinase)	Breast	Inhibited by **trastuzumab** **cetuximab**
Gene for PDGF (c-*sis*)	PDGF (a receptor tyrosine kinase)	Chronic myeloid leukaemia	Inhibited by **imatinib** (aka Gleevec)
c-*ras*	Ras proteins	30% of all tumours	Ras inhibitors in clinical trial
abl	Abl tyrosine kinase (cytoplasmic)	Chronic myeloid leukaemia	Inhibited by **imatinib** (aka Gleevec)
c-*src*	Cytoplasmic tyrosine kinase	Breast, pancreas, bone	Research in progress.
Genes for JAK, Lck		Leukemias	
c-*jun*/c-*fos*	Transcription factors (Jun, Fos, Myc)	Colorectal	
c-*myc*		Lung, neural tissue	

Mutation of the delayed response nuclear proto-oncogenes... can alter expression of the regulators of the cell cycle, e.g. more than 50% *of human tumours have mutations of* the tumour supressor gene that codes for p53 protein

Rang and Dale's Pharmacology, textbook

Some FDA-approved monoclonal antibodies in oncology

			targets
For solid tumors			
trastuzumab	Herceptin	humanised IgG1	HER2
cetuximab	Erbitux	murine IgG1	EGFR Erb1
panitumab	Vectibix	human IgG2	EGFR Erb1
bevacizumab	Avastin	„	VEGF
for hematologic malignant diseases			
rituximab	Mabtera	chimera murine /human	CD20
alemtuzumab	Campath	humanised IgG1	CD52
ofatumab	Arzerra	human IgG1	CD20
Monoclonal antibodies in conjunction with radioisotopes for hematologic malignant diseases			
90Y-ibritumomab	tiuxetan ,Zevalin	murine IgG1	CD20
131I-tositumomab	Bexxar	murine IgG2	CD20

trastuzumab (Herceptin®)

–humanized monoclonal AB

•Pharmacodynamics:
– **inhibitsHER2/neu**
– prevents activation of receptor kinase
– blockade of angiogenetic effect, and tumor growth

•Pharmacokinetics:
– i.v. infusion
– t1/2: 5.8 days
– combination with chemotherapeutics (paclitaxel)

•Adverse effects:
– cardiac failure!, LVF (20% of patients)
– cardiomyopathy

•Therapeutic application:
– metastatic breast cancer (overexpressesHER2/neu)
_ metastatic colon cc

cetuximab (Erbitux®) , panitumumab (Vectibix)

–cetuximab chimerized monoclonal AB
_panitumumab human IgG2

•Pharmacodynamics:
– **inhibition of EGFR erb1**
– prevent activation of receptor kinase, dimerization
– blockade of cell growth

•Pharmacokinetics:
– i.v. infusion
– combination with chemotherapeutics(5-FU)

•Adverse effects:
– hypersensitive reactions

•Therapeutic application:
– squamous cell carcinoma of head and neck(HNSCC)
– metastatic colon cancer

bevacizumab (Avastin®)

Humanized IgG1 immunoglobulin

Effect: as anti-VEGF-A inhibits angiogenesis

reduces tu growth + inhibits metastasis formation

Administration: as an infusion

Toxicity:

- bleeding in lung — life-threatening in 2 % of the patients

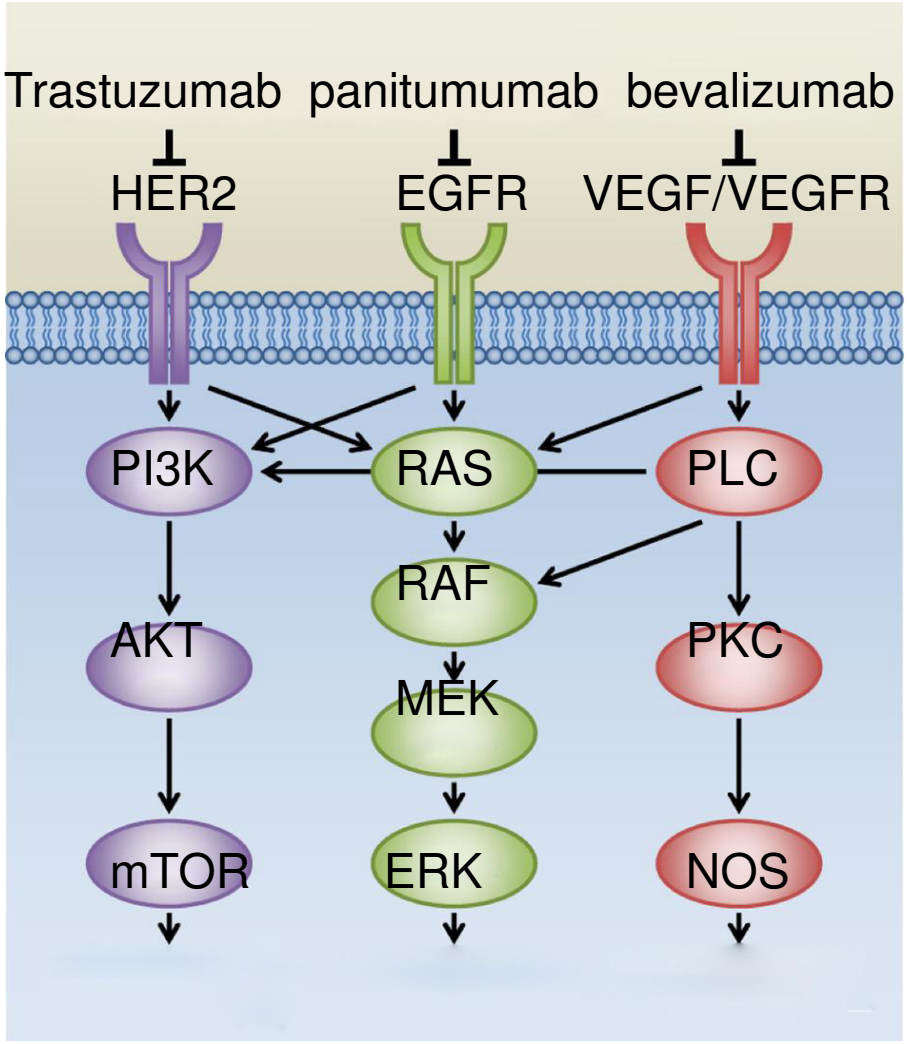
Contraindication: bleeding disorders, hemoptysis, brain metastasis

- Hypertension — endothel NO decreases
- Tromboembolic complications in 3-4 %of the patients

Clinical use: Therapy resistant tumors even with metastasis !!

- renal tumor
- Colon carcinoma breast tu.with metastasis
- Lung cc

Resistance against monoclonal antibody therapy in malignant tumors I.



If we use monoclonal antibodies against mutated growth factor receptor oncogenes, mutations in genes of the molecules along the signaling pathways, which genes generate a constitutively activated tyrosine kinase which renders the tumor insensitive to upstream blockade of the EGFR/RAS/RAF pathway.

Lubner et al. J Gastrointest Oncol 2017; 8(3):499-512

Resistance against monoclonal antibody therapy in malignant tumors II.

Trastuzumab panitumumab:

Changes in target molecules e.g. EGF receptor binding pocket has changed

Amplification of genes of the target molecules
e.g. in case of HER2

Upregulation of HER3
Alternative pathways and increased intracellular signaling

Bevacizumab:

Alternative isoforms of VEGF

Upregulation of HIF-1α (hypoxia inducible factor)
promotion of tumoral vascularization and oxygen delivery

New monoclonal antibodies

nivolumab, pembrolizumab — PD-1 checkpoint inhibitors

against programmed cell death receptor

Effects in human phases: lung cc
melanoma
renal cc

Durable beneficial effects in the 25-30 % of patients

Toxicity: autoimmun responses

onset is very variable, even 6 month after therapy !

Serious side effects in the 20% of the patients :
leukopenia, lymphopenia, hepatotoxicity
GI perforation, toxic megacolon

Adverse effects of monoclonal antibody therapy

-**Autoantibody formation**

-**Cross reactions with own antigenes**

-**Delayed type allergic responses**

-**Neuritis**

-**Demyelinization - even leukoencephalitis**

-**Immunosuppression with infections**

BIOLOGICAL THERAPY WITH CYTOKINES

CYTOKINES

glikoproteins

Physiological functions:

cell to cell communications and control

control of cell cycle, proliferation, differentiation and survival

Classification

growth factors

colony stimulating factors

interleukins

interferons

chemokines

Cytokines with antitumor effects

Interferon – alpha

The IFN-α proteins are produced by leukocytes.
They are mainly involved in innate immune response against viral infection.
At least 13 subtypes

Complex anticancer effect:

stimulation of host-mediated antitumor mechanisms

antiproliferative effect

Clinical use:

hairy cell leukemia, melanoma, follicular non-Hodgkin's lymphoma

IL-2

Frequent >30% of patents serious side effects!!

immunosuppression
Capillary leak sy – breath difficulties

In melanoma as a local treatment IL-2 is well tolerated

Common side effects in cytokine therapies

Acute :

flu-like syndrome
capillary leak syndrome with generalized edema – pulmonary edema

Sweet's syndrome due to immuncomplex formation

Delayed type serious systemic allergic reactions

Stevens Johnson sy
exfoliative dermatitis

GENE THERAPY

1. Antisense therapy (oligonucleotid therapy) against the mutated oncogenes

Targets: **DNA**
mRNA

Gene therapy by antisense molecules with tyrosine kinase inhibitory effect :
oligonucleotids against mRNA in CML
In Philadelphia chromosome in the breakpoint of BCR gene t (9;22) BCR/ABL locus is responsible for the high tyrosine kinase activity

2. Gene substitution therapy:

Replaced the mutated tumor suppressor gene that produces a nonfunctional protein with a normal version of the gene. As tumor suppressor genes (e.g., *P53*) play a role in preventing cancer, restoring the normal function of these genes may inhibit cancer growth or promote cancer regression.

Now there are no such products in clinical practice in cancer chemotherapy.

Vaccines against tumors under investigation

rindopepimut (CDX-110)

effectiveness in gliomas in recidiva

Mechanism of action:

rindopepimut is a peptide which consist of 14 amino acids
enhancement of immune reaction against EGFRvIII

EGFRvIII the epidermal growth factor III. mutant variant

glioblastomas are rich in EGFRvIII

In vivo experiments, increase of antibodies against tumor was observed in mice, rabbits and macaco monkeys