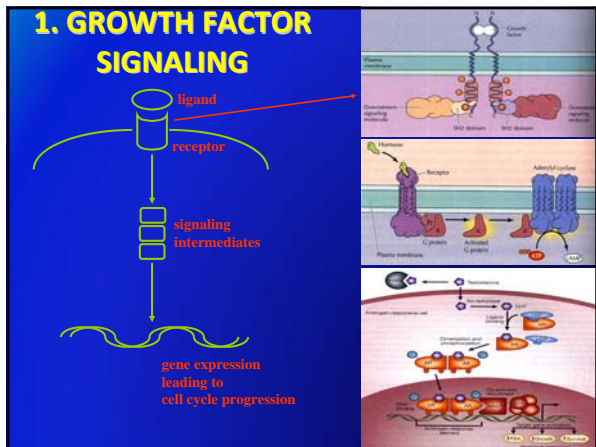
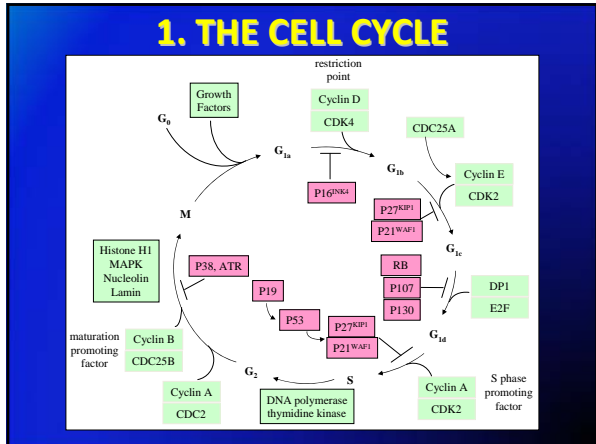
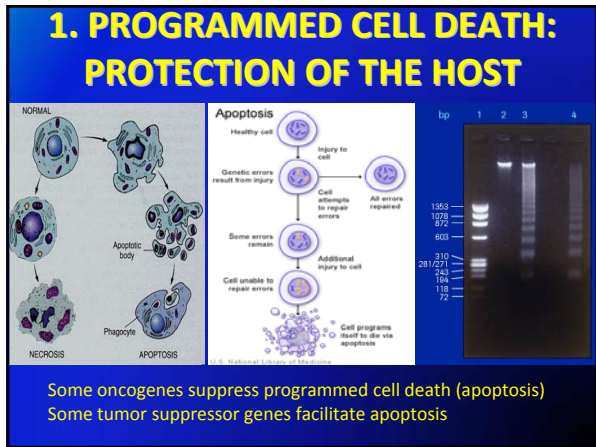


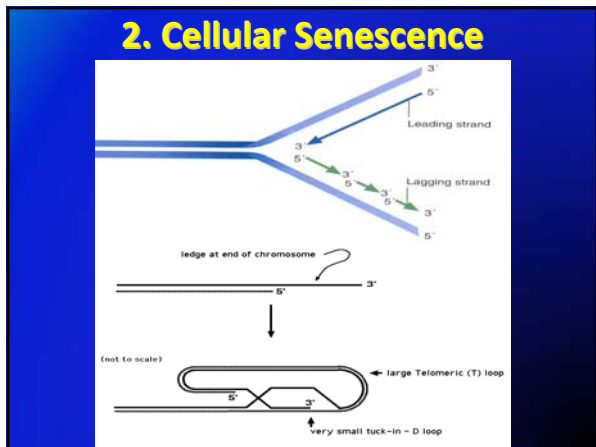


| PHENOTYPIC CHARACTERISTICS OF CANCER | GENETIC BASIS OF CANCER |
|--------------------------------------|---|
| 1. EXCESSIVE GROWTH | ONCOGENES (growth factors and receptors, signaling molecules, apoptosis inhibitors) TUMOR SUPPRESSOR GENES (mediators of cell cycle arrest, mediators of apoptosis) |
| 2. EXTENSION OF LIFE SPAN | SENESCENCE GENES (cell cycle regulators) SENESCENCE SUPPRESSOR GENES (regulators of telomere length) |
| 3. METASTASIS FORMATION | METASTASIS GENES (homing receptors, their ligands, secreted proteases) METASTASIS SUPPRESSOR GENES (adhesion molecules, inhibitors of motility, protease inhibitors) |
| 4. TUMOR-HOST INTERACTIONS | |

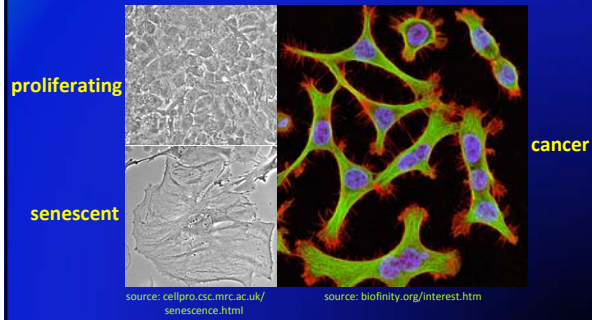






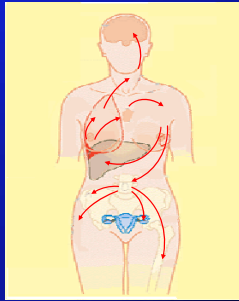


2. Cellular Senescence



3. THE SPREAD OF CANCER

What is Metastasis?



3. METASTASIS MOLECULES

1. EXTRACELLULAR MATRIX DEGRADING ENZYMES

- 1.1. Matrix Metalloproteinases
- 1.2. Proteinases of the fibrinolytic system
- 1.3. Cathepsins
- 1.4. Elastase, Heparanase, and others

2. HOMING RECEPTORS AND THEIR LIGANDS

- 2.1. Selectins
- 2.2. Immunoglobulin superfamily receptors
- 2.3. Integrins
- 2.4. Carbohydrate-rich proteins
- 2.5. Chemokine Receptors

3. SIGNALING MOLECULES ASSOCIATED WITH HOMING RECEPTORS

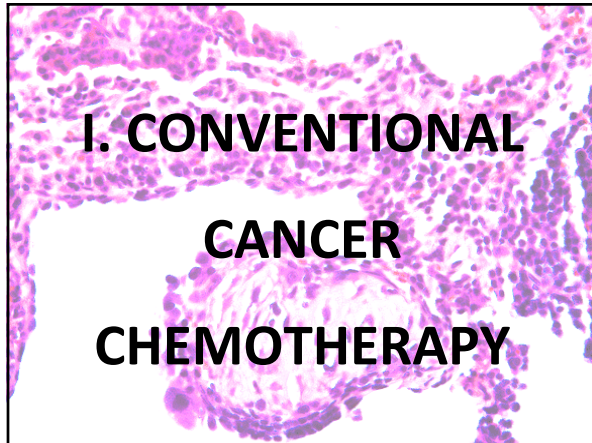
4. TUMOR-HOST INTERACTIONS

1. ANGIOGENESIS once a tumor grows to a certain size, about 1-2 mm diameter, the generation of new blood vessels is a prerequisite for further growth

2. IMMUNE SYSTEM INTERACTIONS immune surveillance protects from tumorigenesis, chronic inflammation can cause DNA damage and increase the susceptibility to transformation, some cancers can induce immune deviation

3. ENDOCRINE FACTORS some tumors - including breast and prostate cancer - grow hormone dependently, some tumors alter the endocrine homeostasis of their hosts

4. STRUCTURAL GROWTH CONTROL the stroma provides important cues that either facilitate or limit tumor growth and dissemination




CLASSES OF ANTI-CANCER DRUGS

Alkylating agents: cross-link two DNA strands
(cyclophosphamide, chlorambucil, BCNU, thiotepa)

Anti-metabolites: have affinity to enzymes of nucleic acid biosynthesis, "false building blocks"
(aminopterin, leucovorin, 5-fluorouracil, mercaptopurine)

Antibiotics: generate free radicals through redox cycles
(adriamycin, mitomycin)

Anti-mitotics: inhibitors of cell division, spindle poisons
(vincristine, vinblastine)



II. NOVEL THERAPEUTIC AGENTS

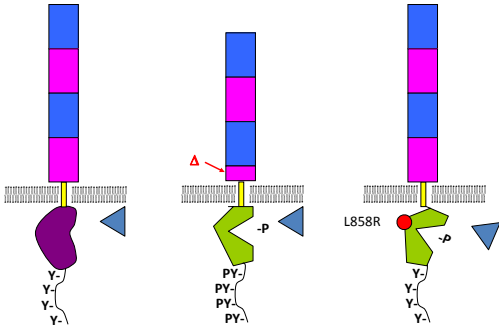
NEW GENERATION ANTI-CANCER DRUGS

1997
NEUTRALIZING ANTIBODIES
(Rituxan, Herceptin, Avastin)

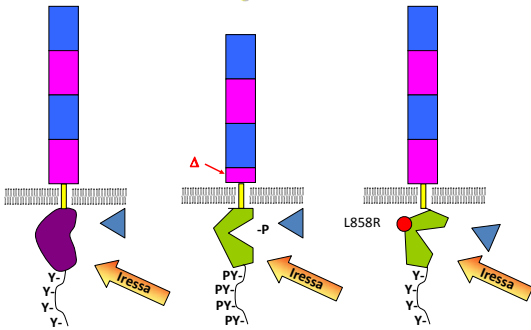
2000
SMALL MOLECULE KINASE INHIBITORS
(ABL inhibitors, EGFR inhibitors, RAS pathway inhibitors)

- EGFR family targets
- Trastuzumab (Herceptin)
 - Cetuximab (Erbix)
 - Panitumumab (ABX-EGF, Vectibix)
 - Nimotuzumab
 - Matuzumab (EMD 72000)
 - Pertuzumab
- Lymphocytic surface targets
- Rituximab (Rituxan) - CD20
 - Tositumomab - CD20
 - Epratuzumab - CD22
 - Lintuzumab (HuM195, SGN-33) (Zamyf) - CD33
 - Siplizumab (MEDI-507) - CD2
 - Alemtuzumab (Campath, Campath-1H, MabCampath) - CD52
- Various targets
- Apolizumab (Remitogen) - HLA-DR
 - CP-751871 - IGF-1R
 - 14G2A - ganglioside GD2
 - Oregovomab (MAb B43.13) (Ovarex) - CA125
 - Bevacizumab (Avastin) - VEGF

EGFR: Gain of Function



Selectivity of Iressa



III. FUTURE DIRECTIONS

Emerging Needs in Cancer Therapy

1. Target survival pathways rather than growth pathways
2. Include telomerase inhibitors
3. Target metastasis
4. Add therapies that modulate the stroma

| | |
|--|---|
| AIDS: Targets: viral entry nucleic acid synthesis reverse transcription Highly active anti-retroviral therapy (HAART) combines 2 to 3 nucleoside analogs With 1 or 2 protease inhibitors or 1 reverse transcriptase inhibitor | Agents: protease inhibitors nucleoside analogs RT inhibitors |
| Tuberculosis: Targets: NAD ⁺ synthesis RNA synthesis RNA translation Combination therapy combines several antibiotics to avoid the development of drug resistance. | Agents: isoniazid rifampicin ethambutol streptomycin |
| Cancer: Targets: DNA damage DNA damage mitosis inhibitors conventional chemotherapy (e.g. COPP, MOPP) combines several DNA damaging agents to limit the impact of their adverse effects. | Agents: redox-cycling antibiotics anti-metabolites (false building blocks) alkylating agents vinca alkaloids |
| Cancer (emerging): Targets: Tumor growth Immortalization Metastasis Host interactions emerging chemotherapy targets major characteristics of transformation to maximize efficacy | Agents: blockers of growth signals inducers of apoptosis telomerase inhibitors homing receptor blockers protease inhibitors angiogenesis inhibitors tumor vaccines |



Leading the REVOLUTION
2009 AACP Annual Meeting and Seminars
July 18–22 • Boston
