New Developments in Cancer Drugs

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**PHENOTYPIC CHARACTERISTICS 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**

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**GENETIC BASIS OF CANCER**

**ONCOGENES** (growth factors and receptors, signaling molecules, apoptosis inhibitors)

**TUMOR SUPPRESSOR GENES** (mediators of cell cycle arrest, mediators of apoptosis)

**SENESCENCE GENES** (cell cycle regulators)

**SENESCENCE SUPPRESSOR GENES** (regulators of telomere length)

**METASTASIS GENES** (homing receptors, their ligands, secreted proteases)

**METASTASIS SUPPRESSOR GENES** (adhesion molecules, inhibitors of motility, protease inhibitors)

**SENEGENCE GENES** (cell cycle regulators)

**SENGENCE SUPPRESSOR GENES** (regulators of telomere length)

**1. GROWTH FACTOR SIGNALING**

Signal

Signal transducers

Gene expression leading to cell cycle progression
1. THE CELL CYCLE

- Growth Factor
- Cyclin D/Cdk4
- Cyclin E/Cdk2
- Cyclin A/Cdk2
- Histone H1
- DNA polymerase thymidine kinase
- P38, ATR
- P53
- P107
- RB
- P130
- P27KIP1
- P21WAF1
- CDC25A
- CDK2
- Cyclin A
- Cyclin B
- E2F
- DP1
- M
- G0
- G1a
- G1b
- G1c
- G1d
- S phase promoting factor

2. PROGRAMMED CELL DEATH: PROTECTION OF THE HOST

Some oncogenes suppress programmed cell death (apoptosis)
Some tumor suppressor genes facilitate apoptosis

3. Cellular Senescence

- End of cell cycle
- Telomere short
- Senescence
- Apoptosis
- Large Tarsier (CT) map
- Small Tarsier (CT) map
- Large Tarsier (T) map
- Small Tarsier (T) map
2. Cellular Senescence

proliferating

senescent

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
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 homoeostasis of their hosts.

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

I. CONVENTIONAL CANCER CHEMOTHERAPY

CLASSES OF ANTI-CANCER DRUGS

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

- **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

### 1997 Neutralizing Antibodies
- Rituxan
- Herceptin
- Avastin

### 2000 Small Molecule Kinase Inhibitors
- ABL inhibitors
- EGFR inhibitors
- RAS pathway inhibitors

### New Generation Anti-Cancer Drugs

#### EGFR family targets
- Trastuzumab (Herceptin)
- Cetuximab (Erbitux)
- Panitumumab (ABX-EGF, Vectibix)
- Nimotuzumab
- Milatuzumab (EMD 72000)
- Pertuzumab

#### Lymphocytic surface targets
- Rituximab (Rituxan) - CD20
- Tositumomab - CD20
- Epratuzumab - CD22
- Lintuzumab (HuMI95, SGN-33) (Zanvil) - CD33
- Siplizumab (MEDI-507) - CD2
- Alemtuzumab (Campath) - 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
Survival versus Growth Pathways

Oncogene over-expression kills tumor cells
Anti-apoptosis leads to tumor cell growth

Challenges and Opportunities for Anti-Metastasis Drug Development

Challenges
Structural diversity: Post-translational modifications regulate function
Importance in immunology: Metastasis molecules execute host defense reactions
Lack of uniqueness for tumors: No mutations but aberrant expression or splicing

Opportunities
Drug targets: Critical functional domains are often small
Specificity: Metastasis molecules are rare in healthy adults (activated only in stress responses)
Accessibility: Promising drug targets are secreted or cell surface molecules

Anti-Metastasis Therapeutics

Early attempts:
* Matrix Metalloproteinase (MMP) inhibitors – unsuccessful
  * bisphosphonates – limited success
  * angiogenesis inhibitors – limited success
  * Cathepsin K inhibitors – in clinical trials
  * inhibitors of cytokine ligands for homing receptors – under investigation
  * 6 Integrin inhibitors in clinical trials: etaracizumab (neutralizing antibody), cilengitide (cyclic peptide)
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, protease inhibitors
- Agents: highly active anti-retroviral therapy (HAART), antiretroviral therapy (e.g. ART, NRTI, NNRTI)

Cancer:
- Targets: DNA damage, telomerase
- Agents: DNA damaging agents, telomerase inhibitors

Tuberculosis:
- Targets: NAD+ synthesis, RNA translation
- Agents: isoniazid, streptomycin, ethambutol

Cancer (emerging):
- Targets: Tumor growth, Immortalization, Metastasis
- Agents: Tumor growth blockers, Immortalization inhibitors, Metastasis homing receptor blockers

Emerging chemotherapy targets major characteristics of transformation to maximize efficacy

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