### Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Usual phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>acute leukemia</td>
<td>precursor</td>
</tr>
<tr>
<td>chronic leukemia</td>
<td>differentiated</td>
</tr>
<tr>
<td>lymphoma</td>
<td></td>
</tr>
<tr>
<td>myeloma</td>
<td></td>
</tr>
</tbody>
</table>

### Total WBC

<table>
<thead>
<tr>
<th>Disease</th>
<th>Blast</th>
<th>Pro</th>
<th>Myel</th>
<th>Meta</th>
<th>Band</th>
<th>Seg</th>
<th>Lymph</th>
</tr>
</thead>
<tbody>
<tr>
<td>leukemoid reaction</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>13</td>
<td>82</td>
<td>3</td>
</tr>
<tr>
<td>acute leukemia</td>
<td>82</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>CML</td>
<td>2</td>
<td>8</td>
<td>13</td>
<td>18</td>
<td>20</td>
<td>37</td>
<td>2</td>
</tr>
<tr>
<td>CLL</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>98</td>
</tr>
</tbody>
</table>
Acute leukemias

- **Major Categories:**

  ALL = acute lymphocytic, lymphoid or lymphoblastic leukemia  
  versus  
  ANLL = acute non-lymphocytic leukemia = acute myeloid leukemia (AML)  
  - includes granulocytic, erythroid, and megakaryocytic lineages
Acute Leukemia

- imbalance between proliferation and differentiation
- majority of cells not dividing
  - therapeutic dilemma

Leukemias - evidence of damage to DNA

- majority have visible chromosome abnormality
- tumor-specific chromosomal translocations, e.g.,
  - t(15;17) acute promyelocytic leukemia
  - t(9;22) chronic myeloid leukemia
  - t(8;14) Burkitt's lymphoma/leukemia

Types of Genetic Damage (DNA mutations)

- rearrangements
- translocations
- point mutations
- deletions
Genetic damage in leukemias

• Causes
  – radiation
  – carcinogens
    » benzene
    » chemotherapy
  – hereditary chromosome disorders
  – hereditary disorders of DNA repair
  – viruses (eg, HTLV-I)

• Proto-oncogenes → oncogenes
• Inactivation of ‘tumor suppressor genes’
• Multiple events

Proto-oncogenes

• Human genes homologous with genes in viruses which cause cancer in animals
  – e.g., abl is homologous with genetic material in the Abelson murine leukemia virus

• Protein product of proto-oncogenes may have an important normal function in humans:
  – e.g., tyrosine kinase activity of abl
  – e.g., transcriptional regulation by myc

• Conversion to oncogenes by mutational events → enhanced or disturbed function

Conversion of proto-oncogene to oncogene

• Possible mechanisms
  – Unaltered gene product (e.g., myc in Burkitt’s)
  – Altered gene product
    » usually a fusion protein (e.g., bcr-abl in CML)
Gene Products of Oncogenes

- Growth factors
- Receptors for growth factors
- Molecules involved in signal transduction
- Proteins that bind DNA and regulate nuclear functions (e.g., transcription factors)

Oncogene Activation

<table>
<thead>
<tr>
<th>Translocation</th>
<th>Disease</th>
<th>Proposed mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(8;14)</td>
<td>some B-cell lymphomas, ALL</td>
<td>↑ expression of transcription factor (myc)</td>
</tr>
<tr>
<td>t(9;22)</td>
<td>CML, some ALL</td>
<td>chimeric signalling molecule (bcr-abl)</td>
</tr>
<tr>
<td>t(15;17)</td>
<td>acute promyelocytic leukemia</td>
<td>chimeric transcription factor (pml-rarα)</td>
</tr>
</tbody>
</table>
Acute Promyelocytic Leukemia

- about 7% of all ANLL
- malignant clone shows early differentiation
- cells often contain multiple Auer rods
- disseminated intravascular coagulation common
- t(15;17) almost always present
- sensitivity to arsenical trioxide and retinoic acid
Acute Promyelocytic Leukemia (t(15;17))

- Retinoic acid receptor-α (RAR-α) gene on 17q in normal cells
- RAR-α gene product is a nuclear receptor protein acting as transcription enhancer in myeloid differentiation when bound to retinoic acid
- In t(15;17), part of RAR-α gene on 17q is translocated to 15q and fused to another gene, PML
- PML is normally a tumor suppressor gene which modulates transcriptional activation and promotes apoptosis
- The fusion gene product (pml-rar) of APL causes failure of promyelocytes to differentiate and blocks apoptosis

Retinoic acid induces remissions in APL

- Marrow hypoplasia not mandatory
- Malignant clone matures to PMN
- Leukemic clone replaced by normal cells in marrow
- t(15;17) no longer readily detected
- 'Differentiating agent'
- Relapse occurs, necessitating chemotherapy
Tumor-suppressor genes

- inactivation of both alleles of gene allows tumor growth
  - minor DNA damage - promotes repair
  - major DNA damage - promotes apoptosis
  - e.g., retinoblastoma gene
  - modulates cell cycling
- ? deleted in therapy-related acute leukemia

How is Lineage & Stage Specificity Achieved?

<table>
<thead>
<tr>
<th>Acute non-lymphocytic leukemia</th>
<th>clonal marker expressed in:</th>
<th>progenitor cell of origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>most patients</td>
<td>neutrophils, monocytes</td>
<td>granulocyte-monocyte progenitor</td>
</tr>
<tr>
<td>minority</td>
<td>neutrophils, monocytes, RBC's, platelets</td>
<td>multipotent hemato-poietic progenitor</td>
</tr>
</tbody>
</table>
Lineage & Stage Specificity in ALL

Acute lymphocytic leukemia

- usually arises in early progenitor B or T cell
- B:T 4:1
- occasional mixed B and T cell phenotype, suggesting malignant event at earlier multipotent lymphoid progenitor cell

<table>
<thead>
<tr>
<th>Feature</th>
<th>ALL</th>
<th>ANLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>usual age group</td>
<td>children</td>
<td>adults</td>
</tr>
<tr>
<td>myeloperoxidase stain</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Auer rods</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>terminal transferase (TdT)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>cell surface Ag’s</td>
<td>B or T</td>
<td>myeloid</td>
</tr>
<tr>
<td>Ig or T cell receptor gene rearrangement</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Flow cytometry in acute monocytic leukemia
Acute Leukemia

**Event**
- Marrow failure
- Hyperuricemia
- DIC

**Consequences**
- Neutropenia
- Anemia
- Platelets
- Tubular damage
- Acute renal failure
- Platelets
- Abnormal clotting
- Infection
- Weakness, fatigue
- Bleeding
- Acute renal failure
- Bleeding

**Organ infiltration**
- Marrow involvement
- Bone pain
- Enlarged liver, spleen, nodes
- Hypertrophied gums
- Meningeal infiltration
- Headache, cranial nn. palsy
Acute Leukemia

- blast leukocytosis

- leukostasis in small blood vessels:
  - tachypnea
  - dyspnea
  - tinnitus
  - lethargy
  - stupor
Acute Leukemia - treatment

• intensive combination therapy
• chemotherapy continued beyond remission
• central nervous system prophylaxis (ALL)
• bone marrow transplantation in selected patients
• therapy is dangerous
• supportive measures
  – allopurinol
  – rbc and platelet transfusions
  – antimicrobials
Acute Leukemia - results of treatment

<table>
<thead>
<tr>
<th></th>
<th>ALL children</th>
<th>ALL adults</th>
<th>ANLL children</th>
<th>ANLL adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>complete remission</td>
<td>90%</td>
<td>75%</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>median survival</td>
<td>6+ yrs</td>
<td>1-2 yrs</td>
<td>1-2 yrs</td>
<td></td>
</tr>
<tr>
<td>5 yr disease-free survival</td>
<td>70%</td>
<td>20-45%</td>
<td>10-20%</td>
<td></td>
</tr>
</tbody>
</table>