Cancer

The fundamental defect is 

unregulated cell division.

Properties of Cancerous Cells
Altered growth and proliferation
  Loss of growth factor dependence
  Loss of contact inhibition
  Immortalization
Altered cell adhesion (associated with Metastasis)
  Poor adhesion, altered CAM expression
  Increased ECM proteolysis, lower ECM secretion
Increased membrane transport & radiation resistance

Causes of Cancer
EM radiation - X-rays, Gamma rays, UV
Chemical carcinogens
Viruses
  Insertional mutagenesis
  Expression of viral oncogenes
“Multiple Hit” Theory of Cancer

Many mutations are required to make a cancerous cell.
Cancer incidence increases with age.

Types of Cancer

Carcinomas - epithelial in origin, most common type
Sarcomas - derived from ‘connective tissue’
Leukemias and lymphomas - immune cell derived
Teratomas - germ cell derived; rare but fascinating.
Figure 19.10 Photomicrograph of a Section Through a Teratocarcinoma

Molecular Genetics of Cancer

Oncogenes

Proto-oncogenes

Tumor Suppressor Genes

Oncogenes - when inappropriately activated or over-expressed, promote unregulated cell division.

Proto-oncogenes - normal cellular versions that can be mutated to become oncogenes

Viral Oncogenes - acquired cellular proto-oncogenes are mutated to permanently activate or over-express
Examples of viral oncogenes:

\( \nu\text{-erbB} \) is a truncated EGF receptor, with permanently activated internal tyrosine kinase domain.

See also Fig 6.10 in Gilbert.
Examples of viral oncogenes

\[ \nu \text{-src} \] is an intracellular tyrosine kinase (cytoplasmic),
also constitutively active.

Normal cellular counterparts of viral oncogenes

\[ c \text{-erbB} \] is a normal cellular EGF receptor
\[ c \text{-src} \] is cellular intracellular tyrosine kinase, normally activated
by a growth factor signaling pathway

Discovery of viral oncogenes and their origins led to awarding
of Nobel Prize (Physiology or Medicine) in 1989 to
J. Michael Bishop & Harold E. Varmus
Many proto-oncogenes are in signal transduction pathways

Growth factors
Growth factor receptors
Intracellular signaling proteins
Transcription factors
(Regulators of apoptosis)
(Cell cycle regulators)

int2 is FGF-like
wnt1 is wingless-like protein, first discovered as an oncogene activated by insertion of mouse mammary tumor virus (MMTV) near normal gene
(trivia: originally called int1, for "integration").

trkA (NGF receptor)
erbB (EGF receptor)
ptc (Patched - Shh receptor)
Many proto-oncogenes are in signal transduction paths

- Growth factors:
- Growth factor receptors:
- Intracellular signaling proteins:
  - ras - GTP binding protein
  - raf - intracellular ser/thr kinase - acts just downstream of ras in RTK pathway
  - src - intracellular tyrosine kinase
  - abl - intracellular tyrosine kinase
Molecular Genetics of Cancer - Src functions

Src protein interacts in many pathways including with integrins

Src protein interacts in many pathways

See Fig. 6

G1 phase → S phase
Molecular Genetics of Cancer

Intracellular signaling proteins:
  
  abl - intracellular tyrosine kinase

Causes Chronic Myeloid Leukemia (CML) via novel fusion protein formed by t(9:22) translocation

\[ \text{t(9:22) translocation - the "Philadelphia chromosome"} \]

Fusion protein blocked by Gleevec

Many proto-oncogenes are in signal transduction pathways

Growth factors:
Growth factor receptors:
Intracellular signaling proteins:
Transcription factors:
  
  myc - basic Helix-loop-helix (bHLH)

  fos, jun - basic Leucine zipper (bZIP), together form AP1

  \( \beta \)-catenin - Wnt signaling pathway TF (can promote transcription from myc gene)
Figure 6.24(1) The Wnt Signal Transduction Pathway

Figure 6.24(2) The Wnt Signal Transduction Pathway

APC = adenomatosis polyposis coli (tumor suppressor)

Figure 21.18 Differentiation of Osteogenic Sarcomas in Mice Due to Inactivation of the Myc Transcription Factor
### Molecular Genetics of Cancer

Many proto-oncogenes are in signal transduction paths

- **Growth factors:**
  - *wnt-1, int-2*

- **Growth factor receptors:**
  - *trkA, erbB, ptc*

- **Intracellular signaling proteins:**
  - *ras, raf, src, abl*

- **Transcription factors:**
  - *myc, fos, jun, β-catenin*

- **Regulators of apoptosis:**
  - *bcl-2*

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### Tumor Suppressor Genes

- Normally function to inhibit cell proliferation (or promote apoptosis)
- Loss-of-function mutations promotes cancer (recessive)
- Both copies of tumor suppressor gene must be lost for complete loss-of-function ("2 hit" process)
- Inherited mutation in one allele means only single loss of remaining good allele can promote cancer ("LOH")

The **p53 gene** - mutated in ~50% of all human cancers

- (Non-heritable, somatic mutations)
Molecular Genetics of Cancer

Heritable p53 gene mutation causes high cancer risk.

Li Fraumeni syndrome
- rare genetic condition resulting in high cancer rate
  (soft tissue sarcomas, breast cancer, leukemia, brain tumors, melanoma, etc.)
- mainly caused by missense mutations changing single AA, but also simple deletions
- some mutations create dominant-negative protein
  (blocks function of normal, wild-type p53 protein)

(p50% of patients have cancer by age 40, 90% by age 60)

Molecular Genetics of Cancer - Tumor Suppressor Genes

p53 protein
- regulates progression through the cell cycle, especially at the G1-S checkpoint.
- blocks entry into S phase if DNA is damaged, allowing time for repair
- if repair fails, then p53 promotes apoptosis

p53 protein - is a transcription factor
p53 core DNA-binding domain + DNA
Yellow - most commonly mutated aa's in human cancer
Red - Zn ion
p53 protein
- is a transcription factor
- turns on p21 (aka WAF1, CIP1) - a **cyclin-dependent kinase inhibitor**
- p21 blocks activity of cyclinE-cdk2 (among others), the main regulator of entry into S phase.

### Figure 8.2(2) Cell Cycles of Somatic Cells and Early Blastomeres

- MPF - G2-M checkpoint regulator
- G1-S checkpoint regulator
- Cyclin B + cdk1
- Cyclin B
- Cyclin E + cdk2
- Cyclin E
- Cyclin D + cdk4,6
- Cyclin D
- Cyclin A
- Cyclin A
- cdk2
- cdk2
- cdk2
- G2
- Interphase
- Mitosis

- if repair fails, then p53 promotes apoptosis
- activate bax gene (pro-apoptotic)
- repress bcl-2 gene (anti-apoptotic)
p53's apoptotic function is, however, largely non-transcriptional (not well understood).
Other cdk inhibitors are needed:

p16 (Ink4a) is also a cdk inhibitor (especially cdk4), is mutated in malignant melanomas