Cancer results from a breakdown of the regulatory mechanisms that govern normal cell behavior: proliferation, differentiation and survival of cells of a multi-cellular organism must be carefully regulated to meet the needs of the whole organism. Cancer derives from errors at the molecular and cellular level -> abnormal proliferation of a type of cell.

Student Learning Outcomes:
1. to explain the development and causes of cancer – from a single altered cell (caused spontaneously or by chemicals, radiation or viruses)
2. to describe some tumor viruses, their transforming proteins and types of cancers they cause, and the usefulness of these viruses as model systems.
3. to explain the essential features of oncogenes and of tumor suppressors, and how different, and sequential mutations lead to malignant cancers.
4. to describe some modern molecular approaches to detecting and treating cancer.

Important Tables are is Tables 1, 2, 3, 4, 5, 6; Figures are 2, 4*, 5, 6, 7*, 8, 10*, 12*, 17*, 18*, 19, 20, 21*, 22*, 23*, 24*, 26, 28, 31, 32, 33*, 36*, 37*, 38, 39, 40
Relevant questions at end of chapter are all.

Continual unregulated proliferation of cells
Is the fundamental abnormality resulting in cancer.
The cells no longer respond appropriately to external signals.
The final metastatic cancer reflects accumulated abnormalities in multiple regulatory systems.
1.4 x 10^6 cases/year; 560,000 deaths,
Incidence increases with age (Fig. 3)

Types of cancer (Table 1 – can be any cell type)
Tumor – abnormal proliferation of cells
   Benign tumor – confined to original site (ex. skin wart)
   Malignant tumor – invades surrounding tissue
      Spreads throughout body – metastasis
      Only these are referred to as cancers.
   Carcinoma - ~90% of cancers = epithelial cells
   Sarcoma – rare – solid tumors of collective tissue
   Leukemia & lymphomas are tumors of blood-forming cells and immune system cells

Development of cancer
Tumor clonality is fundamental – tumor
   Derives from one initial cell with mutation;
   Then multistep process – original cell becomes
   More aberrant and malignant; (Figs. 2, 4)
   Selection of cells that can reproduce better.

Tumor initiation is 1st genetic change, then progression as additional mutations, selection for faster-growing cells (Fig. 5* Colon cancer is well studied).

**Tumor promoters** cause increased cell division:
- Help cancer cells proliferate.
- Ex. estrogen promotes growth of endometrium.

**Properties of cancer cells:**
Uncontrolled growth from accumulated abnormalities:
- *In vitro* culture (Fig. 7) of normal cells shows Go density-dependent inhibition when crowded.
- Cancer cells keep growing and pile up.

Reduced requirement for extracellular growth factors:
- Or production of autocrine growth stimulation,
- Or unregulated intracellular pathways
  - (ex. mutated Ras always signals).
- Less regulated by cell-cell or cell-matrix interactions:
  - Less adhesive cells lose contact inhibition (Fig. 9)
  - Can invade soft agar

Cancer cells secrete proteases to digest extracellular matrix:
- -> helps them invade nearby tissues.

**Angiogenesis:** cancer cells secrete growth factors to induce new blood vessels (Fig. 5):
- supplies food to tumor and helps metastasis.

Fail to differentiate normally -> keep proliferating.
- Ex. leukemia cells from hematopoietic stem cell line have not finished differentiation to then stop growth (Fig. 10)
- One treatment is agents that cause differentiation.

**Transformation assay** permit experimentally asking what genes or proteins cause cells to be come cancer-like:
- permanent genetic change – altered properties.
- (Fig. 11) study *in vitro* focus assay of tissue culture cells.
- Also test growth in soft agar in Petri plates.
- Ex. Chick embryo fibroblasts and RSV virus
18.2 Tumor viruses (Table 2). Tumor viruses are important experimental model – they grow typically (lytically) in permissive cells; promote tumors in nonpermissive cells. Viral proteins interfere with normal cell regulation, Stimulate cell cycle to increased proliferation.

Hepatitis B and C: (HBV, HBC) infect liver cells; Liver cancer in people with chronic infections.

Simian virus 40 (SV40) [and polyomaviruses] Small DNA viruses (Fig. 13). Transform nonpermissive host (Fig. 12). Important experimental model of cancer: Sv40 T antigen (transforming) binds to and inactivates Rb and p53 tumor suppressors


Adenoviruses – DNA viruses (Fig. 15). Early proteins E1A and E1B bind and Inactivate Rb and p53. ->: transformation.

Herpesviruses – big family of large genome DNA viruses. Herpes simplex I and II (cold sores, genital sores) Kaposi’s sarcoma associated with a herpesvirus. Sarcoma cells secrete growth factors. Epstein Barr virus: virus infects B lymphocytes. (mononucleosis), Burkitt’s lymphoma

Retroviruses may cause cancer (Fig. 16): RNA genome, convert to DNA, integrate host genome Most only have 3 single genes: gag, poly, env: HTLV-1 -?T-cell leukemia HIV kills T cells, and cancers are indirect result Of lack of immune surveillance.

RSV Rous sarcoma virus: RNA genome -> DNA provirus integrates. RSV and others carry oncogenes = variants of normal genes-> tumors. Src (nonreceptor protein tyr kinase) binds to Phosphates of receptors; signals; Has SH2 homology domain
18.3 Oncogenes drive cell proliferation.
Tumor viruses carry particular genes (oncogenes) -> induce cell transformation.
Important model systems for studying cancer.
Studies of viral oncogenes led to cellular oncogenes
And the proto-oncogenes.
Most human cancers do not derive from viral infection, but from radiation, chemicals, spontaneous errors.

Retroviral oncogenes were identified by comparisons of wild-type and mutant viruses (Figs. 17).
RSV -> transformation, and has extra gene Src
    Protein tyrosine kinase
ALV -> does not transform, smaller genome
    Mutant RSV unable to transform confirmed role of Src.

Table 3 lists retroviral oncogenes:
    These genes are not required for viral replication,
    But cause tumors in susceptible animals, cells.
    Note: many, like ras, raf, src are
    Proteins of signal transduction pathways.

Proto-oncogenes are normal cellular versions of oncogenes.
Studies of highly oncogenic viruses showed
    the new protein came from a normal cellular gene
    that was picked up, fused to a viral gene:
Oncogene is over-expressed or aberrant form of proto-oncogene
    (can be fusion or point mutation or other alteration).
    Result is altered cell cycle regulation.
    Ex. Fig. 18 Abelson leukemia virus is gagΔabl;
    Fig. 19 Raf oncogene always kinase signals) (See. Ch. 15)

How do oncogenes cause human cancer?
Different mechanisms were discovered experimentally:
Cell culture permitted extraction of DNA,
Some were related to viral oncogenes:
    – ras (Fig. 21); others were new (Fig. 22).
    RasH oncogene differs 1 point mutation from normal rasH:
        Always active GTP bound state.

Animal models showed chemicals can induce mutations:
Translocations (break/join) of chromosomes -> oncogenes (brc/abl)
    Ex. c-myc (Fig. 22) in Burkitt’s lymphoma: transcription factor
        c-myc is over-expressed in B cells since moved to IgH promoter.
    Ex. bcr/abl fusion protein in chronic myeloid leukemia (CML)
        Fusion protein results in overactive kinase.
Gene amplification can also convert normal gene to oncogene.
Function of oncogene products. About 100 genes are oncogenes:
  Many proto-oncogenes have normal roles
  in cell proliferation, others affect differentiation.

Ex. ERK signaling path by growth factor EGF
  (Fig. 24; Fig. 15.34, 37).
  EGF binds ErbB cell receptor: stimulates via
  Ras/Raf to MEK, ERK -> increase Fos mRNA.
  Mutated or over-expressed proteins always signal.

Ex. mutated tyrosine kinase receptor signals (Fig. 25).
  Tel/PDGFR fusion protein is always active.
Ex. (Fig. 26). Fos/jun (AP-1) activates synthesis
  of cyclin D1 -> transformation. (G1 -> S)
  Gene encoding cyclin D1 is proto-oncogene.
Ex. fusion protein PML/RAR$\alpha$ -> leukemia (APL):
  Blocks differentiation of promyelocytes (Fig. 28).

[some oncogenes block apoptosis path;
Some promote survival PI-3 kinase/AKT]

18.4. Tumor suppressor genes (Table 5).
Proteins whose normal role is inhibition of proliferation,
When inactivated (mutation, deletion) -> promote cancer.

Retinoblastoma important human cancer. (Fig. 31)
Rare inherited susceptibility to eye tumors (dominant disease).
  1970s theory disease caused by inheritance
  of 1 mutated gene (Rb); if other gene was mutated
  (somatic mutation) -> cancer (Fig. 32)
  Therefore, Rb was a tumor suppressor gene.
Rb is mutated in many cancers; target of many viral oncogenes.

Other tumor suppressors are frequently deleted or mutated in cancers.
  Ex. p53, INK4, BRCA1, BRCA2 (Table 5)
These proteins normally inhibit cell proliferation or
  survival, often the same pathways stimulated by oncogenes.

Ex. Rb and Ink4 (p16) inhibit passage through G$_1$
  (inhibit transcription Fig. 16.17).
  Cdk4, 6/cyc D phosphorylates Rb and then progress.
  P16 inhibits Cdk4,6/cycD. (Fig. 36).

Ex. p53 is very important for cell cycle arrest
  -> apoptosis after DNA damage.
  (Fig. 37) p53 is induced by DNA damage
  -> p21 inhibits CDk (Fig. 16.21).

Ex. miRNA regulate expression: let-7 mi RNA
Roles of oncogenes and tumor suppressor genes in tumor development.
Cancer is a multistep process: study with large-scale genomic approaches
Normal cell -> malignant, metastic
requires sequential mutations.

Ex. colon cancer and breast cancer (Fig. 39) sequential mutations:
  - Ras or Raf oncogene activates ERK path
  - Tumor suppressor or oncogene in Wnt path
  - Tumor suppressor involved in TGFB path
P53.

18.5 Molecular approaches for cancer treatment.
Prevention and early diagnosis:
Reduce risk of known carcinogens.
Early detection of small premalignant lesions ->
  - Easier ‘cure’, survival. (Fig. 40)

*** big search to identify susceptible individuals:
  - Mutated tumor suppressors, oncogenes, DNA repair gnees
  - Est. 5% of cancers inherited susceptibility

Molecular diagnosis: chromosomes, molecular markers.
  - Ex. bcr/abl, pml/rar  fusions
  - N-myc amplified in neuroblastoma
  - Use of DNA microarrays permits genetic snapshot expression

Molecular treatment plans: Table 6
Drugs target to oncogene proteins:
  - ex. Imatinib inhibits the abl kinase domain
  - Ex. herceptin monoclonal antibody to
    Erb-2 oncogene for breast cancer.
  - Ex. gefinib specifically binds most common
    mutant EGF receptor (ErbB)
    and inhibits activity. (Fig. 41)