CELL TRANSFORMATION

ONCOGENIC VIRUSES
ONCOGENIC VIRUSES OR TUMOR VIRUSES

– ability to induce cell transformation and to form tumors
Tumor Viruses

For most viruses:

Genome → viral proteins

Replication → Lysis → Progeny virions

Lytic Life Cycle
Tumor Viruses

Latent Life Cycle

Virus

Cell

Integration (usually)

Transformation

Virus-specific proteins expressed - No mature virus
Changes in the properties of host cell - TRANSFORMATION
Both DNA and RNA tumor viruses can transform cells. Integration of the viral genome into the host cell DNA occurs (usually) by similar mechanisms.

**VIRAL TRANSFORMATION**

The changes in the biological functions of a cell that result from regulation of the cell’s metabolism by viral genes and that confer on the infected cell certain properties characteristic of neoplasia.
Major human Oncogenic Viruses

**DNA Viruses**

Small DNA tumor viruses
- Adenovirus
- SV40
- Human Papilloma virus (HPV)

Herpesviruses (large)
- Epstein Barr virus (EBV)
- Kaposi’s Sarcoma Herpesvirus (KSHV)

Other
- Hepatitis virus B

**RNA viruses**

Retroviruses - Human T-cell Leukemia Virus 1 and 2 (HTLV1, HTLV2)
Hepatitis virus C
Tumor Viruses

Transformation:

Loss of growth control

Ability to form tumors - viral genes interfere with control of cell replication
Control of cell replication

Two categories of cell regulatory genes

- Proto-oncogenes (cellular oncogene, c-onc)
- Tumor suppressor genes

- Proto-oncogenes code for
  - Growth factors
  - Receptors
  - Signal-relay or transduction factors

- Tumor suppressor genes code for factors that down-regulate the cell cycle
  - P53
  - Rb
TRANSFORMATION

Properties of the TRANSFORMED CELL are:

• Loss of growth control (loss of contact inhibition in cultured cells)
• Cell morphology changes
• Tumor formation
• Transformed cells frequently exhibit chromosomal aberrations
• Mobility
• Reduced adhesion
Figure 28.2 Normal fibroblasts grow as a layer of flat, spread-out cells, whereas transformed fibroblasts are rounded up and grow in cell masses. The cultures on the left contain normal cells, those on the right contain transformed cells. The top views are by conventional microscopy, the bottom by scanning electron microscopy. Photographs kindly provided by Hidesaburo Hanafusa and J. Michael Bishop.
Changes When a Cell Becomes Cancer Cell

Multiple Genetic Changes

Changes lead the conversion of normal cells → transformed cells:
  Multiple genetic changes: 6-7 events over 20-40 years

Factors (carcinogens) that increase the conversion:
  Initiate/Promote suggest stages in cancer development

Genes that cause transformation:
  **Oncogenes** (100+)
    Viral oncogenes and cellular counterparts (proto-oncogenes)
    Gain-of-function or **Activated**
  **Tumor suppressor genes** (~10)
    Loss-of-function or **Inactivated**
Tumor Viruses

Mechanisms of oncogenesis:

- Presence of viral oncogene (v-onc)
- Activation of cellular proto-oncogenes or inactivation of tumor suppressor genes
V-onc

- early viral genes
- altered form of c-onc

**Figure 28.5** Cells transformed by polyomaviruses or adenoviruses have viral sequences that include the early region integrated into the cellular genome. Sites of integration are random.

SV40 T/t antigens
Adenovirus E1A, E1B
Activation of proto-oncogenes

- mutation
- amplification
- translocation
- insertion of viral genome
Inactivation of tumor suppressor genes

- mutation
- viral oncoproteins
- viral degradation
Anti-Oncogenes

Retinoblastoma

Rb Gene

Rb protein

Rb

105kD

Stops replication

Adenovirus E1A

Cell cycle continues
Anti-Oncogenes

p53

P53 gene

Hepatitis C

P53 gene

P53 gene

P53

DNA

Stops replication

replication

replication

Papilloma proteolysis
DNA Tumor Viruses

DNA genome

Integration

TRANSFORMATION

-Typically nonproductive infections
-Transformation of nonpermissive cells
- usually only **EARLY** functions are expressed
DNA Tumor Viruses In Human Cancer

HUMAN PAPILLOMAVIRUSES

urogenital cancer

benign warts malignant squamous cell carcinoma

Papilloma viruses are found in 99.7% of women with cervical cancer

Squamous cell carcinoma:
Larynx
Esophagus
Lung

All histologically similar

10% of human cancers may be HPV-linked
HUMAN PAPILLOMAVIRUSES

• 118 types identified - most common are benign types 6 and 11
• most cervical, vulvar and penile cancers are ASSOCIATED with types 16 and 18

EPIDEMIOLOGICAL STUDIES BUT:
HPV 16 and HPV 18 do transform human keratinocytes

The important transforming genes in papilloma viruses are the non-structural regulatory genes, E6 and E7 – inactivation of tumor supressor genes (Rb, p53)
DNA Tumor Viruses In Human Cancer

ADENOVIRUSES

Highly oncogenic in animals
Only part of virus integrated
Always the same part
Early functions
E1A region: 2 T antigens
E1B region: 1 T antigen

E1A and E1B = Viral Oncogenes
Considerable evidence for role in human cancer

- Some very tumorigenic in animals
- Viral DNA found in small proportion of tumor cells: “hit and run”
  
  (Virus cause mutation in cell genes and then virus is no longer needed)
HERPES VIRUSES

Epstein-Barr Virus

- Burkitt’s Lymphoma
- Nasopharyngeal cancer
- Lymphomas
- Transforms human B-lymphocytes *in vitro*

Human herpes virus 8 (HHV8)

- Kaposi’s Sarcoma Herpesvirus (KSHV)
Gene translocation

Burkitt’s Lymphoma
8:14 translocation
Break in chromosome 14 at q32
HEPATITIS B VIRUS

Strong correlation between HBV and hepatocellular carcinoma

- Mechanism of carcinogenesis still unknown
- X gene – oncogene?
- activation of proto-oncogenes?
RNA Tumor Viruses

- Retroviruses
- Hepatitis C virus
Transducing retroviruses

“typical retrovirus”

R U5 GAG POL ENV U3 R

“transducing retrovirus” Have v-onc instead of env

R U5 GAG POL V-onc U3 R

Rous Sarcoma Virus

R U5 GAG POL ENV SRC U3 R

Have an extra gene (v-onc)
Cis-acting retroviruses

- Nondefective viruses
- Near c-onc and LTR activation
- Insertional inactivation of tumor suppressor genes
- Chronic-transforming
Trans-acting retroviruses

R U5 GAG POL ENV U3 R

TAX

C-onc
Retroviruses known to cause human cancer

- **Human T cell lymphotrophic virus -1 (HTLV-1)**
  
  Adult T cell leukemia, Sezary T-cell leukemia
  
  Africa, Caribbean, Some Japanese Islands

- **Human T cell lymphotrophic virus -2 (HTLV-2)**
  
  Hairy cell leukemia
RNA Tumor Viruses In Human Cancer

HEPATITIS C VIRUS

Strong correlation between HCV and hepatocellular carcinoma

- Mechanism of carcinogenesis still unknown
- Inactivation of p53?