What is Cancer or Oncogenesis?

Is a disruption of the normal restrains on cellular proliferation

An abnormal growth of tissue resulting from uncontrolled, progressive multiplication of cells and serving no physiological function; a neoplasm

Oncogenesis
onkos (greek) : tumor, mass
genesis: root, origen

Tumor Progression: Evolution at the Cellular Level

Benign tumor (polyp in epithelial cells) is confined by basal lamina; then additional mutation occurs. Malignant tumor (carcinoma in epithelial cells) grows very fast, becomes invasive, and metastasizes.
Genes and Cancer

- Mutations that result in cancer typically occur in 3 types of genes
- Proto-oncogenes (genes whose products stimulate cell multiplication)
- Tumor-suppressor genes (genes whose products inhibit cell multiplication)
- Mutator genes (genes whose products ensure accurate DNA replication and DNA repair)

Definitions

- Transformation: the virus takes up residence in a cell and alters the host’s properties.
- Oncogene: region of the viral genome that can cause a tumor. The foreign gene causes changes in the properties of the cell (ex. Immortalization)
- Proto-oncogene: genes that are found in all cells and its homologous is carried by a virus (viral-oncogene).
- Tumor Suppressor: gene products whose loss contributes to the development of cancer.

History

- First detected Early 20th century
  Human warts, Chicken sarcoma, Chicken leukemia.
- 20 years of GLORY days of isolation of animal viruses.
- 1964 EBV – Burkitt’s Lymphoma
  HBV virion – human sera
  - HTLV-1: patients with T-cell lymphoma leukemia 1980/82
  - HIV: individuals with AIDS 1983/84
  - HCV: post-transfusion patients (infected sera) 1989
  - HHV-8(KSHV): AIDS-associated Kaposi’s sarcoma 1994

End 20th century Viruses recognized as cancer causing agents in Humans (HBV,EBV,HPV,HTLV-1,HCV)
Peyton Rouse and the cancer causing chicken virus

Rockefeller University 1912

Acquired capabilities of cancer

Self-sufficiency in growth signals
Insensitivity to anti-growth signals
Evading options
Sustained angiogenesis
Tissue invasion & metastasis
Limitless replicative potential

Cell (2000) 100:57-70

GENERAL FEATURES OF VIRUSES

1. **Small size** (10-300nm)
   - bacteria: 1000nm
   - erythrocytes: 7500nm

2. **Genome** (DNA or RNA)

3. **Metabolic senescence**
   - Use of metabolic mechanisms and enzymes of the host cell

[Image of a virus particle]
Structure of viruses

1. Virion
2. Capsid
3. Capsomere
4. Genome
5. Nucleocapsid
6. Envelope

DNA containing viruses
- Adeno-
- HBV
- Papilo-
- HSV
- Parvo-

RNA containing viruses
- Entero-
- Paramyx-
- rota-
- influenza
- rvf
Two Major Classes of Tumor Viruses

**DNA Tumor Viruses**

- DNA-dependent DNA polymerase (Host or viral)
- Host RNA polymerase
- Viral mRNA
- Viral protein

**RNA Tumor Viruses**

- Viral RNA genome
- Reverse transcriptase (Virus-encoded)
- Viral DNA genome (integrated)
- DNA-dependent RNA polymerase (Host RNA pol II)
- Viral genomic RNA
- Splicing (Host splicing enzymes)
- messenger RNA
- viral protein
- Virus

Important: Use HOST RNA polymerase to make its genome

An enzyme that normally makes mRNA

Cell cycle of RNA viruses
Visualisation of HSV-1 infection in live cells: the development of replication compartments by recruitment of ICP4, a protein known to be recruited onto replicating viral DNA.

Virus vECFP-ICP4 expresses ICP4 linked to ECFP from an otherwise normal normal ICP4 gene in the correct genomic location. Note that ICP4 forms discrete dots early in infection, some of which develop into replication centres.

Sourcevios & Everett, EMBO J, 2002

Classes of Tumor Viruses

- **DNA viruses**
  - Viral oncoprotein expression
  - Pro-viral gene acquisition
    - Transforming
    - Non-Transforming

- **RNA viruses** (Retroviruses)
  - Viral oncogene
  - Pro-viral insertion near cellular oncogene
    - Transforming
    - Non-Transforming
Characterization

- **Viral oncogene:**
  * Acquisition of a cellular oncogene
    - Usually mutated in the process.
    - Viral genes are usually lost as a result.
    - Expressed under the control of LTR
    - Transformation of target cell.
  * Proviral Insertion:
    - Activate cellular proto-oncogenes.
    - Replication competent.
    - Induce tumors with long latent periods *in vivo.*
- **Viral oncoproteins:**
  - Virus-encoded non-structural proteins.
  - Target tumor suppressor proteins of the host cell.

Oncogenic viruses

- Impairment of Signal Transduction pathways upon viral infection and expression of viral proteins.
- Inactivation of tumor suppressors through their association with viral transforming proteins.

Mechanism for viral-oncogenesis

- Oncogenes affect the signal transduction process in an aberrant manner.
  (RNA tumor viruses)
  - Growth factor expression
  - Growth factor receptor
  - Cytoplasmic or membrane-bound kinases
  - Transcription factors
- Inactivation of Tumor-suppressor genes
  (DNA tumor viruses)
  - Uncontrolled proliferation
  - Inhibition of Apoptosis
Oncogenes

**Acute- vs. slow-transforming viruses**

- **Normal c-myc**
  - Acute transforming virus
    - Mutant cell line
    - Overexpression
  - Slow transforming virus
    - Insertion
    - Normal protein
    - Overexpression
- Overexpressed normal protein

**Cellular Genes altered in the Signal Transduction Pathway**

- Akt, PI3K, RAS, MEK
- c-fos, c-jun
- Apoptosis inhibitors
- Mitogen-activated protein kinases
- MAPK
- Cytoplasmic proteins
- Extracellular factors
Selected signaling pathways and transcription factors activated by HCMV-binding to EGFR and TLR-2

Oncogenes in Ras signalling pathway dictate host-cell permissiveness to herpes simplex virus 1 (1)

Oncogenes in Ras signalling pathway dictate host-cell permissiveness to herpes simplex virus 1 (2)
Oncogenes in Ras signalling pathway dictate host-cell permissiveness to herpes simplex virus 1 (3)

Raf promotes human herpesvirus-8 (HHV-8/KSHV) infection

ERK1/2 and MEK1/2 Induced by Kaposi’s Sarcoma-Associated Herpesvirus (Human Herpesvirus 8) Early during Infection of Target Cells Are Essential for Expression of Viral Genes and for Establishment of Infection
Retroviruses containing cellular oncogenes

<table>
<thead>
<tr>
<th>General class</th>
<th>Oncogene</th>
<th>Virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-receptor tyrosine kinase</td>
<td>c-myc</td>
<td>Rous sarcoma virus (RSV)</td>
</tr>
<tr>
<td>Receptor tyrosine kinase</td>
<td>c-erbB, c-sis</td>
<td>Avian erythroblastosis (AEV-ES4)</td>
</tr>
<tr>
<td>Serine/Threonine kinase</td>
<td>c-ras</td>
<td>Murine sarcoma virus (MSV5611)</td>
</tr>
<tr>
<td>Growth factor</td>
<td>c-myc</td>
<td>Simian sarcoma virus (SSV)</td>
</tr>
<tr>
<td>G protein</td>
<td>c-Kras</td>
<td>Kirstein murine sarcoma virus (KI-MSV)</td>
</tr>
<tr>
<td>Transcription factor</td>
<td>c-myb</td>
<td>MC29 Avian myelocytoma virus (MC29)</td>
</tr>
</tbody>
</table>

Cellular oncogenes activated by insertion of retrovirus

<table>
<thead>
<tr>
<th>General class</th>
<th>Oncogene</th>
<th>Virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-receptor protein tyrosine kinase</td>
<td>c-fos</td>
<td>Moloney murine sarcoma virus (Mo-MSV)</td>
</tr>
<tr>
<td>Receptor protein tyrosine kinase</td>
<td>c-sis, c-fms</td>
<td>Rous-associated sarcoma virus 1 (RAV-1)</td>
</tr>
<tr>
<td>Serine/Threonine protein kinase</td>
<td>c-myc</td>
<td>Moloney murine sarcoma virus (Mo-MSV)</td>
</tr>
<tr>
<td>Growth factor</td>
<td>c-myc</td>
<td>Friend murine leukemia virus (Fr-MLV)</td>
</tr>
<tr>
<td>G protein</td>
<td>c-erbB</td>
<td>Moloney murine sarcoma virus (Mo-MSV)</td>
</tr>
<tr>
<td>Transcription factor</td>
<td>c-myb</td>
<td>Moloney murine sarcoma virus (Mo-MSV)</td>
</tr>
</tbody>
</table>

Oncoproteins
Tumor Suppressor

- **gatekeepers**
  * Directly suppress cell proliferation
  (RB, p53, APC, NF1)

- **caretakers**
  * Maintain integrity of the genome
  (BRCA1,2)

---

**Rb Protein is Inactivated By CDK-Cyclin During G1 → S**

- G1
- pRB: Inactive complex
- Cyclin-CDK complex (phosphorylates pRB)
- pRB
  - p21:
  - Active transcription factor
  - Gene expression: cell progresses through cell cycle
- Target gene

---

**The p53 Signaling Pathway**

- Genetic damage → DNA repair
- DNA damage
- p53
- p21
- Cell cycle arrest
- Apoptosis
- p53 degradation
DNA virus oncoproteins and cellular protein interaction

<table>
<thead>
<tr>
<th>Virus</th>
<th>Oncoprotein</th>
<th>Cellular Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV40</td>
<td>Large T ag, Small T ag</td>
<td>p53, pRb, PP2A</td>
</tr>
<tr>
<td>HPV</td>
<td>E6, E7</td>
<td>p53, pRb</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>E1A, E1B-55K</td>
<td>pRb, p53</td>
</tr>
<tr>
<td>EBV</td>
<td>LMP1</td>
<td>TRAFs</td>
</tr>
</tbody>
</table>

Functional Domains of p53

Tumor suppressor genes

p53

- P53 gene
- P53 gene
- P53 gene
- P53 gene
- P53 gene
- HPV

- P53: Replication
- P53: Replication
- P53: Replication
- P53: Replication
- P53: Replication
- Papilloma proteolysis

- P53: DNA
- P53: Stopped replication
Tumour suppressor gene

Retinoblastoma

Rb Gene

Adenovirus E1A

Rb protein

Rb 105kD

Stops replication

Cell cycle continues

P53/Rb - virus interaction

Adenovirus infection
Potential mechanisms by which miRNAs can affect virus replication

a) miRNA targets viral RNA

b) Viral genome

Host cell genome

Viral miRNA inhibits viral replication

Viral RNA inhibits viral replication

Host cell miRNA inhibits viral replication

MicroRNAs can function as tumour suppressors and oncogenes

<table>
<thead>
<tr>
<th>HCMV miRNAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>MicroRNAs can function as tumour suppressors and oncogenes</td>
</tr>
<tr>
<td>The future: Silencing MicroRNAs with Antagomirs</td>
</tr>
</tbody>
</table>
HPV

- DNA Tumor virus
  - Over 100 HPV types
    - infect different areas of skin
    - 38 genital HPV types
    - do not circulate in blood
- Not easy to grow
  - Test for HPV DNA in patient samples

HPV Genome

- E6 & E7 genes
  - code for proteins that inactivate human tumor suppressor proteins
- L1 gene
  - codes for a protein that self-assembles into the shell (capsid) of the virus
  - empty shells (capsids) are called virus–like particles (VLPs)

HPV life cycle

- E6, E4, E1, L1
- Virus Release
- Packaging
- Genome Amplification
- Proliferation
- Genome Maintenance
- E4, E5, E7, L1, L2
HPV L1 Virus-Like Particle (protein from the L1 gene of HPV)

HPV Papilloma Viruses
urogenital cancer
wart → Malignant Squamous cell carcinoma

Squamous cell carcinoma:
- Larynx
- Esophagus
- All histologically similar
- Lung

10% of human cancers may be HPV-linked

Model of the roles of UV irradiation and HPV infection in skin cancer development

UVB → DNA repair → Downregulation of DNA damage → Residual lesions → Apoptosis → Survival → UV-driven clonal expansion → SCC
A. Cells have been infected with empty retrovirus → normal epithelium
B. Cells have been infected with retroviruses expressing HPV E6/E7 → parakeratosis
C. Normal human skin
D. Characteristic CPE pf HPV8 (pronounced vacuolation of the keratinocytes)

HPV infection in non melanoma skin cancer

HPV DNA was detected in 27% of the non melanoma skin cancer

Highest prevalence for HPV 8 vs HPV 18

Cervical carcinogenesis

Schematic presentation of the morphological alterations seen in consecutive premalignant cervical lesions and correlation of the cervical intraepithelial neoplasia (CIN) classification with squamous intraepithelial lesions (SILs)
Deregulated HPV 16 E6/E7 expression in lower, dysplastic cell layers of a CIN 2 lesion at the transition to normal cervical epithelium.

Left panel: Haematoxylin–eosin (HE)-stained section.
Right panel: E6/E7 RNA in situ hybridization (RISH).

HPV-mediated carcinogenesis

Alignment of the different steps during cervical carcinogenesis (upper part) and in vitro transformation of epithelial cells mediated by high risk HPV (lower part). Potential relevant genetic alterations are indicated in red. Chromosomes are indicated by '#'.

Compl. = complementation

Progression model of cervical cancer based on in vitro transformation steps and data from clinical samples. Potential relevant genetic alterations are indicated in red. TSGs = tumour suppressor genes. ↑ indicates increased activity resulting from (epi)genetic alteration(s). ↓ indicates decreased activity resulting from (epi)genetic alteration(s), such as deletion or promoter hypermethylation.
EBV Latency Proteins

Cohen NEJM 2000

EBV enters resting B-cells by interaction of the viral gp350/220 with the receptor CR2/CD21. After viral genome uncoat and transferred to the nucleus, a cascade of events leads to virus latent gene expression. The EBV nuclear antigen (EBNA) leader protein (EBNA-LP) and EBNA2 – the first latent proteins to be detected – are sufficient to advance the cells to early G1 phase of the cell cycle. Later, all other known EBV latent genes are expressed. These include: EBNA1, EBNA3A, -3B and -3C; latent membrane protein-1 (LMP1) and LMP2; and a species of non-translated RNAs, referred to as the EBERs (EBV-encoded RNAs).
Pathogenesis of EBV Infection

EBV Transforms B Cells In Vitro and the Cells Express Limited Viral and Cellular Proteins

Table 2: Latency types according to state of B-cell differentiation

<table>
<thead>
<tr>
<th>Latency type and EBV protein present</th>
<th>Stage of B-cell differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency 0 (LMP 2, EBNAs)</td>
<td>Memory B-cell</td>
</tr>
<tr>
<td>Latency I</td>
<td>General center B-cell</td>
</tr>
<tr>
<td>Latency II (EBNAs, LMP 1, LMP 2)</td>
<td>II-cell blast</td>
</tr>
<tr>
<td>Latency III (EBNAs, EBNAs, EBNAs-LF, EBNAs, I, II, III, LMP 1, LMP 2)</td>
<td>Latent membrane protein</td>
</tr>
</tbody>
</table>

EBNA, Epstein-Barr virus nuclear antigen; LF, leader protein; LMP, latent membrane protein.

Table 3: Latency types characteristic of different Epstein-Barr virus-associated tumors

<table>
<thead>
<tr>
<th>Latency type and EBV protein present</th>
<th>Tumor type displaying latency patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency I (EBNAs)</td>
<td>Burkitt's lymphoma</td>
</tr>
<tr>
<td>Latency II (EBNAs, LMP 1, LMP 2)</td>
<td>Undifferentiated nasopharyngeal carcinoma, Hodgkin's lymphoma, T-cell lymphoma</td>
</tr>
<tr>
<td>Latency III (EBNAs, EBNAs-LF, EBNAs, I, II, III, LMP 1, LMP 2)</td>
<td>Immunoblastic lymphoma, post-transplant lymphoma</td>
</tr>
</tbody>
</table>

EBNA, Epstein-Barr virus nuclear antigen; LF, leader protein; LMP, latent membrane protein.
LMP-1 is the EBV Oncogene

Oncogene
Expression in transgenic mice leads to B cell lymphoma; expression in fibroblasts leads to tumors in nude mice

B Cell Proliferation
Upregulates adhesion molecules, CD23, CD40, IL-6, IL-10, etc. Activates NF-κB

Inhibits apoptosis
Upregulates Bcl-2, A20, Mcl-1

Activation of NF-κB in Tumor from Patient with Post-Transplant EBV Lymphoproliferative Disease

Lane 1: EBV- B cell
Lane 2: EBV+ B cell
Lane 3: EBV- LPD
Lane 4: EBV+ LPD

Liebowitz NEJM 1998

Cancers often result from gene translocations

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

Acute myelocytic leukemia
7:15
8:19
11:15:17
Diseases Associated with EBV

EBV in B Cell
- Infectious mononucleosis
- X-Linked Lymphoproliferative Disease
- Chronic active EBV
- Hodgkin Disease
- Burkitt Lymphoma
- Lymphoproliferative disease

EBV in Other Cells
- Nasopharyngeal carcinoma
- Gastric carcinoma
- Nasal T/NK cell lymphomas
- Peripheral T cell lymphomas
- Oral hairy leukoplakia
- Smooth muscle tumors in transplant patients

Hodgkin Disease

EBV+: 60-70% of cases in developing countries
35-50% cases in US
EBV in Reed-Sternberg cells
Therapy: Chemotherapy, radiation
Anti-EBV CTLs effective in some cases

EBV-Associated Smooth Muscle Tumors

Occur in transplant recipients, AIDS patients, congenital immunodeficiency
Pathology: leiomyosarcomas and leiomyomas in various organs (especially transplant) and lymph nodes
Some tumors regress with reduced immunosuppression
Methotrexate, but not other Immunosuppressants, Induces EBV Lytic Replication

Feng et al JNCI 2004

Polyoma Viruses

- Small DNA Tumor Viruses
- Infect vertebrates with species-specificity
- Etiologic agents of benign diseases and malignancy

Biophysical/Genetic Characteristics

Capsid: Non-enveloped; icosahedral (T=7d); ~45 nm diameter.
Major capsid protein (VP1) self-assembles into homopentameric capsomeres; capsids contain 72 capsomeres
Genome: Covalently closed, circular, superhelical, dsDNA (~5,000 bp), Forms "viral mini-chromosome" (with host histones H2A, H2B, H3 and H4)
Replicates in the nucleus of the infected host cell
DNA replication and RNA Transcription are bi-directional

SV40 Virions
**Py Host Range:**

<table>
<thead>
<tr>
<th>Virus</th>
<th>Host</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simian virus 40 (SV40)</td>
<td>Human, Rhesus monkey</td>
</tr>
<tr>
<td>Simian Agent 12 (SA12)</td>
<td>Baboon</td>
</tr>
<tr>
<td>Lymphotropic Papovavirus (LPV)</td>
<td>African green monkey</td>
</tr>
<tr>
<td>JC virus (JCV)</td>
<td>Human</td>
</tr>
<tr>
<td>BK virus (BKV)</td>
<td>Human</td>
</tr>
<tr>
<td>Bovine polyomavirus (BPy)</td>
<td>Cattle</td>
</tr>
<tr>
<td>Rabbit polyomavirus (RKV)</td>
<td>Rabbit</td>
</tr>
<tr>
<td>Murine Polyoma virus (Py)</td>
<td>Mouse</td>
</tr>
<tr>
<td>Kirsten virus (KV)</td>
<td>Mouse</td>
</tr>
<tr>
<td>Hamster polyomavirus (HaPy)</td>
<td>Hamster</td>
</tr>
<tr>
<td>Rat polyomavirus (RPV)</td>
<td>Rat</td>
</tr>
<tr>
<td>Budgerigar fledgling disease virus</td>
<td>Parakeet</td>
</tr>
</tbody>
</table>

**Pathogenesis**

This family causes sub-clinical persistent infections

Some transmitted transplacentally, Polyoma and SV40 viruses

Pathology only after immunosuppression

eg. Progressive multifocal leucoencephalopathy caused by JCV

tumors caused by Polyomavirus in mice

**Polyomavirus (SV40) Genomic Organization**
### Polyomavirus proteins and functions

<table>
<thead>
<tr>
<th>Protein</th>
<th>Function(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large T Ag</td>
<td>DNA binding activity (5'-GAGGC-3'); ATP-dependent helicase; initiation/elongation of viral DNA replication; Inactivation of p53 (bypass p53-mediated G1 arrest or apoptosis); Inactivation of pRB family of proteins (releases E2F transactivator); Interaction with other cell regulatory factors (p300; TBP; AP2; TEF-1); Activation/Repression of viral/cellular transcription; Stimulates resting cells to enter the cell cycle and replicate their DNA; Binding to Topoisomerase I; TAF-like function in complex with TFIIID; &quot;Classical&quot; nuclear localization signal (NLS) sequences (Arg/Lys)</td>
</tr>
</tbody>
</table>

---

### Functional Regions of SV40 Large T Antigen

SV40 T-ag disrupts cell growth control mechanisms primarily by interfering with the normal functions of tumor suppressor proteins p53 and Rb family members.

Three essential regions of T-ag are required for transformation:

- The first is an N terminal domain (amino acids 1-82) that binds a chaperone protein (hsc70) involved in assembly/disassembly of protein complexes.
- A second domain (amino acids 102-115) is required for binding to Rb-related tumor suppressor proteins (Rb, p107, and p130/pRb2).
- A third region contains p53 binding sites (aa 350-450 and 533-626).

Functional Activities of SV40 Large T Antigen (cont.)

- T-ag binds hypophosphorylated Rb and thus disrupts the role of Rb in coordinating cell cycle progression.
- Rb normally binds transcription factor E2F in early G1 phase of the cell cycle.
- Rb phosphorylation by cyclin-dependent kinases releases E2F to activate expression of growth-stimulatory genes.
- T-ag causes dissociation of Rb-E2F complexes, thus releasing active E2F.

Functional Activities of SV40 Large T Antigen (cont.)

- Wild-type p53 senses DNA damage and either causes a pause in late G1 phase for DNA repair or directs the cell to undergo apoptosis.
- p53 induces transcription of p21 cyclin-dependent kinase inhibitor, which blocks the activity of cyclin-cdk complexes and arrests progression in G1.
- T-ag binding sequesters p53, thus allowing cells with genetic damage to survive and enter S phase.
- Accumulation of T-ag-expressing cells with genomic mutations may promote tumorigenesis.
- Binds protein phosphatase-2A (PP2A), which activates the mitogen-activated protein (MAP) kinase pathway and growth stimulation of quiescent cells.

- Activates AKT and telomerase and induces anchorage-independent growth of human epithelial cells.
SV40 Late Gene Expression

Detection of BK Virus in Prostate Cancer

Figure 1: BKV VP1 + - - - - + - + - + + - - prostate samples 14-23, 2% agarose gel.

Figure 2: Sensitivity Assay, pBK-VP1 containing plasmid, (3 X 10^{-11} minimum conc.).

Expression of human BK virus sequences in neoplastic prostate tissues

Colocalization of BK Virus TAg and p53 expression in prostate samples
RNA Tumor Viruses

A normal retrovirus has:
- 3 genes
- GAG: internal proteins
- ENV: Envelope glycoproteins
- POL: Enzymes
  - Reverse transcriptase
  - Integrase
  - Protease

The viral genome

A retrovirus virion
How do retroviruses cause cancer?

Some retroviruses have an extra gene

“typical retrovirus”

<table>
<thead>
<tr>
<th>R</th>
<th>U5</th>
<th>GAG</th>
<th>POL</th>
<th>ENV</th>
<th>U3</th>
<th>R</th>
</tr>
</thead>
</table>

Rous Sarcoma Virus

<table>
<thead>
<tr>
<th>R</th>
<th>U5</th>
<th>GAG</th>
<th>POL</th>
<th>ENV</th>
<th>SRC</th>
<th>U3</th>
<th>R</th>
</tr>
</thead>
</table>

Feline Sarcoma Virus (FSV)

| R | U5 | dGAG | FMS | dENV | U3 | R |

Avian Myeloblastosis Virus

| R | U5 | GAG | POL | MYB | U3 | R |

Avian Myelocytoma Virus (MC29)

| R | U5 | dGAG | MYC | dENV | U3 | R |
Retroviruses and cancer

Transduction of oncogenes

Activation of oncogenes

Inactivation of tumour-suppressors

Other transduced oncogenes

1. Sis - platelet derived growth factor (PDGF) cDNA by wooly monkey or cat in simian sarcoma and feline sarcoma viruses

Cell transformed by SSV

Proliferation

Sis protein