Predicted RSV converted its genome into DNA to become part of host chromosome; later discovered reverse transcriptase.
1975 Nobel Laureates in Physiology or Medicine

David Baltimore  Renato Dulbecco  Howard Temin

"for their discoveries concerning the interaction between tumour viruses and the genetic material of the cell".
Discovery of reverse transcriptase

1970: H. Temin Lab at Wisconsin
    D. Baltimore Lab at MIT
1975: Nobel prize

Gene information flow concept revised
Dogma: DNA to RNA to protein
New: RNA to DNA to protein
Life cycle of an RNA tumor virus

Key enzyme: Reverse transcriptase

introduction of nucleocapsid into cell

association of reverse transcriptase and integrase with viral RNA

synthesis of (-) strand viral DNA by reverse transcriptase

removal of viral RNA and synthesis of (+) strand viral DNA by reverse transcriptase

integration of viral dsDNA into cell chromosome to form provirus

host cell chromosomal DNA

transcription of provirus by host cell RNA polymerase II

new viral RNA

assembly of viral proteins and viral RNA genomes into progeny virions

translation of viral RNA to make new viral proteins

cytoplasm

nucleus

progeny virions leave cell and initiate new infectious cycles

Figure 3.18 The Biology of Cancer (© Garland Science 2014)
Genome structure of ALV (avian leukosis virus) and RSV (Rous sarcoma virus)
Src in different RSV strains
**Origin of Oncogenes**

*Oncogene hypothesis:*
Hubner and Todaro, 1969

*Provirus/protovirus hypothesis:*
Temin, 1971

*Experimental proof of cellular origin of the RSV src and other retroviral oncogenes:*

**Physical presence in normal cells:**
Bishop, Varmus, Stehelin, 1976

**Recovery of functional src gene from cells:**
Hanafusa, 1977

**Identification of retroviral oncogenes in human cancers:**
Weinberg, Scolnick, Aaronson, Cooper, Wiegler, 1980’s

**Promoter-insertion and activation of proto-oncogene:**
Hayward, 1981
Presence of RSV $src$ gene in normal uninfected cells
Nature 1975

1989 Nobel prize

J. Michael Bishop

Harold Varmus
The Nobel Prize in Physiology or Medicine 1989

J. Michael Bishop
Prize share: 1/2

Harold E. Varmus
Prize share: 1/2

The Nobel Prize in Physiology or Medicine 1989 was awarded jointly to J. Michael Bishop and Harold E. Varmus "for their discovery of the cellular origin of retroviral oncogenes"
Preparation of Src-specific DNA probe

1. Wild-type viral RNA is reverse transcribed to cDNA.
2. The RNA is destroyed.
3. The cDNA is hybridized to the viral RNA of a td mutant.
4. The ds RNA:DNA hybrids are discarded.
5. The remaining DNA (src-specific probe) is used to detect src sequences in other DNAs.
6. The normal cell DNA is tested for the presence of src sequences.

Figure 3.20 The Biology of Cancer (© Garland Science 2007)
Figure 3.20 (part 1 of 2) The Biology of Cancer (© Garland Science 2007)
Figure 3.20 (part 2 of 2)  The Biology of Cancer (© Garland Science 2007)
<table>
<thead>
<tr>
<th>Species</th>
<th>Extent of Hybridization</th>
<th>Melting Temp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV-rat</td>
<td>70%</td>
<td>82°</td>
</tr>
<tr>
<td>emu</td>
<td>16%</td>
<td>75.5°</td>
</tr>
<tr>
<td>quail</td>
<td>48%</td>
<td>78°</td>
</tr>
<tr>
<td>chicken</td>
<td>54%</td>
<td>80°</td>
</tr>
<tr>
<td>turkey</td>
<td>53%</td>
<td>78°</td>
</tr>
<tr>
<td>duck</td>
<td>46%</td>
<td>76°</td>
</tr>
</tbody>
</table>

Figure 3.21  The Biology of Cancer (© Garland Science 2007)
Capture (transduction) of c-src proto-oncogene by ALV
How cellular src gene was captured into RSV?
Transduction of the c-src gene by src-deletion mutants of Rous sarcoma virus

Origin of Recovered Avian Sarcoma Viruses (rASV’s)

Hanafusa et al 1977
Wang L-H. et al 1978
The Genomic Structure of rASV3812

rASV3812

LTR gag Δpol XbaI NcoI src LTR

c-src

500bp 196 bp 384 bp

exon 1 Intron 1 exon 2
Nucleotide Sequence Flanking the Recombination Site on rASV3812 Genome

3379  \[\text{pol}\]

\begin{align*}
td109: & \quad \text{CTAGACATGA AAATGCGCTG GAGAGAGATC GTACGCTCA GCACCACGGC} \\
rASV3812: & \quad \text{CTAGACATGA AAATGCGCTG GAGAGAGATC GTACGCTCA GCACCACGGC} \\
td109: & \quad \text{TGCCTTGGAAC GATGGGACC CTGCCGTGCC TCTGGAAGGA GCCGTGCTCA} \\
rASV3812: & \quad \text{TGCCTTGGAAC GATGGGACC CTGCCGTGCC TCTGGAAGGA GCCGTGCTCA} \\
td109: & \quad \text{GATGGAACA GGGGCAATA GGGTCTGGG GACAGGGACT GTTGCAACAC} \\
rASV3812: & \quad \text{GATGGAACA GGGGCAATA GGGTCTGGG GACAGGGACT GTTGCAACAC} \\
td109: & \quad \text{CCAAGGCCAT GCTTGCTGTT ATTCCTCACC} \\
rASV3812: & \quad \text{CCAAGGCCAT GCTTGCTGTT ATTCCTCACC} \\
c-src: & \quad \text{CCAAGGCCAT GCTTGCTGTT ATTCCTCACC} \\
rASV3812: & \quad \text{CCAAGGCCAT GCTTGCTGTT ATTCCTCACC} \\
c-src: & \quad \text{TACTAGGAG ATTTCTCCACC TCGTTTCTCC ATCCGTCCAT GCCTATCCTA} \\
rASV3812: & \quad \text{TACTAGGAG ATTTCTCCACC TCGTTTCTCC ATCCGTCCAT GCCTATCCTA} \\
c-src: & \quad \text{GCCTAAATAT TCTCCCTCGGT AGCTTCAAGGA CGCTGCTGTG TATCCTGCA} \\
rASV3812: & \quad \text{GCCTAAATAT TCTCCCTCGGT AGCTTCAAGGA CGCTGCTGTG TATCCTGCA} \\
c-src: & \quad \text{TCTTTGAGA CTGCGAAATA TCTCCCTCTT TCATTTATAT CATTACCCTG} \\
rASV3812: & \quad \text{TCTTTGAGA CTGCGAAATA TCTCCCTCTT TCATTTATAT CATTACCCTG} \\
c-src: & \quad \text{GAGCCCAACCA CCATG} \\
rASV3812: & \quad \text{GAGCCCAACCA CCATG}
\end{align*}

\[\text{c-src Exon 2}\]
Recombination Junctions of _fes_ in ST-FeSV and GA-FeSV

A

feline c-fes/fpe ex1

<table>
<thead>
<tr>
<th>GAGCCCCGCAGCAGCTGCCCCGCGG</th>
<th>3'end ex1</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAAACGCCAGCAGCTGCCCCGCGG</td>
<td>1056</td>
</tr>
<tr>
<td>GAAACGCCAGCAGCTTCTCAGA</td>
<td>1621</td>
</tr>
</tbody>
</table>

B

feline c-fes/fpe ex8

<table>
<thead>
<tr>
<th>GAGCTCCAGAAGCGGAGCAGAGAAC</th>
<th>ACCAACCCCGGGGAGG</th>
<th>123</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTCATTAGCAGATTTCTGAGCA</td>
<td>ACCACCCCCGGGCA</td>
<td>905</td>
</tr>
<tr>
<td>GTGATTGAGACATTTCCCTGAGC</td>
<td>ACCACCCCCGGGCA</td>
<td>1470</td>
</tr>
</tbody>
</table>

C

feline c-fes/fpe ex19

<table>
<thead>
<tr>
<th>CCTCGACACGGCAAGATGATAC</th>
<th>CCTCTCCCAAGCTCCGCCA</th>
<th>211</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTTGACACGGCAAGATGATAC</td>
<td>CTCTCCCAAGCTCCGCCA</td>
<td>2393</td>
</tr>
<tr>
<td>ACTGGCTCTCTGATGTTGGTGGCTC</td>
<td>CTCTCCCAAGCTCCGCCA</td>
<td>2942</td>
</tr>
</tbody>
</table>

D

feline c-fes/fpe ex5

<table>
<thead>
<tr>
<th>ACAAGAGCCCGAGAGCAGCGA</th>
<th>AGGCCAACAGCAGGATATG</th>
<th>41</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACAAGAGCCCGAGAGCAGCGA</td>
<td>AGGCCAACAGGATATG</td>
<td>1584</td>
</tr>
</tbody>
</table>

feline c-fes/fpe ex9

| AGCGGGAGCGTCTGAGCCAGCTTGC | 130 |

3' Recombination Junction in ASV S1

HAV
GGGAGTGCTACTGCTGTGC
S1
ACCTCGACAGGCCACTGCCTGTGCATAG
c-src
GACAGGCCCAGTACCAGC

S1

3' Recombination Junction in GA/ST-FeSV

feline c-fea/fps mRNA C-G G-G C-G U-A
ST-FeSV CTCGACAGGCCACTGCCTGTGC
GA-FeSV CTCGACAGGCCACTGCCTGTGC
FeLV (GA-strain) ACTGCCCTACTGTTGCTGCTGC

feline c-fea/fps mRNA
A-U C-C C-G C-G C-G
FeLV genomic RNA
A-U C-C C-G C-G C-G

5'-GAUCGUACCUCCCGUGCCC-3'
reverse transcription

5'-GATCGTACCTCTCCTGCCC-3'
(+-)strand synthesis

Model for the Transduction of Proto-oncogenes by Retroviruses
Location and Function of Retroviral Oncogene Products

Receptor PTKs: erbB2, fms, (ros), (kit)

GTP binding: K-ras, H-ras

Serine/Threonine Kinases: mos, rel, mil/raf

DNA binding; Transcription Factors: myc, fos, rel, ski, myb, jun, ets

Non-receptor PTKs: src, fps/fes, yes, fgr, abl

Nucleus

Extracellular

Intracellular

Location and Function of Retroviral Oncogene Products

Receptor PTKs: erbB2, fms, (ros), (kit)

GTP binding: K-ras, H-ras

Serine/Threonine Kinases: mos, rel, mil/raf

DNA binding; Transcription Factors: myc, fos, rel, ski, myb, jun, ets

Nucleus

Extracellular

Intracellular
PTK Receptors & Oncogenes

Kinase

1. src fps
2. fes yes
3. fgr abl
4. fyn syn
5. lyn hck
6. lck tkl
7. etc

EGFR
neu
v-erbB
sea
eph
ltk
etc

InsR
IGF-1R
met
ros
trk

PDGFRs
CSF1R
v-ros

v-fms
Flk
Flt
Tie1
Tie2

FGFR (3 loops)
flg
bek
Pathogenicity of retroviruses

(A) Acute transforming viruses
(containing oncogenes, replication defective with the exception of Rous sarcoma virus)
- Fibrosarcoma: RSV (Repl+ or repl-), Ki-MSV, Ha-MSV, FeSV, SiSV
- Osteosarcoma: FBJ MSV
- Lymphoid leukemia: Abl-MuLV
- Erythroblastosis: AEV
- Myeloblastosis: AMV
- Myelocytomatosis: MC29
- Carcinoma (renal): MH2

(B) Chronic or non-acute transforming viruses (do not contain oncogenes, replication competent)
- Anemia: ALV, FeLV, BLV
- Lymphoid leukosis: ALV
- Lymphoid leukemia: AKR-MuLV, Mo-MuLV
- Lymphosarcoma: FeLV
- Osteopetrosis: MAV-2 (AMV-asso. helper virus)
- Mammary carcinoma: MMTV
- Erythroleukemia/Splenomegaly: Fr-MLV (slow), SFFV (rapid, repl+)
- Neurodegenerative, encephalitis, pulmonary wasting diseases: lentiviruses (visna virus, CAEV)

(C) Human T cell leukemia virus (HTLV): contains viral gene(s) that could modulate host gene
(replication competent) expression leading to T-cell leukemia after long latency

(D) Human immunodeficiency virus (HIV)/AIDS virus: replication and gene expression affect host
(replication competent) immune function
<table>
<thead>
<tr>
<th>Name of virus</th>
<th>Viral oncogene</th>
<th>Species</th>
<th>Major disease</th>
<th>Nature of oncoprotein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rous sarcoma</td>
<td>src</td>
<td>chicken</td>
<td>sarcoma</td>
<td>non-receptor TK</td>
</tr>
<tr>
<td>Y73/Esh sarcoma</td>
<td>yes</td>
<td>chicken</td>
<td>sarcoma</td>
<td>non-receptor TK</td>
</tr>
<tr>
<td>Fujinami sarcoma</td>
<td>fps</td>
<td>chicken</td>
<td>sarcoma</td>
<td>non-receptor TK</td>
</tr>
<tr>
<td>UR2</td>
<td>ros</td>
<td>chicken</td>
<td>sarcoma</td>
<td>RTK; unknown ligand</td>
</tr>
<tr>
<td>Myelocytomatosis 29</td>
<td>myc</td>
<td>chicken</td>
<td>myeloid leukemia</td>
<td>transcription factor</td>
</tr>
<tr>
<td>Mill Hill virus 2</td>
<td>mil</td>
<td>chicken</td>
<td>myeloid leukemia</td>
<td>ser/thr kinase</td>
</tr>
<tr>
<td>Avian myeloblastosis E26</td>
<td>myb</td>
<td>chicken</td>
<td>myeloid leukemia</td>
<td>transcription factor</td>
</tr>
<tr>
<td>Avian myeloblastosis E26</td>
<td>ets</td>
<td>chicken</td>
<td>myeloid leukemia</td>
<td>transcription factor</td>
</tr>
<tr>
<td>Avian erythroblastosis ES4</td>
<td>erbA</td>
<td>chicken</td>
<td>erythroleukemia</td>
<td>thyroid hormone receptor</td>
</tr>
<tr>
<td>Avian erythroblastosis ES4</td>
<td>erbB</td>
<td>chicken</td>
<td>erythroleukemia</td>
<td>EGF RTK</td>
</tr>
<tr>
<td>3611 murine sarcoma</td>
<td>rat</td>
<td>mouse</td>
<td>sarcoma</td>
<td>ser/thr kinase</td>
</tr>
<tr>
<td>SKV770</td>
<td>ski</td>
<td>chicken</td>
<td>endothelioma (?)</td>
<td>transcription factor</td>
</tr>
<tr>
<td>Reticuloendotheliosis</td>
<td>rel</td>
<td>turkey</td>
<td>immature B-cell lymphoma</td>
<td>transcription factor</td>
</tr>
<tr>
<td>Abelson murine leukemia</td>
<td>abl</td>
<td>mouse</td>
<td>pre-B-cell lymphoma</td>
<td>non-receptor TK</td>
</tr>
<tr>
<td>Moloney murine sarcoma</td>
<td>mos</td>
<td>mouse</td>
<td>sarcoma, erythroleukemia</td>
<td>ser/thr kinase</td>
</tr>
<tr>
<td>Harvey murine sarcoma</td>
<td>H-ras</td>
<td>rat, mouse</td>
<td>sarcoma</td>
<td>small G protein</td>
</tr>
<tr>
<td>Kirsten murine sarcoma</td>
<td>K-ras</td>
<td>mouse</td>
<td>sarcoma</td>
<td>small G protein</td>
</tr>
<tr>
<td>FBJ murine sarcoma</td>
<td>fos</td>
<td>mouse</td>
<td>osteosarcoma</td>
<td>transcription factor</td>
</tr>
<tr>
<td>Snyder–Theilen feline</td>
<td>fes</td>
<td>cat</td>
<td>sarcoma</td>
<td>non-receptor TK</td>
</tr>
<tr>
<td>McDonough feline sarcoma</td>
<td>fms</td>
<td>cat</td>
<td>sarcoma</td>
<td>CSF-1 RTK</td>
</tr>
<tr>
<td>Gardner–Rasheed feline</td>
<td>fgr</td>
<td>cat</td>
<td>sarcoma</td>
<td>non-receptor TK</td>
</tr>
</tbody>
</table>
Table 3.3 Acutely transforming retroviruses and the oncogenes that they have acquired

<table>
<thead>
<tr>
<th>Name of virus</th>
<th>Viral oncogene</th>
<th>Species</th>
<th>Major disease</th>
<th>Nature of oncoprotein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hardy–Zuckerman feline sarcoma</td>
<td><em>kit</em></td>
<td>cat</td>
<td>sarcoma</td>
<td>steel factor RTK</td>
</tr>
<tr>
<td>Simian sarcoma</td>
<td><em>sis</em></td>
<td>woolly monkey</td>
<td>sarcoma</td>
<td>PDGF</td>
</tr>
<tr>
<td>AKT8</td>
<td><em>akt</em></td>
<td>mouse</td>
<td>lymphoma</td>
<td>ser/thr kinase</td>
</tr>
<tr>
<td>Avian virus S13</td>
<td><em>sea</em></td>
<td>chicken</td>
<td>erythroblastic leukemia</td>
<td>RTK; unknown ligand</td>
</tr>
<tr>
<td>Myeloproliferative leukemia</td>
<td><em>mpl</em></td>
<td>mouse</td>
<td>myeloproliferation</td>
<td>TPO receptor</td>
</tr>
<tr>
<td>Regional Poultry Lab v. 30</td>
<td><em>eyk</em></td>
<td>chicken</td>
<td>sarcoma</td>
<td>RTK; unknown ligand</td>
</tr>
<tr>
<td>Avian sarcoma virus CT10</td>
<td><em>crk</em></td>
<td>chicken</td>
<td>sarcoma</td>
<td>SH2/SH3 adaptor</td>
</tr>
<tr>
<td>Avian sarcoma virus 17</td>
<td><em>jun</em></td>
<td>chicken</td>
<td>sarcoma</td>
<td>transcription factor</td>
</tr>
<tr>
<td>Avian sarcoma virus 31</td>
<td><em>qin</em></td>
<td>chicken</td>
<td>sarcoma</td>
<td>transcription factor</td>
</tr>
<tr>
<td>As42 sarcoma virus</td>
<td><em>maf</em></td>
<td>chicken</td>
<td>sarcoma</td>
<td>transcription factor</td>
</tr>
<tr>
<td>Cas NS-1 virus</td>
<td><em>cbl</em></td>
<td>mouse</td>
<td>lymphoma</td>
<td>SH2-dependent ubiquitylation factor</td>
</tr>
</tbody>
</table>

*a*Not all viruses that have yielded these oncogenes are indicated here. “Species” denotes the animal species from which the virus was initially isolated.

*b*Ortholog of the mammalian *fes* oncogene.

*c*Also causes carcinomas and endotheliomas.

*d*Ortholog of the mammalian *raf* oncogene.

*e*Ortholog of the avian *mil* oncogene.

*f*Ortholog of the avian *fps* oncogene.

*g*Also causes granulocytic leukemias and sarcomas.

*h*Functions as a transcriptional repressor.

Abbreviations: CSF, colony-stimulating factor; EGF, epidermal growth factor; G, GTP-binding; PDGF, platelet-derived growth factor; RTK, receptor tyrosine kinase; ser/thr, serine/threonine; SH, src-homology segment; TK, tyrosine kinase; TPO, thrombopoietin.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Insertional mutagen</th>
<th>Tumor type</th>
<th>Species</th>
<th>Type of oncoprotein</th>
</tr>
</thead>
<tbody>
<tr>
<td>myc</td>
<td>ALV</td>
<td>B-cell lymphoma</td>
<td>chicken</td>
<td>transcription factor</td>
</tr>
<tr>
<td>myc</td>
<td>ALV, FeLV</td>
<td>T-cell lymphoma</td>
<td>chicken, cat</td>
<td>transcription factor</td>
</tr>
<tr>
<td>nov</td>
<td>ALV</td>
<td>nephroblastoma</td>
<td>chicken</td>
<td>growth factor</td>
</tr>
<tr>
<td>erbB</td>
<td>ALV</td>
<td>erythroblastosis</td>
<td>chicken</td>
<td>receptor TK</td>
</tr>
<tr>
<td>mos</td>
<td>IAP</td>
<td>plasmacytoma</td>
<td>mouse</td>
<td>ser/thr kinase</td>
</tr>
<tr>
<td>int-1</td>
<td>MMTV</td>
<td>mammary carcinoma</td>
<td>mouse</td>
<td>growth factor</td>
</tr>
<tr>
<td>int-2</td>
<td>MMTV</td>
<td>mammary carcinoma</td>
<td>mouse</td>
<td>growth factor</td>
</tr>
<tr>
<td>int-3</td>
<td>MMTV</td>
<td>mammary carcinoma</td>
<td>mouse</td>
<td>receptor</td>
</tr>
<tr>
<td>int-H/int-5</td>
<td>MMTV</td>
<td>mammary carcinoma</td>
<td>mouse</td>
<td>enzyme</td>
</tr>
<tr>
<td>pim-1</td>
<td>Mo-MLV</td>
<td>T-cell lymphoma</td>
<td>mouse</td>
<td>ser/thr kinase</td>
</tr>
<tr>
<td>pim-2</td>
<td>Mo-MLV</td>
<td>B-cell lymphoma</td>
<td>mouse</td>
<td>ser/thr kinase</td>
</tr>
<tr>
<td>bmi-1</td>
<td>Mo-MLV</td>
<td>T-cell lymphoma</td>
<td>mouse</td>
<td>transcription repressor</td>
</tr>
<tr>
<td>tpl-2</td>
<td>Mo-MLV</td>
<td>T-cell lymphoma</td>
<td>mouse</td>
<td>non-receptor TK</td>
</tr>
<tr>
<td>lck</td>
<td>Mo-MLV</td>
<td>T-cell lymphoma</td>
<td>mouse</td>
<td>non-receptor TK</td>
</tr>
<tr>
<td>p53</td>
<td>Mo-MLV</td>
<td>T-cell lymphoma</td>
<td>mouse</td>
<td>transcription factor</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>IAP</td>
<td>myelomonocytic leukemia</td>
<td>mouse</td>
<td>growth factor</td>
</tr>
<tr>
<td>IL2</td>
<td>GaLV</td>
<td>T-cell lymphoma</td>
<td>gibbon ape</td>
<td>cytokine</td>
</tr>
<tr>
<td>IL3</td>
<td>IAP</td>
<td>T-cell lymphoma</td>
<td>mouse</td>
<td>cytokine</td>
</tr>
<tr>
<td>K-ras</td>
<td>F-MLV</td>
<td>T-cell lymphoma</td>
<td>mouse</td>
<td>small G protein</td>
</tr>
<tr>
<td>CycD1</td>
<td>F-MLV</td>
<td>T-cell lymphoma</td>
<td>mouse</td>
<td>G1 cyclin</td>
</tr>
<tr>
<td>CycD2</td>
<td>Mo-MLV</td>
<td>T-cell lymphoma</td>
<td>mouse</td>
<td>G1 cyclin</td>
</tr>
</tbody>
</table>

*a Subsequently renamed Wnt-1.

*b Subsequently identified as a gene encoding a fibroblast growth factor (FGF).

*c Related to notch receptors.

*d Enzyme that converts androgens to estrogens.

*e Cytokines are GFs that largely regulate various types of hematopoietic cells.

Abbreviations: ALV, avian leukemia virus; FeLV, feline leukemia virus; F-MLV, Friend murine leukemia virus; GaLV, gibbon ape leukemia virus; GF, growth factor; IAP, intracisternal A particle (a retrovirus-like genome that is endogenous to cells); Mo-MLV, Moloney murine leukemia virus; MMTV, mouse mammary tumor virus; ser/thr, serine/threonine; TK, tyrosine kinase.

Tumorigenesis by Non-acute Transforming Retroviruses

How can a retrovirus lacking an oncogene in its genome induce tumors?

A) Promoter Insertion
   Insertion of proviral DNA adjacent to a proto-oncogene can lead to activation of the gene due to enhancer and promoter activity of viral LTR. This mechanism has been well documented in avian leukosis virus induced chicken lymphomas, and has also been shown in MuLV and MMTV induced tumors.
   - ALV-induced tumors: $myc$; $erbB$; $myb$.
   - MMTV-induced mammary carcinomas: int1, int2, int3, int4, int5, $abl$
   - MoMuLV induced tumors: $myc$ Tpl-1(ets), Tpl-2(protein kinase), Gfi-1(transcription factor).

B) Recombination between Endogenous Viruses
   Certain non-oncogenic endogenously derived viruses can undergo recombination with other endogenous viruses (ex. xenotropic viruses) and evolve into potent leukemia viruses by expanding their spectrum of target cells and enhancing the tendency of leukemogenicity in the susceptible target tissues. The promoter insertion and activation of relevant proto-oncogene in the right target cells then lead to leukemia. This process is important for mouse AKR virus induced leukemia.

C) "Virocrine" effect
   The gp55 of SFFV (spleen focus forming virus) leads to activation of erythropoietin (EPO) receptor whose signaling and plays an important role for early stage proliferation of the SFFV infected erythroblasts leading eventually to their transformation presumably following subsequent genetic mistake during the proliferation phase. The SFFV gp55 has no effect on EPO R-/- cells. Similarly, gp70 of MCFV (mink cell focus forming virus) associates with IL-2 receptor resulting in its activation.

   Tax of HTLV (human T cell leukemia virus) has been shown to be sufficient for immortalizing lymphocytes and transforming rat fibroblasts. Tax is able to interacts with a variety of cellular proteins involved in regulation of cell cycle progression and apoptosis.
How ALV without an oncogene cause cancer?

Promoter insertion of ALV into host cell chromosomal DNA induces elevated expression of cellular proto-oncogene located downstream of the ALV LTR.
Leukemogenesis by Retroviral Promoter Insertion

Clonal Expansion/ Lymphoid Nodules → 2° Genetic Changes

B Cell Lymphoid Leukemia

c-myc mRNA

(A)n

Clonal Expansion/ Lymphoid Nodules

(Tumor Formation)
Figure 3.23a  The Biology of Cancer (© Garland Science 2007)
Oncogenes and Human Malignancy

*ras:* first oncogene to be implicated in human cancer;
25 to 30% of all tumors have mutated *ras* or elevated expression;
45 to 50% of colorectal carcinoma and 30% of acute myelo-genous leukemia have altered *ras*;
Other tumors including breast, kidney, liver, lung, stomach, lymphoid organs and brain have also been shown to implicate *ras* mutation;
In animal model, 85% and 25% of rat mammary tumors induced by nitrosourea and DMBA, respectively harbor *ras* mutations.

*myc:* also widely implicated in a variety of tumors;
primary targets are lymphoid tissues including Burkitt's lymphoma and certain T-cell leukemia; translocation of *myc* to IgG or T-cell receptor genes frequently observed; amplification of *myc* observed in carcinomas of breast, lung, cervix and neuroblastoma.

*abl:* specifically implicated in CML
96% of Ph+ CML and 17 to 25% of ALL patients contain *abl* translocation to *bcr*; The resulting *bcr-abl* fusion protein has an elevated PTK activity;
*bcr-abl* transgenic mice produced CML-like symptoms.

*erbB2/neu:* amplified in 25% of human mammary carcinoma.
### Table 4.6 Viruses implicated in human cancer causation

<table>
<thead>
<tr>
<th>Virus</th>
<th>Virus family</th>
<th>Cells infected</th>
<th>Human malignancy</th>
<th>Transmission route</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBV</td>
<td>Herpesviridae</td>
<td>B cells oropharyngeal epithelial cells</td>
<td>Burkitt’s lymphoma, nasopharyngeal carcinoma</td>
<td>saliva, saliva</td>
</tr>
<tr>
<td>HTLV-I</td>
<td>Retroviridae</td>
<td>lymphoid T cells</td>
<td>lymphoma&lt;sup&gt;b&lt;/sup&gt;, non-Hodgkin’s lymphoma</td>
<td>Hodgkin’s disease</td>
</tr>
<tr>
<td>HHV-8&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Herpesviridae</td>
<td>endothelial cells</td>
<td>Kaposi’s sarcoma, body cavity lymphoma</td>
<td>venereal</td>
</tr>
<tr>
<td>HBV</td>
<td>Hepadnaviridae</td>
<td>hepatocytes</td>
<td>hepatocellular carcinoma</td>
<td>parenteral, venereal</td>
</tr>
<tr>
<td>HCV</td>
<td>Flaviviridae</td>
<td>hepatocytes</td>
<td>hepatocellular carcinoma</td>
<td>venereal, venereal</td>
</tr>
<tr>
<td>HPV</td>
<td>Papovaviridae</td>
<td>cervical epithelial</td>
<td>cervical carcinoma</td>
<td>parenteral</td>
</tr>
<tr>
<td>JCV&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Papovaviridae</td>
<td>central nervous system</td>
<td>astrocytoma, glioblastoma</td>
<td>?</td>
</tr>
</tbody>
</table>

<sup>a</sup>Most of the viruses carry one or more potent growth-promoting genes/oncogenes in their genomes. However, such genes have not been identified in the genomes of HBV and HCV.

<sup>b</sup>These tumors, which bear copies of EBV genomes, appear in immunosuppressed patients.

<sup>c</sup>Parenteral, blood-borne; venereal, via sexual intercourse.

<sup>d</sup>Also known as KSHV, Kaposi’s sarcoma herpesvirus.

<sup>e</sup>JCV (JC virus, a close relative of SV40) infects more than 75% of the population by age 15, but the listed virus-containing tumors are not common. Much correlative evidence supports the role of JCV in the transformation of human central nervous system cells but evidence of a causal role in tumor formation is lacking.