

VMC 605: SYSTEMATIC ANIMAL VIROLOGY

VIRAL ONCOGENES

Dr Manoj Kumar

Assistant Professor-cum-Junior Scientist

Department of Veterinary Microbiology

Bihar Animal Sciences University



Four classes of oncogenes

Class One: oncogenes that mimic growth factors to induce cell proliferation

Rare – only two have been identified

Sis:

- **from simian sarcoma virus – a secreted protein that mimics PDGF**
- **from PI-FeSV – a cat sarcoma virus**



Class One:
oncogenes that
mimic growth
factors to induce
cell proliferation

- Rare – only two have been identified
- Sis:
- from simian sarcoma virus – a secreted protein that mimics PDGF
- from PI-FeSV – a cat sarcoma virus



Class Two: Mutated Receptors

Oncogenes that result from mutations of cell-surface receptors, usually resulting in an overactive or constitutive protein-tyrosine kinase (PTK).

Examples:

***fms* – from McDonough feline sarcoma virus – CSF-1 receptor**

***erbB* – from avian erythroblastosis virus – epidermal growth factor (EGF) receptor**

***ros* – UR2 avian sarcoma virus – related to insulin receptor**

***sea* – S13 avian sarcoma virus – related to human growth factor (HGF) receptor**



Class Three: Intracellular transducers

4 types of oncogene transducers

- **Protein-tyrosine kinases**
 - add a phosphate to specific tyrosine amino acids
- **Protein-serine/threonine kinases**
 - add a phosphate to specific serine or threonine amino acids
- **G-protein (Ras) proteins**
 - Trimeric GTPases that bind GTP to become active as signal transducers
- **Phospholipase C (PKC)**
 - Activated by certain G-proteins to trigger inositol phospholipid signaling pathway



Class Four: transcription factor oncogenes

Examples:

Jun  **Transcription factor AP1**
Fos 

**Myc (many examples in chicken, cat
leukosis viruses)**

Myb (chicken myeloblastosis virus)

**Rel (NF-kB family - turkey
reticuloendotheliosis virus)**

**erbA (thyroid hormone receptor – from
chicken erythroblastosis virus)**



How do viruses transform cells?

- Virus infection provides a “hit” towards the genesis of cancer.
 - Act as a “mutagen”
 - Other cofactors (genetic, immunological, or environmental) may be needed for development of cancer
- Cell transformation is accompanied by the persistence of all or part of the viral genome and continual expression of a limited number of viral genes.
- Viral oncogenes are expressed that alter normal cellular gene expression and signal transduction pathways.



Oncogenesis by virus insertion

An alternative to the acute transforming retroviruses.

Most retroviruses cannot transform cells.

Non acute (chronic) transforming viruses don't carry oncogenes – can't transform cells in culture.

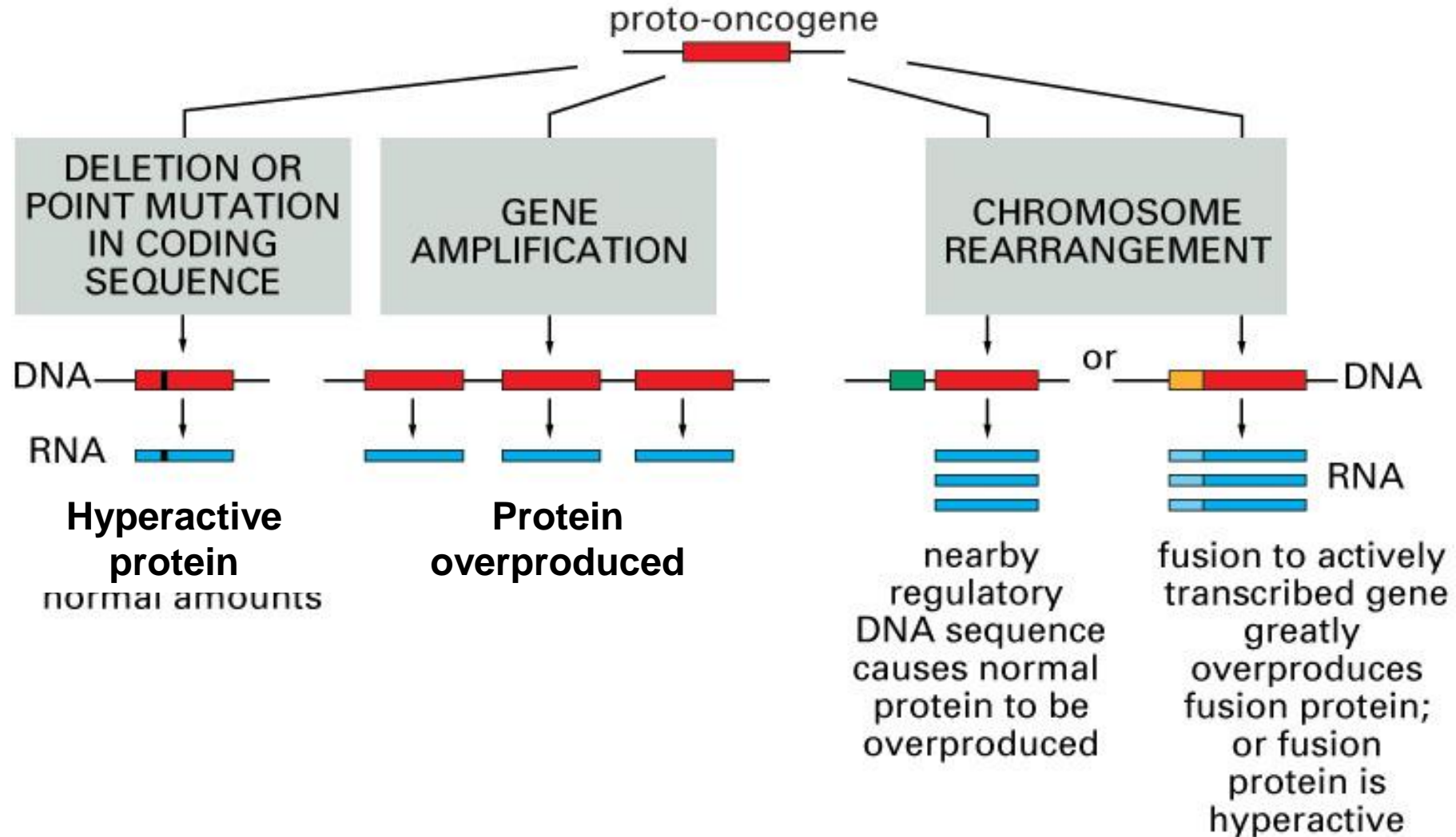
Non acute transforming viruses are still capable of replication.

Non acute transforming viruses can cause tumors in animals but over a 1-2 year time frame.

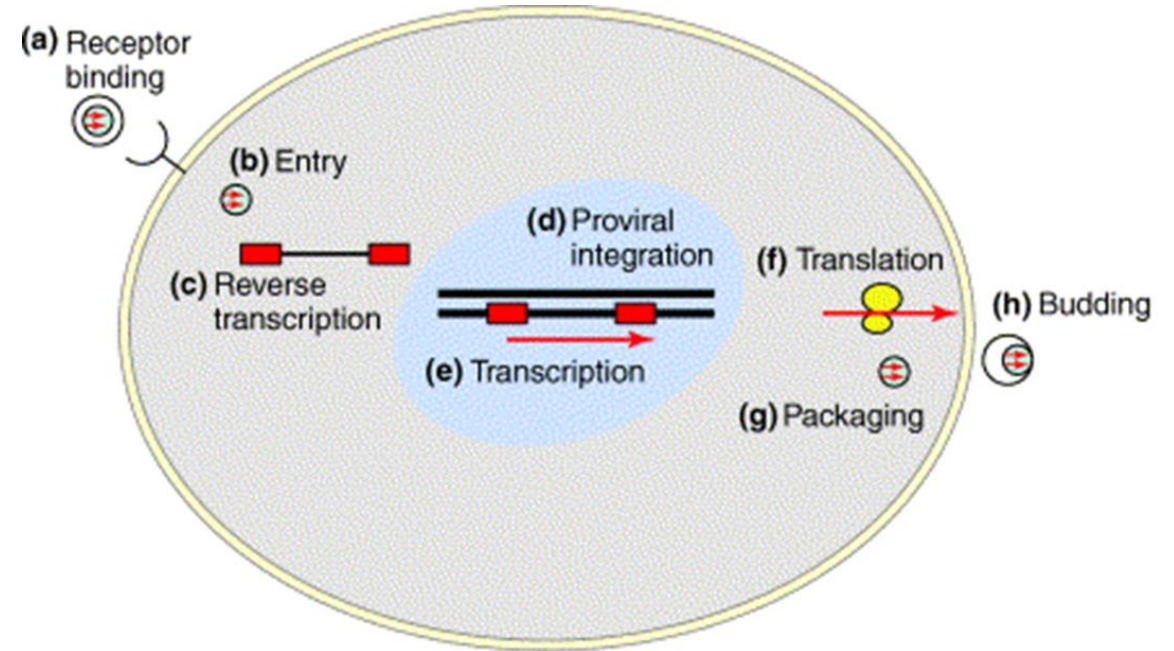
These viruses transform cells by insertional mutagenesis:

1. Avian leukosis virus – insert near myc
2. Mouse mammary tumor virus - int-1, int-2

How do tumors (and viruses) overproduce oncogene proteins?

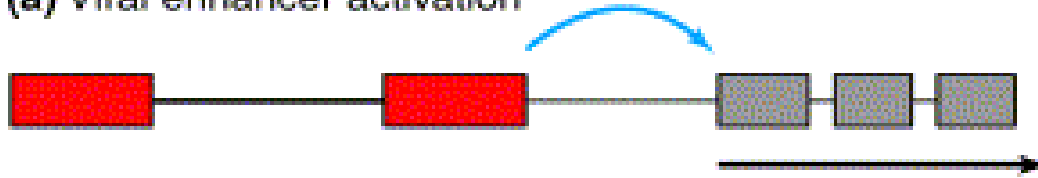


Retrovirus life cycle requires integration into the chromosome



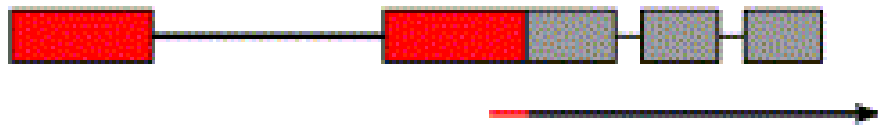
Insertional activation of proto-oncogenes

(a) Viral enhancer activation



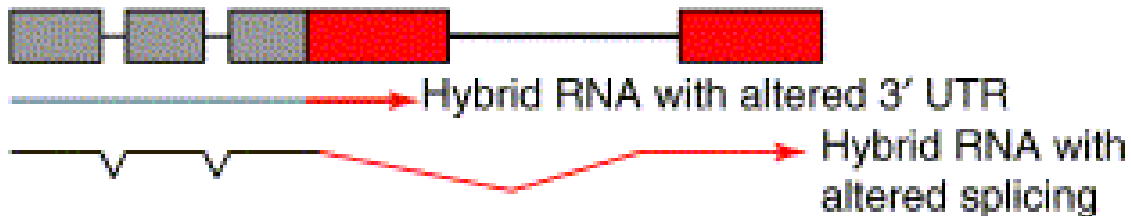
Viral enhancer acts on a nearby gene (dominant)

(b) Viral promoter insertion



Viral promoter transcribes a nearby oncogene (dominant)

(c) Post-transcriptional dysregulation



Altered transcription, processing, or stability (dominant)

(d) Insertional inactivation or gene truncation



Inactivate a gene (recessive mutation)

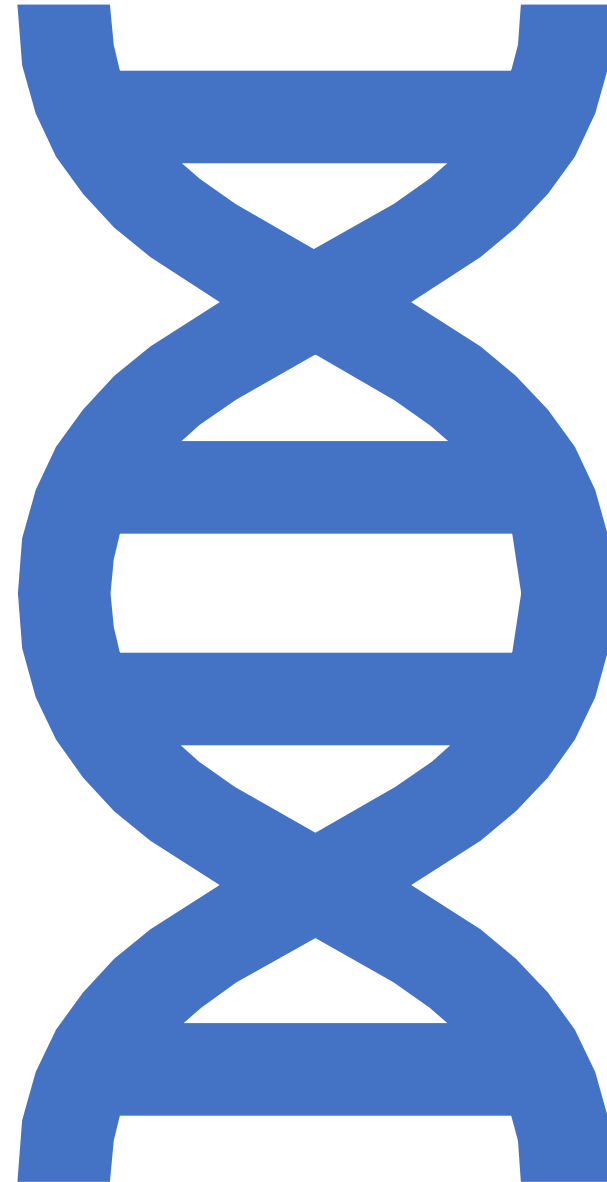


Summary

- RNA and DNA tumor viruses have helped define oncogenes and tumor suppressors
- RNA tumor viruses generally exert their effects through growth signaling pathways, turning them on in the absence of growth stimuli.
 - “add gasoline to the system”
- DNA tumor viruses generally act by sequestering proteins that control cell proliferation (Rb, p53), to shift the cells into S phase
 - “release the brakes”



RNA TUMOR VIRUSES



Retroviruses

RNA tumor viruses “create” oncogenes by acquiring, modifying, deregulating cellular genes (proto-oncogenes)

- v-onc not essential viral gene & unrelated to strategy of viral replication
- Replication of RNA viruses is not cytotoxic nor is it required for tumorigenesis

Mechanisms of cell transformation by retroviruses

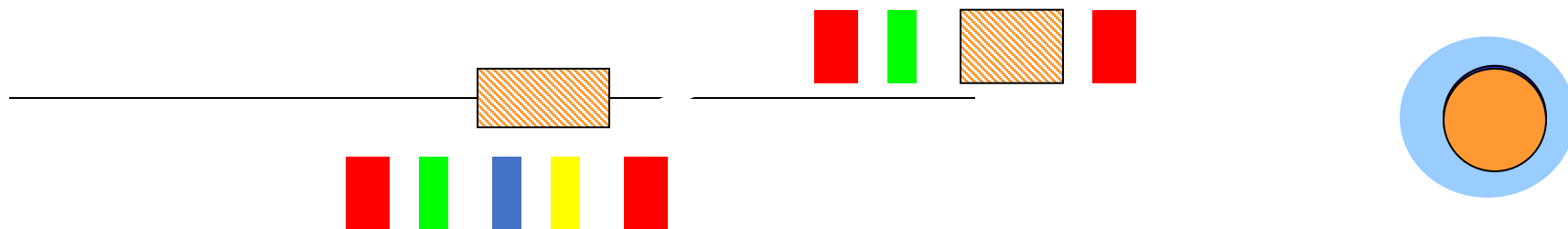
Retroviral transduction of oncogene (transducing retrovirus)

2) Oncogene activation by retroviral insertion (*cis*-acting / nontransducing retrovirus)

3) Oncogenesis mediated by essential retrovirus proteins (*trans*-activating / nontransducing long-latency retrovirus)

Transducing retroviruses

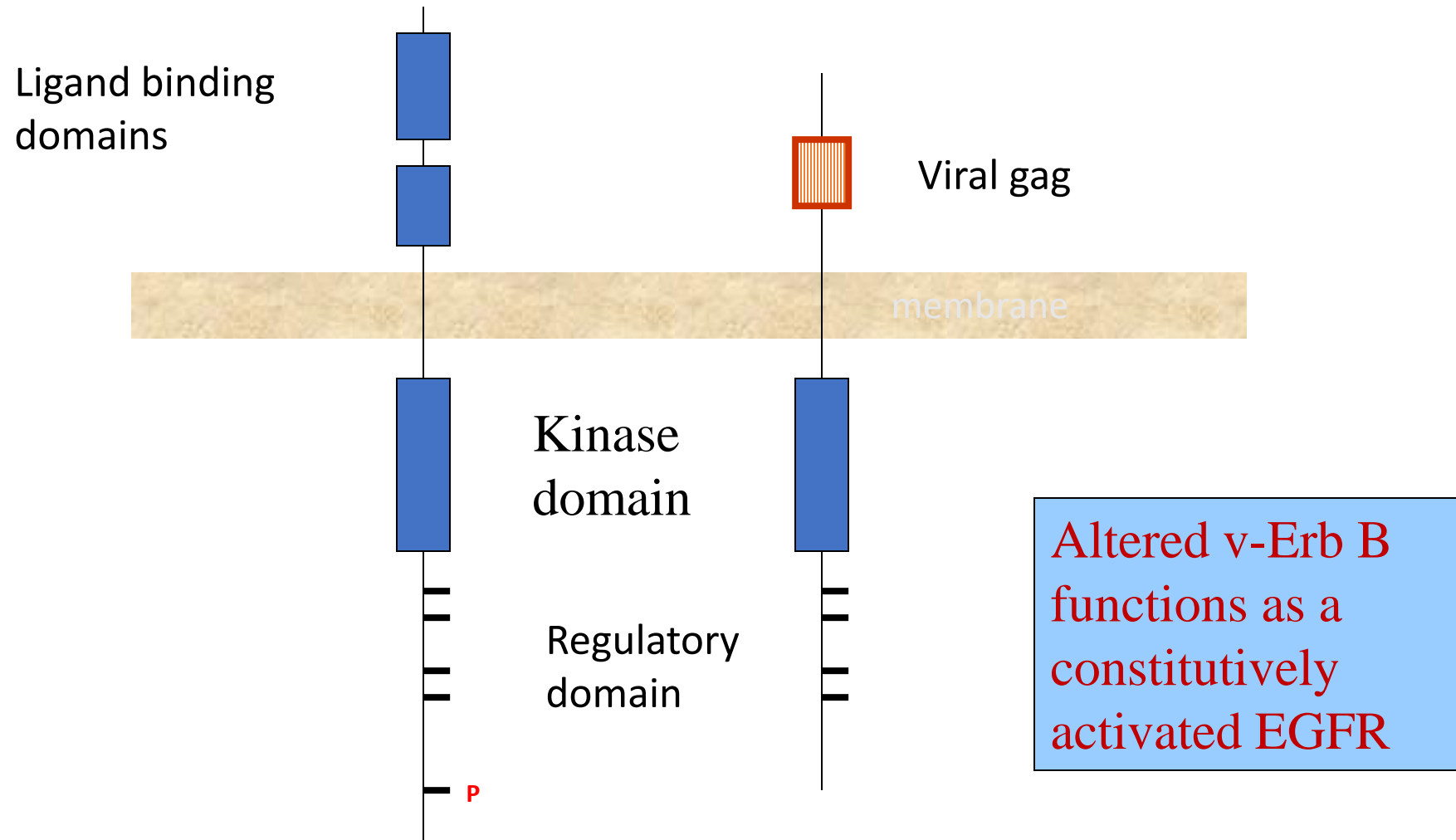
- Viral acquisition of cellular proto-oncogene with capacity to transform if deregulated, usually replacing viral coding sequences (exception is RSV=src oncogene)
- Overexpression versus structural change in v-onc
mos vs src
- Becomes replication defective, secondary to the loss of viral coding information; requires helper virus



Acquired Genes Are Components of Signaling Networks

- External signal molecules or growth factors (receptor ligands *(sis)*)
- Cellular receptors (*erbB, fms, kit*)
- Second messengers in signaling cascade (kinases: *src, abl, fgr, yes; mos raf*)
- Transcription factors (*jun, fos, myc, myb, ets, rel*)

Structural Changes in an Acquired vOnc



Outcome of Retroviral Transduction

Single hit” carcinogenesis (one event)

- Polyclonal: tumor growth initiated in every infected cell
- Tumors form within days
- Characteristic of animal retroviruses

Mechanisms of cell transformation by retroviruses

) Retroviral transduction of oncogene (transducing retrovirus)

Oncogene activation by retroviral insertion (*cis*-acting / nontransducing retrovirus)

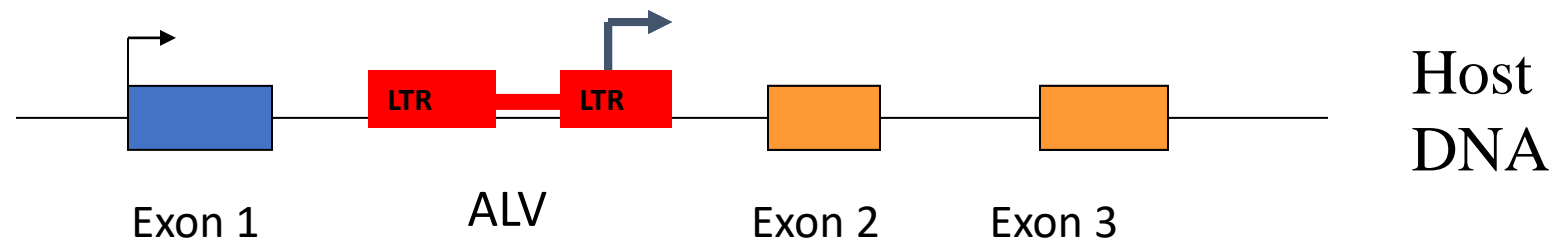
Oncogenesis mediated by essential retrovirus proteins (*trans*-activating / nontransducing long-latency retrovirus)

Cis-acting retroviruses

- Do not carry oncogenes
- Retain all viral genes
- Are replication-competent

Mechanism of cell transformation for cis-acting retroviruses

- Random retroviral integration into cell DNA
- Insertional activation (or inactivation)
- Cis activation by promoter or enhancer insertion next to proto-oncogene (encoded by exons 1-3)



Outcome of Oncogene Activation by Retrovirus Insertion

- Cell transformation rare event because insertion near potential oncogenes is infrequent
- Monoclonal tumors: proviral sequences integrated at same chromosomal site
- Tumors induced more slowly (months) since tumor derived from single cell

Mechanisms of cell transformation by retroviruses

- 1) Retroviral transduction of oncogene (transducing retrovirus)
- 2) Oncogene activation by retroviral insertion (*cis*-acting / nontransducing retrovirus)
- 3) Oncogenesis mediated by essential retrovirus proteins (*trans*-activating / nontransducing long-latency retrovirus)

Mechanisms of cell transformation by retroviruses

Virus category	Tumor latency period	Efficiency of tumor formation	Oncogenic effector	Infecting viral Genome	Transform cultured cells?
Transducing retrovirus	Short (days)	High (can reach 100% of animals)	Cell-derived oncogene carried in viral genome	Viral-cellular chimera, replication defective	Yes
Cis-acting/nontransducing	Intermediate (wk, mo)	High to intermediate	Cellular oncogene activated in situ by provirus insertion	Intact, replication competent	No
Trans-activating/nontransducing long latency	Long (mo, yr)	Very low (<5%)	Virus-coded Transcriptional regulatory protein	Intact, replication competent	No



Any questions???

Thanks