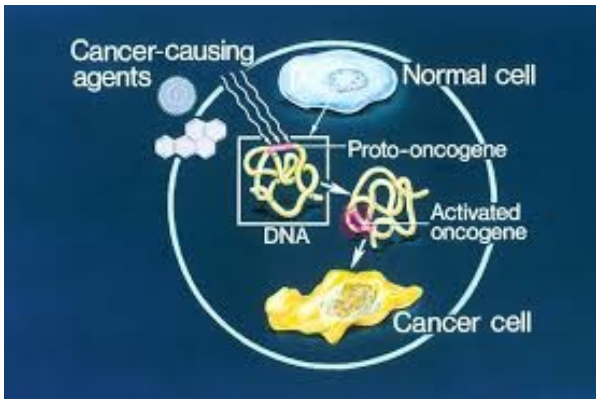
Tumor Viruses and Cellular Oncogenes

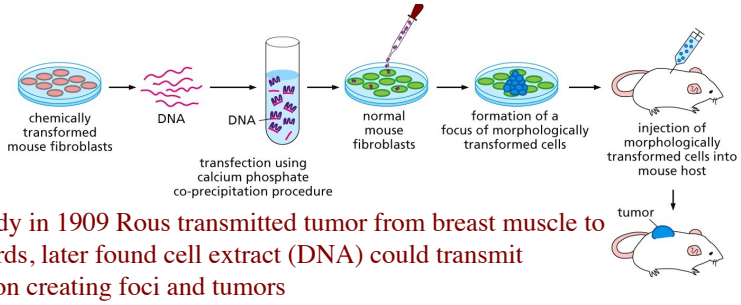


1

Viral sources of Cancer

Viruses were first found in chickens in 1908 by Ellerman and Bang (erythroid leukemia) and in 1911 (soft cell carcinoma) by Peyton Rous.

Initial "war on cancer" was thought to be primarily viral



- Initial study in 1909 Rous transmitted tumor from breast muscle to similar birds, later found cell extract (DNA) could transmit information creating foci and tumors
- Showed use the information of cancers was very small (filterable through sand) was a virus.
- At the time (1911) all/most diseases were thought to be infectious in nature – cancer was considered another such disease

2

Viruses Implicated in Human Cancer Causation

Virus[a]	Virus family	Cells infected	Human malignancy	Transmission route
EBV[b]	Herpesviridae	B cells	Burkitt's lymphoma	saliva
		oropharyngeal epithelial cells	nasopharyngeal carcinoma	saliva
		lymphoid	Hodgkin's disease[c]	
HTLV-I	Retroviridae	T cells	non-Hodgkin's lymphoma	parenteral, venereal[d]
HHV-8[e]	Herpesviridae	endothelial cells	Kaposi's sarcoma, body cavity lymphoma	venereal, vertical[d]
HBV	Hepadnaviridae	hepatocytes	hepatocellular carcinoma	parenteral, venereal
HCV	Flaviviridae	hepatocytes	hepatocellular carcinoma	parenteral
HPV	Papillomaviridae	cervical epithelial	cervical carcinoma	venereal
JCV[f]	Polyomaviridae	central nervous system	astrocytoma, glioblastoma	?

3

Protoncogenes / Oncogenes

Virus/Retrovirus use proto-oncogenes as a strategy for survival and propagation, but most cancers are not viral in nature

- **Proto-oncogene: a normal cellular gene that upon alteration of DNA can acquire the ability to function as an oncogene**
- **Oncogene: a protein capable of inducing cancer (can transform cells).**
  - **c-ZYZ indicates a cellular, yet to be oncogenic (mutated) proto oncogene of cellular origin vs**
  - **v-XYZ is a viral oncogene origin (not often used)**
  - **Non-human oncogenes are in italics *Xyz***
  - **Oncoproteins (not genes) start with capitals followed by lower case Xyz vs XYZ**

4

Genetic Basis of Cancer

-Viral oncogenes - insert mutated DNA into cell and create oncogenes

-Translocation of chromosomes - movement of one segment of a chromosome to another

–- not normally a cause of cancer but used to find cellular proto oncogenes and study their effects

-Point Mutations - Alterations in specific sequences of critical genes (proto oncogene activation)

- usually needs several mutations with one or more critical requirements for cancer to develop

-Alteration in promoter/enhancers - can occur due to chromosomal translocation (expression)

-Gene amplification (expression)

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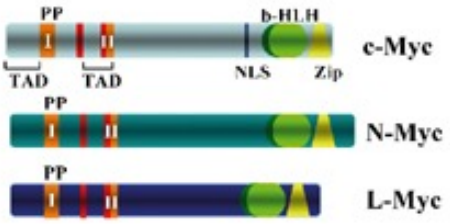
Retroviral – Gene Amplification

Increased copy number of a gene can lead to transformation, proliferation and cell migration or enhanced survival.

- **Lead to increased protein production and as a result higher signaling**

Myc – first found via avian MC29 **my**elo**c**ytomatosis transforming virus is 10-20 extra copies in leukimia and many other cancers



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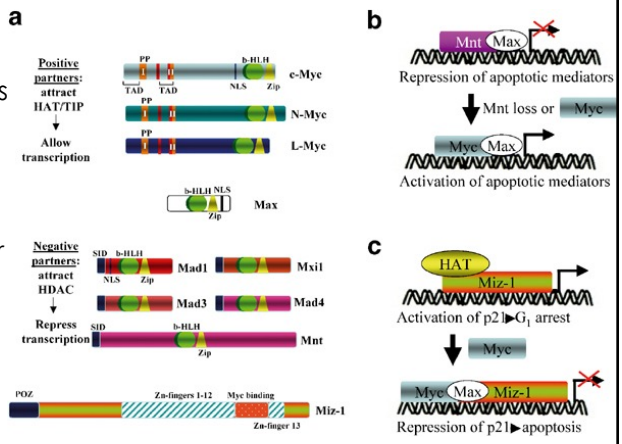
Retroviral – Gene Amplification

Myc –cellular (c-Myc) homolog and isoforms N, L and other Myc forms expresed and activated in nearly 70% of cancers.

•Is a transcription factor (helix-loop-helix leucine zipper) found in most organisms.

- Leads to activation via binding partners to activate proliferation and several signaling cascades – promising target for therapy as small inhibition seems to reduce tumor formation



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Gene Amplification

erbB – first discovered in avian erythroblastosis virus – increased copy number in stomach, breast and brain tumors and many others.

- aka – Neu/Her/erbB: EGFR over expression – separate from mutation/truncation. Several subforms generate protein tyrosine kinase receptors.
  - Gene is amplified in 30% of breast cancers and are the target of several antibody drugs (biologics) Herceptin.

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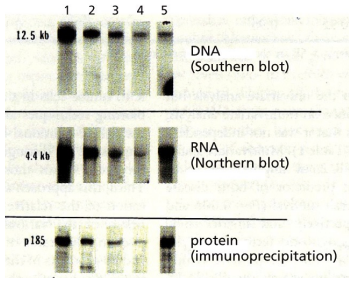
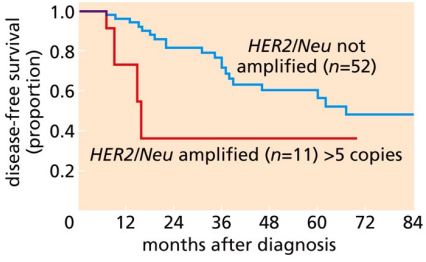
Gene Amplificaton

Direct correlation of amplification with poor breast cancer prognosis

- > 5 copies increases tumor formation and decreases 5 year survival rate by nearly half.
- Gene amplification alone can't explain breast cancer
  - DNA amplification increases protein but mRNA can be increased independently.
  - Some amplifications stretch beyond Myc to enhance other oncogenes providing a synergistic effect





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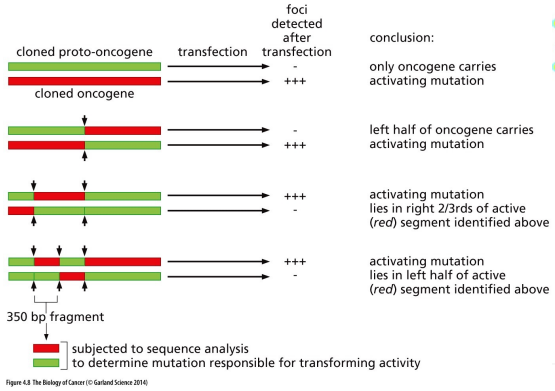
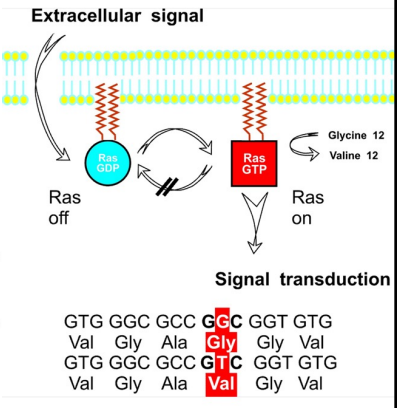
Gene mutations – may cause protein structural changes in oncogene activation

Point mutation – single DNA base pair can lead to altered amino acid and protein function. **Ras is an example of a somatic mutation leading to cancer**





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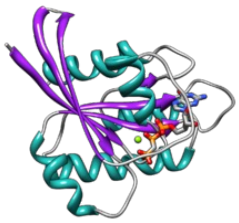
Point Mutation - Ras

Rat Sarcoma discovered by Jennifer Harvey and Werner Kirsten



Three human Ras isoforms (3 different genes)

- NRas – initially found in neuroblastomas
- Kras – Kirsten – sarcomas
- Hras – Harvey rat sarcomas.

P-loop

- Binds second phosphate of GTP
- Gly-Val mutation decreases GTPase activity leaving Ras active

Tumor type	Proportion (%) of tumors carrying a point-mutated *ras* gene[a]
Pancreas	90 (K)
Thyroid (papillary)	60 (H, K, N)
Thyroid (follicular)	55 (H, K, N)
Colorectal	45 (K)
Seminoma	45 (K, N)
Myelodysplasia	40 (N, K)
Lung (non-small-cell)	35 (K)
Acute myelogenous leukemia	30 (N)
Liver	30 (N)
Melanoma	15 (N)
Bladder	10 (H, K)
Kidney	10 (H)

[a]H, K, and N refer to the human *H-RAS*, *K-RAS*, and *N-RAS* genes, respectively.

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Enhanced gene – protein activity via translocation

Placement of oncogene in front of active gene/chromosomal arm will increase protein expression without gene copy

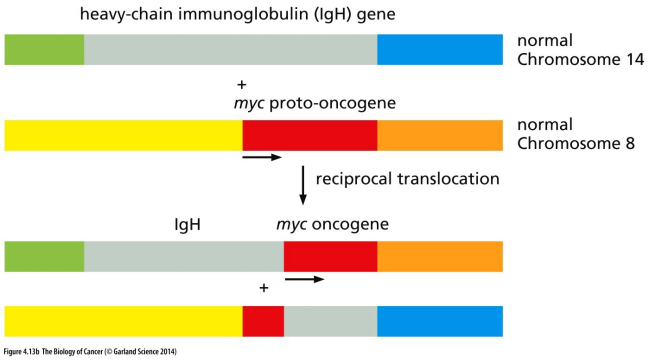

Figure 4.13b The Biology of Cancer (© Garland Science 2014)

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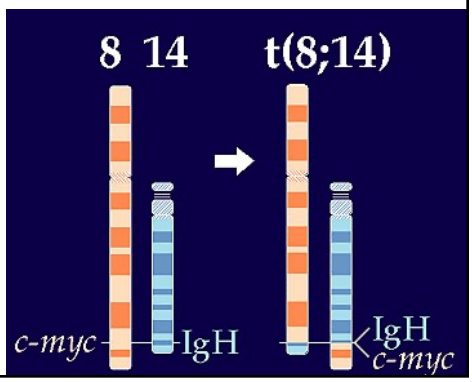
Chromosomal Translocation:

Translocation between chromosomes 8 and 14 found in Burkitt's lymphoma (lymph system cancer / leukemia)

Burkitt's lymphoma is a B cell neoplasm characterized by small noncleaved cells that are uniform in appearance. This neoplasm is one of the fastest growing malignancies in humans.

Burkitts lymphoma is characterized by a specific cytogenetic defect, a balanced, reciprocal translocation of genetic material from the long arm of chromosome 8 to the long arm of chromosome 14.



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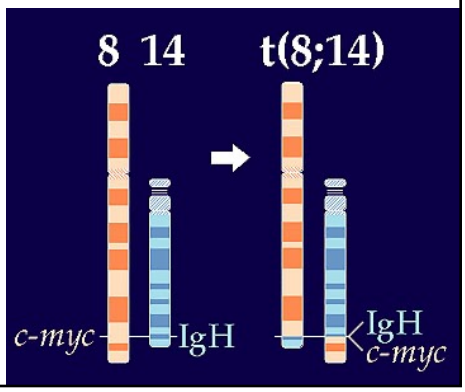
Chromosomal Translocation:

lymphoma are characterized by a specific cytogenetic defect, a balanced, reciprocal translocation of genetic material from the long arm of chromosome 8 to the long arm of chromosome 14. Two variants of Burkitt's lymphoma are recognized: African and non- African; although very similar in histologic and cytologic features, they have very different epidemiologic patterns and clinical presentations. African Burkitt's lymphoma presents most often as a jaw or orbital tumor and occurs endemically in central Africa. In contrast non- African Burkitt's lymphoma presents primarily as an abdominal mass.



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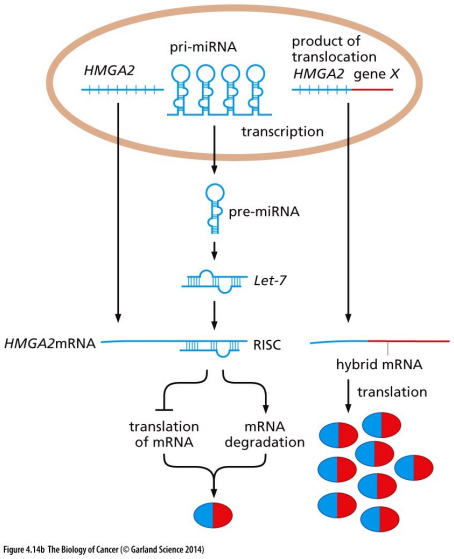
Translocation – micro RNA

- Nuclear Protein HMGA – translocates in a non-protein coding region to another gene producing a hybrid protein.
- Micro-RNA silencing (shRNA/RNAi) DNA is left behind.
- Loss of degredation of mRNA for HMGA leads to enhanced and extended protein levels



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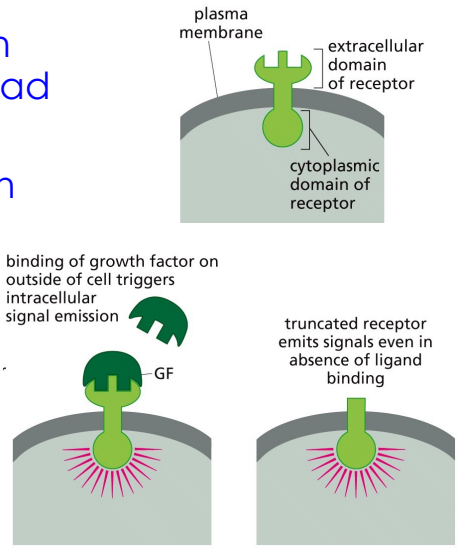
Proto-oncogene activation: Point mutations or translocations – lead to truncation or fusion proteins

- Mutations (point mutation or translocation) can lead to a loss of regulation.
  - "false" stop codons can be added or pauses in mRNA reading frames lead to truncated proteins
  - Examples include EGFR



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Mistakes in Somatic Cells

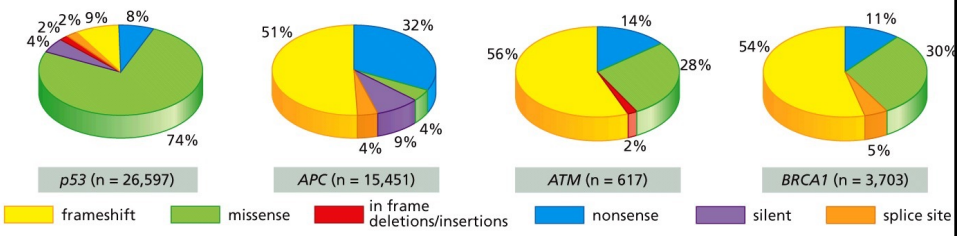

Figure 9.6a The Biology of Cancer (© Garland Science 2014)

Frameshift – addition or deletion of one or two bp
Missense – one bp leading to a single aa change
Nonsense – a single bp change leading to a truncation

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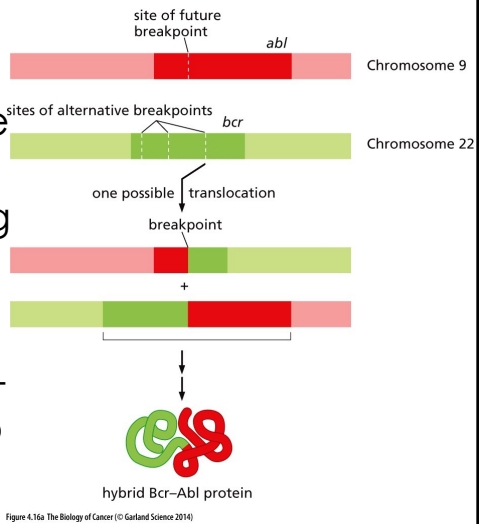
Translocaton within genes produce new oncogene

Two proto-oncogenes are "mixed and matched" to generate unregulated kinase expressed in the wrong tissue

- Abl and Bcr

Imatinib/GLEEVEC – Bcr-Abl specific inhibitor to treat myolegenous leukemia



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