

Dominant Acting Oncogenes

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Oncogenes are altered forms of normal cellular genes called proto-oncogenes that are involved in pathways regulating cell growth, differentiation, and survival.

More than 100 oncogenes identified to date.

Dominant mutations in proto-oncogenes contribute to deregulated cell growth.

Mutations are somatic, and affect only one allele, and are dominant and oncogenic.

Activation of cellular proto-oncogenes to oncogenes

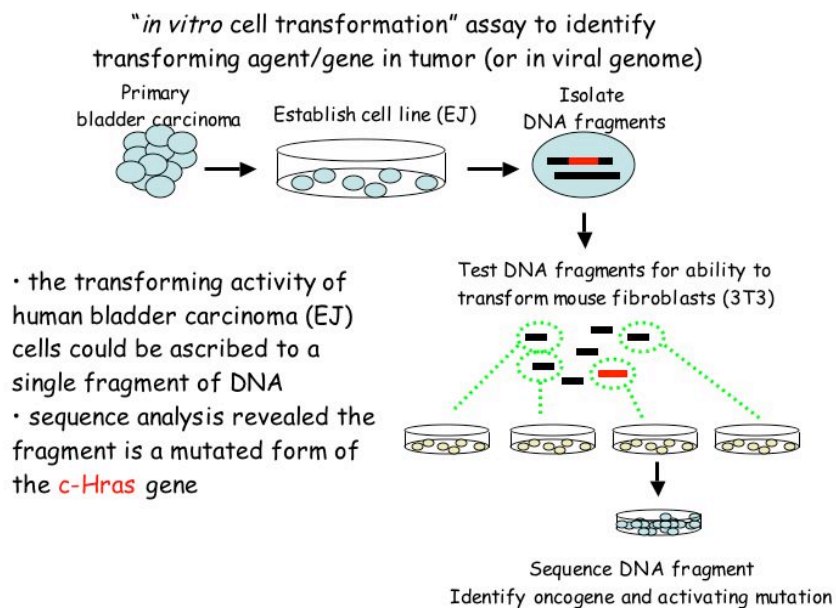
There are three primary mechanisms by which oncogene activation occurs:

1. Point Mutation- affects activity of the protein, typically increasing its activity, e.g Ras.
2. Amplification affects amount of oncoprotein by increasing transcription of the gene.
3. Chromosomal translocation-deregulation of expression or function.

How was active Ras identified?

Separately, Robert Weinberg and Michael Wigler proposed that there must be dominant active oncogenes in human tumors.

They isolated DNA from human tumor cell lines, and transfected into mouse fibroblasts.



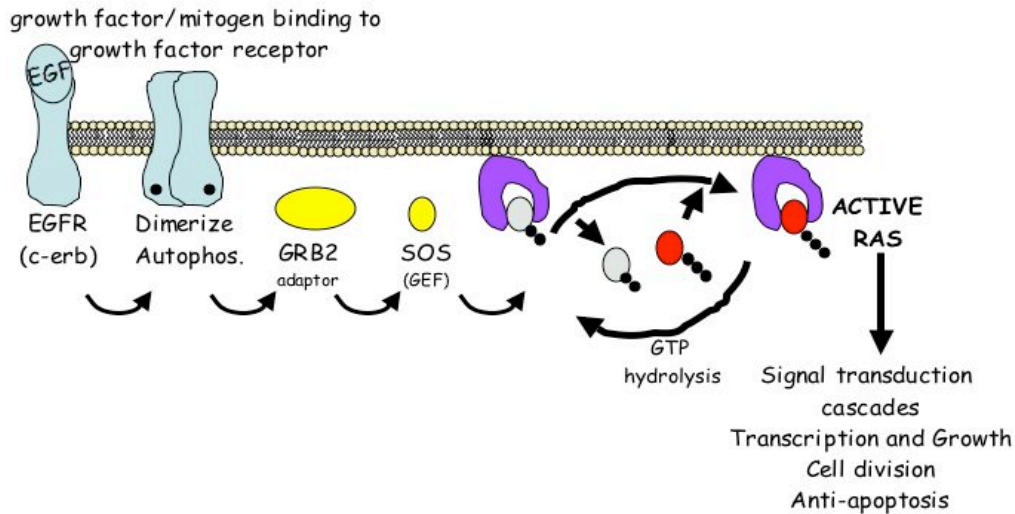
They eventually found that a single mutated gene was responsible for the oncogenic transformation of the fibroblasts. They used the basic assay described in the figure shown.

RAS mutations in a broad spectrum of tumors

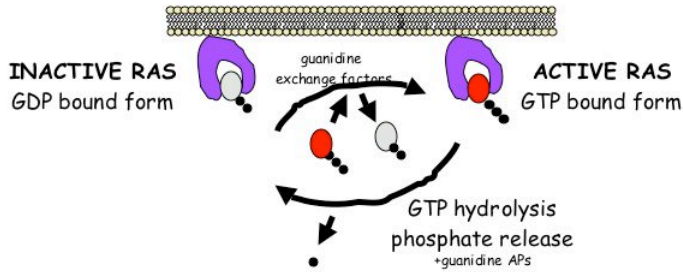
~15% of tumors harbor a mutant RAS gene family member
almost all contain codon 12, 13, or 61 point mutations

Tumor type	Mutation Frequency	Mechanism
Pancreas	>80%	point mut.
Cervical	20-80%	point mut.
Thyroid (follicular)	50-80%	point mut.
Thyroid (papillary)	60%	point mut.
Cholangiocarcinoma	>50%	point mut.
Colon	50%	point mut.
Skin (non melanoma)	30-50%	point mut.
Skin (melanoma)	5-35%	point mut.
Lung carcinoma (NSLC)	30-50%	point mut.
Endometrial	20-40%	point mut.

RAS signaling pathway: activation of RAS



RAS activation and the consequence of codon 12, 13, 61 mutations

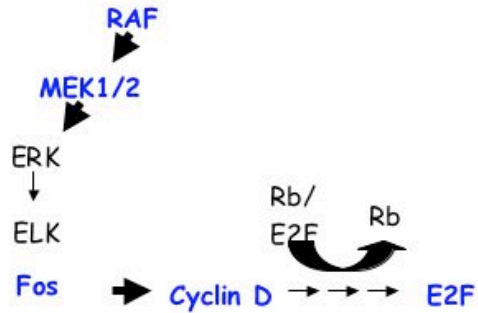


RAS codons 12, 13, 61 code for amino acids that bind the GTP molecule
Mutations significantly reduce/abolish ability of RAS to hydrolyze GTP
Thus, a more active RAS to signal growth



Proteins in **blue** have been implicated as oncogenes

- Growth factors
- Growth factor receptors
- Intracellular transducers
- Nuclear transcription factors
- Regulators of apoptosis
- Negative regulators of tumor suppressors

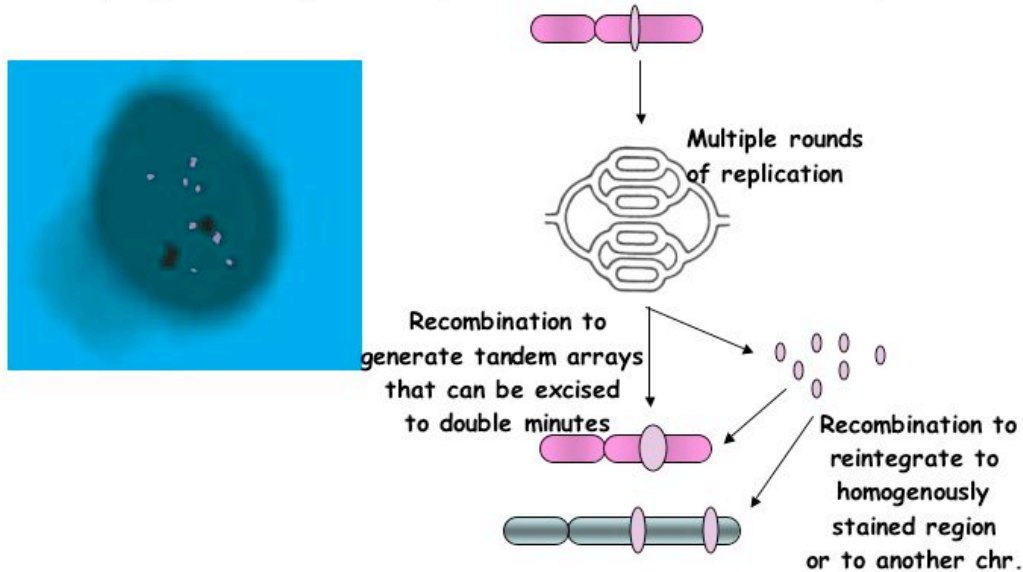


transcription of genes
for DNA synthesis,
cell cycle progression

Activation by Amplification of the DNA

Amplification affects amount of oncoprotein by increasing the number of copies of the gene, thereby increasing transcription. e.g. -Myc, cyclin D

Disease progression by transcriptional deregulation: DNA amplification

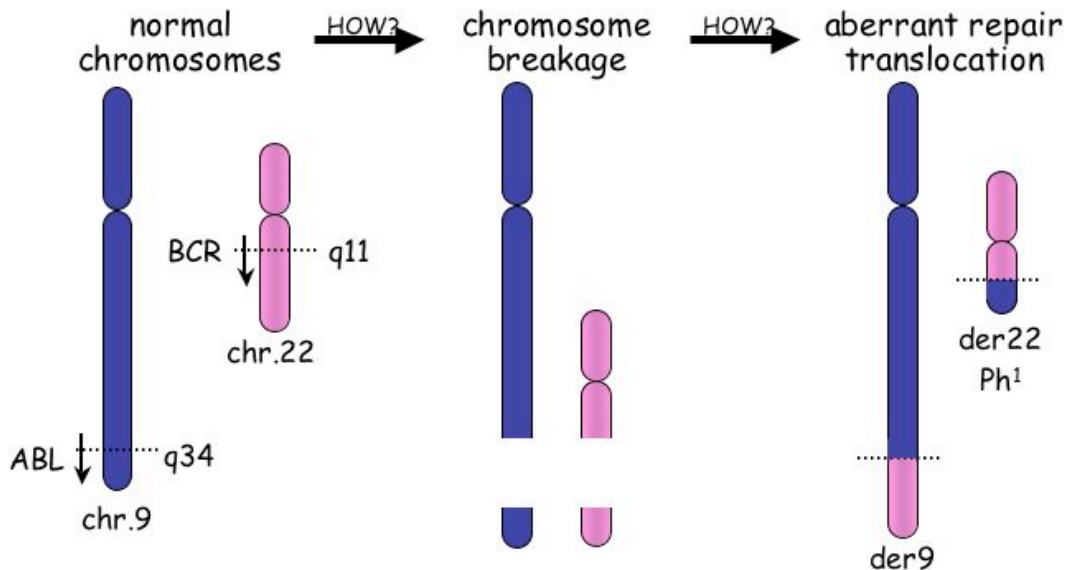


Chromosomal translocation-deregulation of expression or function, e.g. Bcr-abl in CML, Myc in Burkitts lymphoma.

Chromosome translocations activate proto-oncogenes by one of two mechanisms

1. By generating an aberrant fusion gene comprised protein portions of two genes, usually leading to constitutive activation of a kinase that was previously regulated by a signal . (Bcr-Abl)
2. By transcriptional deregulation of a proto-oncogene at one chromosome breakpoint by juxtaposition with regulatory sequences from the other breakpoint. Thus, one gene and its protein are normal, it is either over-expressed or expressed inappropriately leading to trouble. (Myc)

**Disease initiation by gene fusion: Philadelphia (Ph¹) chromosome
observed in 95% of CML cases**



The der22 (identified by Nowell in 1960 because of its small size) contains the activated BCR-ABL fusion oncogene/protein responsible for growth stimulation, anti-differentiation, and anti-apoptosis in certain hematopoietic cells, ultimately leading to leukemia.

Disease initiation by gene fusion: Philadelphia chromosome fusion protein of BCR-ABL results in activation of proto-oncogene ABL

the normal ABL protein

- a non-receptor protein tyrosine kinase
- phosphorylation of ABL substrates promotes cell growth
- enzymatic activity of normal ABL is tightly controlled

the BCR-ABL fusion protein

- the tyrosine kinase activity cannot be downregulated due to replacement of N-terminal ABL sequences with BCR sequences
- the fusion protein constitutively promotes cell growth.

Thus BCR-ABL is the malignantly activated form of the ABL proto-oncogene.

Disease initiation by transcriptional deregulation: Burkitt's lymphoma and MYC

Burkitt's lymphoma is a B cell malignancy endemic in the malarial belt and common in immunosuppressed populations.

Virtually all patients associated with BL have a common chromosomal breakpoint at t(8;14)(q24;q32) which leads to the transcription of the Myc gene on chromosome 8 being transcribed by an Immunoglobulin promoter on chromosome 14.

Oncogenic Viruses

There are multiple mechanisms by which viruses can play a pathogenic role in human cancer.

Some viruses directly cause cancer by binding or destroying tumor suppressor proteins, thus acting in a dominant mechanism, e.g HPV.

Other viruses act indirectly, by stimulating chronic inflammation or by immunosuppression of tumors (Hep virus; HIV).

Tumor Viruses: Human Papilloma Virus (HPV)

HPV infects squamous epithelial cells

- > 75% of cervical squamous cell carcinomas are HPV+
- > 50% anorectal squamous cell cancers (HIV+) are HPV+

