Cancer

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Learning Goals for This Lecture

- To recognize that cancer largely is a preventable disease.

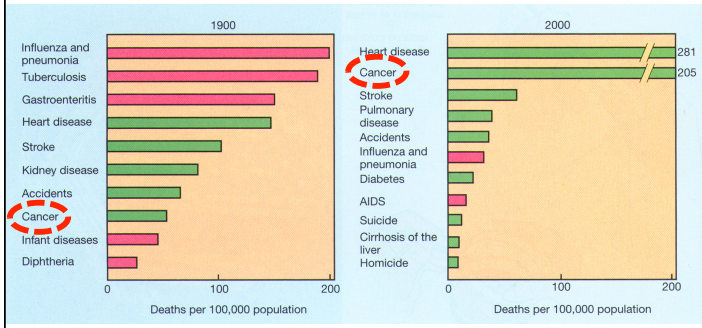
- To recognize that cancer is a disease of our own genes.

- To recognize the differences between oncogenes and tumor suppressors.

- To appreciate the actions of carcinogens in mutating and rearranging DNA.

- To find the link between developmental genes and cancer genes.

Death Rates for the Main Causes of Death in the U.S.



What are the differences 100 years apart?

Leading Sites of New Cases & Deaths
(2015 estimates in the U.S.)

Estimated New Cases*		Estimated Deaths	
Male	**Female**	**Male**	**Female**
Prostate 220,800 (26%)	Breast 231,840 (29%)	Lung & bronchus 86,380 (28%)	Lung & bronchus 71,660 (26%)
Lung & bronchus 115,610 (14%)	Lung & bronchus 105,590 (13%)	Prostate 27,540 (9%)	Breast 40,290 (15%)
Colon & rectum 69,090 (8%)	Colon & rectum 63,610 (8%)	Colon & rectum 26,100 (8%)	Colon & rectum 23,600 (9%)
Urinary bladder 56,320 (7%)	Uterine corpus 54,870 (7%)	Pancreas 20,710 (7%)	Pancreas 19,850 (7%)
Melanoma of the skin 42,670 (5%)	Thyroid 47,230 (6%)	Liver & intrahepatic bile duct 17,030 (5%)	Ovary 14,180 (5%)
Non-Hodgkin lymphoma 39,850 (5%)	Non-Hodgkin lymphoma 32,000 (4%)	Leukemia 14,210 (5%)	Leukemia 10,240 (4%)
Kidney & renal pelvis 38,270 (5%)	Melanoma of the skin 31,200 (4%)	Esophagus 12,600 (4%)	Uterine corpus 10,170 (4%)
Oral cavity & pharynx 32,670 (4%)	Pancreas 24,120 (3%)	Urinary bladder 11,510 (4%)	Non-Hodgkin lymphoma 8,310 (3%)
Leukemia 30,900 (4%)	Leukemia 23,370 (3%)	Non-Hodgkin lymphoma 11,480 (4%)	Liver & intrahepatic bile duct 7,520 (3%)
Liver & intrahepatic bile duct 25,510 (3%)	Kidney & renal pelvis 23,290 (3%)	Kidney & renal pelvis 9,070 (3%)	Brain & other nervous system 6,380 (2%)
All sites 848,200 (100%)	All sites 810,170 (100%)	All sites 312,150 (100%)	All sites 277,280 (100%)

*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

Five-Year Relative Survival Rate (%)

(by stage at diagnosis, 2004-2010 in the U.S.)

	All Stages	Local	Regional	Distant		All Stages	Local	Regional	Distant
Breast (female)	89	99	85	25	Ovary	45	92	72	27
Colon & rectum	65	90	71	13	Pancreas	7	26	10	2
Esophagus	18	40	21	4	Prostate	99	>99	>99	28
Kidney†	72	92	65	12	Stomach	28	64	29	4
Larynx	60	75	43	35	Testis	95	99	96	73
Liver‡	17	30	11	3	Thyroid	98	>99	98	55
Lung & bronchus	17	54	27	4	Urinary bladder§	77	69	34	6
Melanoma of the skin	91	98	63	16	Uterine cervix	68	91	57	16
Oral cavity & pharynx	63	83	61	37	Uterine corpus	82	95	68	18

*Rates are adjusted for normal life expectancy and are based on cases diagnosed in the SEER 18 areas from 2004-2010, all followed through 2011. †Includes renal pelvis. ‡Includes intrahepatic bile duct. §Rate for in situ cases is 96%.

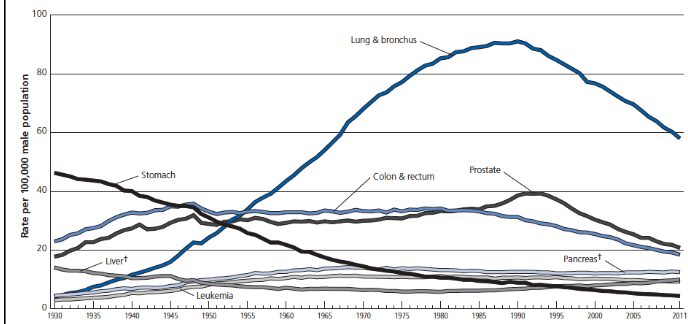
Local: an invasive malignant cancer confined entirely to the organ of origin. **Regional:** a malignant cancer that 1) has extended beyond the limits of the organ of origin directly into surrounding organs or tissues; 2) involves regional lymph nodes; or 3) has both regional extension and involvement of regional lymph nodes. **Distant:** a malignant cancer that has spread to parts of the body remote from the primary tumor either by direct extension or by discontinuous metastasis to distant organs, tissues, or via the lymphatic system to distant lymph nodes.

Source: Howlader N, Noone AM, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2011, National Cancer Institute, Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission.

American Cancer Society, Inc., Surveillance Research, 2015

Trends in Age-adjusted Cancer Death Rates*

(by site, males, 1930-2011, U.S.)



*Per 100,000, age adjusted to the 2000 US standard population. †Mortality rates for pancreatic and liver cancers are increasing.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the liver, lung and bronchus, and colon and rectum are affected by these coding changes.

Source: US Mortality Volumes 1930 to 1959 and US Mortality Data 1960 to 2011, National Center for Health Statistics, Centers for Disease Control and Prevention.

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Lifetime Probability of Developing* & Dying from Cancer

(for 23 Sites, 2009-2011, U.S.)

	MALES				FEMALES			
	Developing		Dying		Developing		Dying	
	%	1 in...	%	1 in...	%	1 in...	%	1 in...
All Sites†	43.3	2	22.8	4	37.8	3	19.3	5
Brain & ONS	0.7	[illegible]	0.5	198	0.6	182	0.4	250
Breast	0.1	[illegible]	0.0	3,083	12.3	[illegible]	2.7	37
Colorectal	[illegible]	21	2.0	[illegible]	[illegible]	[illegible]	1.9	54
Esophagus	[illegible]	[illegible]	0.8	127	[illegible]	[illegible]	0.2	474
Hodgkin lymphoma	[illegible]	[illegible]	0.1	2,191	[illegible]	[illegible]	[illegible]	2,954
Kidney & renal pelvis	[illegible]	[illegible]	[illegible]	163	[illegible]	[illegible]	0.4	289
Larynx	[illegible]	[illegible]	[illegible]	489	[illegible]	[illegible]	[illegible]	1,951
Leukemia	[illegible]	[illegible]	1.0	[illegible]	[illegible]	[illegible]	[illegible]	138
Liver & intrahepatic bile d[illegible]	[illegible]	[illegible]	[illegible]	111	[illegible]	[illegible]	[illegible]	213
Lung & bronchus	[illegible]	[illegible]	[illegible]	15	[illegible]	[illegible]	[illegible]	20
Melanoma of skin‡	[illegible]	[illegible]	0.5	202	[illegible]	[illegible]	[illegible]	414
Myeloma	[illegible]	[illegible]	0.5	[illegible]	[illegible]	[illegible]	0.4	267
Non-Hodgkin lymphoma	[illegible]	42	0.9	115	[illegible]	[illegible]	0.7	144
Oral cavity & pharynx	[illegible]	65	0.4	[illegible]	[illegible]	[illegible]	0.2	551
Ovary	--	--	--	--	[illegible]	[illegible]	1.0	[illegible]
Pancreas	1.5	66	1.4	74	[illegible]	67	[illegible]	[illegible]
Prostate	15.0	7	[illegible]	[illegible]	--	--	[illegible]	[illegible]
Stomach	1.1	[illegible]	[illegible]	[illegible]	0.7	[illegible]	[illegible]	[illegible]
Testis	0.4	[illegible]	[illegible]	[illegible]	--	[illegible]	[illegible]	[illegible]
Thyroid	[illegible]	[illegible]	[illegible]	[illegible]	1.7	[illegible]	[illegible]	[illegible]
Urinary bladder§	3.8	[illegible]	[illegible]	[illegible]	1.1	[illegible]	[illegible]	[illegible]
Uterine cervix	--	[illegible]	[illegible]	[illegible]	0.7	[illegible]	[illegible]	[illegible]
Uterine corpus	--	[illegible]	[illegible]	[illegible]	2.7	[illegible]	[illegible]	[illegible]

1 in 2!

1 in 3!

1 in 4!

1 in 5!

* For those who are cancer free.
† All sites excludes basal cell and squamous cell skin cancer[illegible] and in [illegible] cance[illegible] [illegible]cept urina[illegible] bladder.
‡ Statistics are for whites.
§ Includes invasive and in situ cancer cases.
Source: Software: DevCan: Probability of Developing or Dying of Can[illegible]er Software, Version 6.7.1, National Cancer Institute, 2014.

American Cancer Society, Surveillance Research, 2015

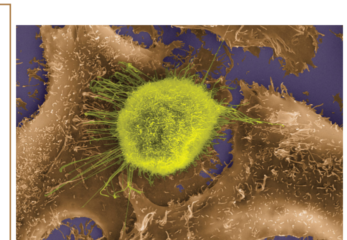
Cancers Are Malignant Tumors

Benign tumors:

- cells resemble their tissue of origin
- grow slowly
- are localized to tissue of origin

Malignant tumors:

- cells do not resemble tissue of origin and has irregular structures
- can invade surrounding tissues and spread to other organs (metastasis)



Cancer cells differ from the normal cells from which they originate:
- cancer cells lose control over cell division
- cancer cells can migrate to other locations in the body (*metastasis*)

Cancer Classification

Carcinoma: epithelial cells

Sarcoma: connective tissues

Lymphoma and leukemia: hematopoietic cells

Germ cell tumor: seminoma (testis) and dysgerminoma (ovary)

Blastoma: embryonic precursors

Cancer development is a multistep process that takes a long time
- involves a series of genetic and cellular changes
- solid tumors need blood vessels to fuel its growth

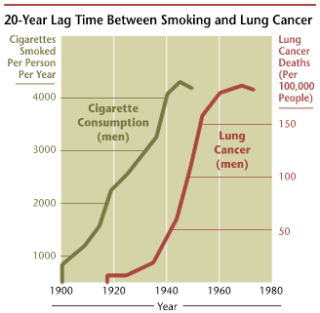
How Do Cancers Arise?
(DNA mutations that impact cell growth)

Environmental factors:
tobacco, diet and obesity, infections, radiation, lack of physical activity and environmental pollutants

Genetics:
only *a small percentage* of cancers are caused by inherited mutations, but our genomes have differences in susceptibility to carcinogens

Many mutagens are carcinogens but not all carcinogens are mutagens (e.g. alcohol is not a mutagen)

How Do Cancers Arise?
(DNA mutations that impact cell growth)



Cancers are primarily an environmental disease, so they are *largely a preventable disease*!

How Do Cancers Arise?
(DNA mutations that impact cell growth)

Contagious cancer in Tasmanian Devils
(Devil Facial Tumor Disease or DFTD)

Naked mole rats live long (32 years) but never develop cancer
(mice live 4 years and often die of cancer)

Cancers are primarily an environmental disease, but we are different in susceptibility

DNA Damage Causes Cancer by Mutating the Genes Controlling Cell Division & Survival

Oncogene proteins:
- positive regulators to stimulate cancer cells to divide more
- mutated to be overly active or are present in excess
- components in signal transduction pathways

Tumor suppressors:
- negative regulators in both cancer and normal cells
- become inactive in cancer cells

The importance of cell death

Somatic mutations: mutation occurs in cells of the body.
Germ line mutations: mutation occurs in the germ cells.

Peyton Rous & the Rous Sarcoma Virus (RSV)
(demonstrated first in 1910 that a virus could cause cancer in birds)

But many were skeptical:

"But, my dear fellow, don't you see, this can't be cancer because you know its cause" – a British oncologist

Rous took a sample of a malignant tumor from the connective tissue of a hen:
- Initially showing the samples could cause cancer in another chicken even after passing them through filters to remove all cancer cells and any bacteria or just using a supernatant of emulsified tumor cells.
- Further showing that such activity was lost after exposing malignant samples to freezing, drying and radiation (to kill the virus).
- Moreover, using tumors from bone, cartilage and blood vessels yielded the same result.
- Finally, the immune systems of the infected chickens were producing an antibody similar to those produced in response to harmful bacteria

Breakthrough in Our Understanding of Cancer Came from Studying Viruses

18.2 *Human Cancers Known to Be Caused by Viruses*

CANCER	ASSOCIATED VIRUS
Liver cancer	Hepatitis B virus
Lymphoma, nasopharyngeal cancer	Epstein–Barr virus
T cell leukemia	Human T cell leukemia virus
Anogenital cancers	Papillomavirus
Kaposi's sarcoma	Kaposi's sarcoma herpesvirus

HPV vaccine is extremely effective in preventing cervical cancer

Peyton Rous & the Rous Sarcoma Virus (RSV)
(demonstrated first in 1910 that a virus could cause cancer in birds)

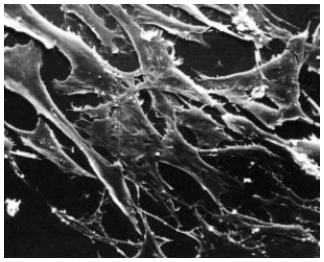
"The product of his diligence in pursuing a single chicken tumor nearly eighty years ago (1), Rous' virus remains the only retrovirus that could have satisfied the genetic and biochemical criteria for the work we accomplished in the era that preceded molecular cloning." – H. Varmus

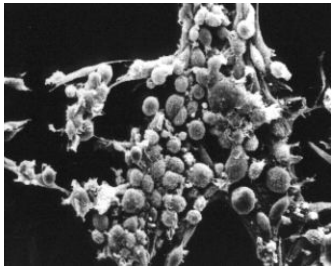
Nobel Prize at the Age of 85 (Physiology or Medicine, 1966)

[1]Rous P. (1911) A sarcoma of the fowl transmissible by an agent separable from the tumor cells. *J. Exp. Med.* 13:397–411

The principle of delayed gratification in science!

Normal Cells Can Be Transformed





Normal Cells
(contact inhibition of growth)

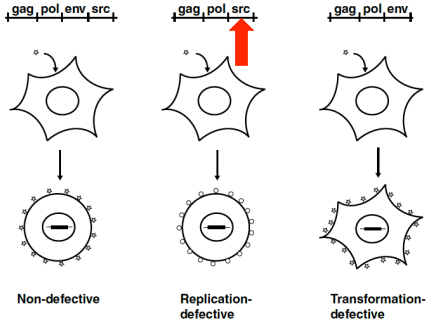
Transformed Cells
(no contact inhibition)

Photos: G. Steven Martin

How Does RSV Cause Cancer?
(developing simpler assays to examine viral activity)

The viral sequence responsible for transformation appeared to reside in a single contiguous segment near the 3' terminus, most likely a single gene.

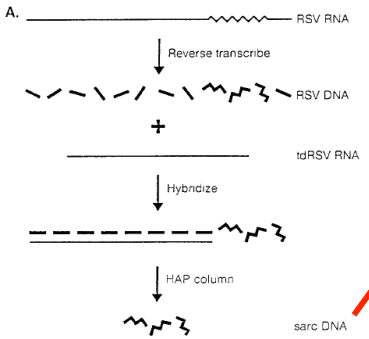
(Wang *et al*. *PNAS* 73:447-451, 1976)



- Isolation of transformation-defective viral strains (unable to transmit tumor)
- Virus replication and transformation could be dissociated

Martin. (2004) *Oncogene* 23:7910-7917

How Does RSV Cause Cancer?
(comparing the genetic differences among viral strains)



Detected conserved sequence in normal chicken DNA!

Stehelin *et al*. (1976)
J. Mol. Biol. 12:983–992
Nature 260:170-173

RSV is a retrovirus
(using RNA as genetic material)

How Does RSV Cause Cancer?
(the discovery of oncogene and protooncogene)

Nobel Prize
(Physiology or Medicine, 1989)

J. Michale Bishop **Harold E. Varmus**

"My commitment to experimental science occurred, by today's standards, dangerously late in a prolonged adolescence. As an undergraduate … was devoted to Dickensian novels … marginally fulfilling pre-medical requirements … then indulged myself with a year of Anglo-Saxon and metaphysical poetry at Harvard graduate school, before beginning medical studies …" – Harold Varmus

How Does RSV Cause Cancer?
(the discovery of v-Src & c-Src)

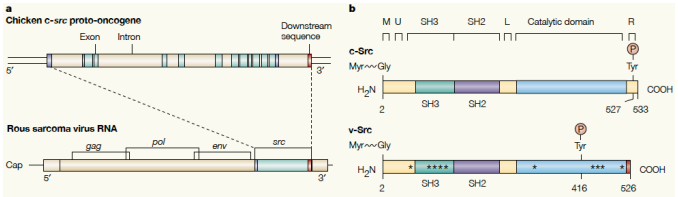


Figure 2 | **Comparison between v-Src and c-Src. a** | The v-*src* and c-*src* genes. The v-*src* gene (bottom) lacks the introns present in c-*src* (top), and in v-*src* the 3′-terminal sequence of c-*src* is replaced by a downstream sequence. In addition, several activating point mutations are present within v-*src* (not shown). A non-defective Rous sarcoma virus strain, such as that shown, contains the viral structural genes (*gag*, *pol* and *env*), plus the viral-transforming gene, v-*src*. The Bryan strain is replication-defective and lacks a functional *env* gene; some variants of the Bryan strain are also defective in *pol*. **b** | Structural features of c-Src and v-Src proteins. Residue numbers and other details are specific to chicken c-Src and the v-Src protein of the Schmidt–Ruppin strain of RSV. The amino terminus of the protein is myristoylated at Gly2. Positions of the membrane-binding (M), unique (U), SH2, SH3, linker (L), catalytic and regulatory (R) domains of c-Src are shown; the substituted carboxy-terminal sequences in v-Src are shown in red. Asterisks represent amino acid substitutions in v-Src.

Martin. (2001) *Nat. Rev. Mol. Cell Biol.* 2:467-475

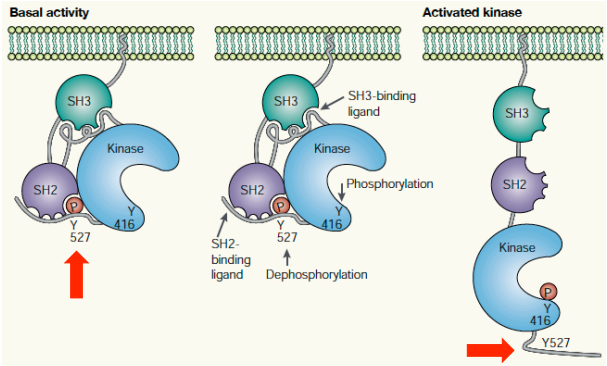
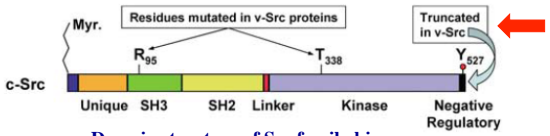


Figure 3 | **Activation of c-Src.** The left panel represents the inactive conformation of Src, in which Tyr527 (chicken c-Src) interacts with the SH2 domain, positioning the SH3 domain to interact with the linker between the SH2 and catalytic domains. The middle panel illustrates different mechanisms involved in the activation of Src, and the right panel represents the open or active conformation. Adapted from REF. 107, on the basis of work in REFS 65–69.

Martin. (2001) *Nat. Rev. Mol. Cell Biol.* 2:467-475

How Does RSV Cause Cancer?
(the discovery of v-Src & c-Src)



Domain structure of Src family kinases
(Parsons & Parsons. *Oncogene* 23:7906-7909, 2004)

- **The *v-src* gene in RSV is required for the formation of cancer and that the other genes have no role in oncogenesis (H. Hanafusa, R. Erikson and others)**
- ***c-src* is a gene encoding a normal cellular protein that shares strong amino acid sequence homology with v-Src (J. M. Bishop and H. Varmus)**
- **The v-Src protein lacks the inhibitory phosphorylation site (tyrosine-527) near the C-terminus and is constitutively active. Normal c-Src is only activated under circumstances where it is required (e.g. growth factor signaling)**
- ***v-src* is an *oncogene* whereas *c-src* is a *proto-oncogene***

Scientific advance is a result of both the brilliance of one person & team Work!

Figure 1 | **Memorial symposium in honour of Teruko Hanafusa.** Together with her husband, Hidesaburo Hanafusa, Teruko Hanafusa was responsible for many key insights into the biology of Rous sarcoma virus and the origin and function of *src*. Many members of the Src community who are mentioned in this review gave presentations at this symposium, held in May 1997. Attendees included, from left to right: front row, Michinari Hamaguchi, Bob Weinberg, Michiyuka Matsuda, Lu-Hai Wang, Mina Bissell, Joan Brugge; second row, Anindya Datta, the author, Hidesaburo Hanafusa, Raymond Birge; third row, Irwin Gelman, Harold Varmus, Bruce Mayer, Masabuyl Shibuya, Peter Vogt, Tom Parsons; back row, Stu Aaronson, Jim Darnell, Ray Erikson.

Martin. (2001) *Nat. Rev. Mol. Cell Biol.* 2:467-475

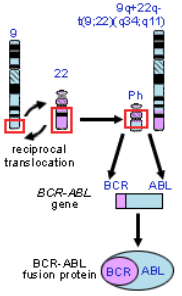
How Do Viruses and Carcinogens Cause Cancer?

Viruses

- Incorporate a proto-oncogene into its viral genome
- Insert next to proto-oncogene in host DNA

Carcinogens

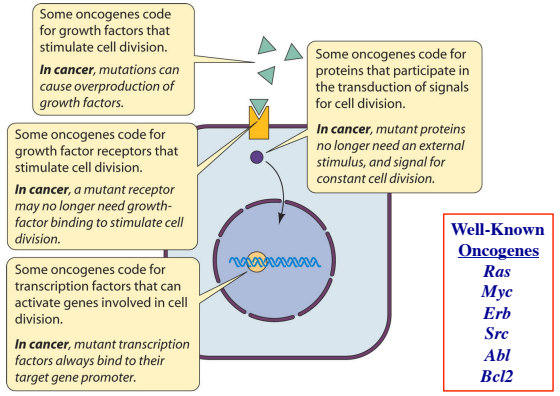
- Cause chromosome translocation
- Mutate DNA by making deletions or changing nucleotides



Leukemic white blood cells in CML contain a Philadelphia (Ph) chromosome, the result of a translocation between the long arms of chromosomes 9 and 22. The resulting fusion gene (*BCR-ABL*) produces an altered protein believed to play a key role in the development of CML.

Philadelphia Chromosome (makes a fusion gene (BCR-ALB)

The Normal Function of Proto-Oncogenes Is to Control Cell Growth & Proliferation



Well-Known Oncogenes

Ras
Myc
Erb
Src
Abl
Bcl2

Ras Was the First Known Mutated Human Oncogene

Human EJ bladder carcinoma oncogene is homologue of Harvey sarcoma virus *ras* gene

Luis F. Parada, Clifford J. Tabin, Chiaho Shih & Robert A. Weinberg

Center for Cancer Research and Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA

Examination of homologies between retroviral oncogenes and transforming sequences defined by transfection reveals that the human bladder carcinoma (EJ) oncogene is homologous to the Harvey sarcoma virus oncogene (ras). Structural analysis limits the region of homology to a 3.0-kilobase SacI *fragment of the EJ oncogene. Both EJ and ras DNA probes detect similar transcripts in transfectants derived from bladder carcinoma cell lines.*

A point mutation is responsible for the acquisition of transforming properties by the T24 human bladder carcinoma oncogene

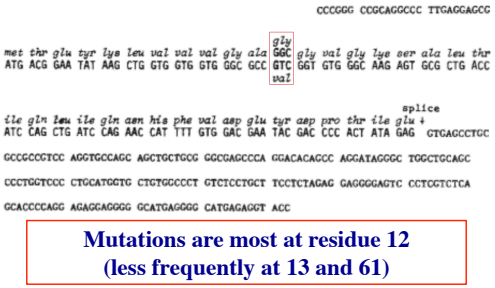
E. Premkumar Reddy, Roberta K. Reynolds, Eugenio Santos & Mariano Barbacid

Laboratory of Cellular and Molecular Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20205, USA

The genetic change that leads to the activation of the oncogene in T24 human bladder carcinoma cells is shown to be a single point mutation of guanosine into thymidine. This substitution results in the incorporation of valine instead of glycine as the twelfth amino acid residue of the T24 oncogene-encoded p21 protein. Thus, a single amino acid substitution appears to be sufficient to confer transforming properties on the gene product of the T24 human bladder carcinoma oncogene.

Changing A Single Amino Acid Makes Normal Ras Oncogenic

(mutations found in many human cancers)



Mutations are most at residue 12 (less frequently at 13 and 61)

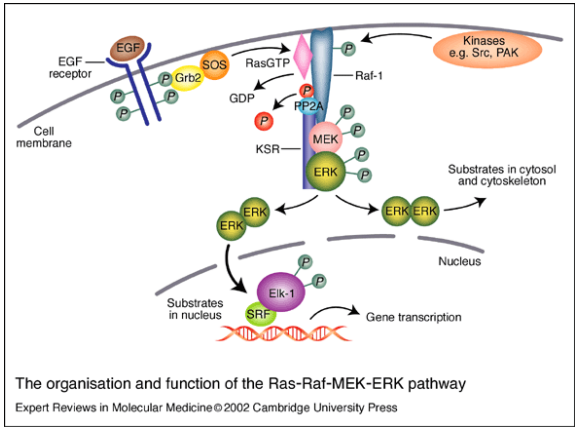
H-RAS GOF mutation at the same codon as the worm homologue (let-60) GOF

Table 1 | **Ras mutations in human cancers**

Tissue	H-Ras	K-Ras	N-Ras
Adrenal gland	1%	0%	5%
Biliary tract	0%	32%	1%
Bone	2%	1%	0%
Breast	1%	5%	1%
Central nervous system	0%	1%	2%
Cervix	9%	8%	1%
Endometrium	1%	14%	0%
Eye	0%	4%	1%
Gastrointestinal tract (site indeterminate)	0%	19%	0%
Haematopoietic and lymphoid tissue	0%	5%	12%
Kidney	0%	1%	0%
Large intestine	0%	32%	3%
Liver	0%	7%	4%
Lung	1%	17%	1%
Meninges	0%	0%	0%
Oesophagus	1%	4%	0%
Ovary	0%	15%	4%
Pancreas	0%	60%	2%
Parathyroid	0%	0%	0%
Peritoneum	0%	6%	ND
Pituitary	2%	0%	0%
Placenta	0%	0%	0%
Pleura	0%	0%	0%
Prostate	6%	8%	1%
Salivary gland	16%	4%	0%
Skin	5%	2%	19%
Small intestine	0%	20%	25%
Stomach	4%	6%	2%
Testis	0%	5%	4%
Thymus	0%	15%	0%
Thyroid	4%	3%	7%
Upper aerodigestive tract	9%	4%	3%
Urinary tract	12%	4%	3%

Data derived from the Catalogue of Somatic Mutations in Cancer (COSMIC) of the Wellcome Trust Sanger Institute, Cambridge, UK. ND, not determined.

The Ras Signaling Pathway

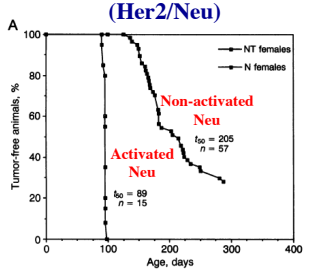


The organisation and function of the Ras-Raf-MEK-ERK pathway

Expert Reviews in Molecular Medicine © 2002 Cambridge University Press

Oncogenes Can Initiate Tumorigenesis

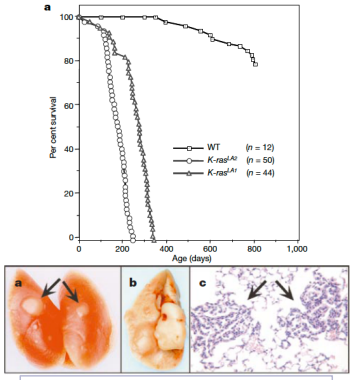
EGF Receptor (Her2/Neu)



Trastuzumab (Herceptin) is effective in treating breast cancer (a mono-clonal antibody against Neu)

Guy *et al*. (1992) *PNAS*. 89:10578-10582

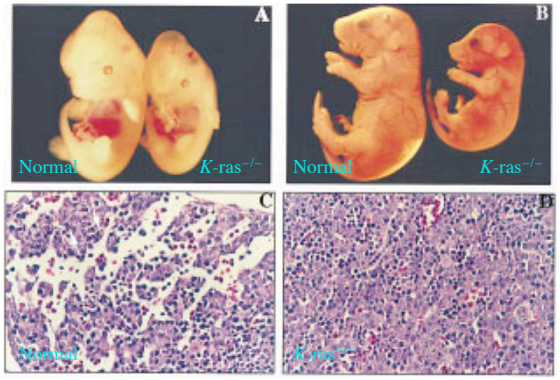
K-Ras



Johnson *et al*. (2001) *Nature*. 410:1111-1116

K-ras Is Essential for Development

(humans and mice have 3 *ras* genes: *H-ras*, *N-ras* and *K-ras*)



Johnson *et al*. (1997) *Genes Dev*. 11:2468-2481

How Do Cancers Arise?

(it takes more than just one mutation)

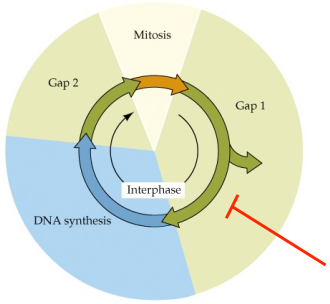
The efficiency of the *ras* lesion in initiating cellular transformation in primary cells was soon questioned when it was discovered that a *ras* oncogene could not transform freshly isolated rodent embryo cells. Consequently, three reports that were published in 1983 described the ability of H-Ras-Val12 to transform primary cells that had previously been immortalized by either carcinogens or transfection with *myc*, SV40 large T antigen or adenovirus *E1A* oncogene. These findings extended the concept of multistep carcinogenesis and suggested that mutant Ras proteins can only transform (to a tumorigenic state) cells that have undergone predisposing changes.

Karnoub & Weinberg. (2008) *Nat. Rev. Mol. Cell Biol*. 9:517-531

A single oncogenic event is not sufficient for carcinogenesis

How Do Cancers Arise?
(tumor suppressors)

- Activation of one oncogene allele is sufficient
- Disruption of both tumor suppressor alleles is needed



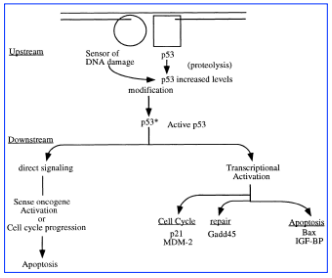
There are "checkpoints" to prevent inappropriate proliferation

Well-Known Tumor Suppressors
(all are essential for embryonic development except *TP53*)

- ***Rb*** **and** ***TP53*** **are the most frequently mutated genes in human cancers.**
- ***TP53*** **encodes the p53 protein that responds to DNA damage. Upon sensing DNA damage, p53 is activated, resulting in either G1 cell cycle arrest or apoptosis.**
- ***PTEN*** **encodes a phosphatase that inhibits kinase signaling.**
- ***BRCA1*** **and** ***BRCA2*** **encode DNA binding proteins required for DNA damage repair.**

TP53 **homozygous mutant mice show no developmental defects but all develop and die of cancer during adult life**

How Do Cancers Arise?
(p53 and tumor suppressors)

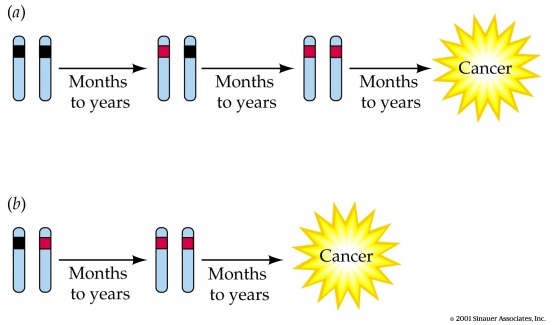


Lane & Levine. (2010)
Cold Spring Harb. Perspect. Biol.
doi: 10.1101/cshperspect.a000893

When it was discovered in 1979 p53 was thought to be another oncogene, but it was later shown to be a tumour suppressor. This finding, along with the identification of the recessive gene involved in retinoblastoma, helped to kick-start a new research field in cancer biology.

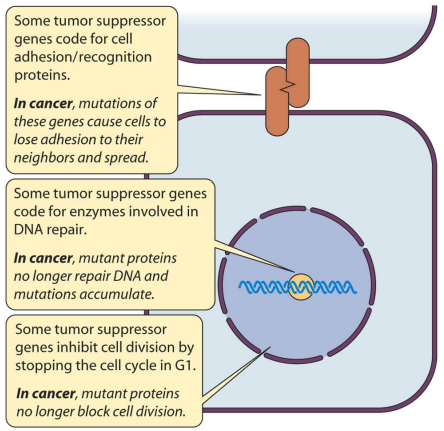
Although the function of p53 has been the subject of intensive research since 1979, and we have some understanding of its function in maintaining genomic stability and modulating apoptosis, its multifaceted qualities have meant that new findings have not declined with age. For example, in the past 15 years p53 has been shown to be part of a family — reflecting the evolution of p53 in multicellular organisms. How p53 activates target genes has also become a complex issue, and roles for p53 independent of its activities as a transcription factor have also been described. Indeed, as the diversity of p53-dependent activities widens to include key roles in metabolism (both endogenously and in response to stress), fecundity and development, old debates continue about how p53 suppresses tumour development. For example, how important is its role in maintaining genomic stability to tumour suppression? What is the significance of its crosstalk with other pathways, such as the E2f–Rb pathway? How is one p53-dependent response selected from many possible options? One thing is clear: p53 is therapeutically important. Numerous approaches are being taken to reconstitute the expression of p53 in tumours and to use the function of the p53 pathway as an indicator of prognosis and response to therapy.

How Do Cancers Arise?
(The Two-Hit Hypothesis by Alfred Knudson)

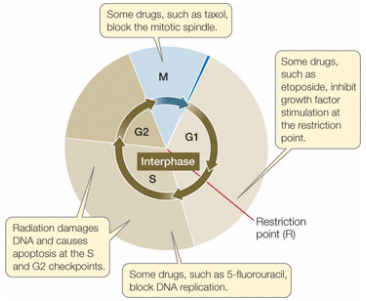


Knudson A. (1971) *Proc. Natl. Acad. Sci. USA* 68:820–823

Tumor suppressors come in many different flavors



How to Target Cancer Cells



Prevention

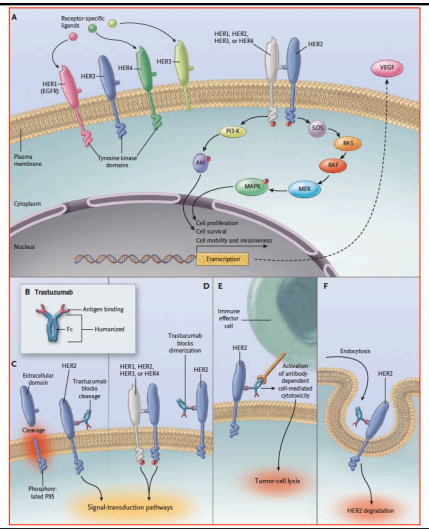
Palliative care

Surgical removal

Chemotherapy

Radiation (ionizing)

Targeting Breast Cancer



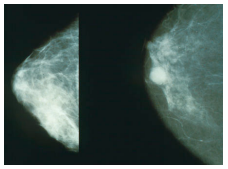
Hudis C. A., NEJM (2007)

How to Target Cancer Cells

BRCA1 and BRCA2
tumor suppressors (genetic diagnosis)

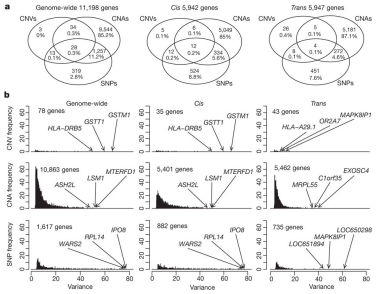
Human Epidermal Growth Factor Receptor type 2 (Her2/Neu)
- **overexpressed in 20-30% of invasive breast carcinomas and gene amplification**
- **promotes cell proliferation (Ras-MAPK)**
- **inhibits cell death (PI3K/Akt)**

Trastuzumab (Herceptin)
a mono-clonal antibody against Her2



Understanding cancer risks, signaling pathways and individualized treatment!

Oncogenomics: Genetic Diversity & Refined Classification
(whole-genome analyses of different breast cancers)



Germline and somatic variants influence tumour expression architecture

Curtis et al., Shah et al., Sephens et al., Ellis et al, and Banerji et al., *Nature*, 2012

Understanding cancer risks and signaling pathways for individualized treatment!

Key Concepts from This Lecture

1. **Cancer is a disease of our own genes and cells.**
2. **Carcinogens are compounds that cause cancer by mutating our genes.**
3. **Proto-oncogenes normally promote cell division and get amplified/activated to become oncogenes in cancer.**
4. **Tumor suppressors normally act to prevent cell division, and both copies of the genes are lost/deleted in cancer.**
5. **Cancer usually requires activation of oncogenes and loss of tumor suppressors in the same cell.**
6. **Cancer cells can hijack many cellular pathways to fuel their growth in a cancer-specific manner (personalized treatment).**