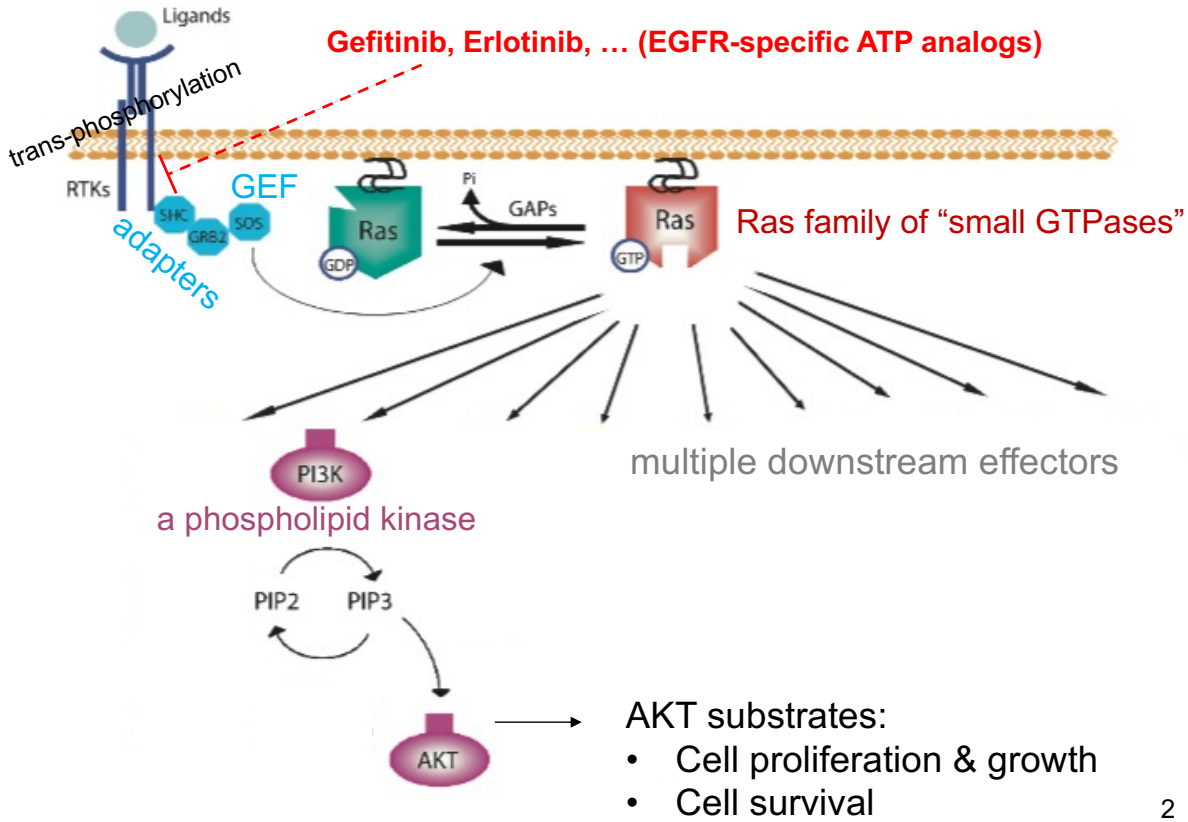
Introduction to Oncology

BIO-392

Previously…



AKT substrates:

- Cell proliferation & growth
- Cell survival

TODAY

Hallmark capability 2: Evading growth suppressors

EXAMPLES:

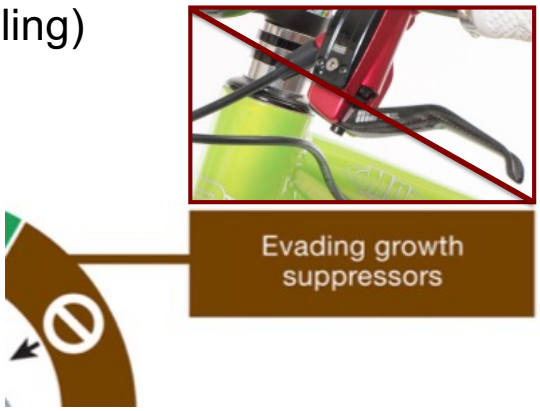
✓ Adenomous Polyposis Coli protein (APC)

◆ NF1 and PTEN (⊣ RTK signaling)

◆ retinoblastoma protein RB1

◆ Tumor Protein p53 (*TP53*)

◆ TGFβ/Smad signaling



Neurofibromatosis type I syndrome

- Autosomal dominant syndrome that affects neural crest derivatives
- Caused by inherited heterozygous mutations in neurofibromin-1 (NF1) diagnosed by "Café au lait" spots (melanocyte pigmentation defects):

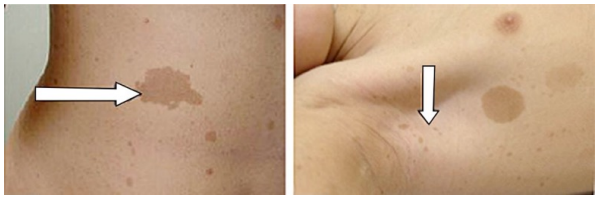
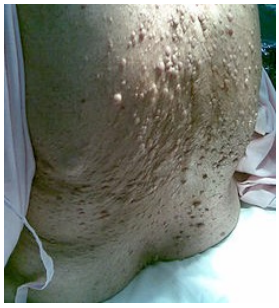


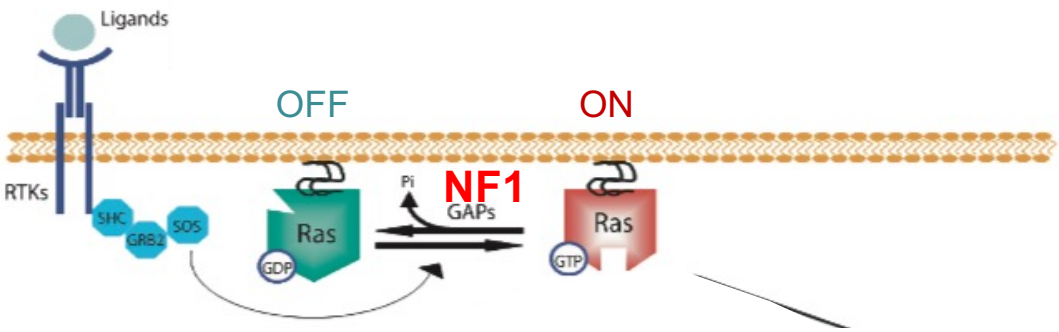
Figure 7.21 *The Biology of Cancer* (© Garland Science 2007)

- Mutation of the residual copy of NF1 (loss of heterozygosity, LOH) in Schwann cells provokes neurofibromas (subcutaneous nodules):

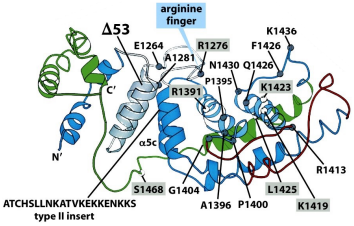


- Neurofibromas can give rise to malignant nerve sheath tumors

Loss of neurofibromin (NF1) hyperactivates Ras



- NF1 is a GTPase Activating Protein (GAP) that is required to *inactivate* Ras in Schwann cells:



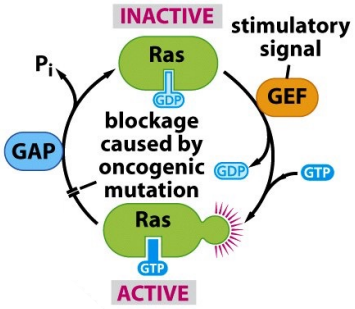
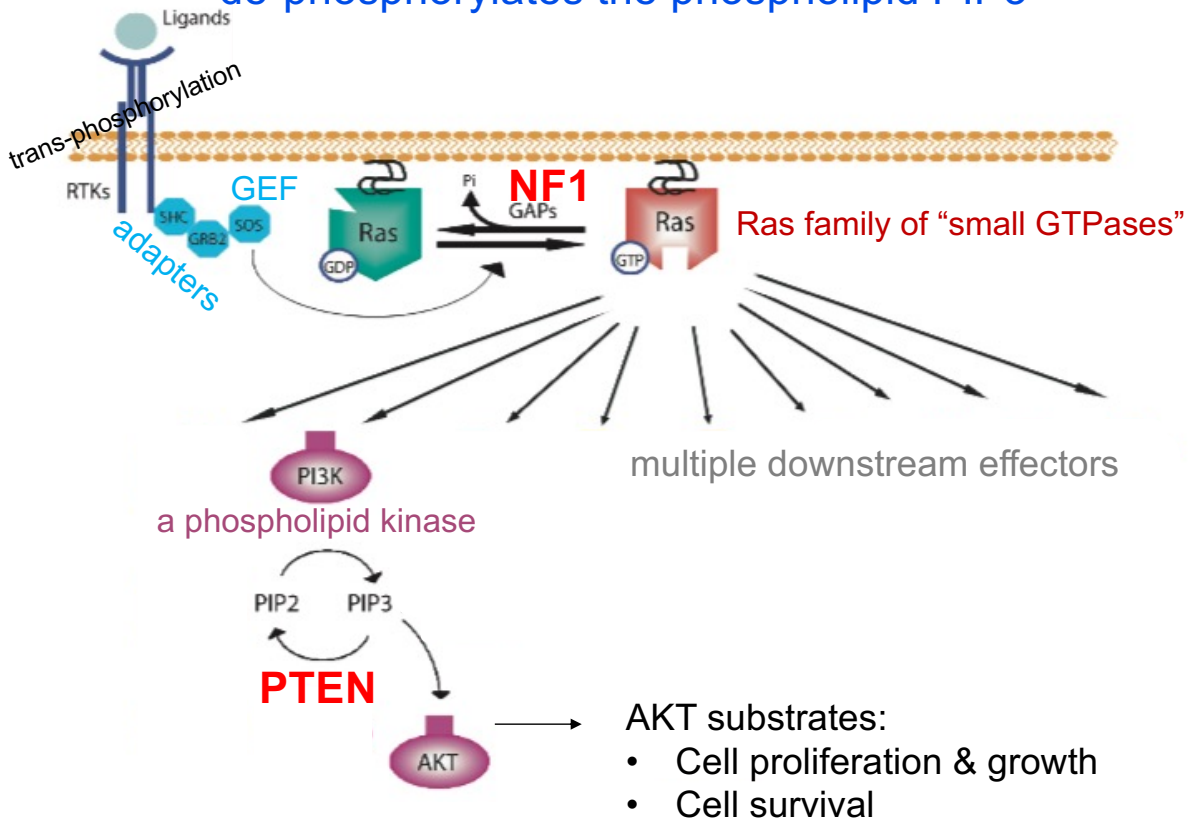


Figure 7.21 *The Biology of Cancer* (© Garland Science 2007)

The phosphatase and tensin homolog PTEN de-phosphorylates the phospholipid PIP3

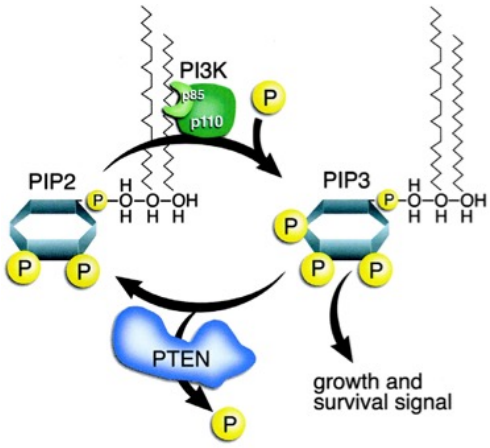


AKT substrates:

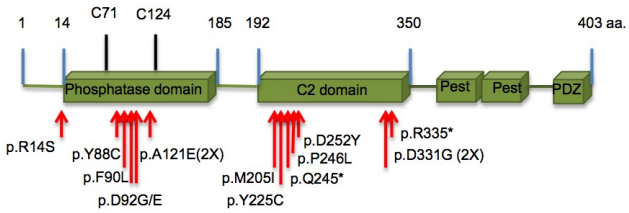
- Cell proliferation & growth
- Cell survival

PTEN is essential to protect against cancer

- Inactivated by ***germline mutations*** in Cowden syndrome (increased tumor risk in breast, thyroid, uterus)
- ***Somatic mutations*** in glioblastoma, prostate carcinoma, head & neck cancer
- Frequently ***downregulated*** expression in breast and lung cancer



membrane targeting **C2 domain**



PTEN is essential to dampen growth and survival signals

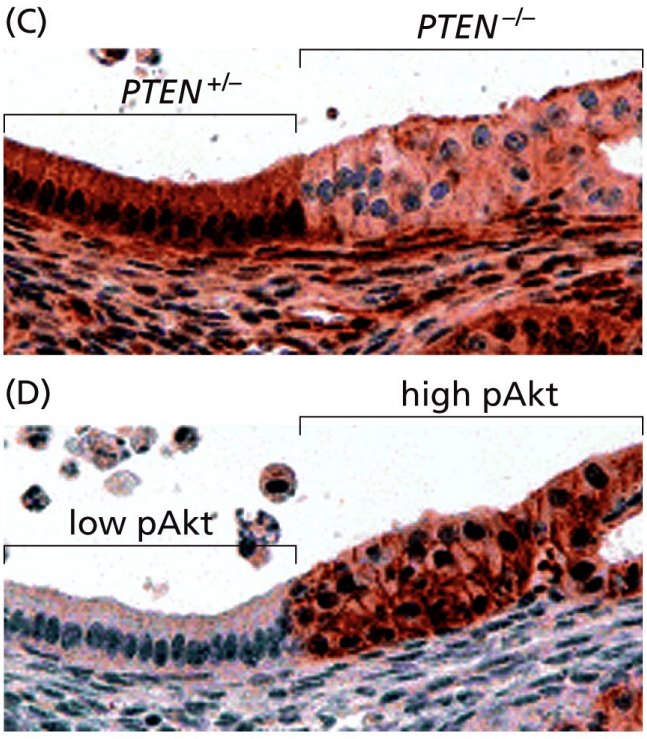


Figure 6.19cd The Biology of Cancer (© Garland Science 2014)

Left: PTEN immunostaining in the uterus of PTEN+/- mice.

Right: Sporadic loss of the remaining WT allele gives rise to PTEN-negative hyperplasias.

Phospho-Akt staining: Reveals Akt hyperactivation specifically in PTEN-negative hyperplastic uterine epithelial cells *(right panel).*

Concept: Tumor suppressors and oncogenes

Examples:

Function	Type of alteration	Genes
oncogene	gain-of-function (GOF)	β-catenin, PI3K, Ras,...
tumor suppressor	loss-of-function (LOF)	APC, PTEN, SMAD4, TP53...

- 1914: Postulated by Theodor Heinrich Boveri

Theodor Boveri (1914) predicted the genetic origin of cancer from embryological studies in sea urchin

Observation:
Mechanical shaking at 1-cell stage can induce unequal chromosome segregation, leading to diverse malformations.

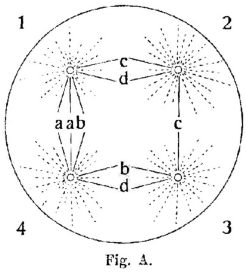


Fig. A.

Interpretation:
"...unrestrained proliferation is due either to an excess or to a stable reinforcement of specific stimulatory chromosomes. ...this model...might explain the emergence of... tumours that are benign."

"Malignant tumours would be defined by the fact that, in addition to having an excess of stimulatory chromosomes, they have lost certain other chromosomes."

- A genetic cause can explain the origin of *familial* cancers
- However, it did not seem to explain the increased prevalence of cancer at old age.
- Until more accurate epidemiologic data revealed:

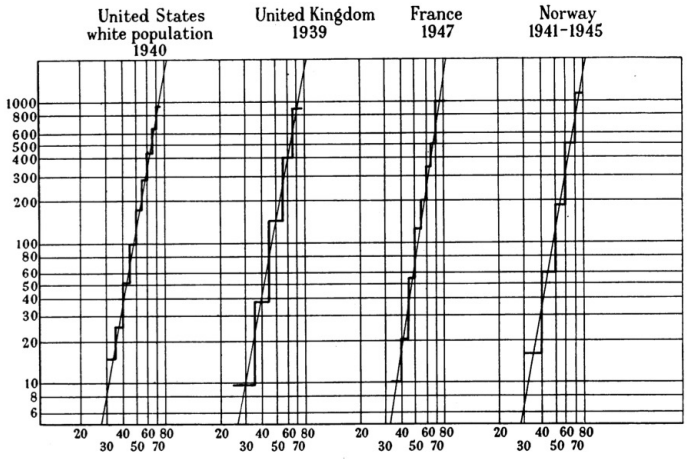


FIG. 1.—Diagram drawn to double logarithmic (log/log) scale showing the cancer death-rate (in the case of the United Kingdom, the carcinoma death-rate) in males at different ages. Deaths per 100,000 males are shown on the vertical scale, age figures on the horizontal scale.

Carl O. Nordling (1953)

"Cancer mortality in males increases according to a certain power (the sixth) of age."

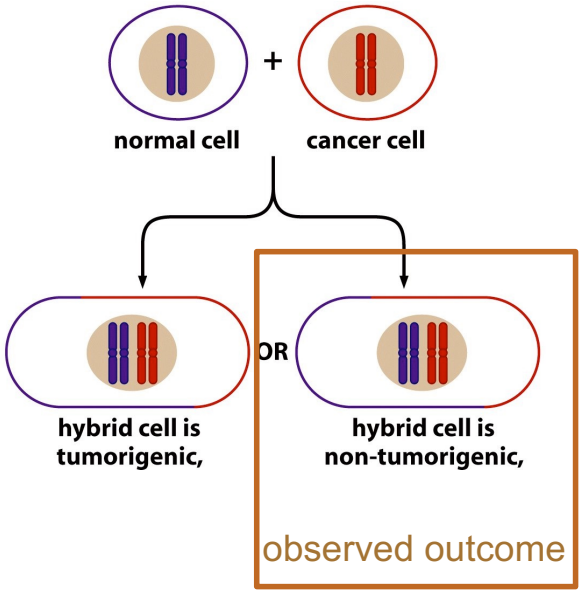
=> Hypothesis:

"...the cancerous cell contains not one but a number of mutated genes"

Nordling 1953 Br. J. Canc.

Cell fusion experiments

Harris et al. (1969) Nature 223, 363-368



⇒ Theory (David Comings, 1973):

"...all cells possess multiple genes capable of coding for transforming factors.

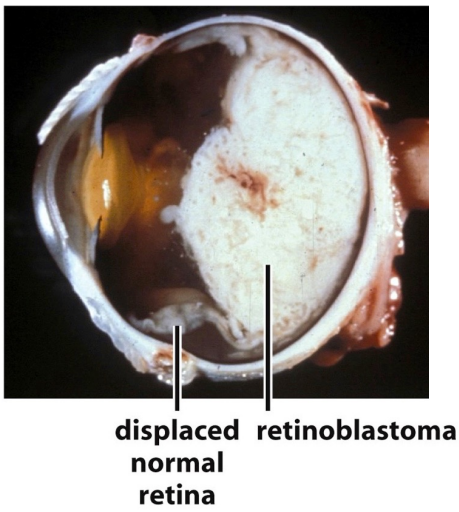
In adult cells they are suppressed by diploid pairs of regulatory genes"

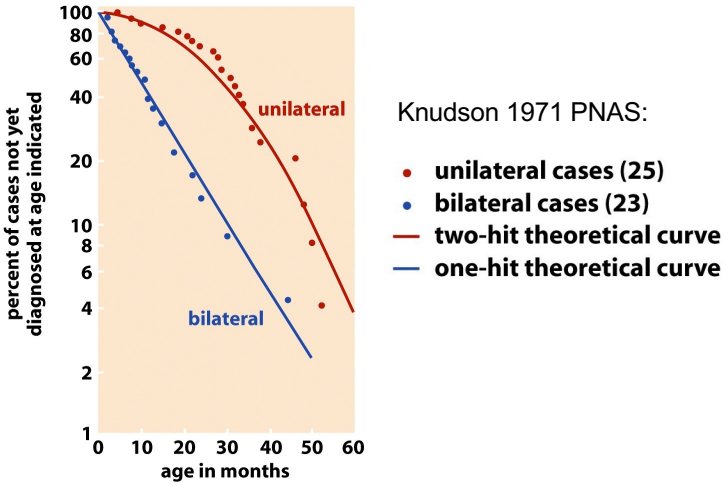
Figure 7.3 *The Biology of Cancer* (© Garland Science 2007)

First evidence for a recessive tumor suppressor gene

Retinoblastoma

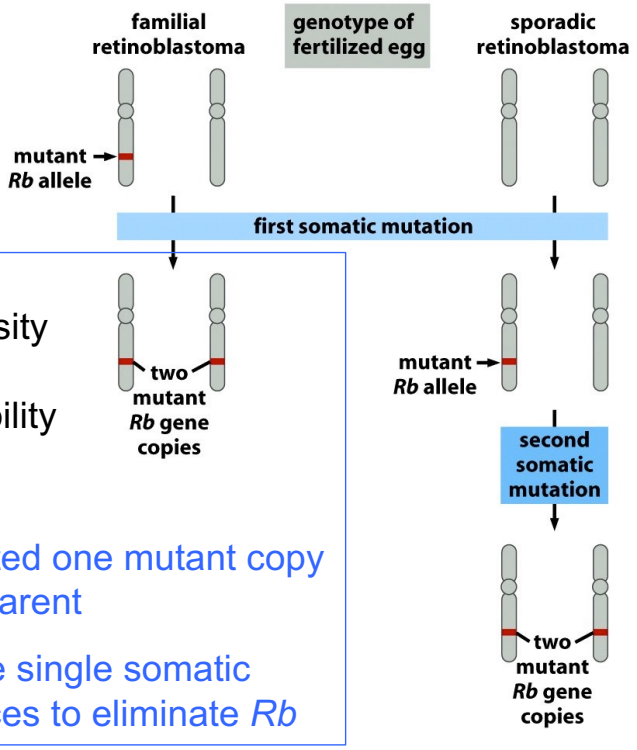
- arise from retinal stem cells in 1/20'000 *children*
- ***sporadic*** forms affect only one eye, and they appear later in childhood
- ***familial*** forms: Multifocal (bilateral) & also predispose for other cancers





Figures 7.4b & 7.7 *The Biology of Cancer* (© Garland Science 2007)

Knudson hypothesis (1971): Two-hit inactivation model



loss of heterozygosity (LOH): *High* probability

Familial form:
All cells inherited one mutant copy of *Rb* from a parent

Therefore, one single somatic mutation suffices to eliminate *Rb*

loss of heterozygosity (LOH): *Low* probability → delayed, lower frequency, unilateral

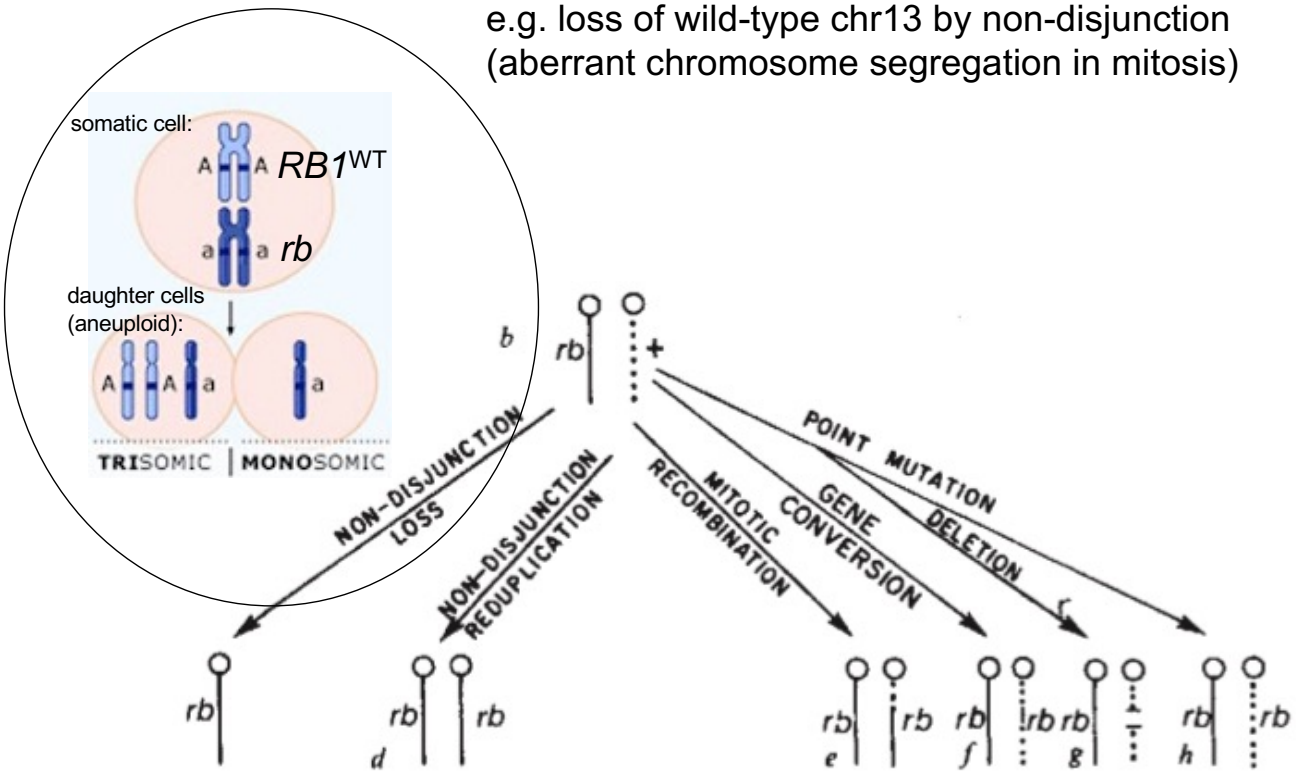
Figure 7.7 *The Biology of Cancer* (© Garland Science 2007)

Mutant tumor suppressor genes can be inherited through the germ line from parents.

By contrast, heritable driver mutations in proto-oncogenes have not been found. Why not?

Loss of heterozygosity (LOH) can occur by various mechanisms

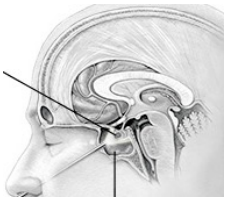
e.g. loss of wild-type chr13 by non-disjunction (aberrant chromosome segregation in mitosis)

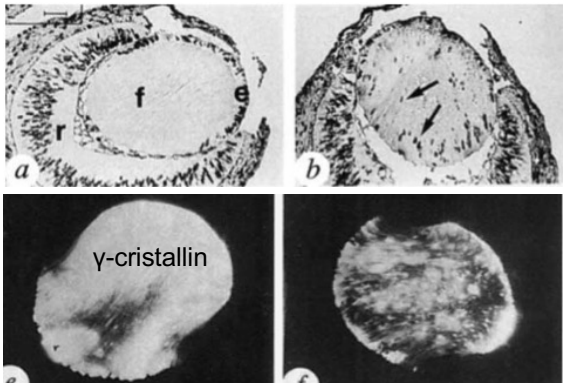


Cavenee et al. 1983 Nature

Rb regulates cell proliferation and differentiation *in vivo*

- $Rb^{+/-}$ mice are at risk to develop *pituitary* adenocarcinoma
- $Rb^{-/-}$ mouse embryos die before E15, with impaired red blood cell maturation and eye phenotype at E14:





BrdU incorporation (marks DNA synthesis) increased in -/- vs. +/+

Immunofluorescent staining of the late differentiation marker γ-cristallin was diminished

Rb ⊣ cell proliferation ⊣ cell differentiation

- No *retinal* dysplasia in either $Rb^{+/-}$ or $Rb^{-/-}$ mice => Why not?

Morgenbesser et al. 1994 Nature

Summary 1: Characteristics of tumor suppressors

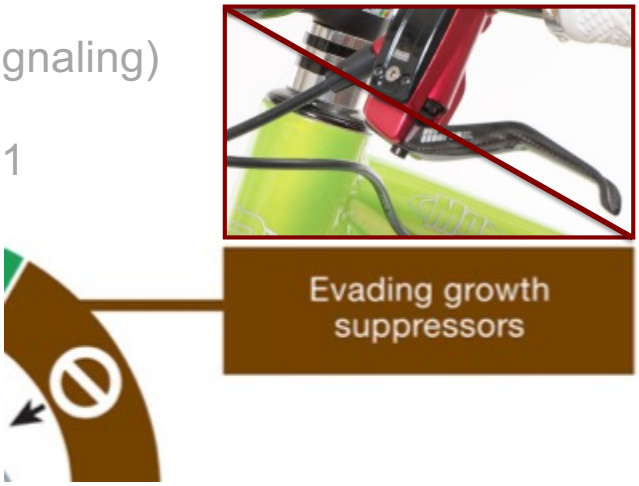
- Tumor suppressor genes (TSGs) encode inhibitors of proliferation, growth & survival signaling pathways (e.g. APC –l β-cat, NF1 –l RasGTP, PTEN –l PIP3,…)
- The existence of TSGs was predicted already >100 years ago (Theodor Boveri)
- Epidemiologic data (Nordling), cell fusion experiments (Harris), and a comparison of familial versus sporadic retinoblastoma (Knudson) later confirmed the existence of TSGs
- Mutations in TSGs, unlike oncogenes, can be inherited
- Loss of TSG function by mutation typically requires a second hit in the same gene (loss of heterozygosity), *or* inhibition of TSG expression
- Tumor aggressiveness increases progressively as additional TSGs are mutated (e.g. in colorectal cancer, see below)

TODAY

Hallmark capability 2: Evading growth suppressors

EXAMPLES:

- ✓ NF1 and PTEN (⊣ RTK signaling)
- ✓ retinoblastoma protein RB1
- ◆ Tumor Protein p53 (*TP53*)
- ◆ TGFβ/Smad signaling



Article

Pan-cancer analysis of whole genomes

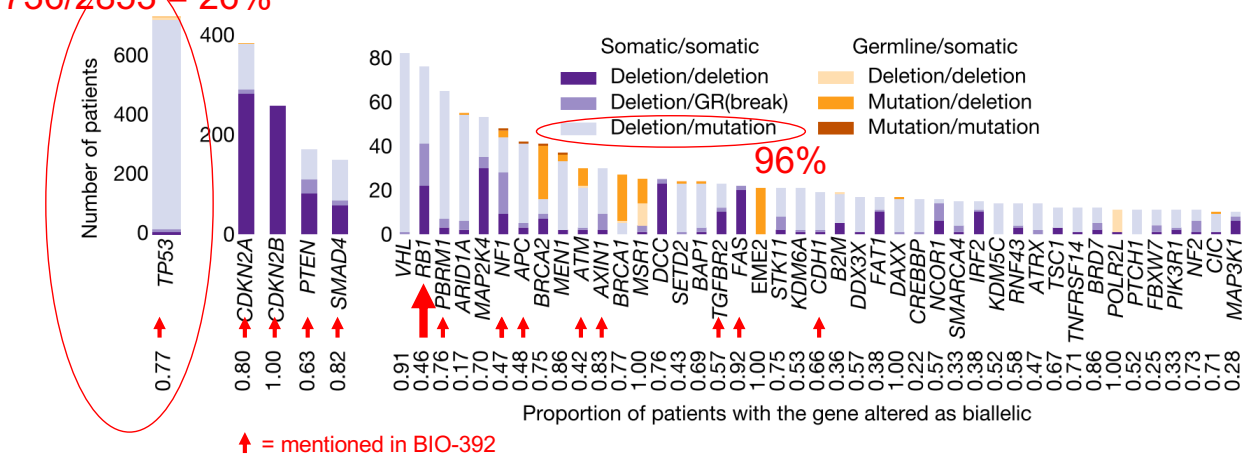
https://doi.org/10.1038/s41586-020-1969-6
Received: 29 July 2018
Accepted: 11 December 2019
Published online: 5 February 2020
Open access

The ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium

Cancer is driven by genetic change, and the advent of massively parallel sequencing has enabled systematic documentation of this variation at the whole-genome scale[1–3]. Here we report the integrative analysis of 2,658 whole-cancer genomes and their matching normal tissues across 38 tumour types from the Pan-Cancer Analysis of Whole Genomes (PCAWG) Consortium of the International Cancer Genome Consortium (ICGC) and The

Tumour-suppressor genes with biallelic inactivation in ≥10 patients (of 2853):

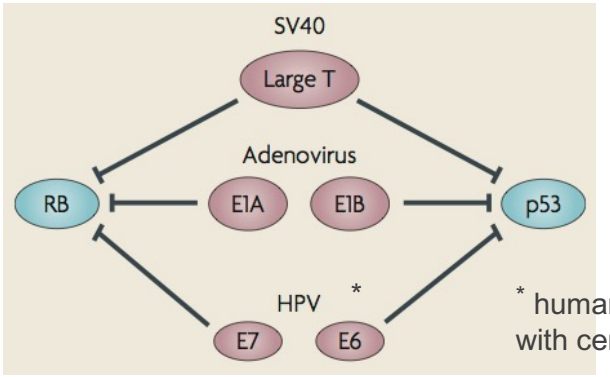
736/2853 = 26%



↑ = mentioned in BIO-392

Combined inhibition of the tumor suppressors RB1 and p53 by mutations or by oncogenic DNA viruses

Human carcinomas (e.g. lung, breast, pancreas) frequently harbor mutations in ***both*** RB1 *and* p53



Oncogenic DNA viruses make poteins that bind and inhibit both RB1 *and* p53

* human papilloma virus (associates with cervical cancer)

Polager & Ginsburg 2009 Nat Rev Cancer

Important:
Mutation is *not* the only way to evade tumor suppressors

Mutations

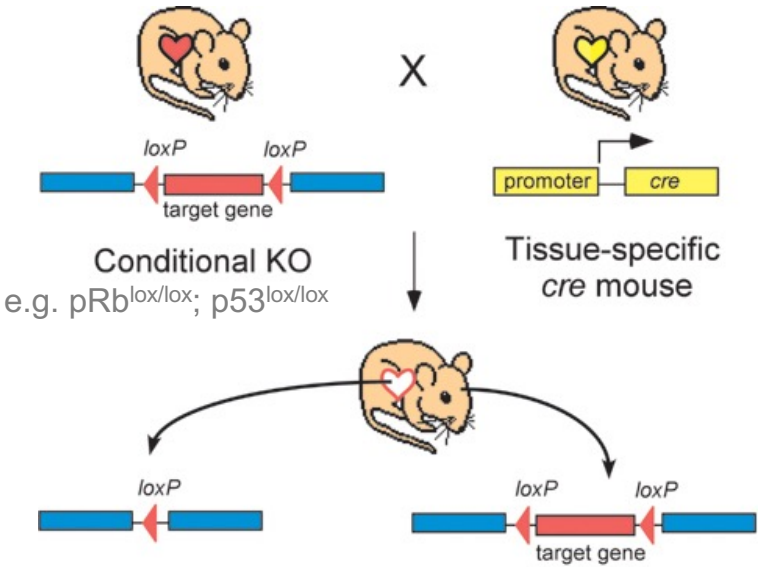
Epigenetic silencing
- promoter methylation
- miRNAs

Tumor suppressors

oncogenic small DNA viruses

Upregulation of specific inhibitors
- ubiquitin ligases
- kinases
- specific interacting proteins

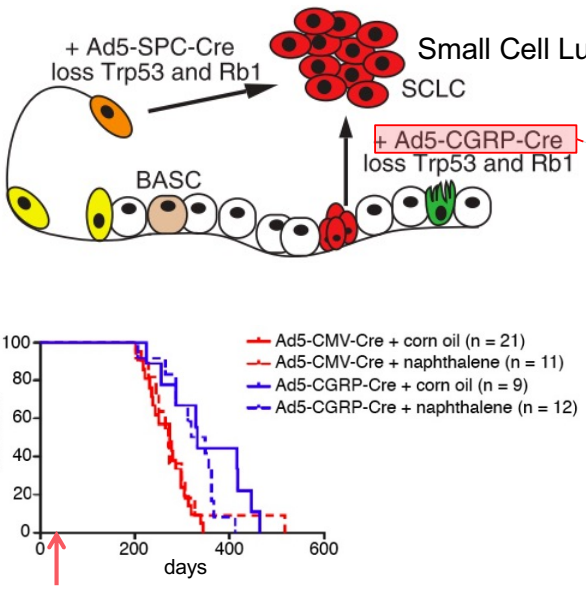
Mouse tumor models:
Tissue-specific deletion of Rb1 and p53 by cre/lox technique



e.g. heart-specific knock-out

All cells other than heart

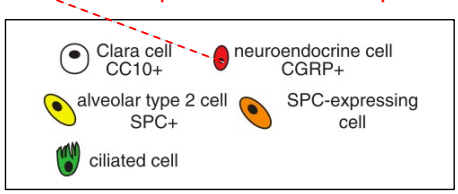
Combined deletion of Rb1 and p53 in lungs provokes SCLC



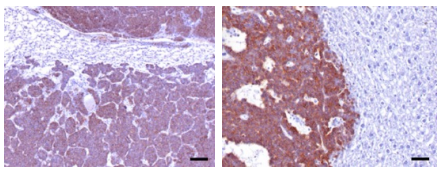
Intratracheal instillation of Ad5 adenovirus carrying the Cre transgene:

- CMV promoter: Active in *all* infected cells
- CGRP promoter: Only active in NE lineage

Calcitonin-gene related peptide (CGRP) promoter: NE cell-specific



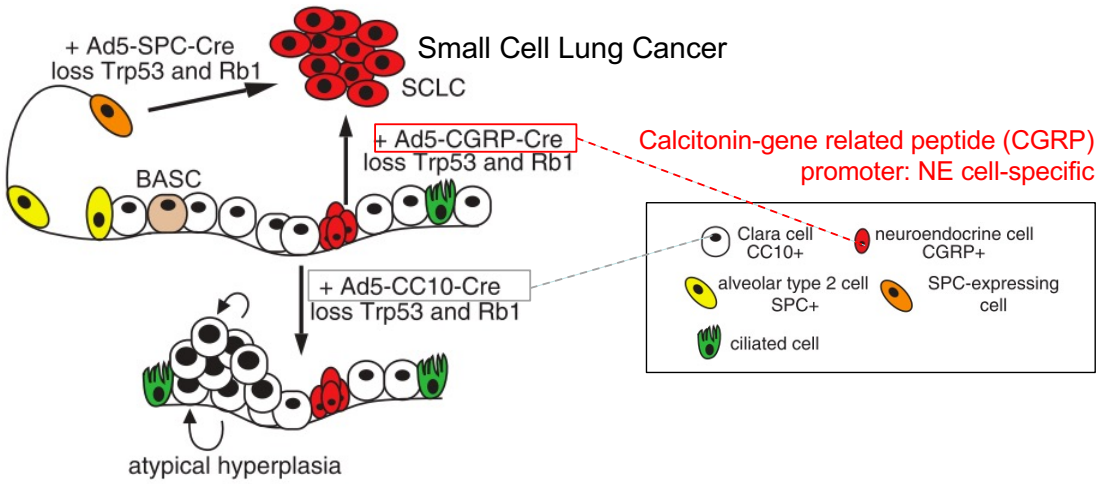
NCAM1 (brown) marker confirms neuroendocrine origin:



Primary SCLC Liver metastasis

Sutherland et al. 2011 Cell 19:754-764

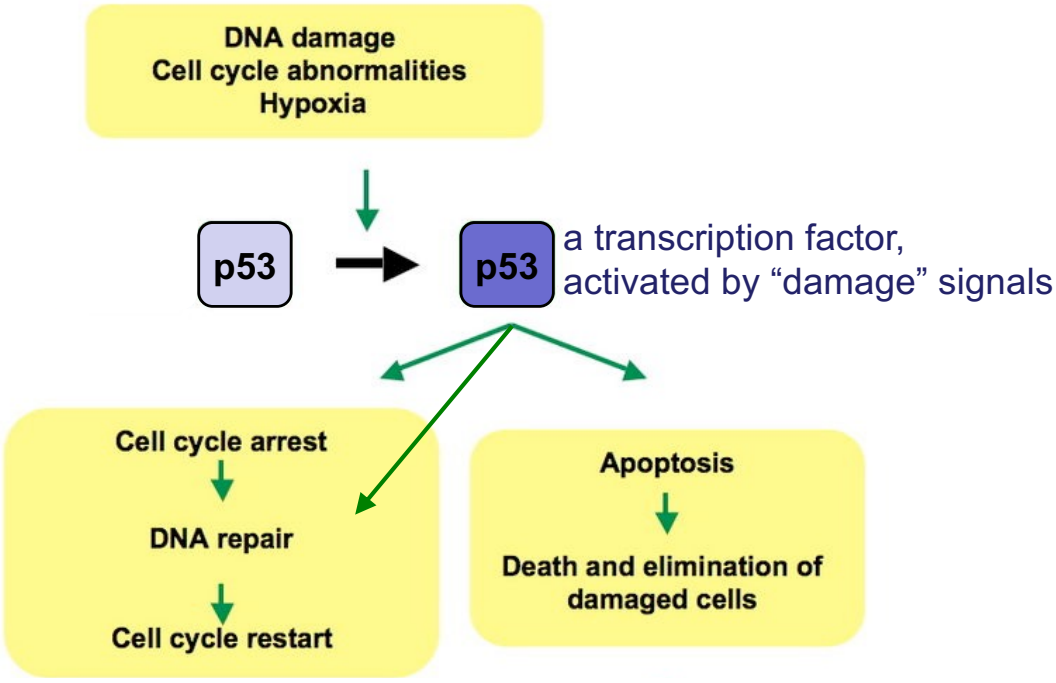
Combined deletion of Rb1 and p53 provokes SCLC
…depending on the mutated cell type!



- Likely explanation for this cell type-specific difference:
  In neuroendocrine cells, Rb1 mediates *terminal* differentiation

Sutherland et al. 2011 Cell 19:754-764

p53 fulfills *several* essential tumor suppressive functions



After wikipedia

Transcription of *Mdm2* by wt p53 mediates *negative feedback*

p53 tetramer:

- a transcription factor
- induces *Mdm2*

Mouse Double Minute 2 (MDM2):

- an E3 ubiquitin ligase
- targets p53 for degradation:

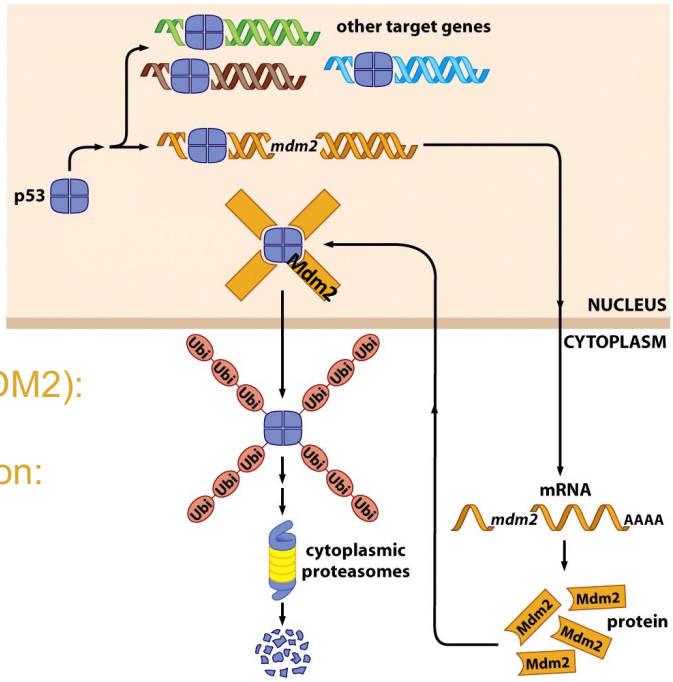
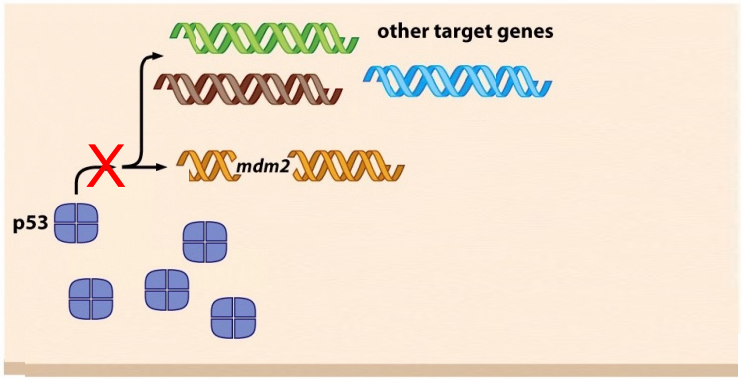


Figure 9.11 *The Biology of Cancer* (© Garland Science 2007)

Transcription of *Mdm2* by wt p53 mediates *negative feedback*

90% of p53 mutations are in its DNA-binding domain and thus block *Mdm2* induction:

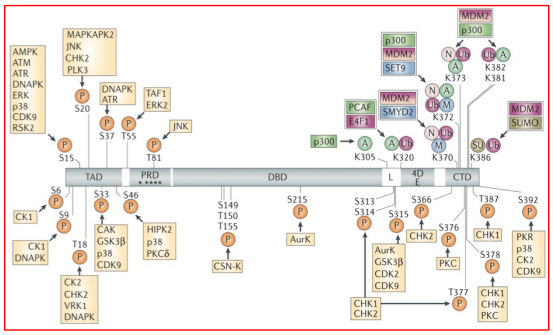


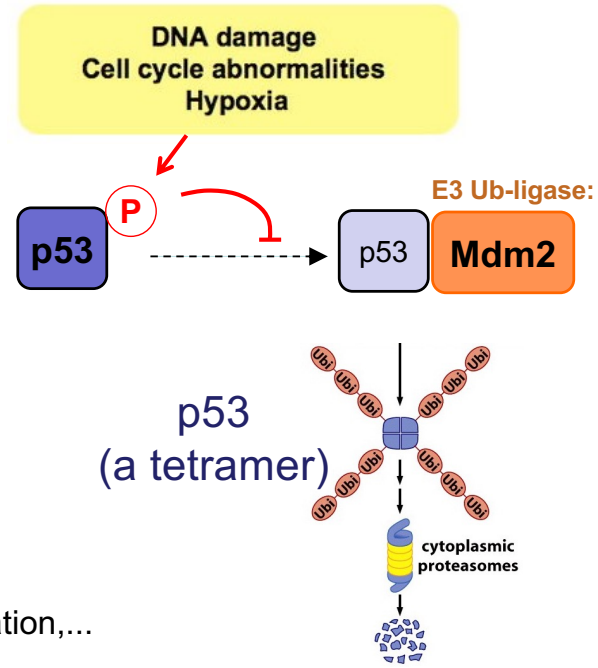
➔ How will such mutations affect the levels of the p53 protein itself?

Figure 9.11 *The Biology of Cancer* (© Garland Science 2007)

p53 is critically regulated at the level of protein turnover

DNA damage-induced phosphorylation stabilizes p53 by inhibiting access of Mdm2:





Post-translational modifications:
Phosphorylation, methylation, acetylation,...

Toledo & Wahl 2006 Nat Rev Canc

Important:
Mutation is *not* the only way to evade tumor suppressors

Mutations

Epigenetic silencing
- promoter methylation
- miRNAs

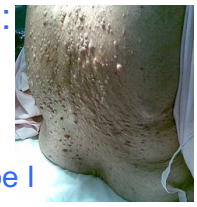
Tumor suppressors

oncogenic small DNA viruses

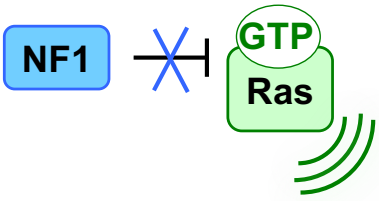
Upregulation of specific inhibitors
- ubiquitin ligases
- kinases
- specific interacting proteins

CONCEPT:
Hallmarks often result from defects in regulators of regulators

a) Loss of GAP activity (GTPase activating protein) by NF1 mutations:

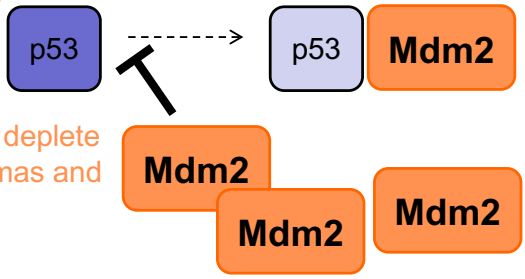


Neurofibromatosis type I



Sustaining proliferative signaling

b) Increased expression of the E3 Ub ligase **Mdm2 (proto-oncogene)**

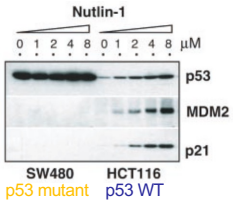


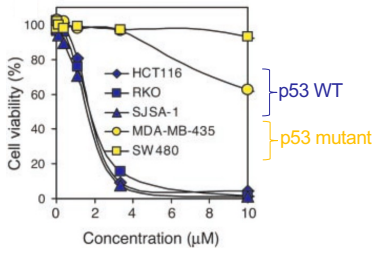
=> *excess* MDM2 can deplete wt p53 in some sarcomas and breast cancers

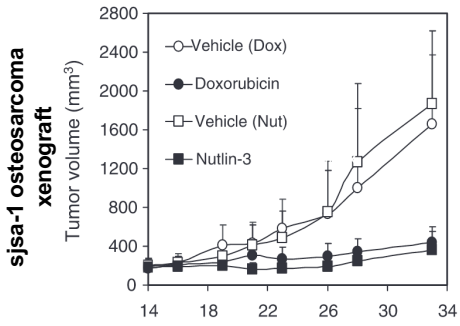
Evading growth suppressors

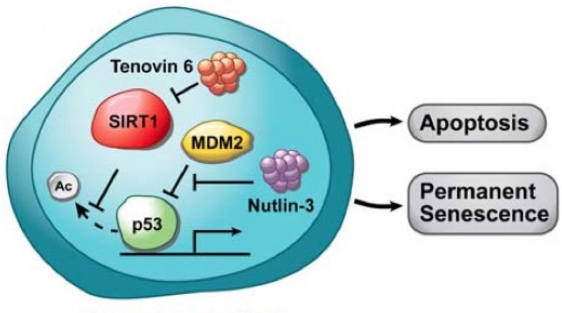
Drugs to protect wild-type p53 against excessive degradation

p53 target genes (MDM2 and p21):









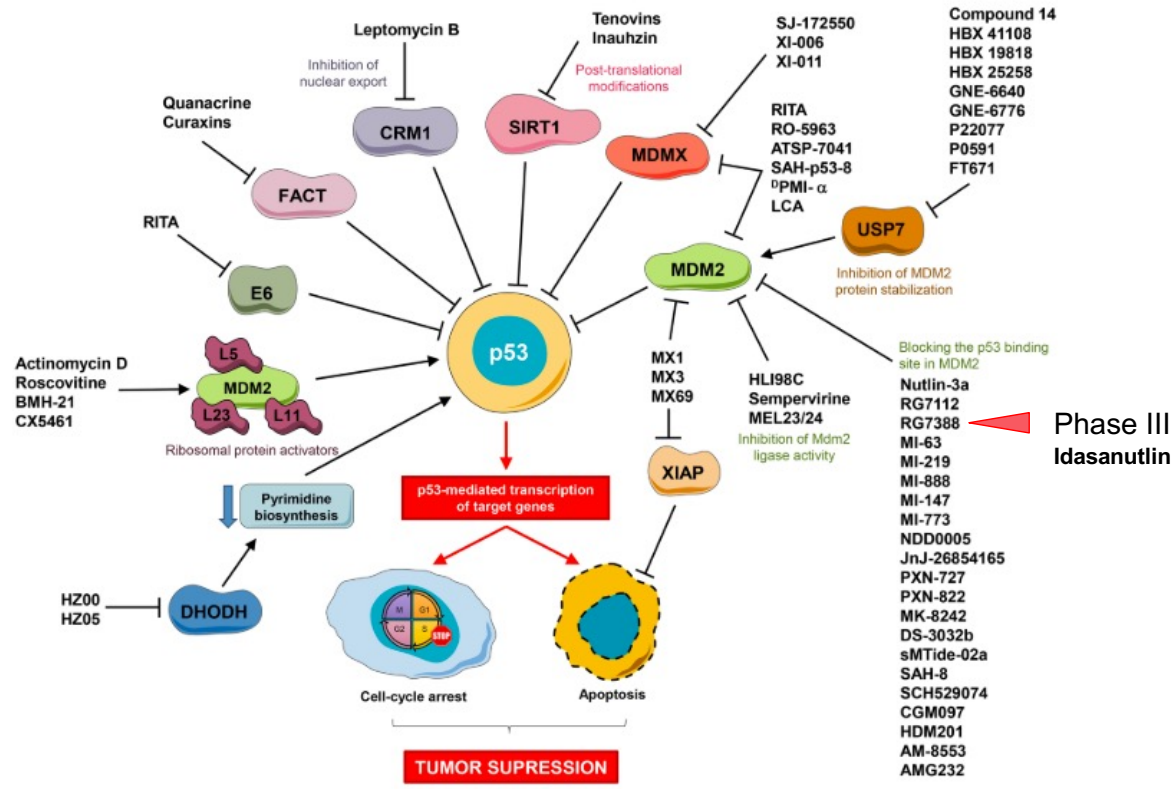
Drug → p53 → transcription:

- cell cycle inhbition genes
- cell death
- cell senescence

- Proof-of-concept: A chemical library screen identified "nutlins"
  Vassilev et al. 2004 Science
- Inhibitors of p53 deacetylation by Sirtuins
  Lain et al. 2008 Cancer Cell

Schug 2011 Annals Med.; Künkele et al. 2012 Neuro Oncol

Drugs under development to target p53-regulatory proteins



Sanz et al. 2019 J Mol Cell Biol 7:586-599

Cell

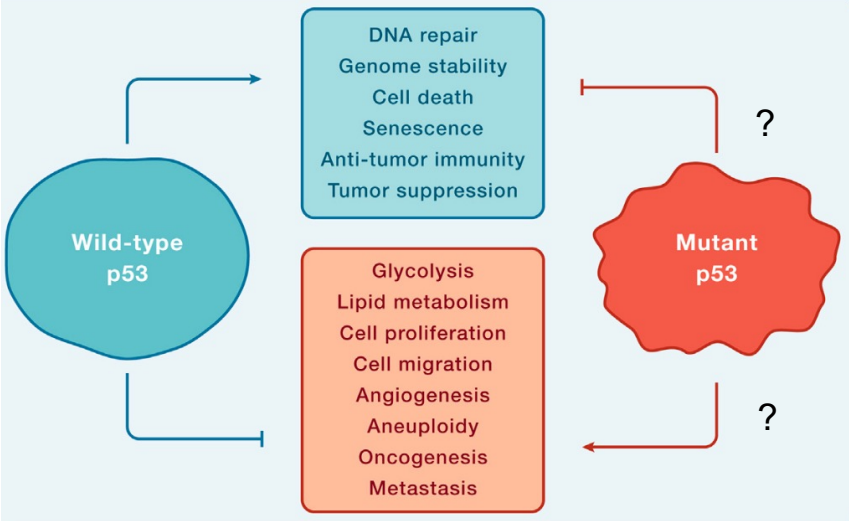
CellPress

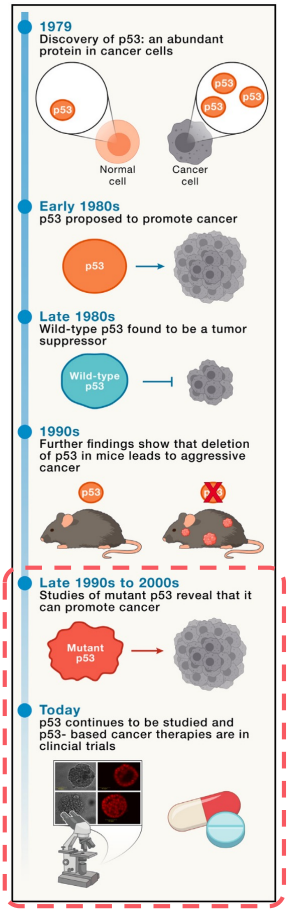
Volume 187, Issue 7, 28 March 2024, Pages 1569-1573

BenchMarks

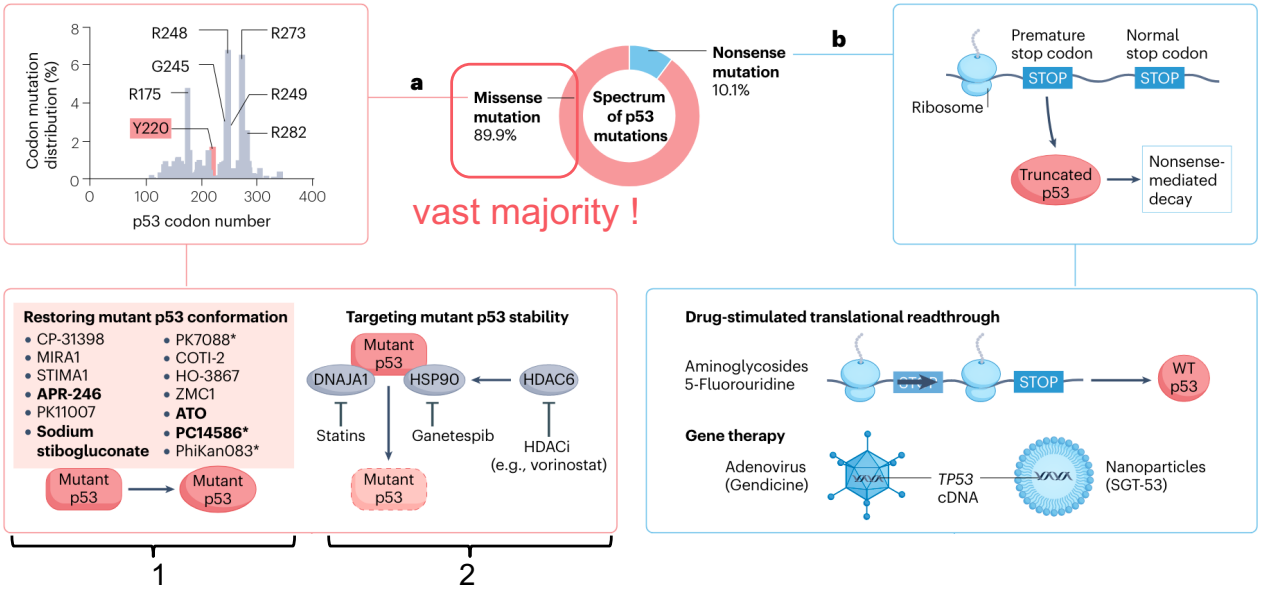
p53: A tale of complexity and context

Moshe Oren [1], Carol Prives [2]





Drugs to target *mutant* p53



1: Rescue the *folding* of mutant p53 and DNA binding to restore tumor-suppression

2: *Degrade* mutant p53 independently of *MDM2* induction to block oncogenic effects

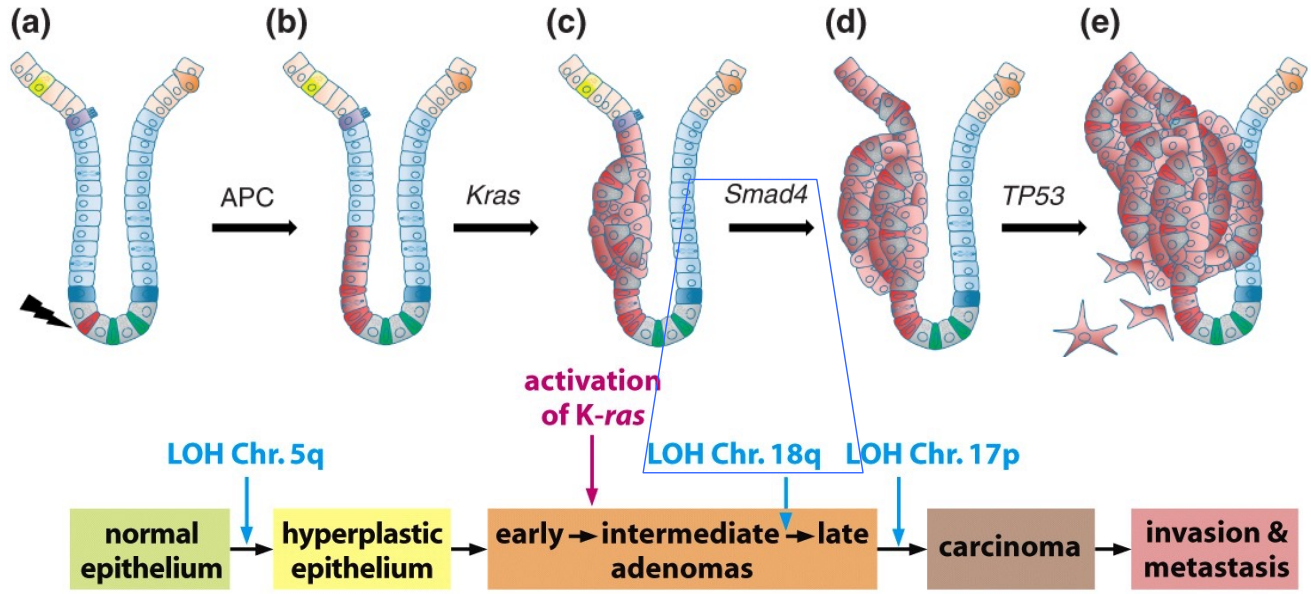
Ongoing clinical trials for drugs that target *mutant* p53

Table 1 | Select clinical trials of p53-based therapeutics for cancer

Therapeutic agent	Mechanism of action	Cancer type	Phase	Status	Clinical trial identifier
Targeting mutant p53					
APR-246 +DNMTi Aza	Generic; restoration of mutant p53 structure via binding to thiol groups in the DBD	AML, MDS	II	Completed	NCT03072043
APR-246+Aza		AML, MDS	II	Completed	NCT03588078
APR-246+Aza		MDS	III	Completed	NCT03745716
APR-246+ICI pembrolizumab		Advanced solid cancers	I/II	Completed	NCT04383938
APR246 +BTK inhibitor acalabrutinib or APR246+BCL-2 inhibitor venetoclax and CD20 antibody rituximab		NHL, CLL, mantle cell lymphoma	I/II	Suspended	NCT04419389
APR-246+Aza		MDS, AML after HSCT	II	Completed	NCT03931291
APR-246+venetoclax		AML	I	Completed	NCT04214860
PC14586	Selectively restores the structure of the Y220C p53 mutant by binding to a crevice created by the mutation	Solid cancers	I	Recruiting	NCT04585750
ATO+DNMTi decitabine	Restores the structure of moderately destabilized p53 mutants by binding to cysteines in the DBD	AML, MDS	I	Recruiting	NCT03855371
ATO		Ovarian and endometrial cancers	NA	Unknown	NCT04489706
		Refractory solid cancers	II	Unknown	NCT04695223
		Refractory solid cancers	II	Recruiting	NCT04869475
Sodium stibogluconate	Stabilizes the structure of 65 temperature-sensitive p53 mutants by non-covalent binding	AML, MDS with defined p53 mutations	II	Recruiting	NCT04906031

Questions ?

The « Vogelgram » of colon tumor progression



after Bert Vogelstein (Johns Hopkins)

Figure 11.9 *The Biology of Cancer* (© Garland Science 2007)

TODAY

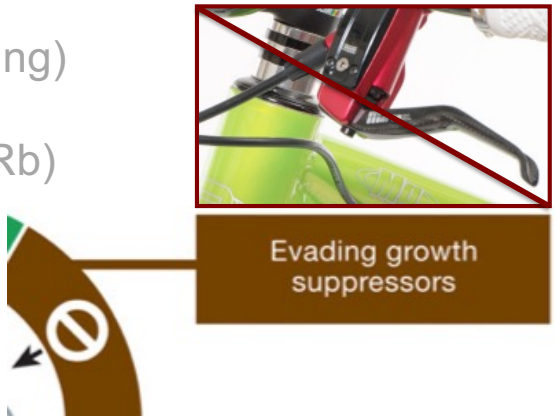
Hallmark capability 2: Evading growth suppressors

EXAMPLES:

✓ NF1 and PTEN (⊣ RTK signaling)

✓ retinoblastoma protein RB1 (pRb)

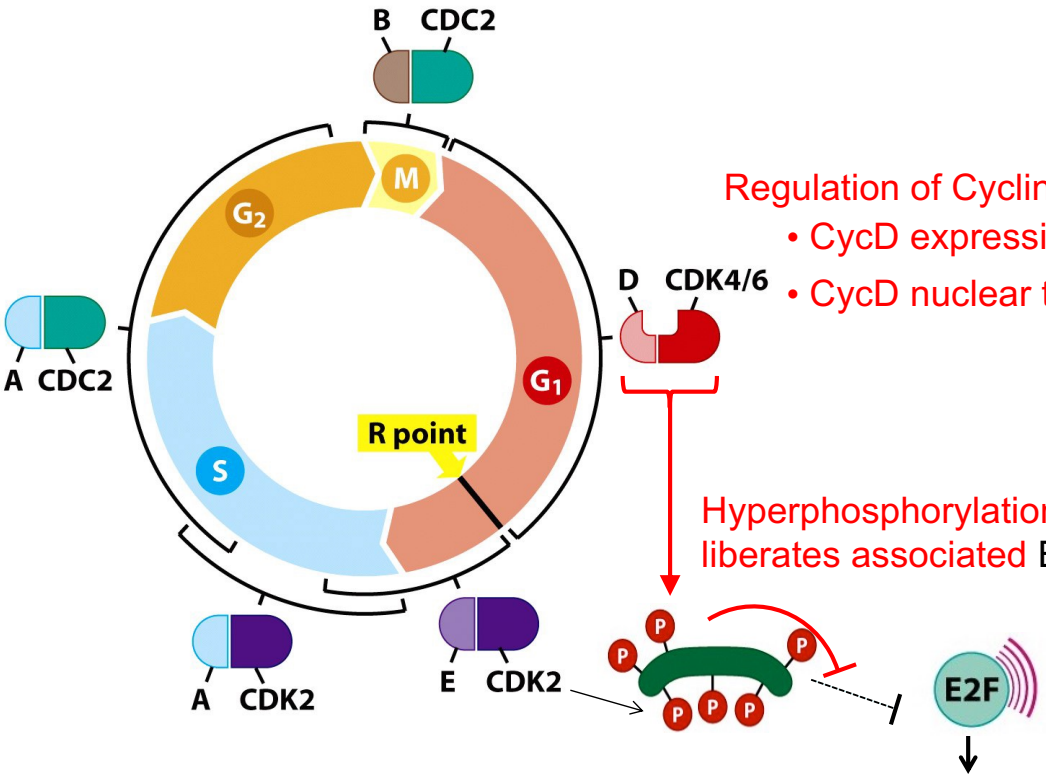
✓ Tumor Protein p53 (TP53)



◆ TGF-β/Smad signaling

- Induction of cell cycle inhibitors
- Core pathway components mutated in human cancers
- Validation of tumor-suppressive TGF-β signaling in mouse models

Phosphorylation by CyclinD/CDK4,6 complex inactivates RB1

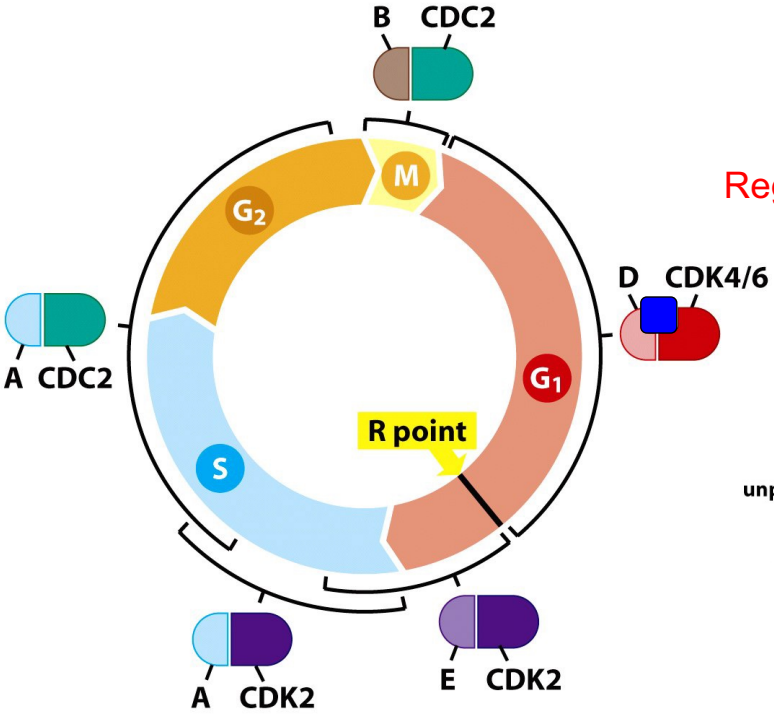


Regulation of CyclinD/Cdk4,6
- CycD expression levels
- CycD nuclear translocation

Hyperphosphorylation of **RB1** liberates associated E2F:

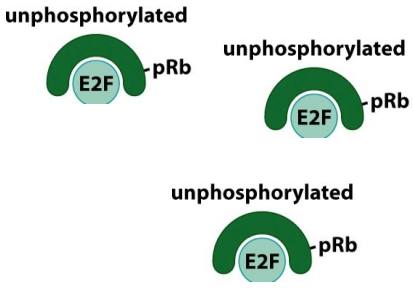
=> Free E2F activates transcription of DNA replication and cell cycle genes

Specific CDK inhibitors (CKI) *inhibit* cell proliferation



Regulation of CyclinD/Cdk4,6:

- CycD expression levels
- CycD Nuclear translocation
- **Inhibitors (CKI)**



=> When bound to *hypo*phosphorylated Rb, E2F *represses* target genes

Several CDK inhibitors for different occasions...

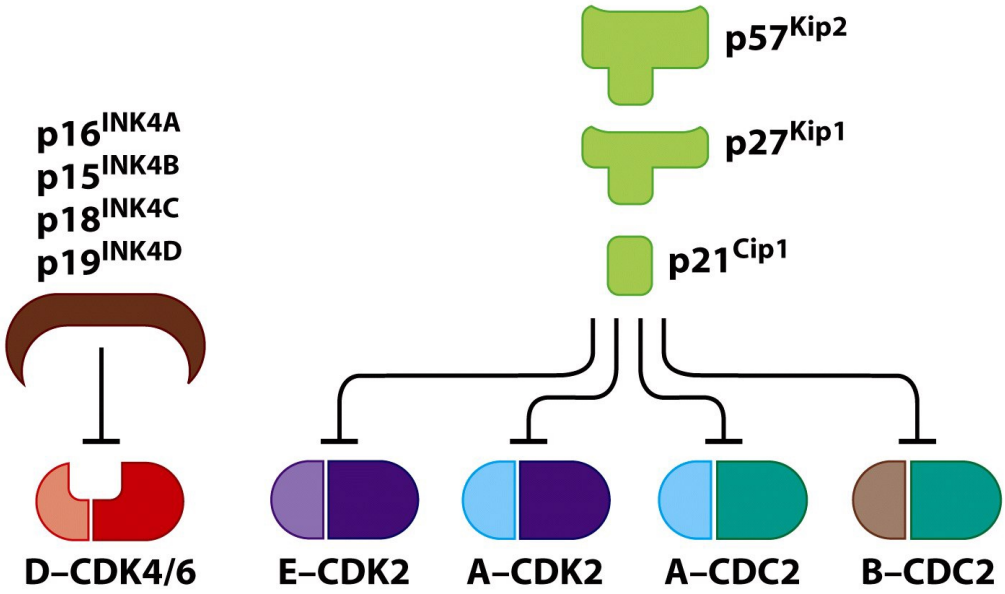


Figure 8.13a *The Biology of Cancer* (© Garland Science 2007)

TGF-β blocks the cell cycle by inducing several CDK inhibitors

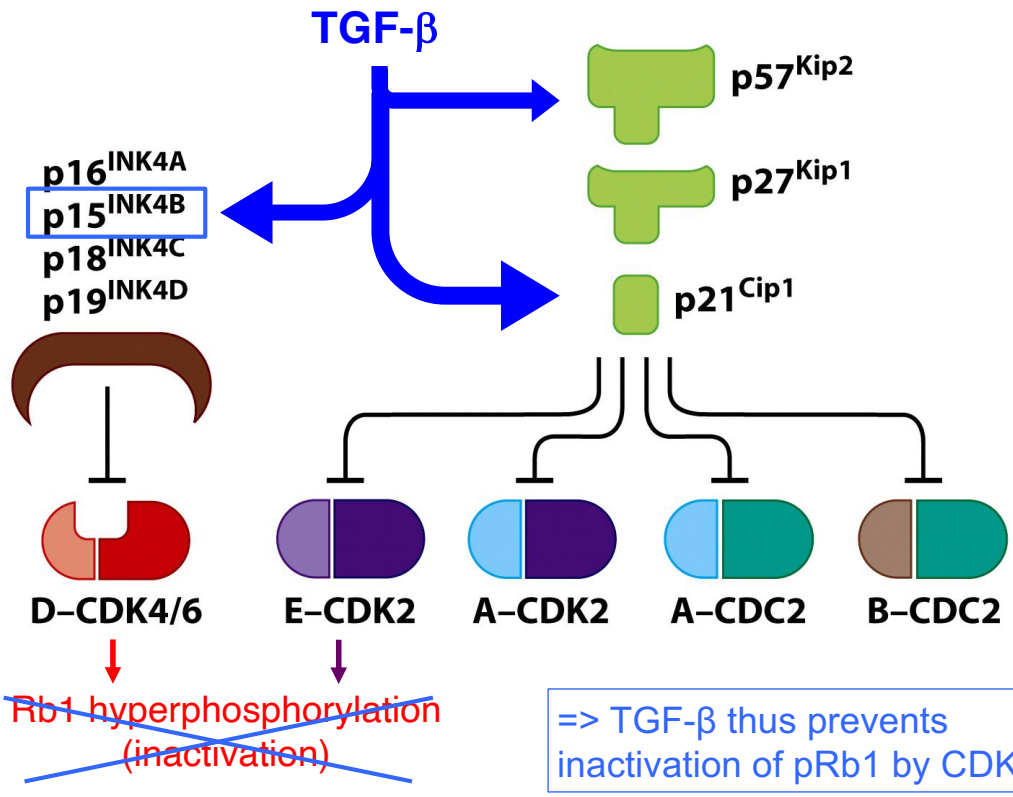


Figure 8.13a *The Biology of Cancer* (© Garland Science 2007)

Transforming Growth Factors

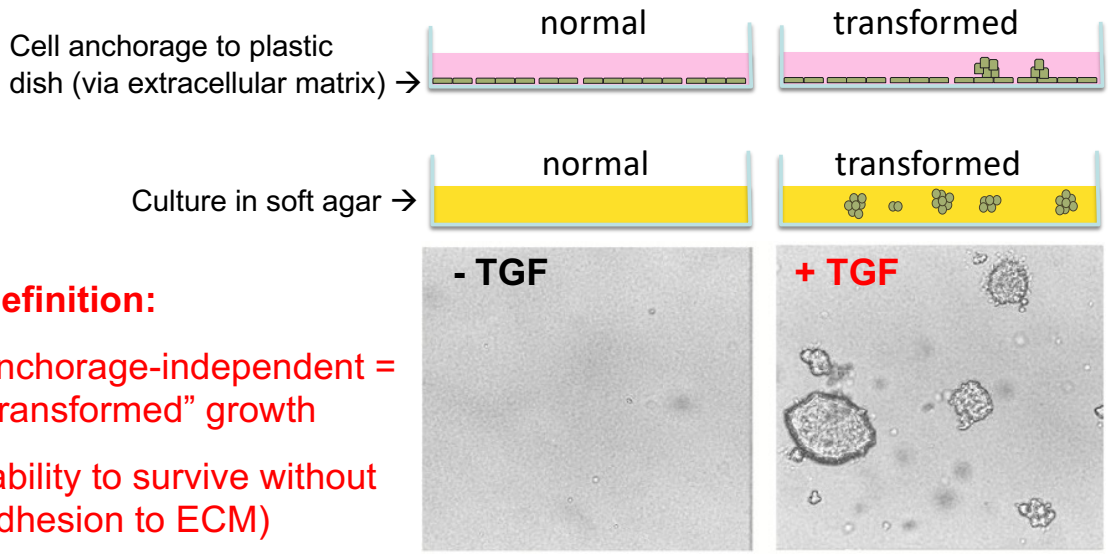
TGF-β is secreted, but *unrelated* to TGF-α (a ligand of the EGF family activating EGFR).

It only shares with TGF-α the potential to induce

transformed growth

Transformed growth has been recognized long ago as a distinctive characteristic of many cancer cells in culture

Transforming growth factor-β activity



Definition:

anchorage-independent = "transformed" growth

(ability to survive without adhesion to ECM)

1981 TGF-β *transforms* the growth of normal *fibroblasts*

1984 Paradox: In *epithelial* cells, TGF-β *inhibits* proliferation
= a tumor suppressor ?

Today: TGF-β has pleiotropic functions (# of PubMed entries ≈ p53)

Smads transduce signals mediated by TGF-β family members

Dimeric ligands

Heterotetrameric receptor complexes (dimers in cartoon for simplification)

Type II receptors *transphosphorylate* type I

Type I receptor phosphorylates « R-Smads » (e.g. TGF-β itself: Smad2 and Smad3)

Phosphorylated R-Smads associate with the "co-Smad" Smad4 to regulate promoters of target genes

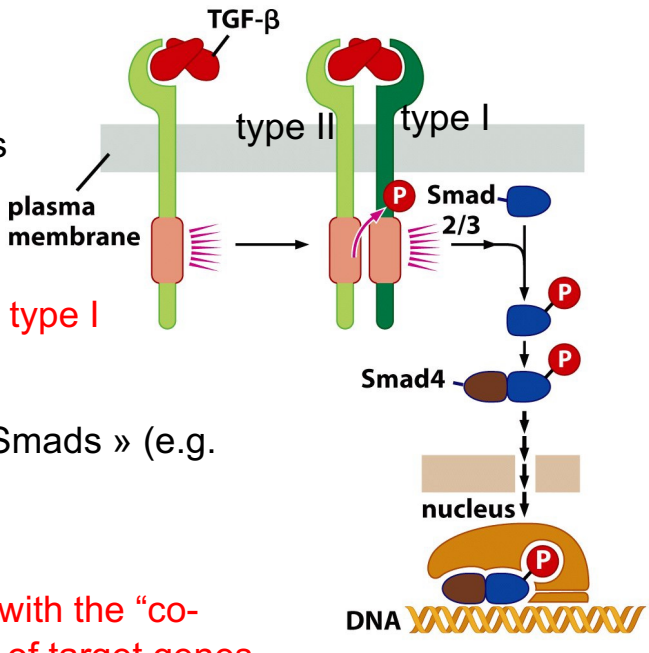
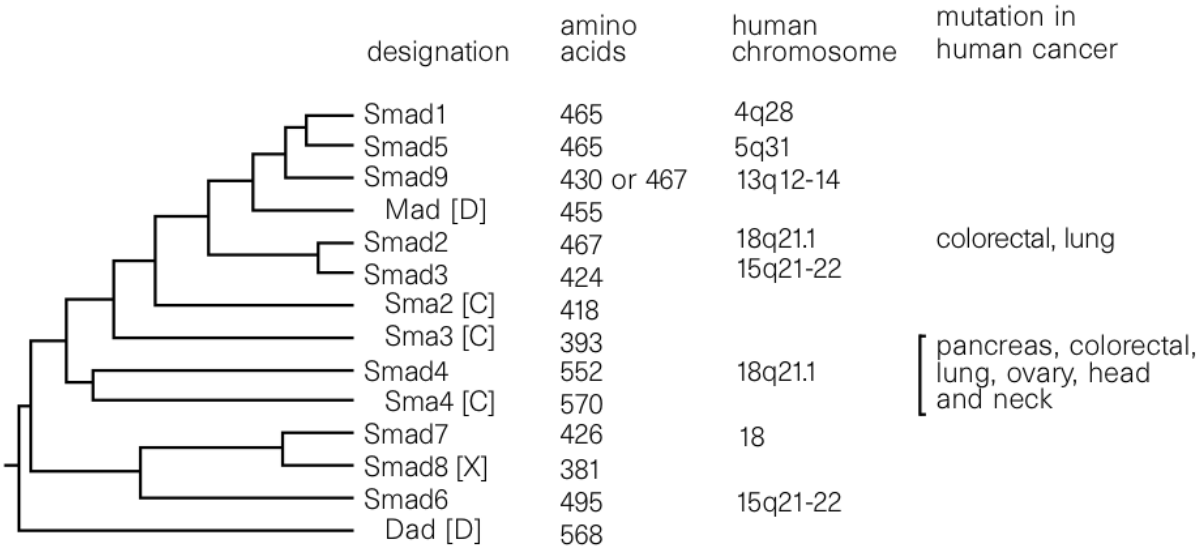


Figure 6.29d *The Biology of Cancer* (© Garland Science 2007)

LoF Mutations in SMAD4 and less frequently SMAD3 or SMAD2 occur in several human tumor types

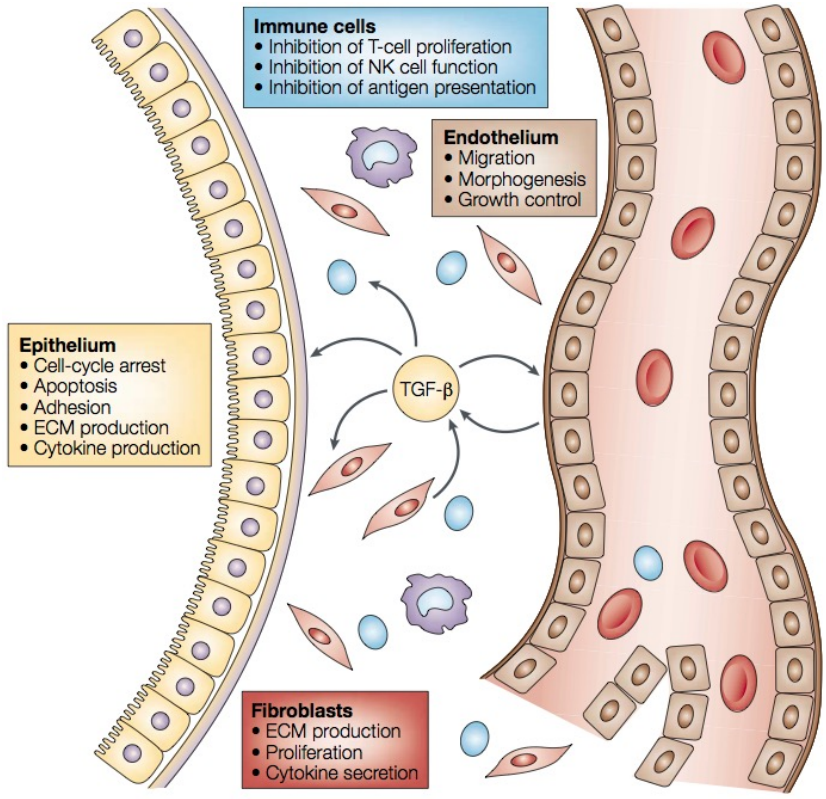


designation	amino acids	human chromosome	mutation in human cancer
Smad1	465	4q28	
Smad5	465	5q31	
Smad9	430 or 467	13q12-14	
Mad [D]	455		
Smad2	467	18q21.1	colorectal, lung
Smad3	424	15q21-22	
Sma2 [C]	418		
Sma3 [C]	393		
Smad4	552	18q21.1	pancreas, colorectal, lung, ovary, head and neck
Sma4 [C]	570		
Smad7	426	18	
Smad8 [X]	381		
Smad6	495	15q21-22	
Dad [D]	568		

Combined prevalence: E.g. 15% of all primary sporadic CRCs have SMAD4, SMAD2, or SMAD3 mutated (Fleming et al. 2013 Cancer Res)

Nature 390, 465-471(4 December 1997)

TGF-β: a Jack of all trades

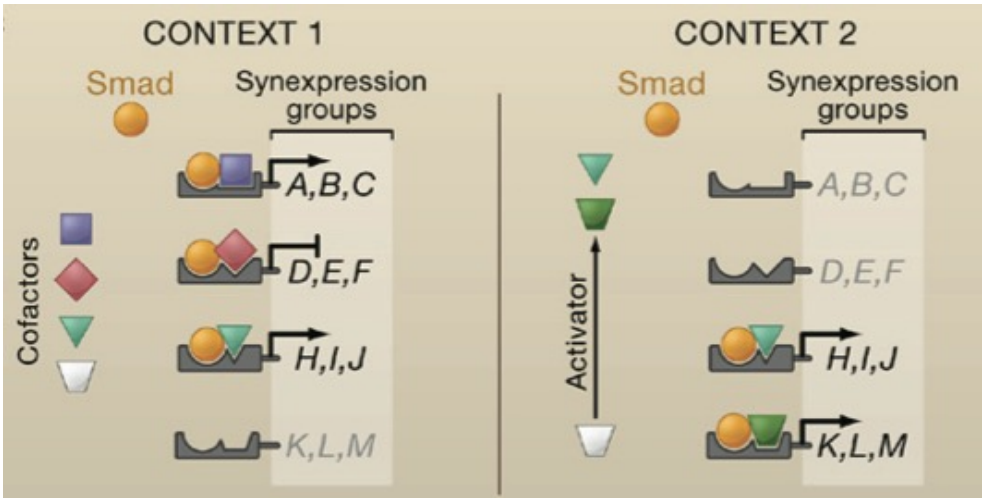


Signal outputs depend on context:

- Ligand diversity
- Types of co-receptors
- SMAD co-factors
- integration with other inputs (RTK, Wnt,...)

Siegel & Massagué 2003 Nat Rev Cancer

SMADs bind different target genes, depending on co-factors



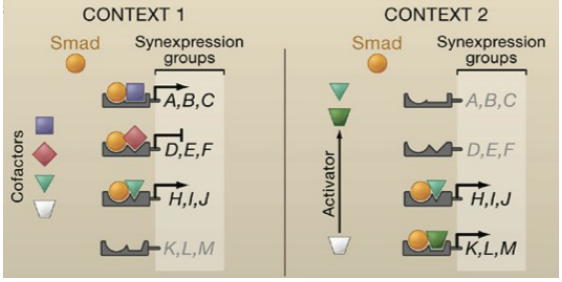
- SMADs alone have only low DNA binding affinity
- Co-activators and co-repressors direct Smads to context-specific subsets of target genes (synexpression groups)

Massagué 2008 Cell 134:215-230

Specific co-activators and co-repressors that bind Smad2&3 determine which CKI is induced by TGFβ in a given context

B

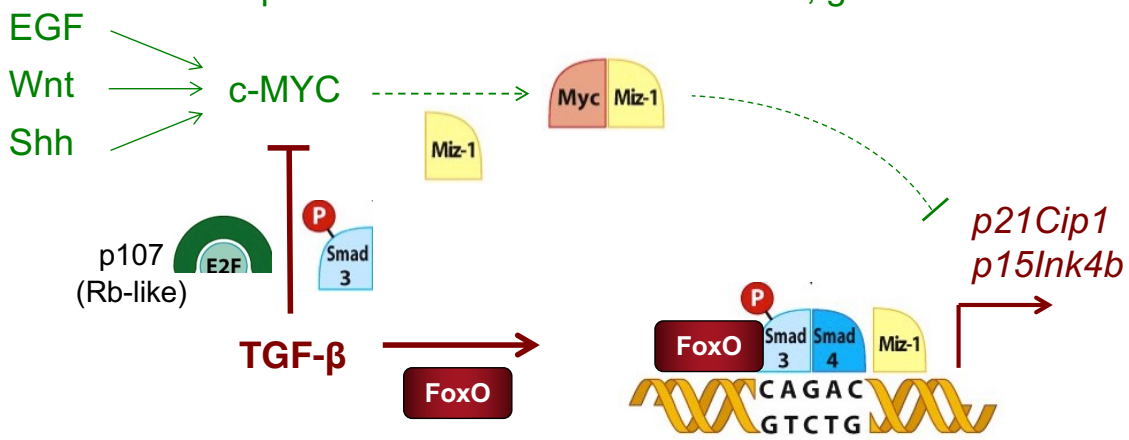
TGFβ target genes:	*p15INK4b*	*p21CIP1*	*p57KIP2*	*c-MYC*
Epithelial progenitors	up	up		down
Neural progenitors, Astrocytes	up	up		down
Hematopoietic progenitors			up	down
T cells		up		down



In addition, p-Smad3 inhibits cell proliferation also by repressing c-MYC

Illustrative example of intricate intracellular signaling circuitry

- **c-Myc**
  - a bHLH transcription factor
  - binds Max or Miz1 to induce or repress target genes
  - discovered as a proto-oncogene in Burkitt's lymphoma
  - important in cancers for cell division, growth & survival



- TGF-β-mediated repression of c-MYC potentiates induction of the CDK inhibitors p21 and p15

Cytostatic co-factors of Smad2,3 are tumor suppressors

FoxO: Subclass of forkhead box transcription factors regulating cell growth, proliferation, apoptosis and longevity; frequently inactivated in cancers by mutation or Akt phosphorylation

p53: Can bind Smad2 on the p21 promoter

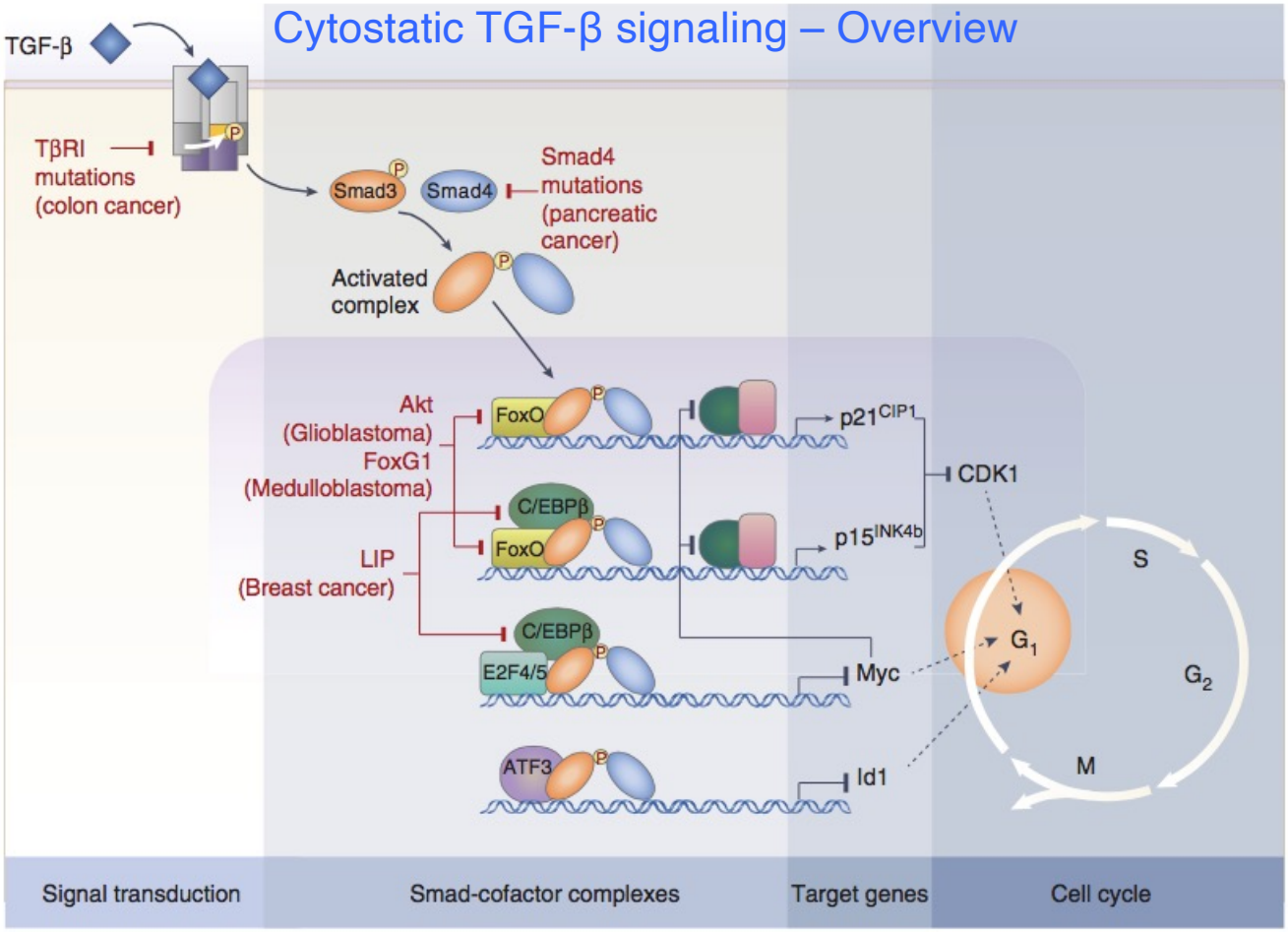
C/EBPβ: CCAAT/enhancer binding proteins are transcriptional coactivators; α and β mediate growth arrest and differentiation of basal keratinocytes

p107: Related to Rb; recruits histone deacetelase (HDAC); required for Smad3-mediated repression of c-Myc

- *No need to memorize them all, but be aware of the concept!*
- *Equally relevant for stem cell quiescence, longevity, metabolism...*

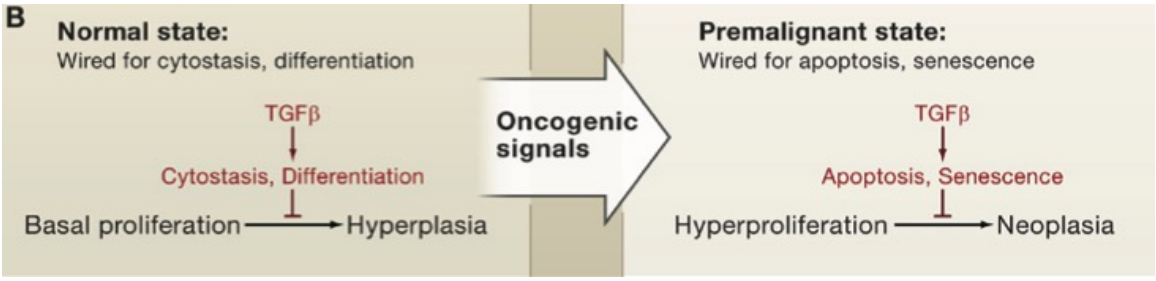
Massagué 2008 Cell 134:215-230

Cytostatic TGF-β signaling – Overview

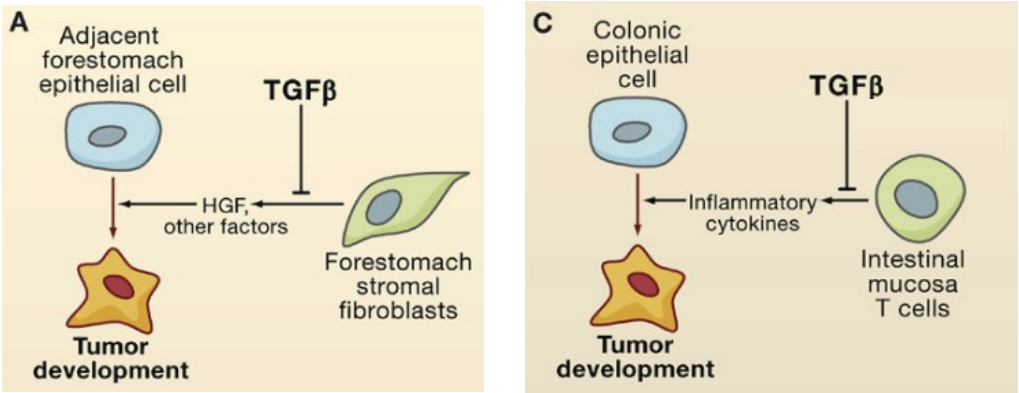


Tumor suppressive functions of TGF-β

- In epithelial cells: Cell cycle arrest, senescence, or even death:

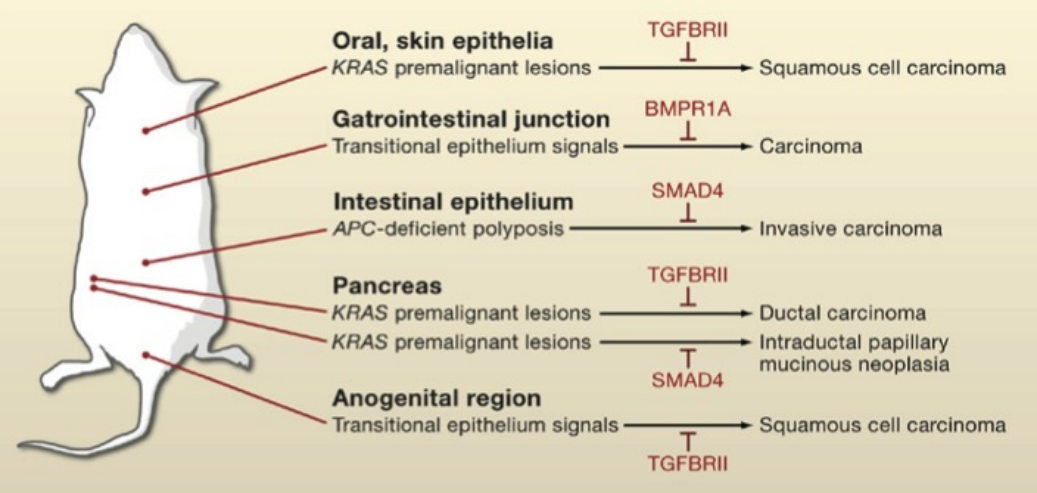


- In stromal cells: Inhibition of secreted oncogenic factors



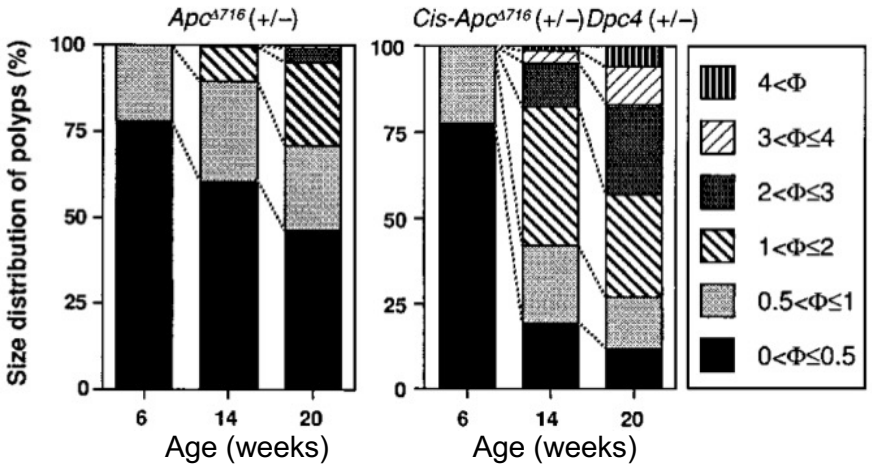
Massagué 2008 Cell 134:215-230

Various mouse models confirmed a role for TGF-β signaling in blocking tumor progression to a malignant state



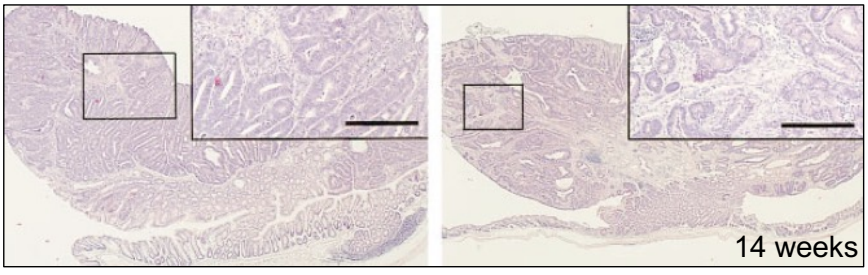
Massagué 2008 Cell 134:215-230

Intestinal polyps in APC+/-; Smad4+/- compound mutants



Mouse APC and Smad4 are in "cis" (=on the same chromosome)

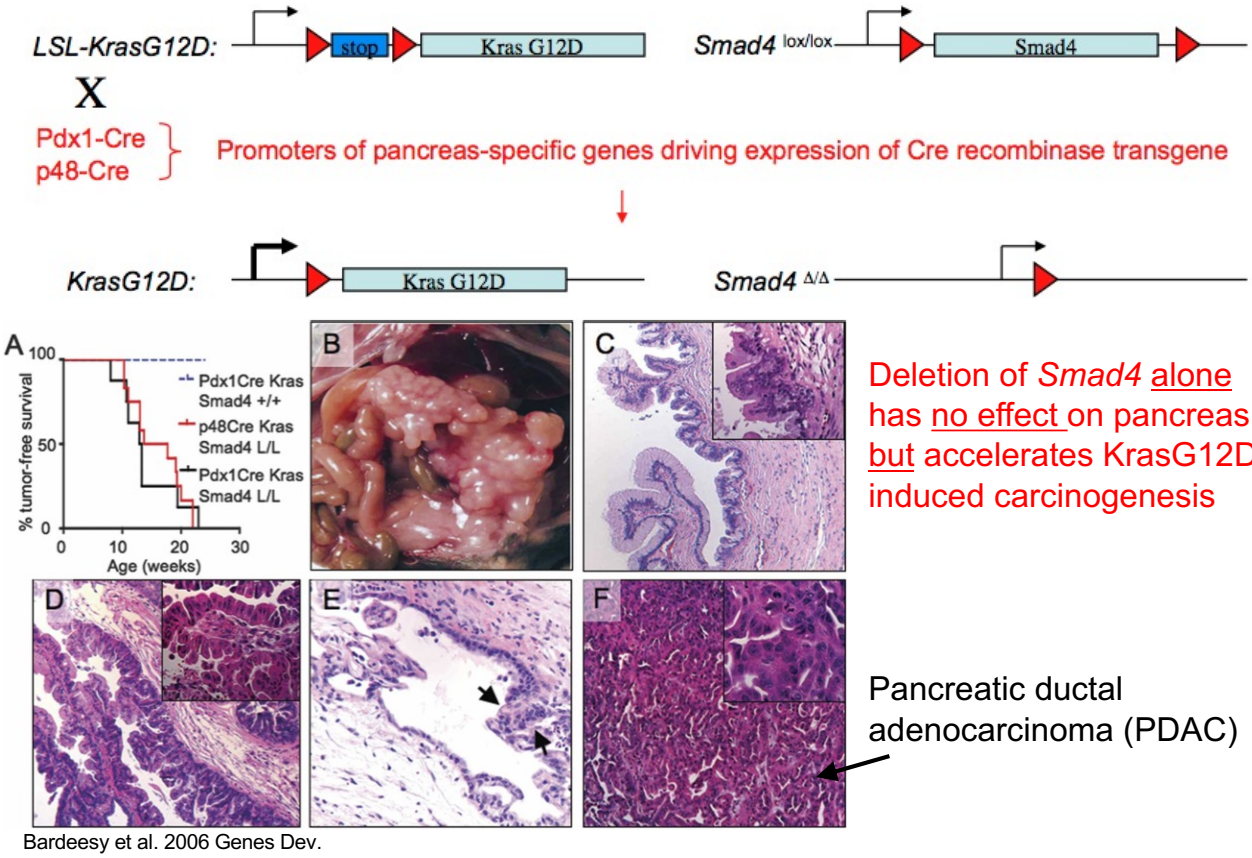
LOH of APC & Smad4 together increases polyp size compared to APC LOH alone



LOH of APC & Smad4 increases stromal content and eventually leads to invasion of mucosa

Takaku et al. 1998, Cell

Smad4 suppresses oncogenicity of mutant K-Ras in pancreas

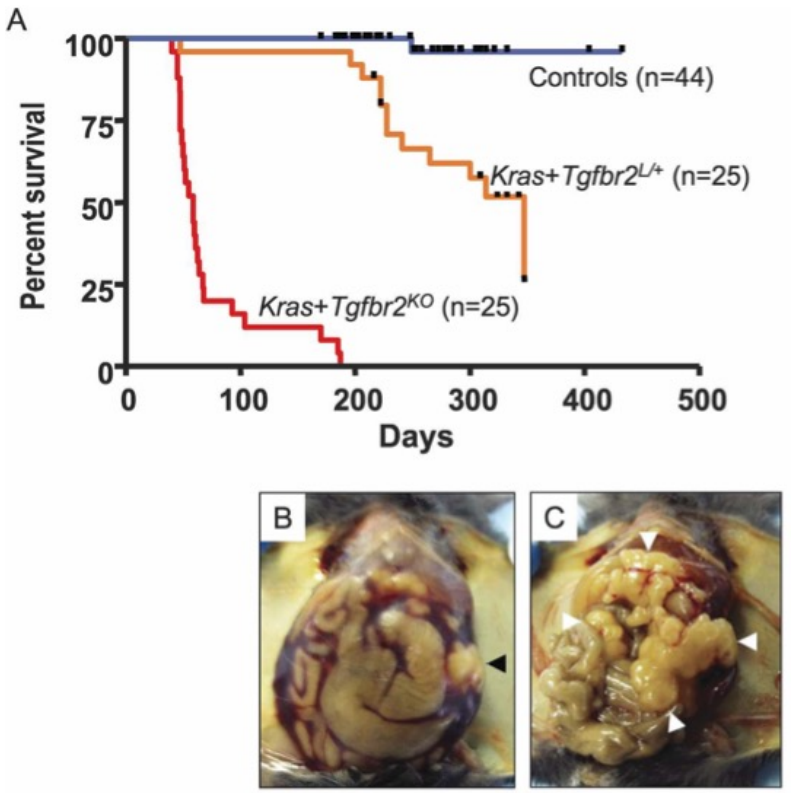


Deletion of *Smad4* alone has no effect on pancreas, but accelerates KrasG12D-induced carcinogenesis

Pancreatic ductal adenocarcinoma (PDAC)

Bardeesy et al. 2006 Genes Dev.

Mutant K-Ras also induces PDAC in *Tgfbr2* cKO pancreas



p48-Cre deletion of floxed *Tgfbr2* similarly increases the tumorigenicity of KrasG12D

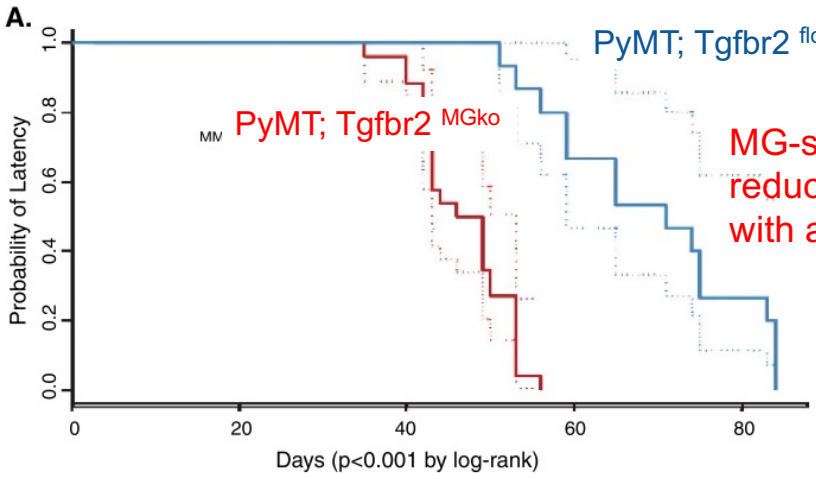
Ijichi et al. 2006 Genes Dev.

Deletion of TβRII in the mammary gland of PyMT tumor mice

Transgenic mice expressing Polyoma virus Middle T antigen (PyMT)

- a viral oncogene that mimics an activated RTK
- promoter/enhancer from mouse mammary tumor virus (MMTV)

→ A widely used mouse model of metastatic breast cancer:



MG-specific deletion of TβRII reduces tumor latency, consistent with a role as a tumor *suppressor*

=> TGF-β signaling in *epithelial* cells *delays* oncogene-induced tumors

Forrester et al. 2005 Cancer Res 65: 2296-2302

Tumor suppressive TGF-β signaling - Summary

- TGF-βs activate heterotetrameric complexes of type I and II Ser/Thr receptor kinases to elicit pleiotropic effects
- Phosphorylation of Smad2&3 by activated type I receptors is necessary to bind Smad4 and/or transcriptional coactivators/repressors on specific target genes
- In epithelial cells, TGF-β inhibits proliferation by inhibiting c-myc and by activating a FoxO synexpression group including the CKIs p21 and p15.
- CKIs inhibit CDK4/6 to prevent RB1 hyperphosphorylation and entry into S-phase
- cytostatic TGF-β/Smad signaling is important to restrain oncogene-induced tumorigenesis, especially in colon, pancreas, and mammary gland

Questions ?

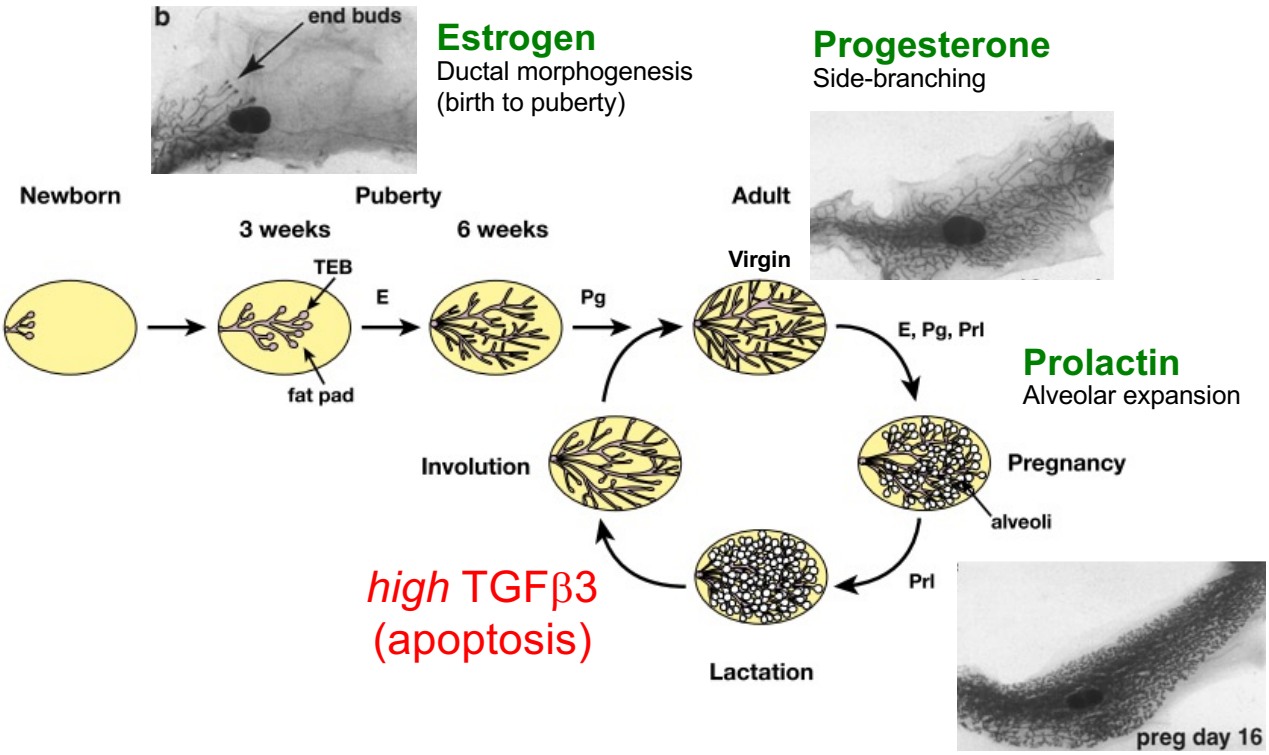
Exercise questions:

Tumor suppressive role of cytostatic TGF-β signaling in the mammary gland epithelium

Introduction:

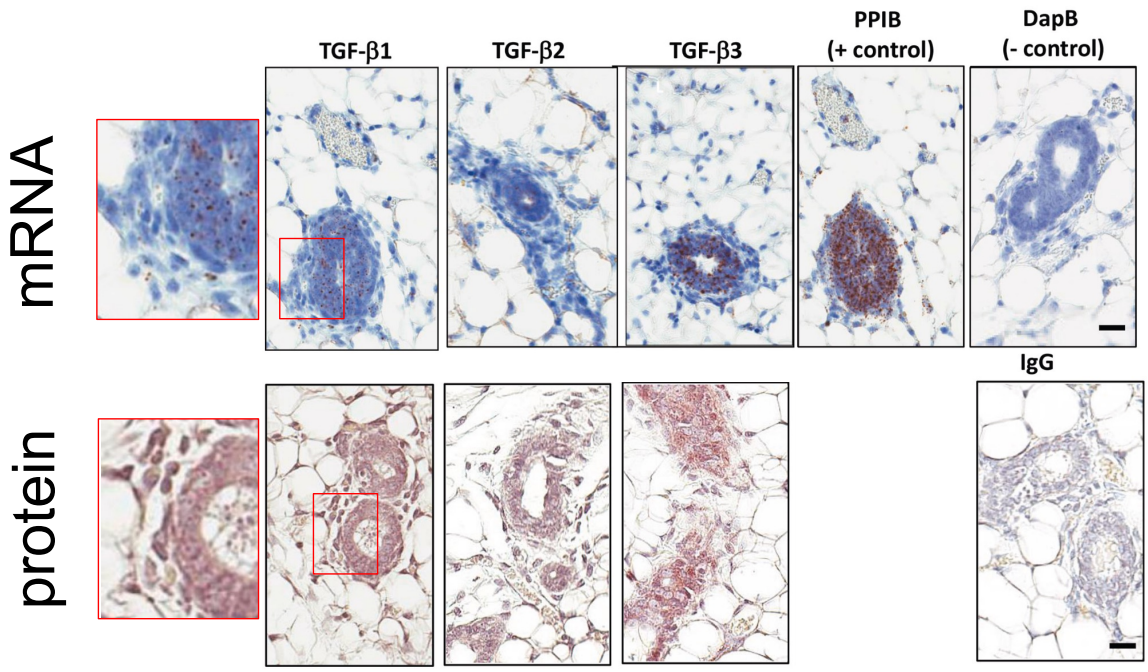
Molecular breast cancer types & estrogen signaling

Mammary gland development



Hennighausen et al. 1998 Genes Dev. 12: 449-455; Visvader & Stingl 2014 Genes Dev

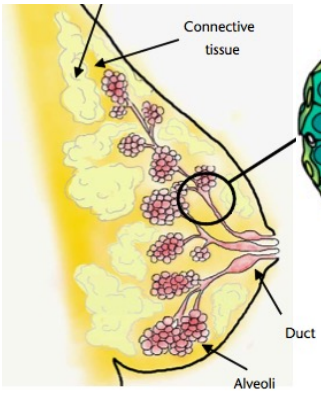
TGF-β mRNAs and proteins in virgin mouse mammary glands

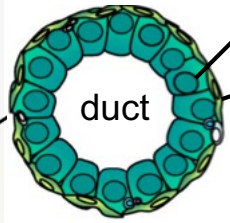


→ *Autocrine* and/or *paracrine* TGF-β1 signaling?
(Exercise)

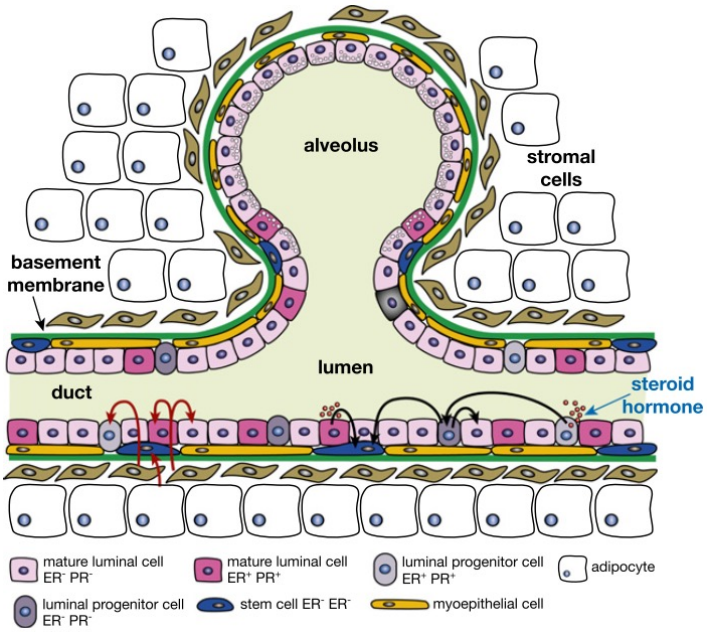
Flanders et al., 2016, Oncotarget 25:38164-38179

Role of hormone receptors in epithelial homeostasis

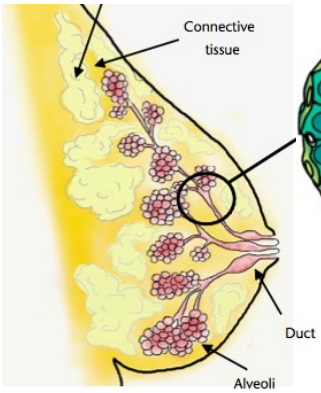


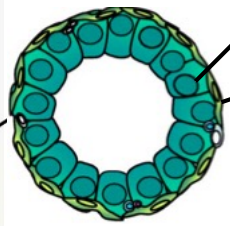


- Heterogenous stem and progenitor cell populations
- Proliferation is regulated by endocrine hormones and paracrine growth factors



Breast cancer classification by gene expression profiling





- ≥18 types of breast cancer
- important distinction: estrogen receptor α status (ERα+ tumors need estrogen to grow)

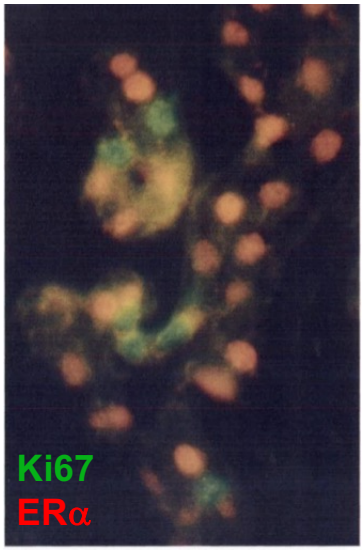
Table 1 Molecular classification of breast cancer

Molecular subtype	Genes overexpressed	Prognosis	Mutations
Luminal-like	ERα, GATA-3 and prolactin receptor	Good	Low rate of p53 mutations
Basal-like	Cytokeratins 5,6 and 17, laminin, c-kit, c-myc and SFRP1	Bad	High rate of p53 and BRCA-1 mutations
HER2 overexpressing	HER2, GRB7, RALB and RAB6A	Bad	High rate of p53 mutations
Normal breast-like	Cytokeratins 5, 17 and genes specific to adipose cells as peroxisome proliferator-activated receptor (PPAR)-γ	Intermediate	Intermediate rate of p53 mutations

Caffaral 2011 Encyclopedia of Life Sciences (ELS). DOI: 10.1002/9780470015902.a0023164

ERα drives mammary epithelial cell proliferation

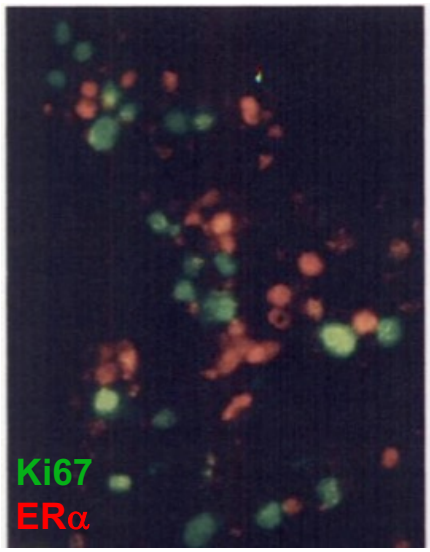
Normal human breast



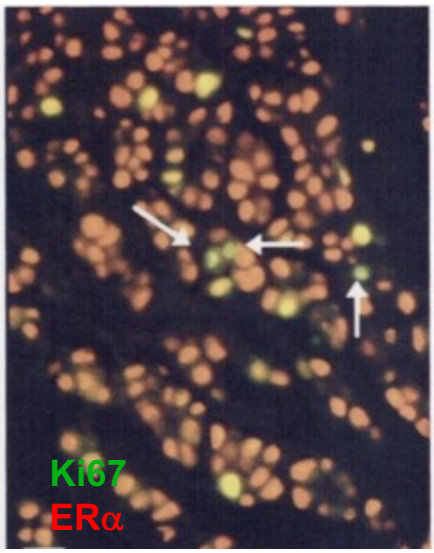
ERα cells *rarely* proliferate

ERα stimulates *neighboring* cells

human breast tumor 1



human breast tumor 2



ERα-positive cells escape from growth arrest in *some* breast cancers

Clarke et al. (1997) Cancer Res 57:4987