Principles and pathology of cancer

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Lecture outline

- Review the “hallmarks” of cancer
- Discuss current views about how cancer starts and progresses
- Introduce the concept of “cancer stem cells” and how they relate to cancer heterogeniety
- Discuss what make cancers lethal – metastasis and other factors
- Goal: to set the stage for the other lectures

Definitions

- Oncogenes: normal genes that promote cancer when they are mutated, translocated, or amplified. They affect proliferative signal transduction pathways
- Tumor suppressor genes: normal genes that promote cancer when they are lost. Most regulate DNA repair and/or cell cycle progression

More definitions

- Amplification: occurs when a region of a chromosome containing an oncogene is multiplied (can be up to 20-fold or more)
- Deletion: occurs when a region of a chromosome containing a tumor suppressor is lost
- Translocation: occurs when part of one chromosome is fused to part of another
- Epigenetic: a change in mRNA expression caused by reversible mechanisms (usually DNA methylation or post-translational modifications of histones)

More definitions

- Tumor progression: occurs as cancers acquire more genetic and epigenetic defects and become clinically aggressive.
- Metastasis: when cancers leave their tissues of origin to colonize other sites within the body. Almost always used when describing solid tumors and not hematopoietic malignancies.
- Grade: appearance of a tumor under a microscope, linked to proliferation.
- Stage: measure of how disseminated a tumor is.

Cancer is a genetic and epigenetic disease

- Defined by the accumulation of “hard-wired” DNA alterations, including mutations, copy number variations (CNVs: amplifications and deletions), and translocations
- Probably occur in punctuated “bursts”
- Nevertheless, tumors are like “wounds that do not heal”, and as is true in wound healing, signals from the tumor microenvironment are critical for the development and progression of cancer

Cell, Vol. 61, 759–767, June 1, 1990, Copyright © 1990 by Cell Press

A Genetic Model for Colorectal Tumorigenesis

Review

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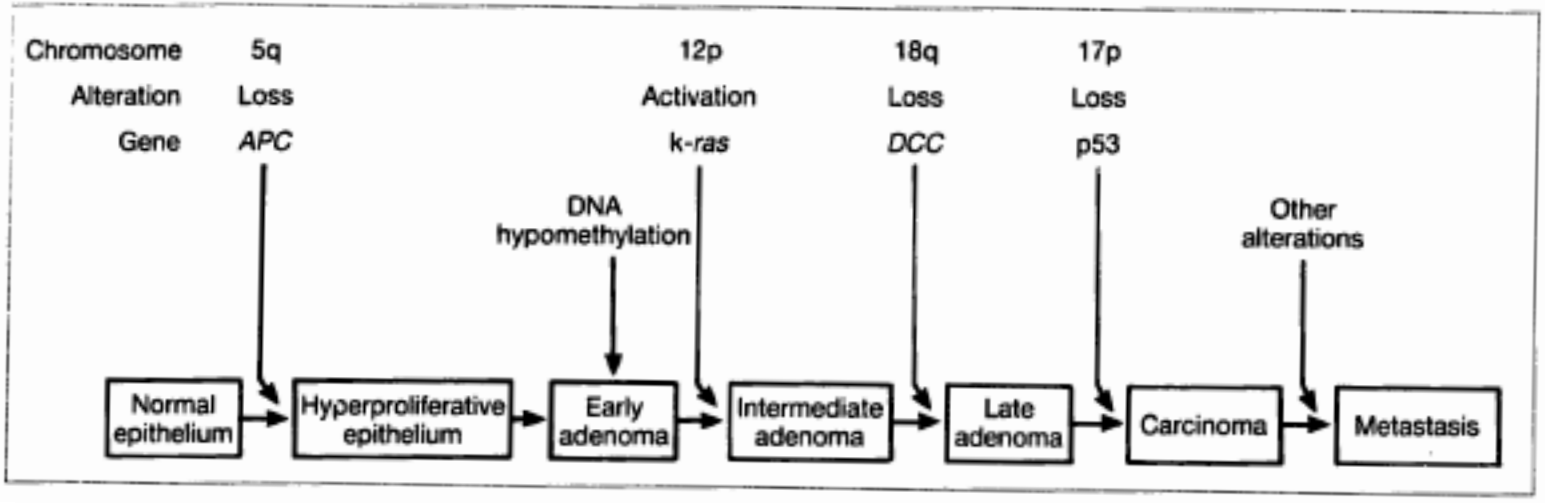
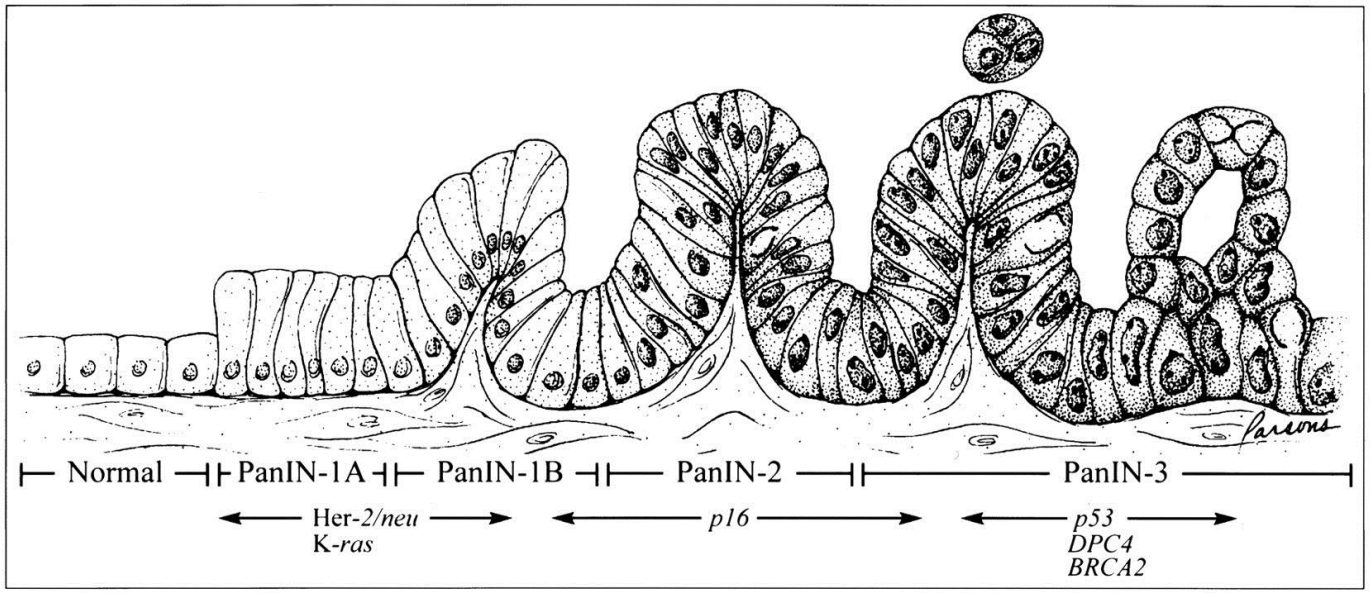


Pancreatic cancer progression



Hruban, R. H. et al. Clin Cancer Res 2000;6:2969-2972

AACR Clinical Cancer Research

Factors that cause cancer

- Familial predisposition (inherited mutations)
- Ageing
- Exposure to viral and bacterial pathogens (chronic inflammation)
- Exposure to natural and man-made toxicants in the environment (UV, certain metals, cigarette smoke carcinogens)
- Oxidative stress

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The Hallmarks of Cancer

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Cell

Leading Edge
Review

Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]
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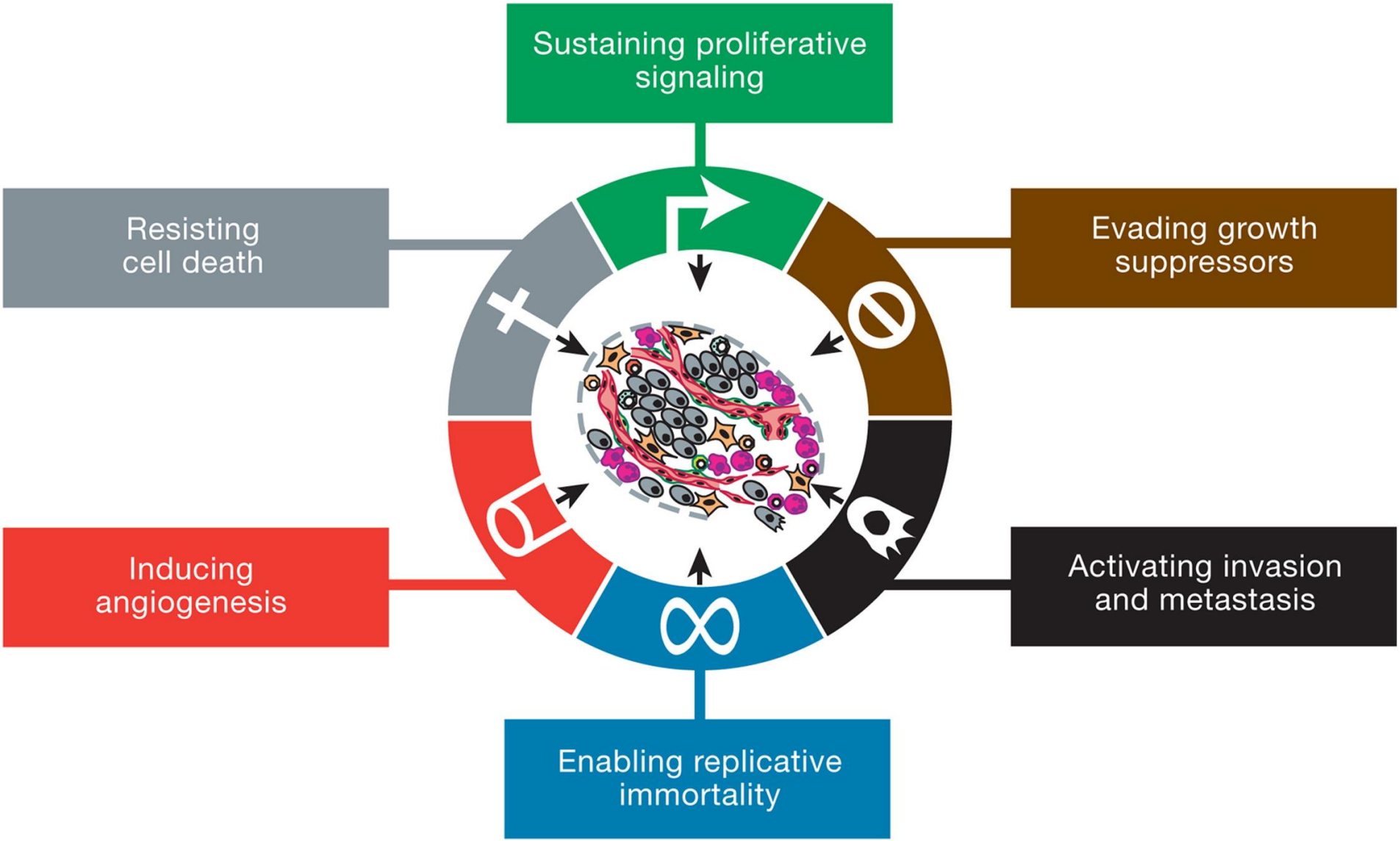
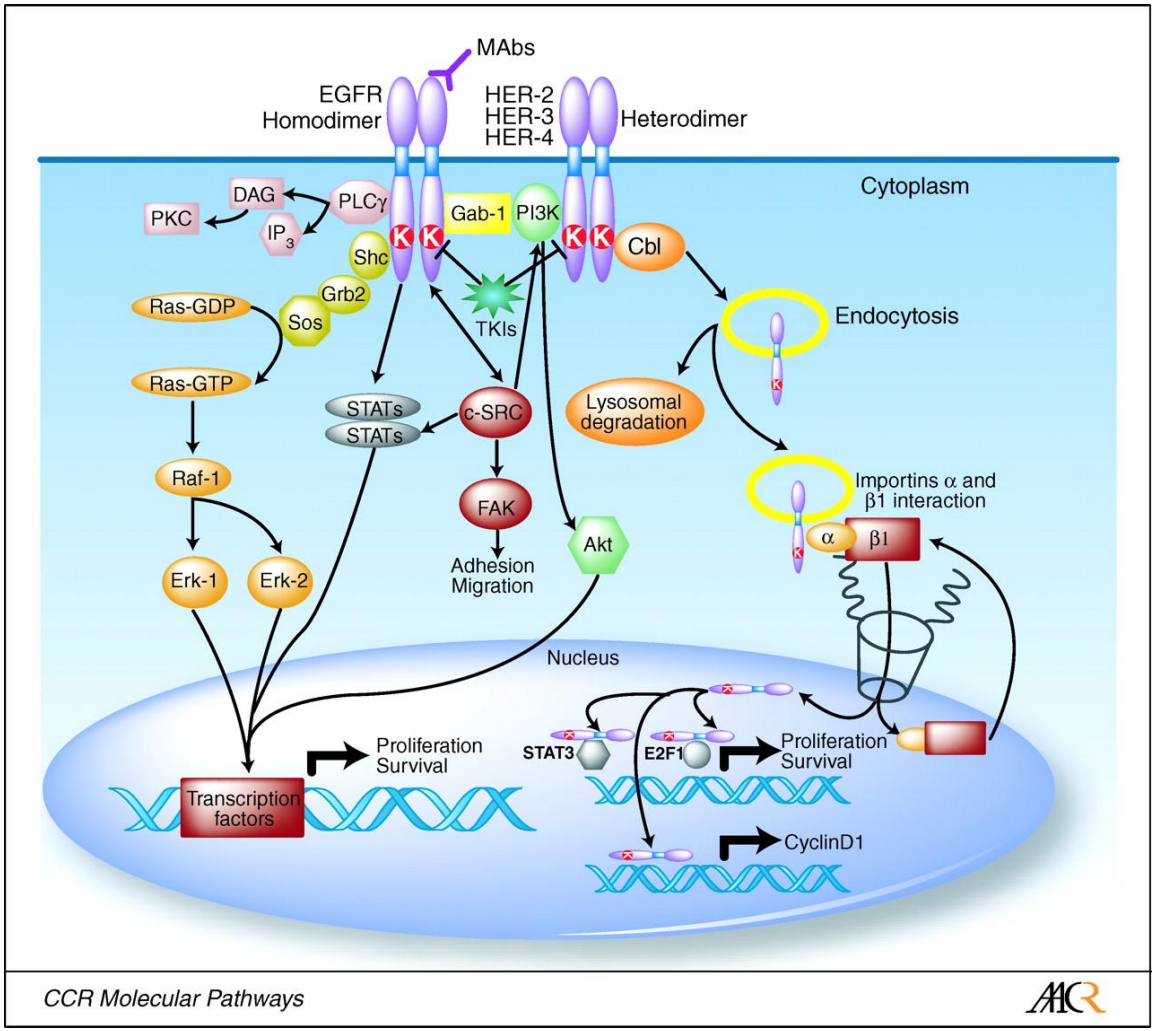

Sustaining proliferative signaling
Evading growth suppressors
Activating invasion and metastasis
Enabling replicative immortality
Inducing angiogenesis
Resisting cell death



Scaltriti, M. et al. Clin Cancer Res 2006;12:5268-5272

Clinical Cancer Research

Sustained proliferative signaling

- Caused by inappropriate activation of growth factor receptors and/or their downstream signal transduction pathways.
- Tumors often make their own growth factors (ex: TGFα-EGFR)
- Growth factor receptors are often amplified (EGFR, HER2, MET, FGFR3, etc)
- Growth factor receptors can be constitutively activated by mutation or chromosomal translocation (EGFR, FGFRs, HER2)
- Downstream signal transduction genes are often mutated or amplified (Ras, PIK3CA, AKT, TSC-1, mTOR, PTEN).
- Genes that promote cell cycle progression are often amplified (Myc, cyclin D, aurora A, etc)

Melanoma genetics and the development of rational therapeutics

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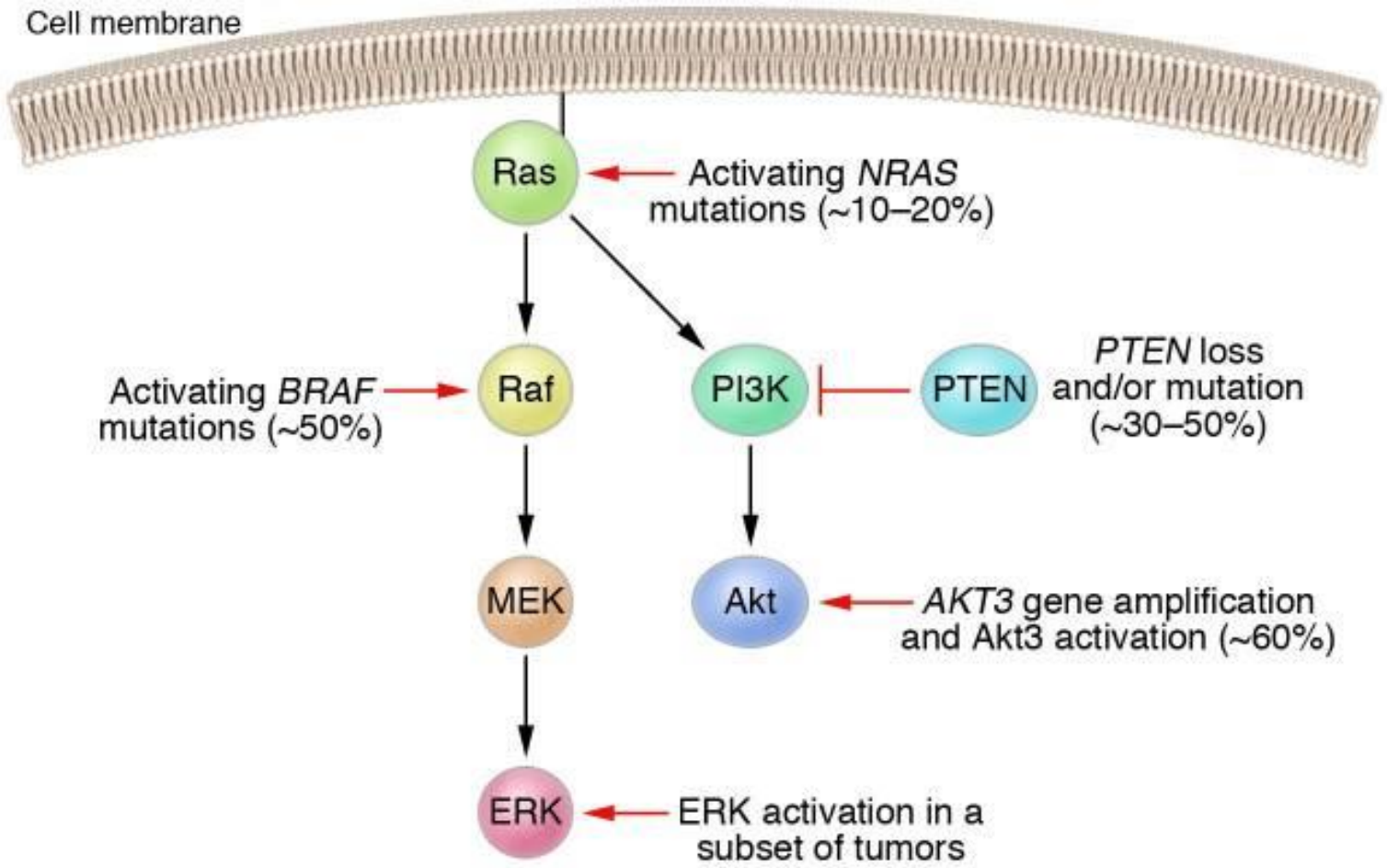
Ras pathway activation in melanoma



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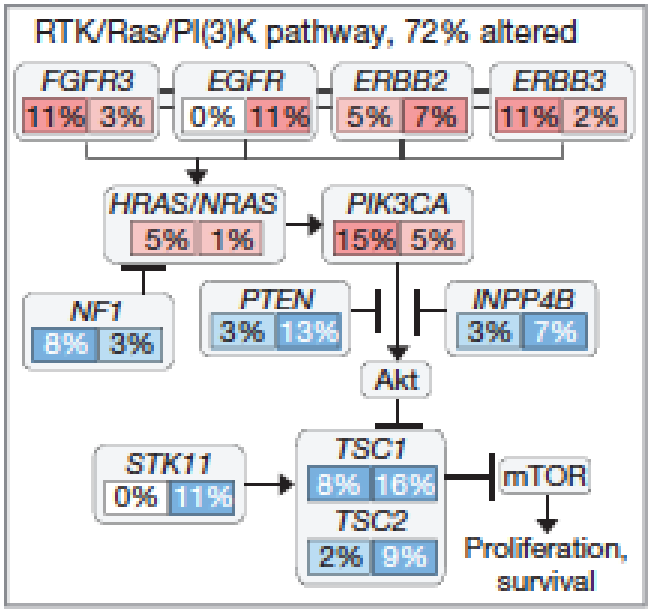
OPEN

doi:10.1038/nature12965

Comprehensive molecular characterization of urothelial bladder carcinoma

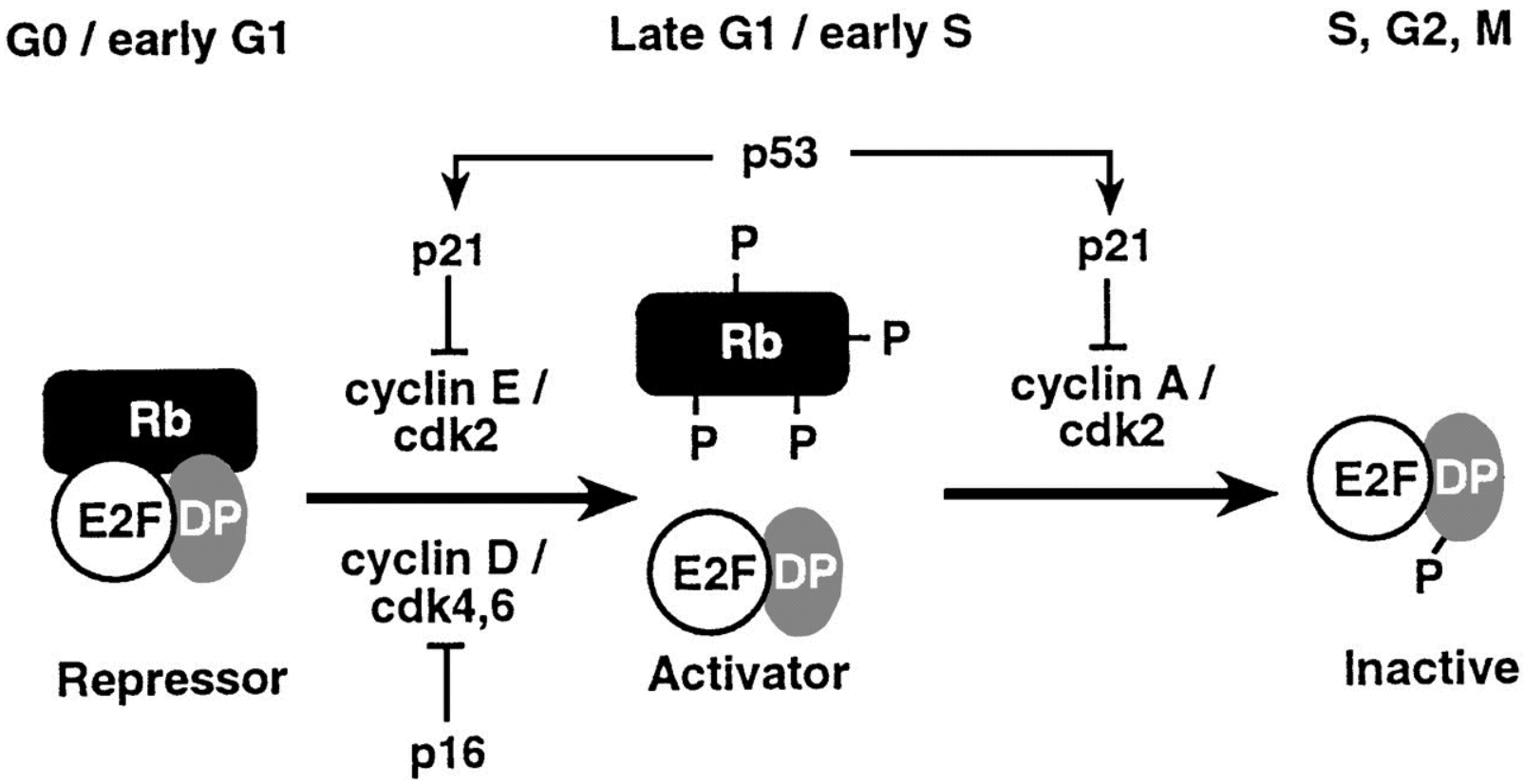
The Cancer Genome Atlas Research Network*



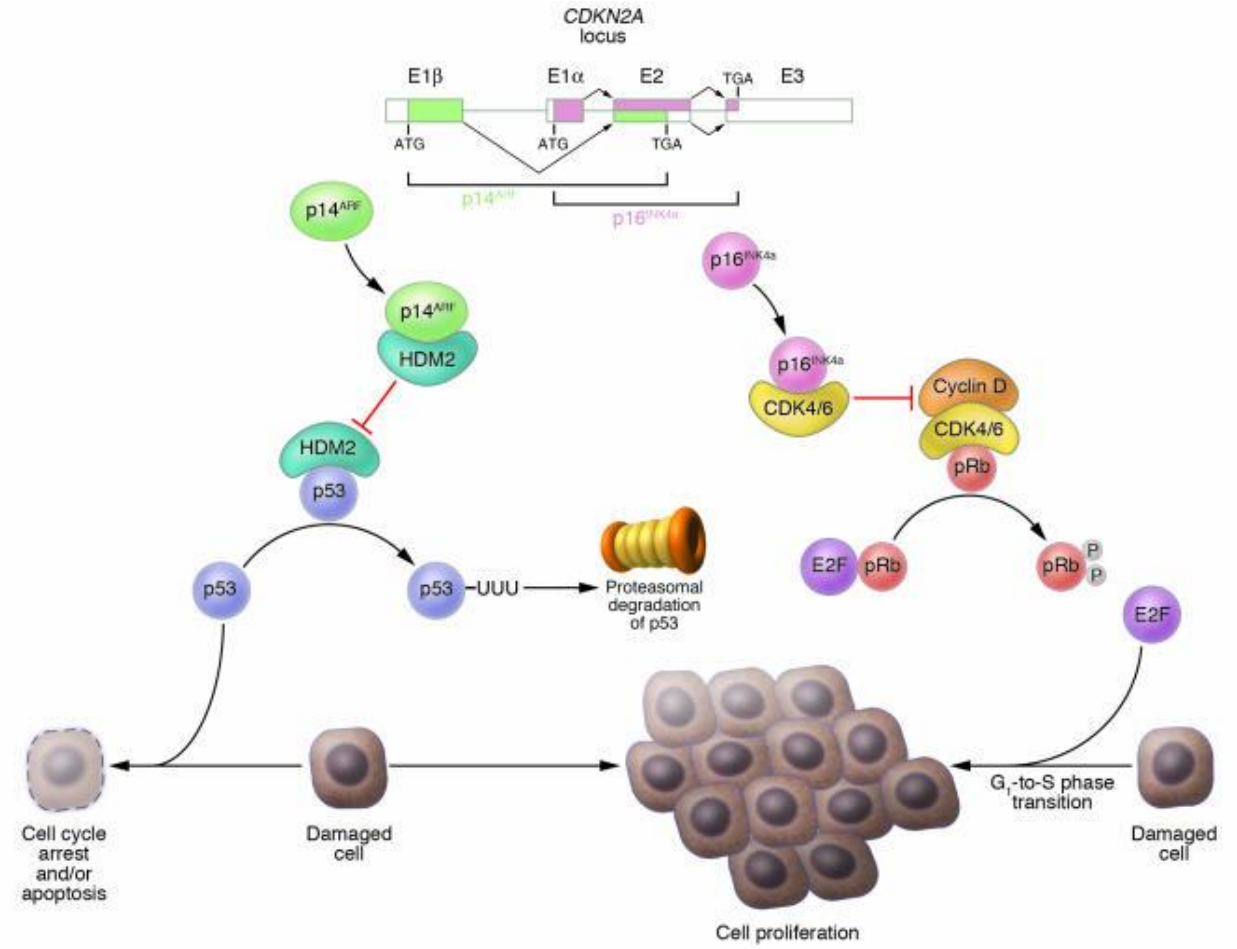
Evading growth suppressors

- Cancers typically inactivate the Rb and p53 pathways
- In normal cells, the Rb pathway is inhibited by growth factor receptors and activated by certain growth-inhibitory cytokines (TGFβ)
- Cancers lose TGFβ responsiveness by acquiring mutations in TGFβ receptors, downstream signal transduction components (SMAD4), or the Rb pathway itself (p16, Rb)
- Cancers lose p53 function by inactivating p53 itself (point mutations, deletions), by amplifying its inhibitor (MDM2), and by silencing p53's effector, p21 (DNA methylation)

Control of Rb function



Functions of p14ARF and p16



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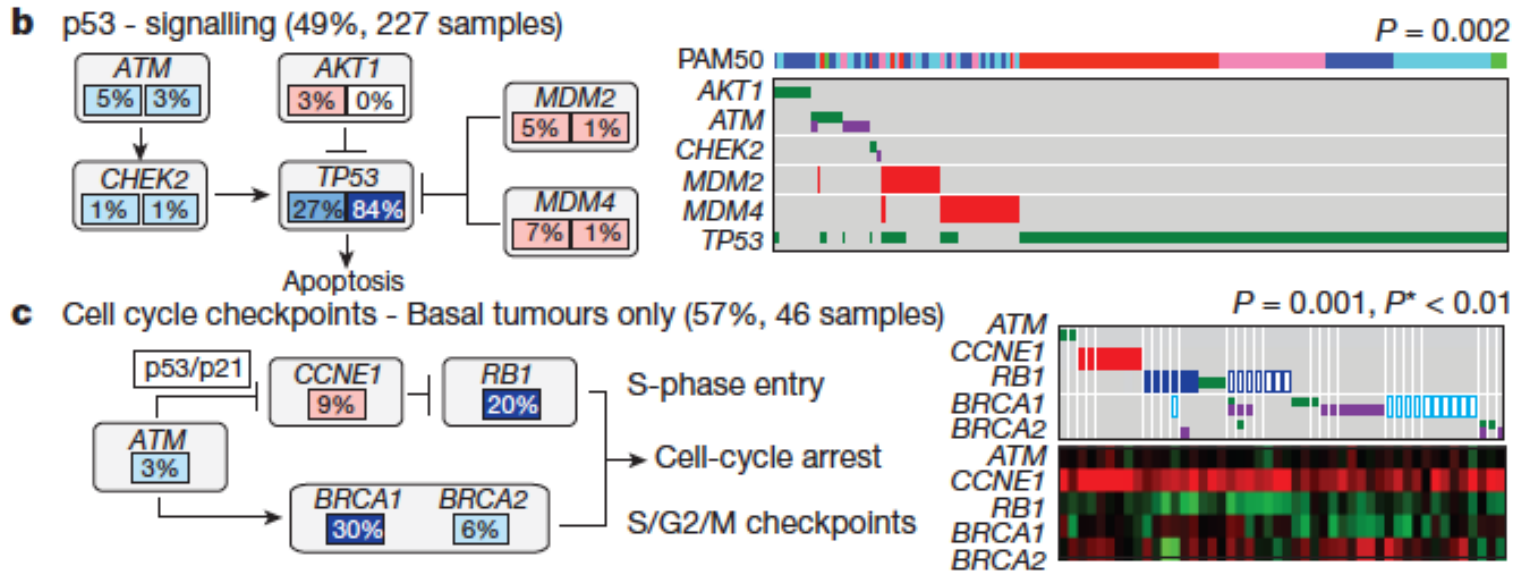
doi:10.1038/nature11412

Comprehensive molecular portraits of human breast tumours

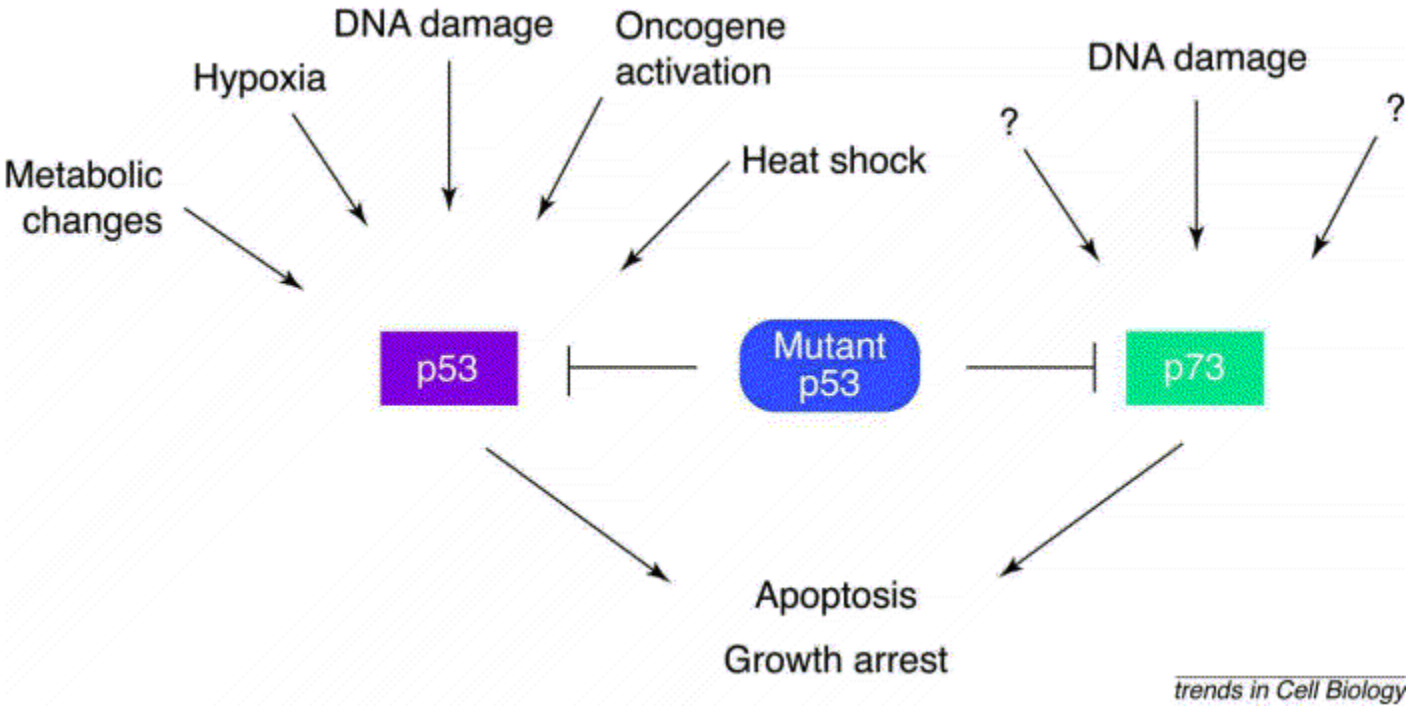
The Cancer Genome Atlas Network*



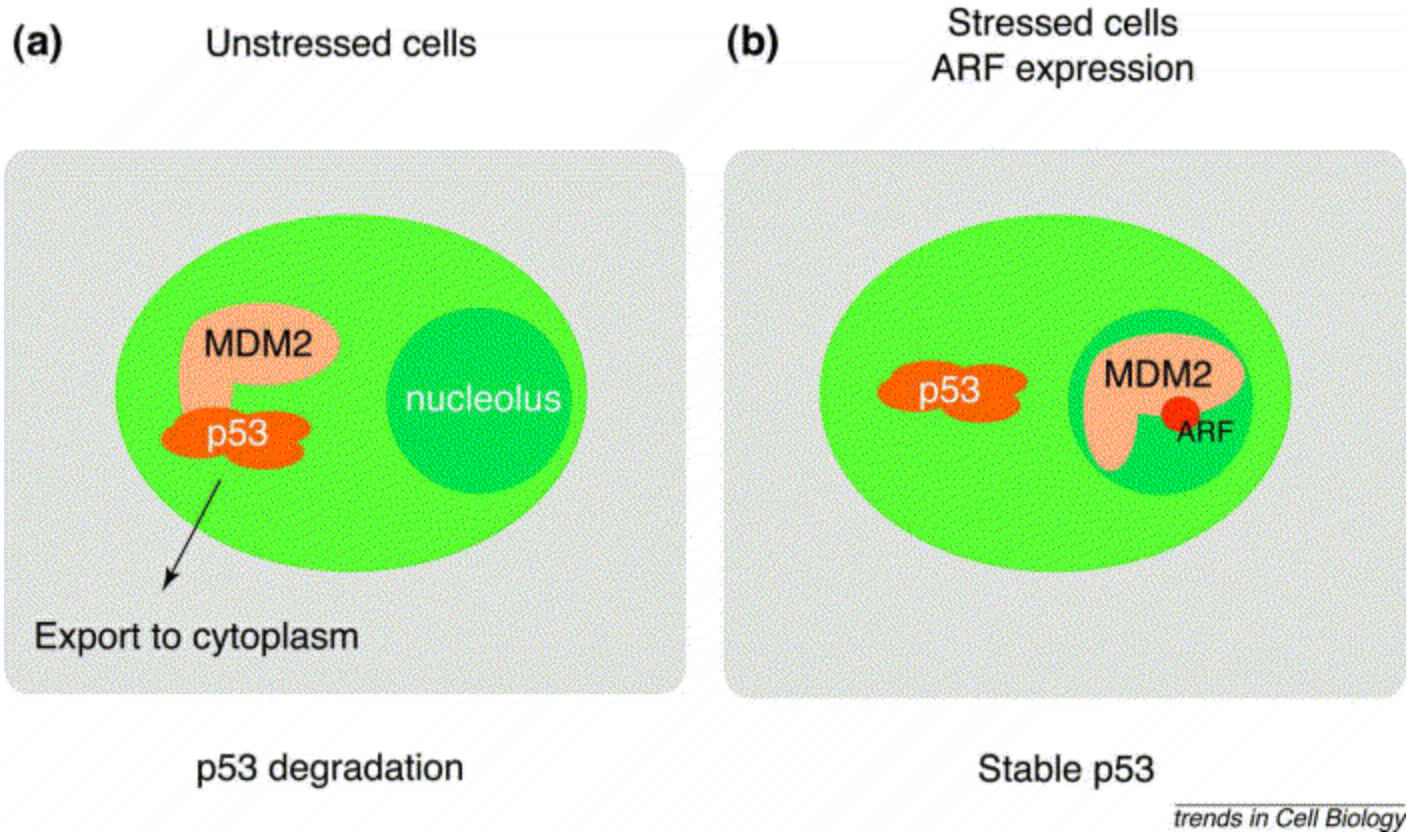
Evading apoptosis

- p53 promotes apoptosis in some normal (especially hematopoietic) cells
- Loss of p53 allows for evasion of apoptosis
- AKT pathway activation – blocks apoptosis induced by growth factor withdrawal
- Exiting the cell cycle ***(quiescence)*** also promotes apoptosis resistance
- ***Autophagy***: can sustain quiescent cells for long periods when nutrients and oxygen are scarce

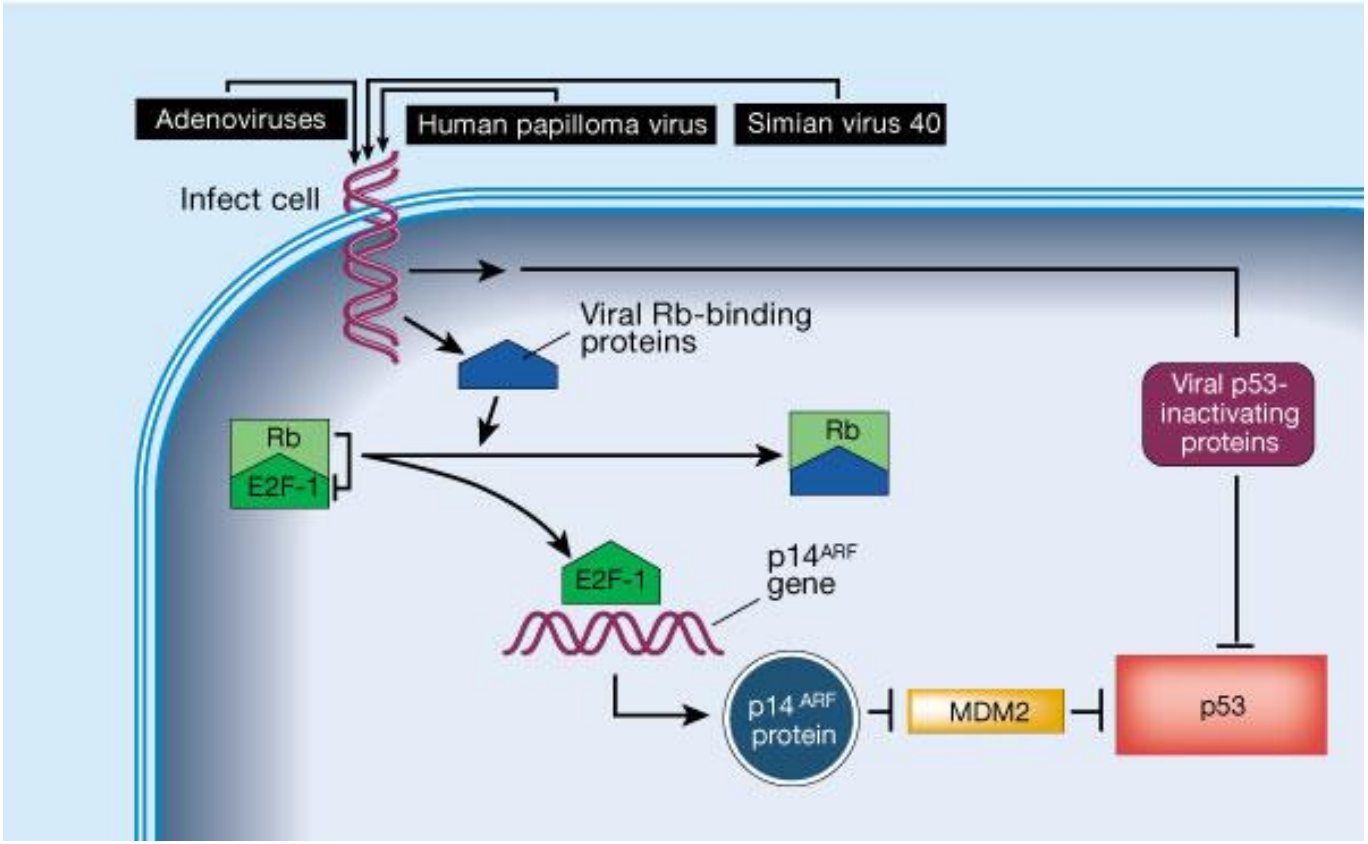
Many stimuli activate p53



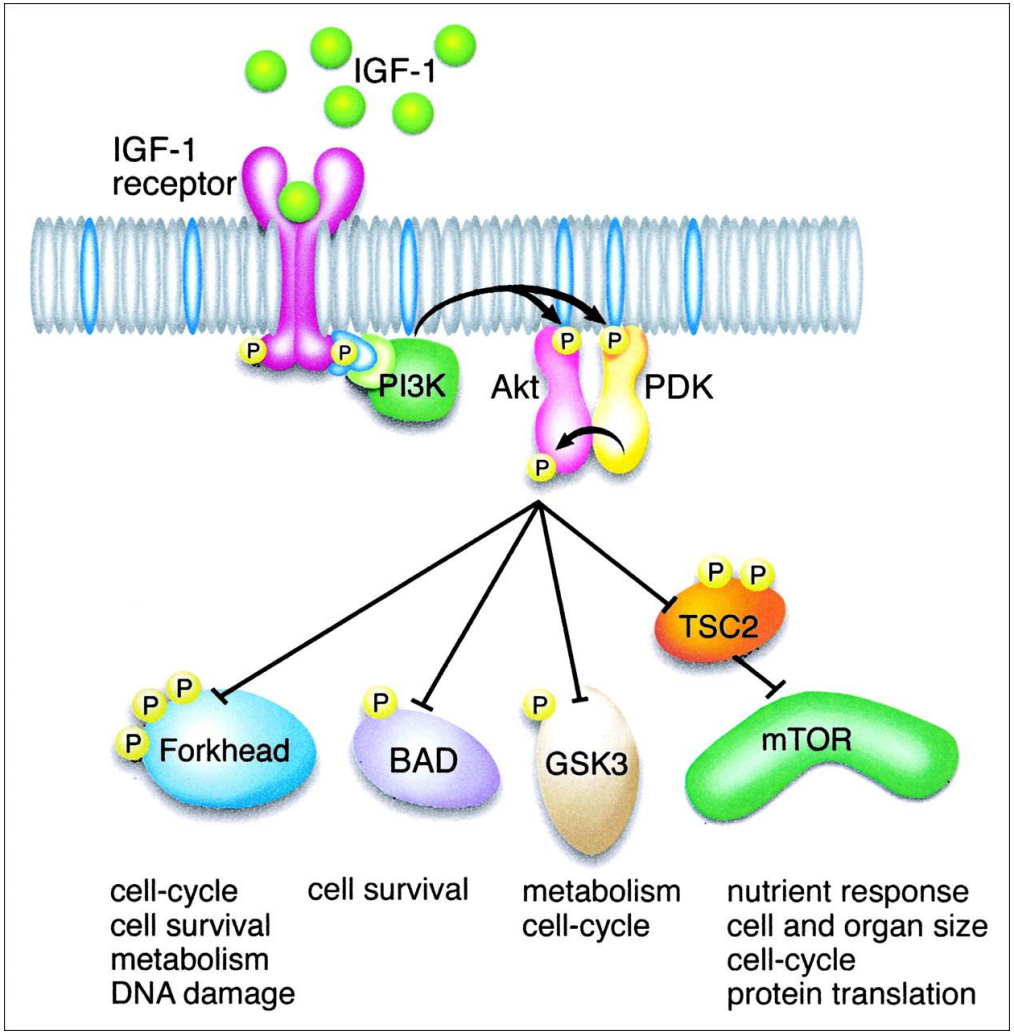
Control of p53 by MDM-2 and p14ARF



Viral disruption of p53 pathway regulation



Binding of growth factor ligands activates kinase receptors leading to recruitment of PI3K to receptor complex

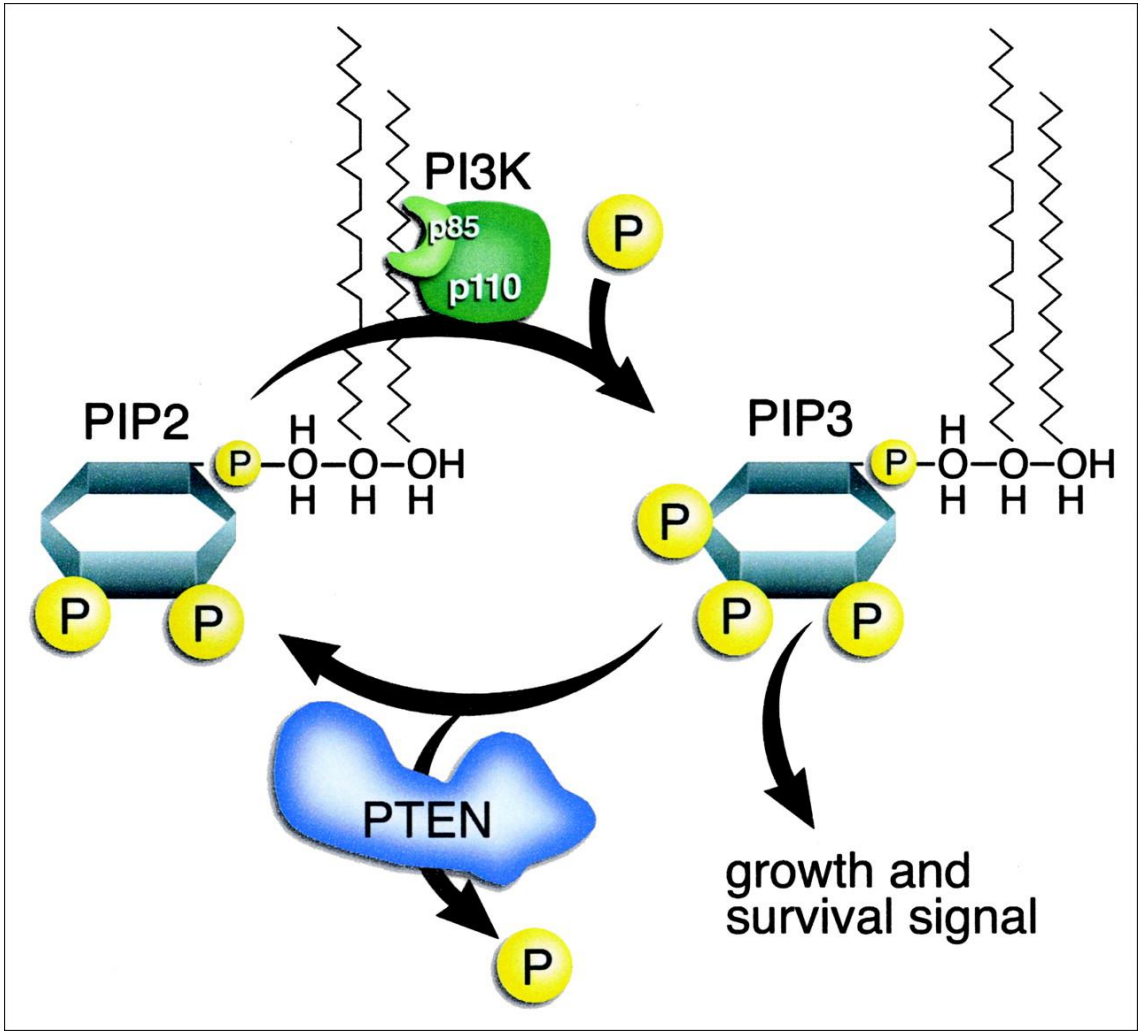


Sansal, I. et al. J Clin Oncol; 22:2954-2963 2004

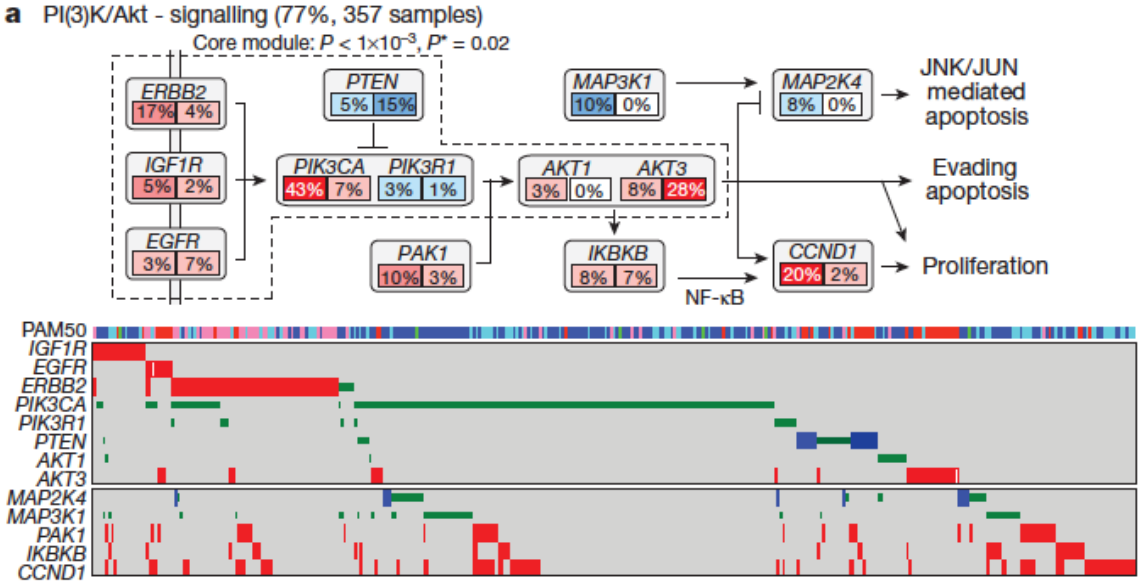
The AKT pathway is negatively regulated by PTEN

- PTEN = phosphatase on chromosome 10
- Also known as MMAC = mutated in multiple adenocarcinomas
- Lipid phosphatase

PTEN (blue), a lipid phosphatase



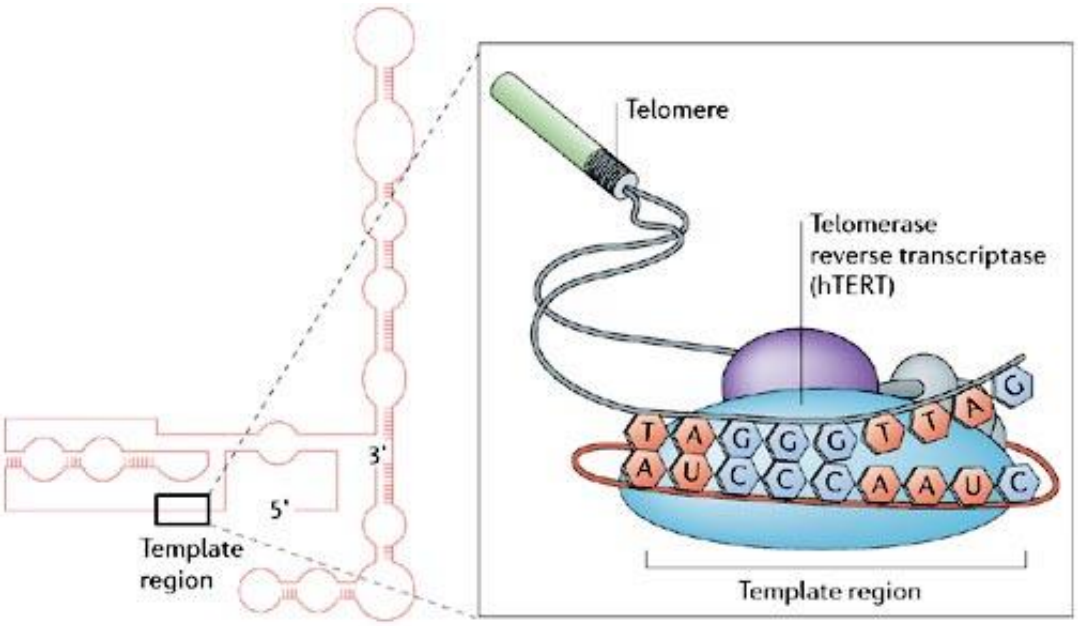
Sansal, I. et al. J Clin Oncol; 22:2954-2963 2004


a PI(3)K/Akt - signalling (77%, 357 samples)
Core module: P < 1×10−3, P* = 0.02
ERBB2 17% 4%
IGF1R 5% 2%
EGFR 3% 7%
PTEN 5% 15%
PIK3CA 43% 7%
PIK3R1 3% 1%
PAK1 10% 3%
MAP3K1 10% 0%
AKT1 3% 0%
AKT3 8% 28%
IKBKB 8% 7%
MAP2K4 8% 0%
CCND1 20% 2%
NF-κB
JNK/JUN mediated apoptosis
Evading apoptosis
Proliferation
PAM50
IGF1R
EGFR
ERBB2
PIK3CA
PIK3R1
PTEN
AKT1
AKT3
MAP2K4
MAP3K1
PAK1
IKBKB
CCND1

Limitless replicative potential

- Hayflick: First recognized that mammalian cells contain an in-built mechanism to limit proliferative potential
- It is now known that the erosion of telomeres is responsible for this phenomenon
- Tumor cells ultimately reach a stage of “crisis” and will undergo mitotic catastrophe if telomere length is not maintained
- Strategies: increase expression of telomerase (85-90%), acquire ALT/recombination-based mechanism

Structure of telomerase



TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal

Patrick J. Killela[a,1], Zachary J. Reitman[a,1], Yuchen Jiao[b,1], Chetan Bettegowda[b,c,1], Nishant Agrawal[b,d], Luis A. Diaz, Jr.[b], Allan H. Friedman[a], Henry Friedman[a], Gary L. Gallia[c,d], Beppino C. Giovanella[e], Arthur P. Grollman[f], Tong-Chuan He[g], Yiping He[a], Ralph H. Hruban[h], George I. Jallo[c], Nils Mandahl[i], Alan K. Meeker[h,m], Fredrik Mertens[i], George J. Netto[h,l], B. Ahmed Rasheed[a], Gregory J. Riggins[c], Thomas A. Rosenquist[f], Mark Schiffman[j], Ie-Ming Shih[h], Dan Theodorescu[k], Michael S. Torbenson[h], Victor E. Velculescu[b], Tian-Li Wang[h], Nicolas Wentzensen[j], Laura D. Wood[h], Ming Zhang[b], Roger E. McLendon[a], Darell D. Bigner[a], Kenneth W. Kinzler[b], Bert Vogelstein[b,2], Nickolas Papadopoulos[b], and Hai Yan[a,2]

Table 1. Frequency of *TERT* promoter mutations

Tumor type*	No. tumors	No. tumors mutated (%)
Chondrosarcoma	2	1 (50)
Dysembryoplastic neuroepithelial tumor	3	1 (33.3)
Endometrial cancer	19	2 (10.5)
Ependymoma	36	1 (2.7)
Fibrosarcoma	3	1 (33.3)
Glioma†	223	114 (51.1)
Hepatocellular carcinoma	61	27 (44.2)
Medulloblastoma	91	19 (20.8)
Myxofibrosarcoma	10	1 (10.0)
Myxoid liposarcoma	24	19 (79.1)
Neuroblastoma	22	2 (9)
Osteosarcoma	23	1 (4.3)
Ovarian, clear cell carcinoma	12	2 (16.6)
Ovarian, low grade serous	8	1 (12.5)
Solitary fibrous tumor (SFT)	10	2 (20.0)
Squamous cell carcinoma of head and neck	70	12 (17.1)
Squamous cell carcinoma of the cervix	22	1 (4.5)
Squamous cell carcinoma of the skin	5	1 (20)
Urothelial carcinoma of bladder	21	14 (66.6)
Urothelial carcinoma of upper urinary epithelium	19	9 (47.3)

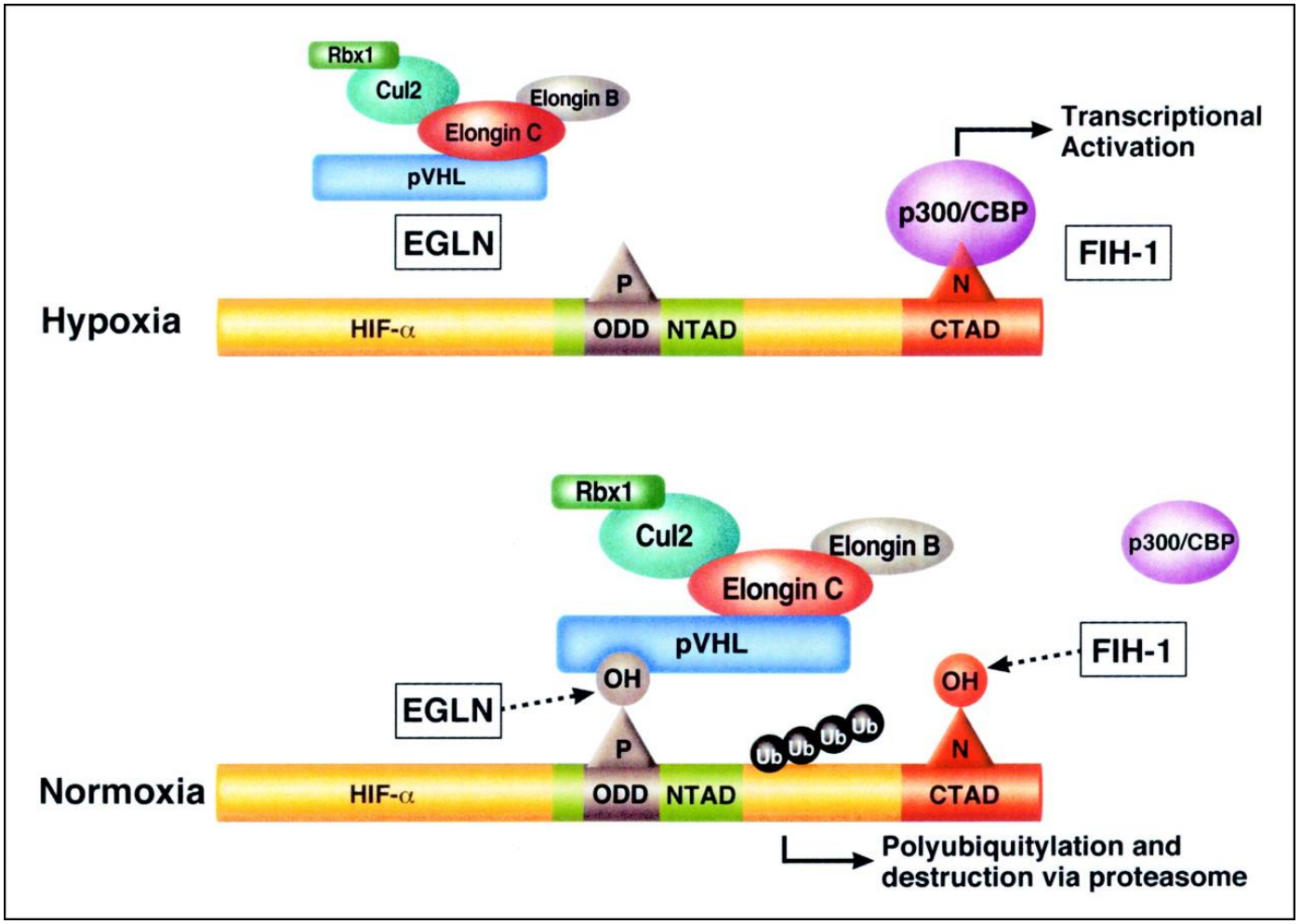
Sustained angiogenesis

- Tumors cannot grow beyond the diffusion distance of oxygen (100 μm)
- Tumor progression therefore involves an "angiogenic switch" (Hanahan), whereby tumors acquire the capacity to stimulate angiogenesis in a malregulated fashion
- Mechanisms: oncogene/growth factor activation, Von Hippel Lindau (VHL) gene inactivation in kidney cancers

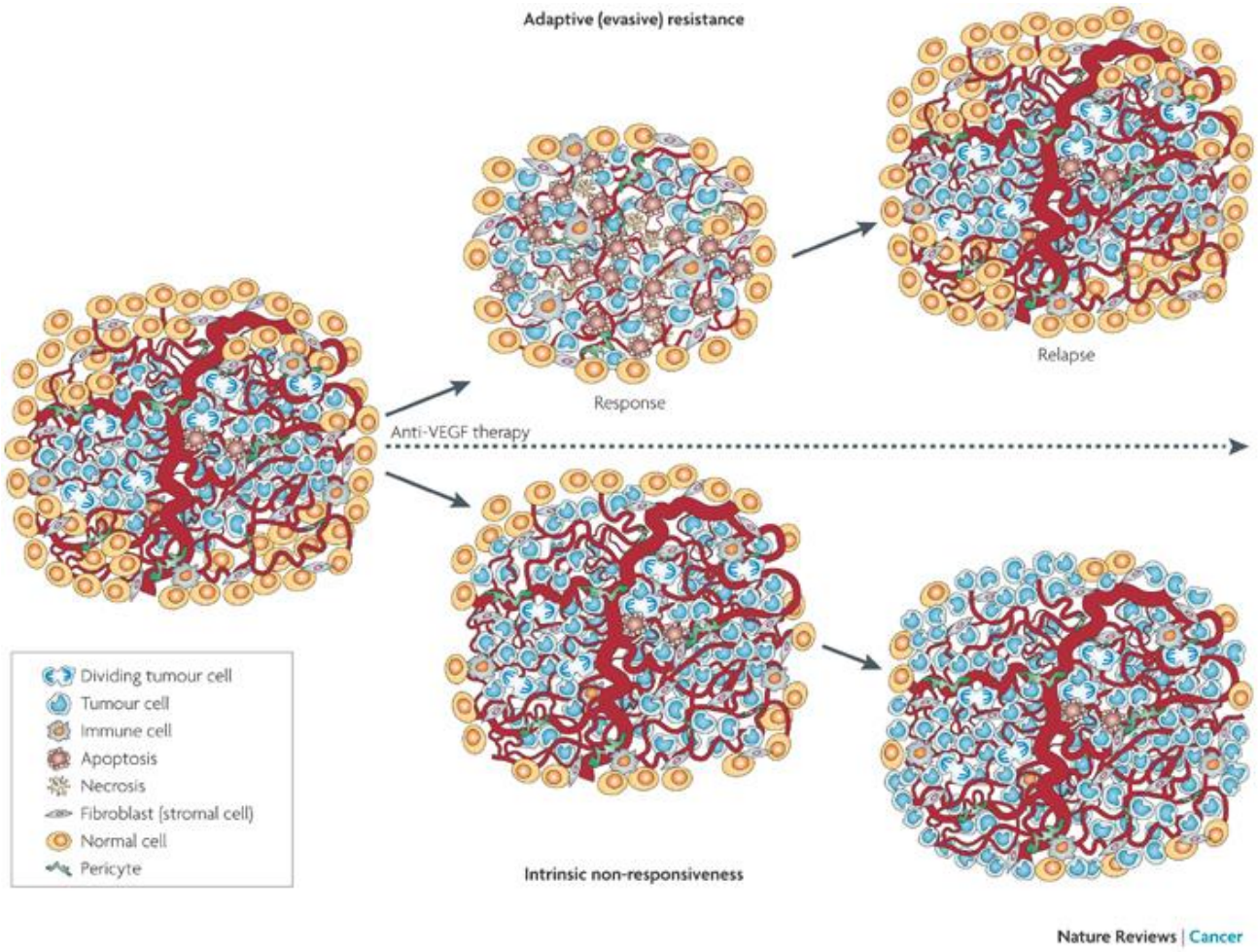
HIF-1α: A key regulator of tumor angiogenesis

- Dimerizes with another protein (ARNT) to form a hypoxia-sensitive transcription factor
- Drives expression of VEGF, TGFα, PDGF, erythropoietin
- Targeted for degradation by the VHL protein
- Kidney cancers are highly angiogenic and sensitive to inhibitors of the VEGF-VEGF receptor pathway

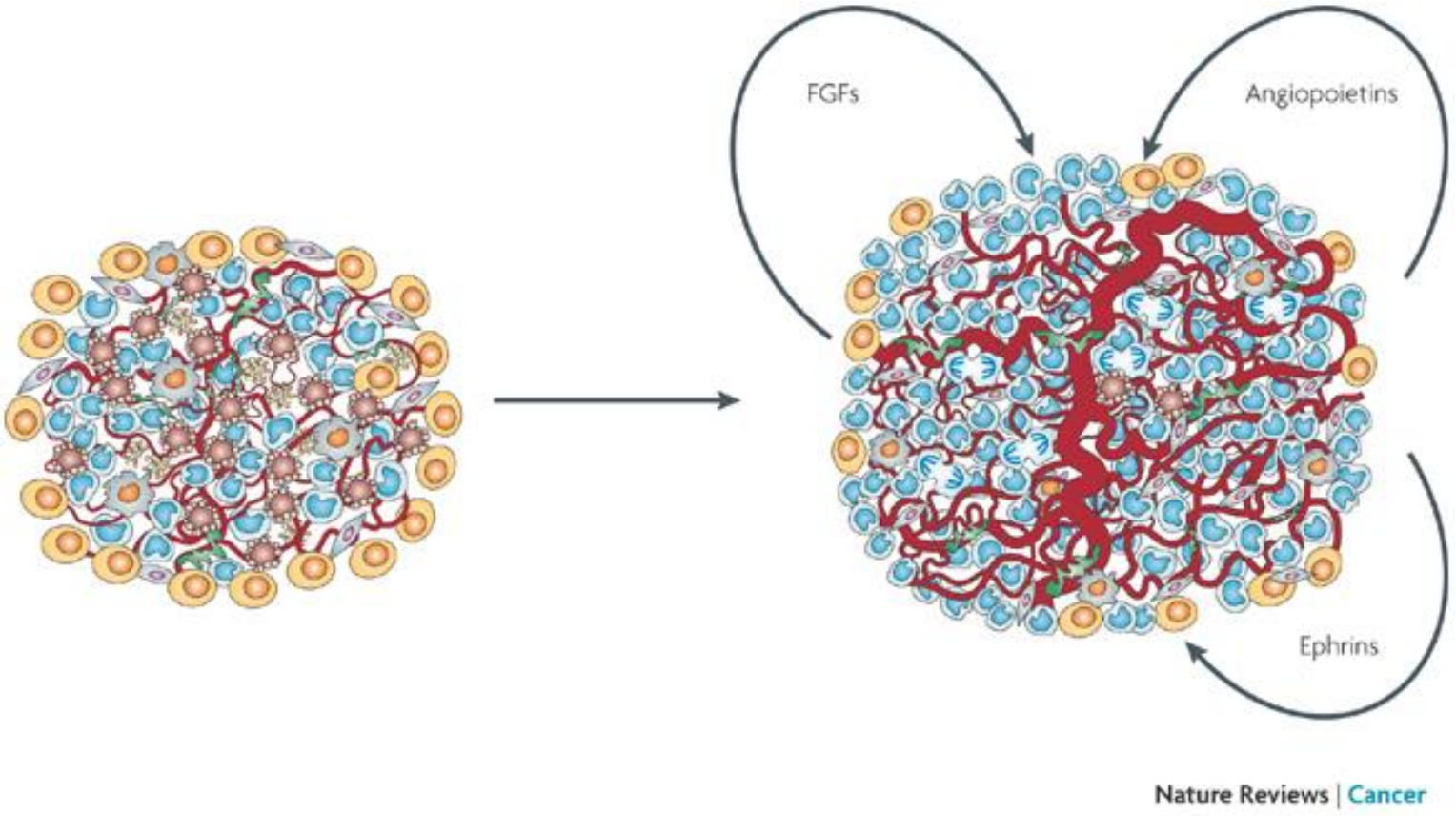
Fig 1. Regulation of hypoxia-inducible factor alpha (HIF{alpha}) by the von Hippel-Lindau tumor suppressor protein (pVHL)



Kim, W. Y. et al. J Clin Oncol; 22:4991-5004 2004



Nature Reviews Cancer ***8, 592-603 (August 2008)***



Nature Reviews Cancer ***8, 592-603 (August 2008)***

Tissue invasion and metastasis

- Shares many similarities with the process of wound healing (“tumors are wounds that don’t heal”)
- Associated with changes in the expression of of adhesion molecules (E-cadherin and integrins) and cell polarity proteins
- Increased motility and invasiveness
- Involves a process known as “epithelial-to-mesenchymal transition” (EMT)

Physiological and pathological roles of EMT

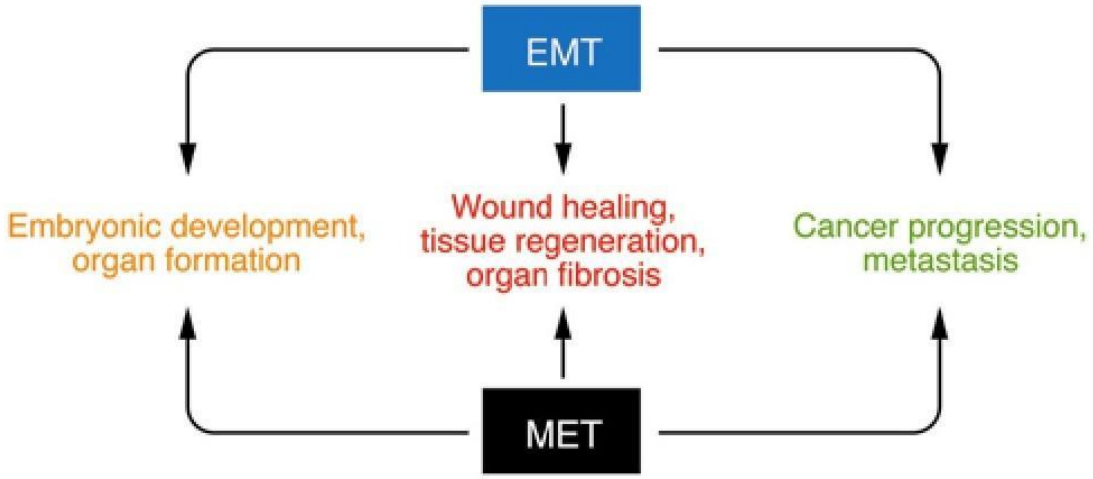


Figure 1
EMT and MET in health and disease. The evidence for EMT is compelling in embryonic development, organ formation, wound healing, tissue regeneration, organ fibrosis, cancer progression, and metastasis. The role for MET in wound healing, tissue regeneration, organ fibrosis, cancer progression, and metastasis is only speculated and rigorous evidence is still lacking.

J Clin Invest, June 1, 2009

Epithelial-to-mesenchymal transition

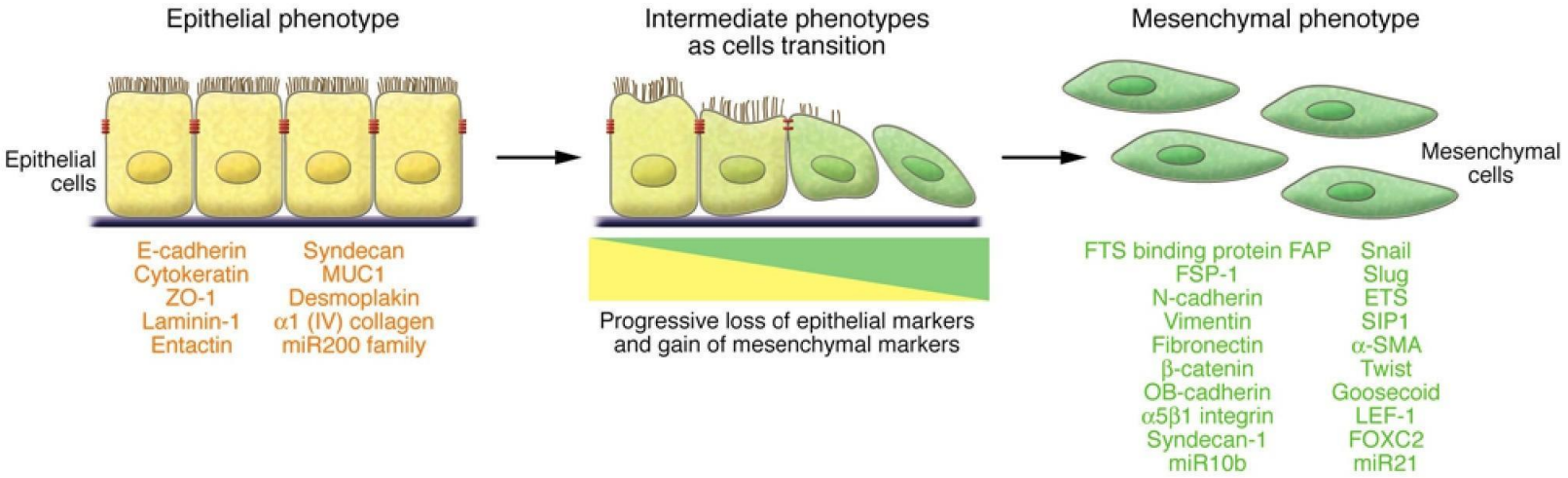


Figure 1
EMT. An EMT involves a functional transition of polarized epithelial cells into mobile and ECM component–secreting mesenchymal cells. The epithelial and mesenchymal cell markers commonly used by EMT researchers are listed. Colocalization of these two sets of distinct markers defines an intermediate phenotype of EMT, indicating cells that have passed only partly through an EMT. Detection of cells expressing both sets of markers makes it impossible to identify all mesenchymal cells that originate from the epithelia via EMT, as many mesenchymal cells likely shed all epithelial markers once a transition is completed. For this reason, most studies in mice use irreversible epithelial cell–lineage tagging to address the full range of EMT-induced changes. ZO-1, zona occludens 1; MUC1, mucin 1, cell surface associated; miR200, microRNA 200; SIP1, survival of motor neuron protein interacting protein 1; FOXC2, forkhead box C2.

J Clin Invest, June 1, 2009

Cancer Cell
Article

Spatiotemporal Regulation of Epithelial-Mesenchymal Transition Is Essential for Squamous Cell Carcinoma Metastasis

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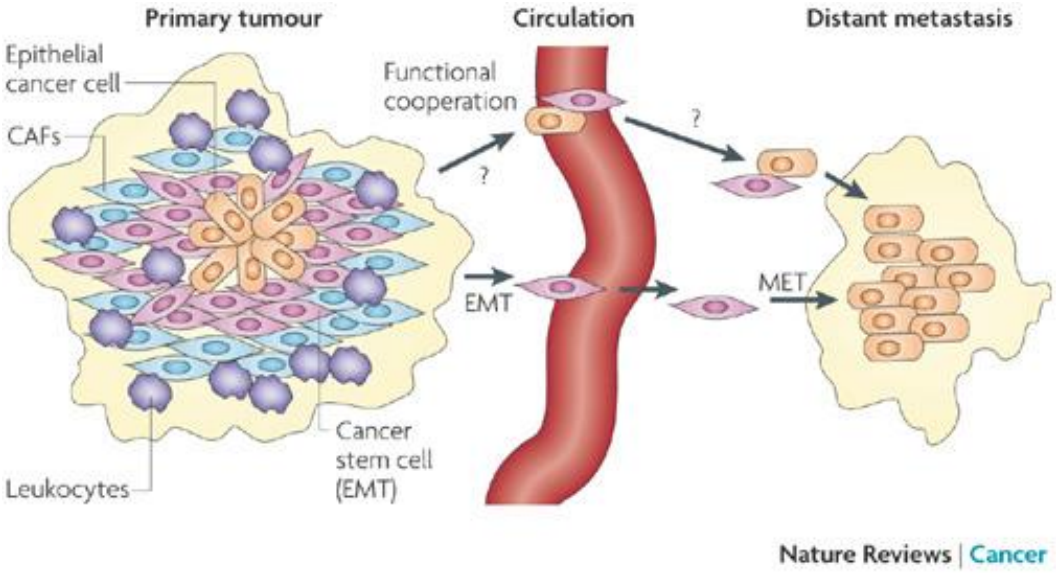
http://dx.doi.org/10.1016/j.ccr.2012.09.022

SUMMARY

Epithelial-mesenchymal transition (EMT) is implicated in converting stationary epithelial tumor cells into motile mesenchymal cells during metastasis. However, the involvement of EMT in metastasis is still controversial, due to the lack of a mesenchymal phenotype in human carcinoma metastases. Using a spontaneous squamous cell carcinoma mouse model, we show that activation of the EMT-inducing transcription factor Twist1 is sufficient to promote carcinoma cells to undergo EMT and disseminate into blood circulation. Importantly, in distant sites, turning off Twist1 to allow reversion of EMT is essential for disseminated tumor cells to proliferate and form metastases. Our study demonstrates in vivo the requirement of "reversible EMT" in tumor metastasis and may resolve the controversy on the importance of EMT in carcinoma metastasis.

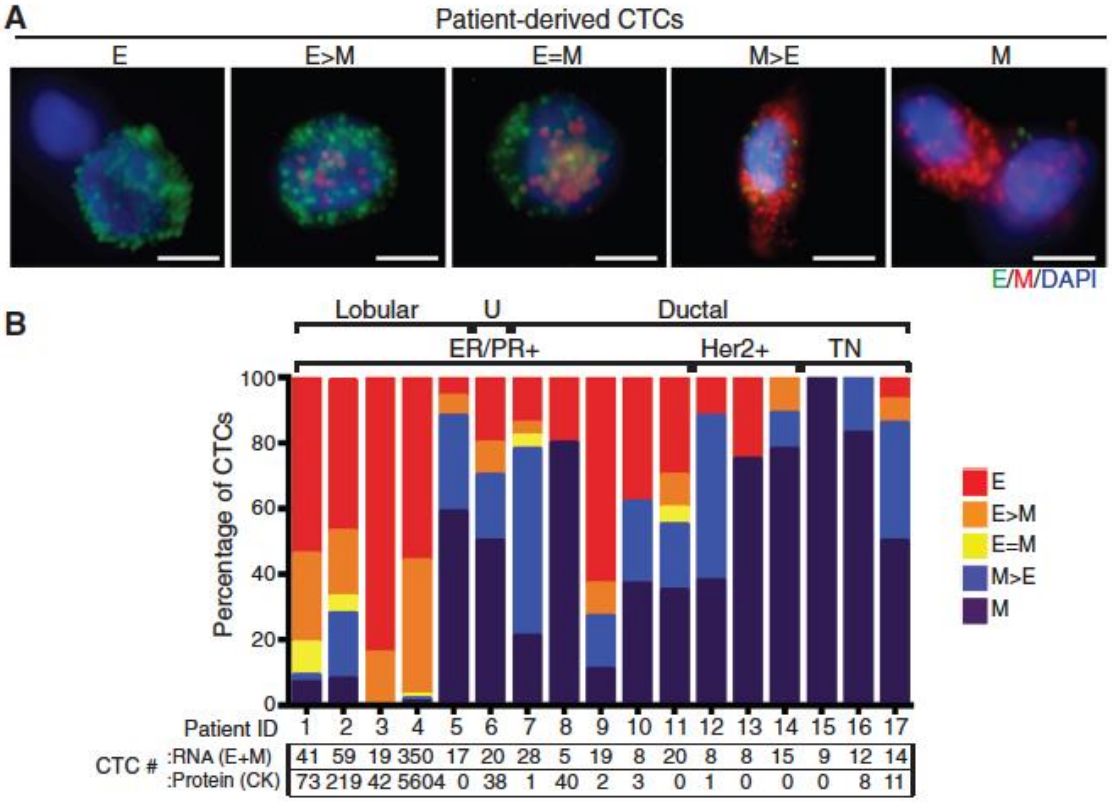
EMT-MET in metastasis



Polyak and Weinberg, Nat Rev Cancer, 2007

Circulating Breast Tumor Cells Exhibit Dynamic Changes in Epithelial and Mesenchymal Composition

Min Yu,[1,6*] Aditya Bardia,[1,3*] Ben S. Wittner,[1] Shannon L. Stott,[1,2] Malgorzata E. Smas,[1] David T. Ting,[1] Steven J. Isakoff,[1,3] Jordan C. Ciciliano,[1] Marissa N. Wells,[1] Ajay M. Shah,[2] Kyle F. Concannon,[1] Maria C. Donaldson,[1] Lecia V. Sequist,[1,3] Elena Brachtel,[1,4] Dennis Sgroi,[1,4] Jose Baselga,[1,3] Sridhar Ramaswamy,[1,3] Mehmet Toner,[2,5] Daniel A. Haber,[1,3,6]† Shyamala Maheswaran[1,5]†



Cancer Cell
Article

Direct Signaling between Platelets and Cancer Cells Induces an Epithelial-Mesenchymal-Like Transition and Promotes Metastasis

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DOI 10.1016/j.ccr.2011.09.009

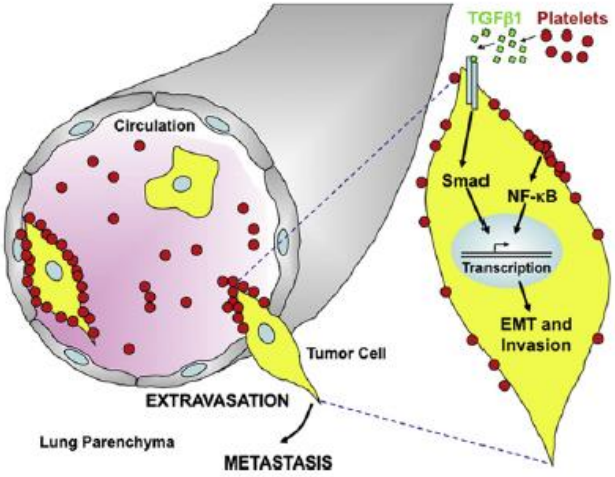
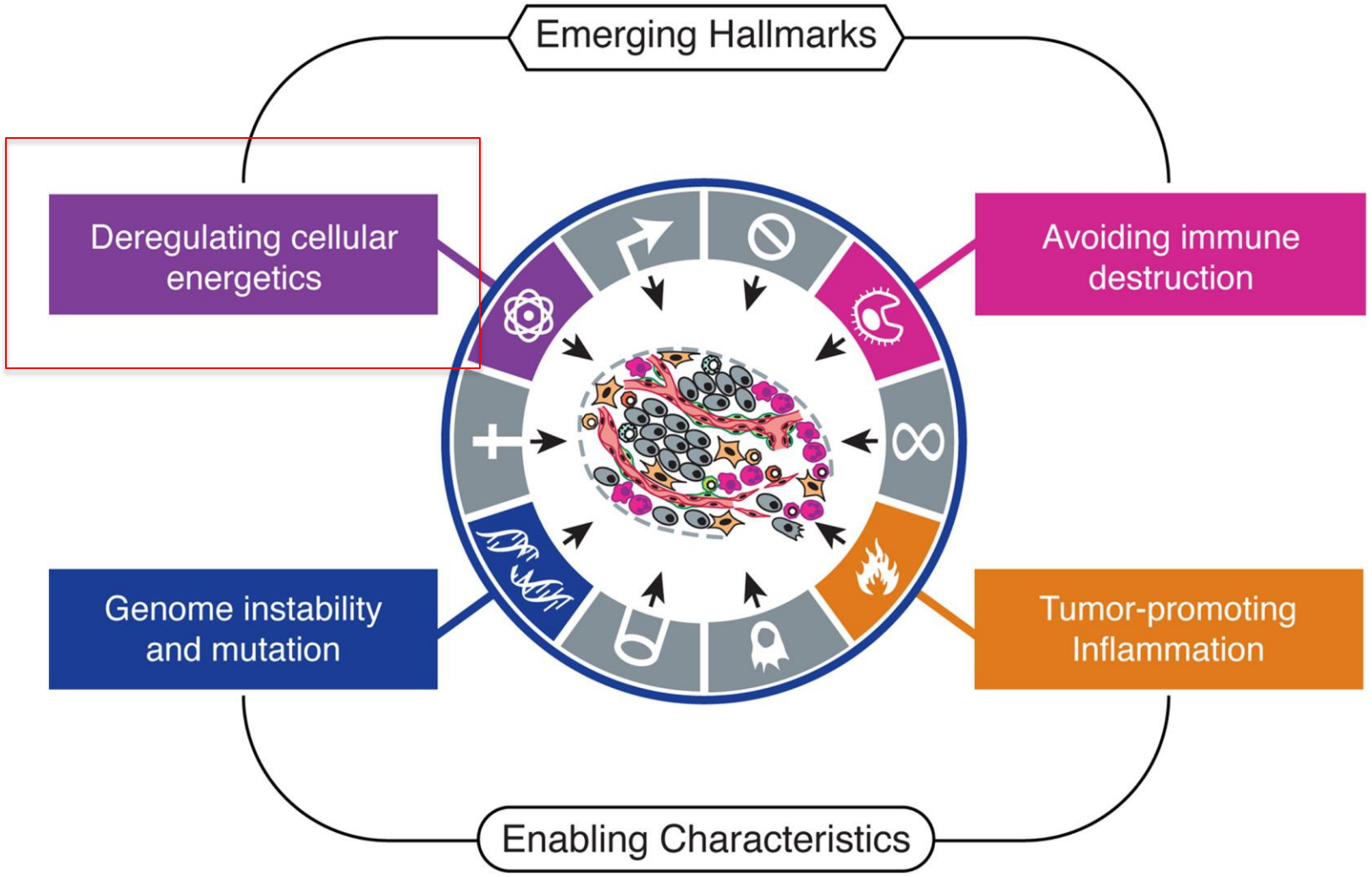


Figure 7. Platelet-Tumor Cell Contact and Platelet-Derived TGFβ1 Synergize to Promote an EMT-Like Transition and Metastasis

Platelets secrete TGFβ1, which activates the TGFβ/Smad pathway in tumor cells. Upon direct platelet-tumor cell contact, the NF-κB pathway is also activated in tumor cells and synergizes with TGFβ/Smad signaling to induce a rapid EMT, enhance invasiveness and promote metastasis. Activation of neither the TGFβ/Smad nor the NF-κB pathway alone is sufficient to promote metastasis. Thus, platelet-tumor cell contact triggers a synergistic interaction between TGFβ/Smad and NF-κB pathways that is necessary for efficient metastasis. The metastatic potential of tumor cells therefore continues to evolve outside of the primary tumor site in response to platelet-to-tumor cell signaling.


Emerging Hallmarks
Deregulating cellular energetics
Avoiding immune destruction
Genome instability and mutation
Tumor-promoting Inflammation
Enabling Characteristics

Cancers use “aerobic glycolysis”

- In terminally differentiated cells, glycolysis is used to generate ATP in response to hypoxia
- Warburg: noted that glycolysis is active in cancer cells even when oxygen is present (“Warburg effect”)
- This property of cancer is exploited in PET imaging (using fluoro-deoxyglucose, or FdG)
- Aerobic glycolysis allows cancers to upregulate biosynthetic pathways (anabolic metabolism)

Cancer Cell
Special Collection
EXCITING CANCER RESEARCH 10 YEARS OF SINCE 2002

Metabolic Reprogramming: A Cancer Hallmark Even Warburg Did Not Anticipate

Patrick S. Ward[1,2] and Craig B. Thompson[1,*]
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DOI 10.1016/j.ccr.2012.02.014

Cancer metabolism has long been equated with aerobic glycolysis, seen by early biochemists as primitive and inefficient. Despite these early beliefs, the metabolic signatures of cancer cells are not passive responses to damaged mitochondria but result from oncogene-directed metabolic reprogramming required to support anabolic growth. Recent evidence suggests that metabolites themselves can be oncogenic by altering cell signaling and blocking cellular differentiation. No longer can cancer-associated alterations in metabolism be viewed as an indirect response to cell proliferation and survival signals. We contend that altered metabolism has attained the status of a core hallmark of cancer.

Metabolic reprogramming in cancer is an active process

- Anabolic metabolism: redirecting energy to building biomolecules (DNA, proteins, lipids)
- The PI3 kinase/AKT/mTOR pathway plays a central role in this “switch”
- Cancer cells still use mitochondria for a significant fraction of their ATP production

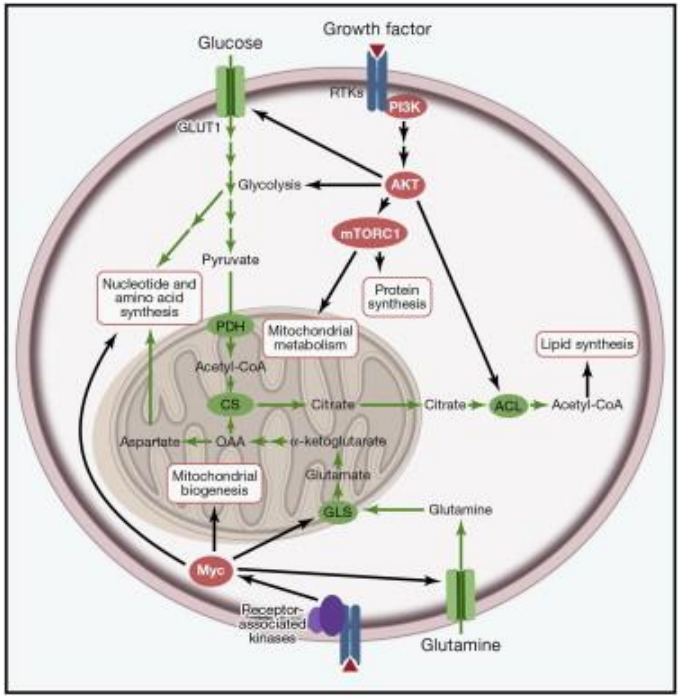

Figure 3 Alterations in Classic Oncogenes Directly Reprogram Cell Metabolism to Increase Nutrient Uptake and Biosynthesis PI3K/Akt signaling downstream of receptor tyrosine kinase (RTK) activation increases glucose uptake through the transporter GLUT1, an...

Patrick S. Ward , Craig B. Thompson

Metabolic Reprogramming: A Cancer Hallmark Even Warburg Did Not Anticipate

Cancer Cell, Volume 21, Issue 3, 2012, 297 - 308

http://dx.doi.org/10.1016/j.ccr.2012.02.014

Cancer cells display altered expression of metabolic enzymes

- Pyruvate kinase: quiescent cells express the M1 isoform, whereas proiferating cells express M2, promoting anabolic metabolism
- Isocitrate dehydrogenase-1 and -2: mutated to versions that produce a novel metabolite (2HG) that inhibits the TET family of enzymes, thereby producing epigenetic changes (i.e., histone modifications) that block differentiation

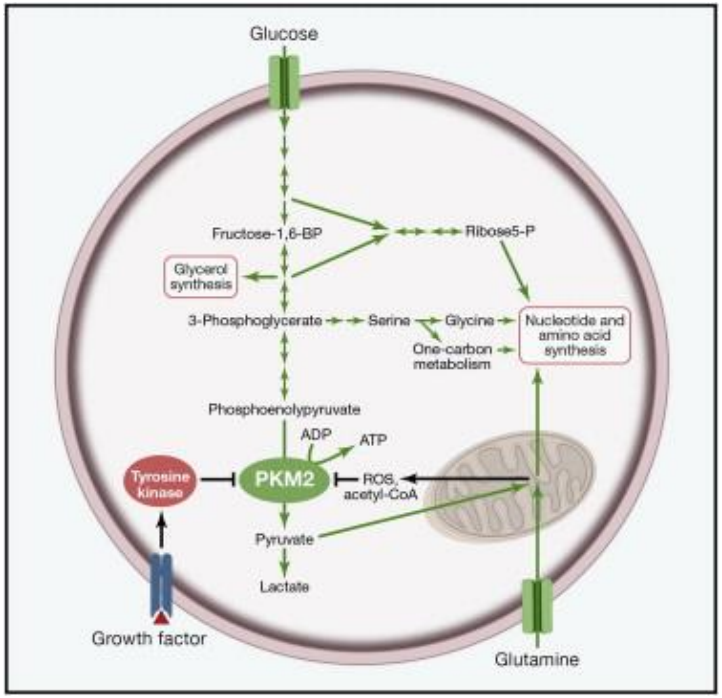

Figure 4 Pyruvate Kinase M2 Expression in Proliferating Cells Is Regulated by Signaling and Mitochondrial Metabolism to Facilitate Macromolecular Synthesis Pyruvate kinase M2 (PKM2) is a less active isoform of the terminal glycolytic enzyme pyruvate kinas...

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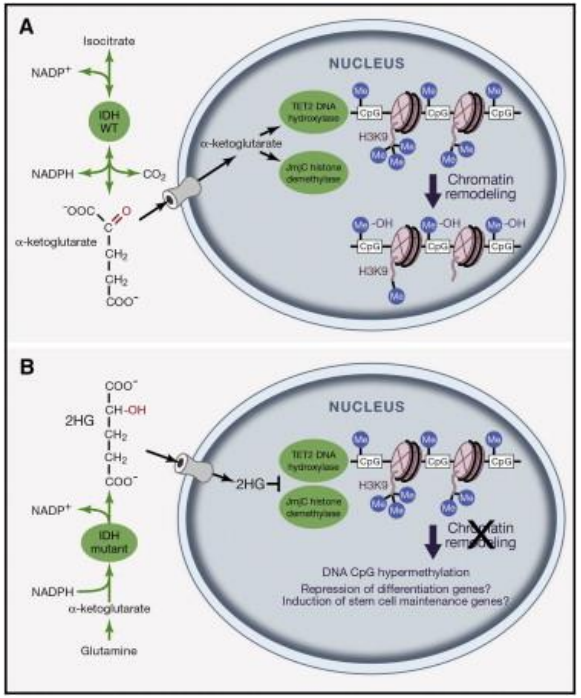

Figure 5 IDH1 and IDH2 Mutants Convert Glutamine Carbon to the Oncometabolite 2-Hydroxyglutarate to Dysregulate Epigenetics and Cell Differentiation (A) α-ketoglutarate, produced in part by wild-type isocitrate dehydrogenase (IDH), can enter the nucleus a...

Patrick S. Ward , Craig B. Thompson

Metabolic Reprogramming: A Cancer Hallmark Even Warburg Did Not Anticipate

Cancer Cell, Volume 21, Issue 3, 2012, 297 - 308

http://dx.doi.org/10.1016/j.ccr.2012.02.014

Article

Cell

Acetate Dependence of Tumors

Sarah A. Comerford,[1,7] Zhiguang Huang,[2,7] Xinlin Du,[2] Yun Wang,[2] Ling Cai,[2] Agnes K. Witkiewicz,[3] Holly Walters,[1] Mohammed N. Tantawy,[4,5] Allie Fu,[4] H. Charles Manning,[4,5,6] Jay D. Horton,[1] Robert E. Hammer,[2] Steven L. McKnight,[2,8,*] and Benjamin P. Tu[2,8,*]

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http://dx.doi.org/10.1016/j.cell.2014.11.020

Article

Cell

Acetate Is a Bioenergetic Substrate for Human Glioblastoma and Brain Metastases

Tomoyuki Mashimo,[1,2,3,11] Kumar Pichumani,[4,11] Vamsidhara Vemireddy,[1,2,3] Kimmo J. Hatanpaa,[2,3,5] Dinesh Kumar Singh,[2,3,6] Shyam Sirasanagandla,[1,2,3] Suraj Nannepaga,[2,3,6] Sara G. Piccirillo,[3,6] Zoltan Kovacs,[4] Chan Foong,[5] Zhiguang Huang,[7] Samuel Barnett,[8] Bruce E. Mickey,[2,3,8] Ralph J. DeBerardinis,[2,9,10] Benjamin P. Tu,[7] Elizabeth A. Maher,[1,2,3,6,12,*] and Robert M. Bachoo[1,2,3,6,12,*]

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http://dx.doi.org/10.1016/j.cell.2014.11.025

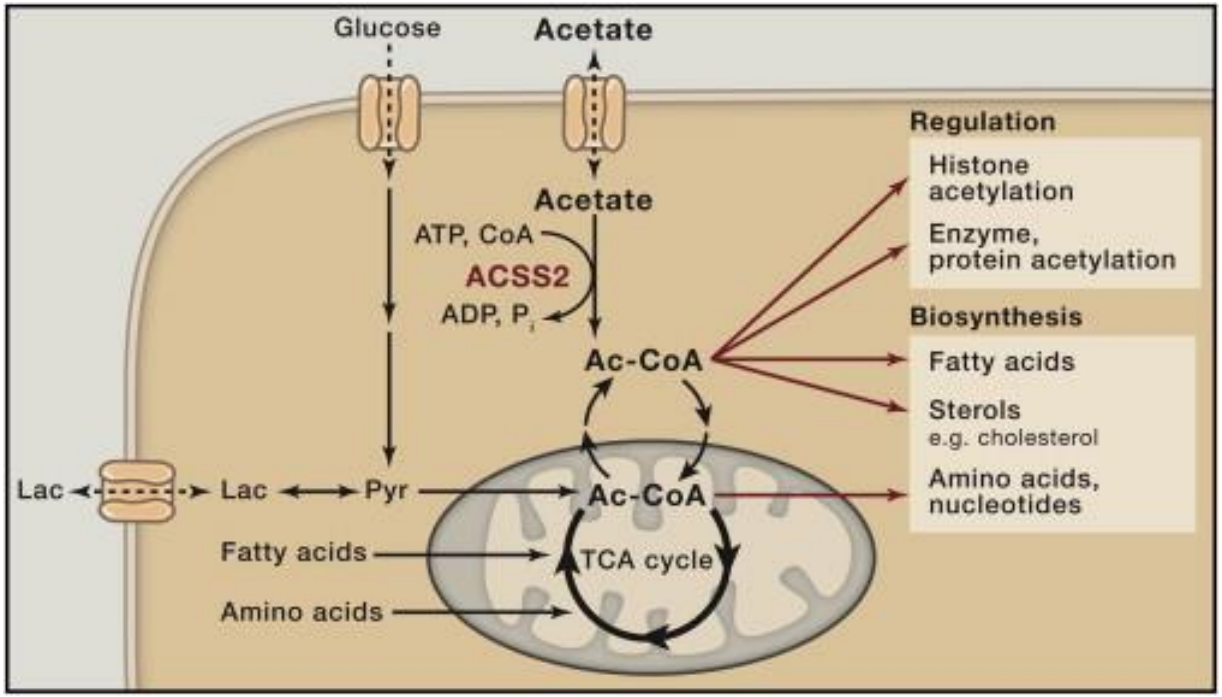


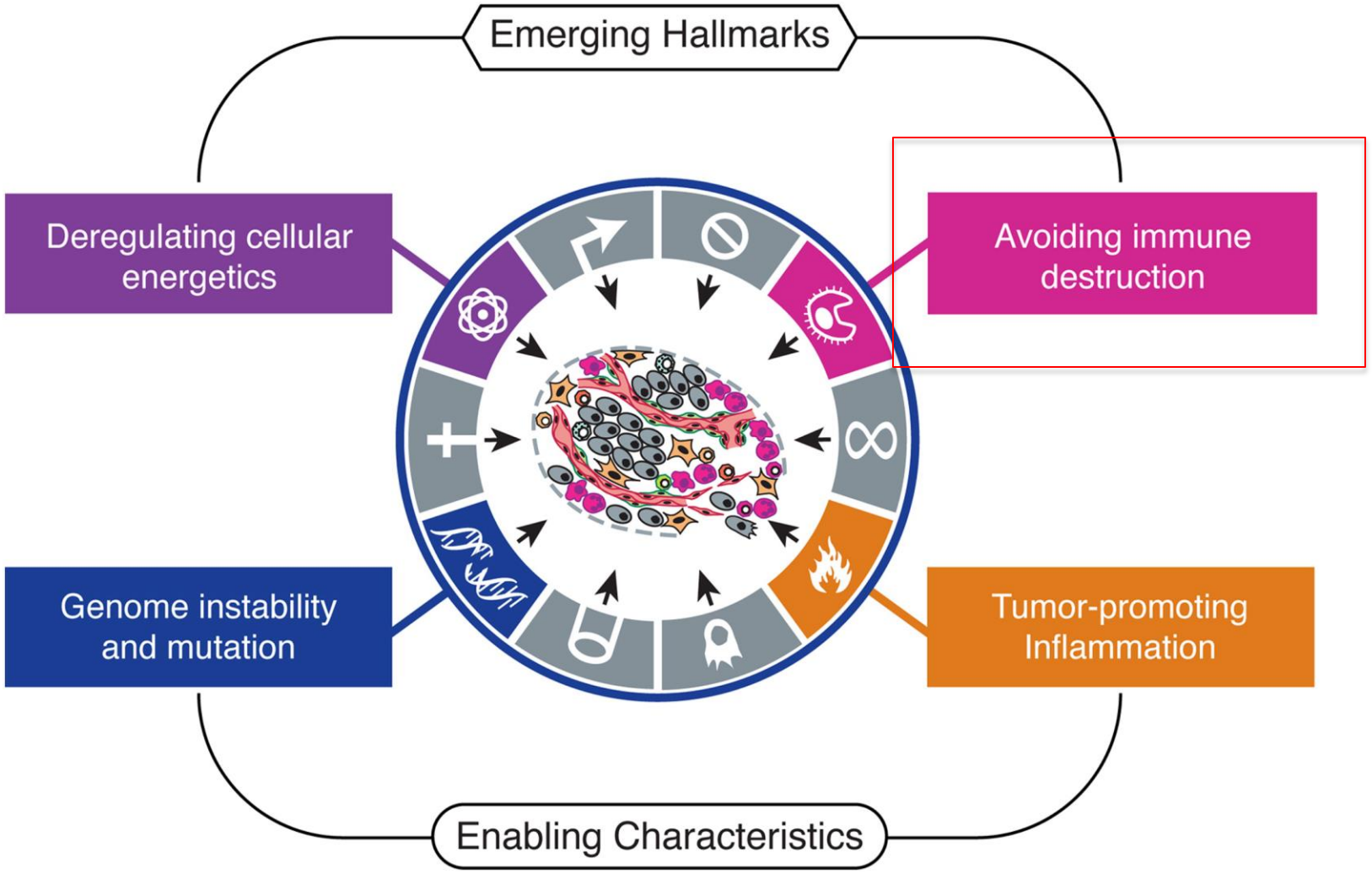
Figure 1 Acetyl-CoA Is a Central Node in Carbon Metabolism Acetyl-CoA plays numerous roles in both regulatory and biosynthetic processes. It can be added in a posttranslational fashion to histone proteins to regulate gene expression or to other proteins a...

Costas A. Lyssiotis , Lewis C. Cantley

Acetate Fuels the Cancer Engine

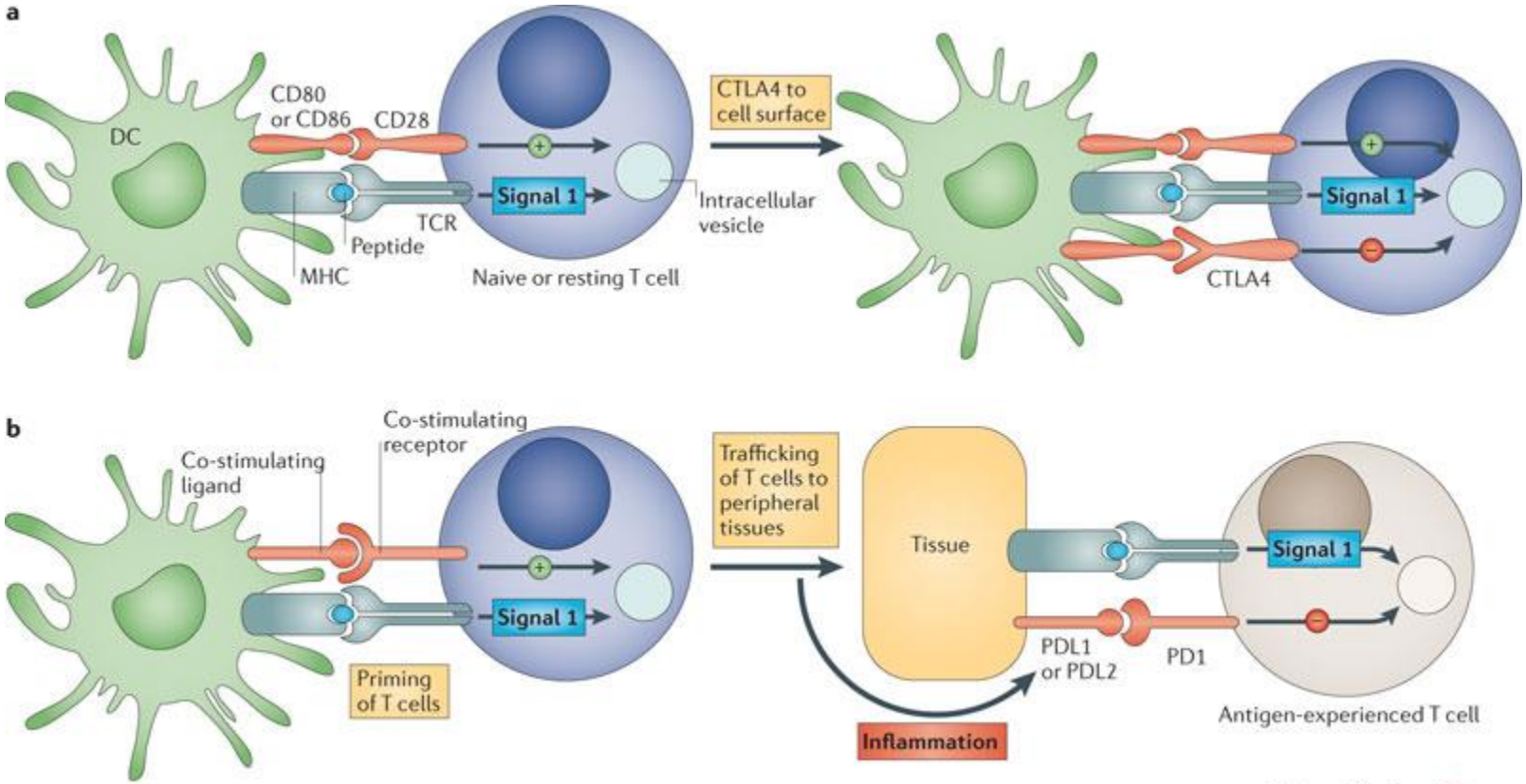
Cell, Volume 159, Issue 7, 2014, 1492 - 1494

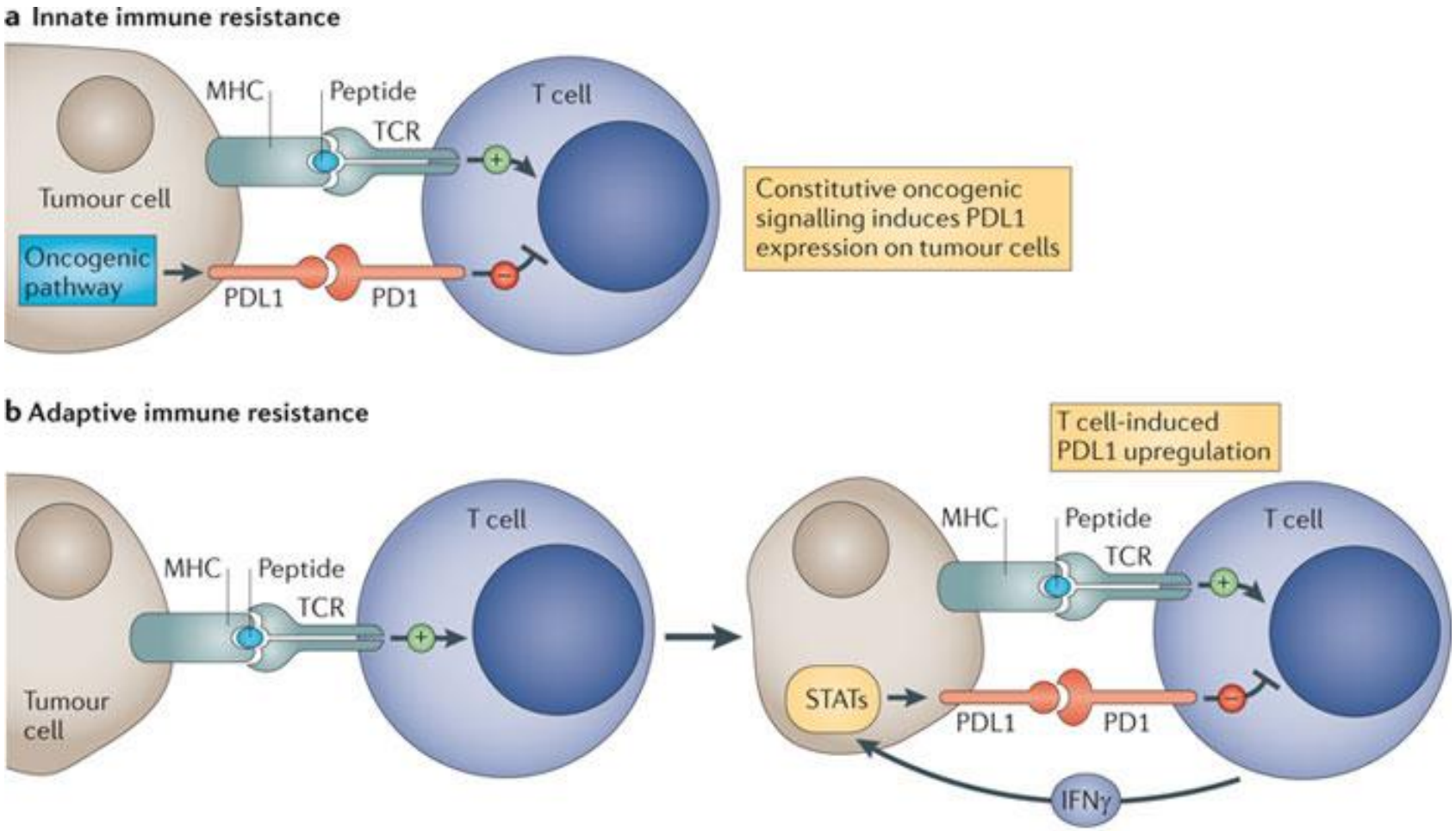
http://dx.doi.org/10.1016/j.cell.2014.12.009


Emerging Hallmarks
Deregulating cellular energetics
Avoiding immune destruction
Genome instability and mutation
Tumor-promoting Inflammation
Enabling Characteristics

Avoiding immune destruction

- Tumors co-opt physiological mechanisms that have evolved to dampen the immune response
- Involve specialized subsets of immune cells (T regulatory cells, myeloid-derived suppressor cells)
- Tumor-induced immune suppression is being aggressively targeted with novel therapies


a
DC
CD80
or CD86
CD28
TCR
Peptide
MHC
Signal 1
Naive or resting T cell
CTLA4 to
cell surface
Intracellular
vesicle
Signal 1
CTLA4
b
Co-stimulating
ligand
Co-stimulating
receptor
Signal 1
Priming
of T cells
Trafficking
of T cells to
peripheral
tissues
Tissue
Signal 1
PDL1
or PDL2
PD1
Antigen-experienced T cell
Inflammation
Nature Reviews | Cancer

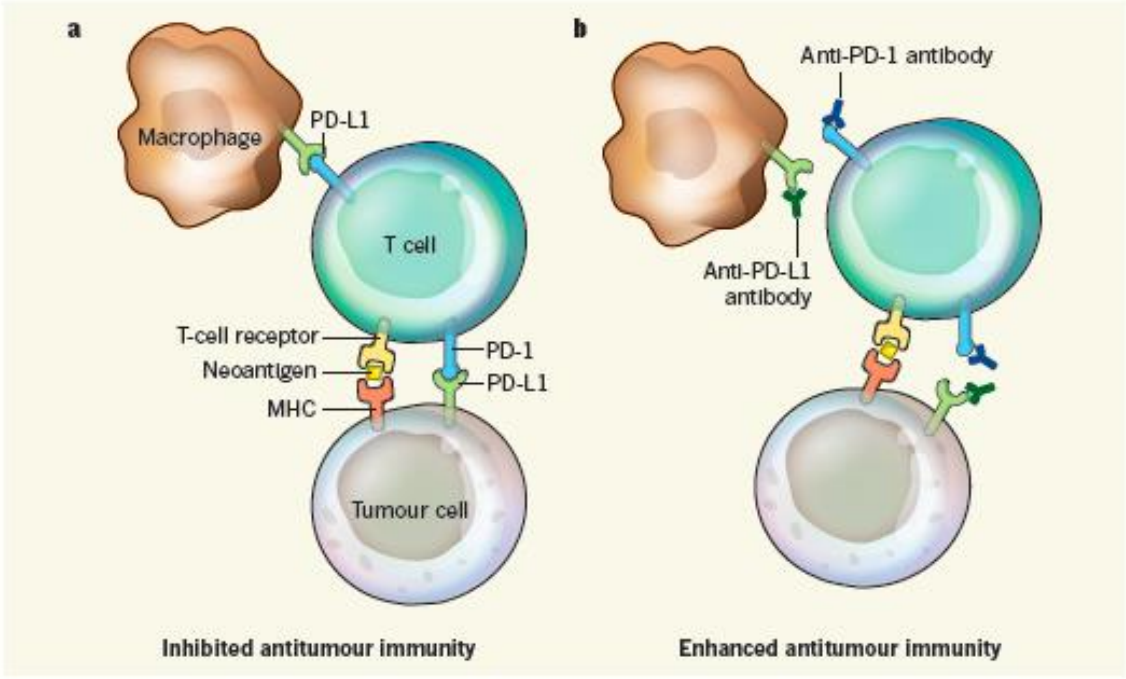

a Innate immune resistance
MHC
Peptide
TCR
T cell
Tumour cell
Oncogenic pathway
PDL1
PD1
Constitutive oncogenic signalling induces PDL1 expression on tumour cells
b Adaptive immune resistance
T cell-induced PDL1 upregulation
MHC
Peptide
TCR
T cell
Tumour cell
STATs
PDL1
PD1
IFNγ

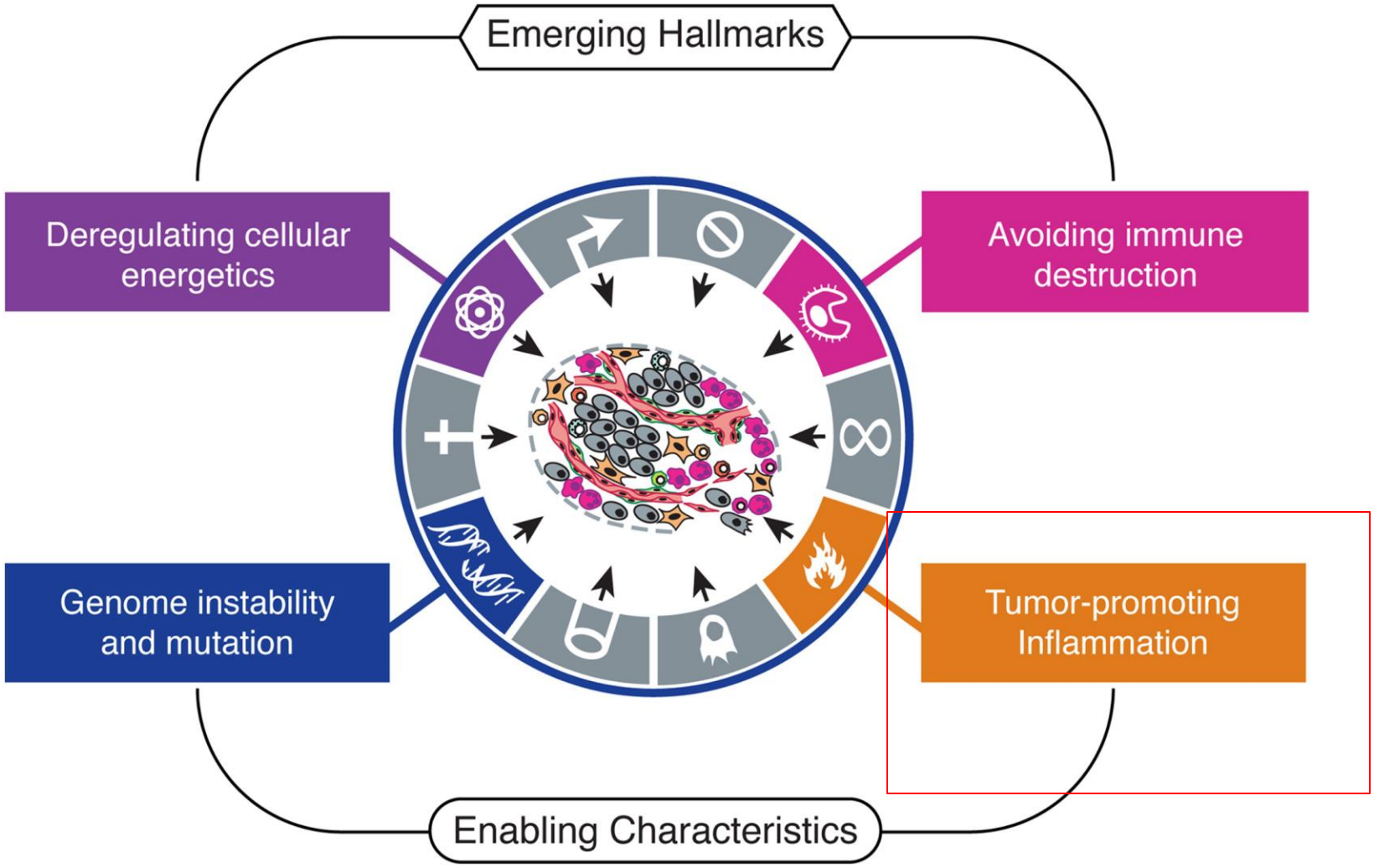
CANCER

Antitumour immunity gets a boost

Five papers extend the list of cancers that respond to therapies that restore antitumour immunity by blocking the PD-1 pathway, and characterize those patients who respond best. SEE LETTERS P.558, P.563, P.568, P.572 & P.577

JEDD D. WOLCHOK & TIMOTHY A. CHAN




Emerging Hallmarks
Deregulating cellular energetics
Avoiding immune destruction
Genome instability and mutation
Tumor-promoting Inflammation
Enabling Characteristics

Tumor-stromal interactions play a crucial role in cancer progression

- Cancer resembles the complex architecture of a tissue, containing many different types of cell
- Cancer cells co-opt the cells in their environments to promote aspects of all of the hallmarks

Developmental Cell
Review

Tumors as Organs: Complex Tissues that Interface with the Entire Organism

Mikala Egeblad,[1,*] Elizabeth S. Nakasone,[1,2] and Zena Werb[3,*]
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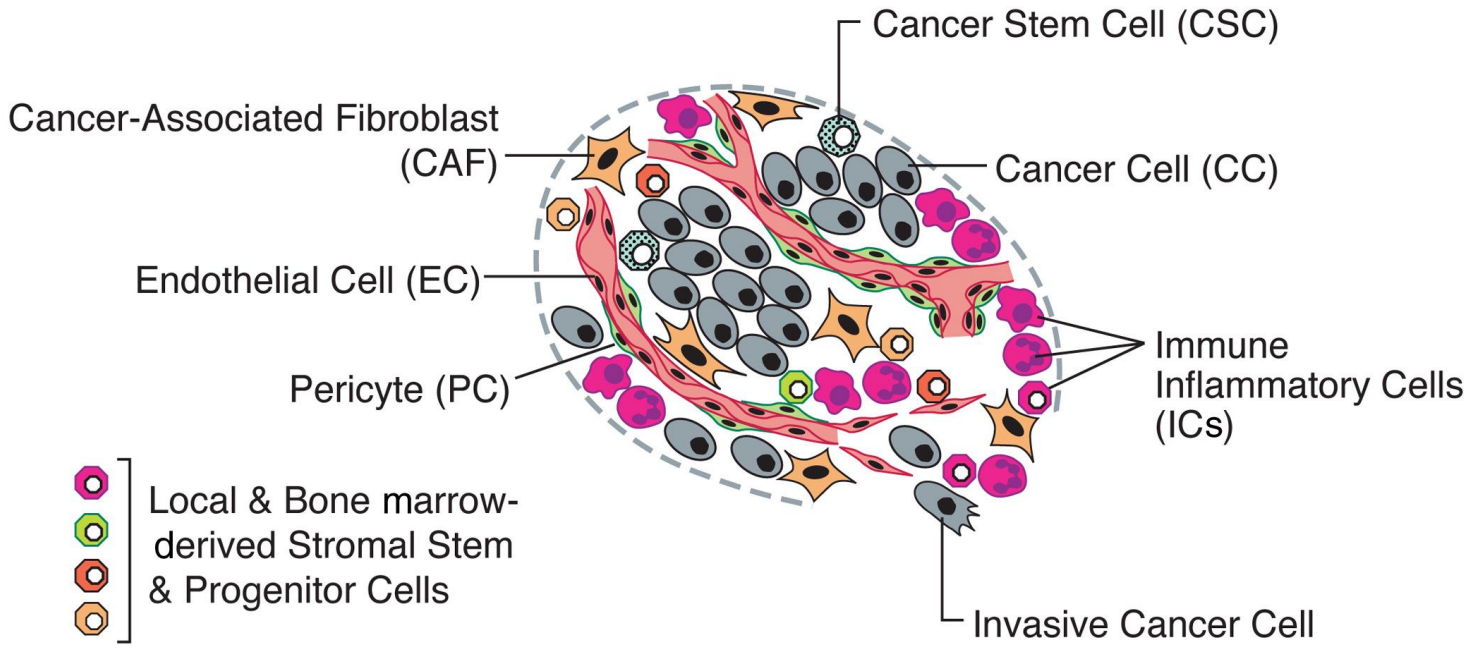
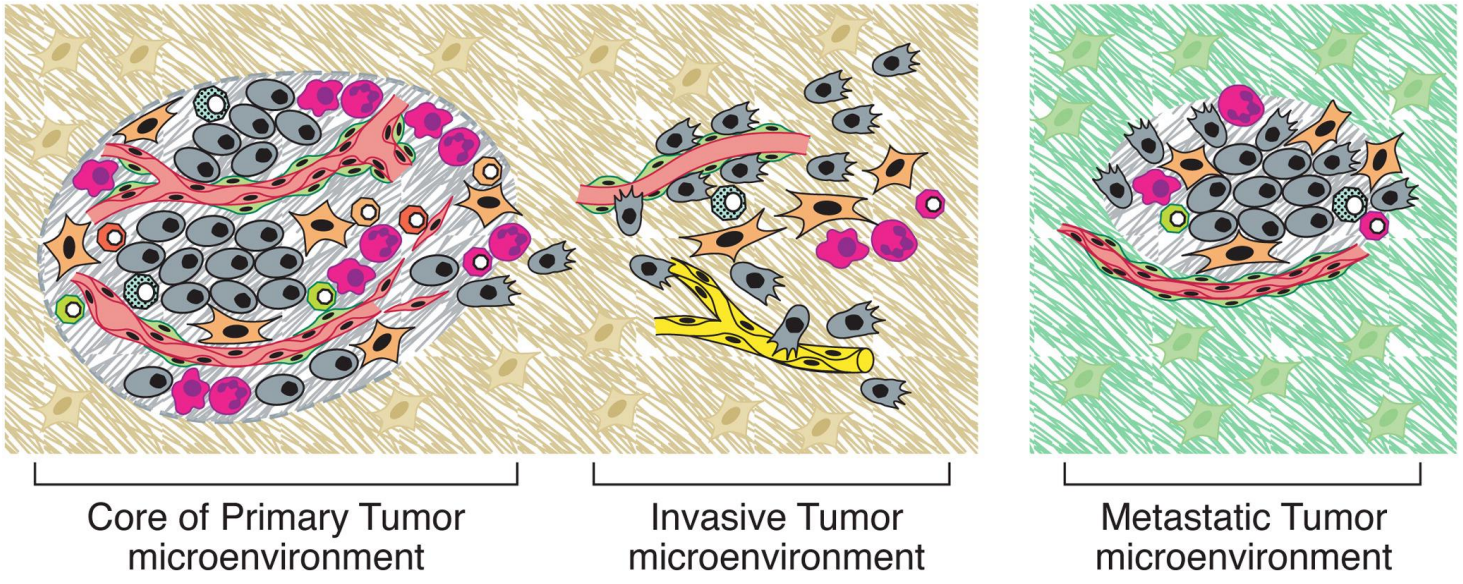
DOI 10.1016/j.devcel.2010.05.012

Stromal cells in cancer

- Endothelial cells
- Lymphocytes
- Macrophages and other cells of the innate immune system (mast cells, neutrophils, etc)
- Smooth muscle cells (pericytes, etc)
- Adipocytes (fat cells)
- Fibroblasts

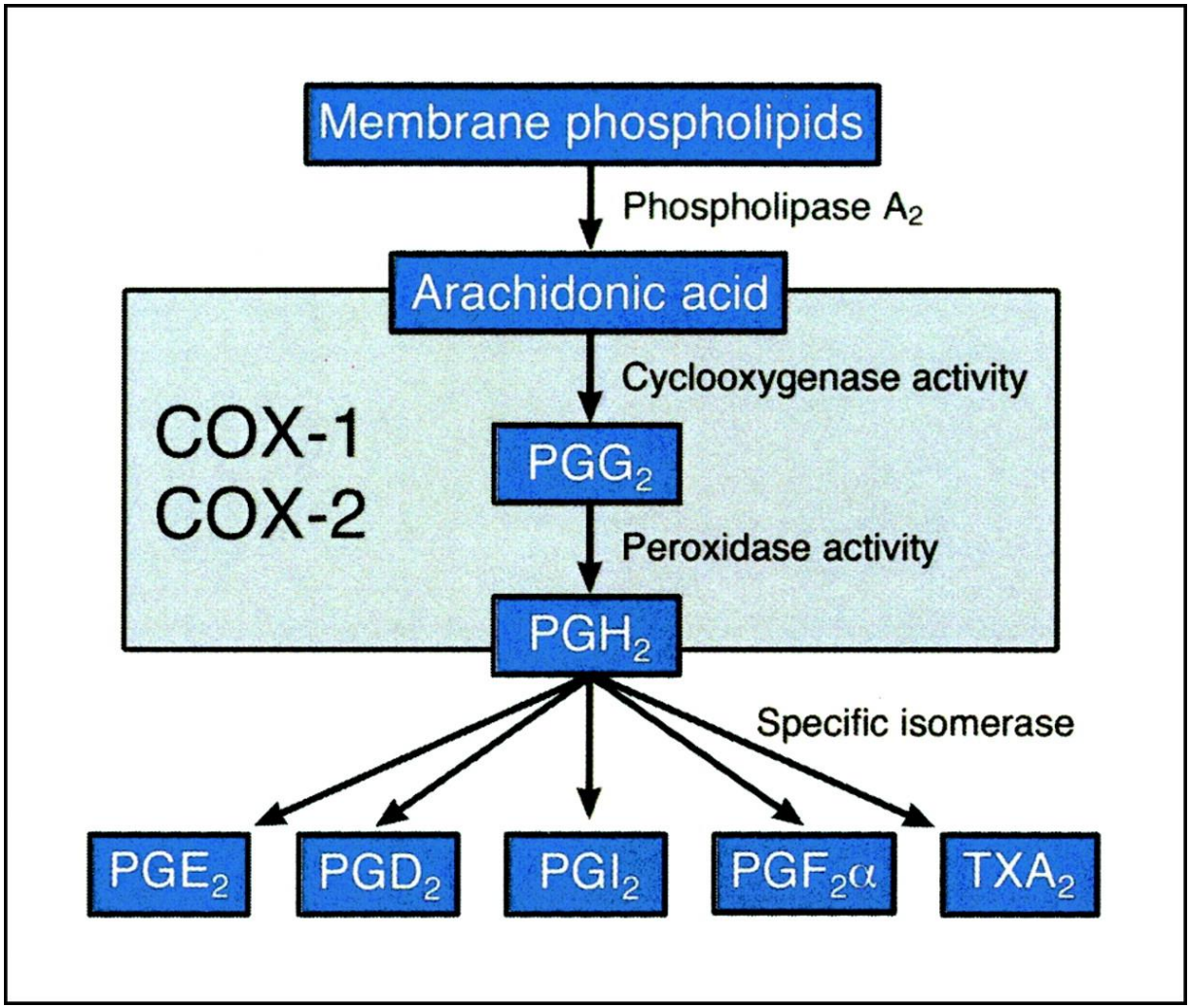

Cancer Stem Cell (CSC)
Cancer-Associated Fibroblast (CAF)
Cancer Cell (CC)
Endothelial Cell (EC)
Immune Inflammatory Cells (ICs)
Pericyte (PC)
Local & Bone marrow-derived Stromal Stem & Progenitor Cells
Invasive Cancer Cell


Core of Primary Tumor microenvironment
Invasive Tumor microenvironment
Metastatic Tumor microenvironment

Inflammation

- Acute response to injury and/or infection
- Mediated by innate immune cells (macrophages, neutrophils, etc) and fibroblasts
- Can lead to scarring or fibrosis
- Long-term (chronic) inflammation – strongly associated with cancer
- Nuclear factor kappa B (NFκB) and cyclooxygenase-2 (COX2) are key regulators

Fig 1. The arachidonic acid cascade

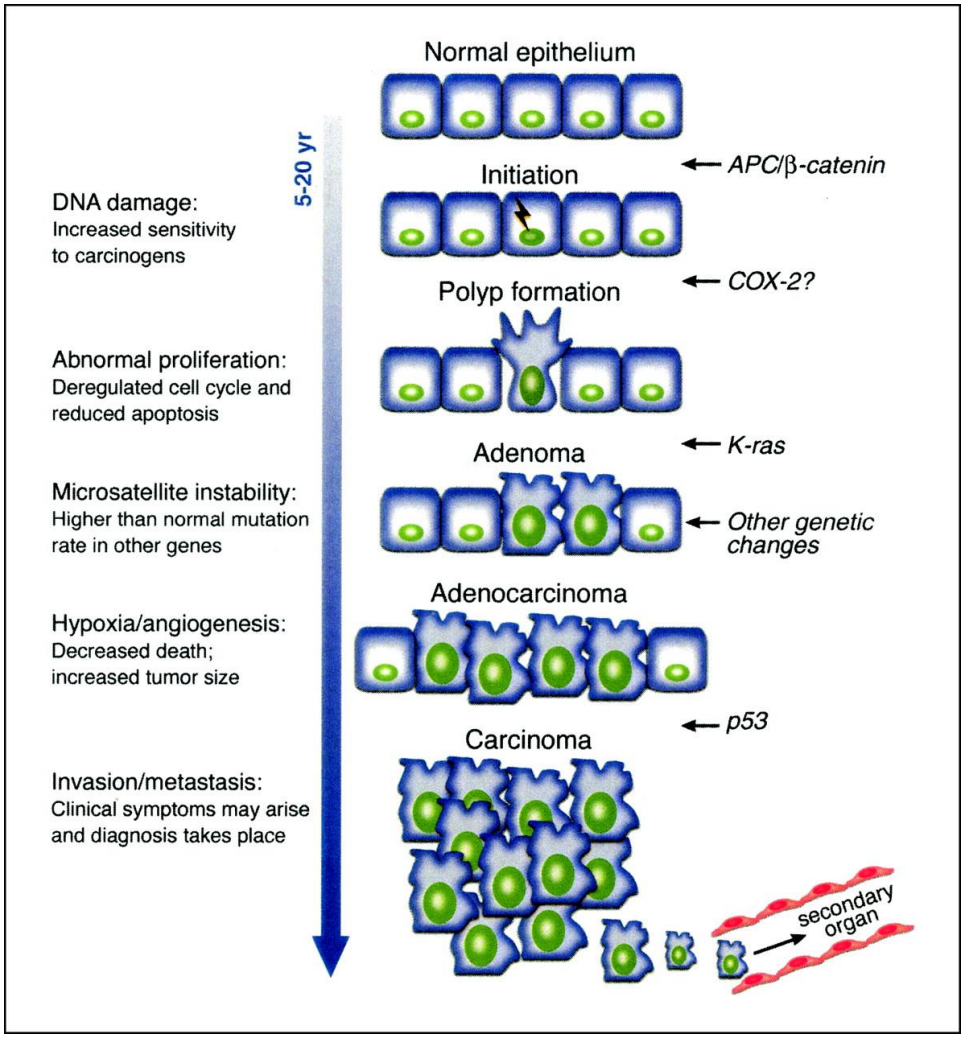


Brown, J. R. et al. J Clin Oncol; 23:2840-2855 2005

Inflammation in colon cancer

- Somatic mutations in APC cause familial predisposition to colon cancer (FAP)
- APC mutations: cause activation of beta-catenin, which drives activation of the Wnt and NFκB pathways
- Alterations in the microbiome
- These effects lead to upregulation of COX2
- Non-steroidal anti-inflammatory drugs (NSAIDS): prevent cancer in animal models and FAP patients

Fig 2. A genetic model for colorectal tumorigenesis illustrating the accumulation of mutations in oncogenes and tumor suppressor genes, which is thought to contribute to tumor progression and the propensity to metastasize



Brown, J. R. et al. J Clin Oncol; 23:2840-2855 2005

Potential role of the “microbiome”

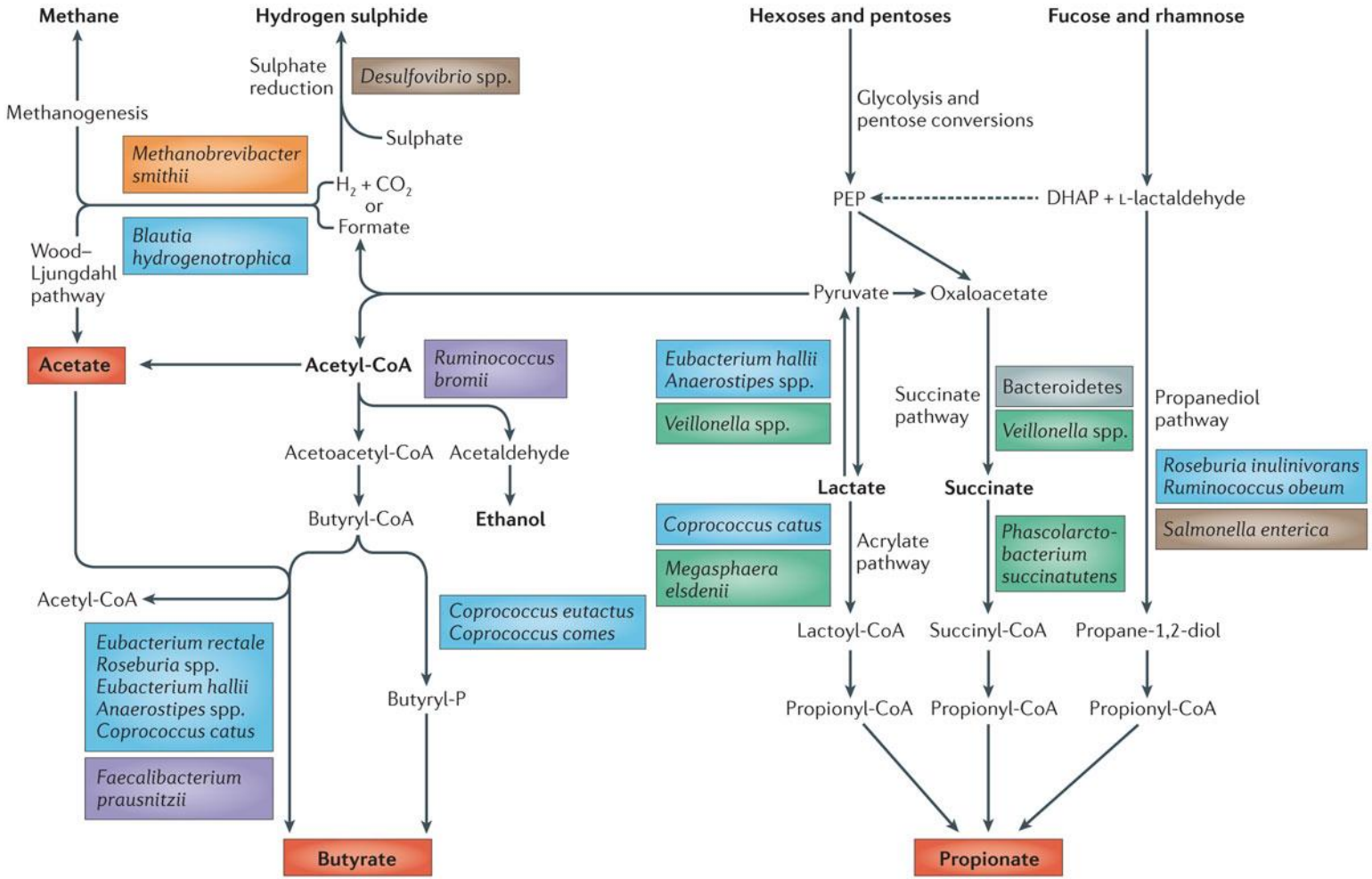
- Recent work indicates that the bacteria that colonize the colon (and other surface-exposed areas of the body) have important effects on many aspects of human health, including obesity, metabolism, and immunity
- Disruption of homeostasis is linked to chronic inflammation and may promote cancer

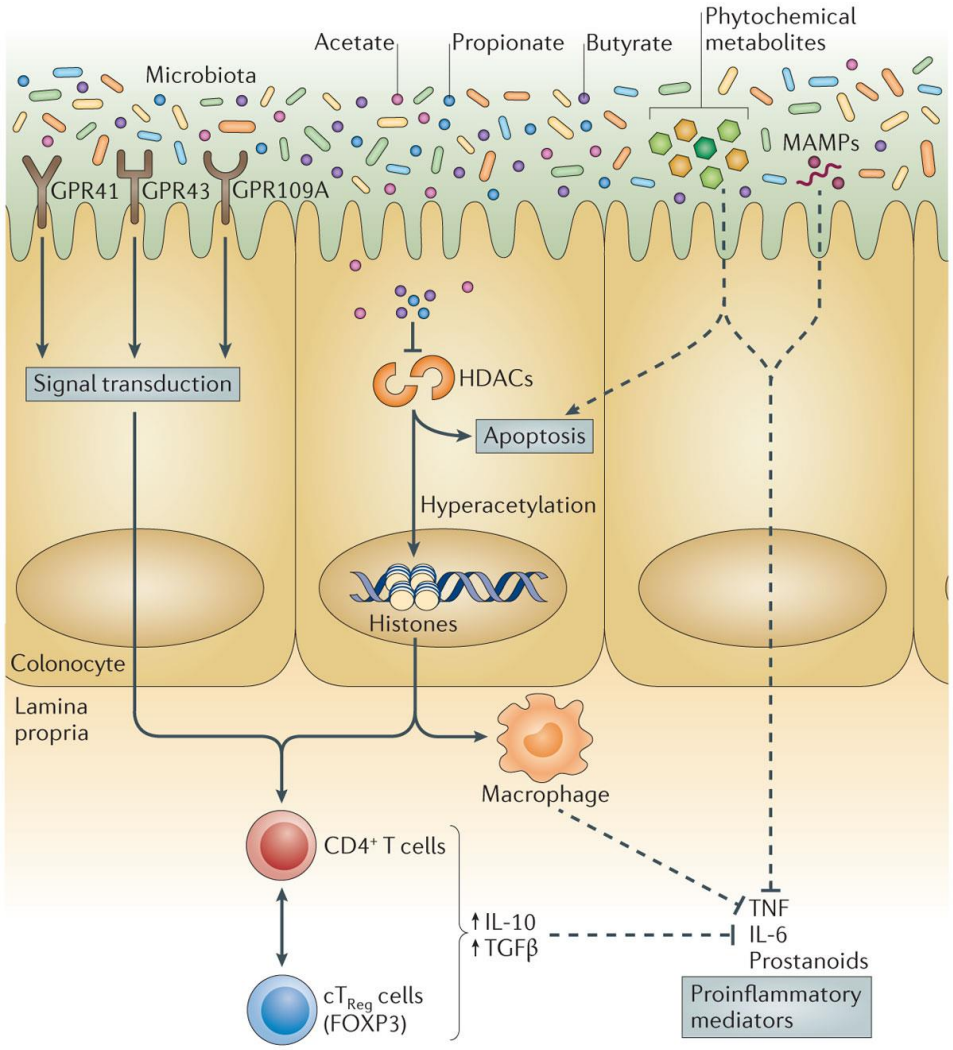
Nature Reviews Microbiology | AOP, published online 8 September 2014; doi:10.1038/nrmicro3344

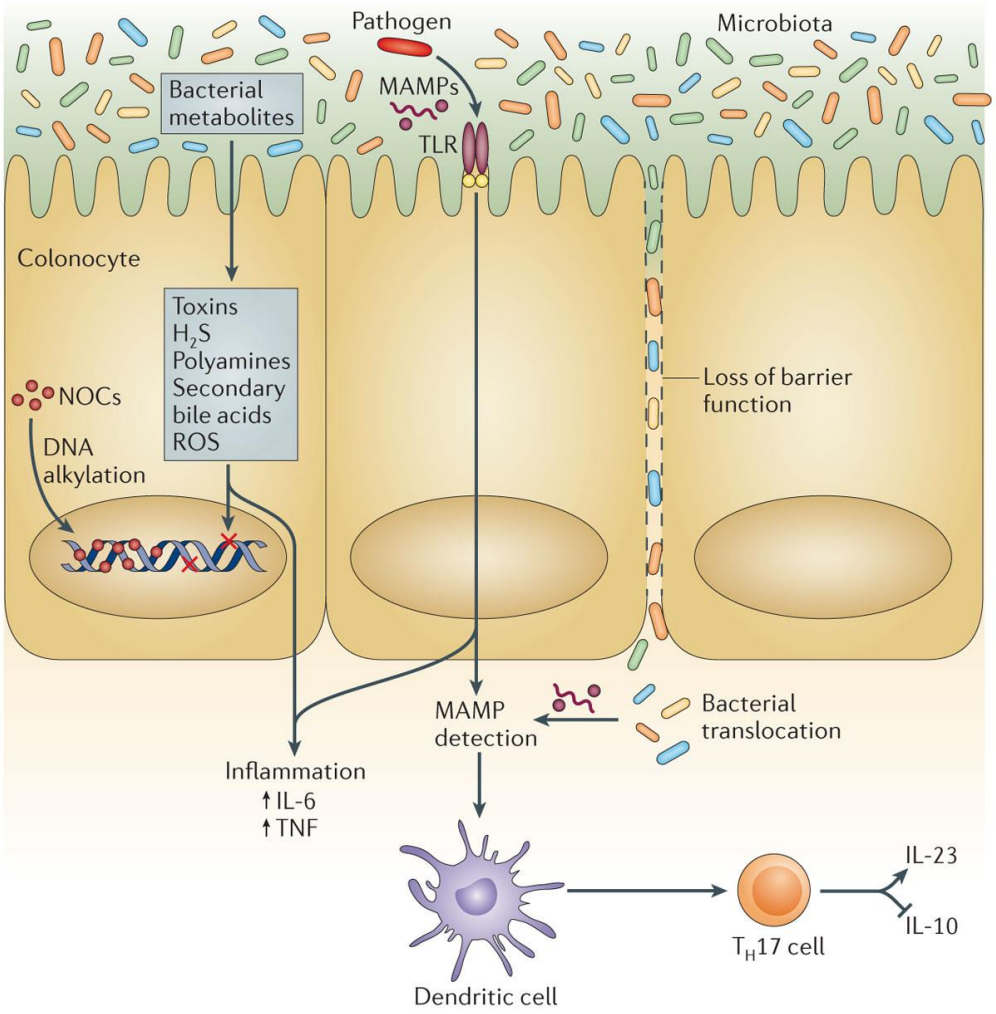
The gut microbiota, bacterial metabolites and colorectal cancer

Petra Louis[1], Georgina L. Hold[2] and Harry J. Flint[1]

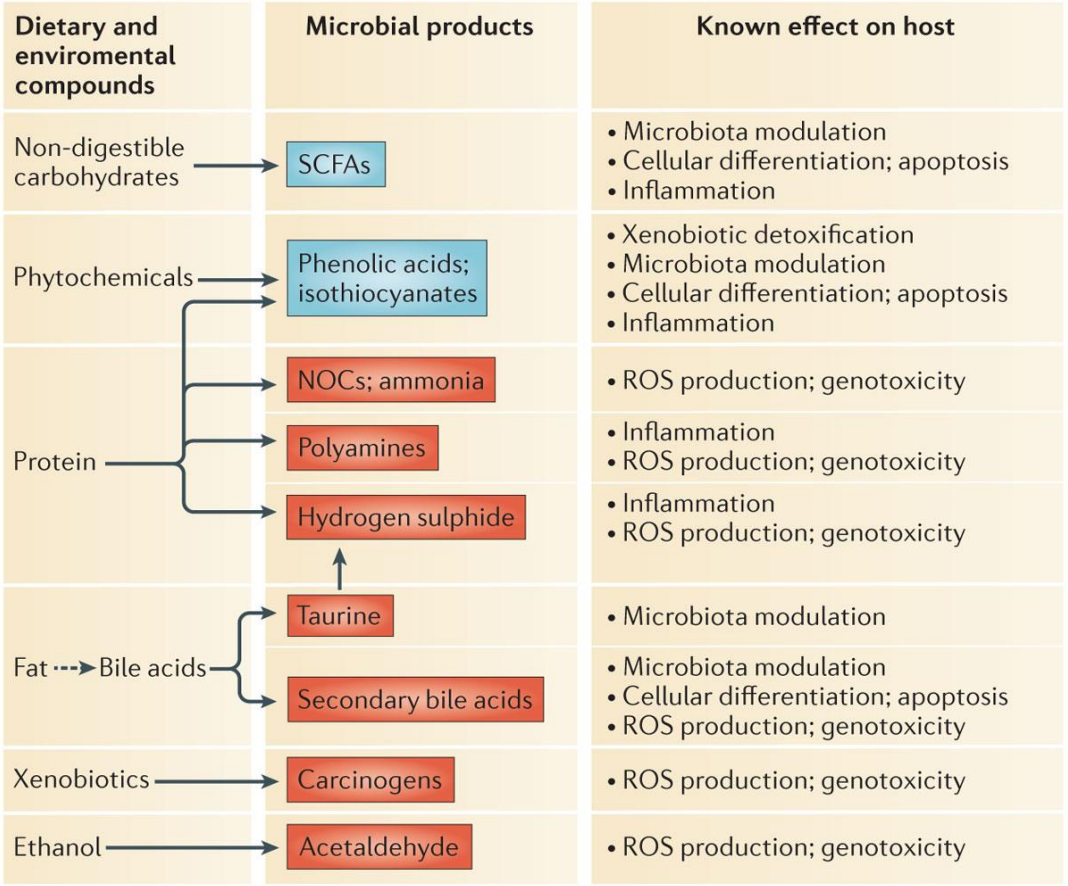
Abstract | Accumulating evidence suggests that the human intestinal microbiota contributes to the aetiology of colorectal cancer (CRC), not only via the pro-carcinogenic activities of specific pathogens but also via the influence of the wider microbial community, particularly its metabolome. Recent data have shown that the short-chain fatty acids acetate, propionate and butyrate function in the suppression of inflammation and cancer, whereas other microbial metabolites, such as secondary bile acids, promote carcinogenesis. In this Review, we discuss the relationship between diet, microbial metabolism and CRC and argue that the cumulative effects of microbial metabolites should be considered in order to better predict and prevent cancer progression.


Methane
Hydrogen sulphide
Hexoses and pentoses
Fucose and rhamnose
Sulphate reduction
Desulfovibrio spp.
Sulphate
Methanogenesis
Glycolysis and pentose conversions
Methanobrevibacter smithii
H2 + CO2 or Formate
PEP
DHAP + L-lactaldehyde
Blautia hydrogenotrophica
Wood–Ljungdahl pathway
Pyruvate
Oxaloacetate
Acetate
Acetyl-CoA
Ruminococcus bromii
Eubacterium hallii
Anaerostipes spp.
Veillonella spp.
Succinate pathway
Bacteroidetes
Veillonella spp.
Propanediol pathway
Roseburia inulinivorans
Ruminococcus obeum
Salmonella enterica
Acetoacetyl-CoA
Acetaldehyde
Lactate
Succinate
Butyryl-CoA
Ethanol
Coprococcus catus
Megasphaera elsdenii
Acrylate pathway
Phascolarcto-bacterium succinatutens
Acetyl-CoA
Coprococcus eutactus
Coprococcus comes
Lactoyl-CoA
Succinyl-CoA
Propane-1,2-diol
Eubacterium rectale
Roseburia spp.
Eubacterium hallii
Anaerostipes spp.
Coprococcus catus
Butyryl-P
Propionyl-CoA
Propionyl-CoA
Propionyl-CoA
Faecalibacterium prausnitzii
Butyrate
Propionate


Acetate
Propionate
Butyrate
Phytochemical metabolites
Microbiota
MAMPs
GPR41
GPR43
GPR109A
Signal transduction
HDACs
Apoptosis
Hyperacetylation
Histones
Colonocyte
Lamina propria
Macrophage
CD4+ T cells
cTReg cells (FOXP3)
↑IL-10
↑TGFβ
TNF
IL-6
Prostanoids
Proinflammatory mediators



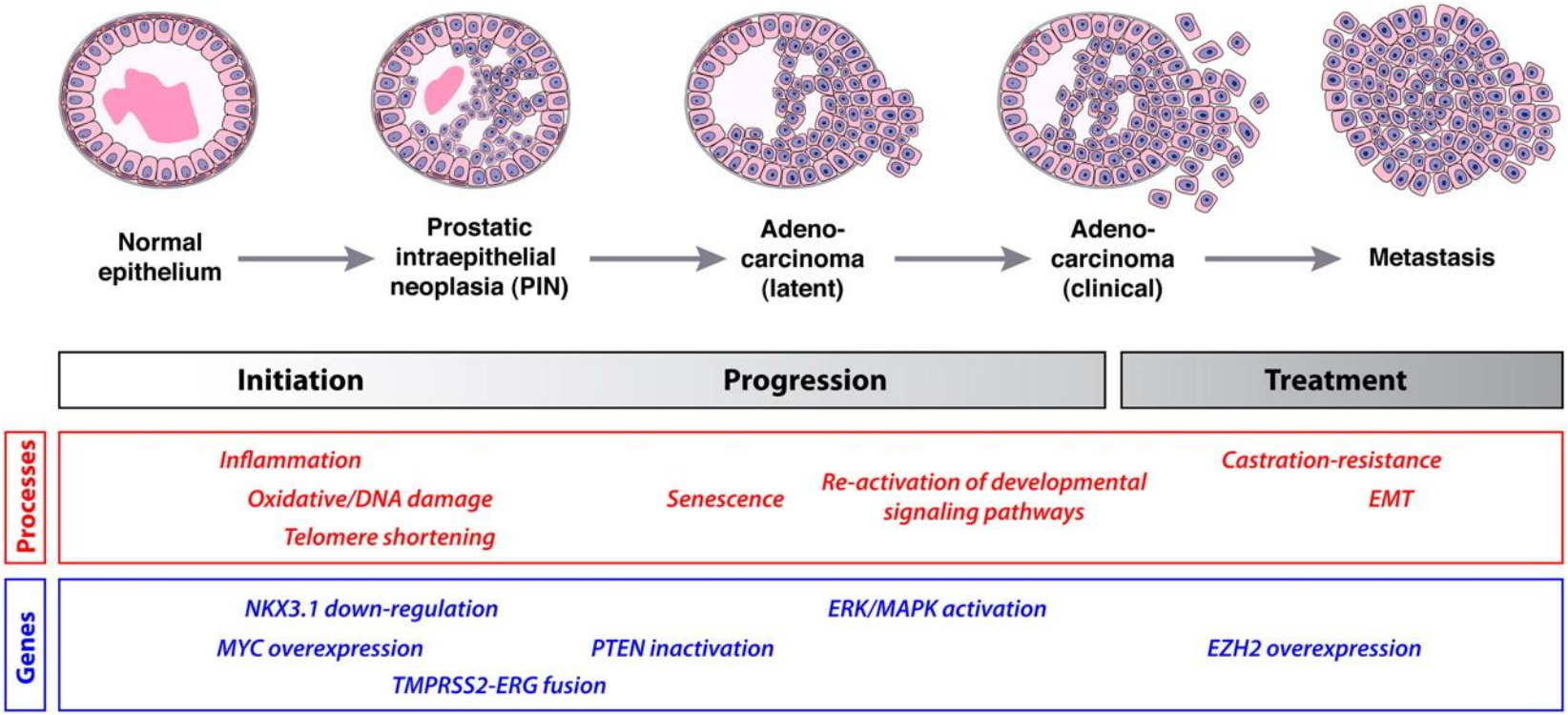
Nature Reviews | Microbiology


Dietary and enviromental compounds
Microbial products
Known effect on host
Non-digestible carbohydrates
SCFAs
• Microbiota modulation
• Cellular differentiation; apoptosis
• Inflammation
Phytochemicals
Phenolic acids; isothiocyanates
• Xenobiotic detoxification
• Microbiota modulation
• Cellular differentiation; apoptosis
• Inflammation
Protein
NOCs; ammonia
• ROS production; genotoxicity
Polyamines
• Inflammation
• ROS production; genotoxicity
Hydrogen sulphide
• Inflammation
• ROS production; genotoxicity
Fat
Bile acids
Taurine
• Microbiota modulation
Secondary bile acids
• Microbiota modulation
• Cellular differentiation; apoptosis
• ROS production; genotoxicity
Xenobiotics
Carcinogens
• ROS production; genotoxicity
Ethanol
Acetaldehyde
• ROS production; genotoxicity

Inflammation and prostate cancer

- The emergence of cancer precursor lesions (prostatic intraepithelial neoplasia, or PIN) is strongly associated with inflammation
- Also associated with focal atrophy
- Referred to as “proliferative inflammatory atrophy” (PIA)

Progression pathway for human prostate cancer.



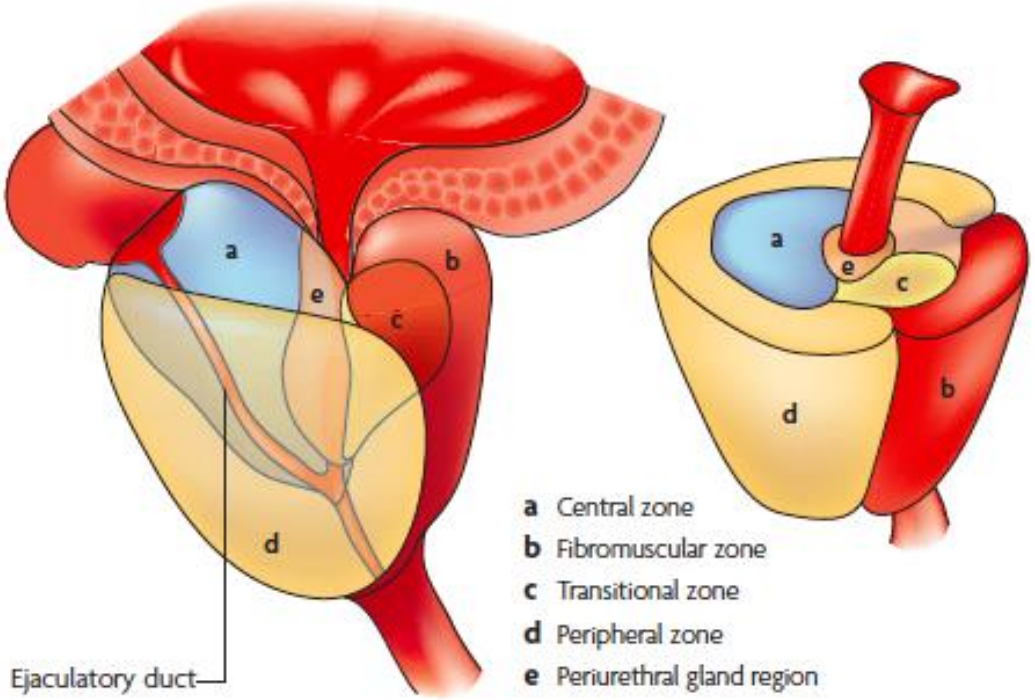
Shen M M , and Abate-Shen C Genes Dev. 2010;24:1967-2000

Inflammation in prostate carcinogenesis

Angelo M. De Marzo[*‡], *Elizabeth A. Platz*[§], *Siobhan Sutcliffe*[§], *Jianfeng Xu*[||], *Henrik Grönberg*[¶], *Charles G. Drake*[‡], *Yasutomo Nakai*[#], *William B. Isaacs*[**] *and William G. Nelson*[‡]

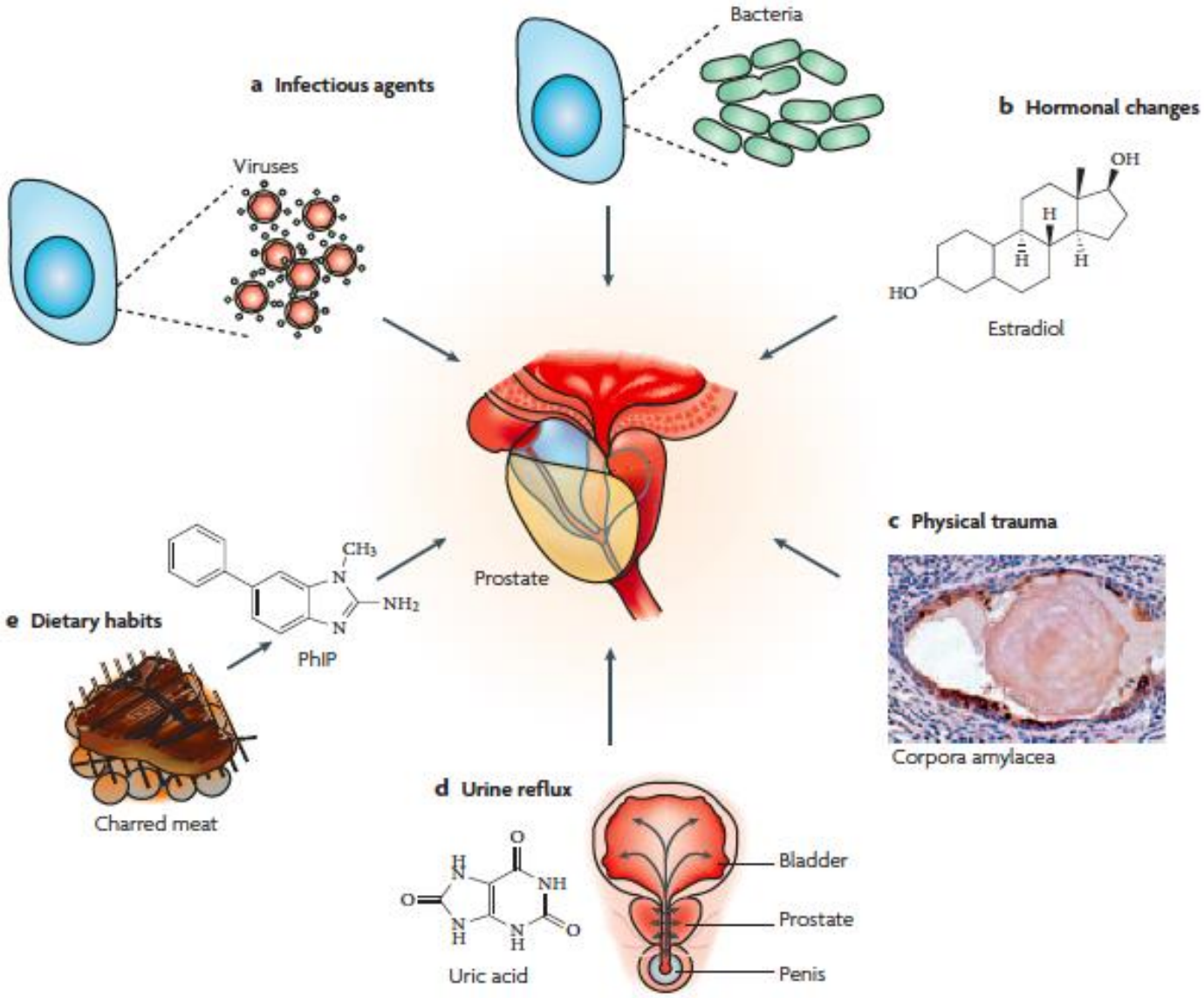
Abstract | About 20% of all human cancers are caused by chronic infection or chronic inflammatory states. Recently, a new hypothesis has been proposed for prostate carcinogenesis. It proposes that exposure to environmental factors such as infectious agents and dietary carcinogens, and hormonal imbalances lead to injury of the prostate and to the development of chronic inflammation and regenerative 'risk factor' lesions, referred to as proliferative inflammatory atrophy (PIA). By developing new experimental animal models coupled with classical epidemiological studies, genetic epidemiological studies and molecular pathological approaches, we should be able to determine whether prostate cancer is driven by inflammation, and if so, to develop new strategies to prevent the disease.

Prostate zones

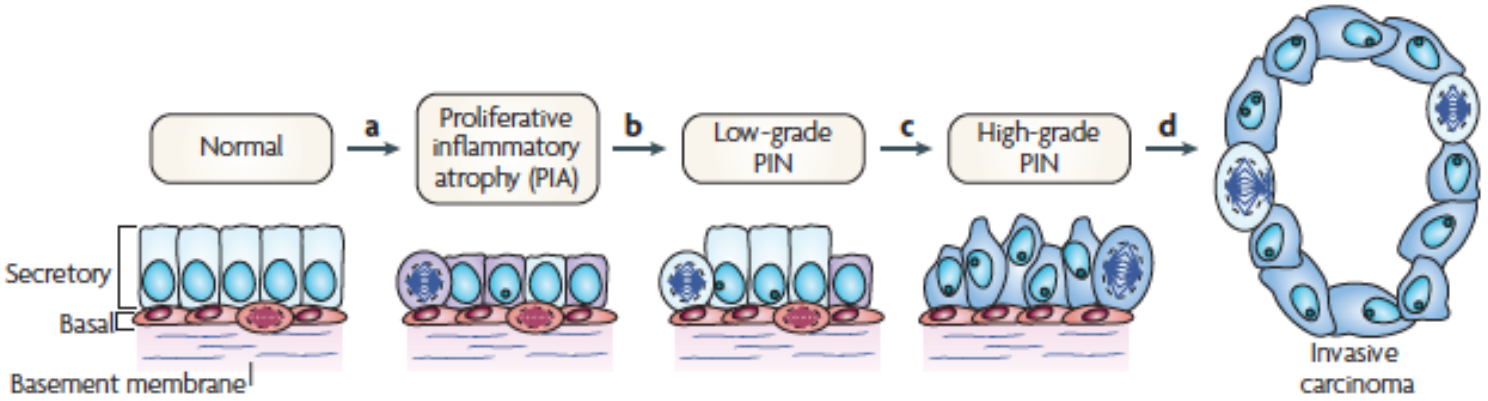


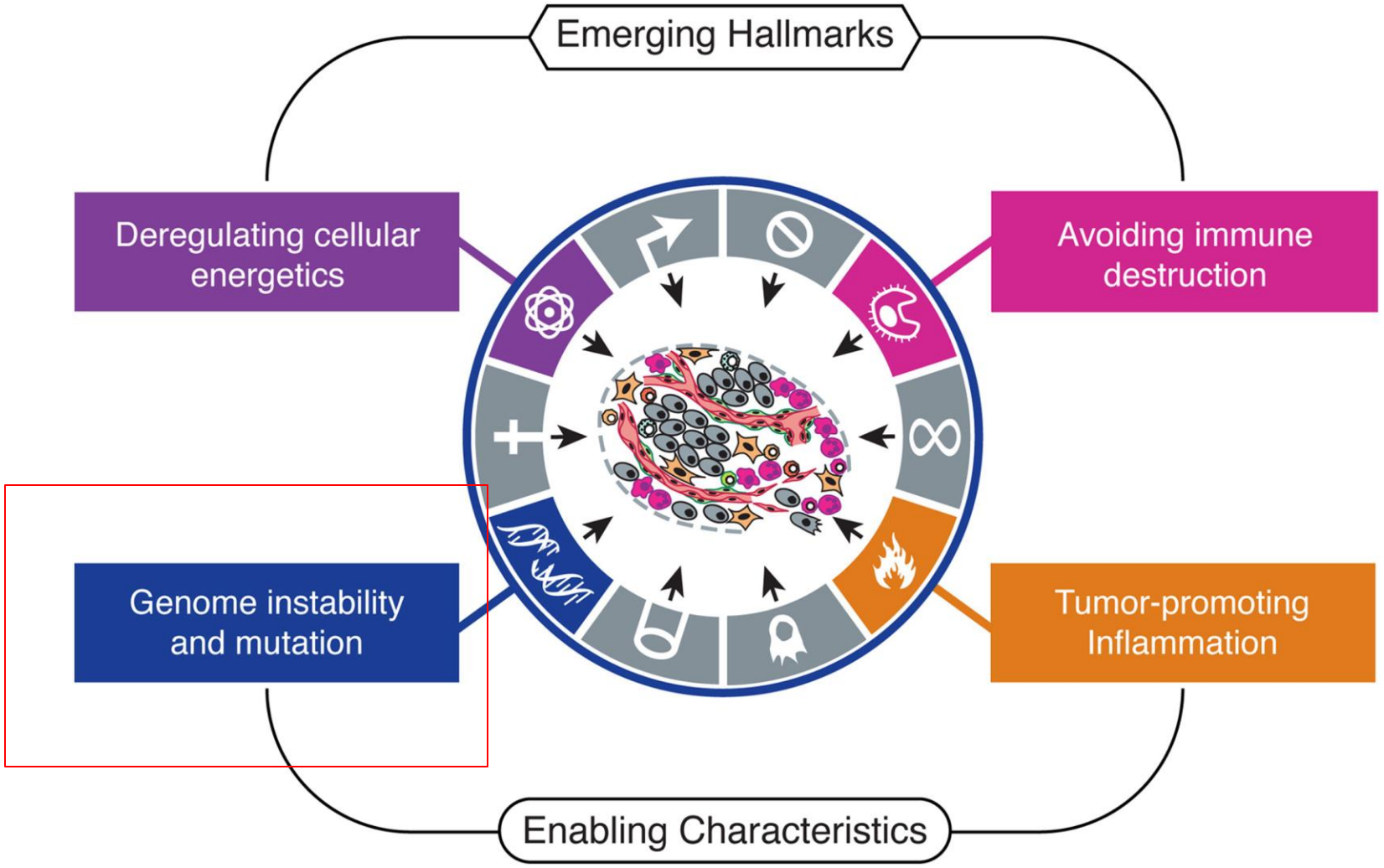
	Prostate zone		
	Peripheral	Transition	Central
Focal atrophy			
Acute inflammation			
Chronic inflammation			
Benign prostatic hyperplasia			
High-grade PIN			
Carcinoma			

High prevalence
Medium-high prevalence
Low prevalence
None


a Infectious agents
Bacteria
Viruses
b Hormonal changes
OH
H
H
H
HO
Estradiol
Prostate
c Physical trauma
Corpora amylacea
e Dietary habits
CH3
N
NH2
N
PhIP
Charred meat
d Urine reflux
O
NH
O
N
H
N
H
O
Uric acid
Bladder
Prostate
Penis

“Proliferative inflammatory atrophy” (PIA)

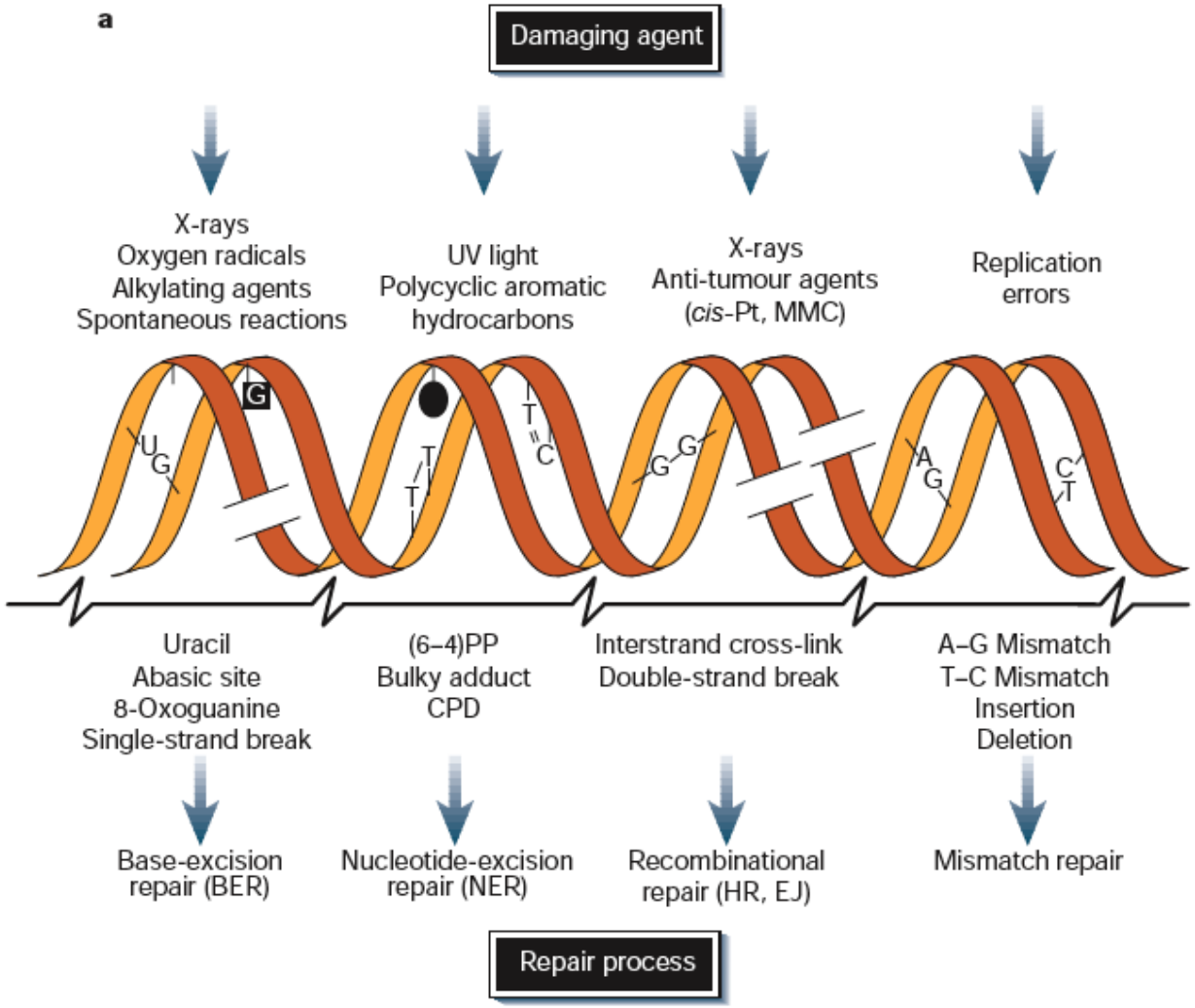



Emerging Hallmarks
Deregulating cellular energetics
Avoiding immune destruction
Genome instability and mutation
Tumor-promoting Inflammation
Enabling Characteristics

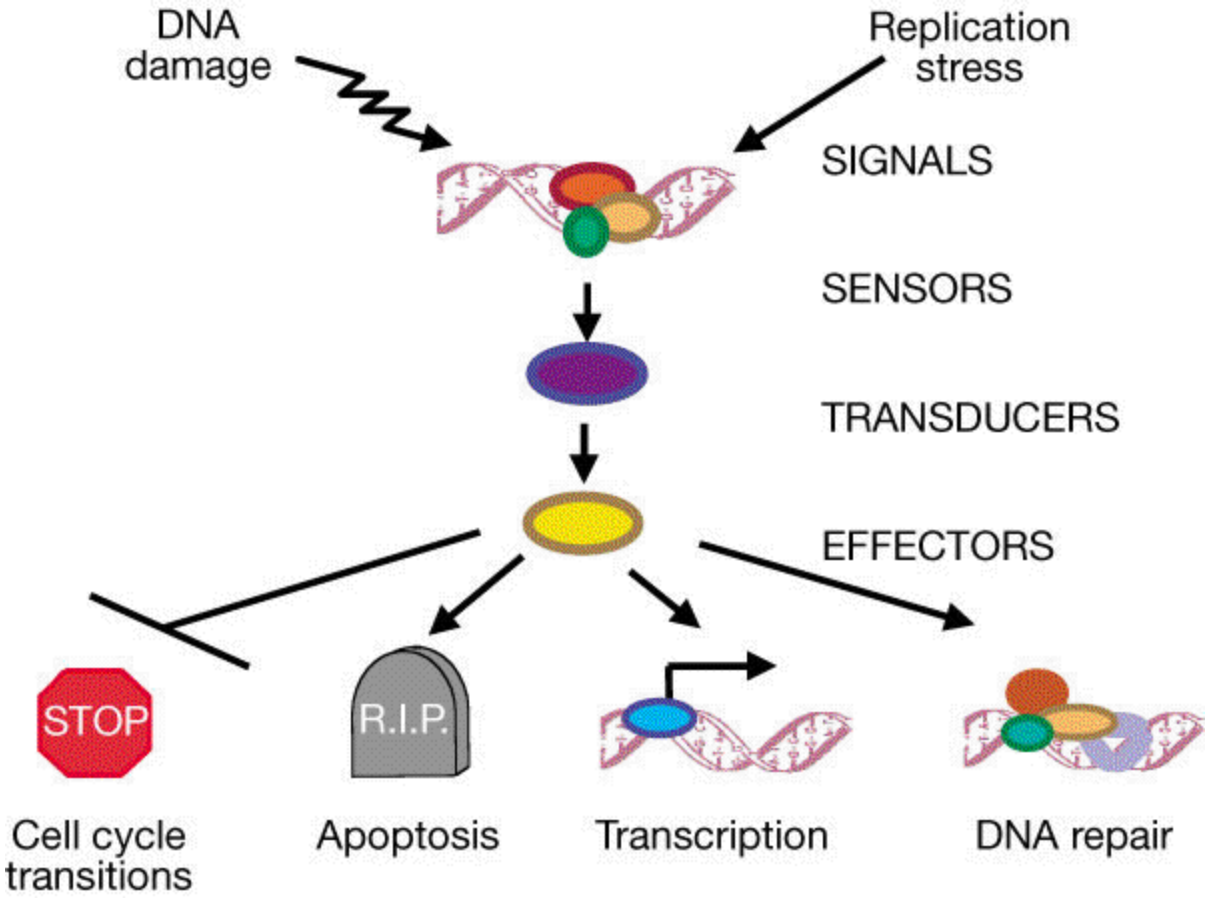
Familial cancer syndromes are caused by DNA repair defects

- Hereditary breast, ovarian, and pancreatic cancers: BRCA1/2
- Hereditary non-polyposis colon cancer/HNPCC: DNA mismatch repair genes
- Li-Fraumeni syndrome: p53
- Ataxia telangectasia: ATM

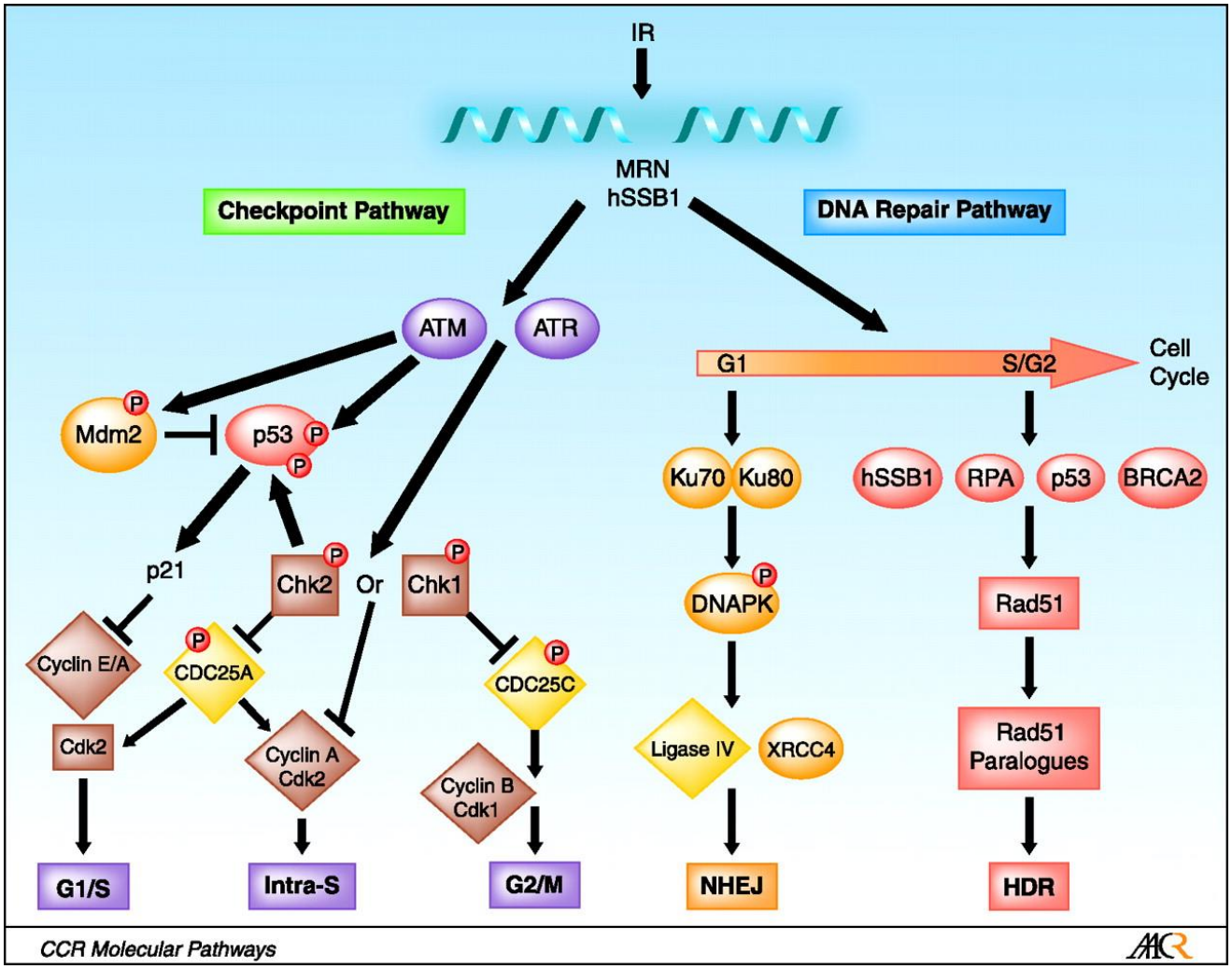
DNA repair pathways



The DNA damage response



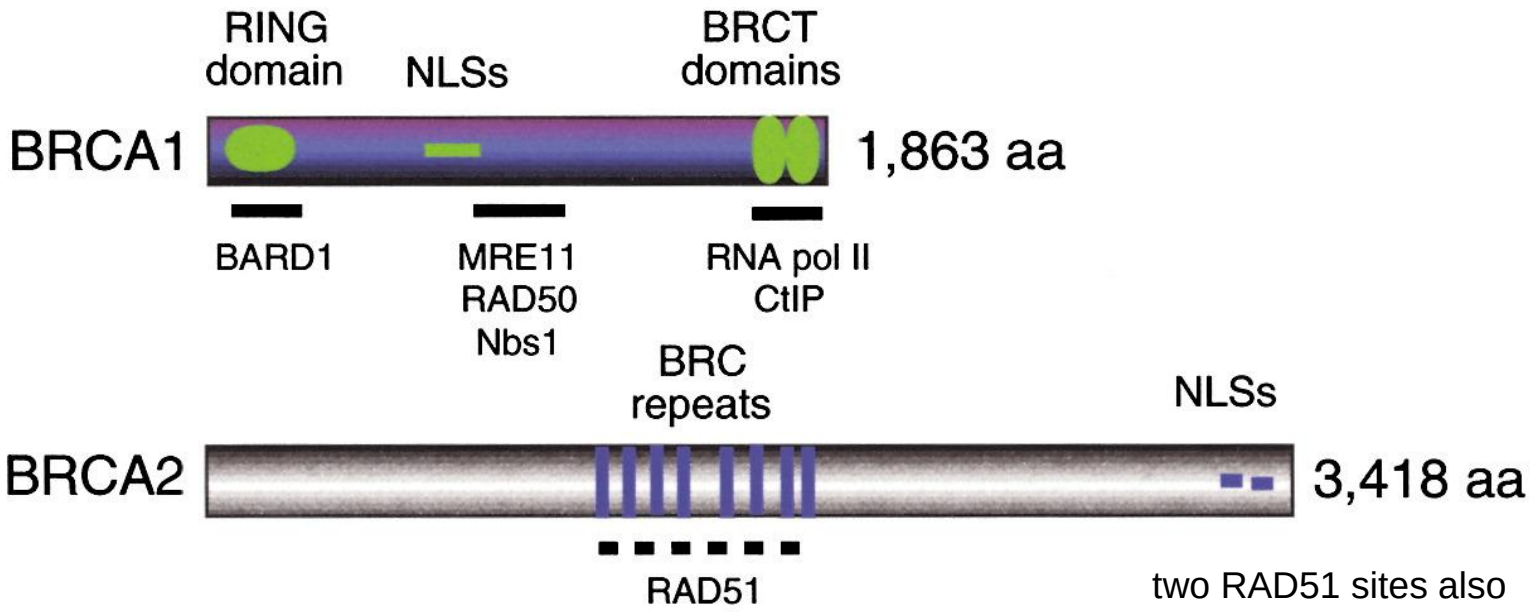
DNA DSB-induced activation of checkpoint and repair pathways



Bolderson E et al. Clin Cancer Res 2009;15:6314-6320

BRCA1 and BRCA2

- Breast cancer susceptibility genes
- Localize to sites of damage (damage foci)
- Both phosphorylated in response to damage
- Defects associated with breast, ovarian, and pancreatic cancer



Venkitanaram, *Cell* 2002, 108, p. 171

VOLUME 26 · NUMBER 22 · AUGUST 1 2008

JOURNAL OF CLINICAL ONCOLOGY

BIOLOGY OF NEOPLASIA

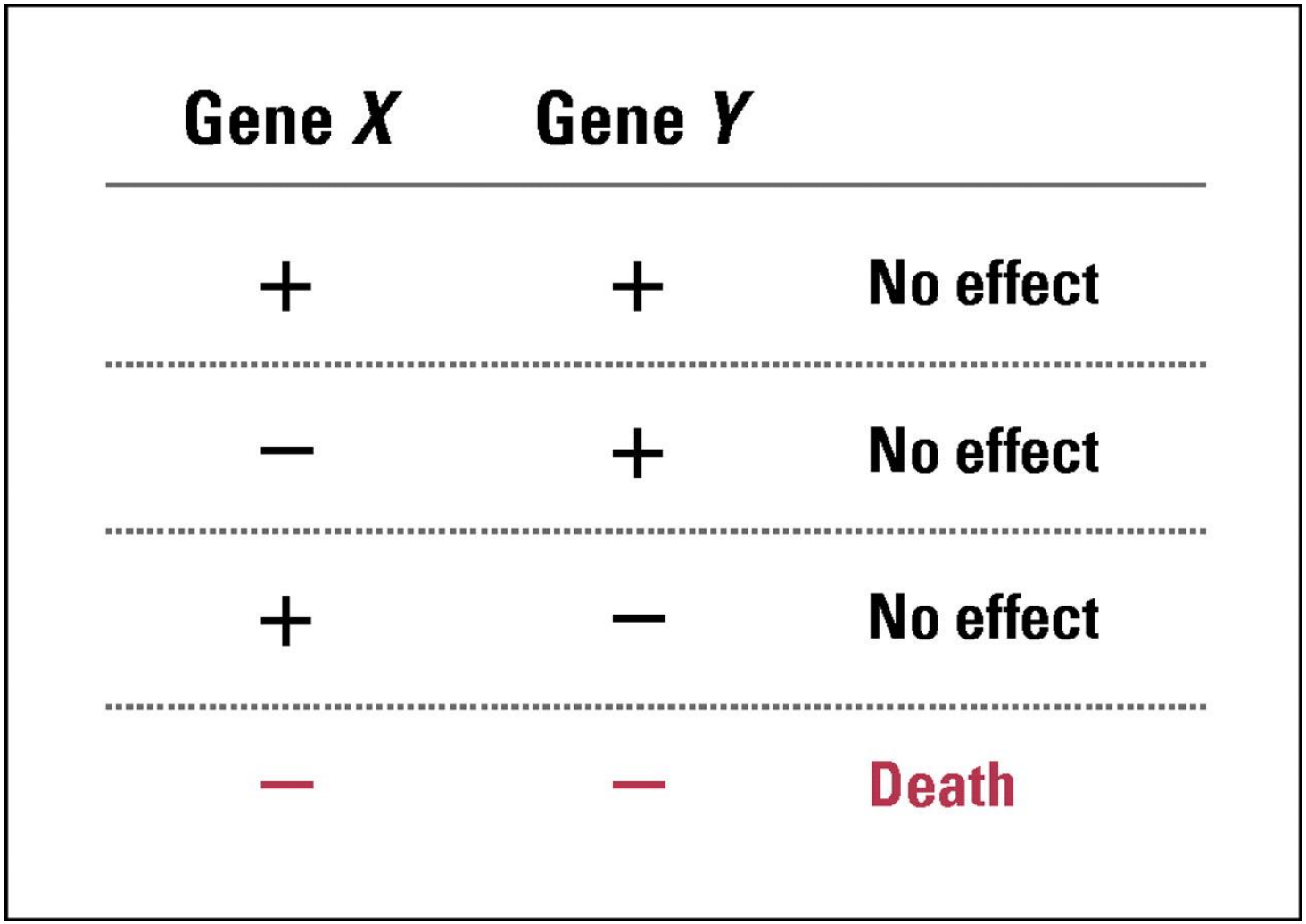
A Synthetic Lethal Therapeutic Approach: Poly(ADP) Ribose Polymerase Inhibitors for the Treatment of Cancers Deficient in DNA Double-Strand Break Repair

Alan Ashworth

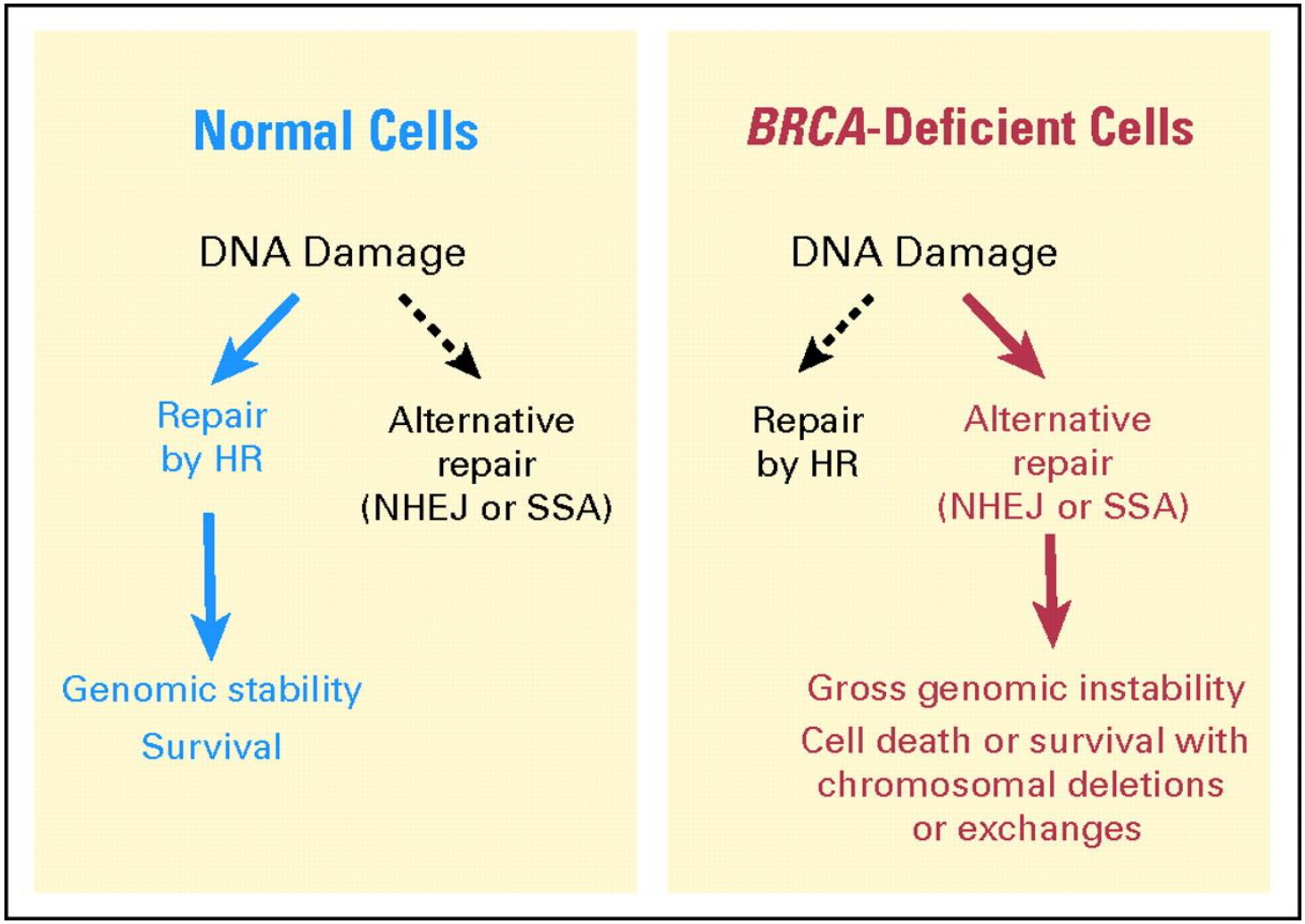
ABSTRACT

Cancer cells frequently harbor defects in DNA repair pathways, leading to genomic instability. This can foster tumorigenesis but also provides a weakness in the tumor that can be exploited therapeutically. Tumors with compromised ability to repair double-strand DNA breaks by homologous recombination, including those with defects in *BRCA1* and *BRCA2*, are highly sensitive to blockade of the repair of DNA single-strand breaks via the inhibition of the enzyme poly(ADP) ribose polymerase. This provides the basis for a novel synthetic lethal approach to cancer therapy.

J Clin Oncol 26:3785-3790.



Ashworth A JCO 2008;26:3785-3790

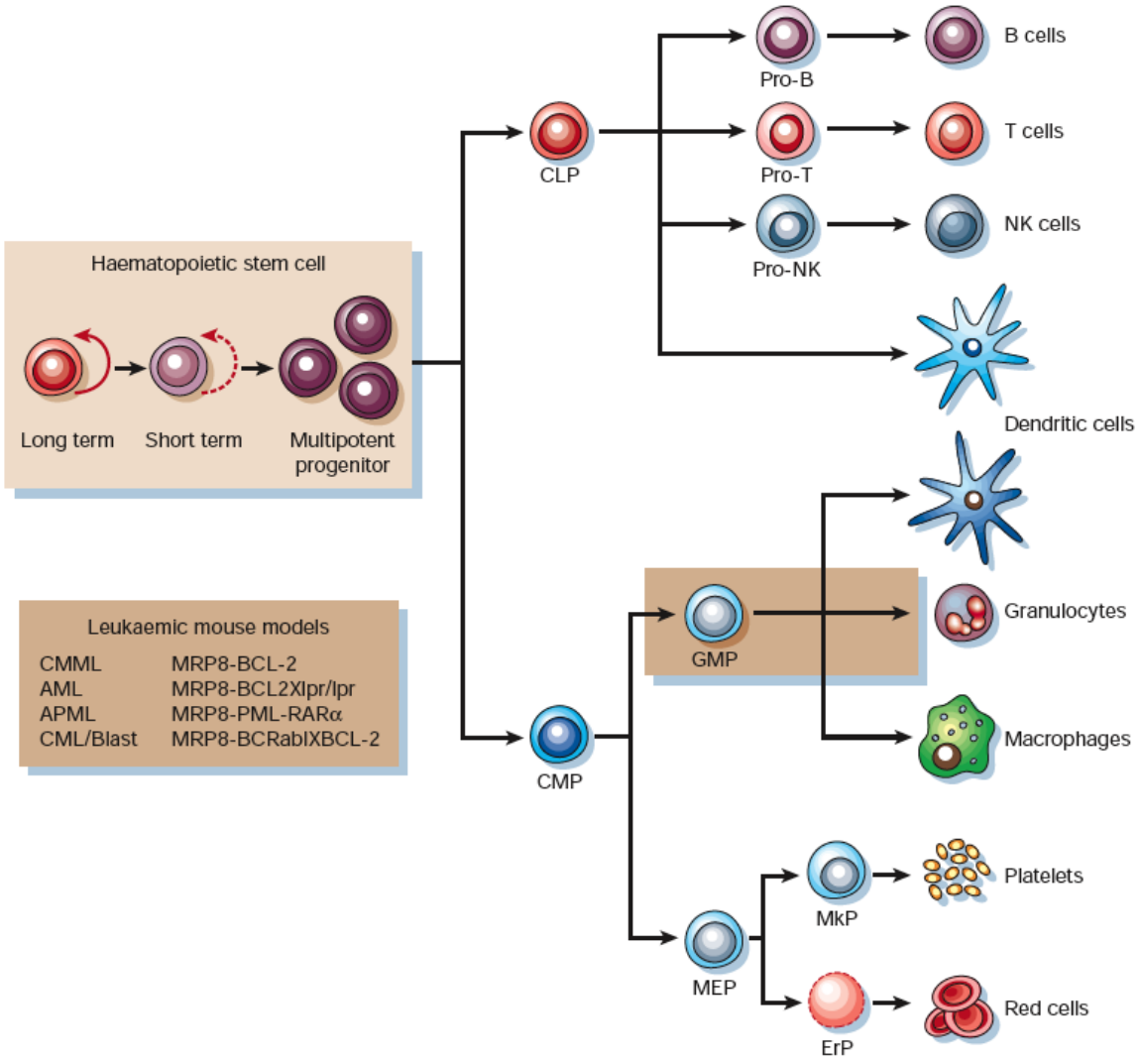


Ashworth A JCO 2008;26:3785-3790

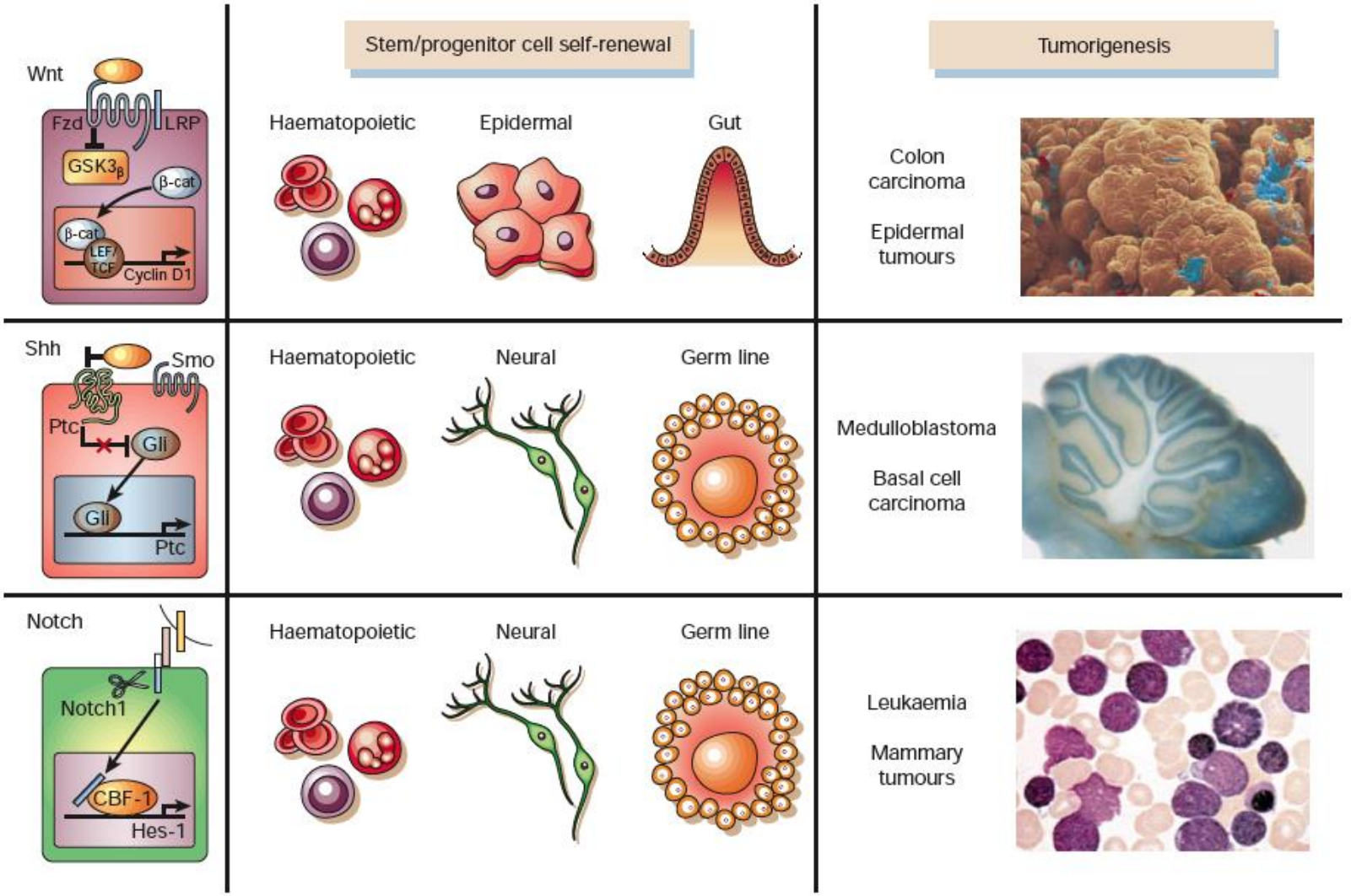
Origins of cancer: Stem cells

- Long-term capacity to repopulate tissues following injury
- Self-renewal: can reproduce themselves without undergoing differentiation
- Also produce “transit amplifying” cells that have high proliferative potential (but cannot repopulate the tissue permanently)
- Their biology is heavily influenced by epigenetic mechanisms

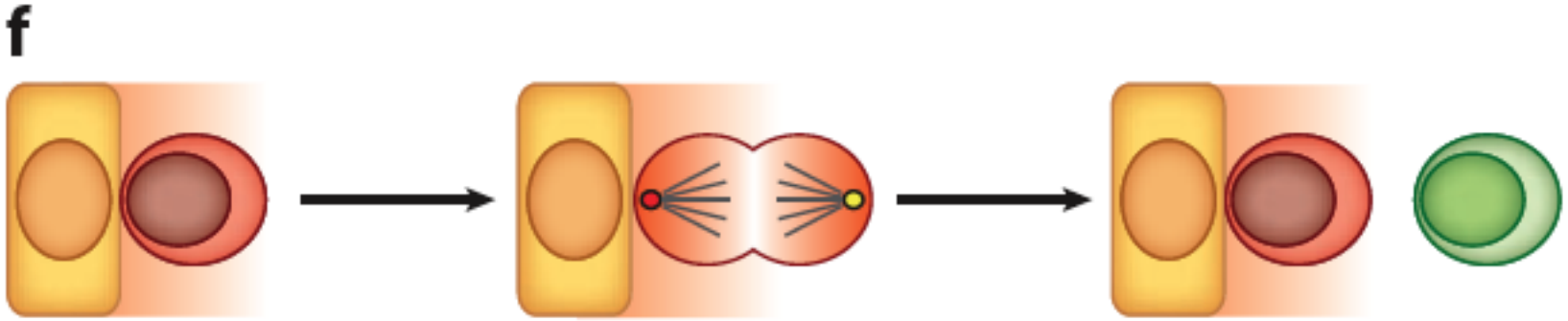
Hematopoietic stem cells



Developmental pathways regulate normal stem cells and cancer



Asymmetric cell division: control by the stem cell niche

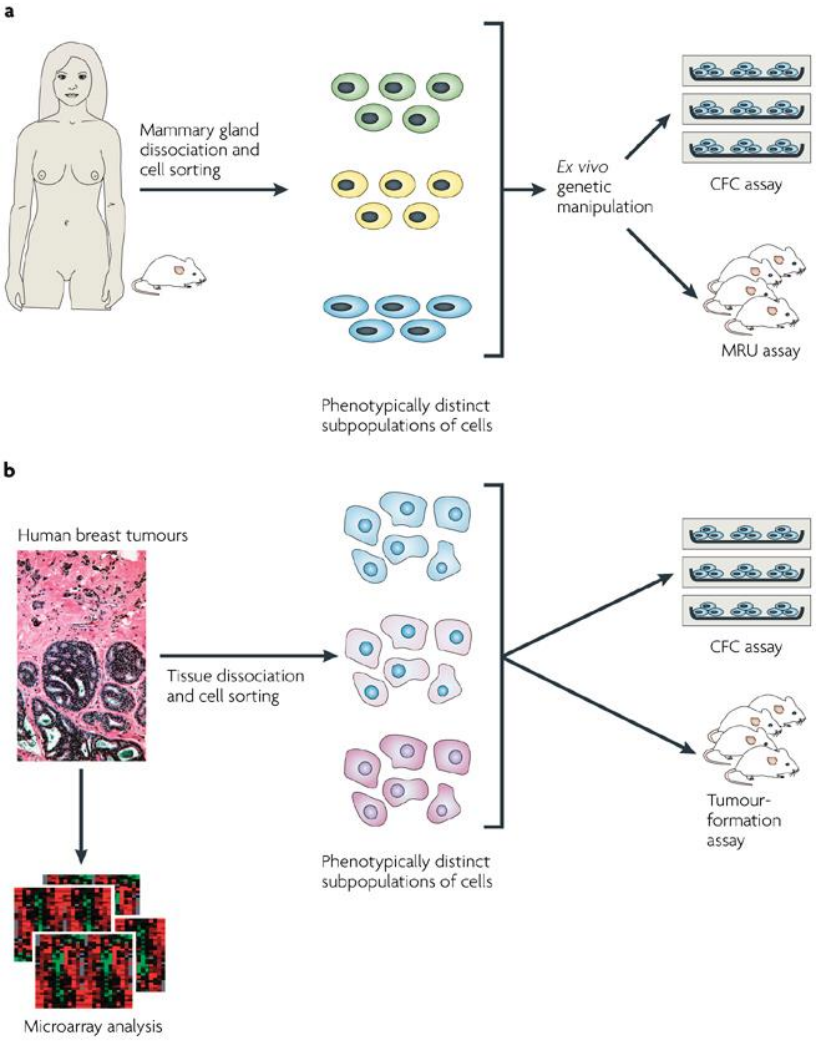


Red cell – daughter cell that remains within the niche.

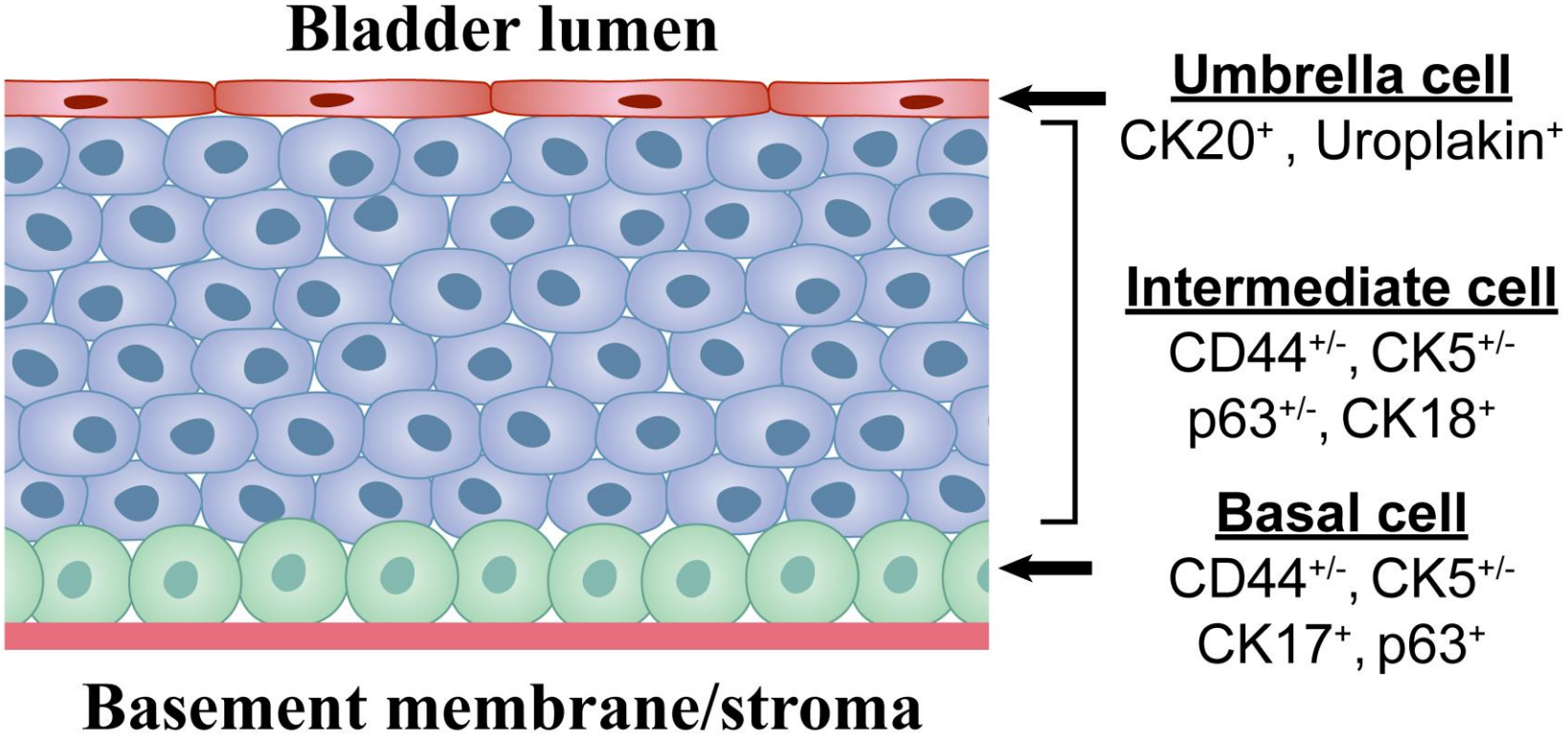
Stem cell niche: the microenvironment in which stem cells reside; promotes stem cell maintenance and regulates stem cell function

Cancers also appear to contain "stem cells"

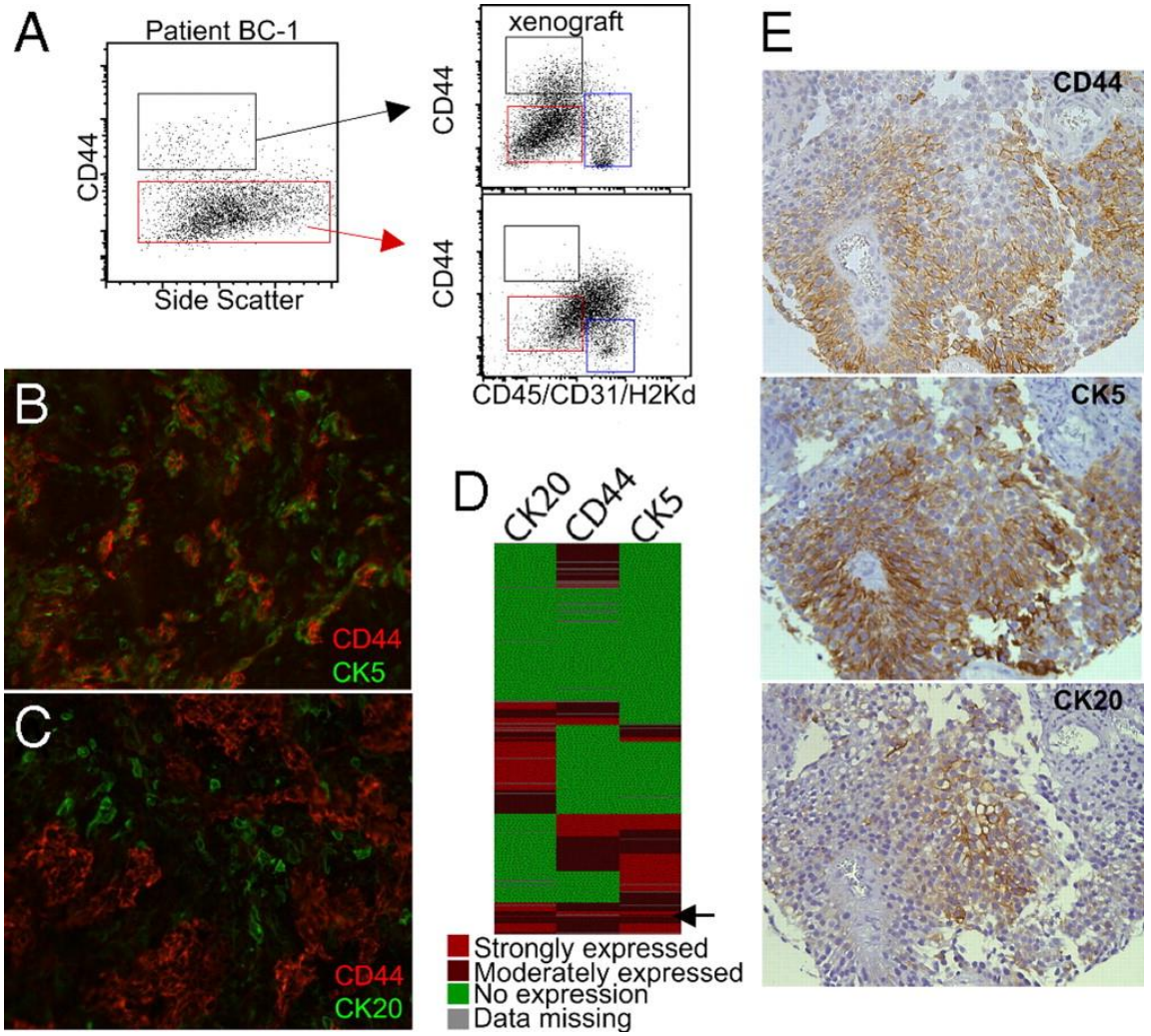
- Subpopulations of cells that can regenerate the whole tumor when transplanted in mice
- The cancer stem cells that have been isolated from different solid tumors and experimentally characterized in mice share biomarkers that are also expressed by the basal layers of surface epithelia
- However, cancers form "intrinsic subtypes" that suggest different cells of origin


a
Mammary gland dissociation and cell sorting
Ex vivo genetic manipulation
CFC assay
MRU assay
Phenotypically distinct subpopulations of cells
b
Human breast tumours
Tissue dissociation and cell sorting
CFC assay
Tumour-formation assay
Phenotypically distinct subpopulations of cells
Microarray analysis

Differentiation in the normal urothelium



Bladder tumor-initiating cells possess cell properties in common with bladder basal cells.



Chan K S et al. PNAS 2009;106:14016-14021

Molecular portraits of human breast tumours

Charles M. Perou*†, Therese Sørlie†‡, Michael B. Eisen*, Matt van de Rijn§, Stefanie S. Jeffrey‖, Christian A. Rees*, Jonathan R. Pollack¶, Douglas T. Ross¶, Hilde Johnsen‡, Lars A. Akslen#, Øystein Fluge☆, Alexander Pergamenschikov*, Cheryl Williams*, Shirley X. Zhu§, Per E. Lønning, Anne-Lise Børresen-Dale‡, Patrick O. Brown¶†† & David Botstein***

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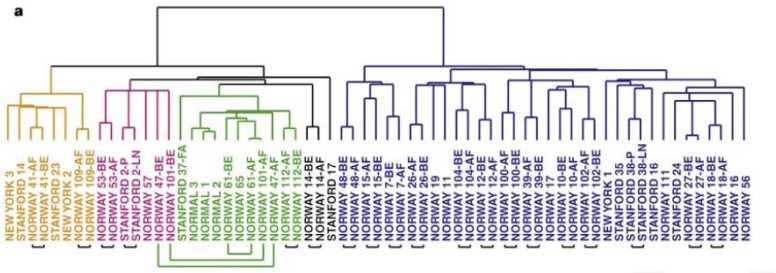
† These authors contributed equally to this work



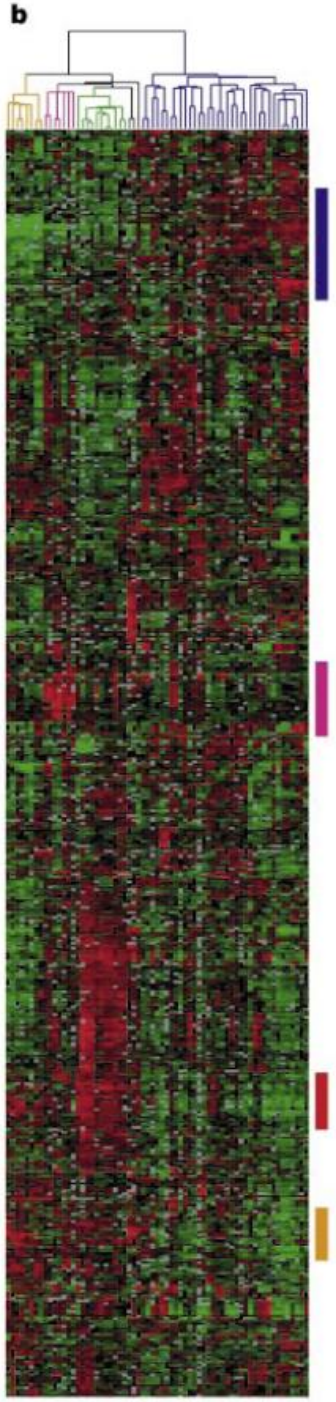
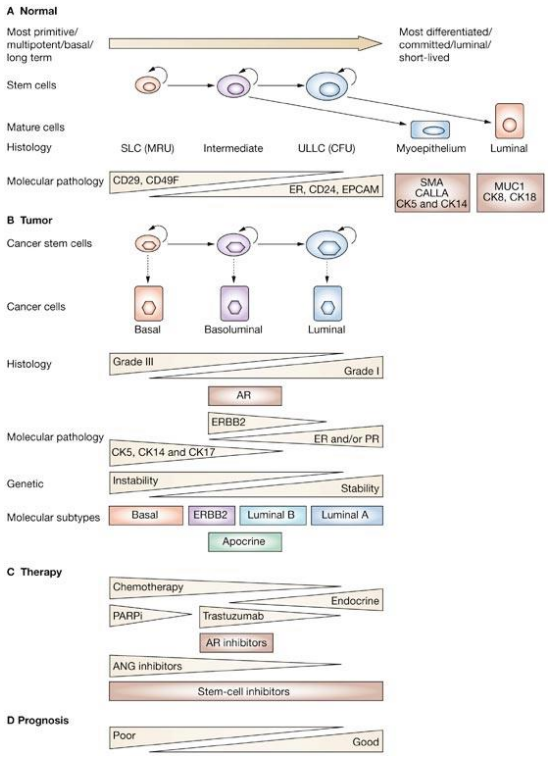


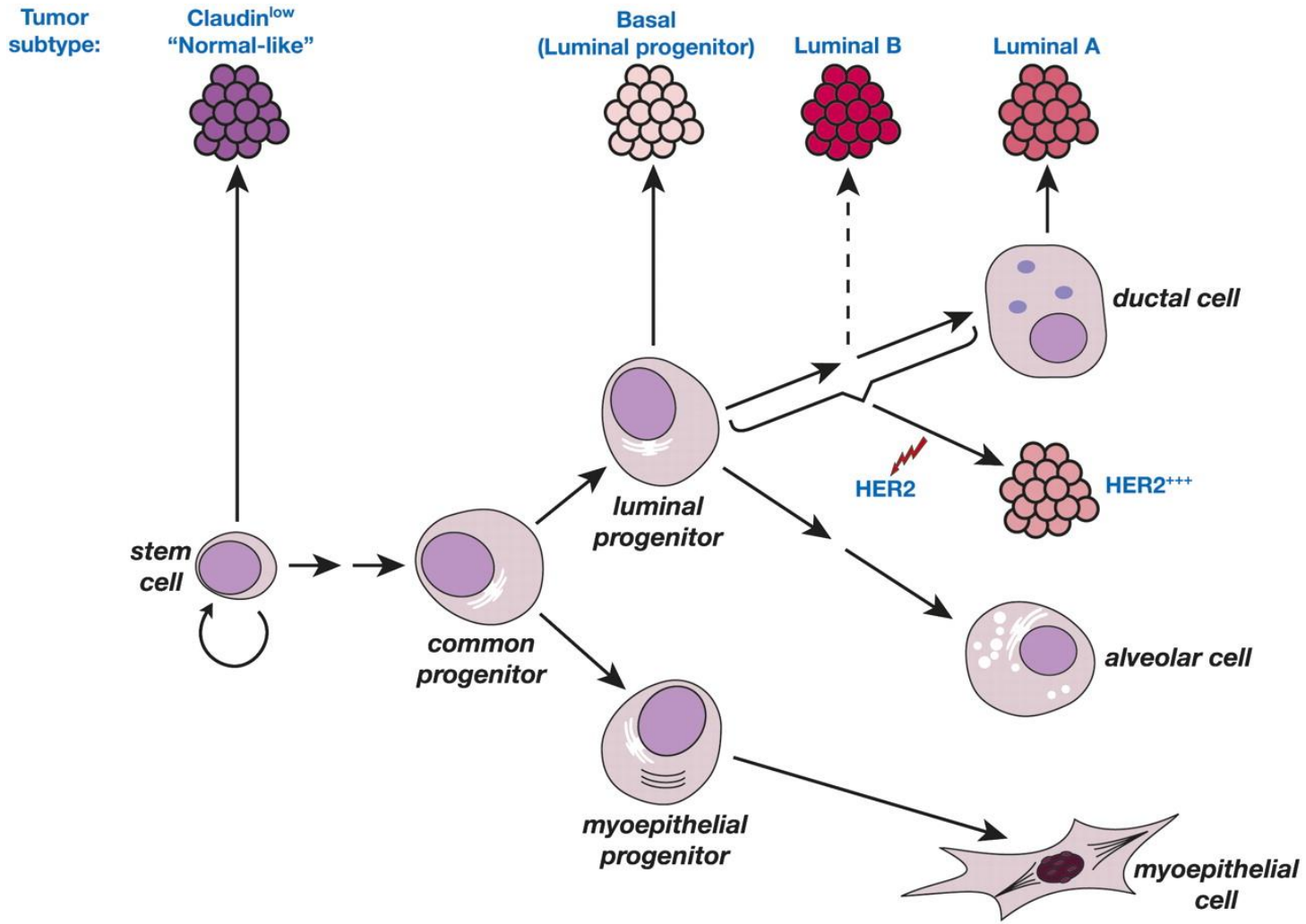
Figure 3 A model of stem-cell hierarchy and how it may account for the origins of different subtypes of breast cancer via cancer stem cells



Sims AH *et al.* (2007) Origins of breast cancer subtypes and therapeutic implications
Nat Clin Pract Oncol **4**: 516–525 doi:10.1038/ncponc0908

nature CLINICAL PRACTICE ONCOLOGY

Schematic model of the human breast epithelial hierarchy and potential relationships with breast tumor subtypes



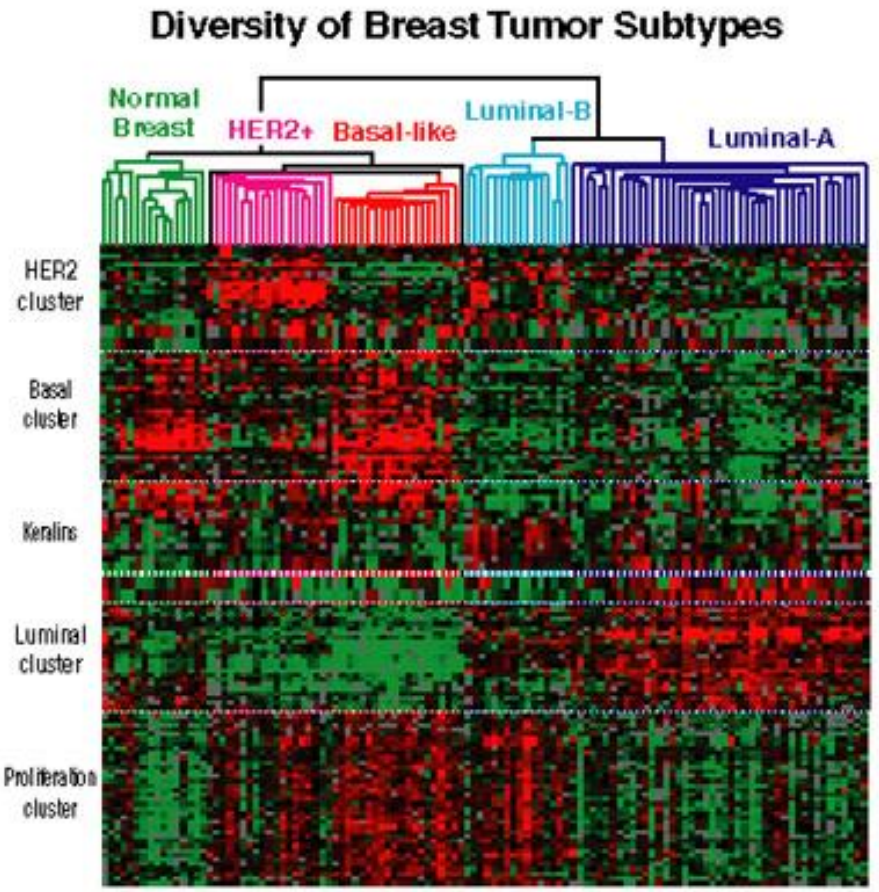
Visvader J E Genes Dev. 2009;23:2563-2577

Subtype Implications

letters to nature

Molecular portraits of human breast tumours

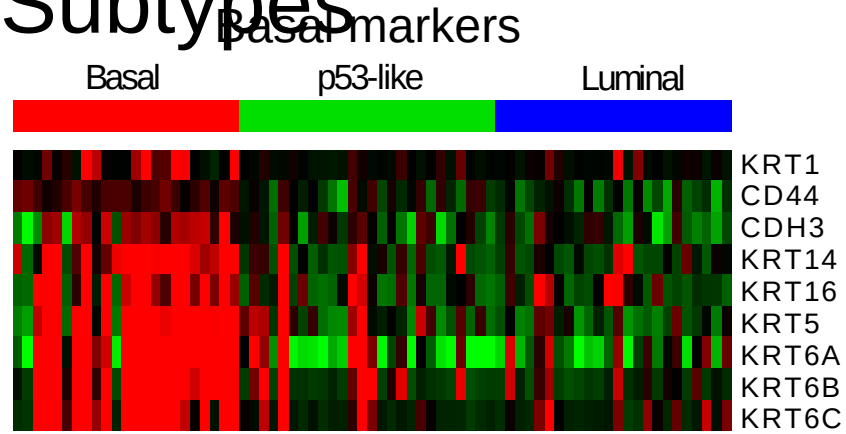
Charles M. Perou*†, Therese Sørlie†‡, Michael B. Eisen*, Matt van de Rijn§, Stefanie S. Jeffrey‖, Christian A. Rees*, Jonathan R. Pollack¶, Douglas T. Ross¶, Hilde Johnsen‡, Lars A. Akslen#, Øystein Fluge☆, Alexander Pergamenschikov*, Cheryl Williams*, Shirley X. Zhu§, Per E. Lønning**, Anne-Lise Børresen-Dale‡, Patrick O. Brown¶†† & David Botstein*

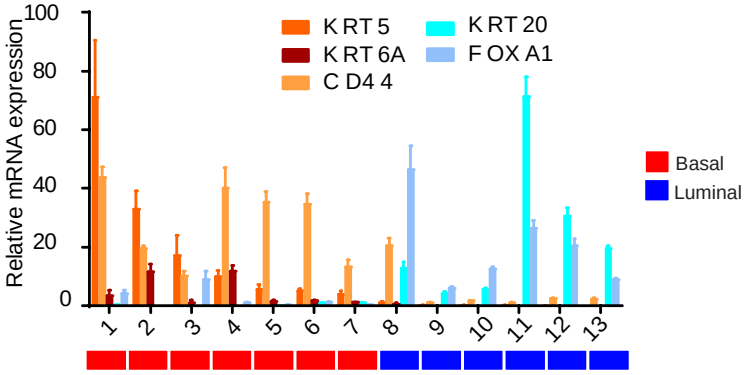


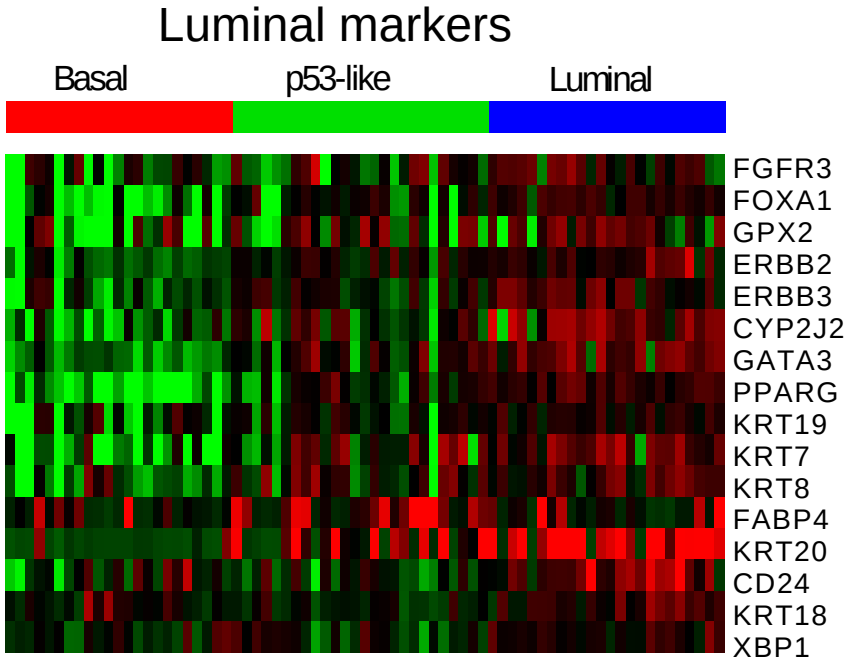
NATURE | VOL 406 | 17 AUGUST 2000 | www.nature.com

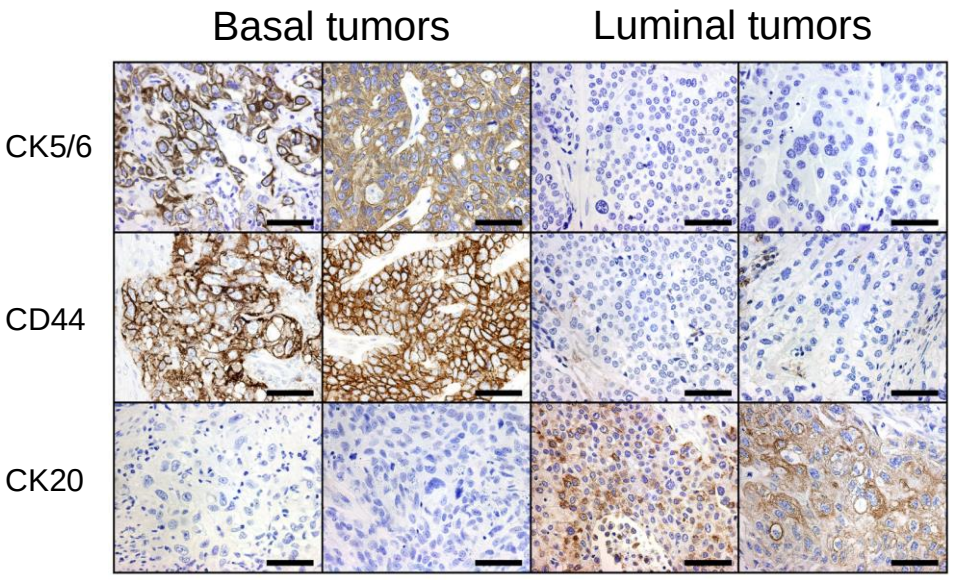
http://genetics.unc.edu/faculty/perou

Expression of Basal and Luminal Markers in Subtypes

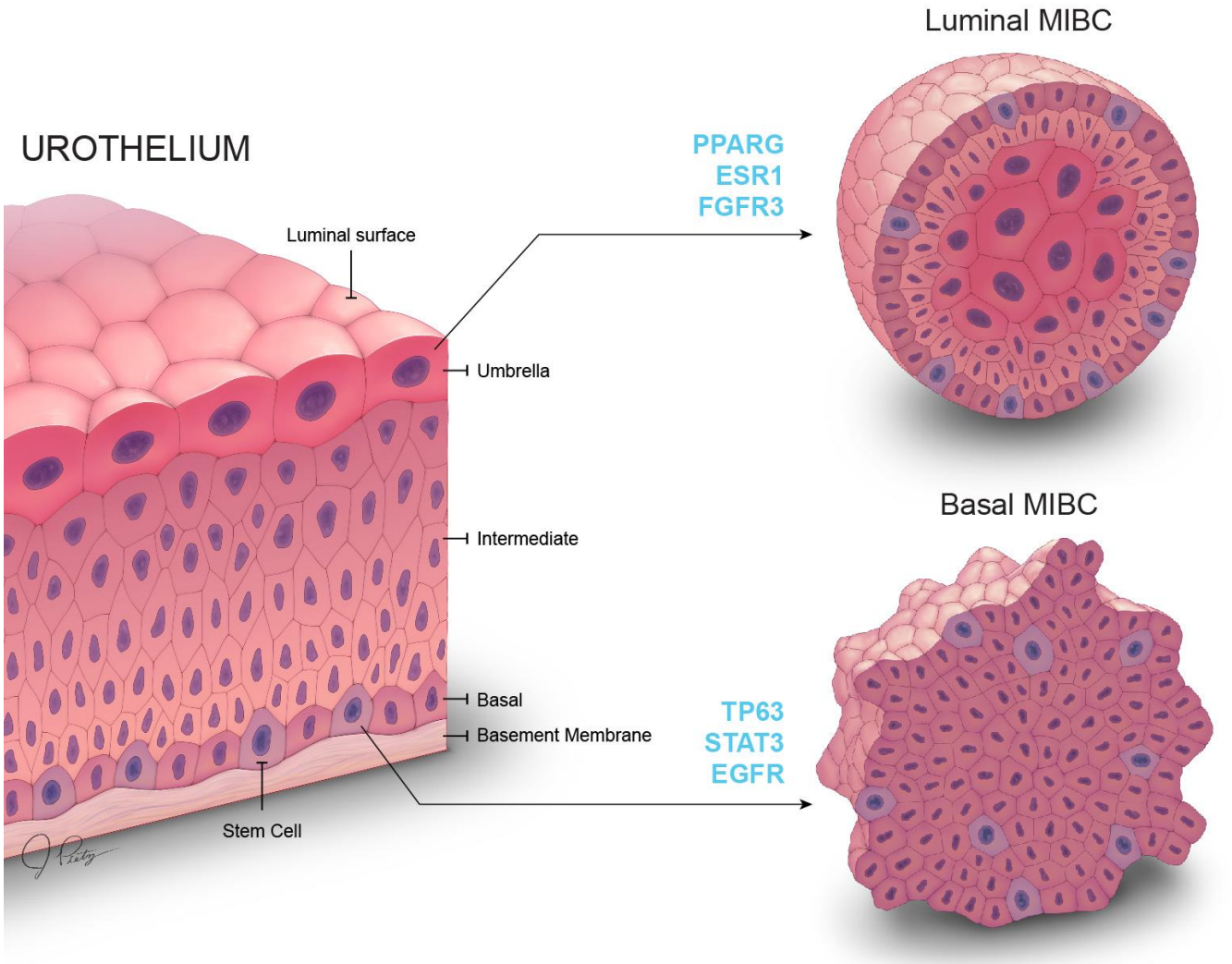








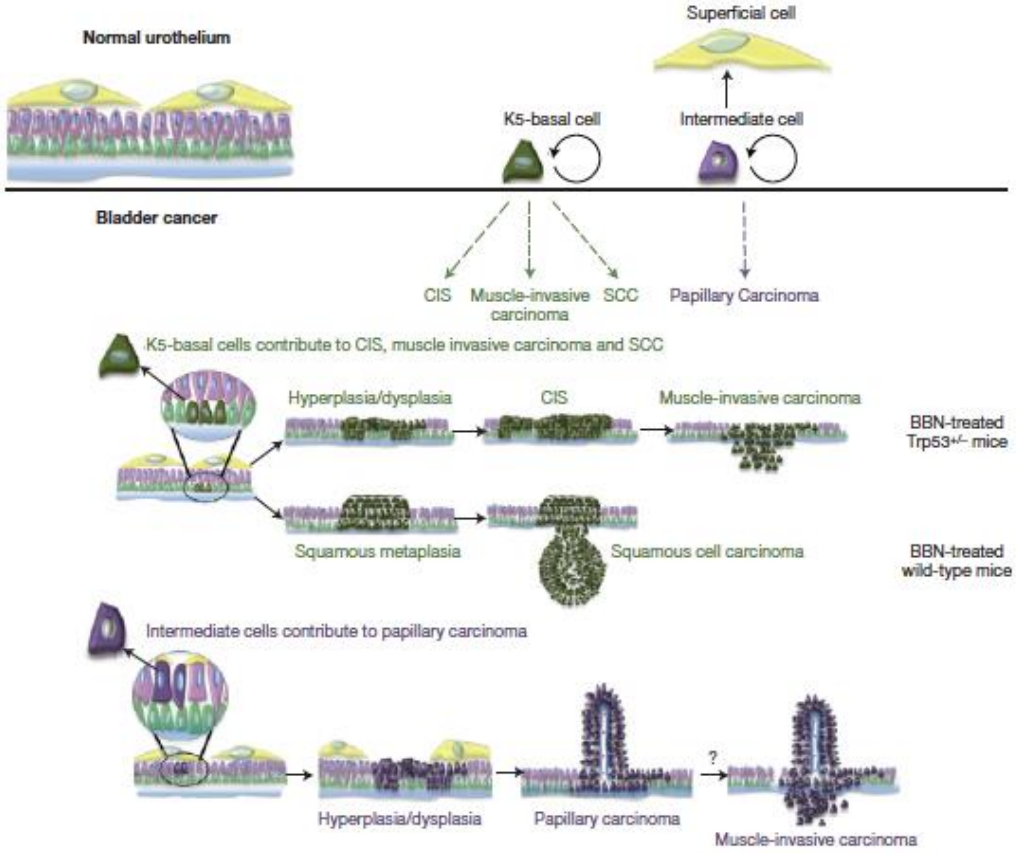
Potential origins of basal and luminal tumors



nature
cell biology

Bladder cancers arise from distinct urothelial sub-populations

Jason Van Batavia[1,6], Tammer Yamany[1,6], Andrei Molotkov[1,6,7], Hanbin Dan[1], Mahesh Mansukhani[2], Ekaterina Batourina[1], Kerry Schneider[1], Daniel Oyon[1], Mark Dunlop[1], Xue-Ru Wu[3,4], Carlos Cordon-Cardo[5] and Cathy Mendelsohn[1,8]



Vol 461|24 September 2009|doi:10.1038/nature08361 nature

ARTICLES

A luminal epithelial stem cell that is a cell of origin for prostate cancer

Xi Wang[1,2,5,6], Marianna Kruithof-de Julio[1,2], Kyriakos D. Economides[5,7]†, David Walker[5,6]†, Hailong Yu[5,6]†, M. Vivienne Halili[5,6]†, Ya-Ping Hu[5,6]†, Sandy M. Price[5,6], Cory Abate-Shen[3,4,5,7] & Michael M. Shen[1,2,5,6]

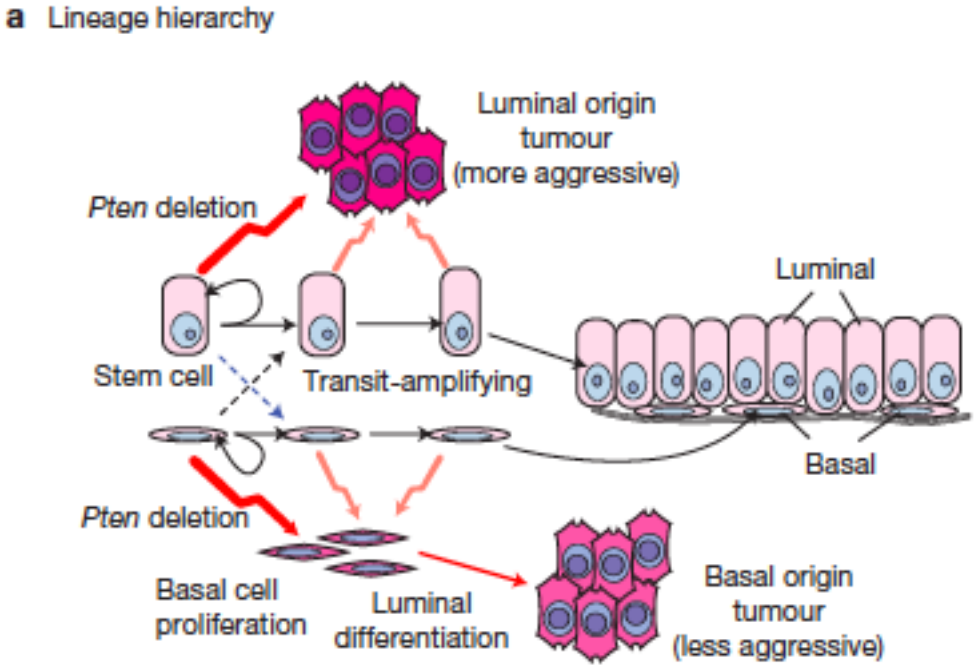
In epithelial tissues, the lineage relationship between normal progenitor cells and cell type(s) of origin for cancer has been poorly understood. Here we show that a known regulator of prostate epithelial differentiation, the homeobox gene *Nkx3-1*, marks a stem cell population that functions during prostate regeneration. Genetic lineage-marking demonstrates that rare luminal cells that express Nkx3-1 in the absence of testicular androgens (castration-resistant Nkx3-1-expressing cells, CARNs) are bipotential and can self-renew *in vivo*, and single-cell transplantation assays show that CARNs can reconstitute prostate ducts in renal grafts. Functional assays of *Nkx3-1* mutant mice in serial prostate regeneration suggest that *Nkx3-1* is required for stem cell maintenance. Furthermore, targeted deletion of the *Pten* tumour suppressor gene in CARNs results in rapid carcinoma formation after androgen-mediated regeneration. These observations indicate that CARNs represent a new luminal stem cell population that is an efficient target for oncogenic transformation in prostate cancer.

Castration-resistant Nkx3-1-expressing cells (CARNs)

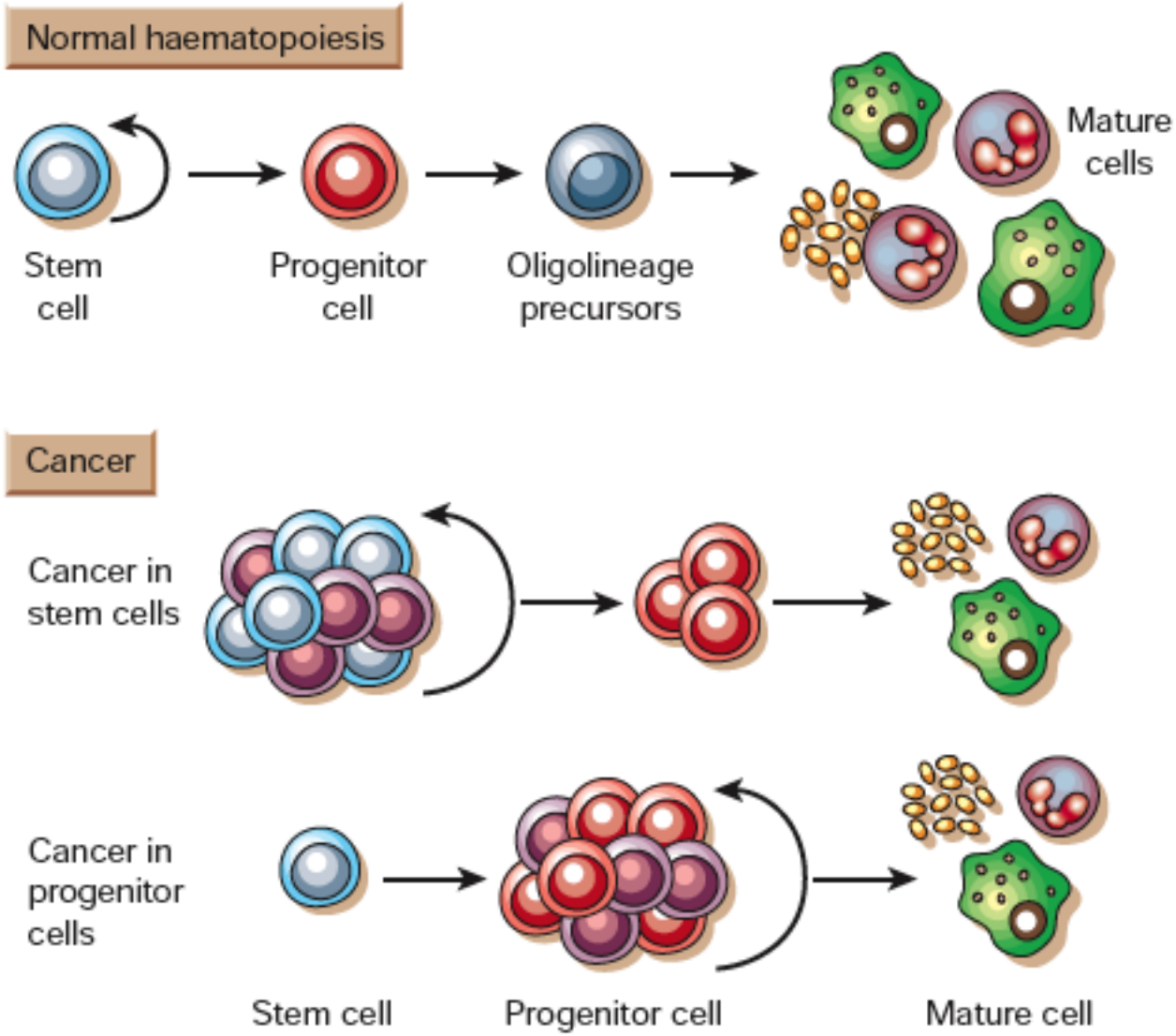
nature cell biology

Lineage analysis of basal epithelial cells reveals their unexpected plasticity and supports a cell-of-origin model for prostate cancer heterogeneity

Zhu A. Wang[1,2], Antonina Mitrofanova[2,3], Sarah K. Bergren[1,2], Cory Abate-Shen[2,4], Robert D. Cardiff[5], Andrea Califano[2,3] and Michael M. Shen[1,2,6]



Stem and committed progenitor cells can both give rise to cancer



Cell

The Epithelial-Mesenchymal Transition Generates Cells with Properties of Stem Cells

Sendurai A. Mani,[1,3,10,*] Wenjun Guo,[1,10] Mai-Jing Liao,[1,10] Elinor Ng. Eaton,[1] Ayyakkannu Ayyanan,[4] Alicia Y. Zhou,[1,2] Mary Brooks,[1] Ferenc Reinhard,[1] Cheng Cheng Zhang,[1] Michail Shipitsin,[5,6] Lauren L. Campbell,[5,7] Kornelia Polyak,[5,6,7] Cathrin Brisken,[4] Jing Yang,[8] and Robert A. Weinberg[1,2,9,*]

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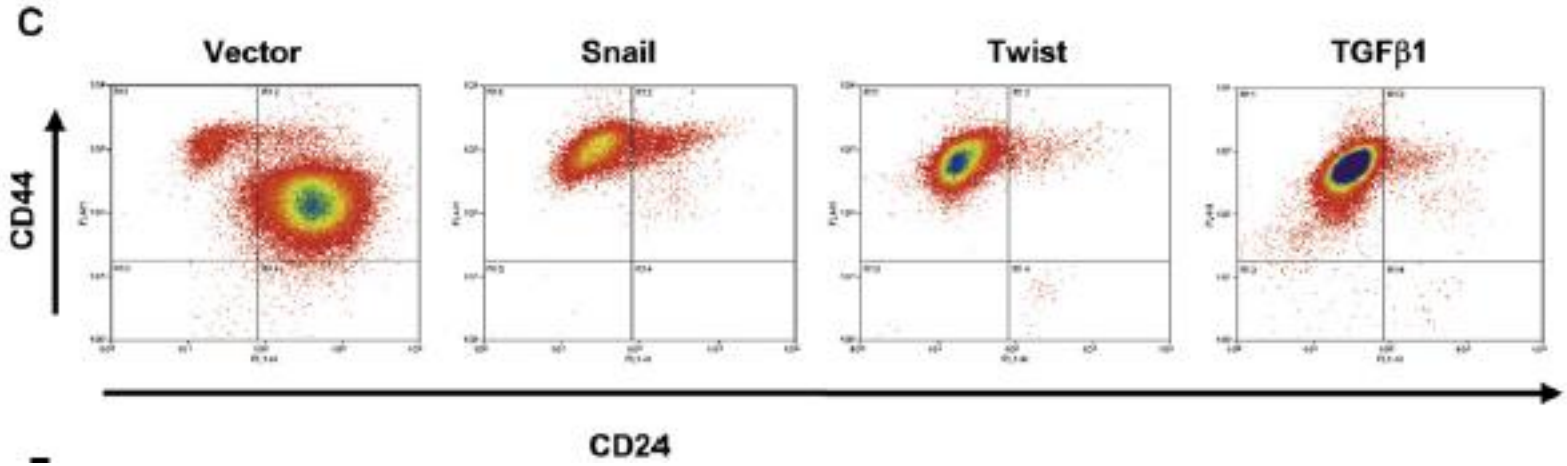
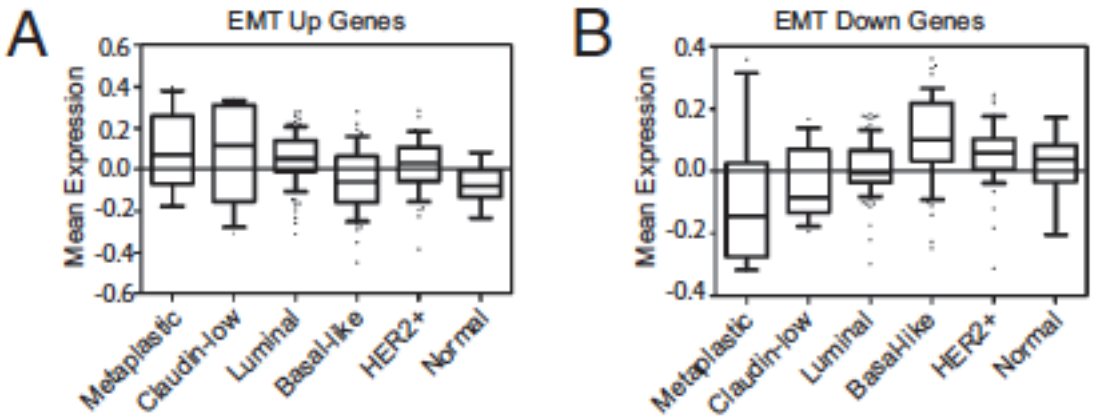
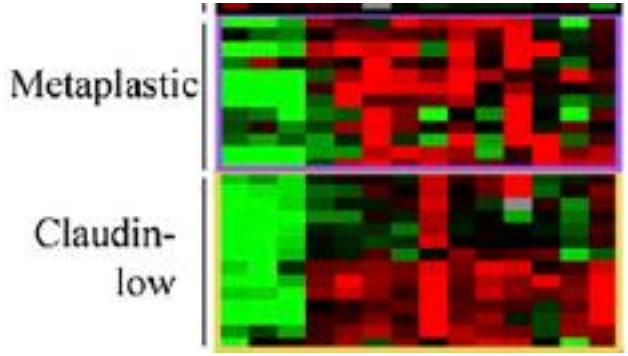
DOI 10.1016/j.cell.2008.03.027



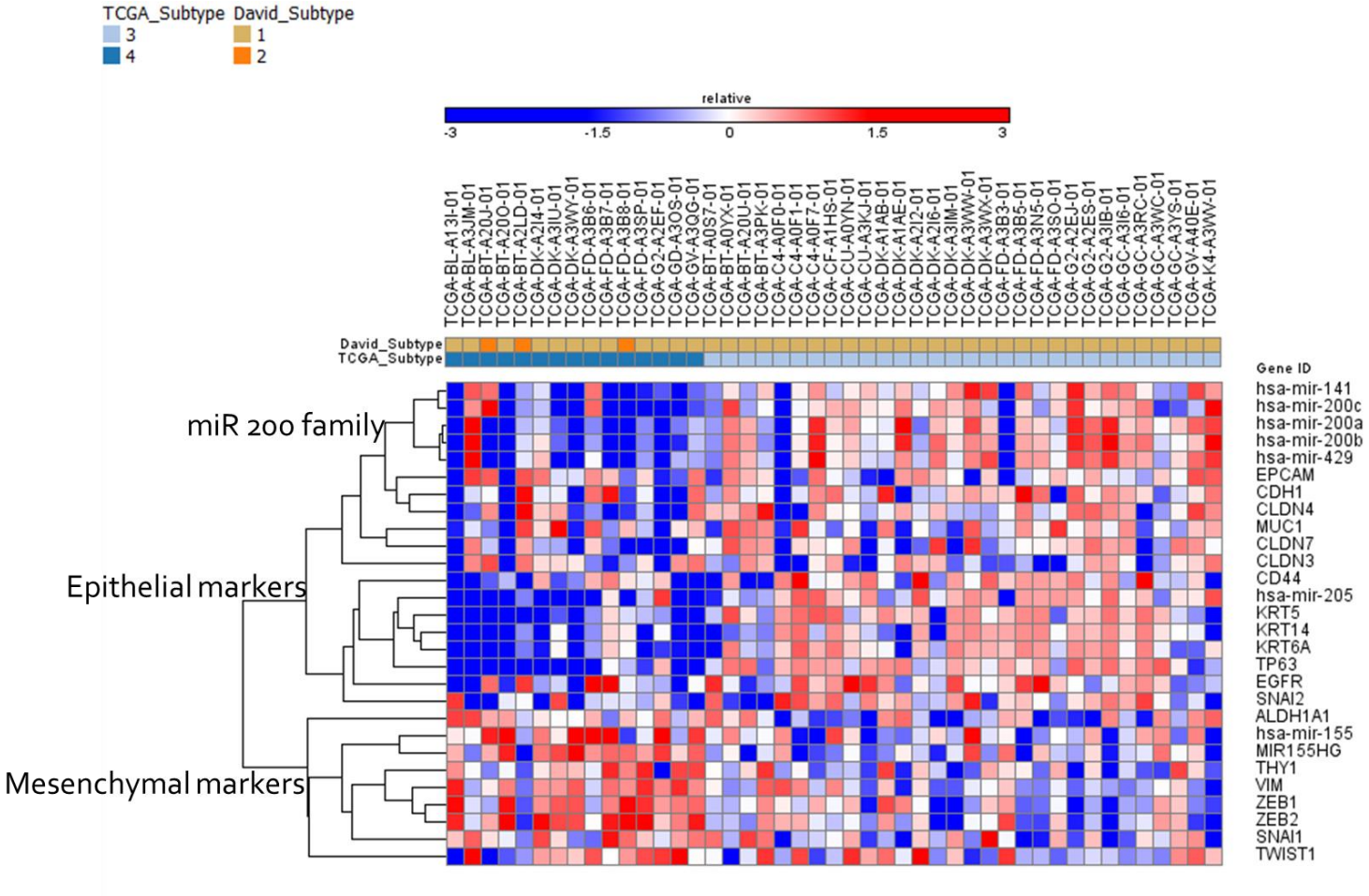
Core epithelial-to-mesenchymal transition interactome gene-expression signature is associated with claudin-low and metaplastic breast cancer subtypes

Joseph H. Taube[a,1], Jason I. Herschkowitz[b,1], Kakajan Komurov[c,1], Alicia Y. Zhou[d,e], Supriya Gupta[f], Jing Yang[g], Kimberly Hartwell[h], Tamer T. Onder[d,e], Piyush B. Gupta[e,f], Kurt W. Evans[a], Brett G. Hollier[a], Prahlad T. Ram[c], Eric S. Lander[d,e,f,i], Jeffrey M. Rosen[b], Robert A. Weinberg[d,e,j,2], and Sendurai A. Mani[a,2]





Claudin-low bladder cancers



TCGA cluster IV = UNC “claudin-low”

Cell

Poised Chromatin at the ZEB1 Promoter Enables Breast Cancer Cell Plasticity and Enhances Tumorigenicity

Christine L. Chaffer,[1,5,*] Nemanja D. Marjanovic,[1,5] Tony Lee,[1] George Bell,[1] Celina G. Kleer,[2] Ferenc Reinhardt,[1] Ana C. D'Alessio,[1] Richard A. Young,[1,3] and Robert A. Weinberg[1,3,4,*]

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[5]These authors contributed equally to this work
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http://dx.doi.org/10.1016/j.cell.2013.06.005

Basal tumor cells can easily switch between “epithelial” and “mesenchymal” states

Stem cell kinetics are associated with cancer incidence

- There is a linear relationship between the odds that a given tissue will produce a tumor and its kinetics of stem cell self-renewal
- In these tissues cancer may be caused by mistakes in the repair of the random DNA damage that occurs during self-renewal rather than to environmental exposures

Rethinking cancer etiology

BIOMEDICINE

The bad luck of cancer

Analysis suggests most cases can't be prevented

By Jennifer Couzin-Frankel

Why? That's the first word on many lips after a cancer diagnosis. "It's a perfectly reasonable question," says Bert Vogelstein, a cancer geneticist at Johns Hopkins University in Baltimore, Maryland, who has spent a lifetime trying to answer it. Thanks to his friendship with a recently minted Ph.D. in applied mathematics, the two now propose a framework arguing that most cancer cases are the result of biological bad luck.

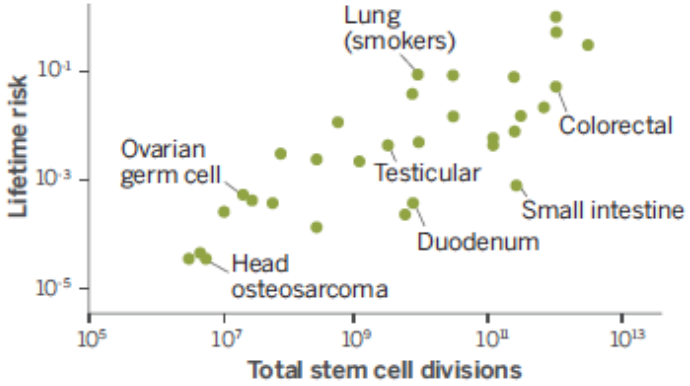
In a paper published on page 78 this week in *Science*, Vogelstein and Cristian Tomasetti, who studies mathematics and biology at Harvard University and has worked with Tomasetti and Vogelstein. "It's a baseline risk of being an animal that has cells that need to divide."

The idea emerged during one of the pair's weekly brainstorming sessions in Vogelstein's office. They returned to an age-old question: How much of cancer is driven by environmental factors, and how much by genetics?

Random mutations in healthy cells may explain two-thirds of cancers, like this one in the colon.

Charting cancer risk

As the number of stem cell divisions in a tissue rises, so does the chance of cancer striking that site.



Science,