INTRODUCTION

How a cell becomes cancerous ?

New cell properties

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Key facts about cancer

Second leading cause of death
after cerebrovascular diseases

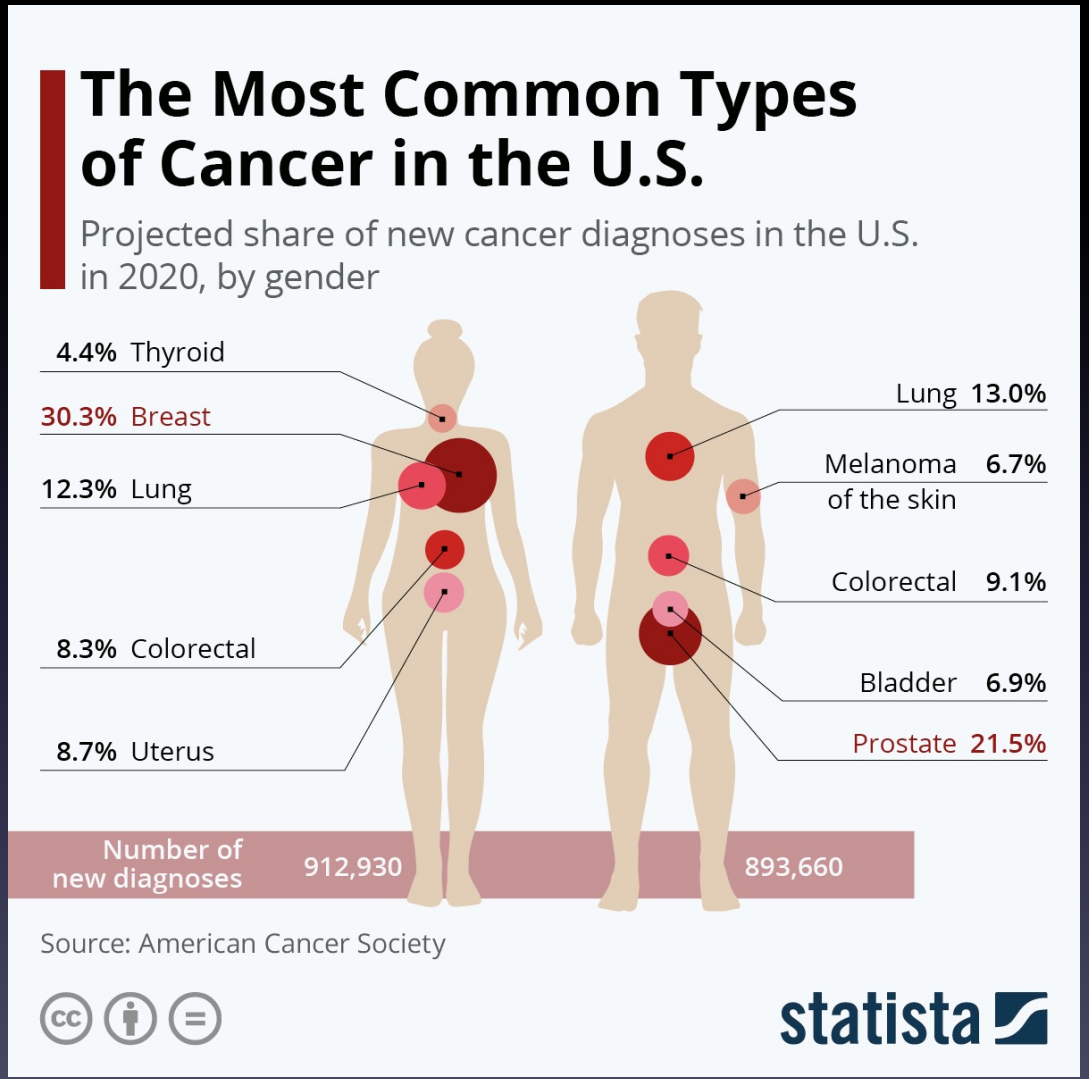
New estimates worldwide
19.3 million cases and
10 million cancer deaths in 2020

GLOBALLY

1 OUT OF 6 DEATHS

is due to **cancer**

World Health Organization



Cancer prognosis evaluation

- ✓ Tumors are classified according to their organ of origin (breast, liver, kidney, bones)

- ✓ Pathological examination to establish the TYPE, GRADE and STAGE of the tumor

  TYPES

  Carcinoma (epithelial tissue), Sarcoma (connective tissue), Lymphoma and Leukemia (blood cells), Neuroblastoma (embryonic tissue), ...

  GRADES *written in Arabic numerals*

  Differentiation, nuclear and cytoplasmic abnormalities, number of mitoses, extension of necrosis...

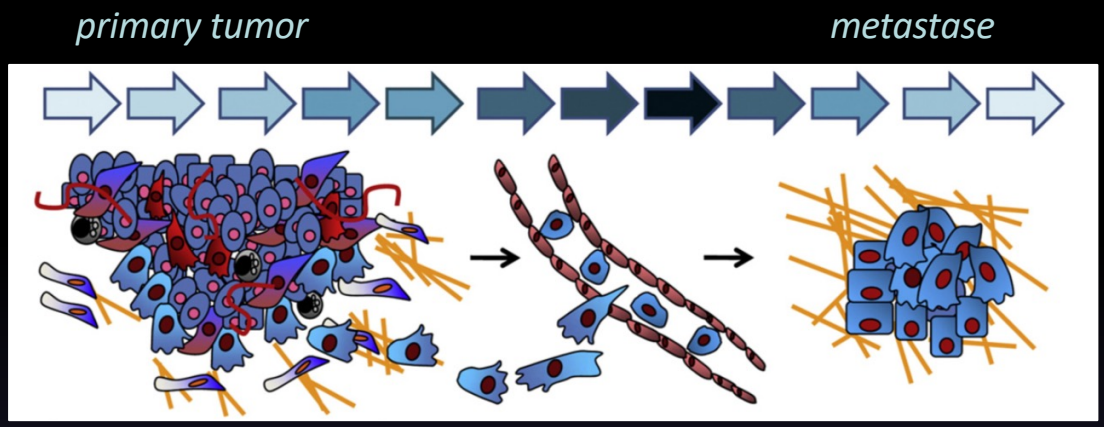
  Example : the Gleason score to grade prostate cancer

  STAGES *represented as Roman numerals*

  TNM classification followed by a number from 0 (no cancer), I to IV, X impossiblity to evaluate
  T: size of the tumor
  N: putative regional lymph node invasion
  M: distant metastases

- ✓ Search for molecular markers allow to precise the spontaneous pronostic or are predictive of an answer to a treatment

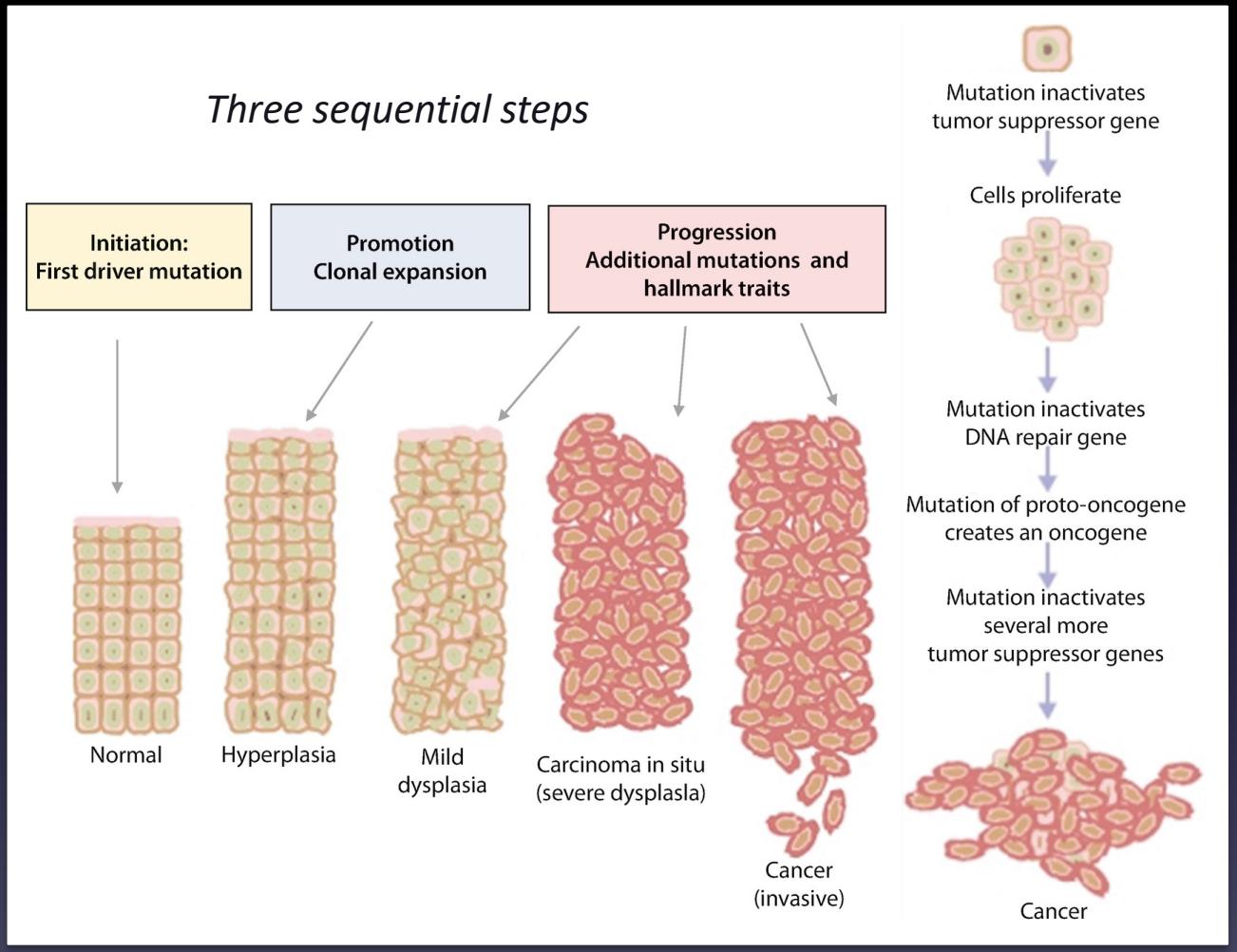
Cancer: a multistep process



Paoli et al., BBA 2013

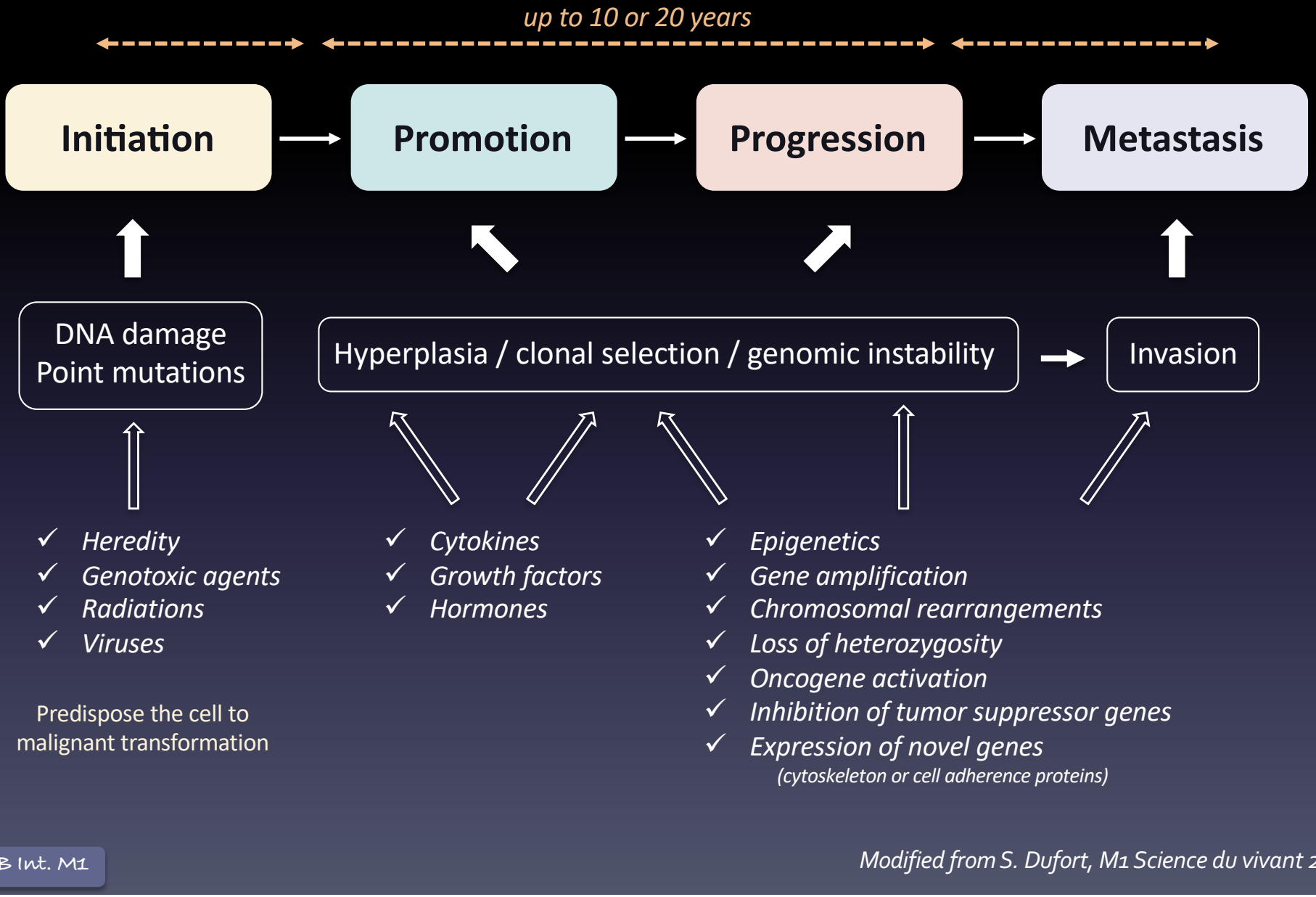
- carcinogenesis in the primary site
- hyperproliferation
- hypoxic environment
- sustained angiogenesis
- crosstalk with parenchymal, stromal, endothelial and inflammatory cells
- migration and invasiveness
- intravasation into the bloodstream
- cell survival in the blood and lymphatic vessels
- extravasation from the circulation
- metastatic niche in which cancer cells should adapt
- growth of the invading cells in the new site

Cancer: a multistep process



Compton, Cancer: The Enemy from Within, Springer Ed., 2020 pp 25-48

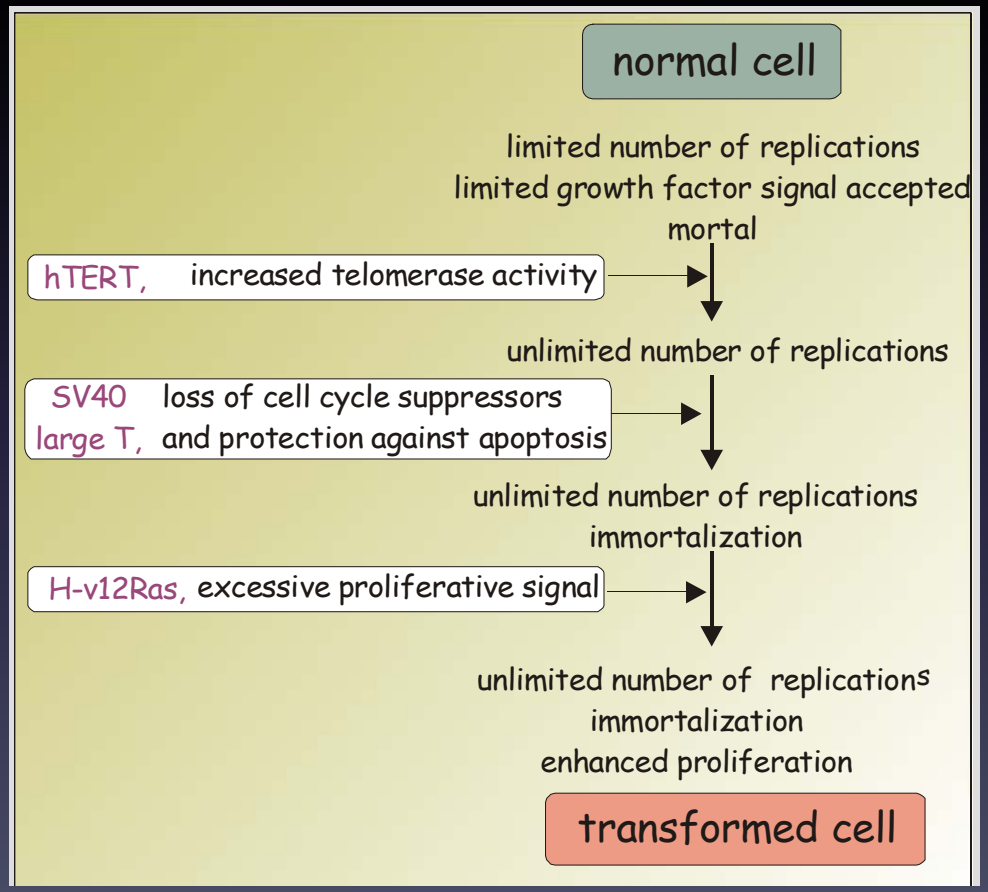
Cancer: a multigenic and multifactorial disease



Modified from S. Dufort, M1 Science du vivant 2008

Transformed cells acquire new properties

Example :
Three specific gene modifications are sufficient to convert a normal cell into a transformed one



Sequential mutations induce new cell properties

- ✓ Immortality
- ✓ Decreased sensitivity to growth suppressors
- ✓ Increased resistance to cell deaths
- ✓ Sustained proliferative signaling
- ✓ Decreased cell-cell and cell-matrix interactions
- ✓ Avoiding immune destruction
- ✓ ...

The Hallmarks of Cancer

Etiology of cancer : a genetic disease

All cancers arise from changes in genes (mutations) but NOT all are inherited

Differentiating hereditary from sporadic cancers

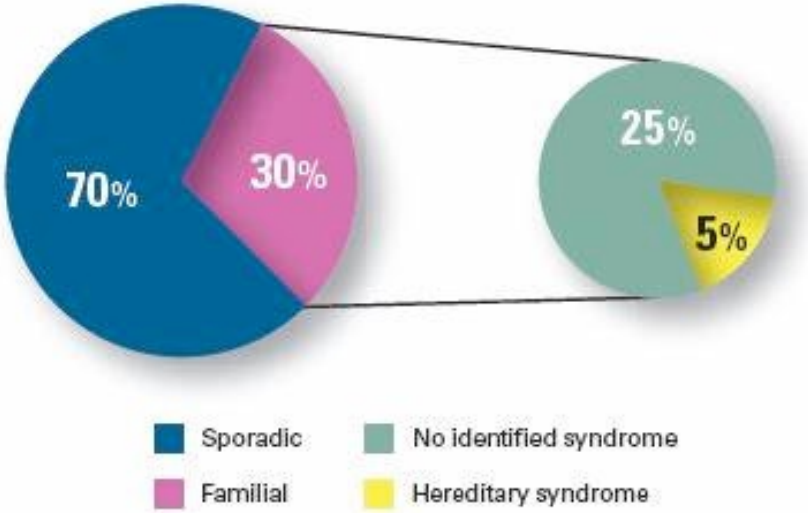


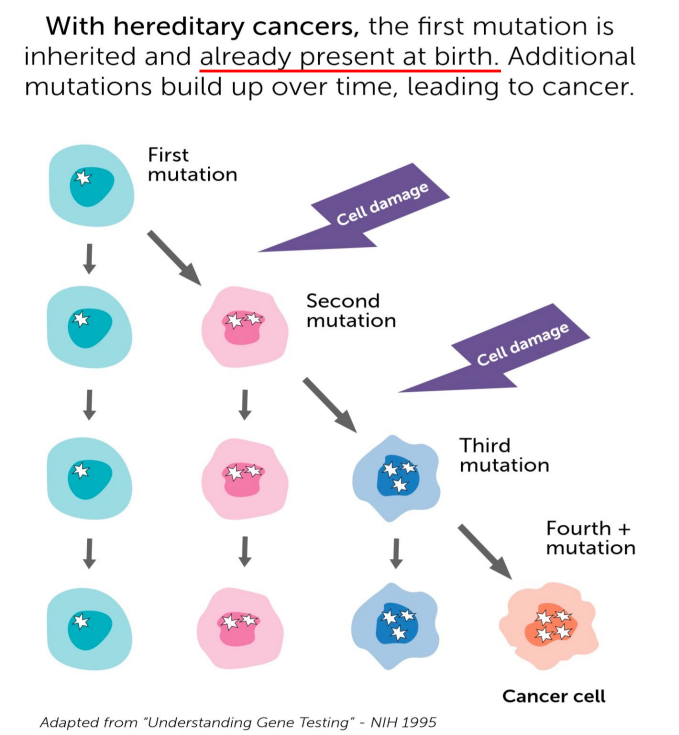
Figure 2. Approximate Prevalence of Sporadic and Familial Colorectal Cancer—Most patients with colorectal cancer have sporadic disease, and only a small fraction of patients with familial colorectal cancer have an identifiable hereditary syndrome.

Data from Grady WM. Gastroenterology. 2003.[12]

Hereditary versus Sporadic cancers

Hereditary cancer

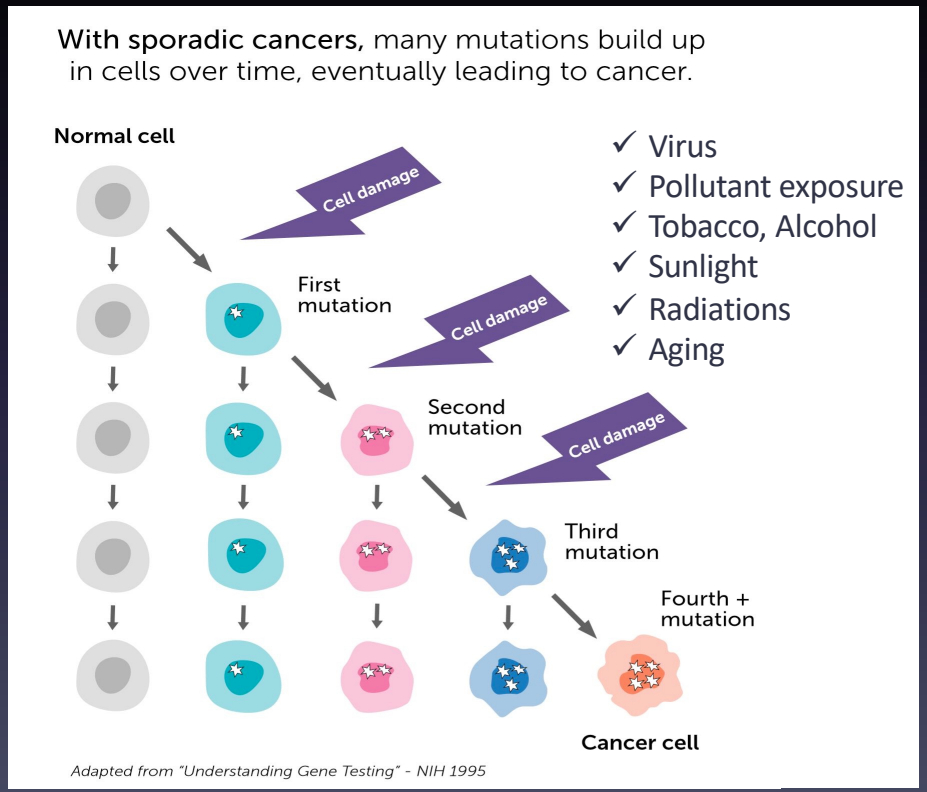
Inherited cancer syndromes are caused by mutations (changes) in certain genes passed from parents to children



→ *Higher risk*

Sporadic cancer

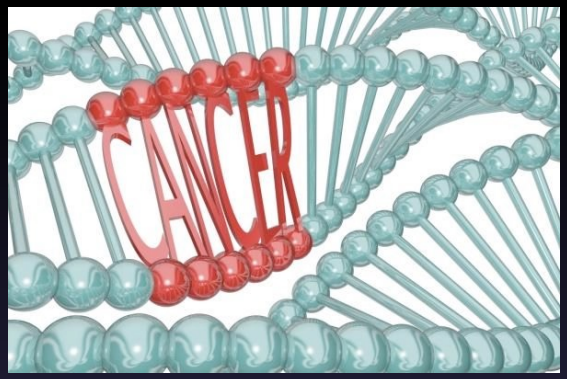
Cancer that occurs in people who do not have a family history of that cancer or an inherited change in their DNA that would increase their risk for that cancer



→ *Generally has a later onset*

Hereditary cancers

Mutations that you have inherited from your parents



- ✓ Breast cancer
- ✓ Familial adenomatous polyposis
  Colon cancer

Both are transmitted in an autosomal dominant pattern

PRÉDISPOSITIONS GÉNÉTIQUES	PRINCIPAUX GÈNES ASSOCIÉS
SYNDROME SEINS-OVAIRES	BRCA1, BRCA2, PALB2, RAD51
SYNDROME DE LYNCH	MLH1, MSH2, MSH6, PMS2, EPCAM
ADÉNOMES HYPOPHYSAIRES FAMILIAUX	AIP
ATAXIE-TÉLANGIECTASIE	ATM, MRE11A
CANCER GASTRIQUE DIFFUS FAMILIAL	CDH1
CARCINOME PAPILLAIRE RÉNAL HÉRÉDITAIRE	FH, MET
HYPERPARATHYROÏDISME	CDC73, CASR
MALADIE DE COWDEN	PTEN, PIK3CA, AKT1
MALADIE DE FANCONI	FANC
MALADIE DE VON HIPPEL-LINDAU	VHL
MÉLANOME MALIN FAMILIAL	CDKN2A, MITF, BAP1, POT1, CDK4
NÉOPLASIES ENDOCRINIENNES	MEN1, RET, CDKN1B
NEUROFIBROMATOSES	NF1, NF2, LZTR1, SMARCB1, SPRED1, SMARCE1
PHÉOCHROMOCYTOME-PARAGANGLIOME HÉRÉDITAIRE	SDH, TMEM127, MAX, EPAS1
POLYPOSES ADÉNOMATEUSES FAMILIALES	APC, MUTYH, POLE, POLD1, NTHL1
RÉTINOBLASTOME	RB1
SYNDROME DE BIRT-HOGG-DUBÉ	FLCN
SYNDROME DE BLOOM	BLM
SYNDROME DE CARNEY	PRKAR1A, ARMC5
SYNDROME DE GORLIN	PTCH1, PTCH2, SUFU
SYNDROME DE LI-FRAUMENI	TP53, CHEK2
SYNDROME DE NIJMEGEN	NBN
SYNDROME DE PEUTZ-JEGHERS	STK11
SYNDROME DE POLYPOSE JUVÉNILE	BMPR1A, SMAD4
SYNDROME DE WERNER	WRN
XERODERMA PIGMENTOSUM	XP

Hereditary cancers : the case of BRCA genes

BRCA1
BReast Cancer 1

BRCA2
BReast Cancer 2

The most well-known genes linked to breast cancer risk

Table 12.1 Human familial cancer syndromes due to germ-line defects in DNA repair

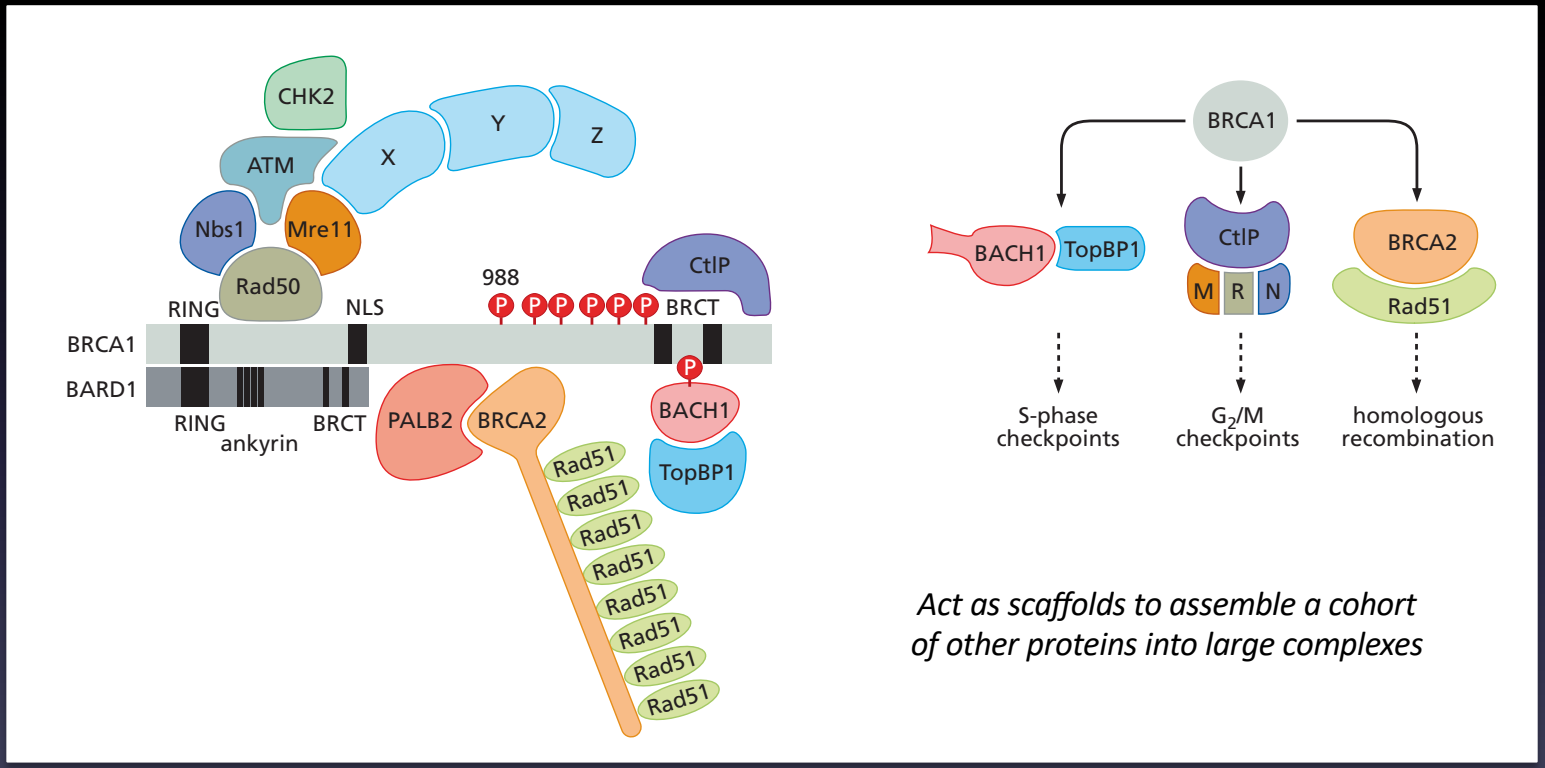
Name of syndrome	Name of gene	Cancer phenotype	Enzyme or process affected
HNPCC/Lynch	(4–5 genes)[a]	colonic polyposis	mismatch repair enzymes
XP[b]	(8 genes)[b]	UV-induced skin cancers	nucleotide-excision repair
ataxia telangiectasia (AT)[c]	*ATM*	leukemia, lymphoma	response to dsDNA breaks
AT-like disorder[c]	*MRE11*	lung, breast cancers	dsDNA repair by NHEJ
Familial breast, ovarian cancer	*BRCA1, BRCA2,*[d] *BACH1, RAD51C*	breast, ovarian, prostate carcinomas	homology-directed repair of dsDNA breaks
Werner	*WRN*	sarcomas, other cancers	exonuclease and DNA helicase,[e] replication
Bloom	*BLM*	leukemias, lymphomas, solid tumors	DNA helicase, replication
Fanconi anemia	(13 genes)[f]	AML, diverse carcinomas	repair of DNA cross-links and ds breaks
Nijmegen breakage[g]	*NBS*	mostly lymphomas	processing of dsDNA breaks, NHEJ
Li–Fraumeni	*TP53*	multiple cancers	DNA damage alarm protein
Li–Fraumeni	*CHK2*	colon, breast carcinomas	kinase signaling DNA damage
Rothmund–Thomson	*RECQL4*	osteosarcoma	DNA helicase
Familial adenomatosis	*MYH*	colonic adenomas	base-excision repair
Familial breast cancer	*PALB2*	breast cancer	dsDNA repair by HR

Weinberg, The Biology of Cancer *Garland Science, Taylor & Francis Group, LLC 2014*

Hereditary cancers : the case of BRCA genes

Loss of BRCA1 partners affects homology-directed repair of dsDNA breaks

Loss of BRCA1 partners affects checkpoint controls in the cell cycle and homologous recombination



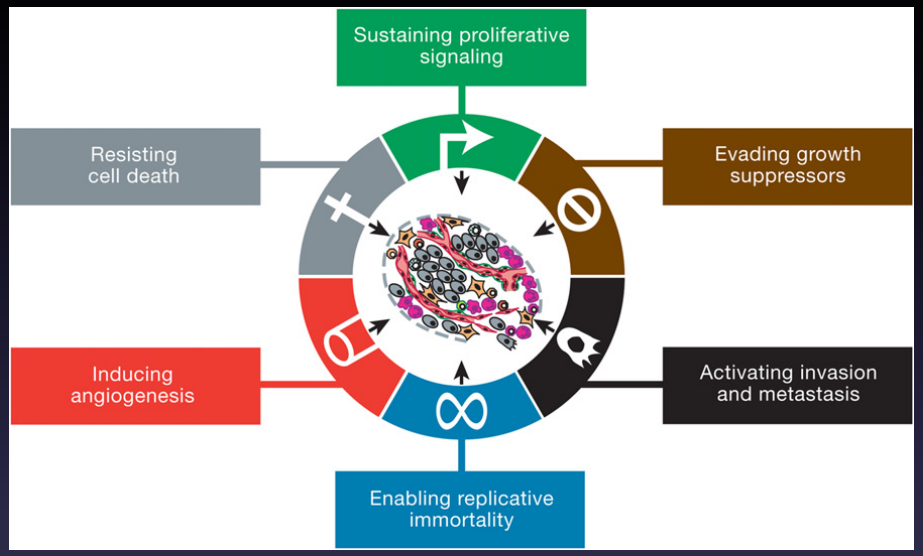
Weinberg, The Biology of Cancer Garland Science, Taylor & Francis Group, LLC 2014

Half of sporadic breast carcinomas carry inactive BRCA1 gene copies, silenced through promoter methylation

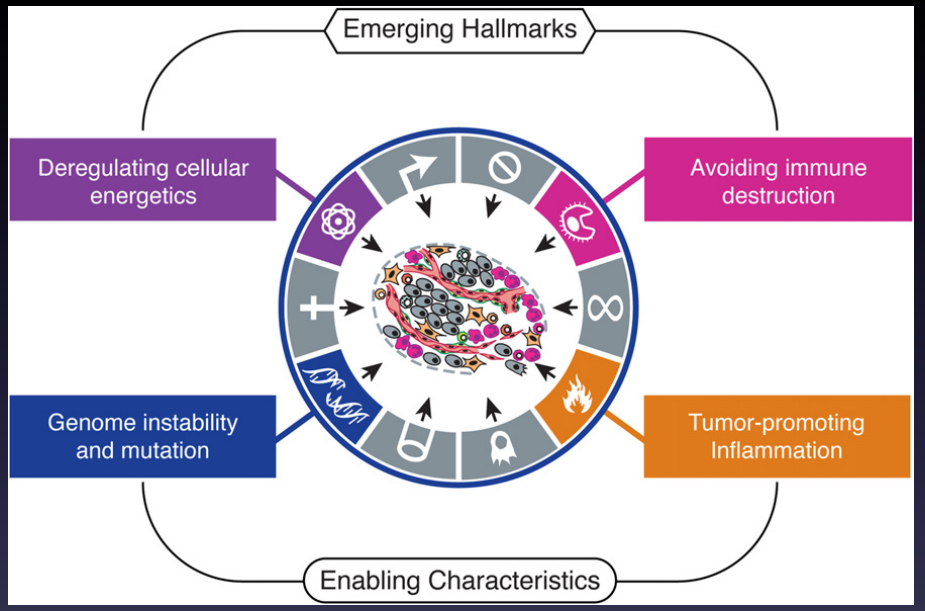
This gene suffers the same fate in ~40% of sporadic epithelial ovarian carcinomas

The Hallmarks of Cancer

Emerging Hallmarks and enabling characteristics due to research progress



Hanahan and Weinberg, Cell 2000



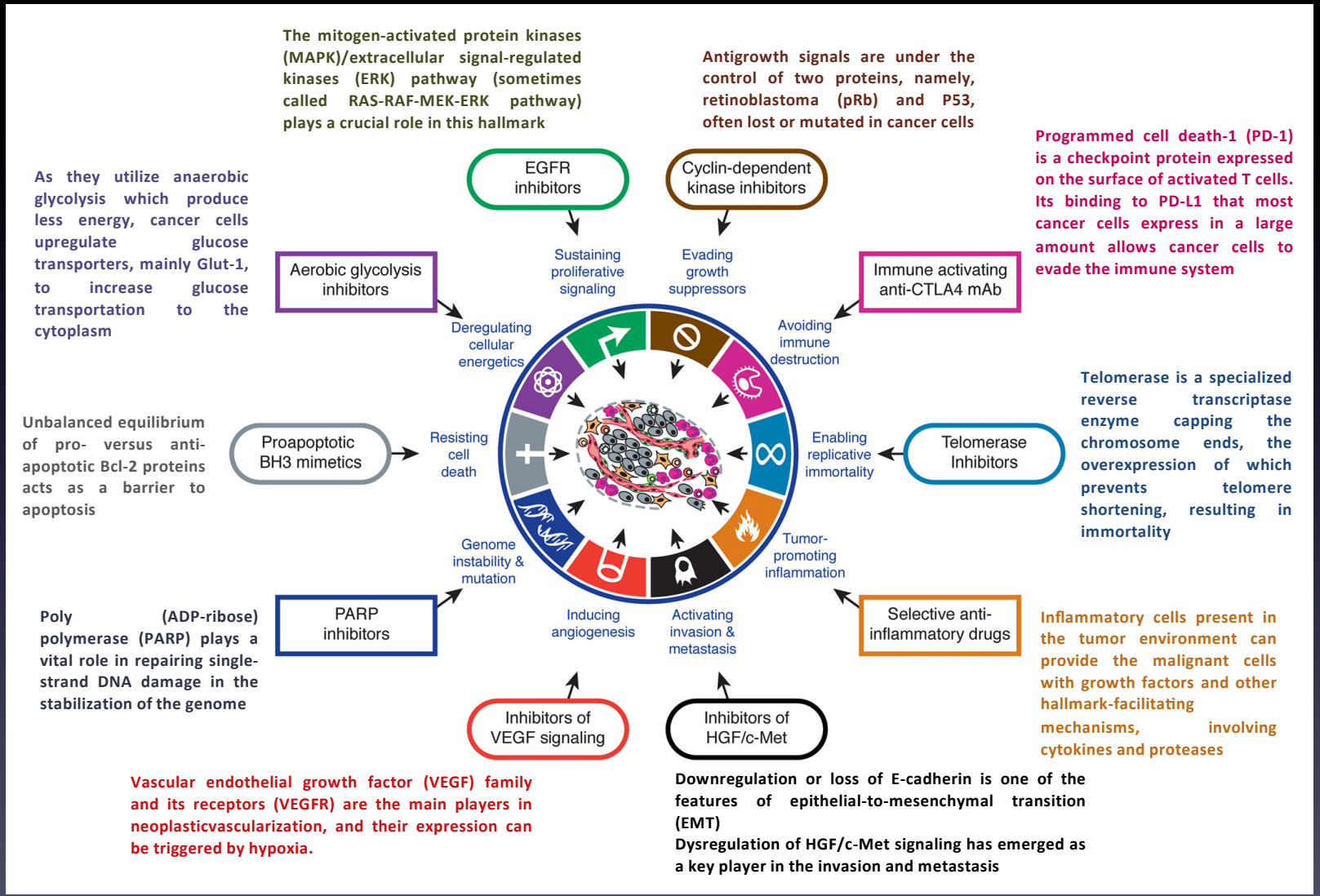
Hanahan and Weinberg, Cell 2011

Six hallmarks capabilities → *Ten hallmarks capabilities*

Targeting these pathways has improved survival dramatically in most cancers

The Hallmarks of Cancer

Main proteins or pathways are dysregulated in the carcinogenesis process



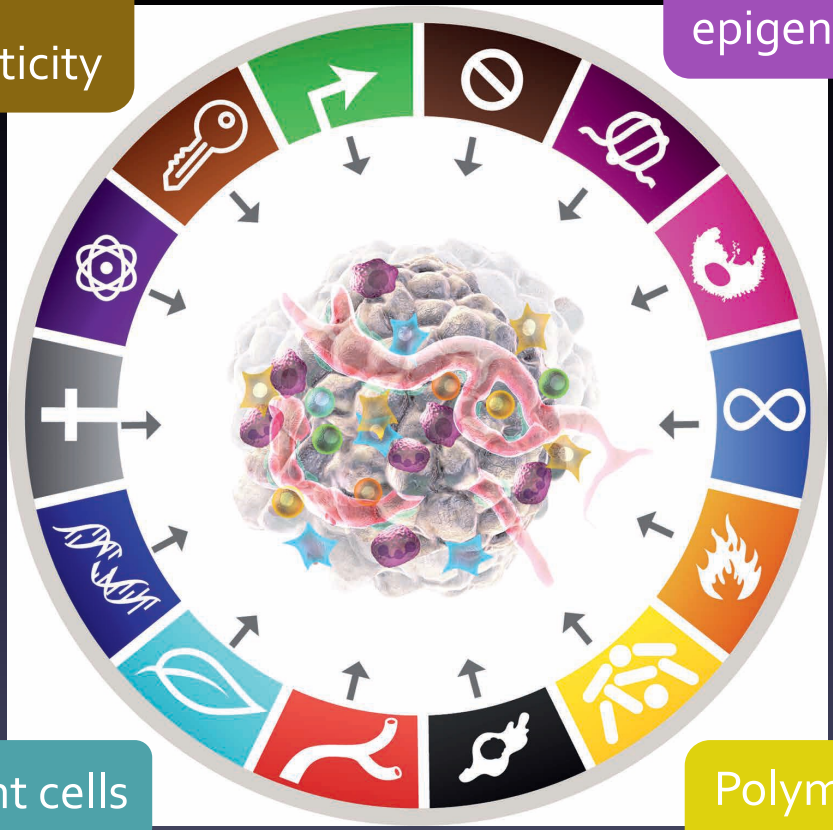
Hanahan and Weinberg, Cell 2011 *Al-Bedeary et al., Iraqi J. Hemat. 2020*

The Hallmarks of Cancer

New additions

Unlocking phenotypic plasticity

Nonmutational epigenetic reprogramming



Senescent cells

Polymorphic microbiomes

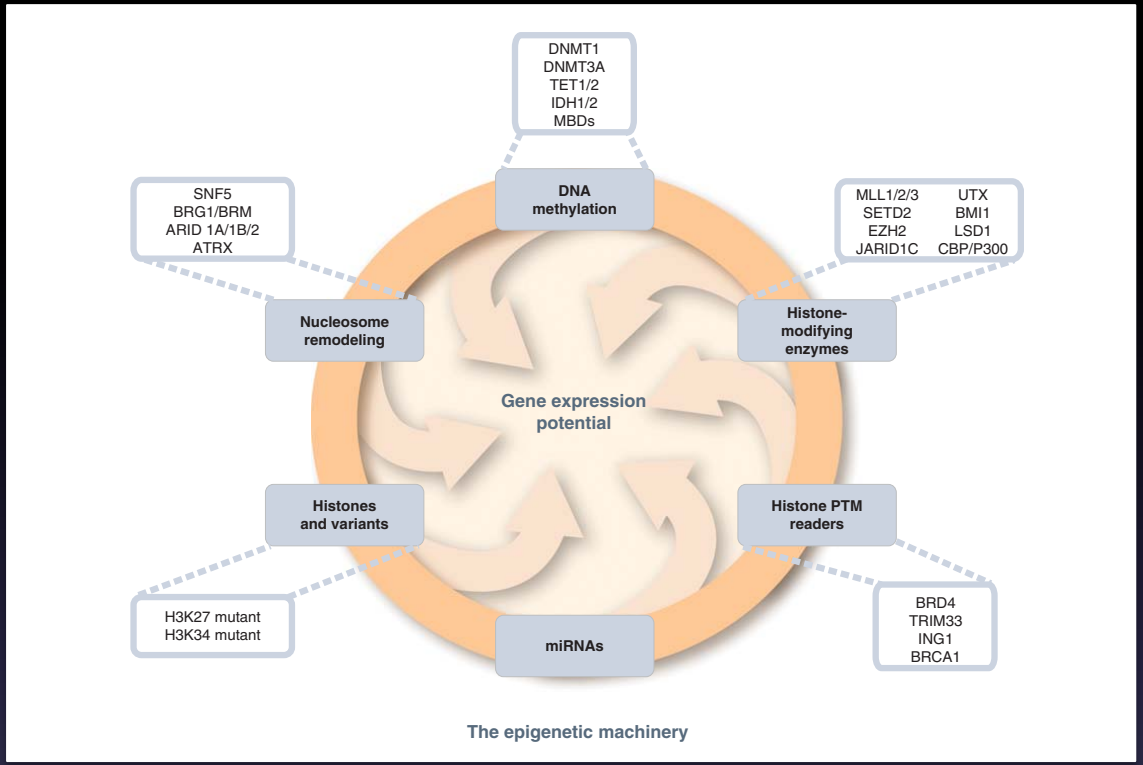
Hanahan, Cancer discovery 2022

Epigenetic reprogramming

Genetic mutations in genes involved in the control of gene expression *(epigenetic modifiers)*

Three main epigenetic mechanisms :

DNA methylation
Histone posttranslational modifications
Noncoding RNAs



Baylin and Jones, Cold Spring Harb Perspect Biol 2016

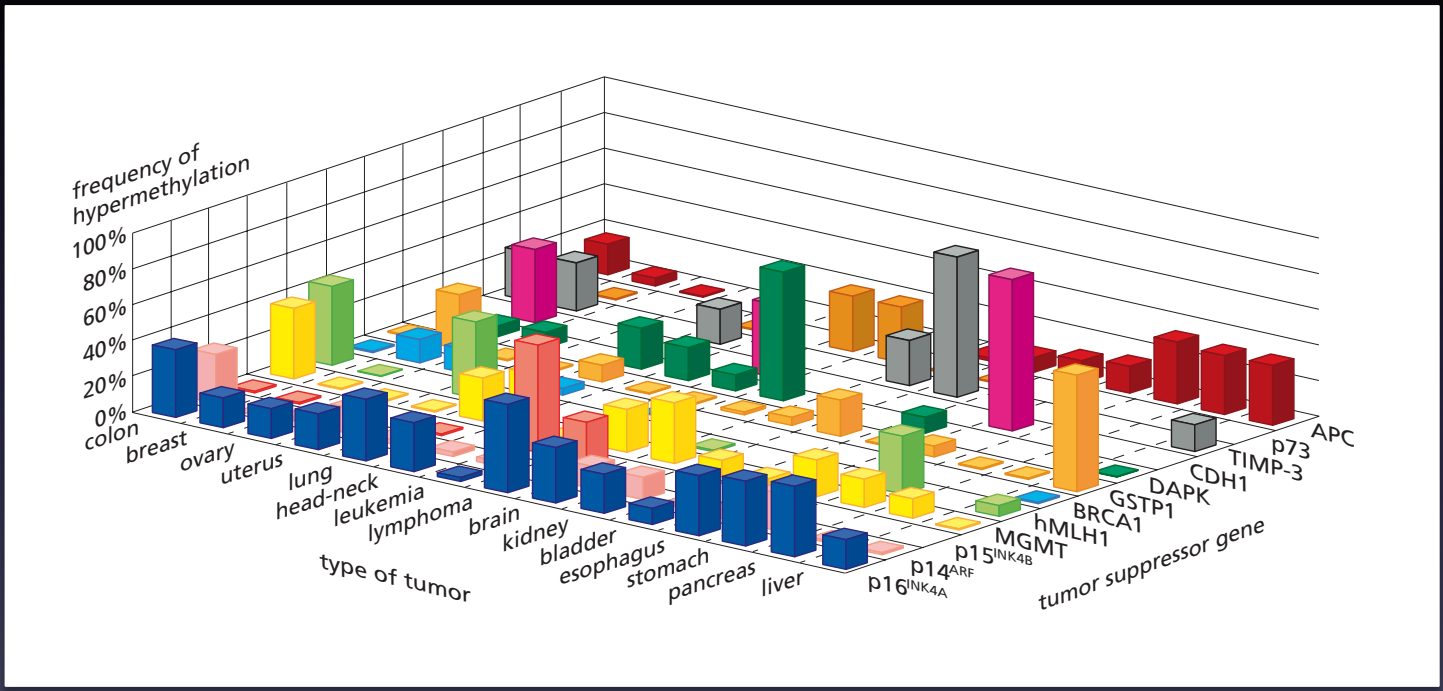
The Cancer Genome Atlas, a database of crucial genomic changes in 33 different cancers
https://cancergenome.nih.gov/

The cBio Cancer Genomics Portal is a web-based platform which offers access to 5000 tumor samples from 20 various cancer studies
http://www.cbioportal.org/

Epigenetic reprogramming

Promoter hypermethylation of genes playing important roles in processes encompassing tumor suppression, cell cycle regulation, apoptosis, DNA repair, and metastastic potential

Hypermethylation signature specific of each cancer types

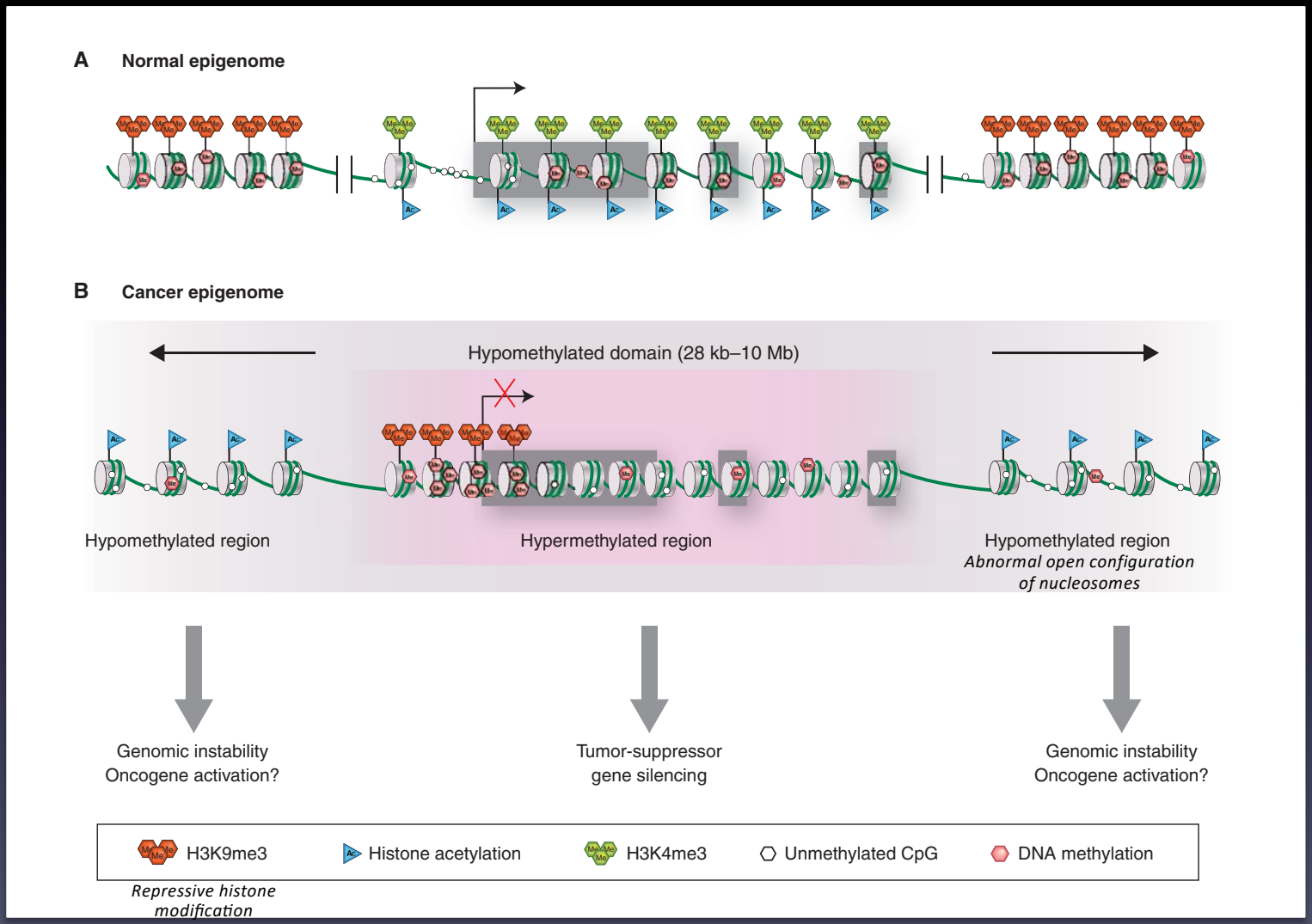


Esteller, Cancer Res. 2001

Epigenetic reprogramming

Chromatin structural changes in cancer cells

Covalent modification of histones is critical in making regions of chromatin more or less hospitable for transcription



Baylin and Jones, Cold Spring Harb Perspect Biol 2016

Epigenetic reprogramming

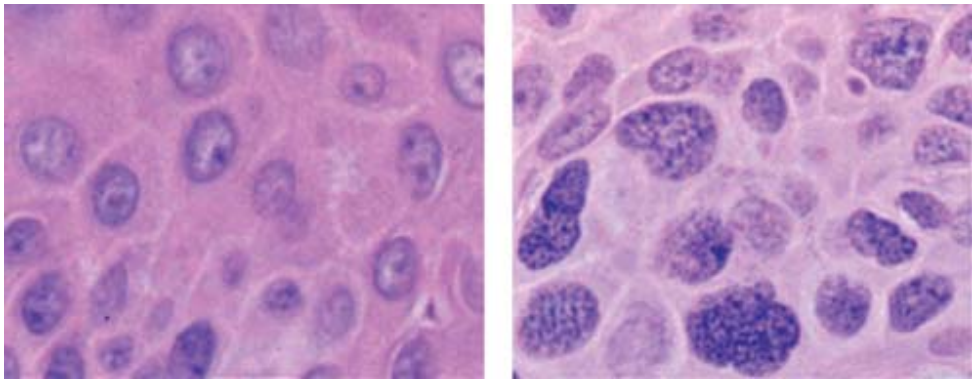


Figure 2. Chromatin structural changes in cancer cells. These two photomicrographs were taken from a patient with a squamous cell carcinoma of the skin. The *left* panel shows normal epidermal cells within one millimeter of the contiguous tumor shown at the same magnification on the *right*. The chromatin, which stains purple as a result of its affinity to hematoxylin, appears much more coarse and granular in the cancer cells than in normal epidermis. Such changes in the staining characteristics of chromatin are used by pathologists as diagnostic criteria for cancer.

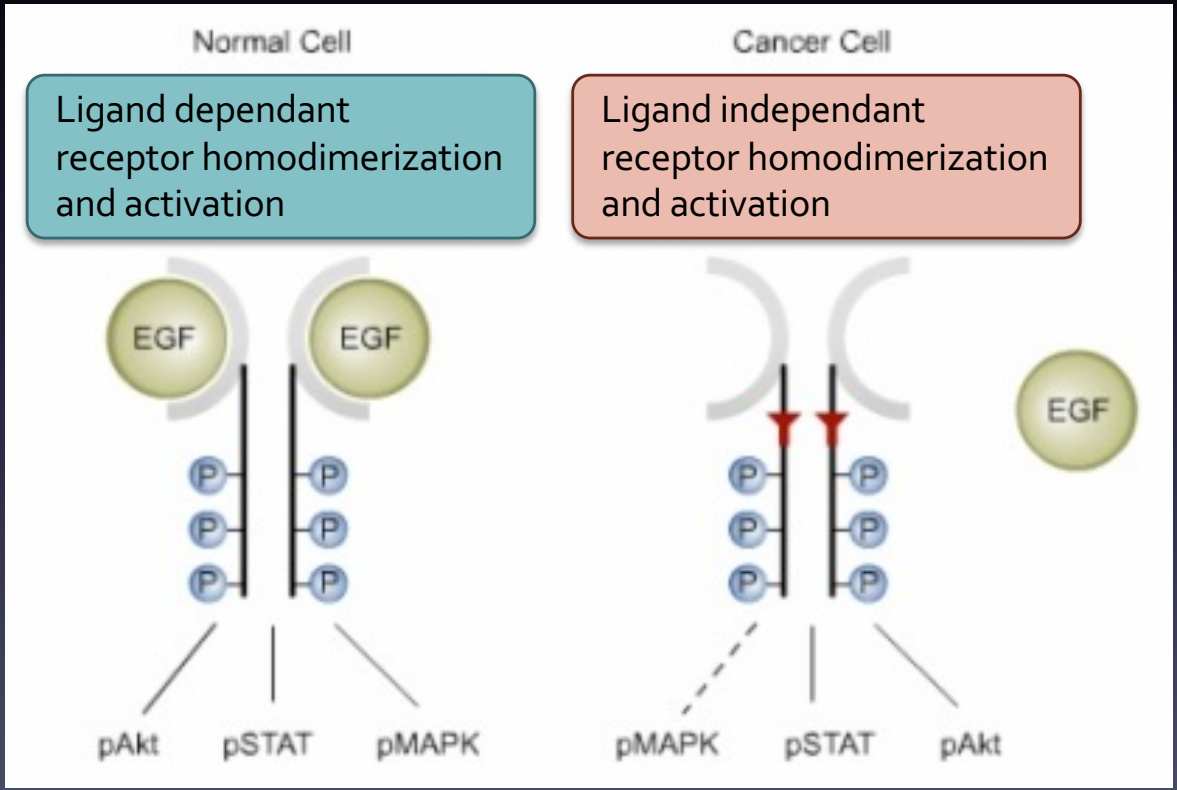
Baylin and Jones, Cold Spring Harb Perspect Biol 2016

Sustained proliferation

Cancer cells produce their own growth signals

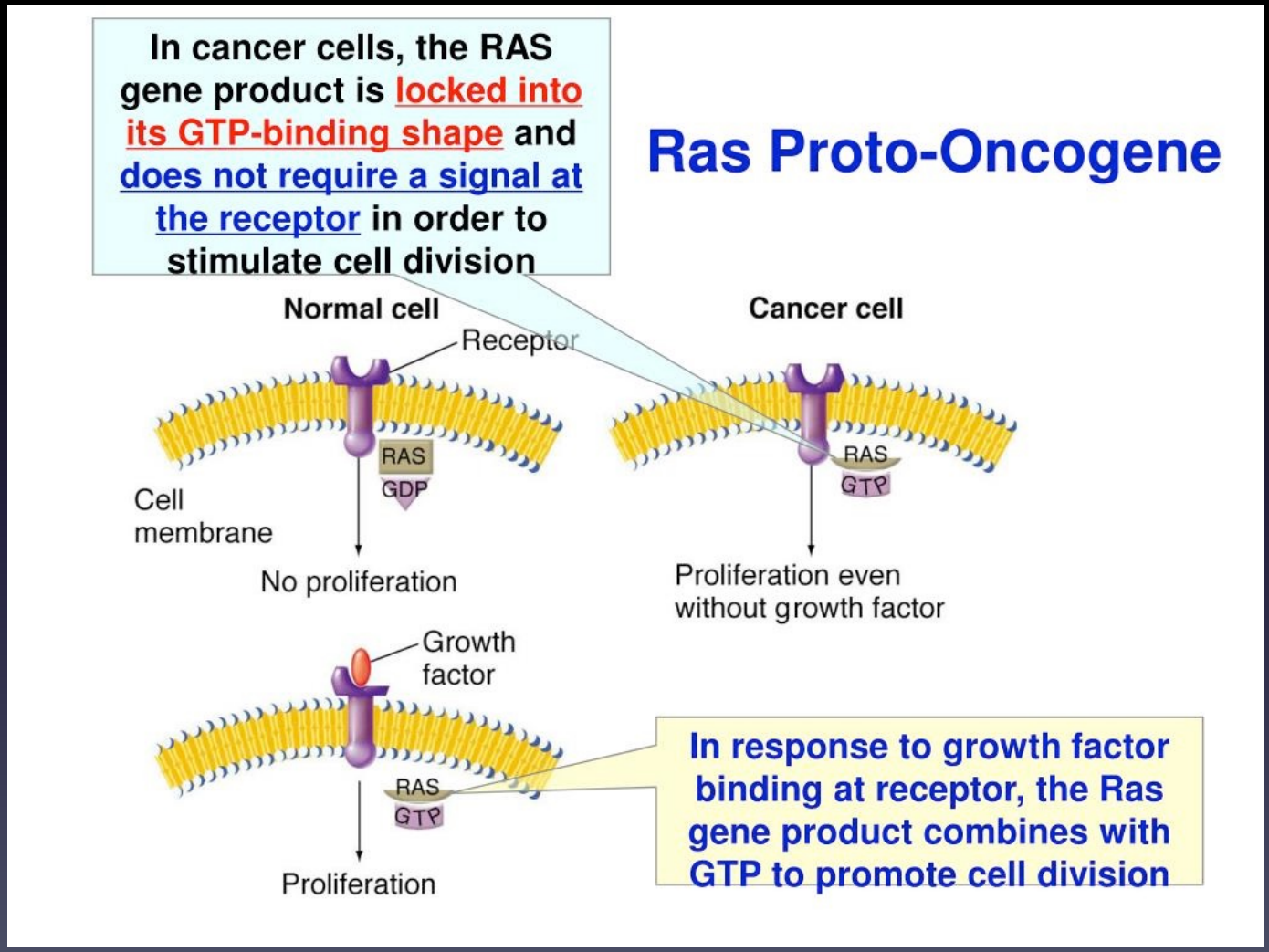
Overexpression of receptors, in particular growth factor receptors like EGF

Ligand independant signaling via constitutively active EGFR

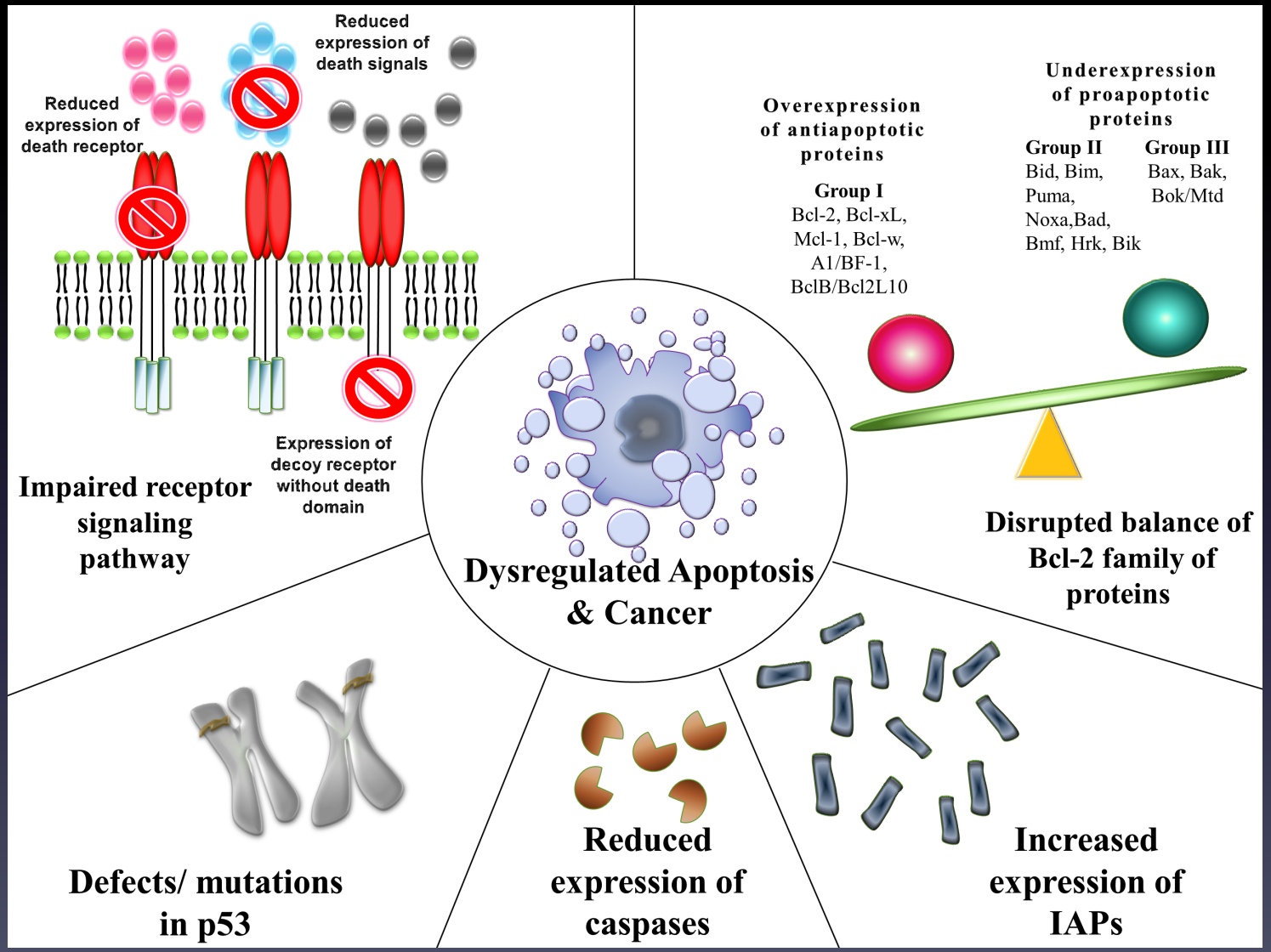


Sustained proliferation

About half of human tumors have mutant Ras oncogene



Dysregulated apoptosis



Wong, Journal of Experimental & Clinical Cancer Research 2011

Changes in tumoral microenvironment

- ✓ immune cells
- ✓ stromal cells
- ✓ blood vessels
- ✓ extracellular matrix

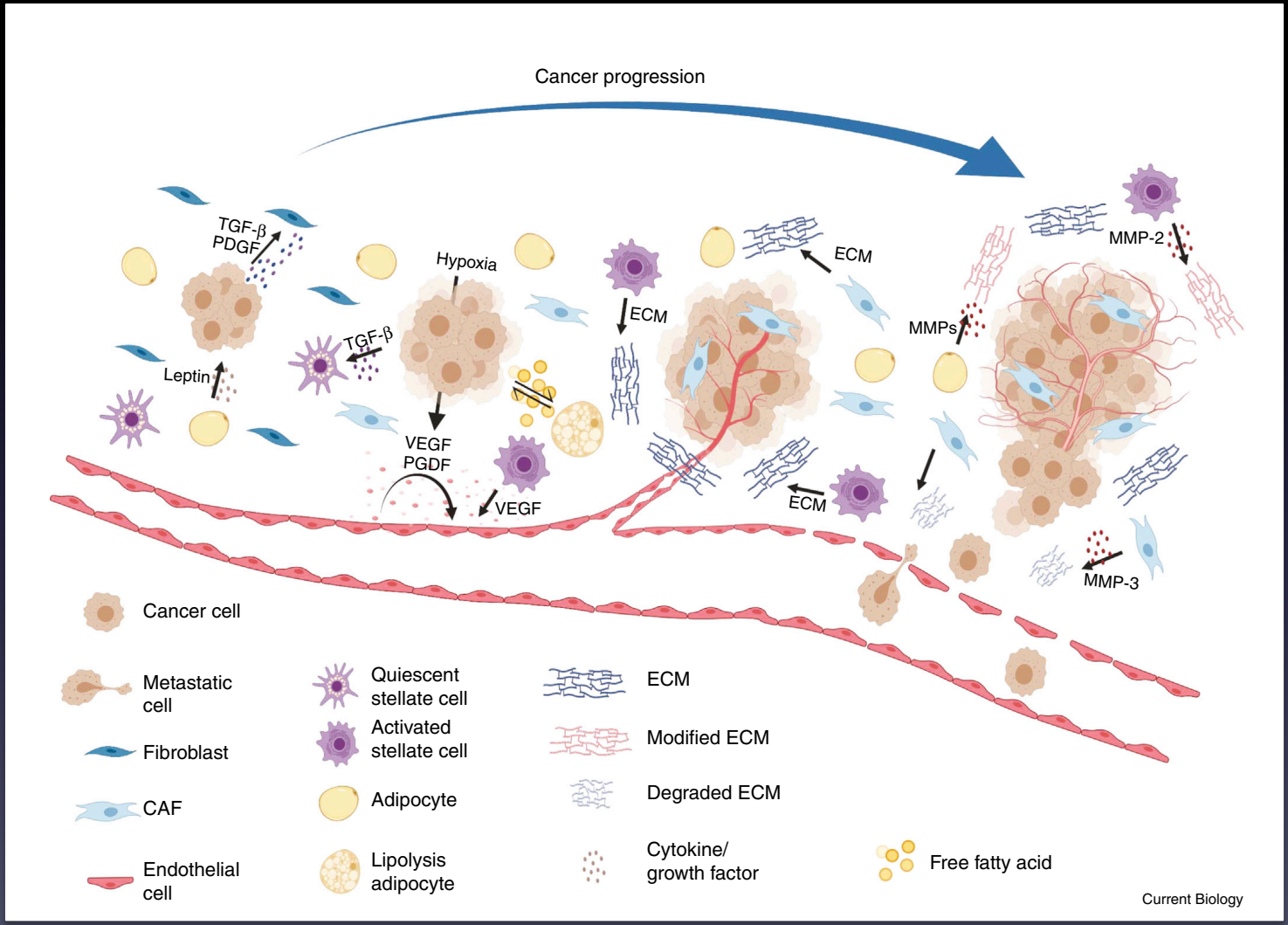
Fibroblasts acquire contractile properties

⬇

Cancer-associated fibroblasts

CAF

The tumor microenvironment orchestrates angiogenesis, proliferation, invasion and metastasis through the secretion of growth factors and cytokines

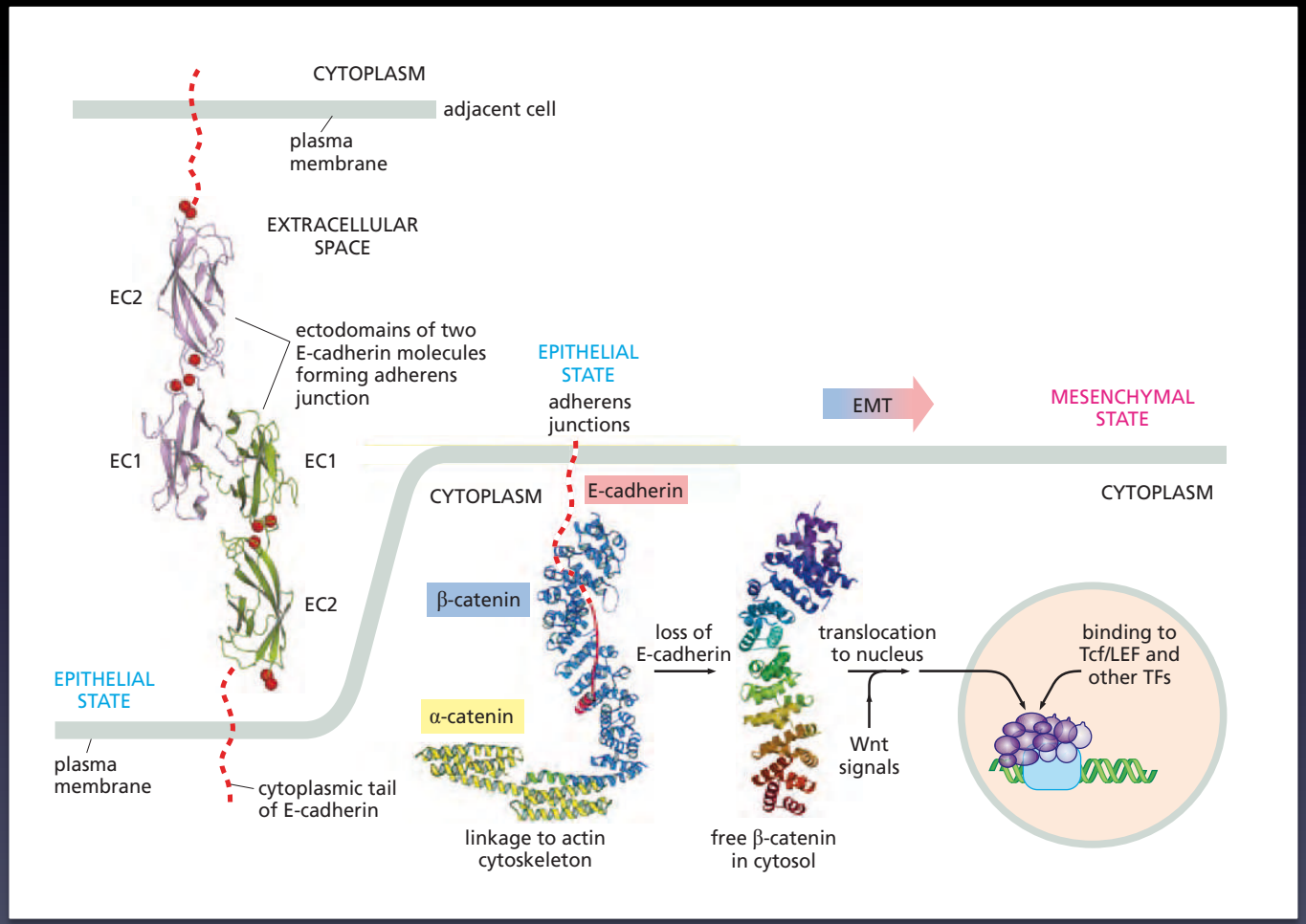


Anderson and Simon, Curr. Biol. 2020

EMT and increased motility and invasiveness

The Epithelial to Mesenchymal Transition (EMT)

A well polarized epithelial cell is converted into a non-polarized cell that gains migratory and invasive properties to become a mesenchymal stem cell



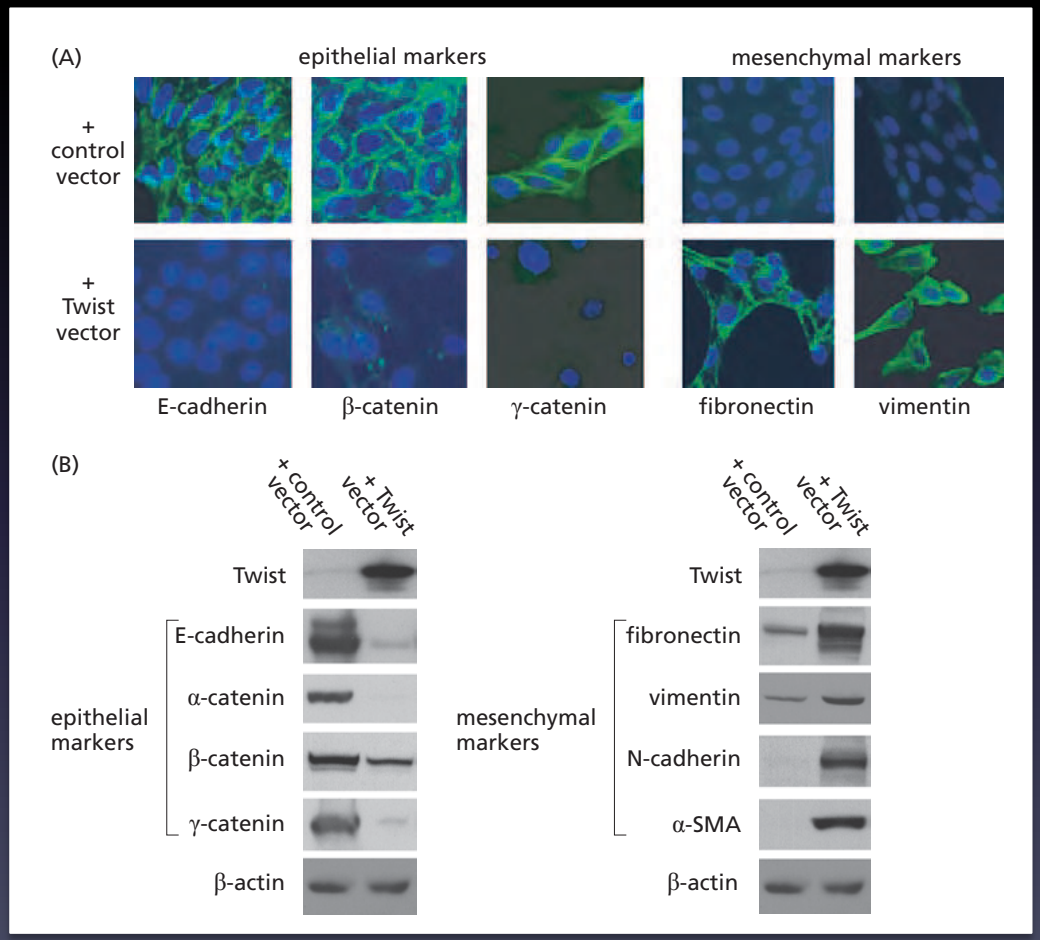
Weinberg, The Biology of Cancer *Garland Science, Taylor & Francis Group, LLC 2014*

Table 14.2 Cellular changes associated with an epithelial–mesenchymal transition

Loss of
Cytokeratin (intermediate filament) expression
Tight junctions and epithelial adherens junctions involving E-cadherin
Epithelial cell polarity
Epithelial gene expression program
Acquisition of
Fibroblast-like shape
Motility
Invasiveness
Increased resistance to apoptosis
Mesenchymal gene expression program including EMT-inducing transcription factors
Mesenchymal adherens junction protein (N-cadherin)
Protease secretion (MMP-2, MMP-9)
Vimentin (intermediate filament) expression
Fibronectin secretion
PDGF receptor expression
$\alpha_v\beta_6$ integrin expression
Stem cell-like traits

EMT and increased motility and invasiveness

Illustration of the loss of cell-cell junctions following ectopic expression of the Twist transcription factor, which mimicks Epithelial to Mesenchymal Transition (EMT)



Expression of epithelial markers, specifically E-cadherin, β-catenin, and γ-catenin, is repressed, while expression of mesenchymal markers, specifically vimentin and fibronectin is induced

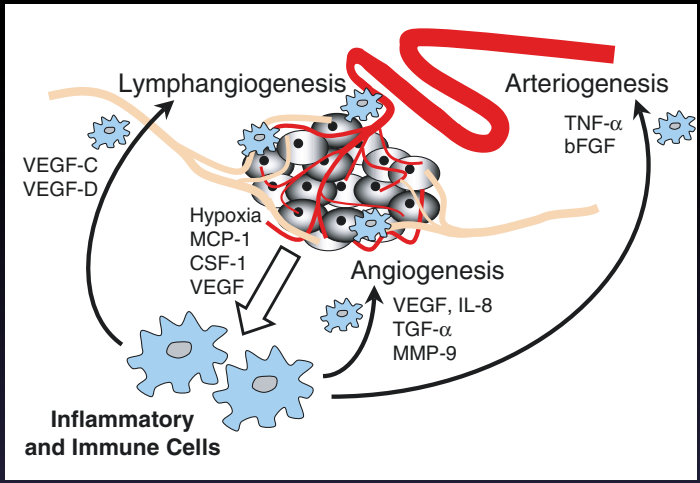
(A) Immunofluorescence
(B) Western blot

Weinberg, The Biology of Cancer Garland Science, Taylor & Francis Group, LLC 2014

Enhanced angiogenesis

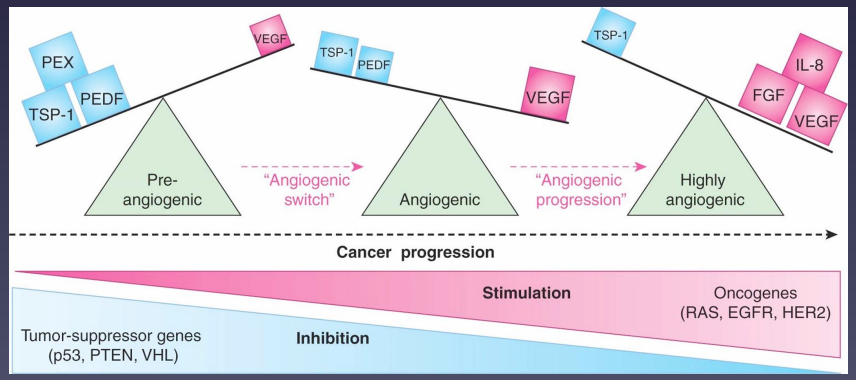
Initiation of tumor vascularization

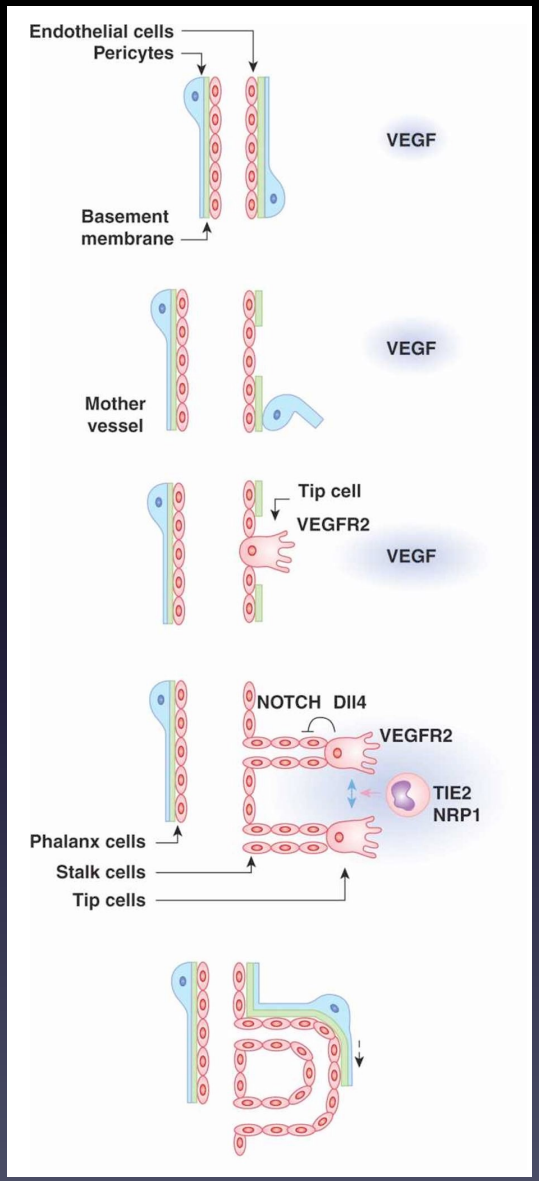
Inflammatory cells by supplying proangiogenic, growth factors, cytokines and proteases…



Yu and Rak, Breast Cancer Res., 2003

… will induce an angiogenic switch…





Angiogenic switch

Endothelial cell stimulation

Formation of endothelial tip cells

Formation of endothelial sprouts

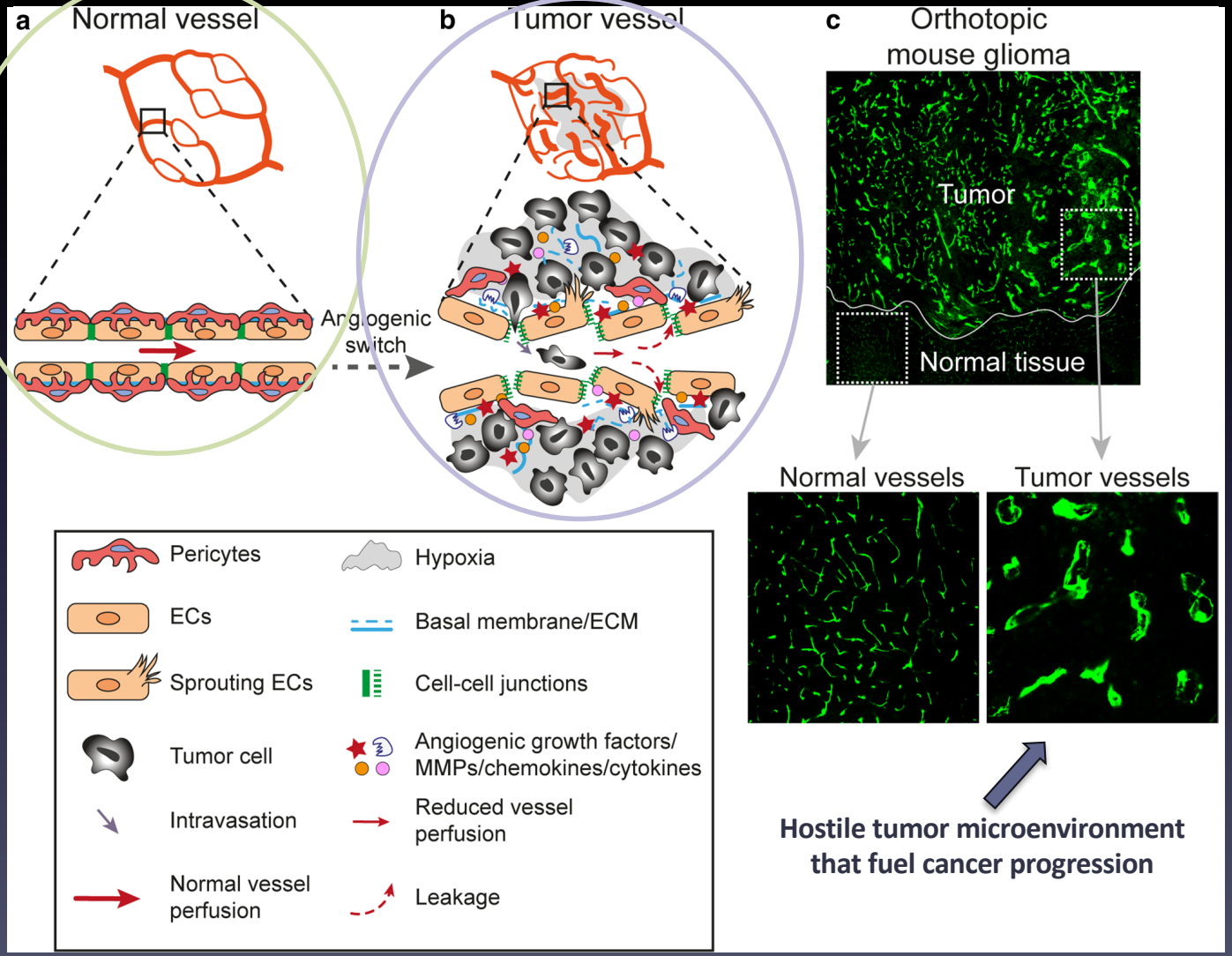
… and promote vessel formation in tumors

Rak, Angiogenesis, Basic Science of Oncology, (McGraw-Hill Int. Editions), 5th Ed.

Enhanced angiogenesis

In normal vessels, endothelial cells are tightly connected by stable cell-cell junctions

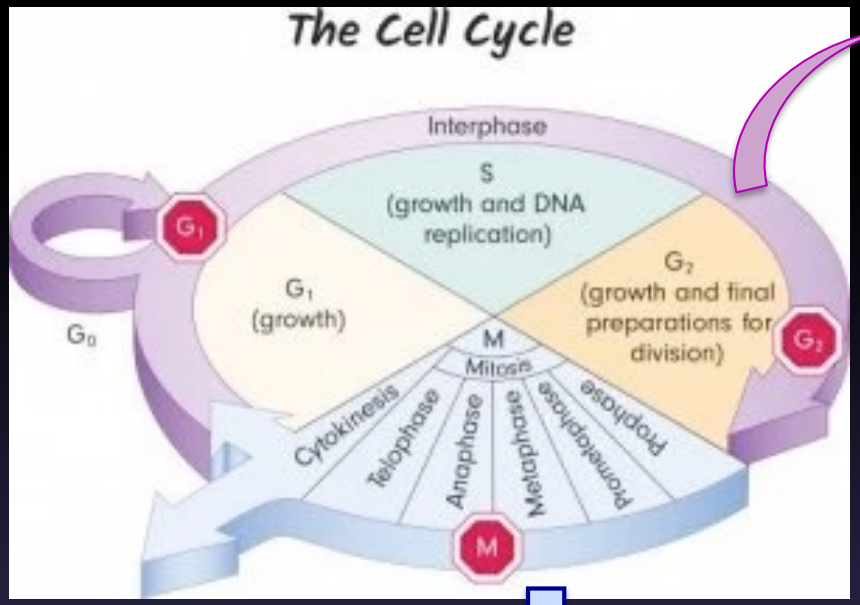
Tumor vessels are characterized by endothelial cell sprouting, disruption of endothelial cell junctions, loss of pericyte coverage and increased vessel leakiness, resulting in intravasation of tumor cells

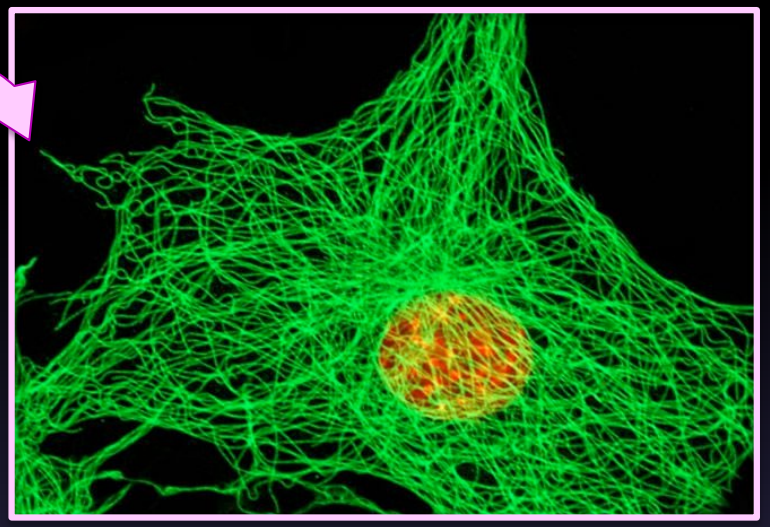


Lugano et al., Cell. Mol. Life Sci. 2020

Rearrangements of cytoskeleton elements

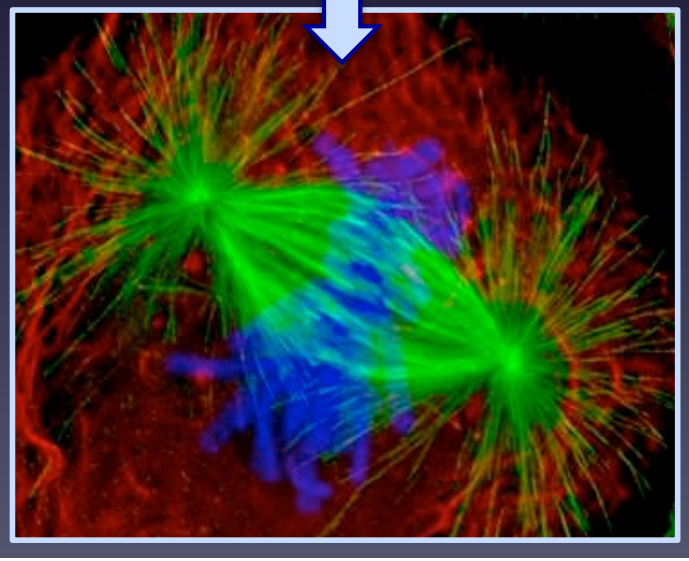
The microtubule network





Interphase

Traffic, Signaling



Are the target of several anticancer drugs

Mitosis

Chromosome alignment and segregation

Rearrangements of cytoskeleton elements

The microtubule network

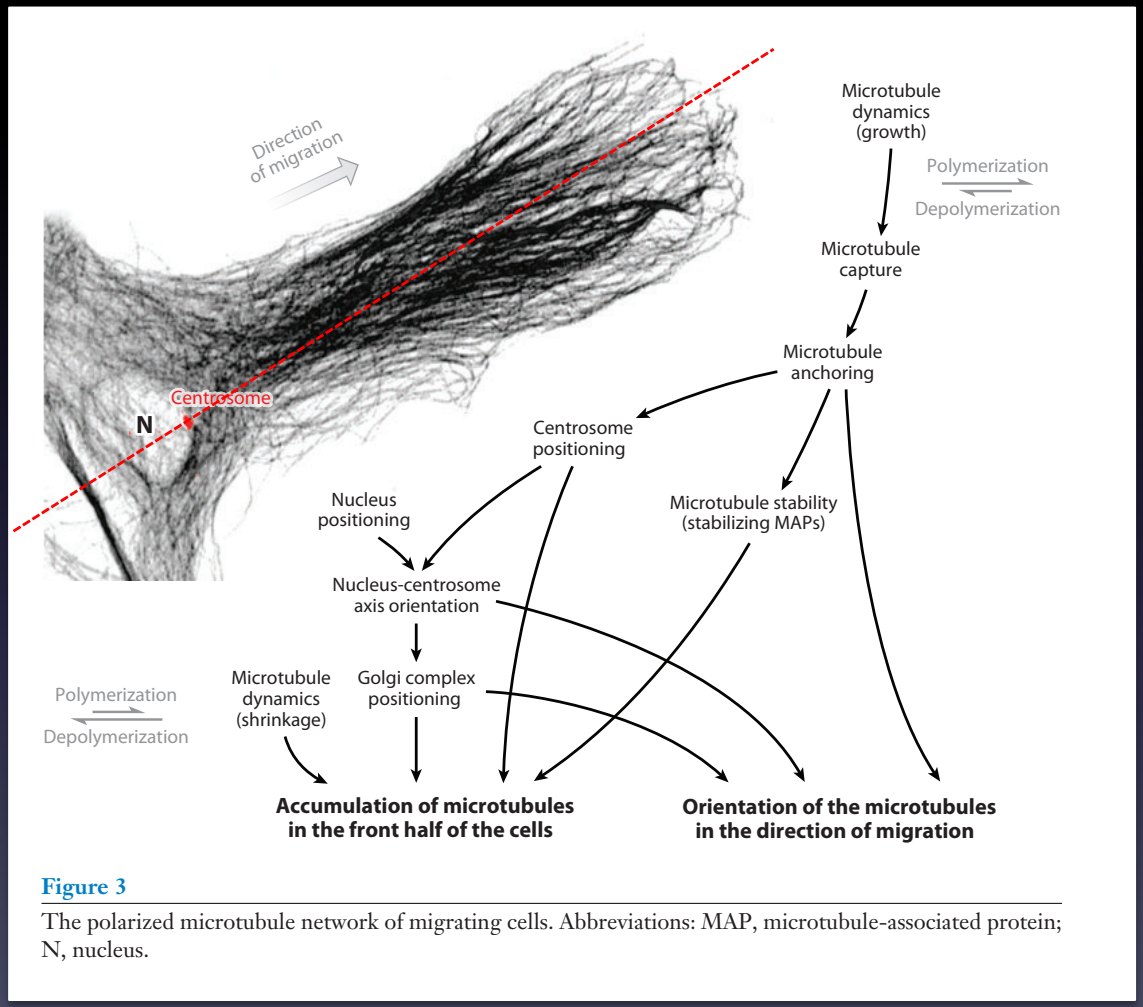


Figure 3

The polarized microtubule network of migrating cells. Abbreviations: MAP, microtubule-associated protein; N, nucleus.

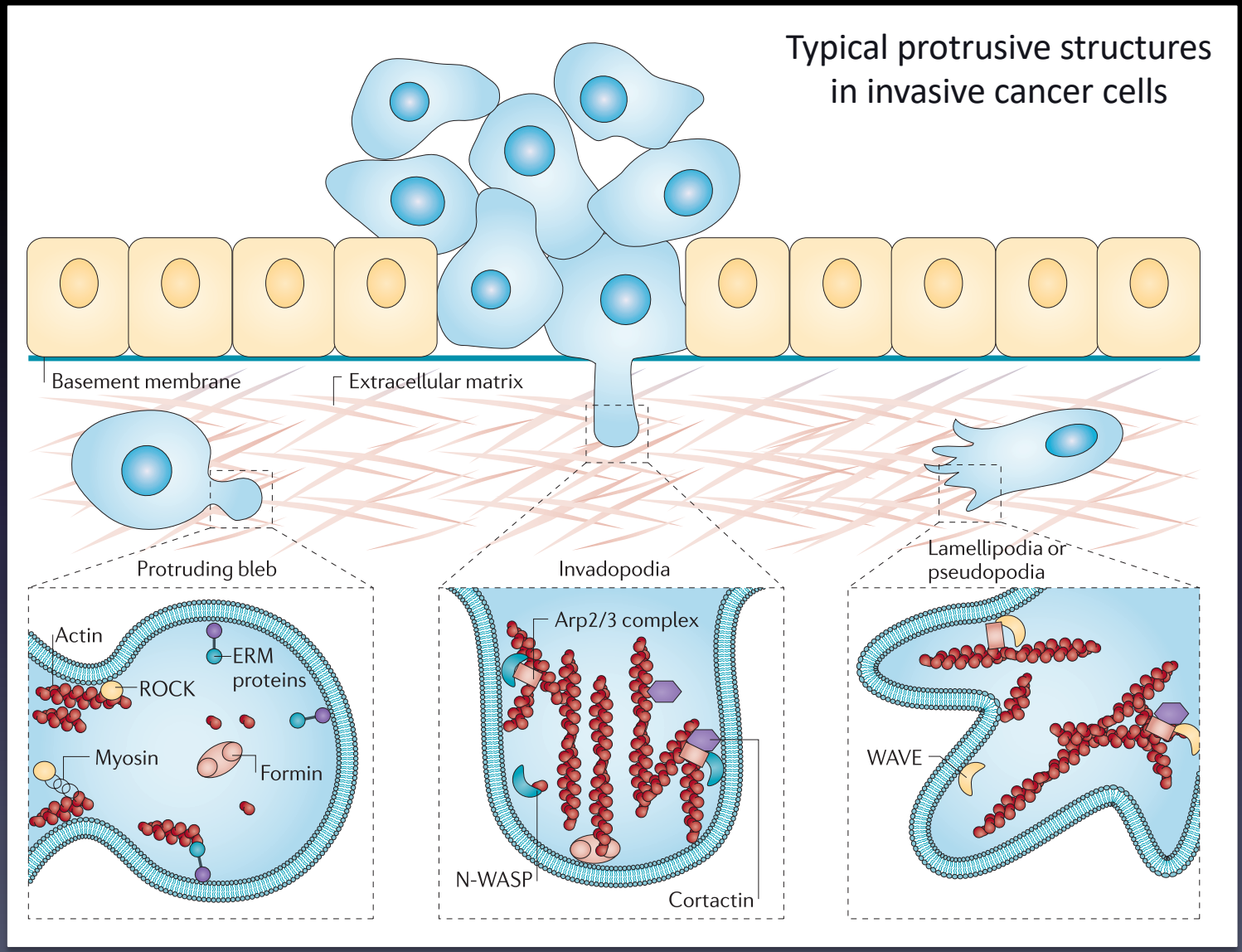
Directional cell migration

Etienne-Manneville et al., Annu. Rev. Cell Dev. Biol. 2013

Rearrangements of cytoskeleton elements

The actin network

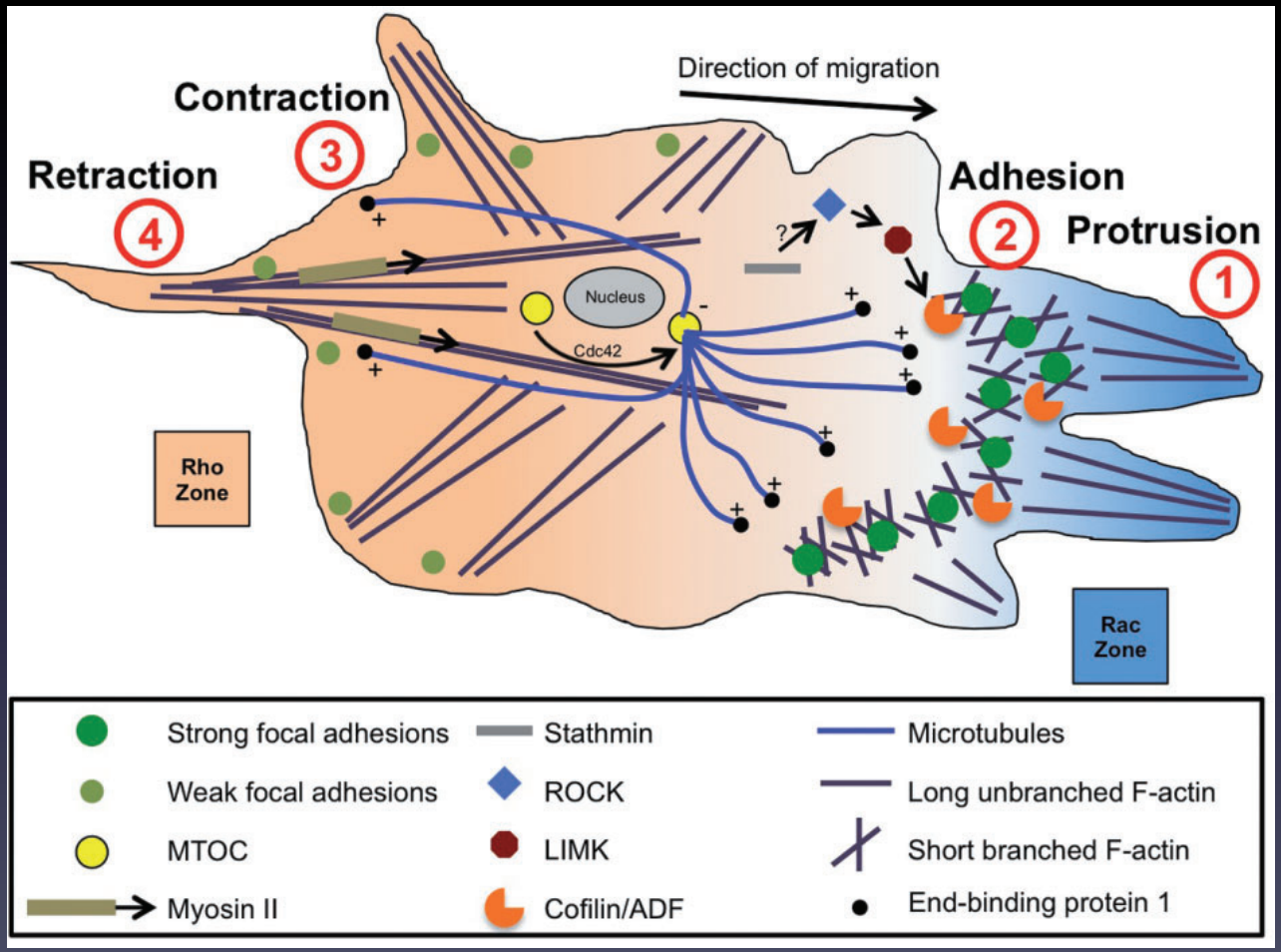
Fife et al., Brit. J. Pharmacol. 2014



Nucleation and assembly of F-actin

Rearrangements of cytoskeleton elements

Actin and Microtubules play a crucial role in directional migration through organization of strong focal adhesions

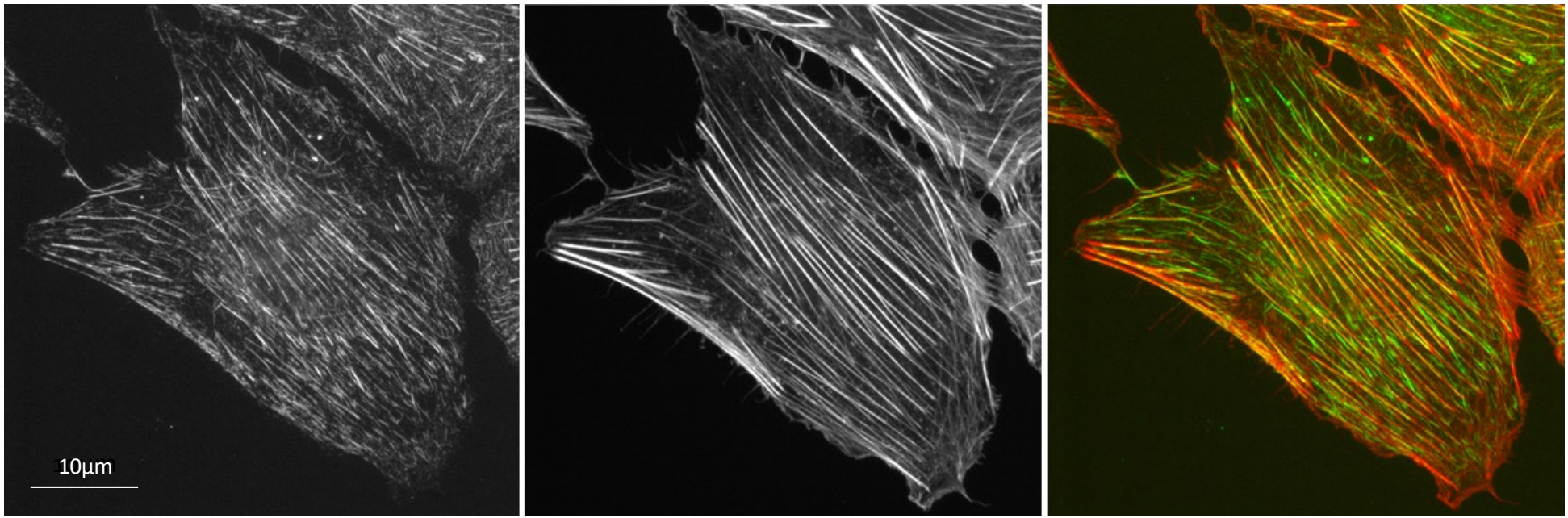


Fife et al., Brit. J. Pharmacol. 2014

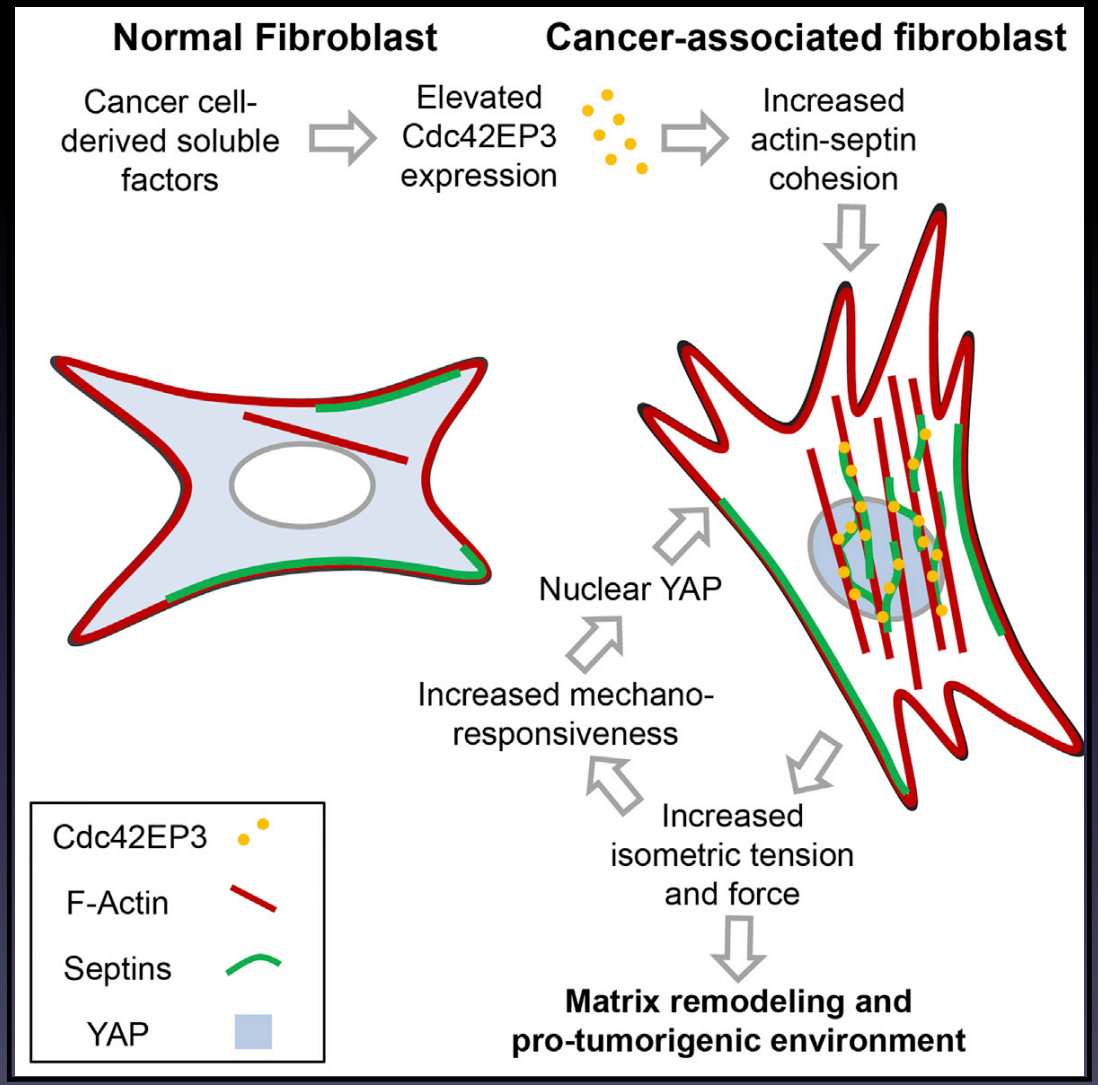
Rearrangements of cytoskeleton elements

Septins : the fourth element of the cytoskeleton

Septins | Actin | Septins | Actin



Rearrangements of cytoskeleton elements



Calvo et al., Cell Reports 2015

Septins,
by strenghtening actin fibers
favors matrix remodeling
and CAF migration

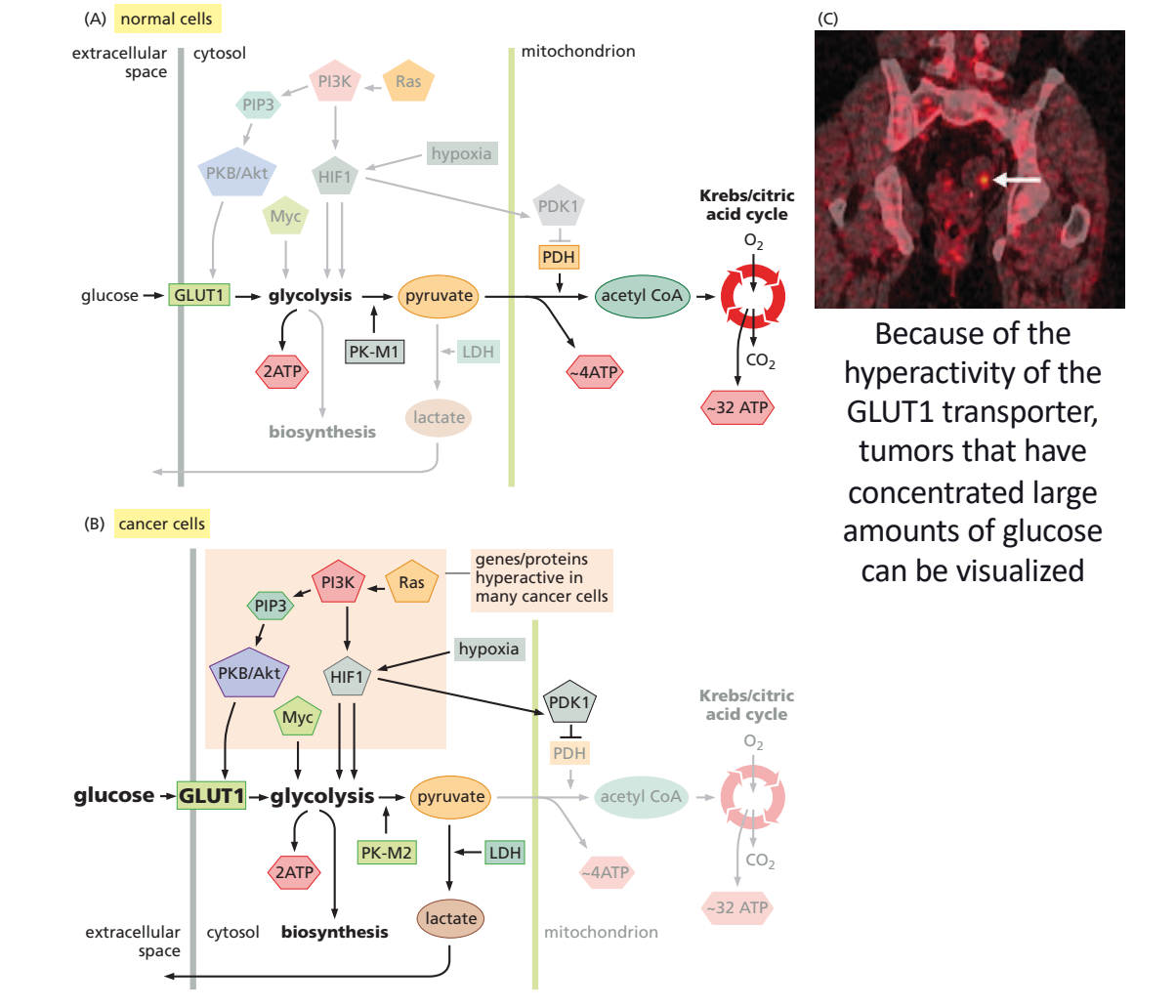
⇩

Pro-tumorigenic environment

Altered energy metabolism

Changes in glucose metabolism in cancer cells

even in the presence of oxygen and fully functioning mitochondria



(C)

Because of the hyperactivity of the GLUT1 transporter, tumors that have concentrated large amounts of glucose can be visualized

The Warburg effect

Increased glucose uptake

Fermentation of glucose to lactate

Weinberg, The Biology of Cancer Garland Science, Taylor & Francis Group, LLC 2014

Escape immune damage

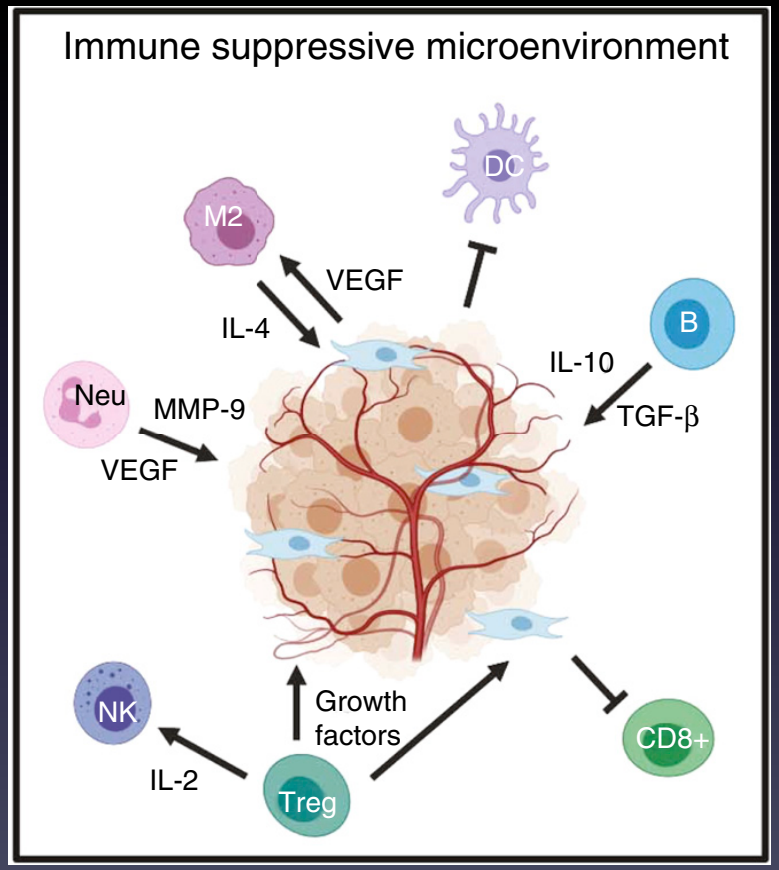
Over time, tumor cells evade immunity by :

- ✓ Downregulating antigen presentation
- ✓ Upregulating expression of inhibitory cell surface molecules that directly kill cytotoxic T cells (PD-L1, FasL)

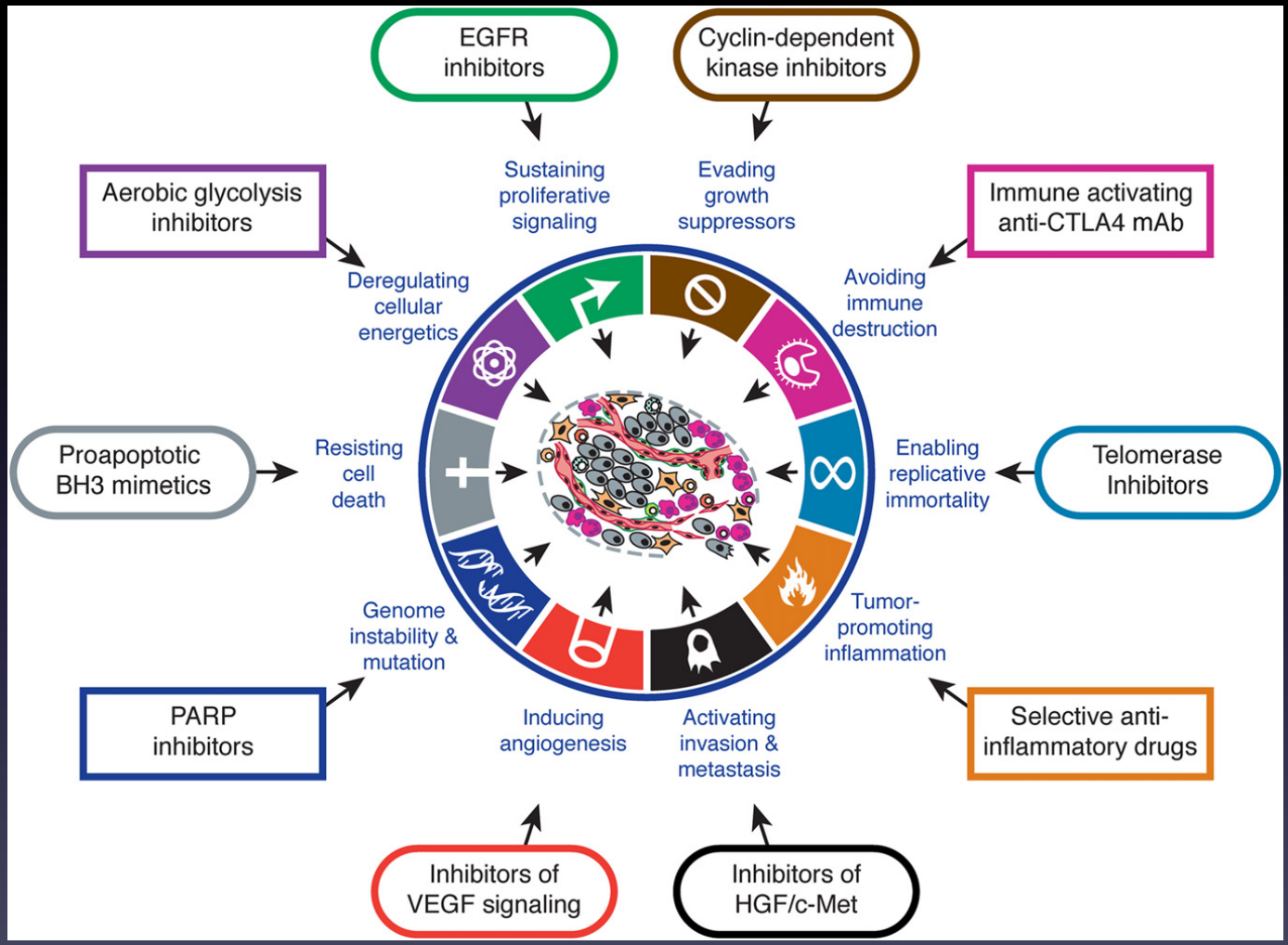
  Binding of PD1 on CD8+ to PD-L1 at the surface of tumor cell inhibits cytotoxicity of T cells
- ✓ Recruiting regulatory cells to attenuate antitumor immunity

  Through the liberation of immunosuppressive cytokines and alterations in the nutrient content of the tumor microenvironment
- ✓ Inhibiting dendritic cells that can no longer produce proinflammatory cytokines to attract macrophages or other immune cells
- ✓ Tregs dampen anti-tumor immune responses and secretion of growth factors

Promote tumorigenesis

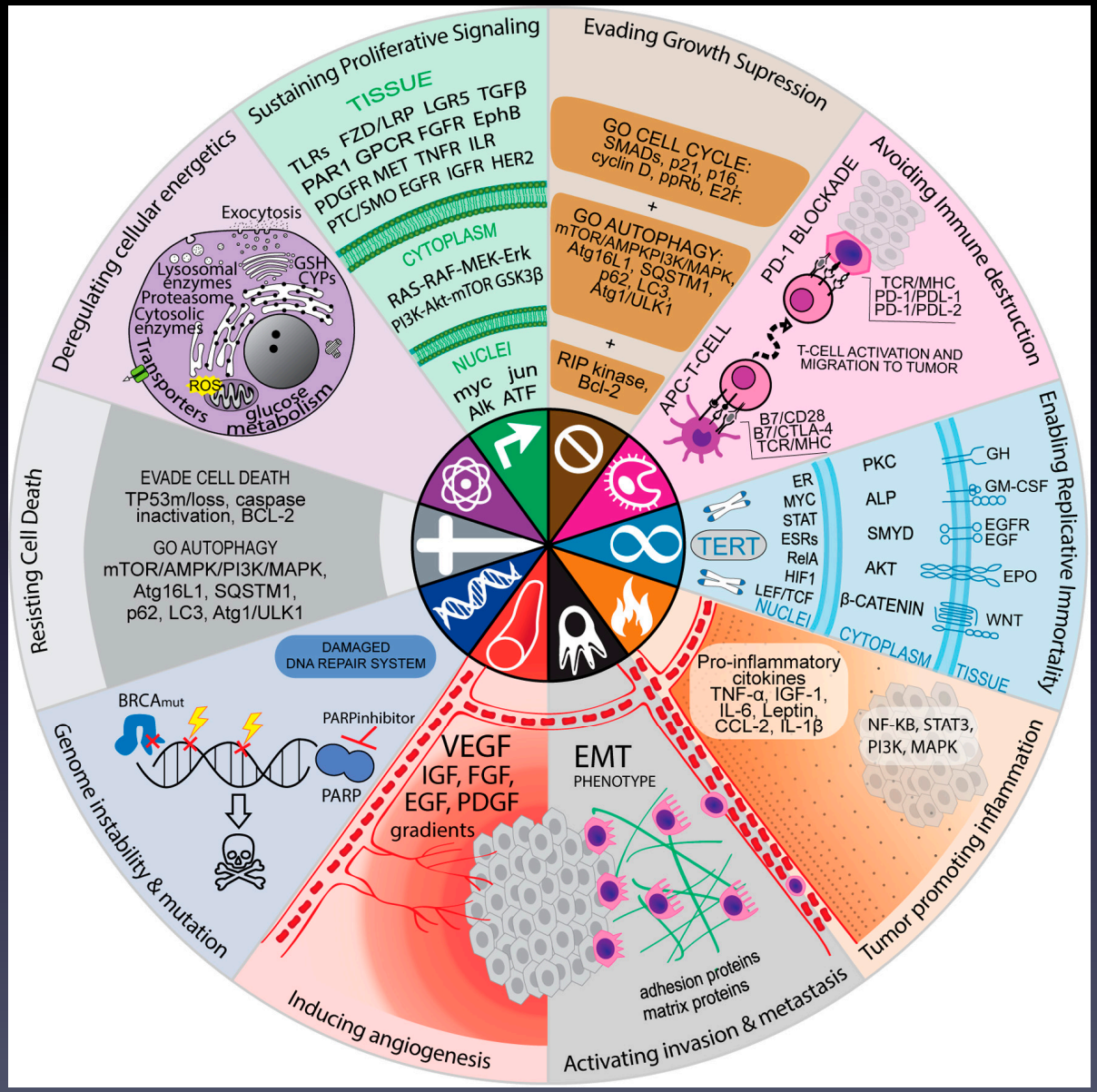


Targeted and combinatorial therapy



Hanahan and Weinberg, Cell 2011

Targeted and combinatorial therapy



Delou et al., Cells 2019

TU05 Cancer Cell Biology

1	How a cell becomes cancerous, new cell properties	Anita BAILLET
2	Epigenetic reprogramming	Anita BAILLET
3	Metabolism, angiogenesis	Christian POÜS
4	Targets and personal therapy, predictive markers, resistance	Christian POÜS
5	Cytoskeleton : microtubule, actin, septin, intermediate filament	Béatrice BENOIT
6	Cell cycle, proliferation, checkpoints, cellular senescence	Béatrice BENOIT
7	Migration, polarity, EMT, metastasis	Béatrice BENOIT
8	Cell deaths : apoptosis, necrosis and autophagy	Béatrice BENOIT
9	Cancer stem cells, tumoral microenvironment, inflammation	Christian POÜS

Thank You