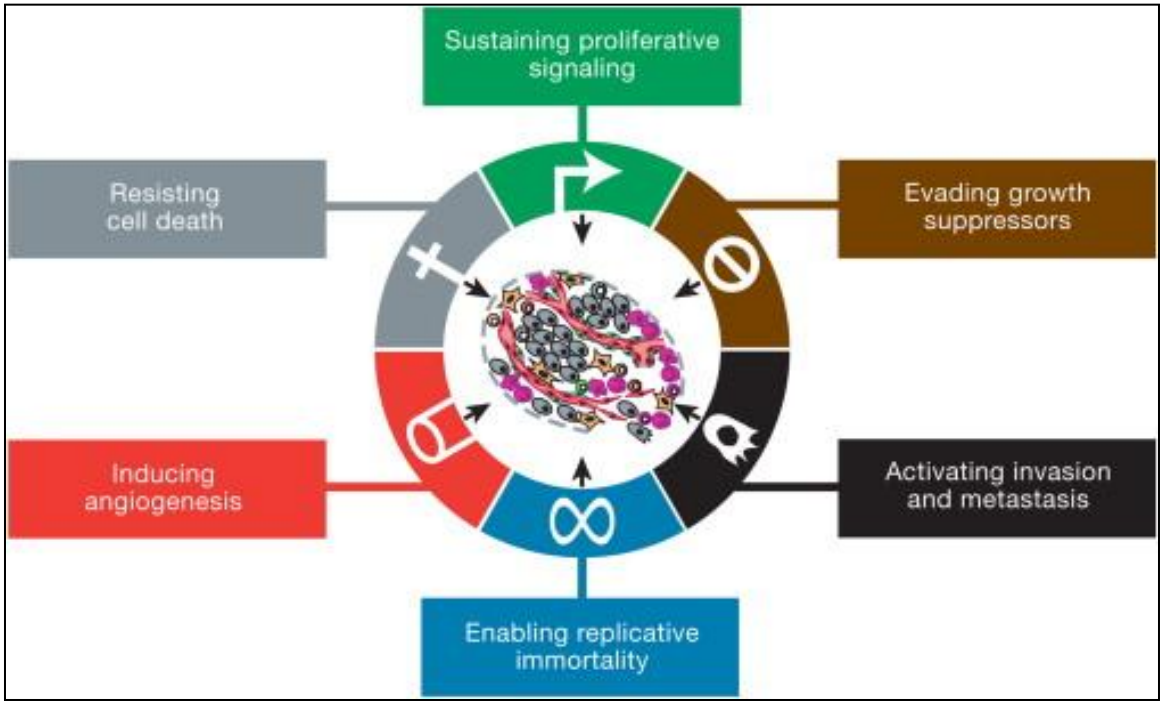
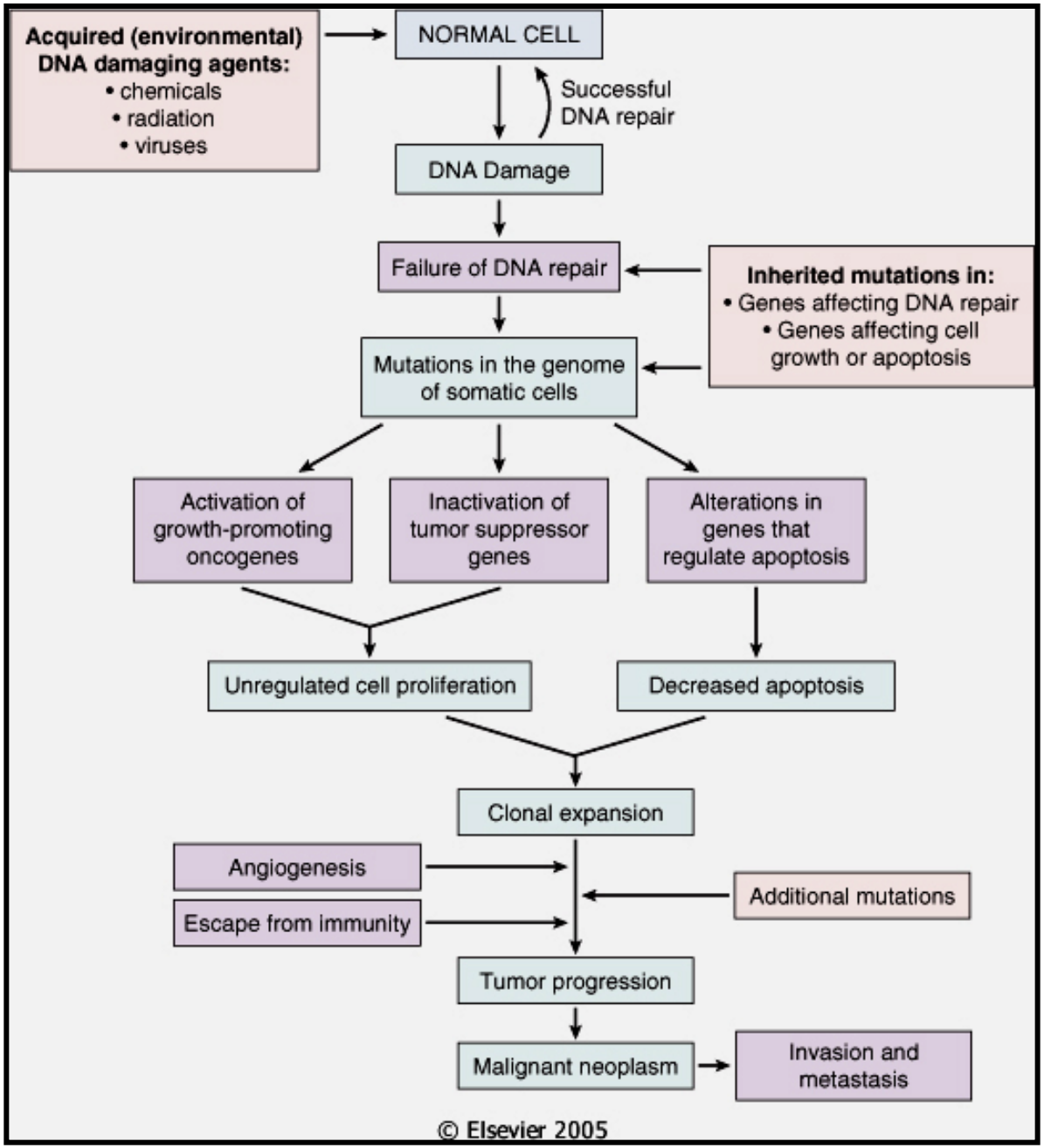
The Hallmarks of Cancer



This illustration encompasses the six hallmark capabilities originally proposed in our 2000 perspective. The past decade has witnessed remarkable progress toward understanding the mechanistic underpinnings of each hallmark.

Hanahan & Weinberg, 2011, Cell 144:646


Acquired (environmental) DNA damaging agents:
• chemicals
• radiation
• viruses
NORMAL CELL
Successful DNA repair
DNA Damage
Failure of DNA repair
Inherited mutations in:
• Genes affecting DNA repair
• Genes affecting cell growth or apoptosis
Mutations in the genome of somatic cells
Activation of growth-promoting oncogenes
Inactivation of tumor suppressor genes
Alterations in genes that regulate apoptosis
Unregulated cell proliferation
Decreased apoptosis
Clonal expansion
Angiogenesis
Escape from immunity
Additional mutations
Tumor progression
Malignant neoplasm
Invasion and metastasis
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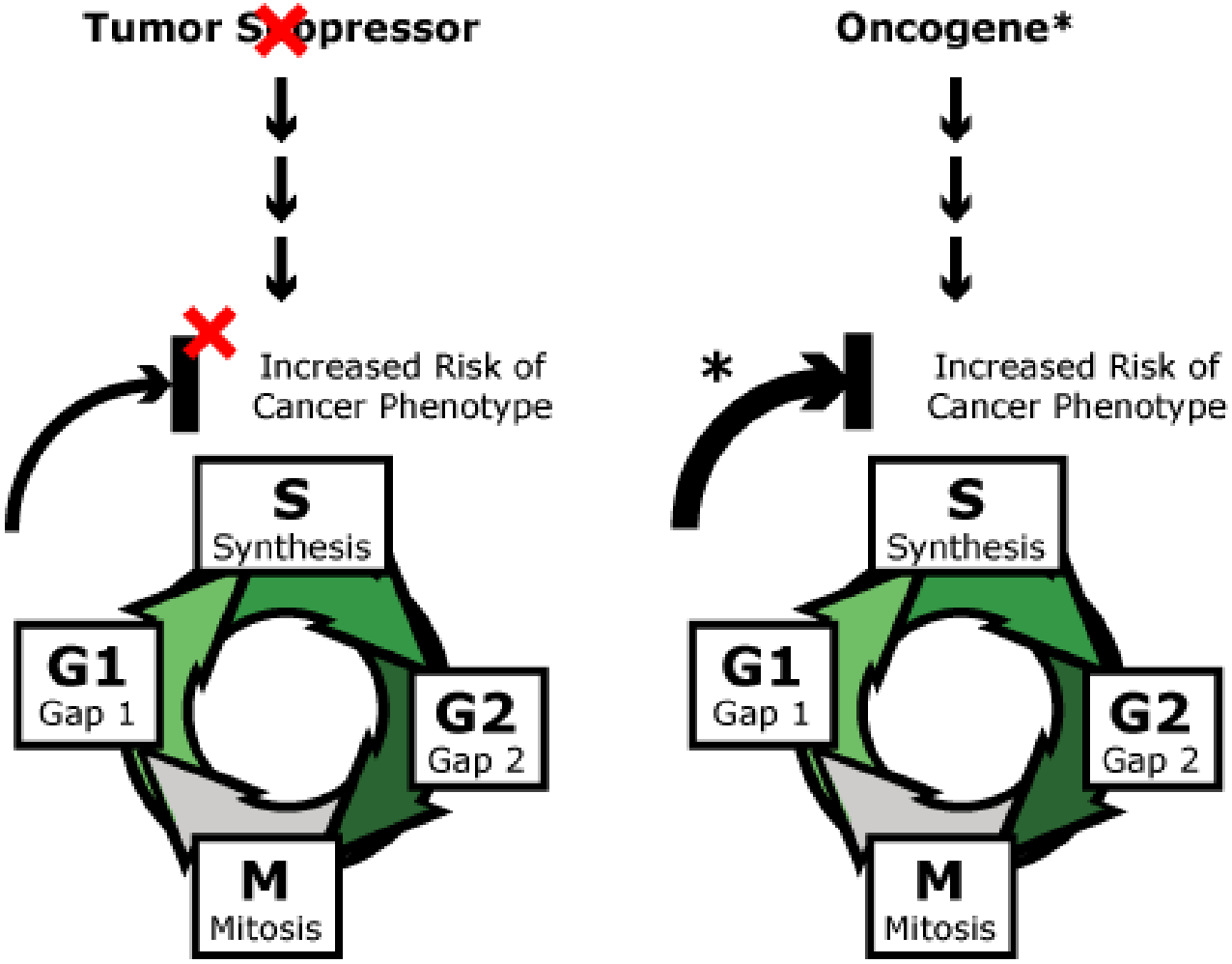
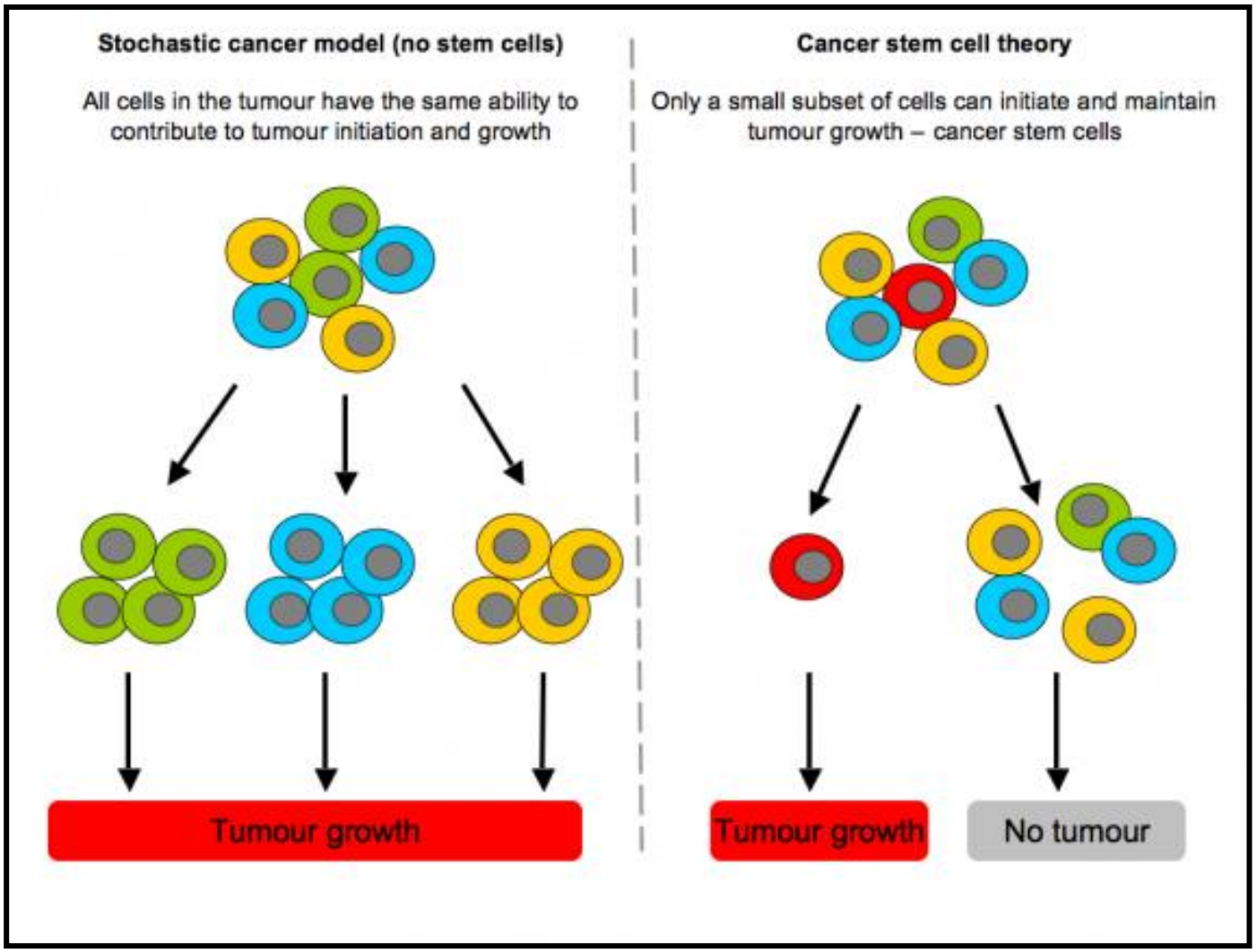


https://www.youtube.com/watch?v=rWnW-5LFLyo

CANCER STEM CELL THEORY

Only few cells in the tumor can:
- self-renew
- indefinitely proliferate
- differentiate



http://www.eurostemcell.org/it/node/14789

ASYMMETRIC CELL DIVISION: THE HALLMARK OF STEMNESS

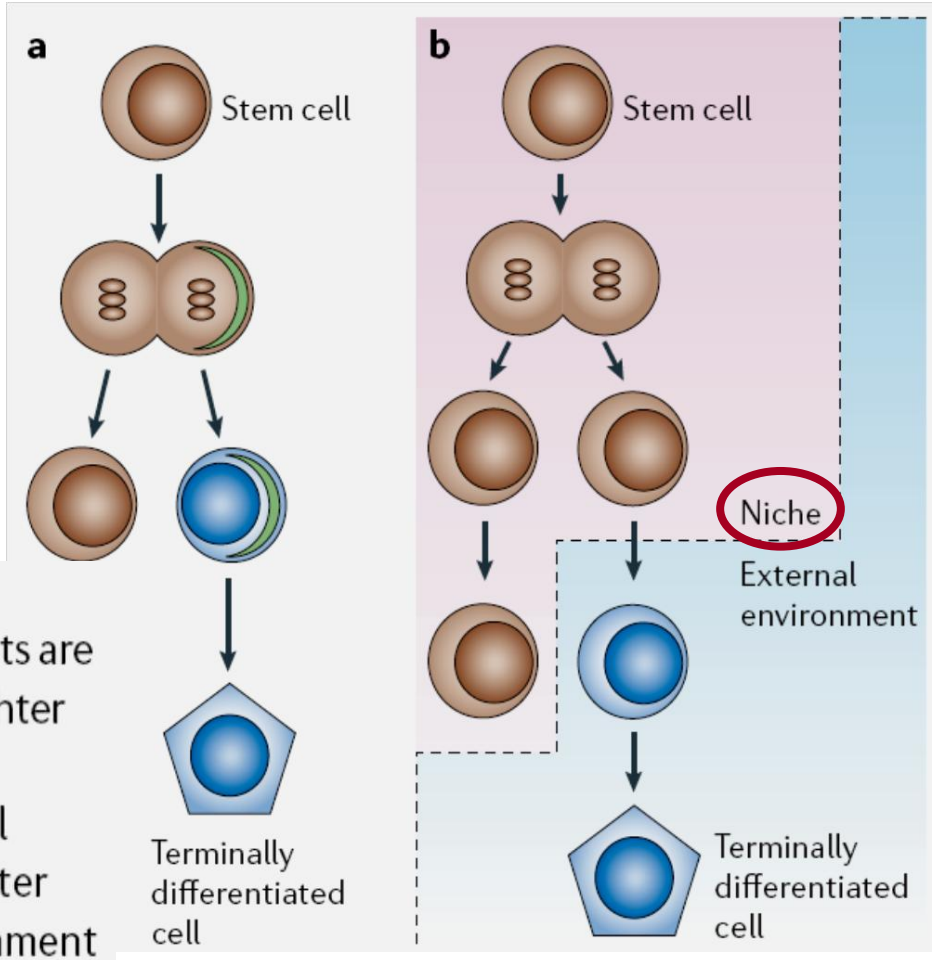


Figure 1 | **A model of asymmetric cell division.** **a** | During divisional asymmetry, cell-fate determinants are asymmetrically localized to only one of the two daughter cells, which retains stem-cell fate, while the second daughter cell differentiates. **b** | During environmental asymmetry, after division, one of two identical daughter cells remains in the self-renewing niche microenvironment while the other relocates outside the niche to a different, differentiation-promoting microenvironment.

Concepts of Cancer Stem Cell

- First formulated in 1875, Julius Cohnheim
  - proposed that stem cell misplaced during embryonal development were the source of tumors later in the life <embryonal-rest theory>
- Decades ago (Xenotransplantation)
  - only a small minority of cancer cells were able to proliferate extensively
- An "operational" & functional term
  - ability to self-renew (long-term repopulating potential)
  - dividing to another malignant stem cell and a cancer cell

Nature 1963;199:79–80
Virchows Arch Pathol Anat Physiol Klin Med 1875;65:64-9

Nature Med 2006;12:296-300
Nature 2001;414:105–111
Nat Rev Cancer 2003;3:895-902

Box 1 | **Discovery of cancer stem cells**

The first evidence supporting the existence of cancer stem cells (CSCs) was reported in acute myeloid leukaemia (AML) in 1994 (REF. 139). A population of primary patient-derived leukaemia cells capable of initiating tumours in immunocompromised mice[139], termed leukaemia stem cells (LSCs), were shown to possess cell surface markers ($CD34^+CD38^-$) and differentiation capacity similar to those of normal haematopoietic stem cells (HSCs). Serial transplantation into secondary recipient mice resulted in engraftment of human cells with similar morphology and cell surface markers to the original leukaemia, thus establishing the gold standard test for assessing CSC self-renewal capacity. Following the initial discovery of AML LSCs, CSCs were discovered in various other blood cancers, such as chronic myeloid leukaemia (CML). In CML, activation of the *BCR–ABL1* fusion oncogene-derived protein tyrosine kinase, P210, was shown to occur at the level of HSCs whereas blast crisis transformation was fuelled by progenitors that had co-opted stem cell self-renewal and survival properties that rendered them impervious to tyrosine kinase inhibitors[7,40,55,99,103,104]. Similar complexity in the CSC hierarchy was reported in solid tumours. For example, breast CSCs were found to be enriched in the $CD44^+CD24^-$ population[140]. Since then, CSC populations have been detected in brain[141], lung[142], colon[143], prostate[144] and ovarian cancers[145]. Whereas these breakthrough studies identified DNA mutations and cell surface phenotypes of relatively rare tumour-initiating cell types, recent research efforts have focused on identifying and understanding the key epigenetic and epitranscriptomic mechanisms that govern CSC evolution.

Jiang et al., 2017

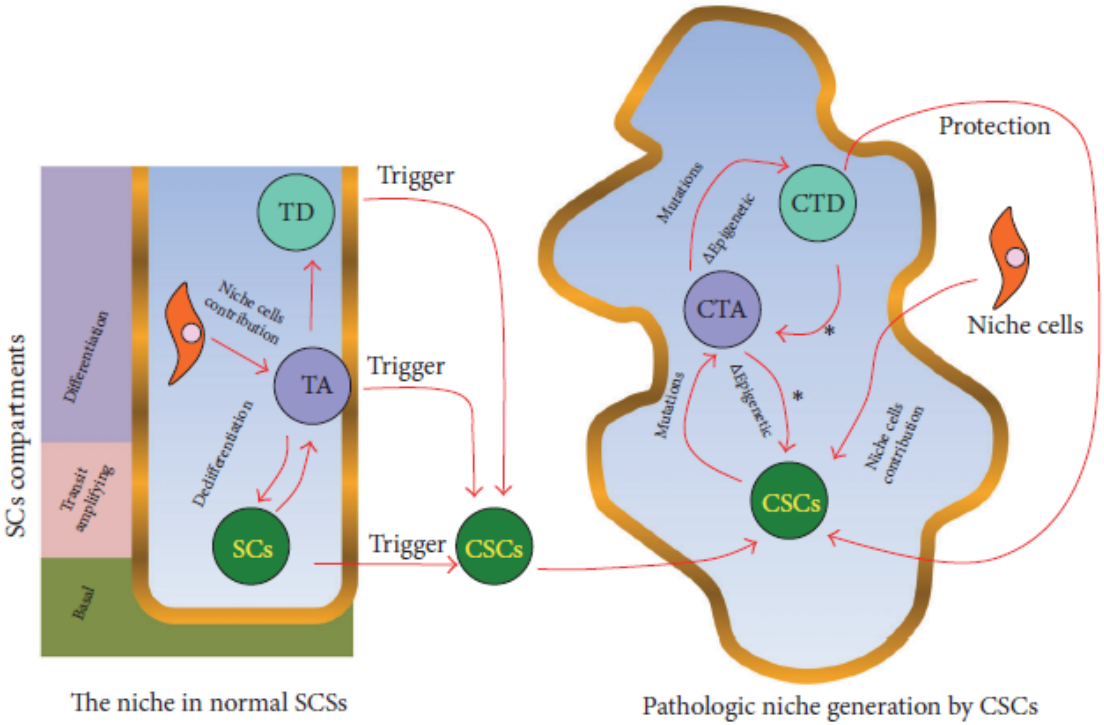


FIGURE 1: The origin of Cancer Stem Cells (CSCs) and Stem Cells (SCs) involvement in the generation of pathological cell hierarchies in tumors. In normal Stem Cell Systems, SCs located at the basal compartment generate committed progenitors (through asymmetrical divisions) which become spatially relocated to the transit-amplifying (TA) compartment. There, progenitors actively divide to produce differentiated daughter cells that carry on the normal physiology of the organ. Under physiological emergencies associated with SC loss, TA cells can dedifferentiate to reload the SC pool. Certain stressful triggers (i.e., chronic inflammation, ROS accumulation, and aging) can promote the transformation of cells in the system and generate CSCs or cancer initiating cells. CSCs remodel the niche and produce a pathological cancer microenvironment and associated hierarchy (pathological Stem Cell System) that resembles the original normal Stem Cell Systems (SCSs). The tumor is a very heterogeneous entity with cells that have accumulated mutations and epigenetic profile changes to secure CSCs survival and thriving. Features typical of SCSs such as niche support, SCs stemness, and dedifferentiation paths (∗) remain in the tumor environment. SCs = Stem Cell; TA = transit-amplifying progenitor; TD = terminally differentiated cell; CSC = Cancer Stem Cell; CTA = cancer transit-amplifying progenitor; CTD = cancer terminally differentiated cell.

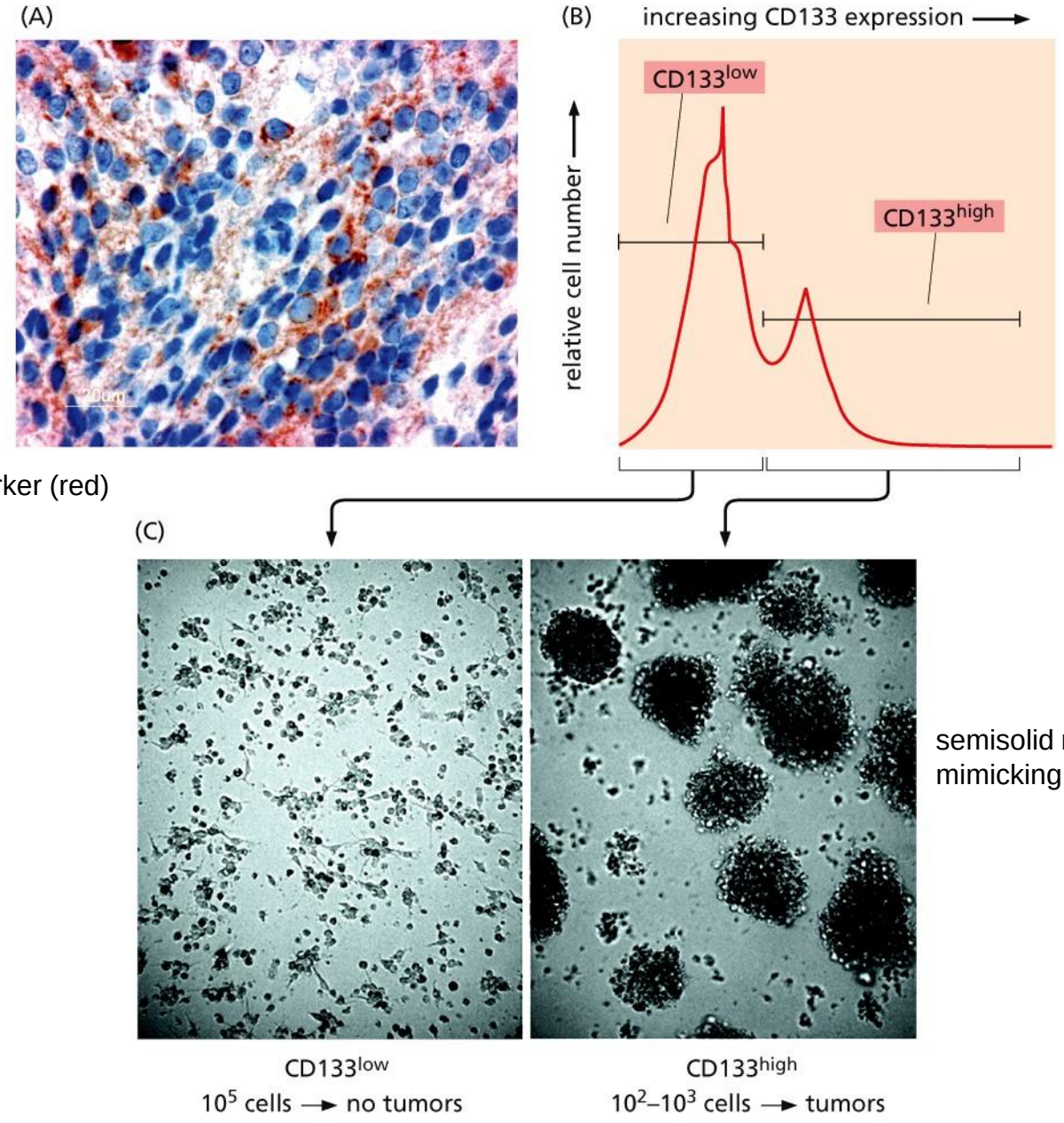
Aponte and Caicedo, 2017

Table 1 Cell Surface Phenotypes of Cancer Stem Cells in Different Tumor Types

Tumor Type	Cell Surface Marker on the CSC
Leukemia[18]	CD34+, CD38–, HLA–DR–, CD71–, CD90–, CD117–, CD123+
Breast[7]	ESA+CD44+CD24–/(low)
Brain[19, 20]	CD133+, CD49f+, CD90+
Lung[21,22]	CD133+, ABCG2(high)
Colon[10,23,24]	CD133+, CD44+, CD166+, EpCAM+, CD24+
Pancreatic[25,26]	CD133+, CD44+, EpCAM+, CD24+
Melanoma[11]	CD20+

ABCG2 = ATP-binding cassette subfamily G member 2; CSC = cancer stem cell; EpCAM = epithelial cell adhesion molecule; ESA = epithelial-specific antigen.

Dawood et al., 2014



CD133: brain stem cell marker (red)

semisolid medium cultures, mimicking *in vivo* tumorigenesis

Figure 11.17 The Biology of Cancer (© Garland Science 2014)

FIGURE 2: Common signaling pathways between Stem Cells (SCs) and Cancer Stem Cells (CSCs) [48]. CSCs share common signaling pathways, like the JAK/STAT, Hedgehog, Wnt, Notch, PTEN/AKT/PI3K, NF-κB, MAPK/ERK, and SMAD. These SCs mechanisms are altered in CSCs and are characteristic of the cancer types mentioned. The JAK/STAT pathway (Janus kinase/signal transducer and activator of transcription) is mainly involved in glioblastoma development and breast CSCs [49–52]. The Hedgehog pathways have effects on the patterning of the embryo but play a crucial role in the induction of myelogenous leukemia. Blocking of the Hedgehog pathway decreases the quantity of CSCs in leukemia, then representing an important target for cancer therapy [53]. The Wnt pathway is an important regulator of SCs and CSCs regarding self-renewal, being perturbed in colon cancer and leukemia [54–56]. The Notch pathway is involved in the development of breast tissue as a regulator of cell fate and differentiation. An excess in the activation of Notch could determine the aggressiveness of breast cancer [55, 57–59]. The phosphatase and tensin homolog (PTEN)/protein kinase B (PKB or AKT)/phosphatidylinositide 3-kinase (PI3K) signaling is a key regulator of self-renewal and maintenance of SCs and CSCs with an important role in the emergence of CSCs in prostate cancer [51, 60]. The NF-κB pathway is crucial for leukemic cells survival and its inhibition affects CSCs development in breast cancer [61]. It has been seen that the increase of neural stem cell (NSC) proliferation is caused by the activation of NF-κB, through the TNF-α signal transduction pathway, but its aberrant regulation could lead to CSCs development in glioblastomas [62, 63]. Blocking the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) results in the growth inhibition of breast cancer and the emergence of CSCs, sensitizing cancer cells to chemotherapy [64–66]. Gastrointestinal SCs can be perturbed, changing their plasticity and differentiation potential by generating an aberrant response to TGF-β affecting the SMAD pathway and generating CSCs [67]. The hepatocellular carcinoma is an aggressive form of cancer in which the TGF-β, Notch, and Wnt are deregulated, also having consequences in the SMAD proteins and changing SCs renewal, differentiation, and survival patterns [68, 69]. In adult and CSCs systems all the mentioned pathways are common and conserved in the control of SCs renewal, proliferation, and differentiation.

Aponte and Caicedo, 2017

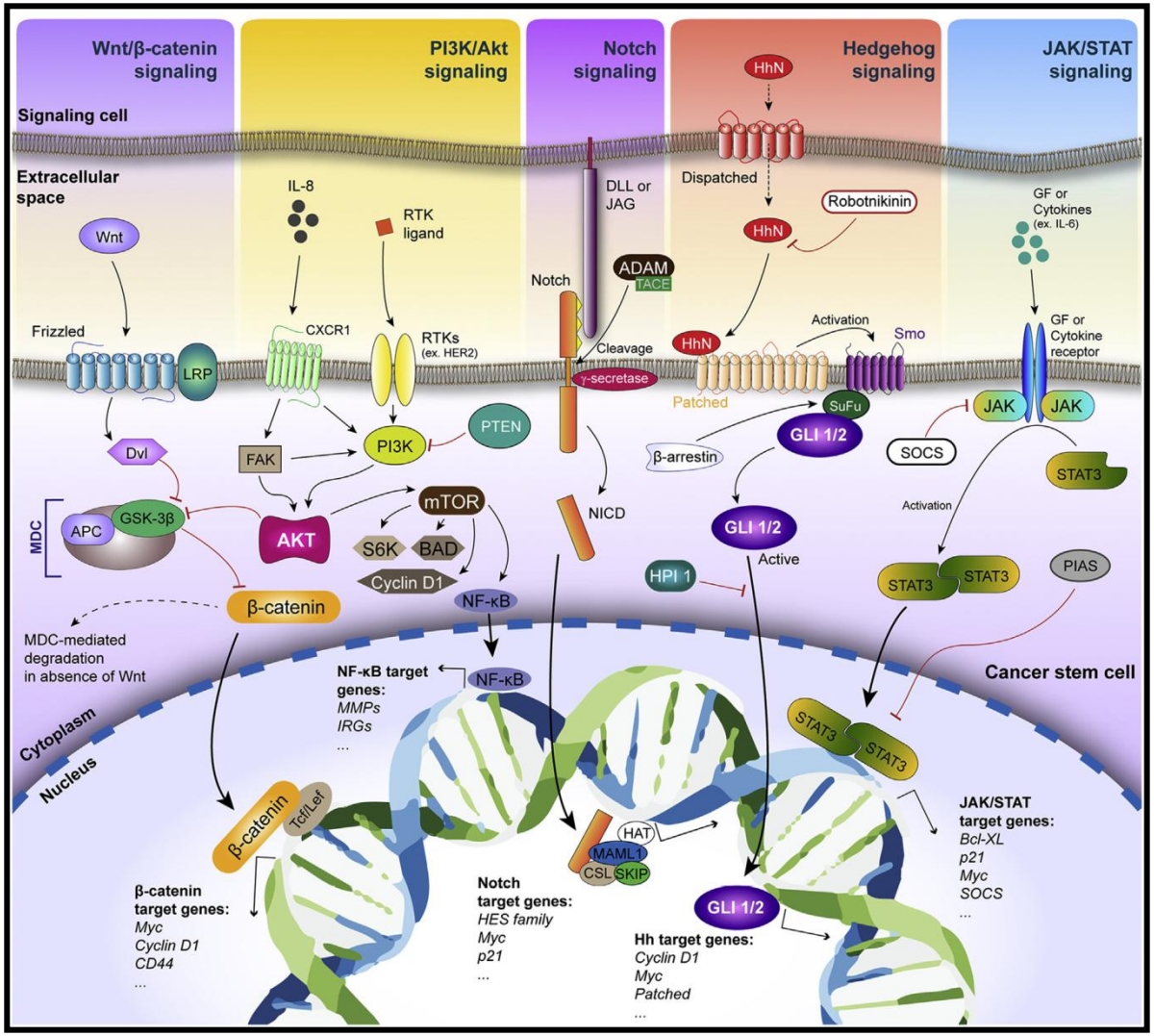


Fig. 2. Fundamental pathways deregulated in cancer stem cells. Developmental signal transduction pathways, including NOTCH, WNT and Hedgehog are highly associatedwith CSC phenotype. Additional signal transduction is mediated by receptor tyrosine kinases (RTK), like HER2, and PI3k/AKT pathway or JAK/STAT pathway. Regulation of CSC through interleukins adds an additional layer to the regulatory network. Abbreviations: ADAM, A disintegrin and metalloproteinase; CSL, CBF1/Su(H)/Lag-1; DLL, Delta-like ligand;Dvl, Disheveled; FAK, focal adhesion kinase; GF, growth factor; HAT, histone acetyltransferase; HhN, Hedgehog ligands; HPI 1, hedgehog protein inhibitor 1; IRGs, inflammation-relatedgenes; JAG, jagged ligands; LRP, low-density lipoprotein receptor-related protein; MAML1, Mastermind-like 1; MDC, multiprotein destruction complex; MMPs, metalloproteinases;NICD, NOTCH intracellular domain; PIAS, protein inhibitors of activated STATs; RTK, receptor tyrosine kinase; SKIP, ski-interacting protein; Smo, smoothened; SOCS, suppressor ofcytokine signaling; SuFu, suppressor of fused, TACE, TNF-¸ converting enzyme; Tcf/Lef, T-cell factor/lymphoid enhancing factor (Fonseca et al., 2017).

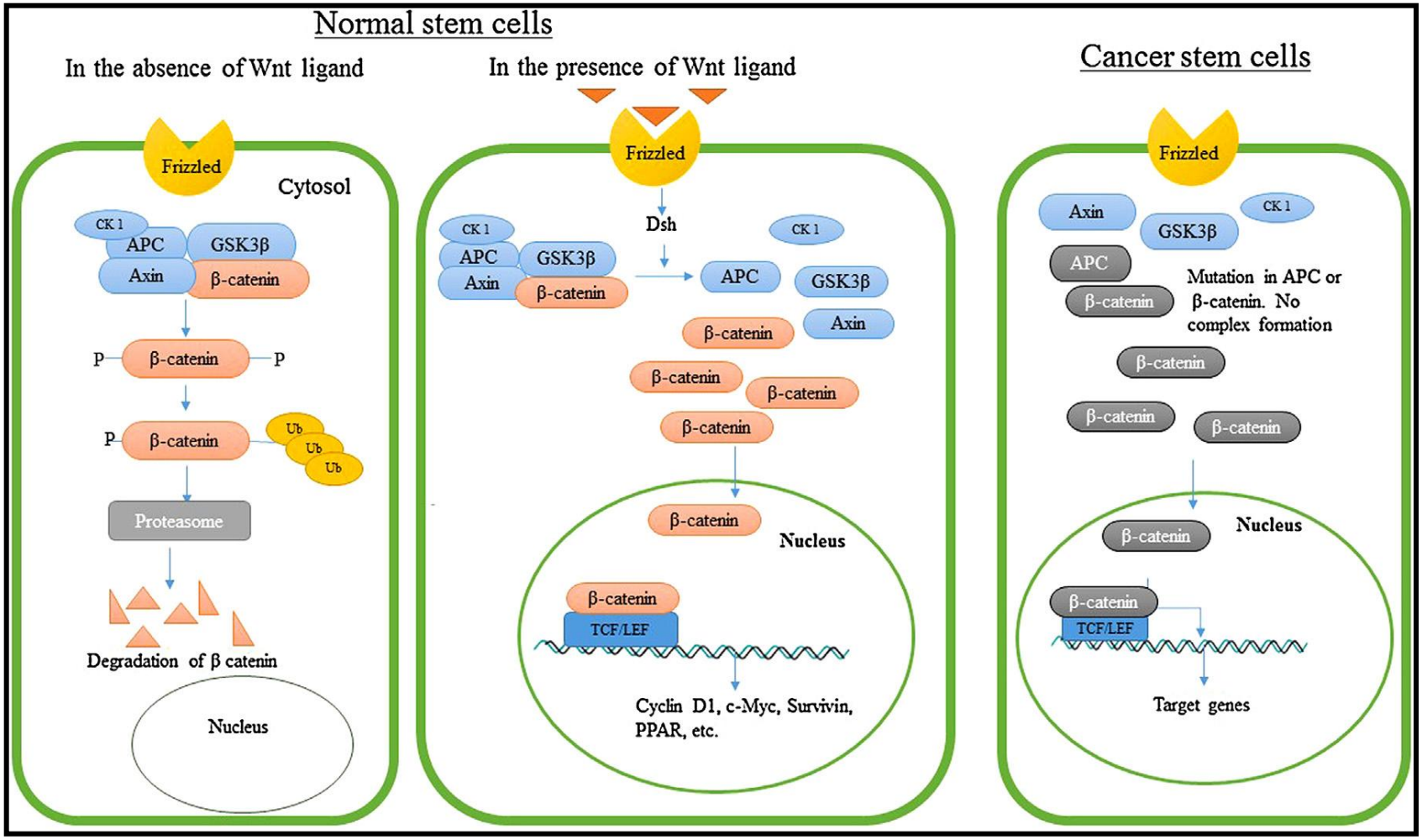


Fig. 1. Mechanism of Wnt/-catenin signalingpathway in colon cancer. In normal stem cells, the Wnt/-catenin signaling pathway starts with the binding of a Wnt ligand to a Frizzled-related protein. After binding of Wnt ligand to receptor, Disheveled (Dsh) gets activated by phosphorylation, this in turn inactivates GSK-3˘, a key modulator of this signaling pathway. As a result, ˘-catenin levels increases intracellularly and allowing translocate into the nucleus. There it interacts with T-cell factor/lymphoid enhancerbinding factor (TCF/LEF) and activates the transcription of Wnt target genes which are necessary for cellular proliferation and survival (cyclin D1, cMyc, etc.). However, in the absence of a Wnt ligand, GSK-3˘ forms destruction complex with proteins of axin, adenomatous polyposis coli (APC) and ˘-catenin. GSK-3˘ activity is switched on and phosphorylates ˘-catenin, which in turn ubiquitinated and degraded via the proteasome. In the case of colon cancer, aberrant Wnt/-catenin signaling contributes to the hyper-proliferative and hypo-apoptotic phenotype, as a result in part of constitutive -catenin or mutated APC may induce transactivation of pro-survival genes (Vadde et al., 2017).

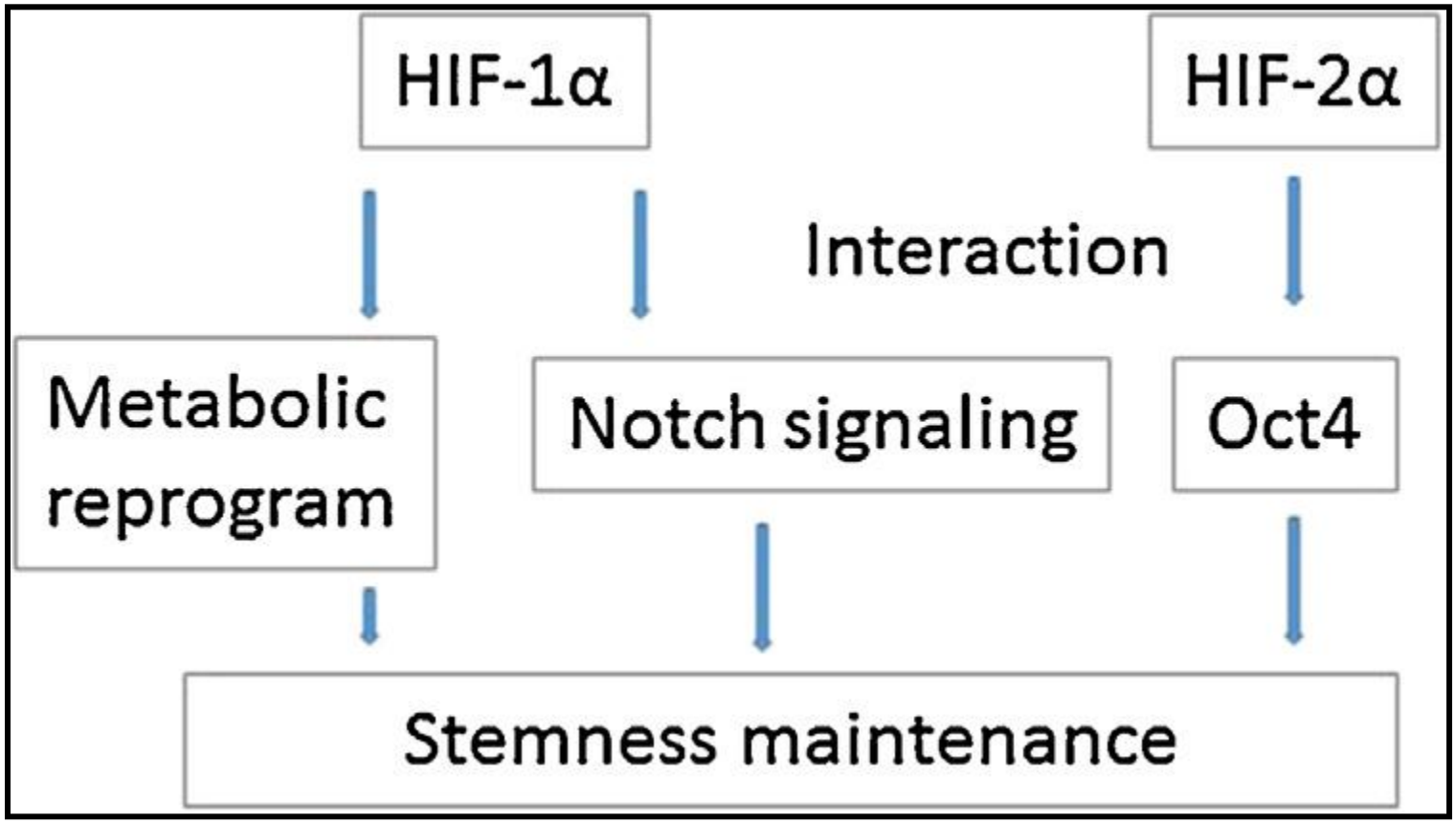


Fig. 3. HIF role in stemness maintenance in stem cells. Under hypoxia conditions, HIF-1 interacts with Notch signaling and influence on the maintenance of stemness by allowing expression of relevant genes and transcription factors involved in stemness maintenance and differentiation. HIF-1 also makes cell survival (stemness) under hypoxic conditions by reprogramming metabolism of glucose. However, the HIF-2 directly involved activation of Oct4 and further responsible for stemness maintenance in stem cells (Vadde et al., 2017).

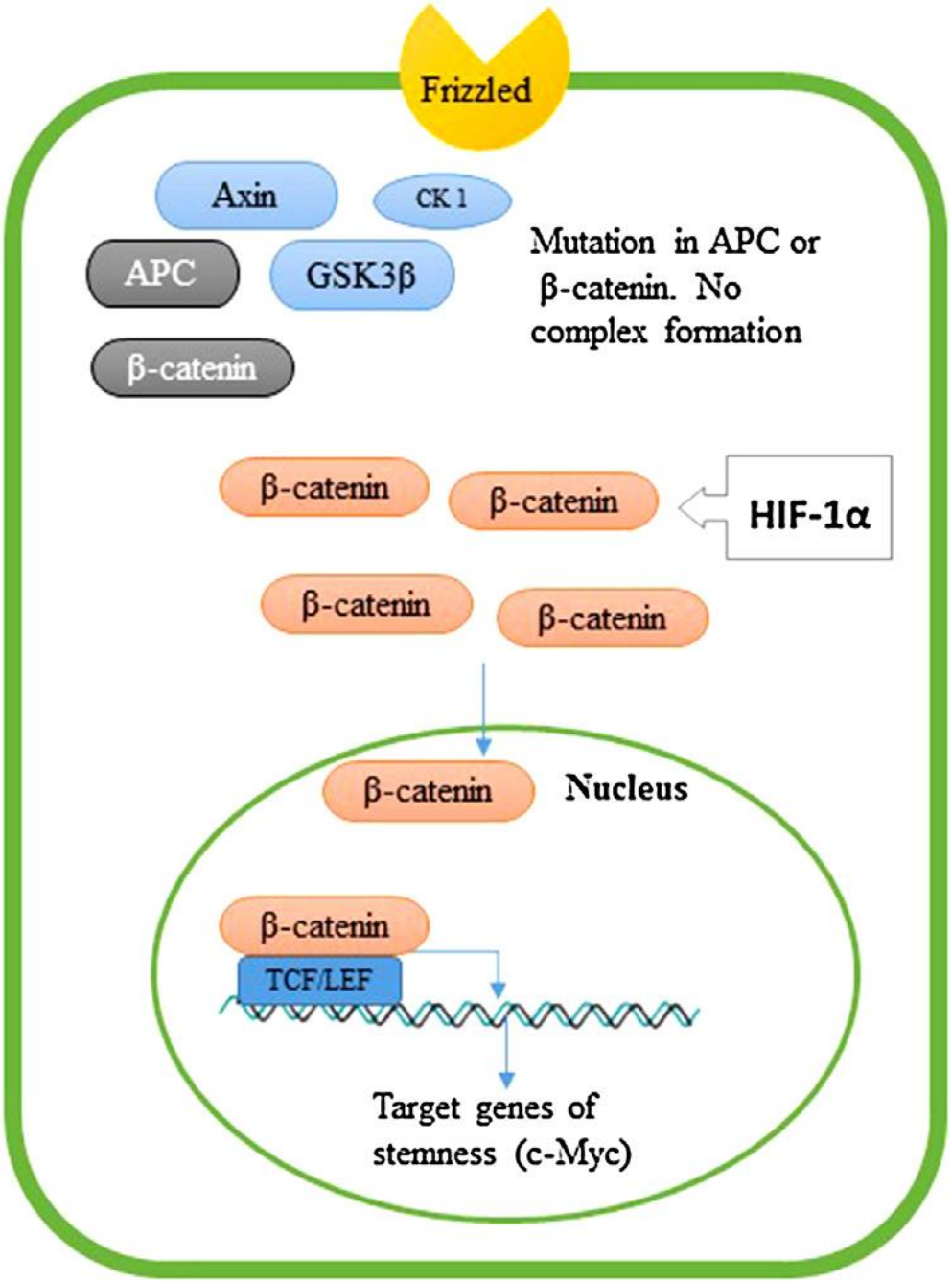


Fig. 4. HIFs in stemness maintenance through Wnt/-catenin signaling.
HIF activates the elevation of β-catenin levels in cytoplasm and translocated in a nucleus. In nucleus, β-catenin binds to TCF/LEF and promotes transcription of all the target genes (c-Myc) involved in stem cell maintenance (Vadde et al., 2017).

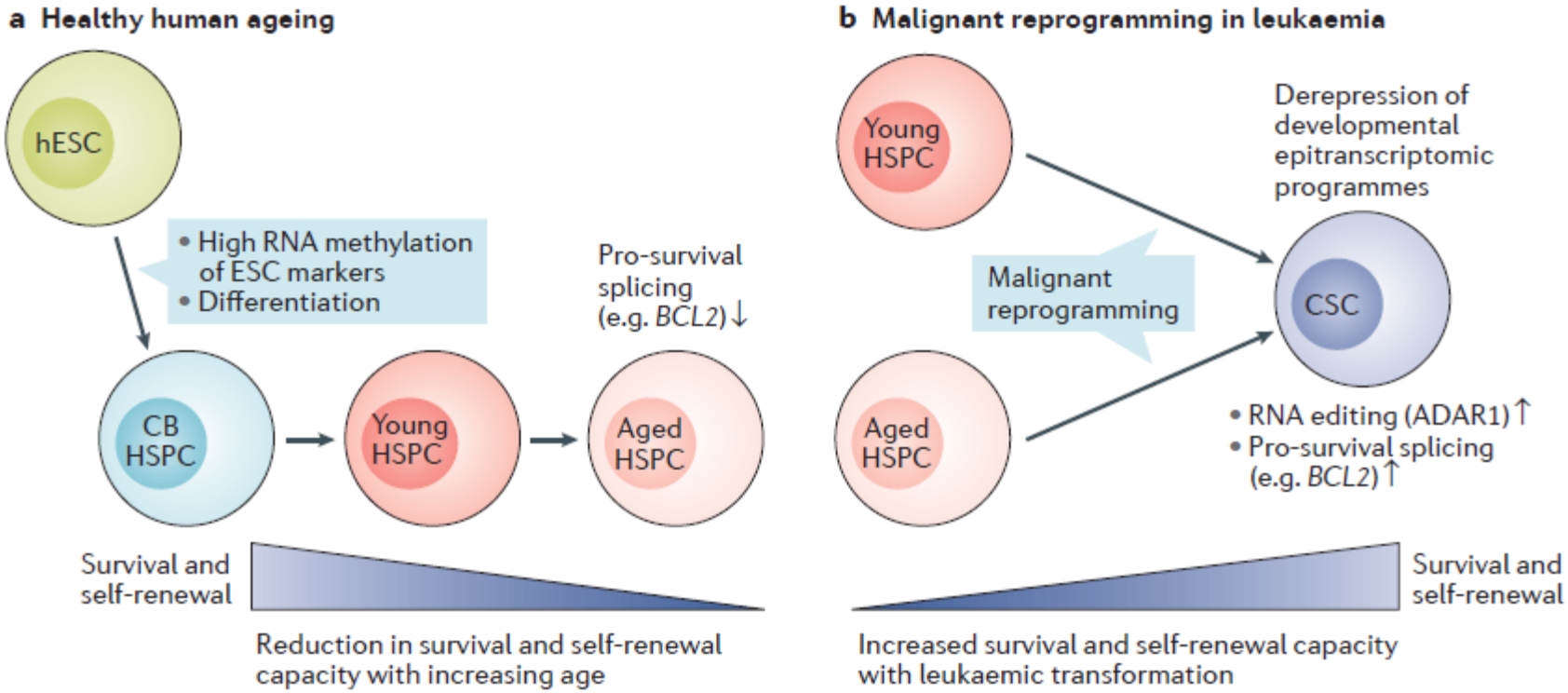


Figure 4 | **RNA processing in normal and malignant haematopoiesis.** RNA processing alterations influence human haematopoietic stem and progenitor cell (HSPC) development, ageing and disease. **a** | In human embryonic stem cells (hESCs), RNA methylation represses pluripotency markers, promoting differentiation along distinct lineages when coupled with derepression of pathway-specific regulatory transcripts. During healthy human development and ageing, precise regulation of stem cell regulatory RNA processing activities such as alternative splicing of pro-survival gene families (for example, *BCL2*) and RNA binding protein activities (including splicing factors) are required to maintain HSPC survival and self-renewal from fetal stages (cord blood (CB)) through adulthood and ageing. **b** | In age-related malignancies such as chronic myeloid leukaemia (CML) and acute myeloid leukaemia (AML), aberrant RNA editing and preferential expression of pro-survival splice isoforms (for example, long isoforms of *BCL2* and *BCL2L1* gene products) promotes malignant reprogramming of progenitors and supports leukaemia cancer stem cell (CSC) survival and self-renewal through derepression of developmental epitranscriptomic programmes. ADAR1, adenosine deaminase acting on double-stranded RNA 1.

Jiang et al., 2017

https://www.youtube.com/watch?v=qszZeZkDysM
Robert Weinberg
Signals Triggering the EMT and Cancer Stem Cell Formation

https://www.youtube.com/watch?v=BK8mDIG3aCE
Irving Weissmann
Cancer Stem Cells: The Origin of Cancer

MULTISTEP CARCINOGENESIS

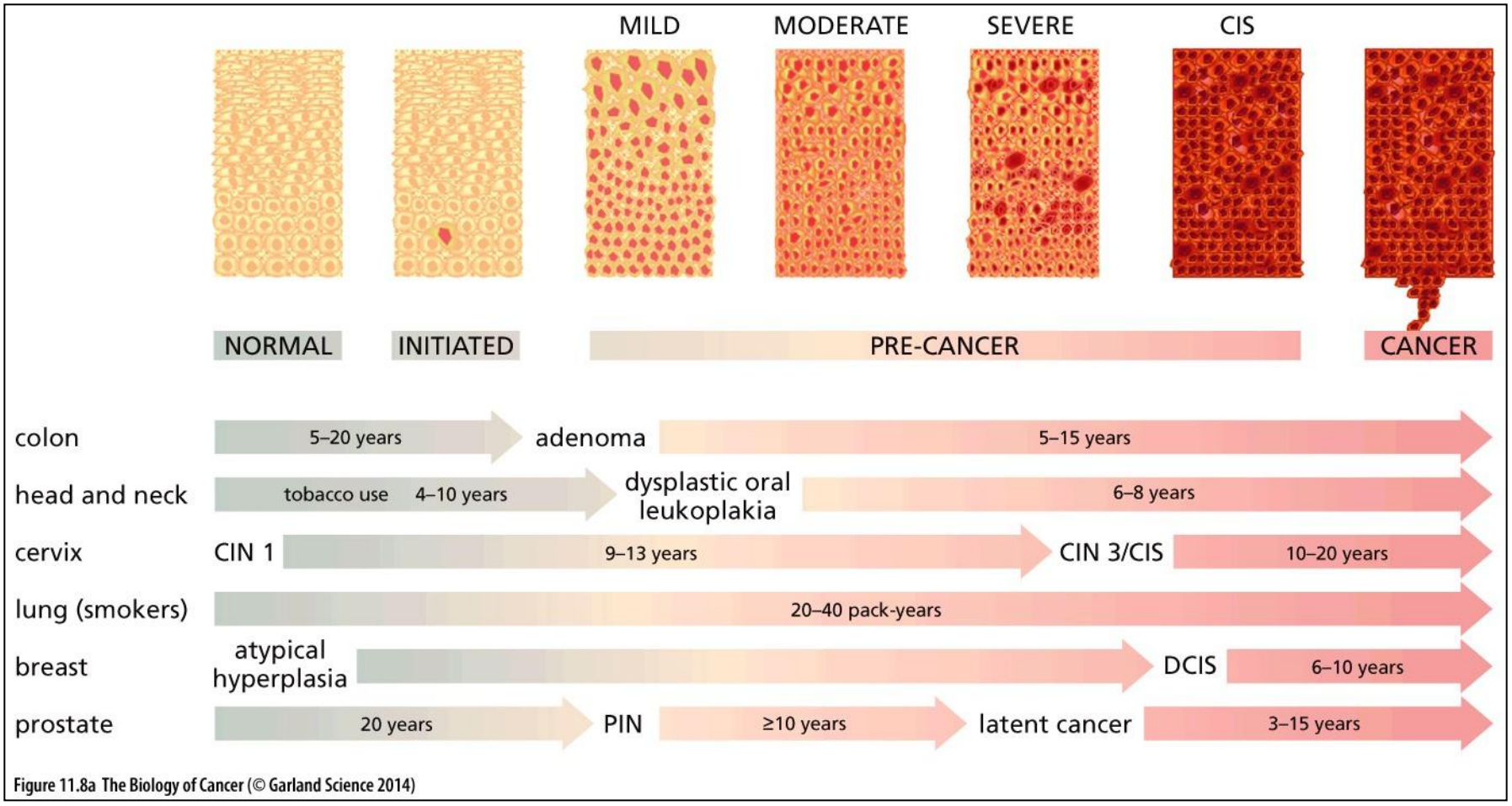


Figure 11.8a The Biology of Cancer (© Garland Science 2014)

NEOPLASTIC TRANSFORMATION: TWO HITS THEORY

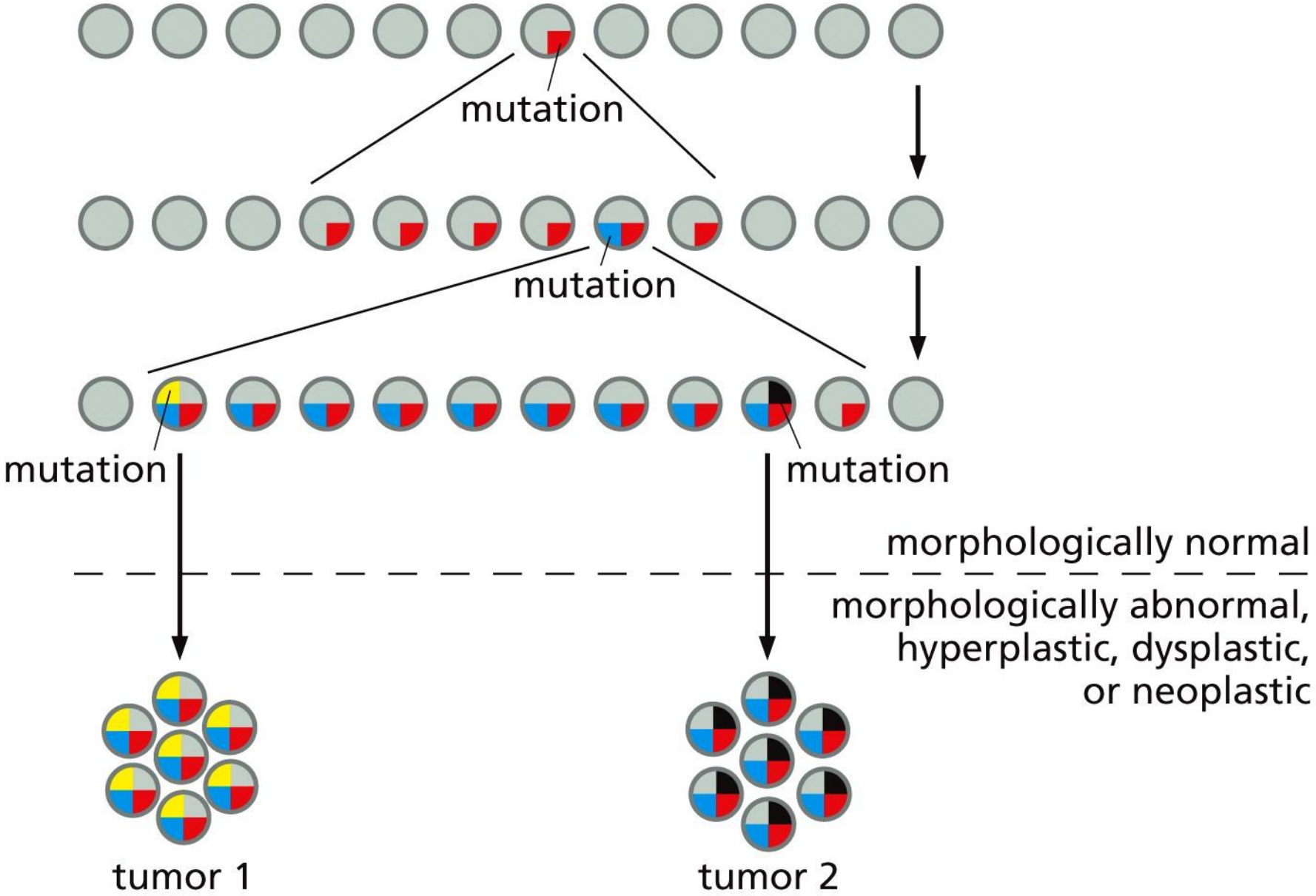
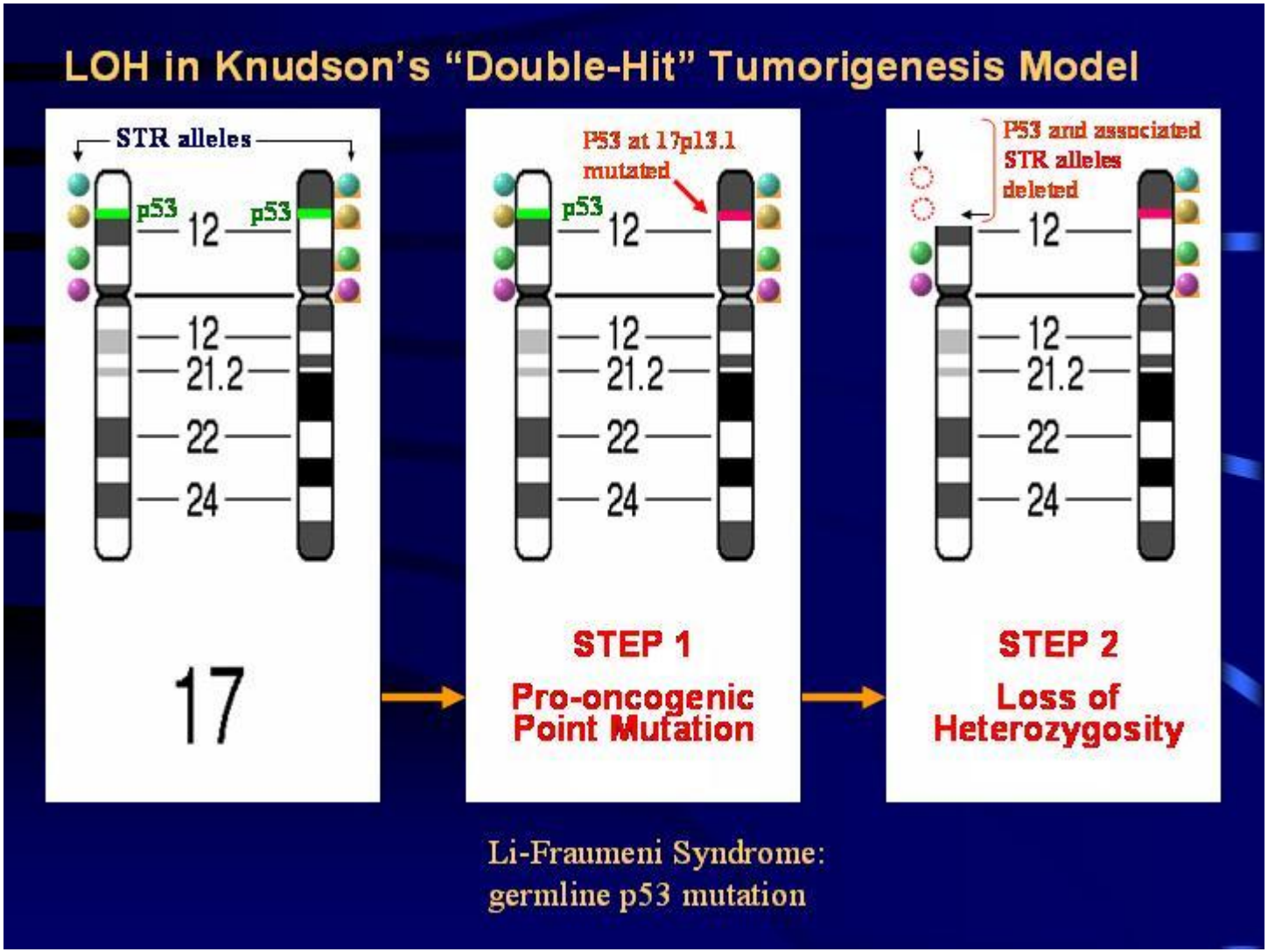


Figure 11.14a The Biology of Cancer (© Garland Science 2014)

LOH: Loss Of Heterozygosity



path.upmc.edu

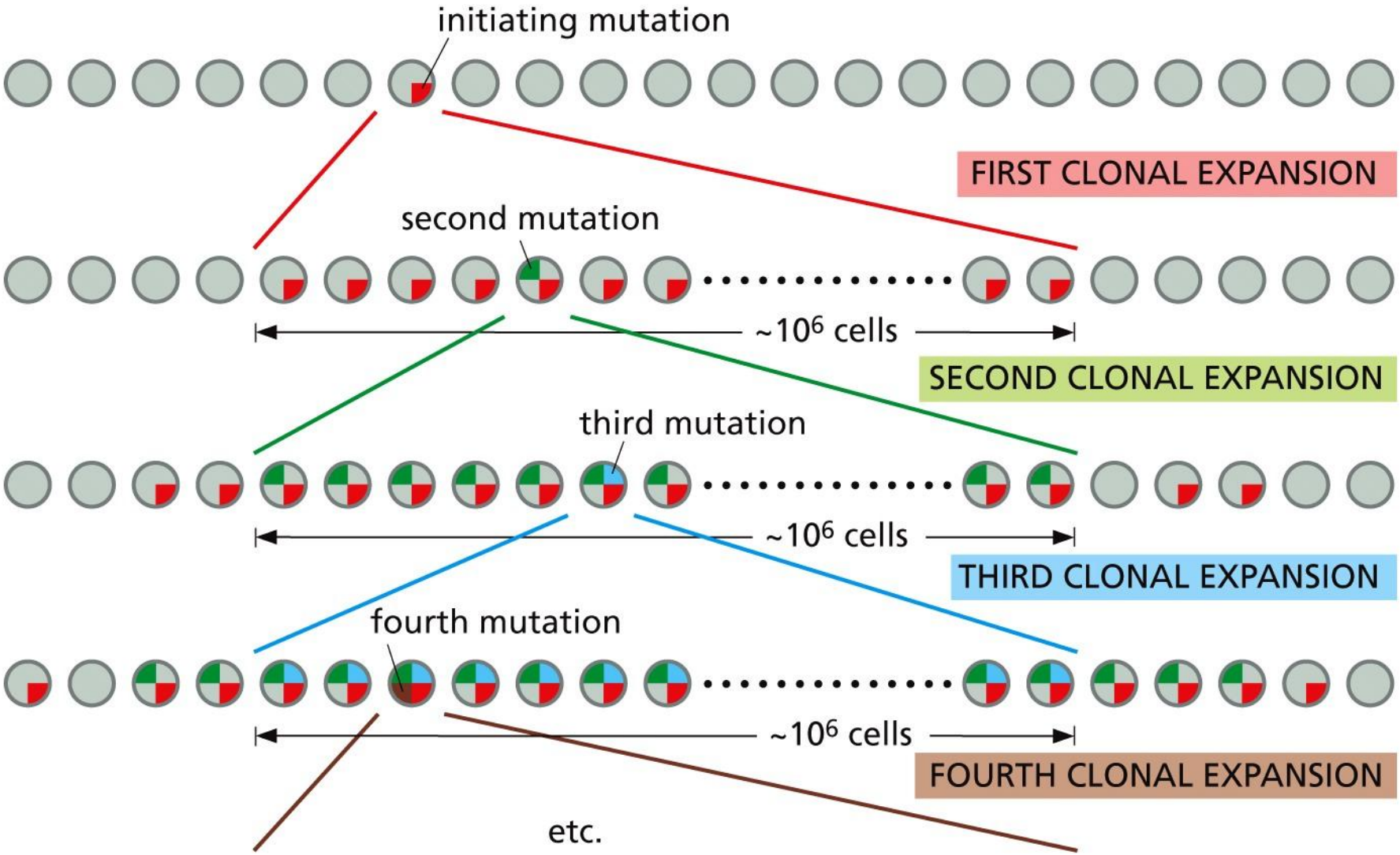


Figure 11.15 The Biology of Cancer (© Garland Science 2014)

PROGRESSIVE GENETIC INSTABILITY

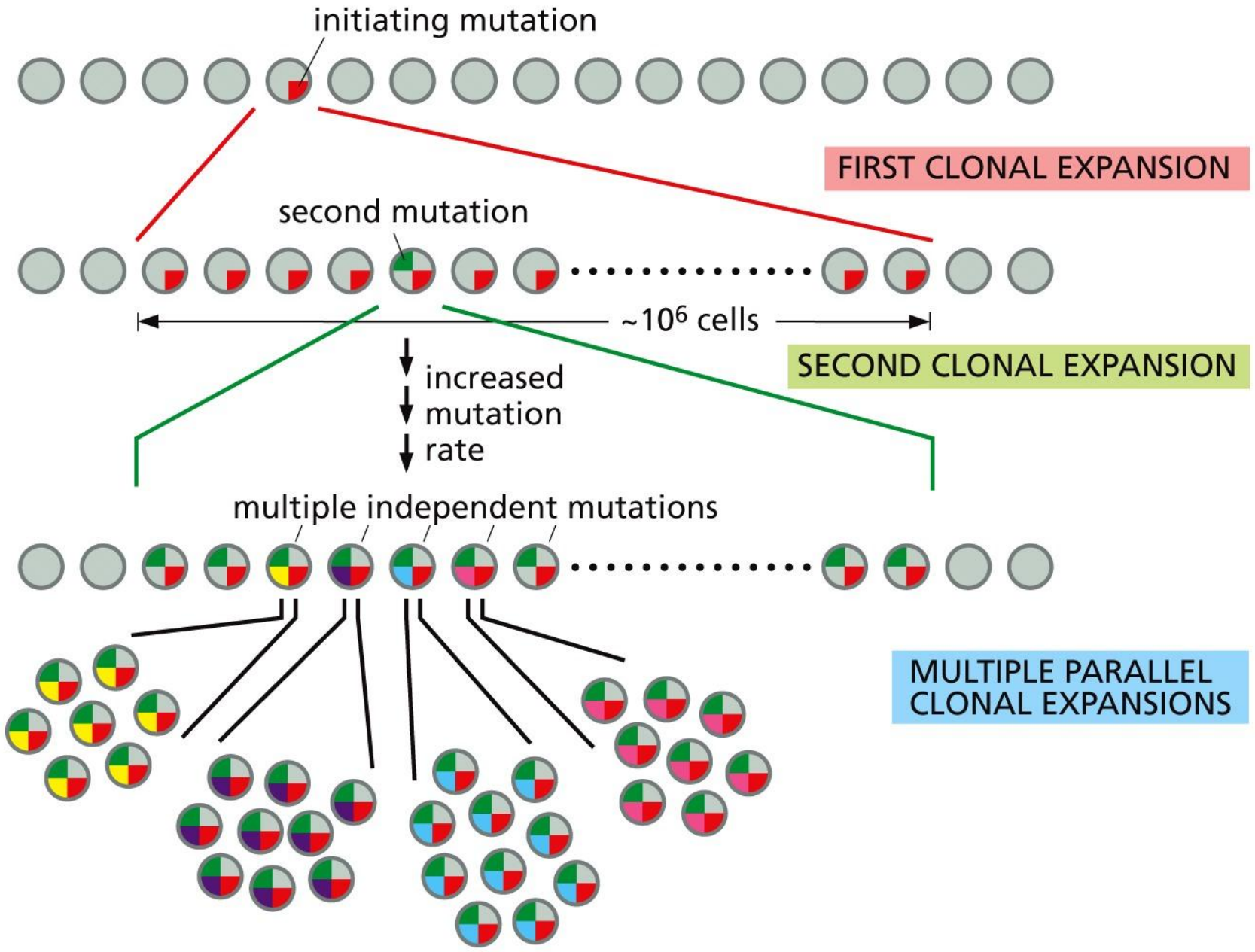


Figure 11.20a The Biology of Cancer (© Garland Science 2014)

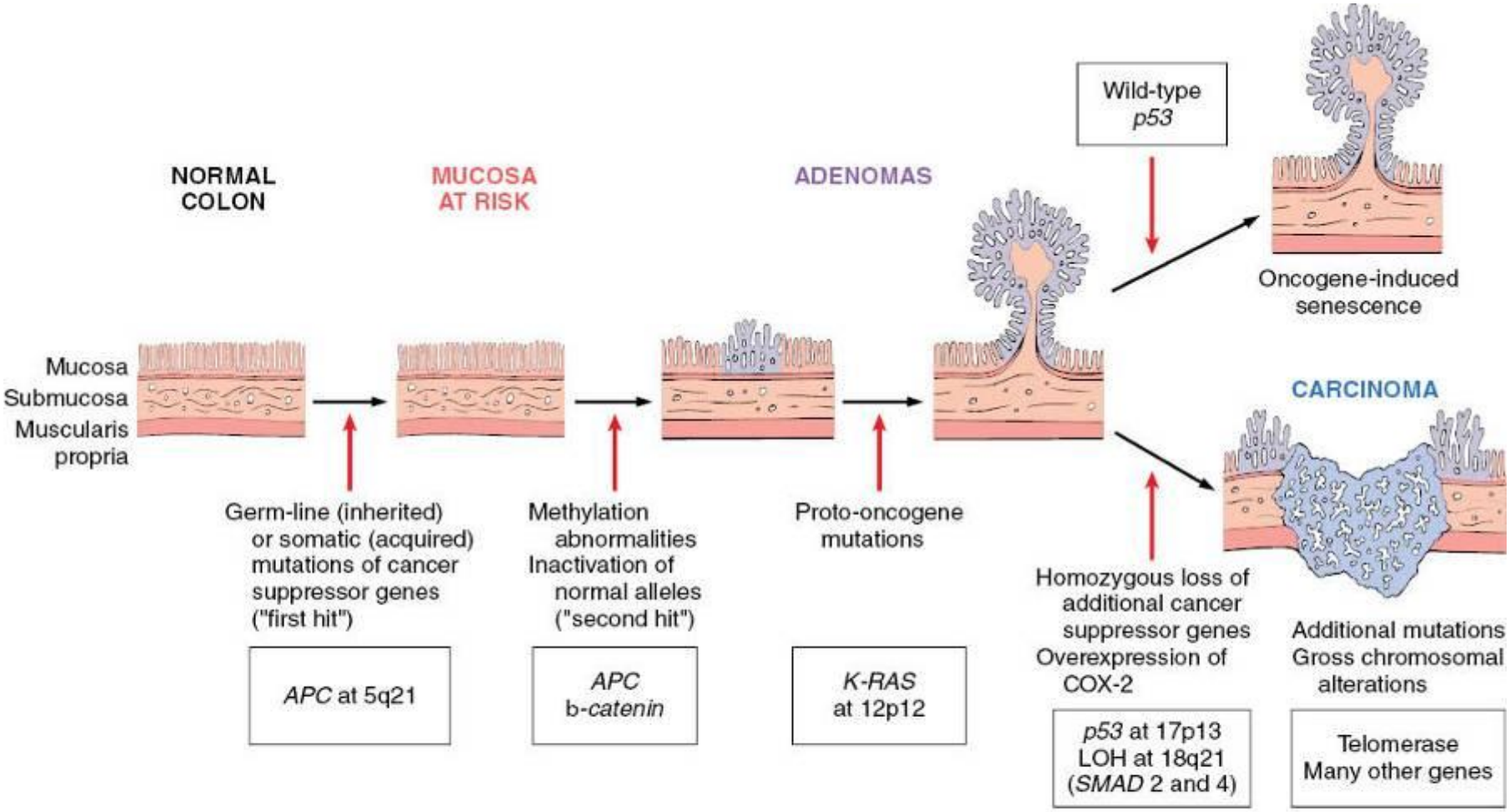


FIGURE 7–40 Molecular model for the evolution of colorectal cancers through the adenoma-carcinoma sequence. Although *APC* mutation is an early event and loss of *p53* occurs late in the process of tumorigenesis, the timing for the other changes may be variable. Note also that individual tumors may not have all of the changes listed. *Top right*, cells that gain oncogene signaling without loss of p53 eventually enter oncogene-induced senescence.

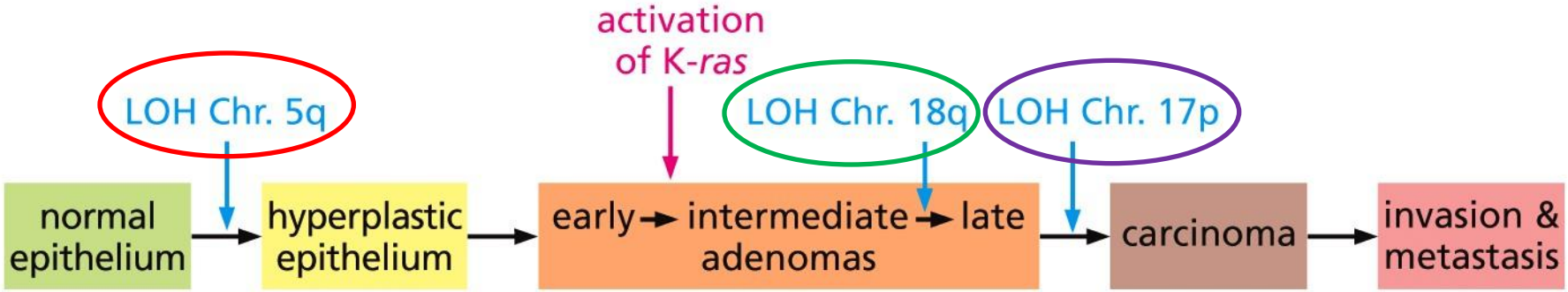


Figure 11.10 The Biology of Cancer (© Garland Science 2014)

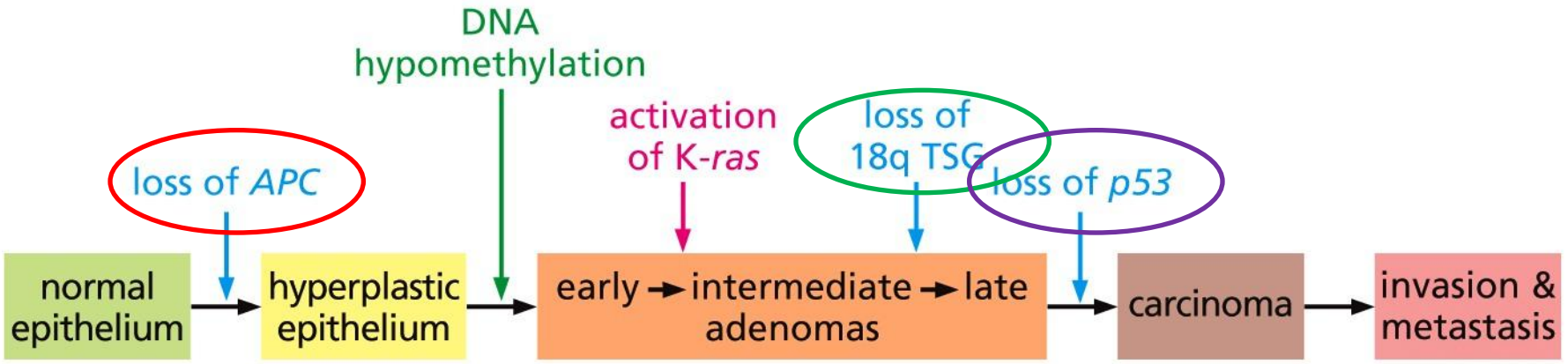


Figure 11.11 The Biology of Cancer (© Garland Science 2014)

TSG = Tumor Suppressor Gene

ALTERNATIVE CHOICES DURING CANCER PROGRESSION

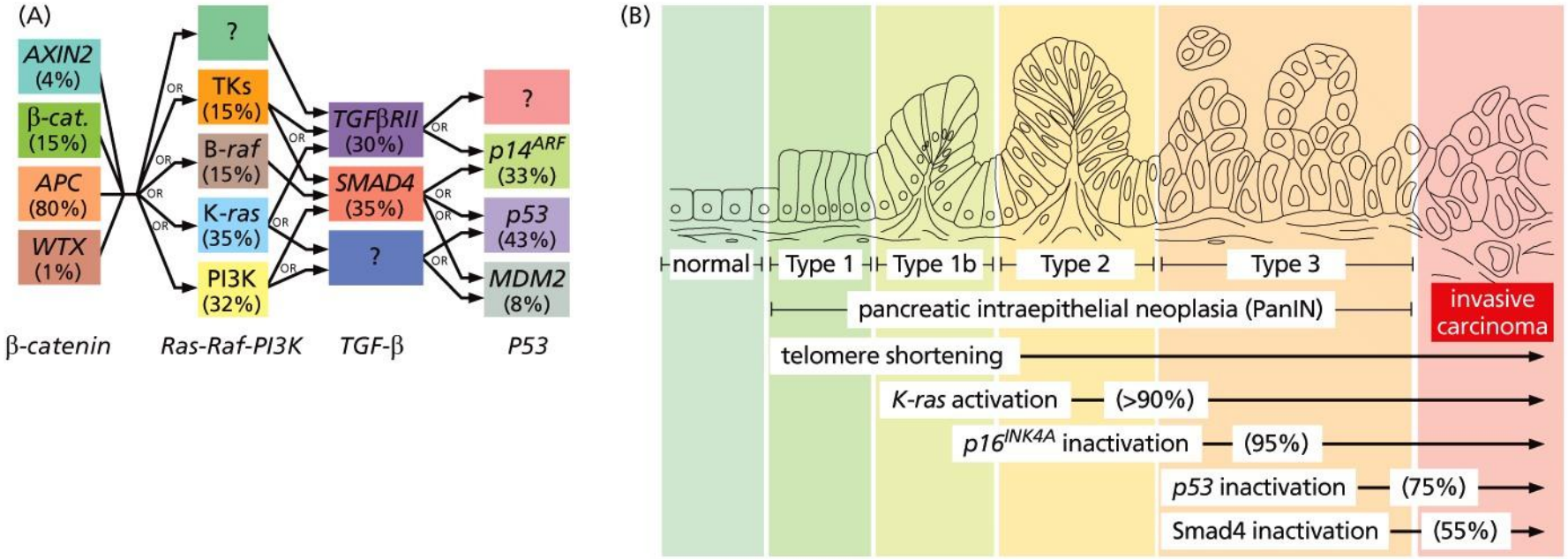


Figure 11.12 The Biology of Cancer (© Garland Science 2014)

Table 11.2 Physiologic mechanisms of oncogene collaboration[a]

Oncogene pair	Cell type	Mechanisms of action
ras + SV40 *large T*	rat Schwann cells	*ras*: proliferation + proliferation arrest
		large T: prevents proliferation arrest and reduces mitogen requirement
ras + *E1A*	mouse embryo fibroblasts	*ras*: proliferation and senescence
		E1A: prevents senescence
erbB + *erbA*	chicken erythroblasts	*erbB*: induces GF-independent proliferation
		erbA: blocks differentiation
TGF-α + *myc*	mouse mammary epithelial cells	*TGF-α*: induces proliferation and blocks apoptosis
		myc: induces proliferation and apoptosis
v-*sea* + v-*ski*	avian erythroblasts	v-*sea*: induces proliferation
		v-*ski*: blocks differentiation
bcl-2 + *myc*	rat fibroblasts	*bcl-2*: blocks apoptosis
		myc: induces proliferation and apoptosis
ras + *myc*	rat fibroblasts	*ras*: induces anchorage independence
		myc: induces immortalization
raf + *myc*	chicken macrophages	*raf*: induces growth factor secretion
		myc: stimulates proliferation
src + *myc*	rat adrenocortical cells	*src*: induces anchorage and serum independence
		myc: prolongs proliferation

[a]In each pair, the first oncogene encodes a cytoplasmic oncoprotein while the second oncogene encodes a nuclear oncoprotein.

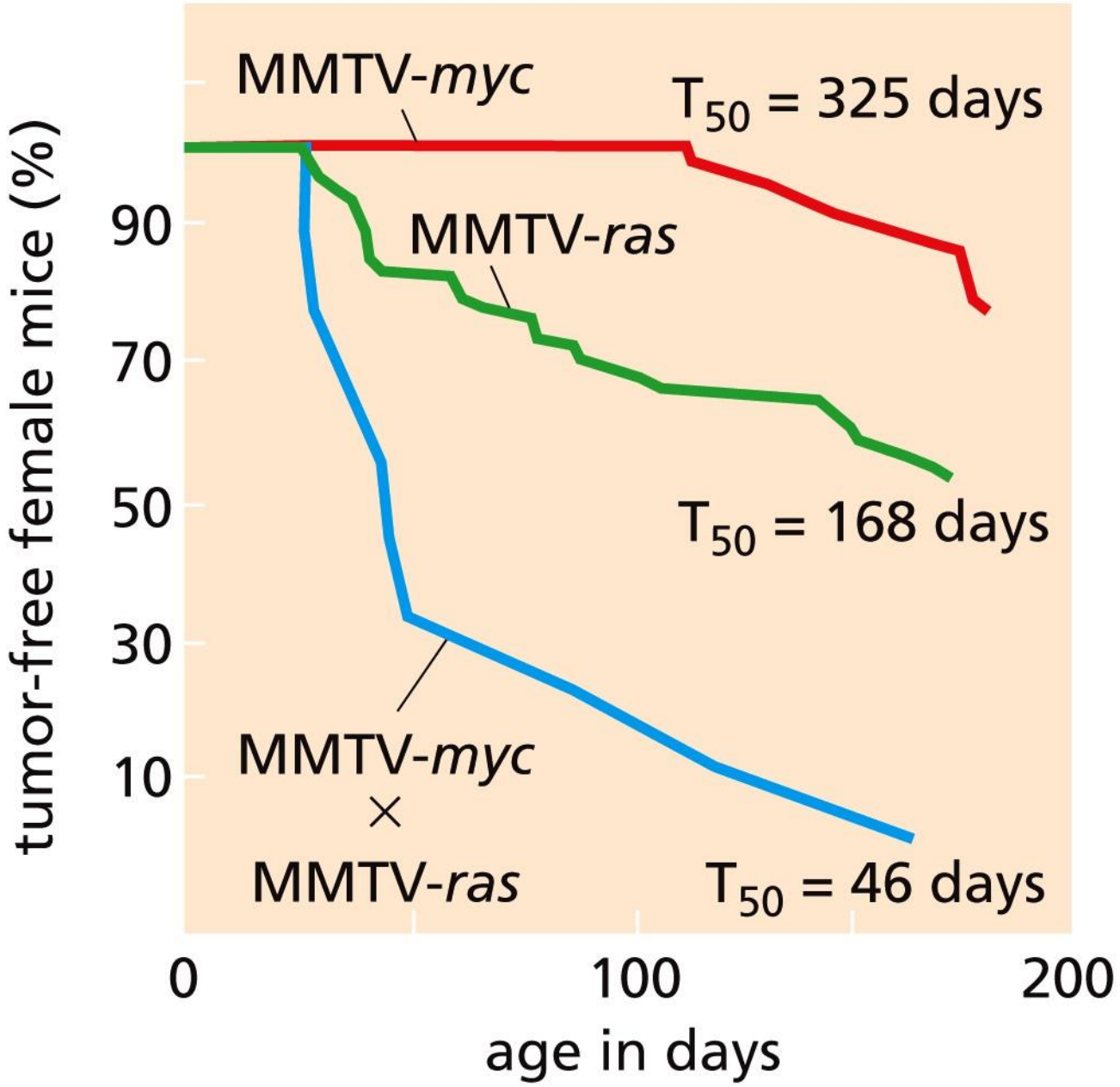


Figure 11.25 The Biology of Cancer (© Garland Science 2014)

CANCER PROGRESSION: THE NATURAL HISTORY OF A TUMOR

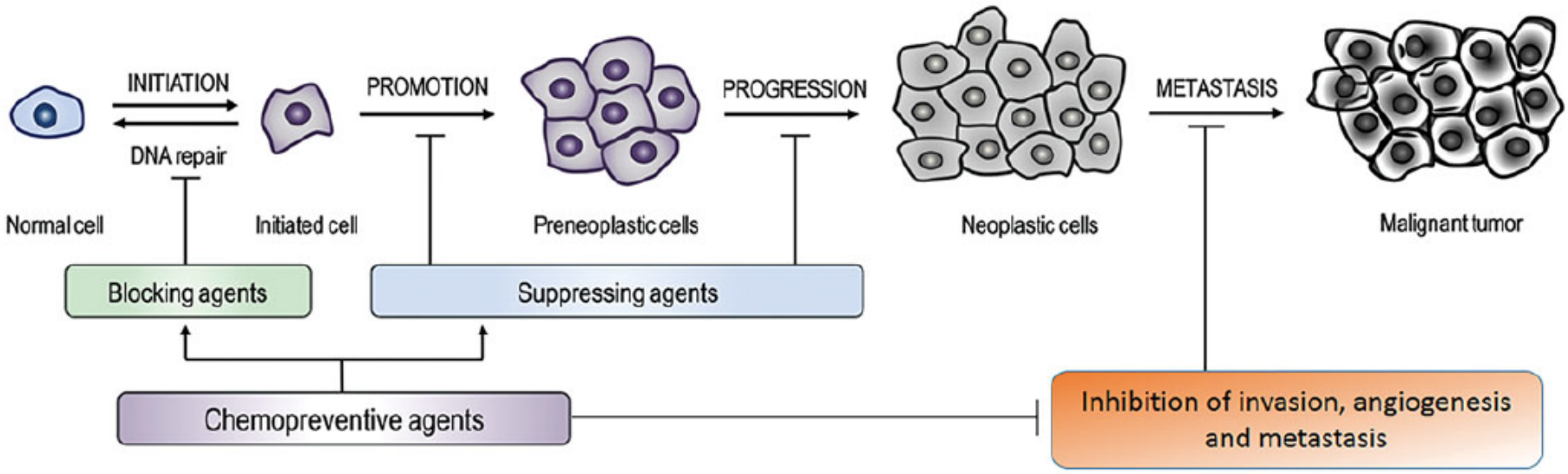


Figure 1. Carcinogenesis phases: initiation, promotion, progression, and metastasis. (A) Initiation involves the alteration, change, or mutation of genes arising spontaneously or induced by exposure to a carcinogenic agent. Genetic alterations can result in dysregulation of biochemical signaling pathways associated with cellular proliferation, survival, and differentiation, which can be influenced by a number of factors, including the rate and type of carcinogenic metabolism and the response of the DNA repair function. (B) The promotion stage is considered to be a relatively lengthy and reversible process in which actively proliferating preneoplastic cells accumulate. Within this period, the process can be altered by chemopreventive agents and affect growth rates. Progression is the phase between a premalignant lesion and the development of invasive cancer. (C) Progression is the final stage of neoplastic transformation, where genetic and phenotypic changes and cell proliferation occur. This involves a fast increase in the tumor size, where the cells may undergo further mutations with invasive and metastatic potential. Chemopreventive agents should be able to preferentially act within the initiation and promotion processes of carcinogenesis. (D) Metastasis involves the spread of cancer cells from the primary site to other parts of the body through the bloodstream or the lymph system. Chemopreventive agents are known to inhibit angiogenesis and invasion of primary tumors, and thus could be utilized to inhibit the metastasis of cancer.

Siddiqui et al., 2015

SKIN: EXPERIMENTAL CARCINOGENESIS

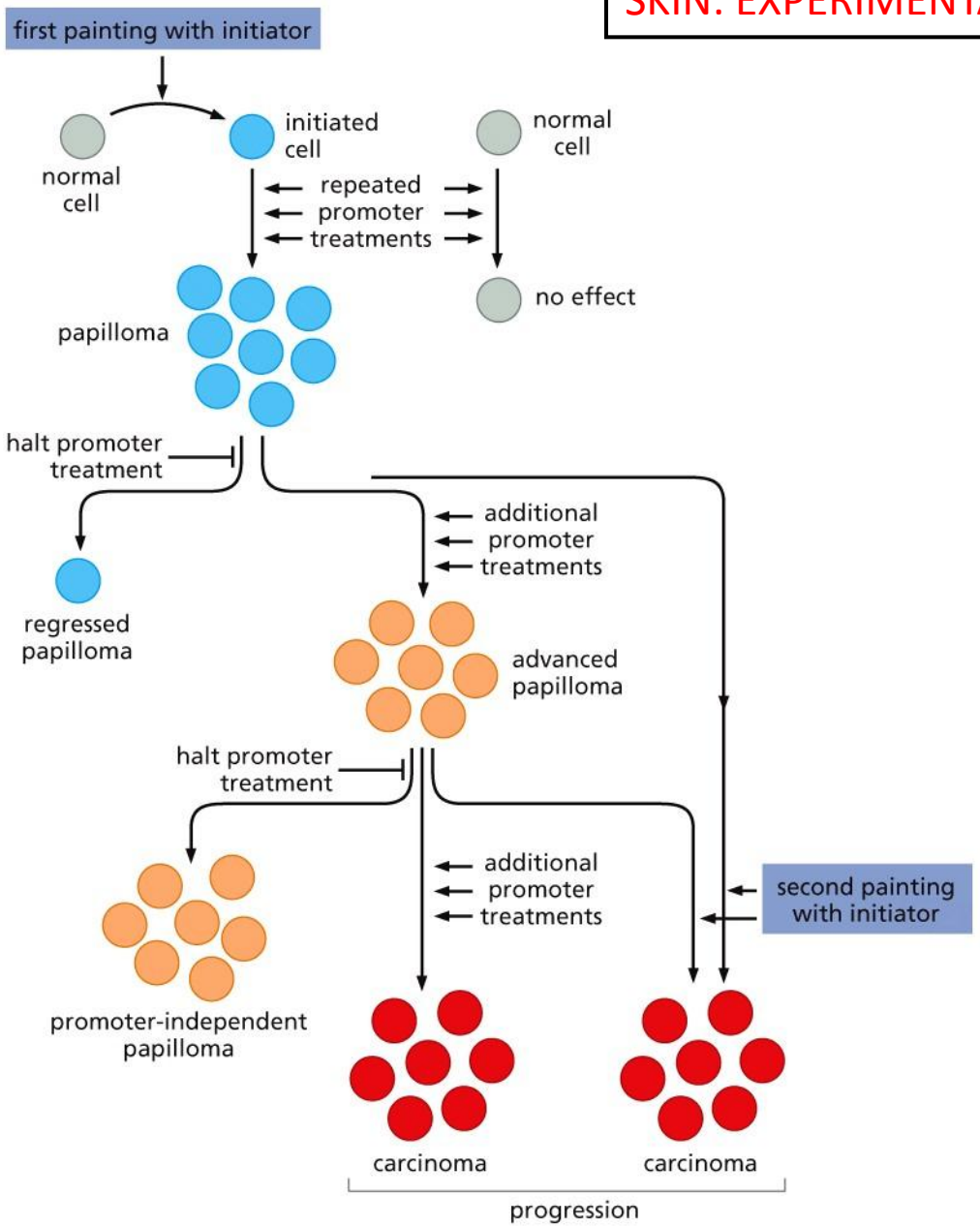


Figure 11.31 The Biology of Cancer (© Garland Science 2014)

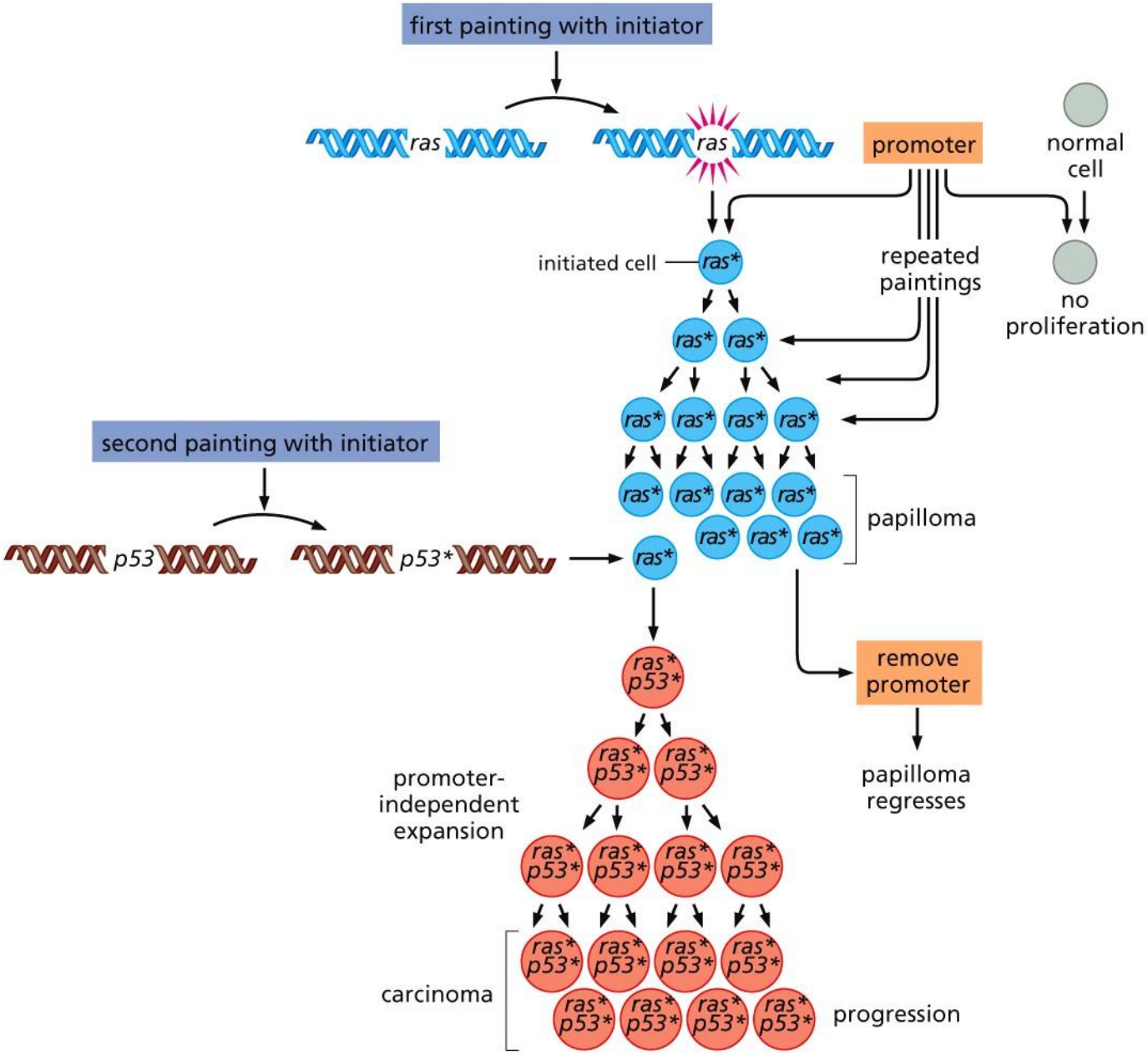


Figure 11.32 The Biology of Cancer (© Garland Science 2014)

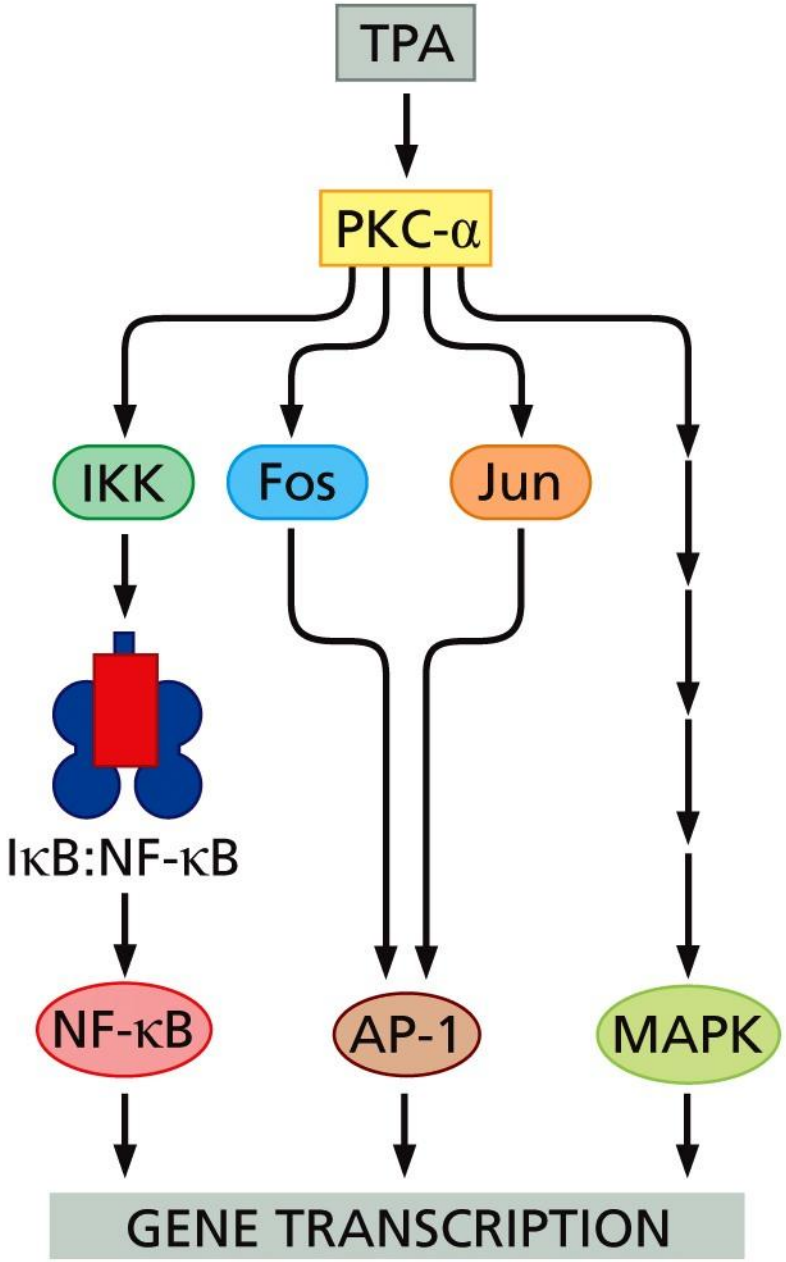


Figure 11.33 The Biology of Cancer (© Garland Science 2014)

Table 11.5 Known or suspected human tumor promoters and their sites of action

Agent or process	Cancer site
Hormones	
Estrogen	endometrium
Estrogen and progesterone	breast
Ovulation	ovary
Testosterone	prostate
Drugs	
Oral contraceptives, anabolic steroids	liver
Analgesics	renal pelvis
Diuretics	kidney
Infectious agents	
Hepatitis B/C viruses	liver
Schistosoma haematobium—blood fluke	bladder
Schistosoma japonicum—blood fluke	colon
Clonorchis sinensis—liver fluke	biliary tract
Helicobacter pylori—bacterium	stomach
Malarial parasites	B cell
Tuberculosis bacillus	lung
Chemical agents	
Betel nut, lime	oral cavity
Chewing tobacco	oral cavity
Bile	small intestine
Salt	stomach
Acid reflux	esophagus
Physical or mechanical trauma	
Asbestos	mesothelium, lung
Gallstones	gallbladder
Coarsely ground corn	stomach
Head injury	meninges
Chronic irritation/inflammation	
Tropical ulcers[a]	skin
Chronic ulcerative colitis	colon
Chronic cystitis	bladder
Chronic pancreatitis	pancreas

[a]Tropical ulcers are caused by chronic infections of the skin, usually of bacterial origin, that do not heal and are associated with poor nutrition and lack of sanitation.

Adapted in part from S. Preston-Martin et al., *Cancer Res.* 50:7415–7421, 1990.

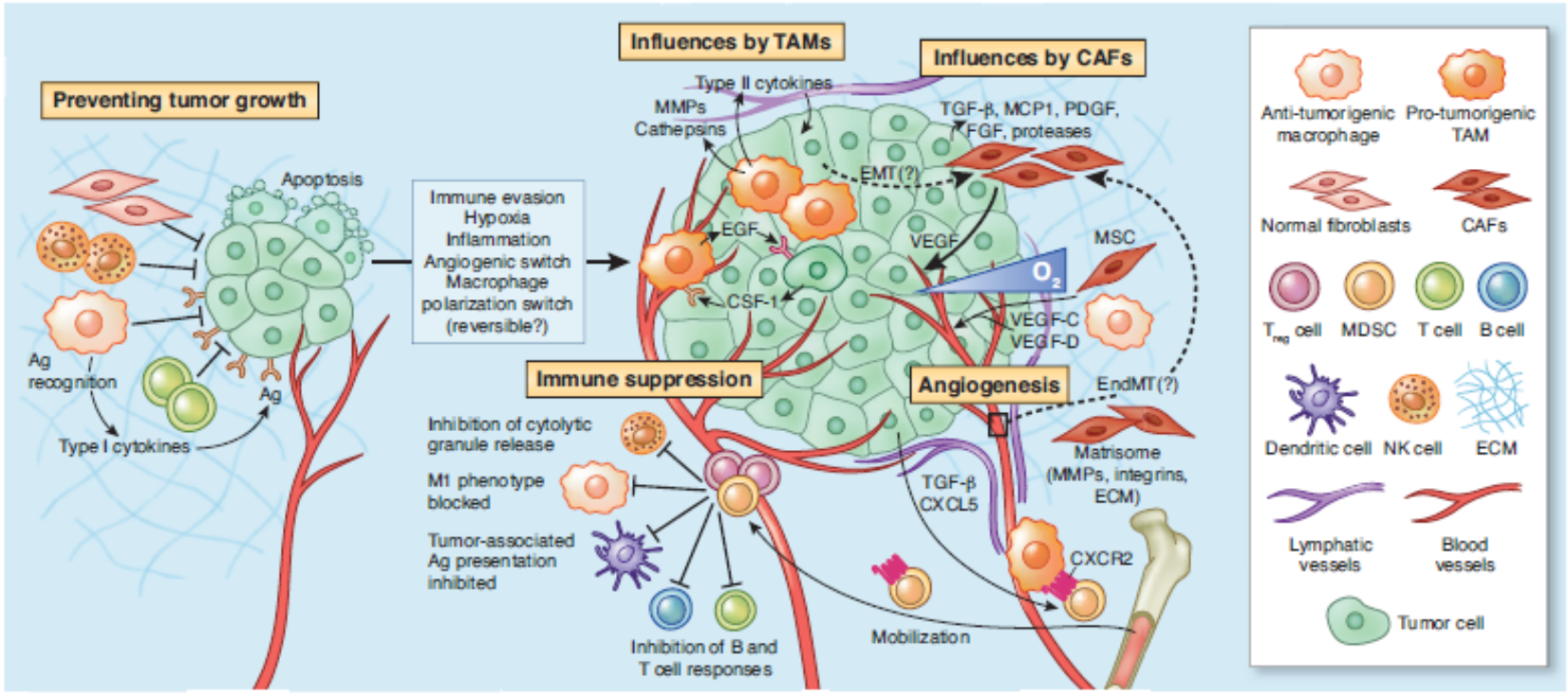
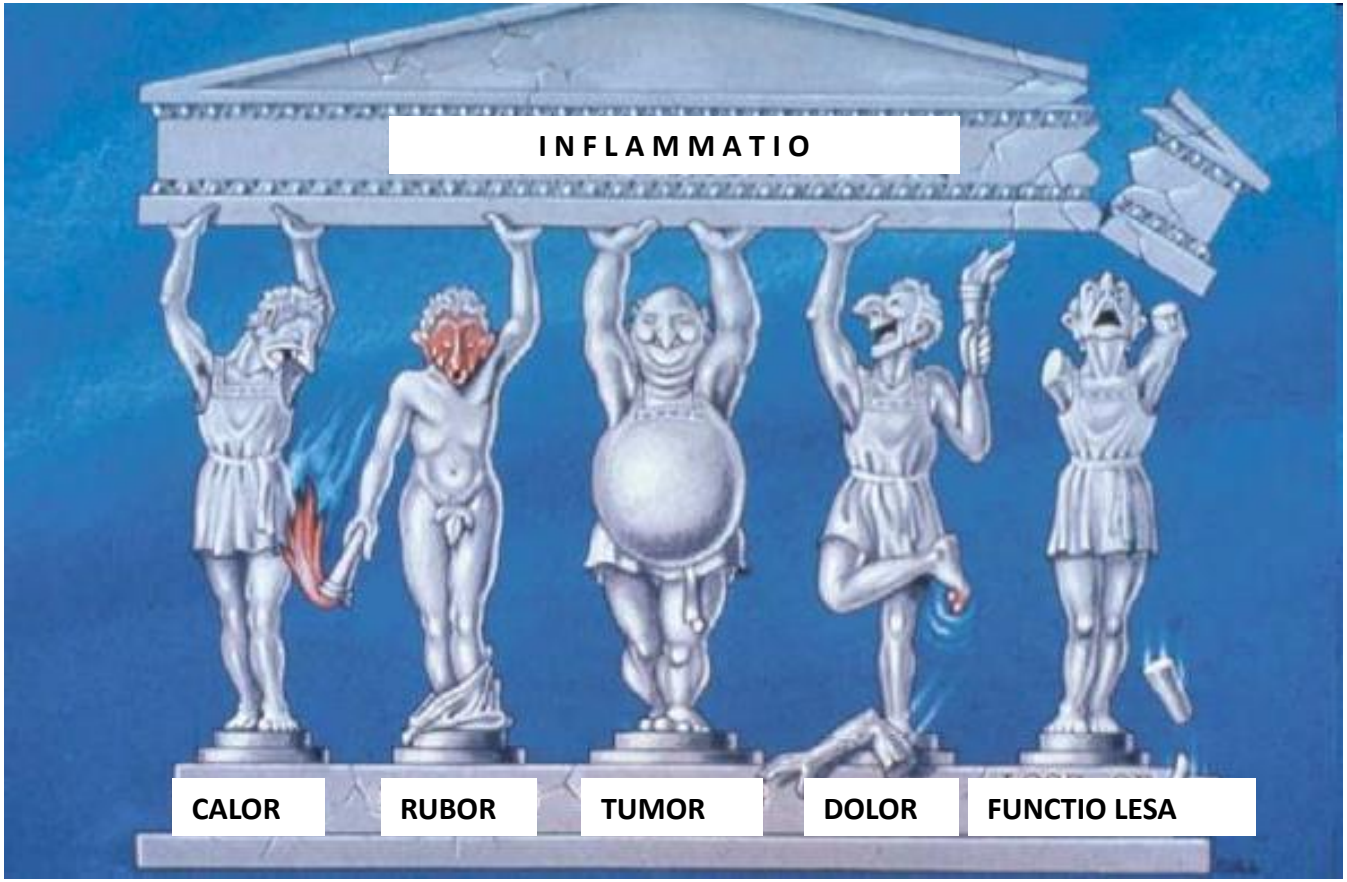


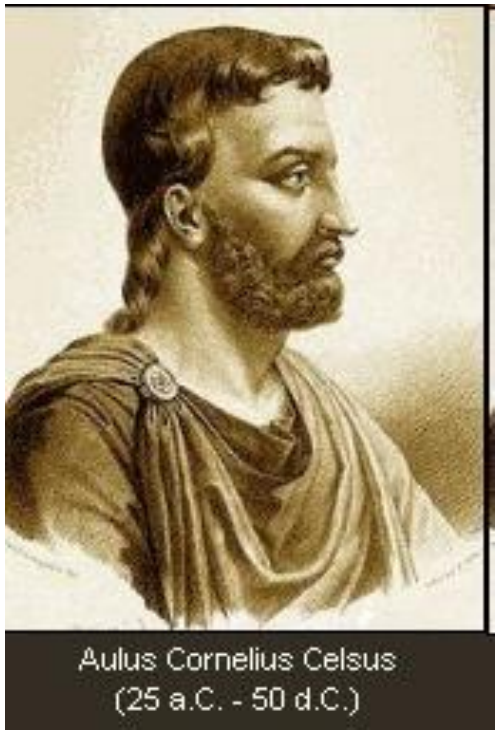
Figure 1 Multiple stromal cell types converge to support a tumorigenic primary niche. After circumventing cell-intrinsic mechanisms of apoptosis, tumor cells are subject to elimination pressures by the immune system. Tumor cell–specific antigens have a role during this process, which are recognized by cytotoxic immune cells, leading to their destruction. Fibroblasts and macrophages within the TME also contribute to a growth-suppressive state; however, these cells may later become educated by the tumor to acquire pro-tumorigenic functions. For instance, TAMs support diverse phenotypes within the primary tumor, including growth, angiogenesis and invasion, by secreting a plethora of pro-tumorigenic proteases, cytokines and growth factors (for example, EGF, which participates in a paracrine signaling loop through tumor-secreted CSF-1). As tumors grow, immune-suppressor cells, including MDSCs and T_{reg} cells are mobilized into the circulation in response to activated cytokine axes that are induced by tumorigenesis (for example, TGF-β and CXCL5-CXCR2). MDSCs and T_{reg} cells infiltrate the growing tumor to disrupt immune surveillance through multiple mechanisms, including, but not limited to, disruption of antigen presentation by DCs, inhibition of T and B cell proliferation and activation or inhibition of NK cell cytotoxicity. CAFs, which become activated by tumor-derived factors (for example, TGF-β, FGF or PDGF, among others), secrete ECM proteins and basement membrane components, regulate differentiation, modulate immune responses and contribute to deregulated homeostasis. CAFs are also a key source of VEGF, which supports angiogenesis during tumor growth. In addition to cellular contributions, several extracellular properties contribute to tumor progression, including low oxygen tension, high interstitial fluid pressure and changes in specific components of the ECM. EndMT, endothelial-to-mesenchymal transition; Ag, antigen.

Quail & Joyce, 2013

INFLAMMATION AND CANCER



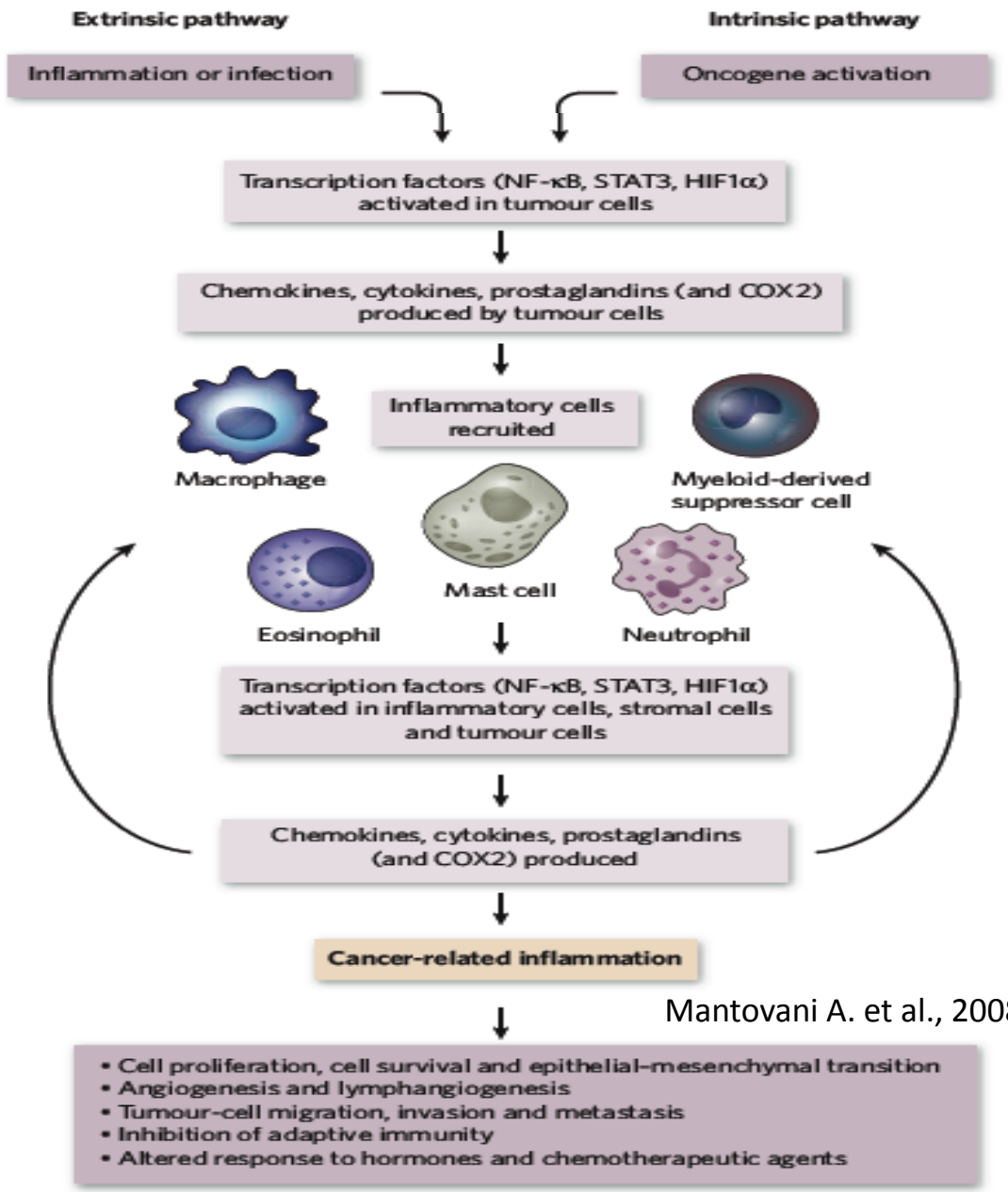
http://www6.ufrgs.br/favet/imunovet/molecular_immunology/inflammation_cartoon.jpg, modified



http://www-1.unipv.it/webchir/neuro/didattica/conoscere/storia/storianch4.htm

INFLAMMATION AND CARCINOGENESIS

- **Rudolph Virchow, 1863**
- **cytokine discovery, 1970-1990**
- **stromal immune cells stimulate tumor growth (Prehn, 1972)**



Mantovani A. et al., 2008

Table 11.3 Inflammatory conditions and tumor development

Human tumor	Inflammatory condition or inflammation-provoking agent
Bladder carcinoma	schistosomiasis, chronic cystitis
Gastric carcinoma	*H. pylori*–induced gastritis
Hepatocellular carcinoma	hepatitis B/C virus
Bronchial carcinoma	silica
Mesothelioma	asbestos
Ovarian carcinoma	endometriosis
Colorectal carcinoma	inflammatory bowel disease
Esophageal carcinoma	chronic acid reflux
Papillary thyroid carcinoma	thyroiditis
Prostate carcinoma	prostatitis
Lung carcinoma	chronic bronchitis
Gallbladder carcinoma	chronic cholecystitis
Squamous cell skin carcinoma	chronic osteomyelitis

Adapted from F. Balkwill, K.A. Charles and A. Mantovani, *Cancer Cell* 7:211–217, 2005.

Table 11.4 Links between inflammation and cancer pathogenesis

Many inflammatory conditions predispose to cancer
Cancers arise at sites of chronic inflammation
Functional polymorphisms of cytokine genes are associated with cancer susceptibility and severity
Distinct populations of inflammatory cells are detected in many cancers
Extent of tumor-associated macrophage infiltrate correlates with prognosis
Inflammatory cytokines are detected in many cancers; high levels are associated with poor prognosis
Chemokines are detected in many cancers; they are associated with inflammatory infiltrate and cell motility
Deletion of cytokines and chemokines protects against carcinogens, experimental metastases, and lymphoproliferative syndrome
Inflammatory cytokines are implicated in the action of nongenotoxic liver carcinogens
The inflammatory cytokine tumor necrosis factor is directly transforming *in vitro*
Long-term NSAID use decreases mortality from colorectal cancer

Courtesy of F. Balkwill. From F. Balkwill and A. Mantovani, *Lancet* 357:539–545, 2001.

CHRONIC LIVER INFLAMMATION AND HEPATOCELLULAR CARCINOMA DEVELOPMENT

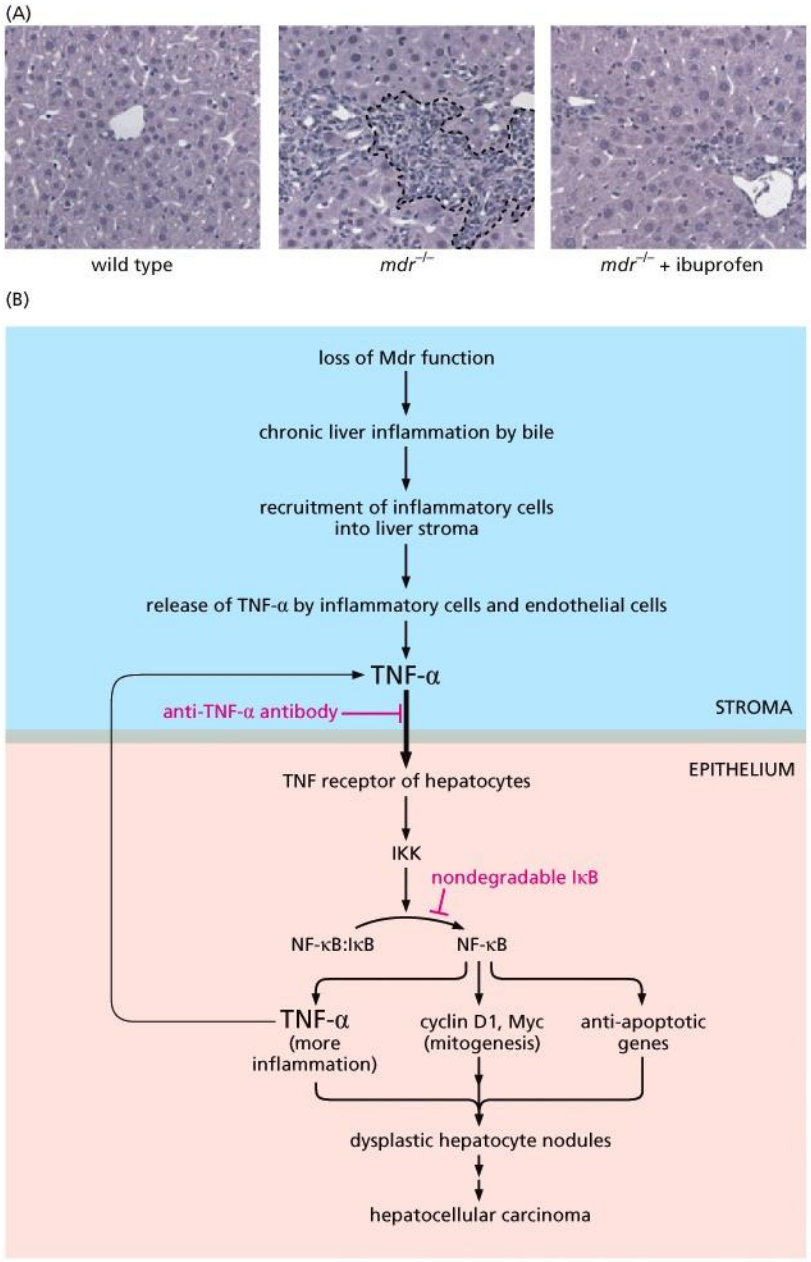
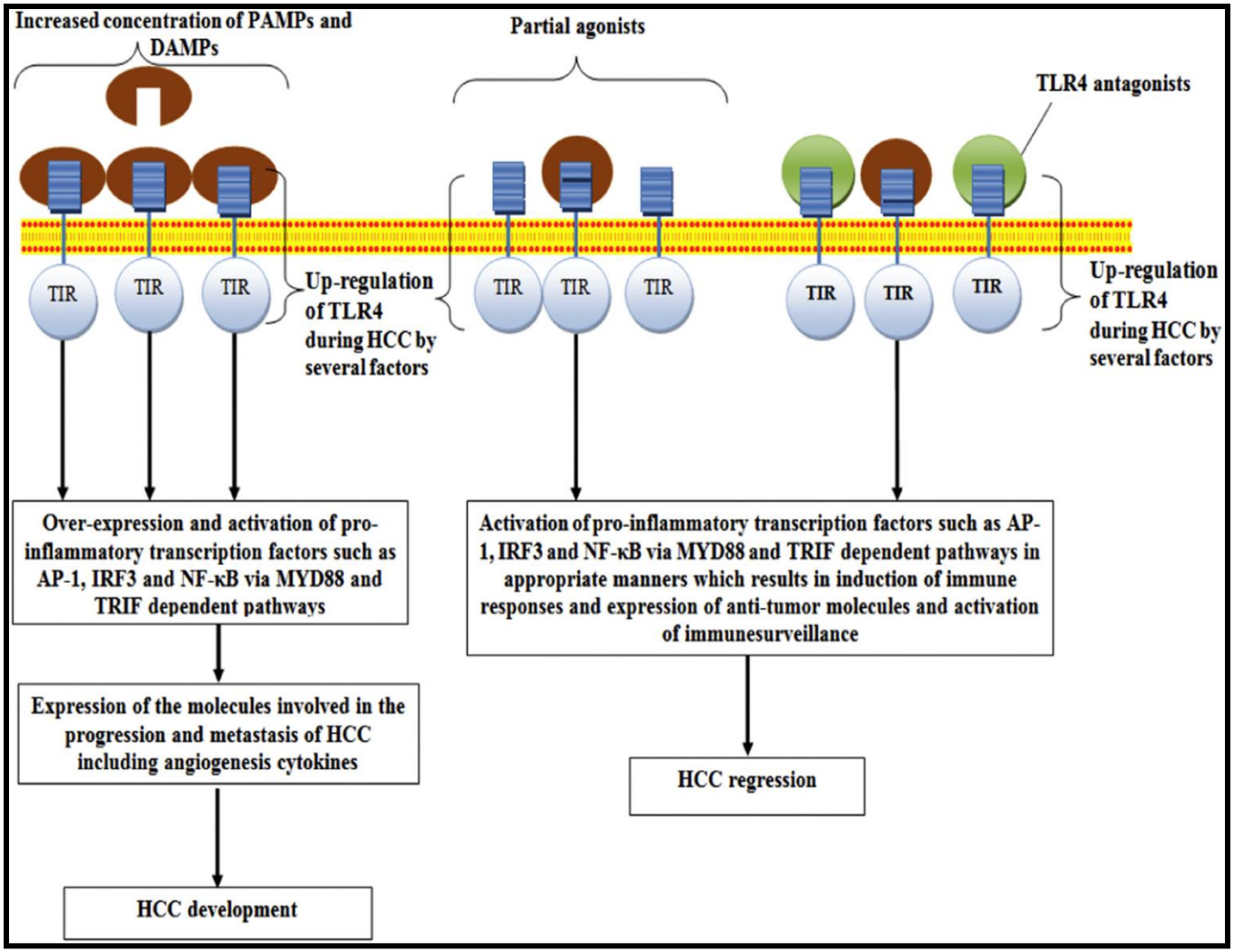


Figure 11.38 The Biology of Cancer (© Garland Science 2014)

mdr: multi drug resistance gene



Up-regulation of TLR4 happened during HCC by several factors which are described in Fig. 3. Hyperactivation of TLR4 by DAMPs and PAMPs is associated with over-expression and activation of pro-inflammatory transcription factors in a considerable manner which is associated with over-expression of the molecules involved in the HCC and development. Using TLR4 antagonists and partial agonists may be associated with involvement of lower expressed TLR4, hence, intracellular signaling has been induced by the limited TIRs which interact with partial agonists. TLR4 antagonists also block the up-regulated TLR4 and decreased the interaction of TLR4 with its ligands. Both strategies, using antagonists and partial agonists lead to under controlled activation of TLR4 which results in induction of appropriate immune responses and consequently HCC regression (Sepheri et al., 2017).

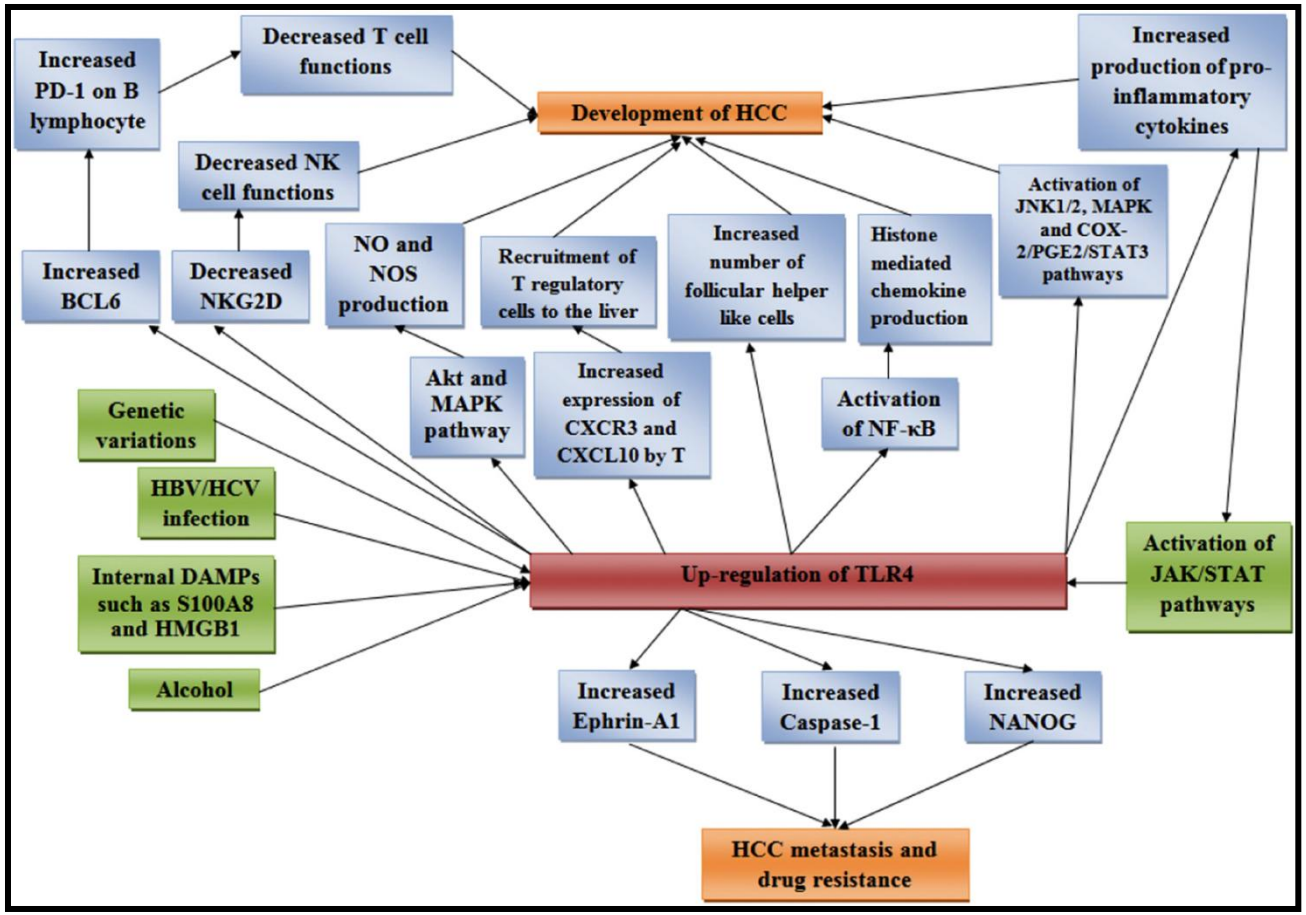


Fig. 3. The mechanisms used by TLR4 in development, metastasis and drug resistance of HCC. Genetic variations, chronic HBV/HCV infection, alcohol, internal DAMPs and chronic inflammation, via activation of JAK/STAT pathways, lead to up-regulation of TLR4. Increased expressions of TLR4 by resident immune cells and also hepatocytes result in increased Ephrin-A1, Casapse-1 and NANOG, which are the main inducers of HCC metastasis and drug resistance. Increased and decreased expressions of BCL6 and NKG2D, respectively, lead to impaired immunosurveillance against HCC development. No, NOS and pro-inflammatory cytokine production are also risk factors for development of HCC. Increased numbers of T regulatory and follicular T helper cells, via up-regulation of chemokines, are other effects of up-regulated TLR4 during HCC, which are associated with development of HCC (Sepheri et al., 2017).

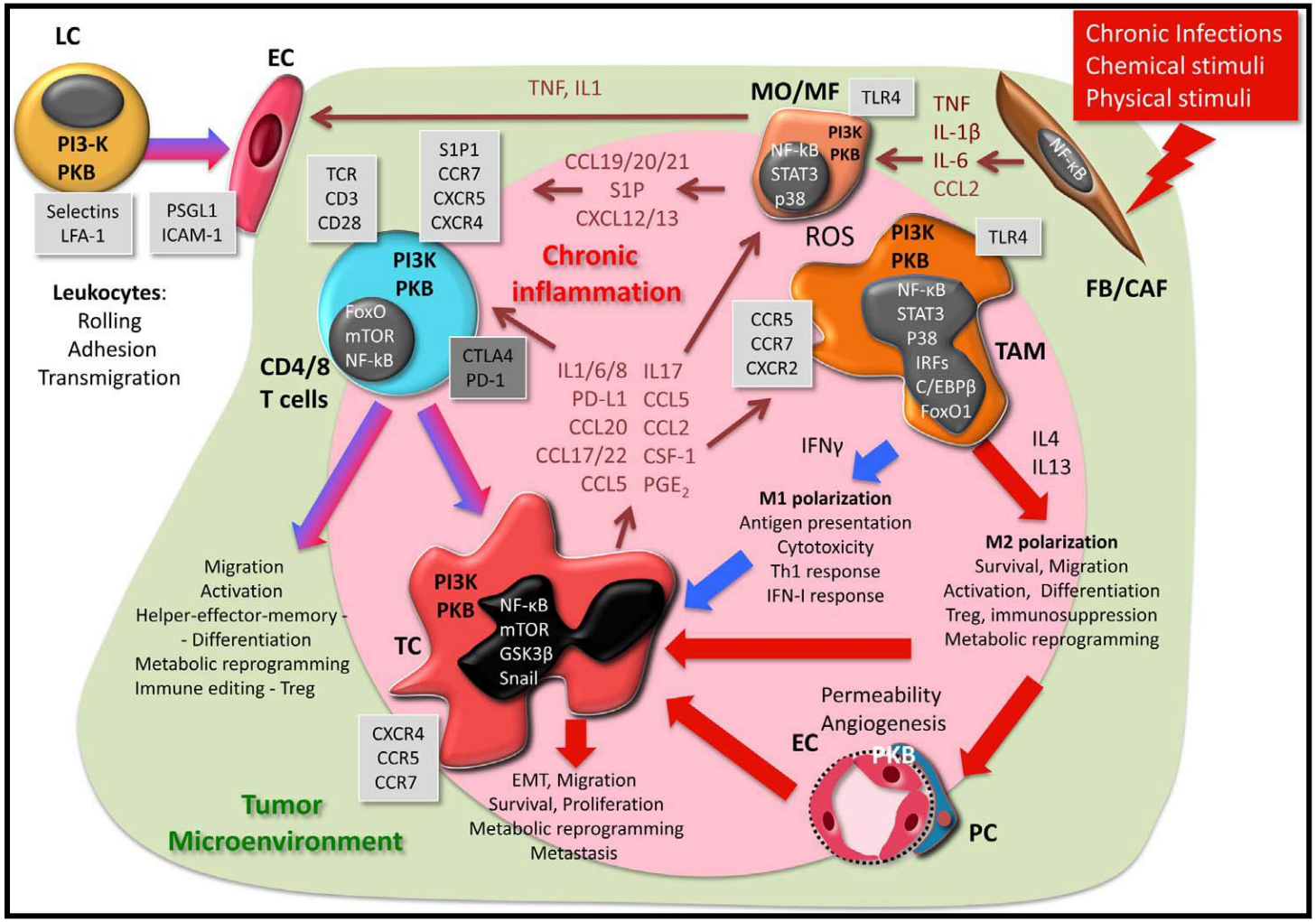


Fig. 2. Cellular effects of PKB in cancer-related inflammation. External persistent stimuli (infectious, chemical or physical) as well as oncogenic signals in tumor cells can initiate chronic inflammation. Additional immune/inflammatory cells are recruited from the blood (T/B cells, NK cells, monocytes, neutrophils) to further sustain chronic inflammation. M2-polarized tumor activated macrophages are main drivers of tumor cell invasion, survival, angiogenesis and immunosuppression. PKB plays key roles in virtually all cells of the tumor microenvironment to promote inflammation and tumor progression, by controlling expression of chemokines and cytokines, as well as mediating some of the effects downstream of their receptors. The PKB effects, however, is contextually regulated by the activation/differentiation state of the effector/target cells and by the concurrent activation of other signaling pathways through additional factors. The list of interactions/effects is non- exhaustive, see text for full explanation. Brown arrows; communication through factors and chemokine; thick arrows, global functional effects (blue, inhibitory effects; red, stimulatory effects). Abbreviations: EC, endothelial cell; EMT, epithelia-to-mesenchymal transition; F/CAF, fibroblast/cancer activated fibroblast; LC, leukocyte; MO/MF, monocyte/macrophage; PC, pericyte; TAM, tumor associated macrophage; TC, tumor cell. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article; Tang et al., 2017.)