Cells and Organisms

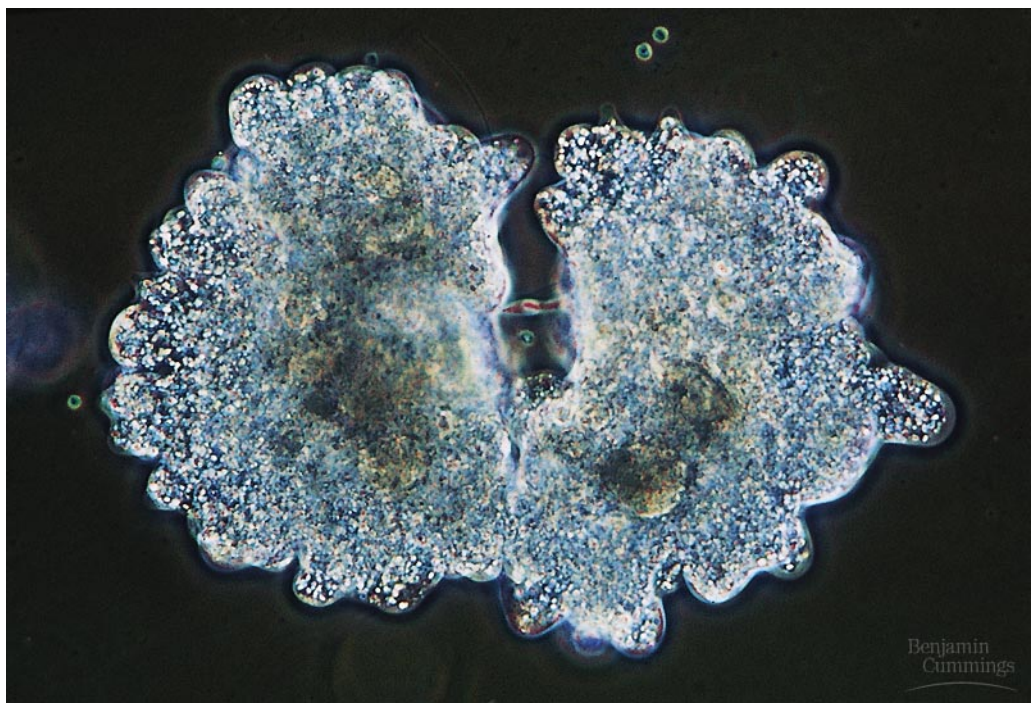
Cell - the basic structural and functional unit of all organisms

Cells of animals form tissues

A tissue is a group of similar cells that perform similar functions

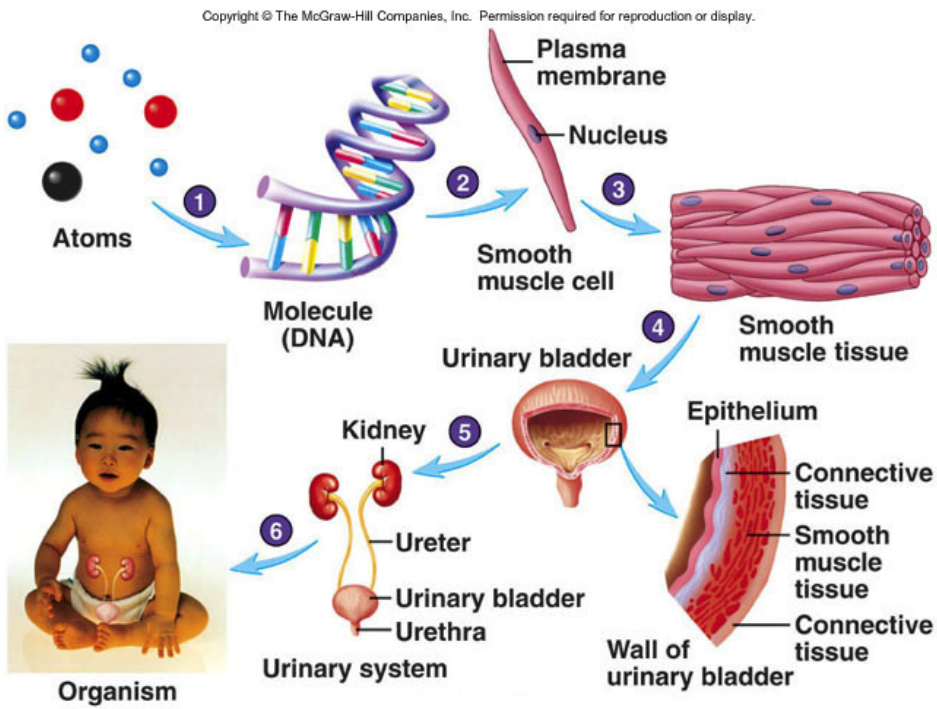
Unicellular Organisms

Multicellular Organisms



Structural & Functional Organizations

- Chemical level
  - –Atoms…Tiny building blocks of matter.
  - –Molecules…Atoms combine to form molecules.
- Cellular Level…Cells are basic units of all living things.
- Tissue Level…Tissue is a group of similar cells e.g. connective, epithelial, etc,.
- Organ Level…Two or more tissue types that perform one or more common functions e.g. heart, bladder, eye, etc.
- Organ System Level…A group of organs that have a common function or set of functions, e.g. skeletal, nervous, etc.
- Organism Level…A living thing considered as a whole e.g. Bacterium, Human.

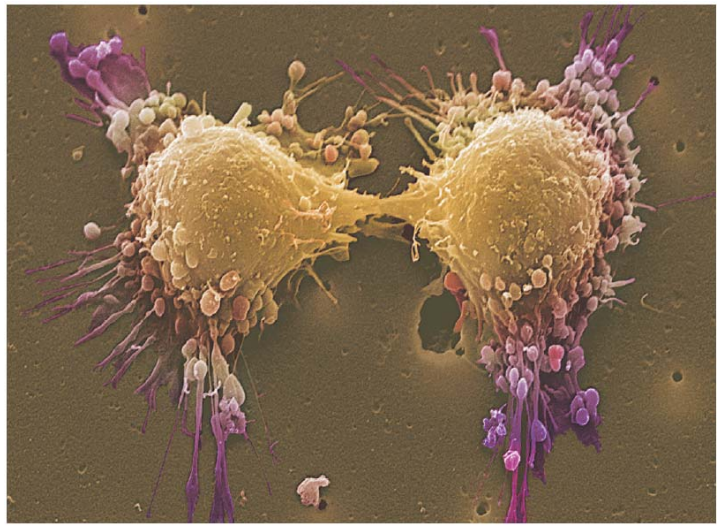


•These organs must communicate to control the development of cells and tissues

•Uncontrolled growth in one part of the body could affect other tissues and normal function of the body can be disrupted

•Organs and tissues in your body have specific functions

The Cell Cycle and Cancer



http://www.insidecancer.org/

The Role of Cell Division

Why do cells divide?

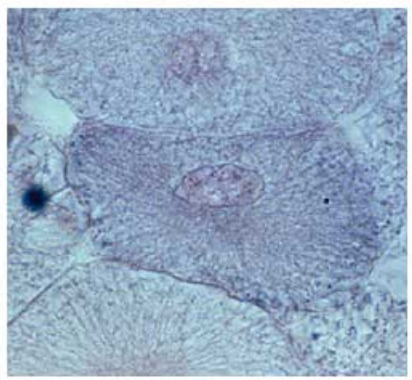
- Growth
- Reproduction
- Replacement of dying cells – skin, RBC
- Reproduction in multi-cellular organisms – gamete formation (meiosis)

In the case of growth, why divide, rather than simply get bigger?

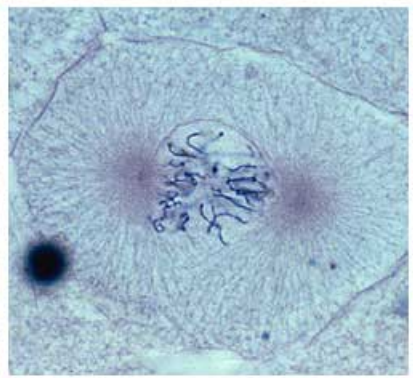
- Surface:volume ratio constraints

Cell division

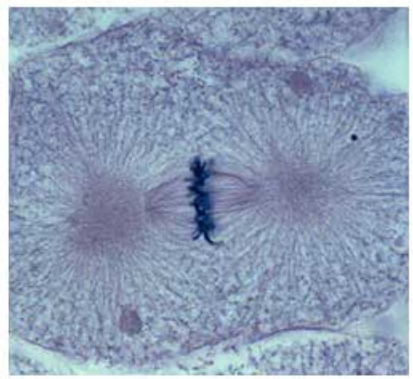
- Mitosis:
  - –Growth, development & repair
  - –Asexual reproduction (yields identical cells)
  - –Occurs in somatic (body) cells
- Meiosis:
  - –Sexual reproduction (yields different cells)
  - –Occurs in specific reproductive cells



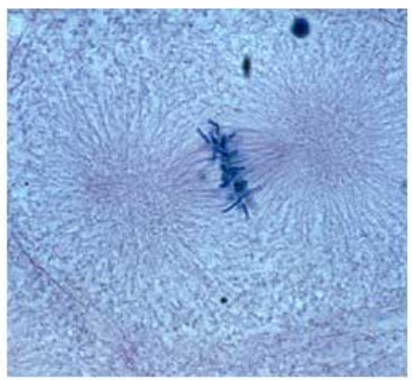
Interphase



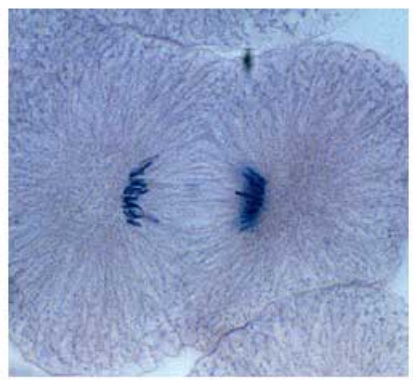
Prophase



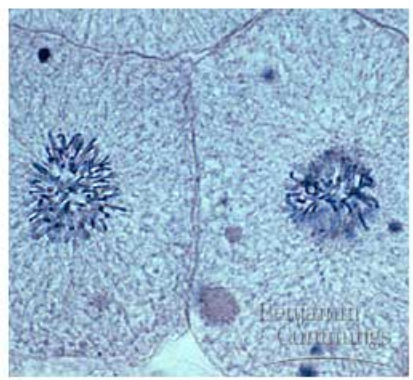
Metaphase



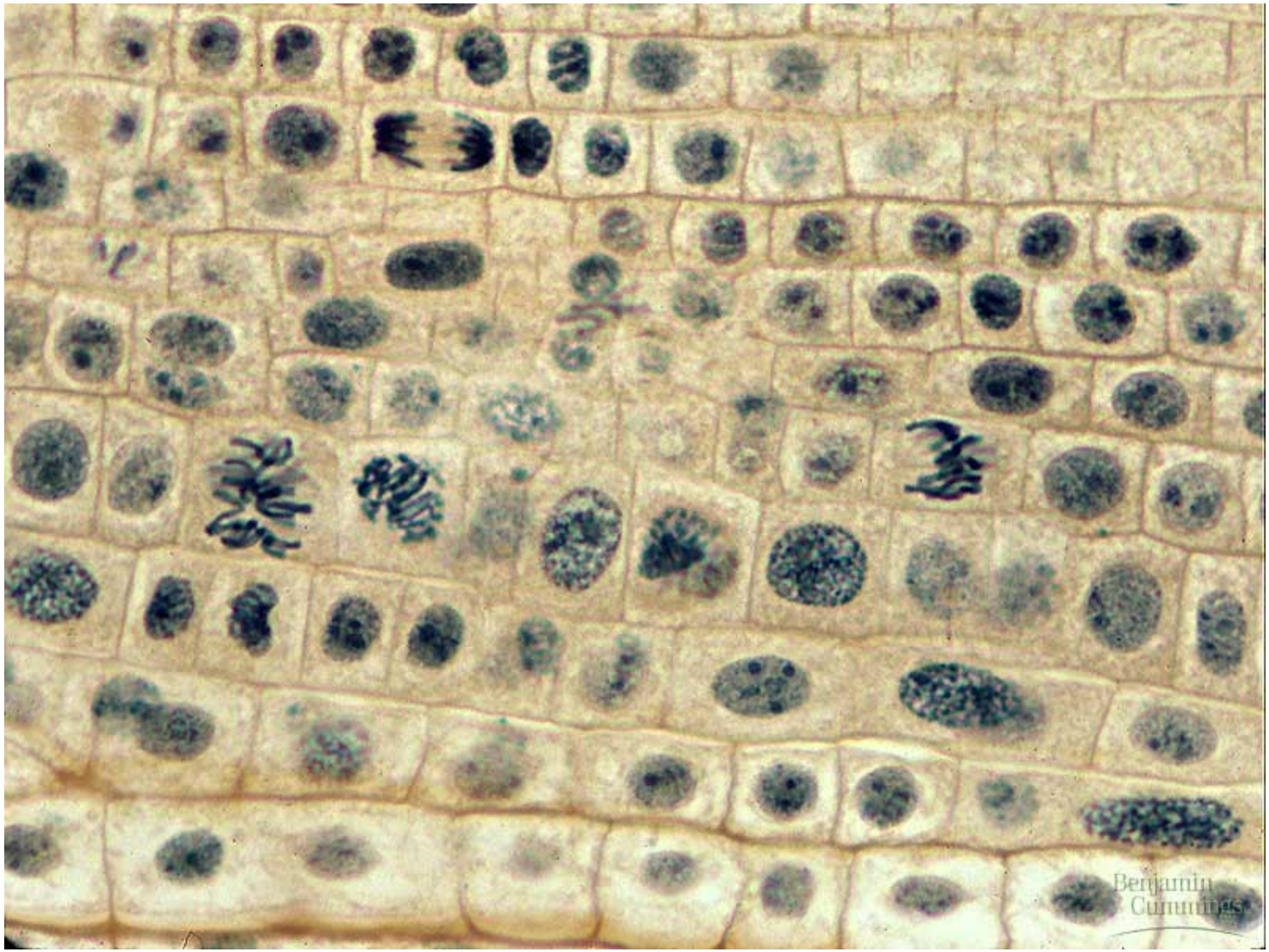
Anaphase



Early Telophase

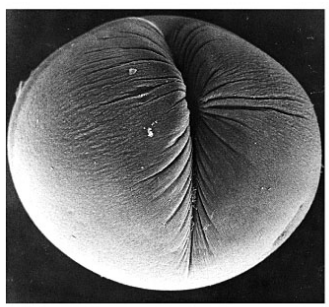


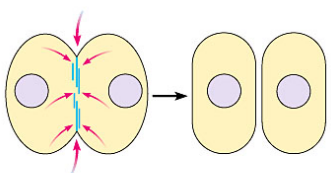
Late Telophase

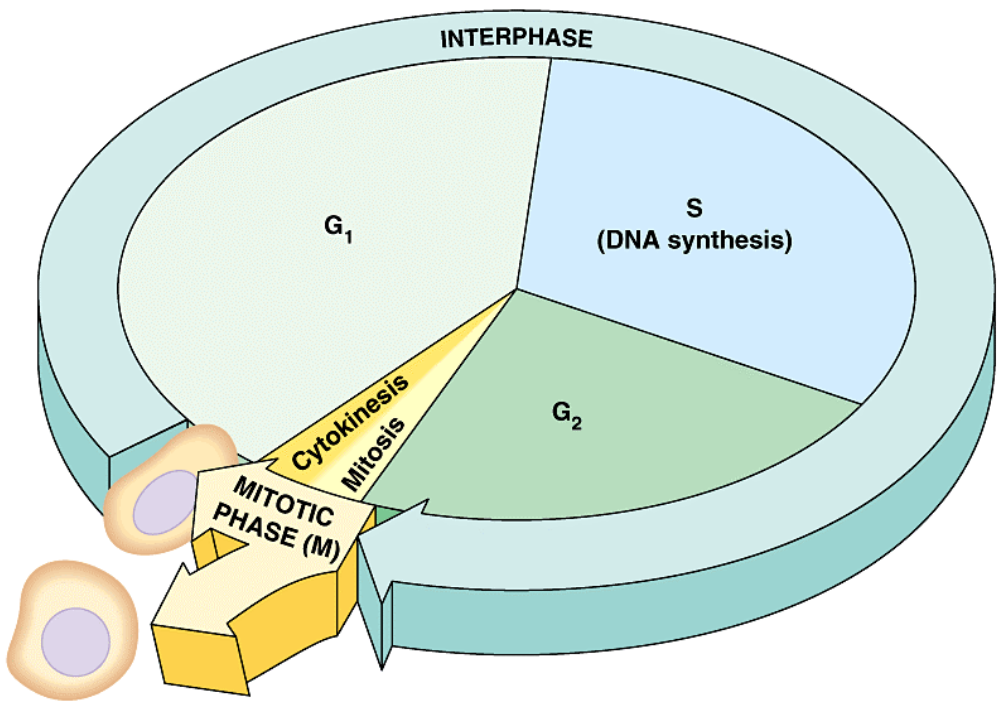

Benjamin
Cummings

- The cell cycle consists of two major phases:
  - Interphase, where chromosomes duplicate and cell parts are made
  - The mitotic phase, when cell division occurs

- Eukaryotic cell division consists of two stages:
  - Mitosis: the duplicated chromosomes are distributed into two daughter nuclei
  - Cytokinesis: divides the cell into two genetically identical cells







The Cell Cycle

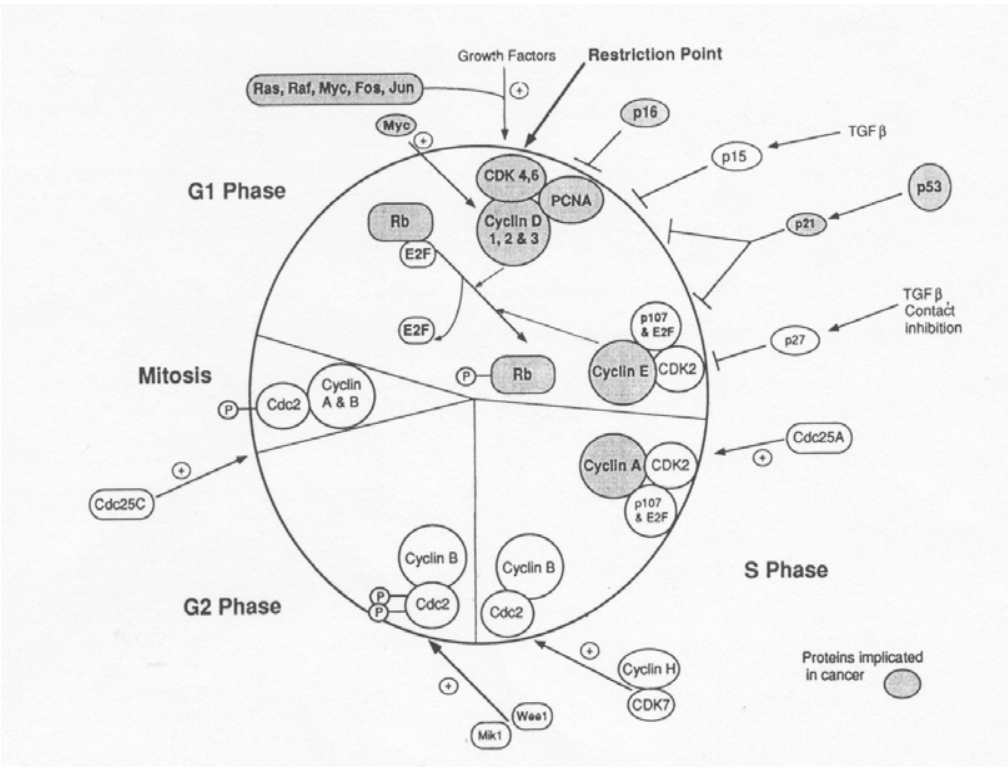
1. G_1 Phase → 1st growth phase
2. S Phase → DNA duplicated
3. G_2 Phase → Final growth phase
4. Mitosis
5. Cytokinesis

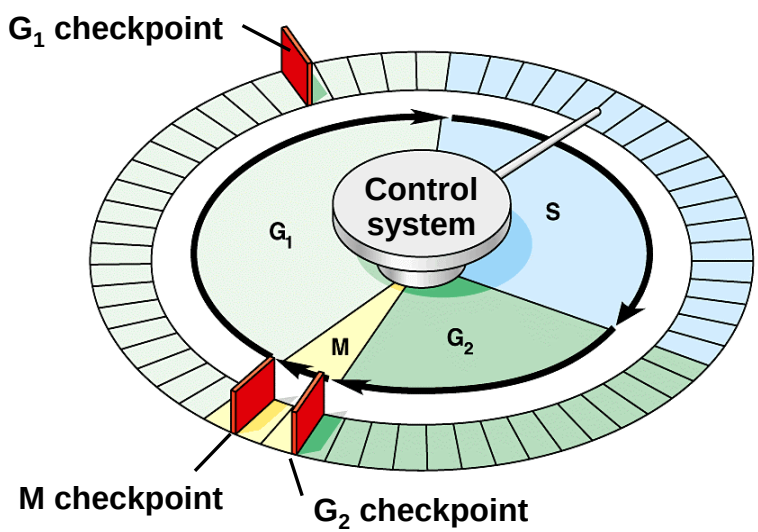
Purpose of the first three phases (Interphase) – to duplicate cell contents; 90% of the cell's growth cycle

Purpose of Mitosis – to divide the genetic material into exact two halves

Purpose of Cytokinesis – to divide all other contents (except nucleus) into two cells

Cell Cycle Regulators and Cancer





DNA Damage - Cell Cycle Arrest
damage dependent checkpoints

G1 - S - G2

G1 - S - G2

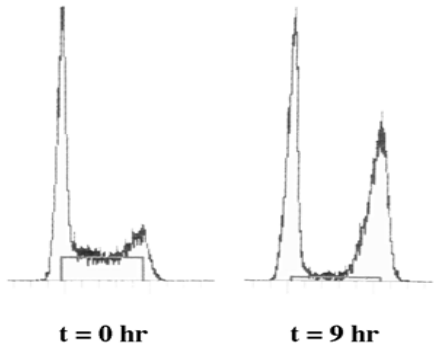
CELL No.

DNA content

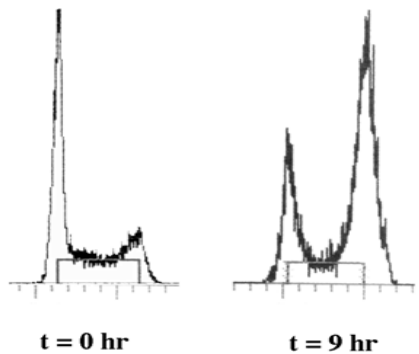
DNA content

asynchronous

X-ray treated
G1/S block
G2/M block
(6-9 hours)



wild-type



loss of G1/S in p53 deficient cells

Two Types of Cell Cycle Control

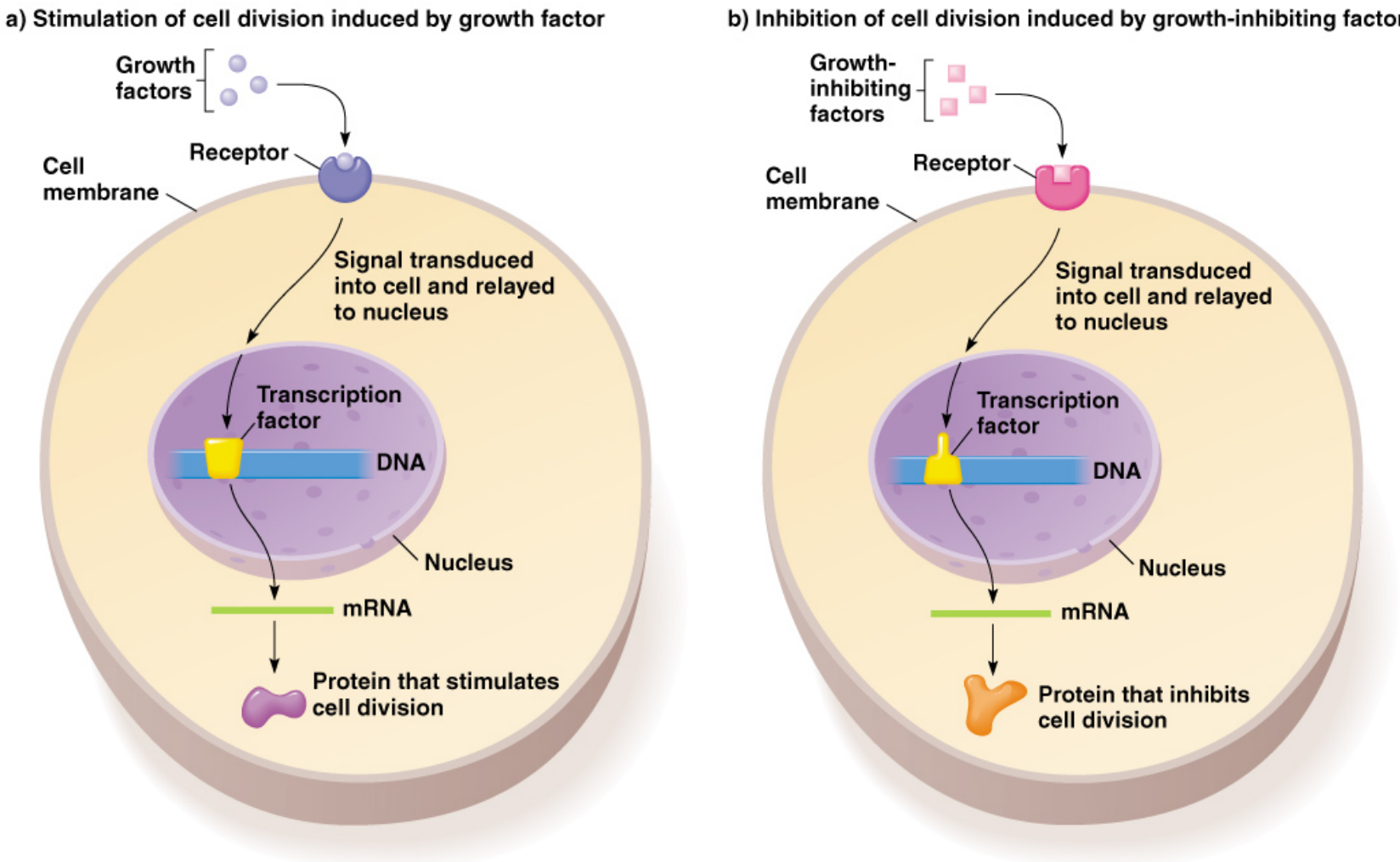
1. A Cascade of Protein Phosphorylations

   Phosphorylation = phosphate groups (PO_4) are added onto substrates by enzymes called kinases

2. Checkpoint Control

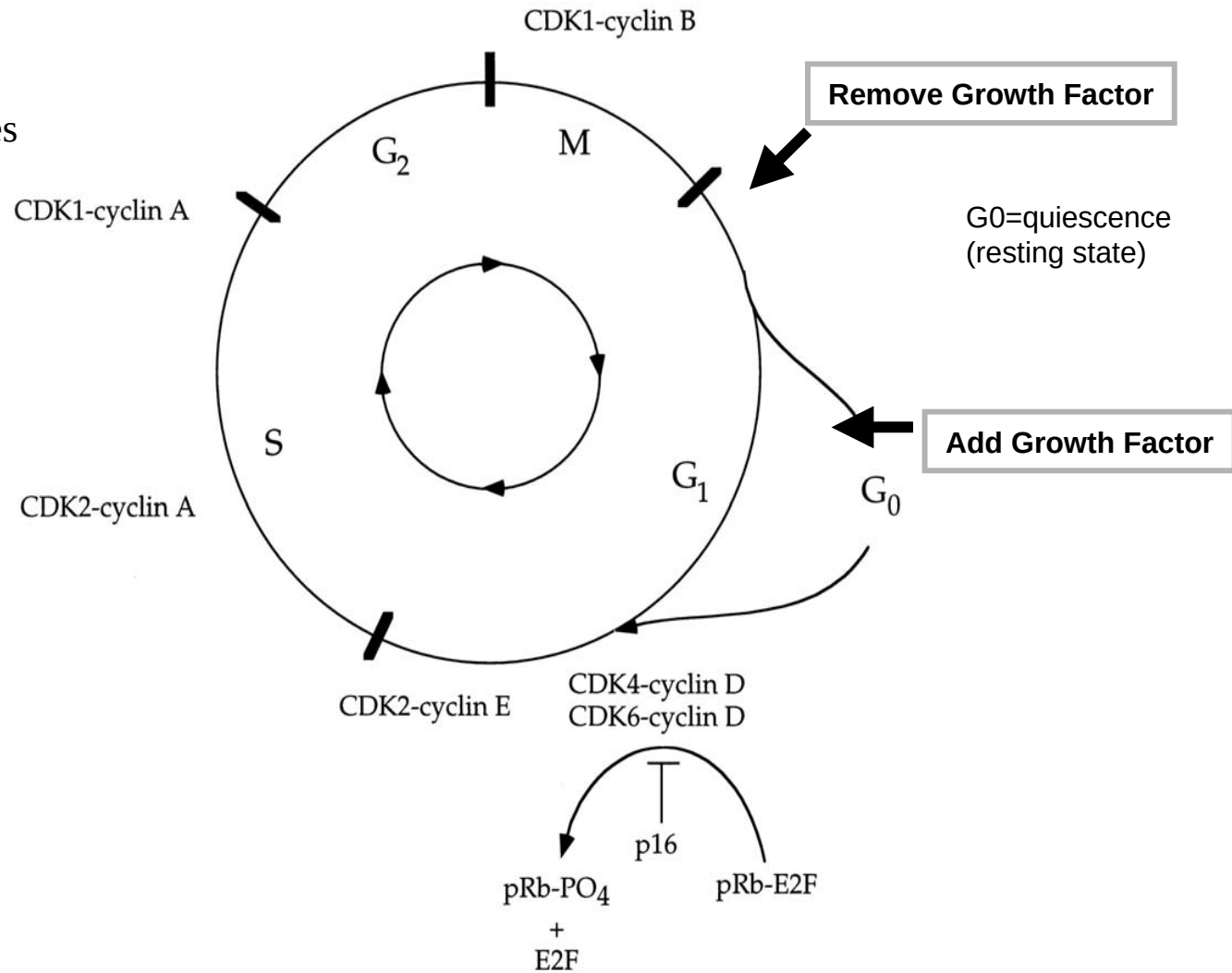
   Checkpoints are places in the cell cycle where a cell will be stopped so that it can be checked for mistakes.

Regulation of cell division by signal transduction

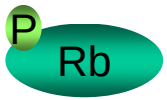


THE CELL CYCLE: 3 basic components

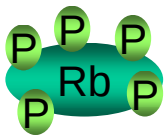
- Cyclin Dependent Kinases (cdk)
- Cyclins
- Regulators of Cyclin/cdk
  - –Activating Phosphatases
  - –Inhibitory Kinases
  - –Non-kinase inhibitors



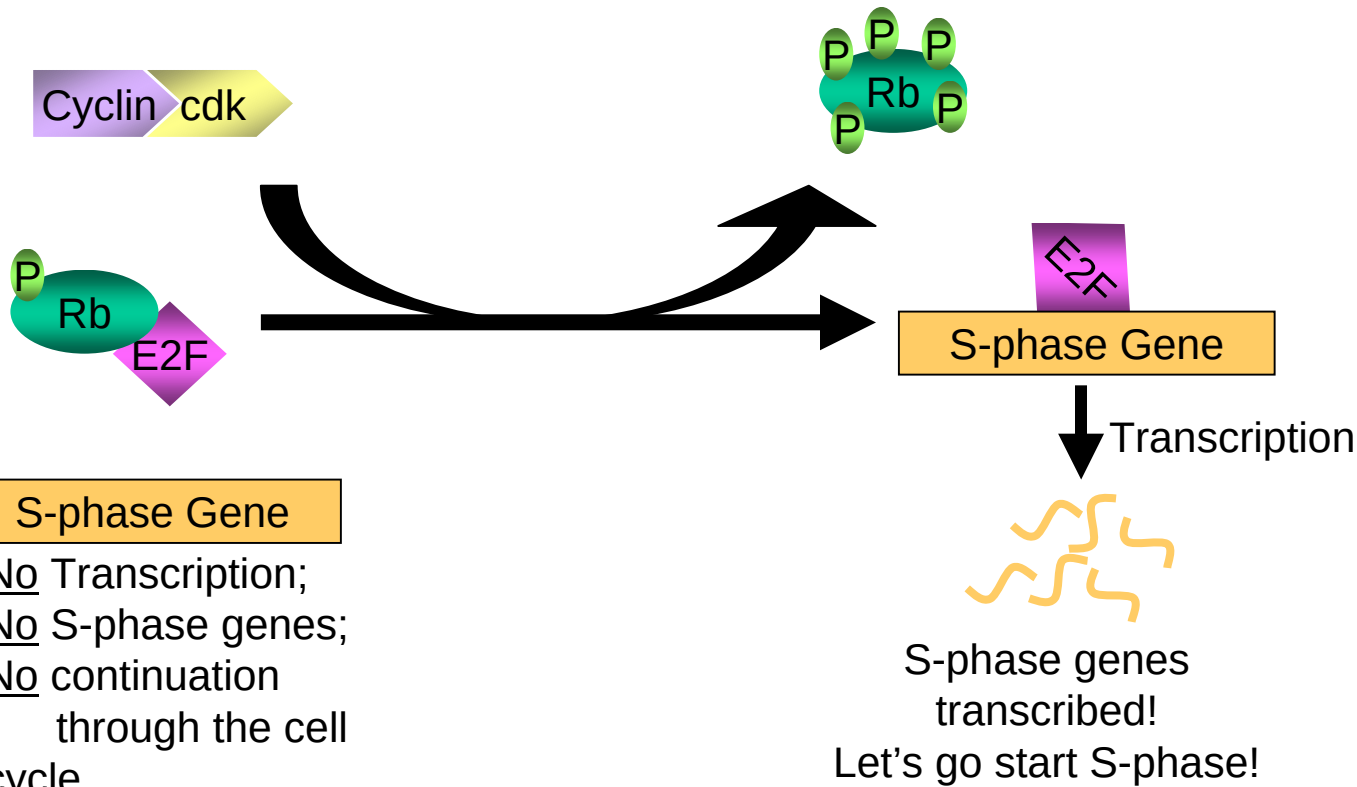
Retinoblastoma Protein (Rb) = an important cell cycle regulator and tumor suppressor that is controlled by how much it is phosphorylated. It is a SUBSTRATE for the enzyme cyclin-dependent KINASE.



= Hypo-phosphorylated (Under-phosphorylated)

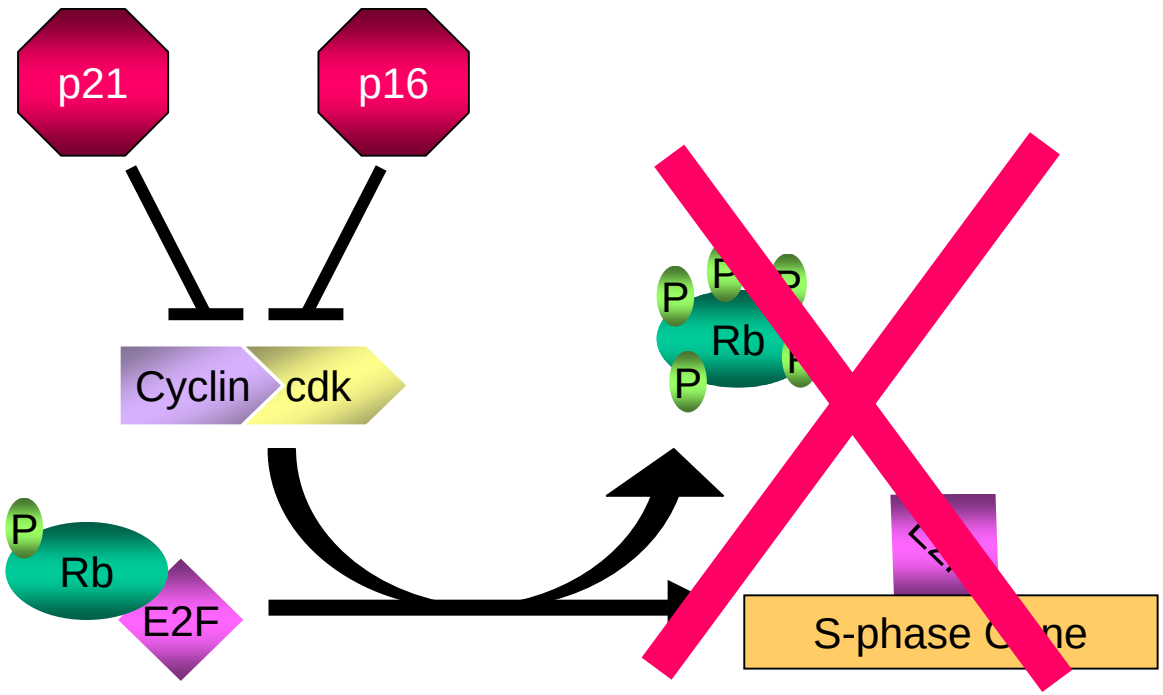


= Hyper-phosphorylated (Over-phosphorylated)

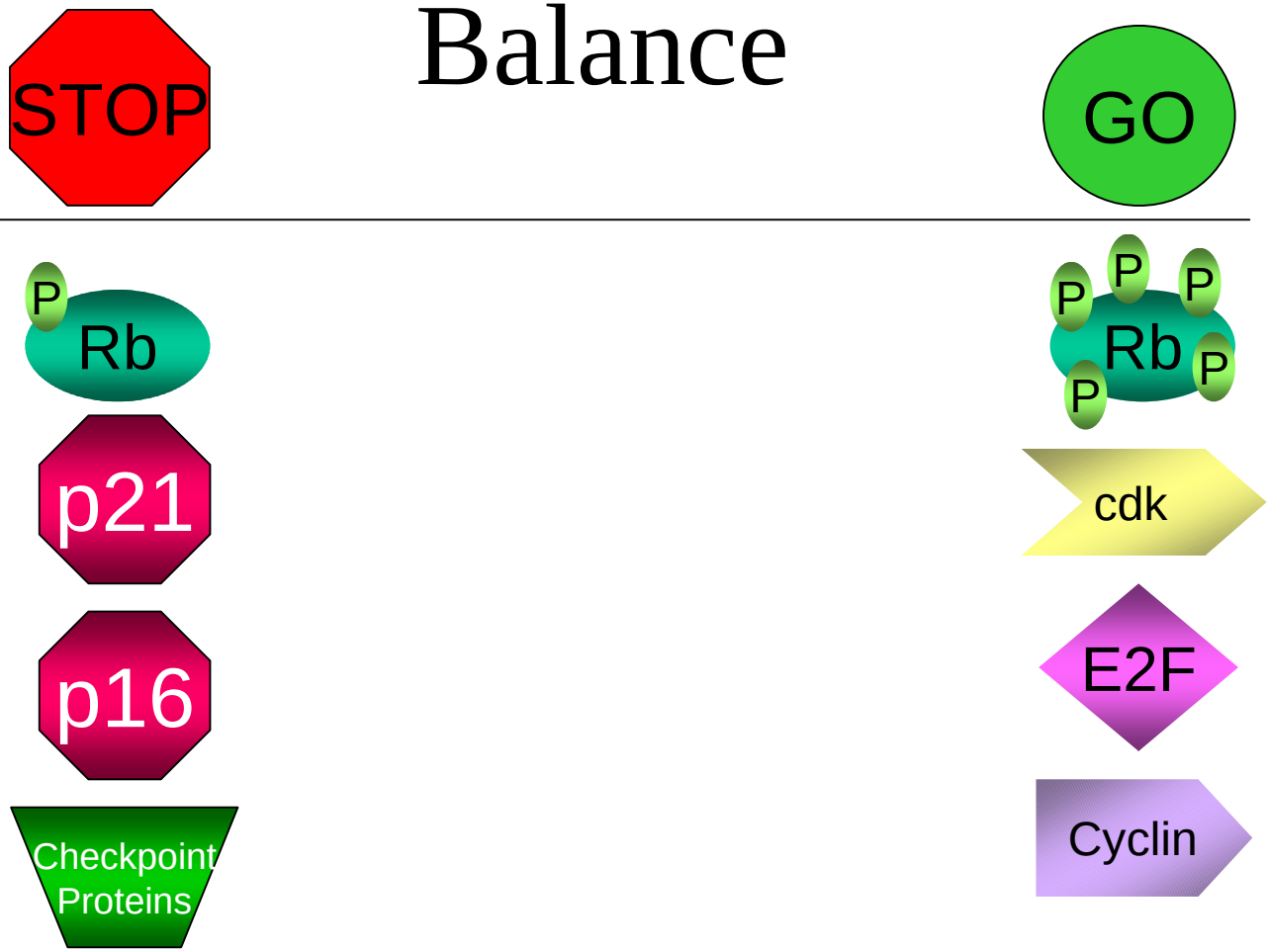


Cdk inhibitors

p21 and p16 are proteins that inhibit the function of cdk's. If you inhibit cdk function, Rb DOES NOT get hyperphosphorylated and E2F is NOT able to transribe genes; when cdk inhibitors are around, the cell cycle is stopped!

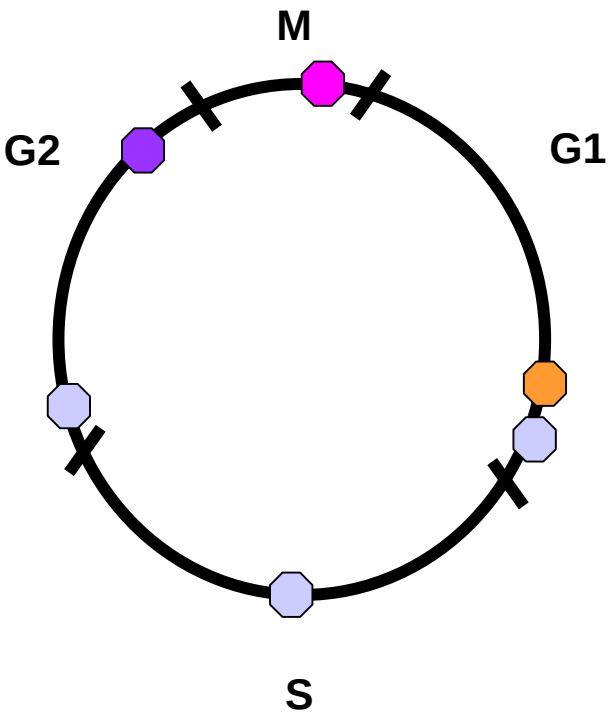


Balance



- loss of control over cell growth

Cell Cycle Checkpoints



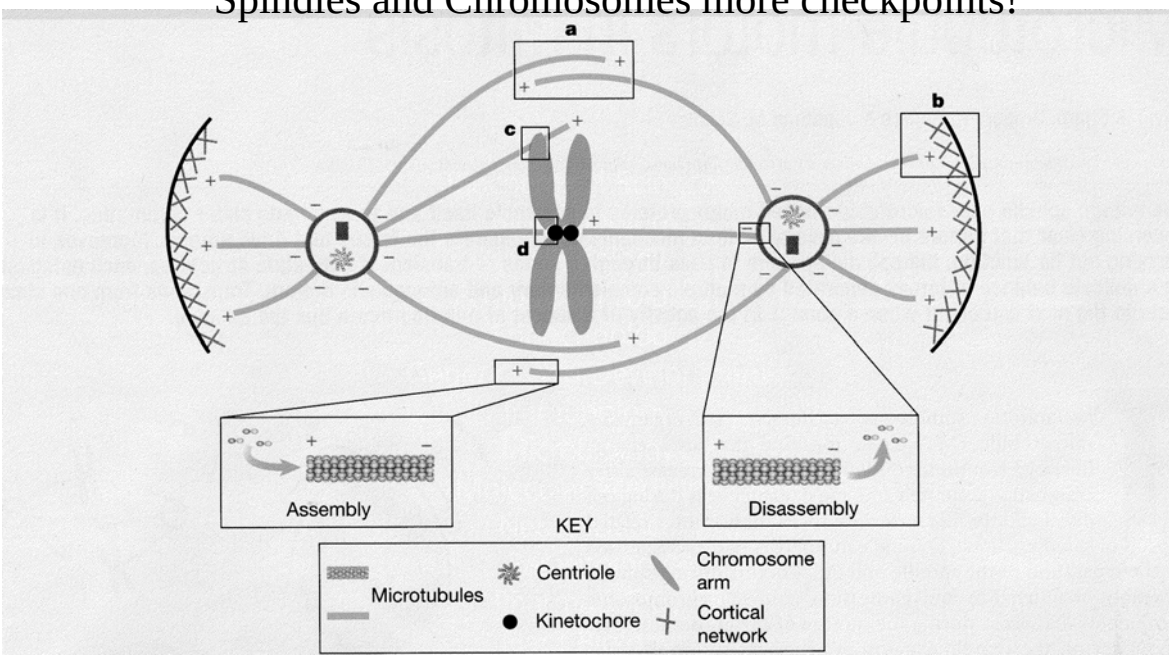
= DNA Damage Checkpoints

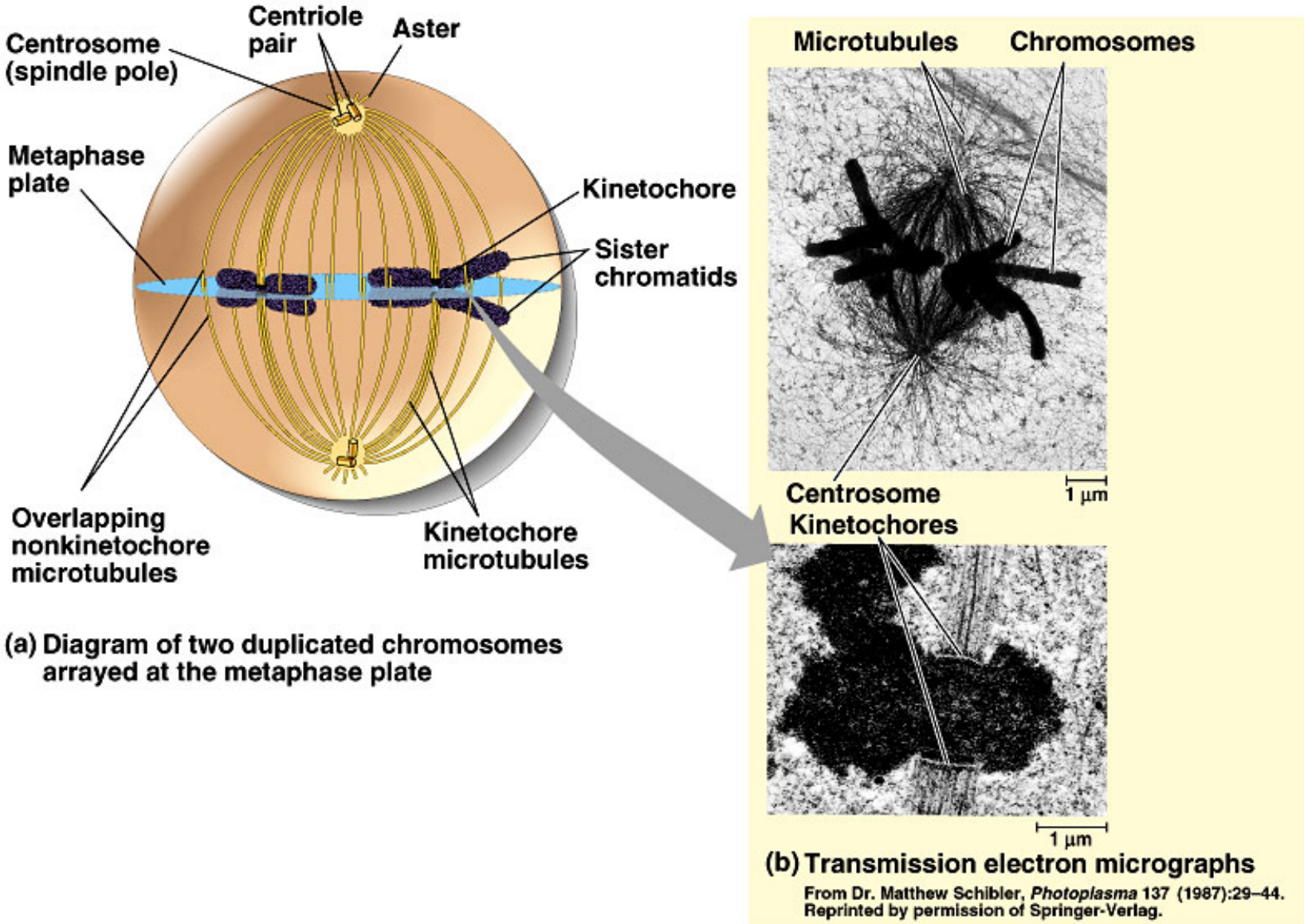
= Spindle Checkpoints

= G1 Checkpoint

= G2 Checkpoint

Spindles and Chromosomes more checkpoints!





Tumors -Masses that show abnormal growth

- Benign tumors
  - –Grow slowly, Remain in place
- Malignant tumors (cancer)
  - –Grow more rapidly, Can metastasize

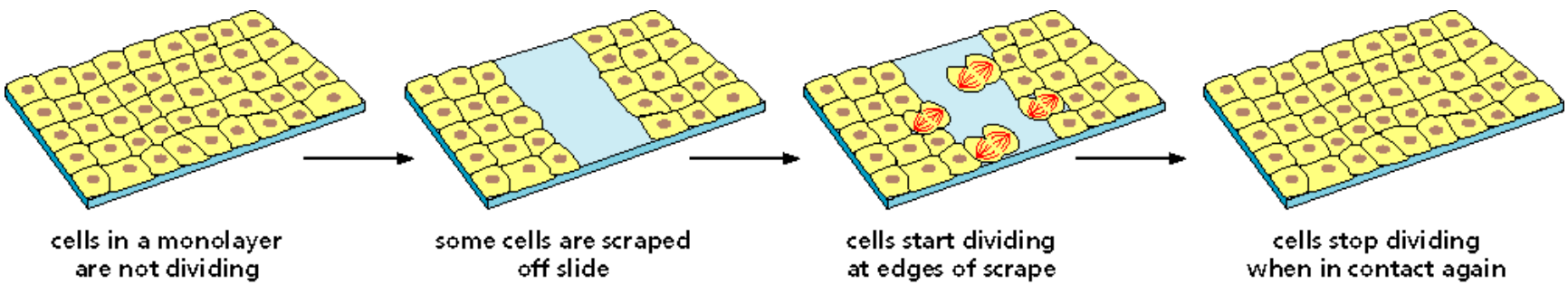
Cancer characteristics

- Plasma membrane and cytoplasm altered
- Cells grow and divide abnormally
- Weakened capacity for adhesion
  - –Can break away and cause new cancers
- Lethal unless eradicated
- have a different metabolism, using glycolysis even when oxygen is available.

Cancer: Contact Inhibition and Anchorage Dependence

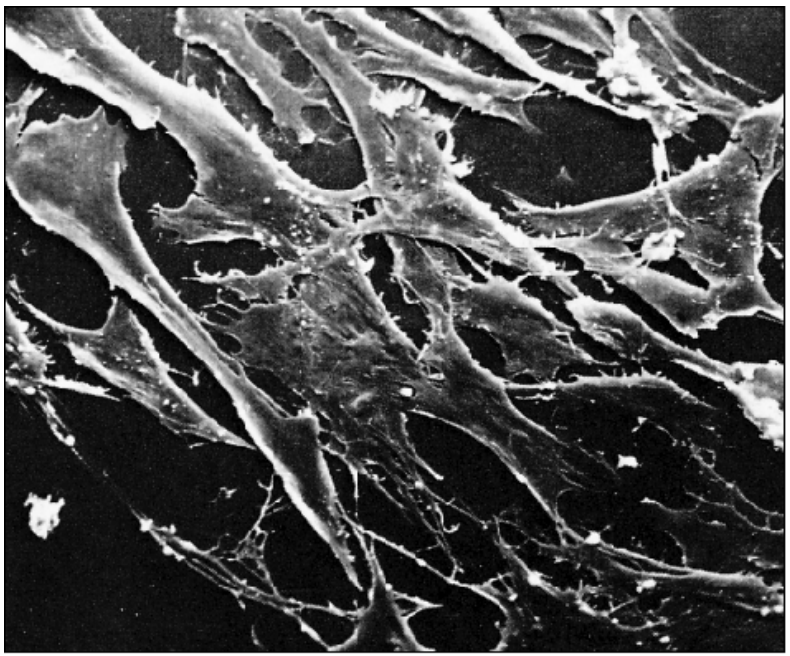
Contact with neighboring cells suppresses cell division in normal cells. This is called Contact Inhibition

Normal cells from many types of tissues have an additional requirement for division called Anchorage Dependence : they (cells) divide only when they are attached to a surface

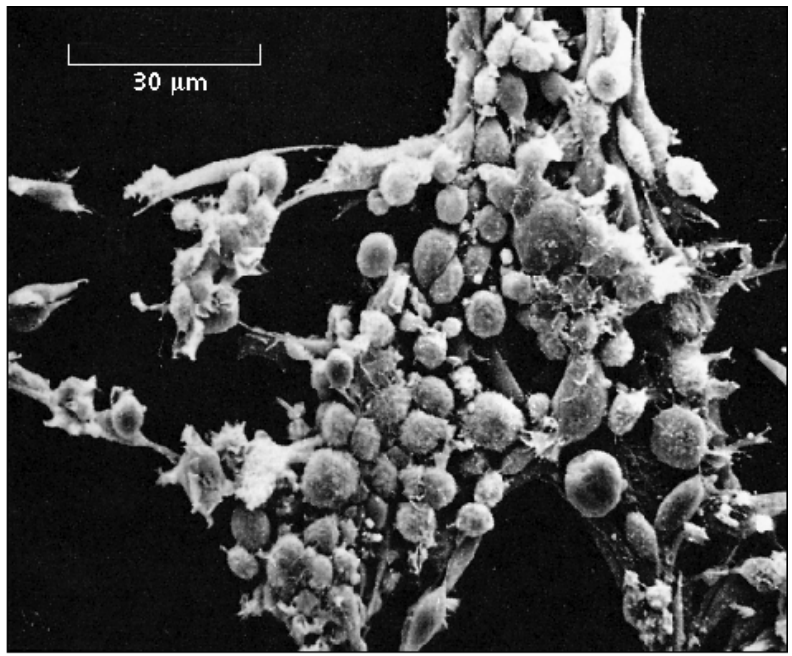


Contact inhibition stops cell division once cells are in contact with each other

Anchorage Dependence

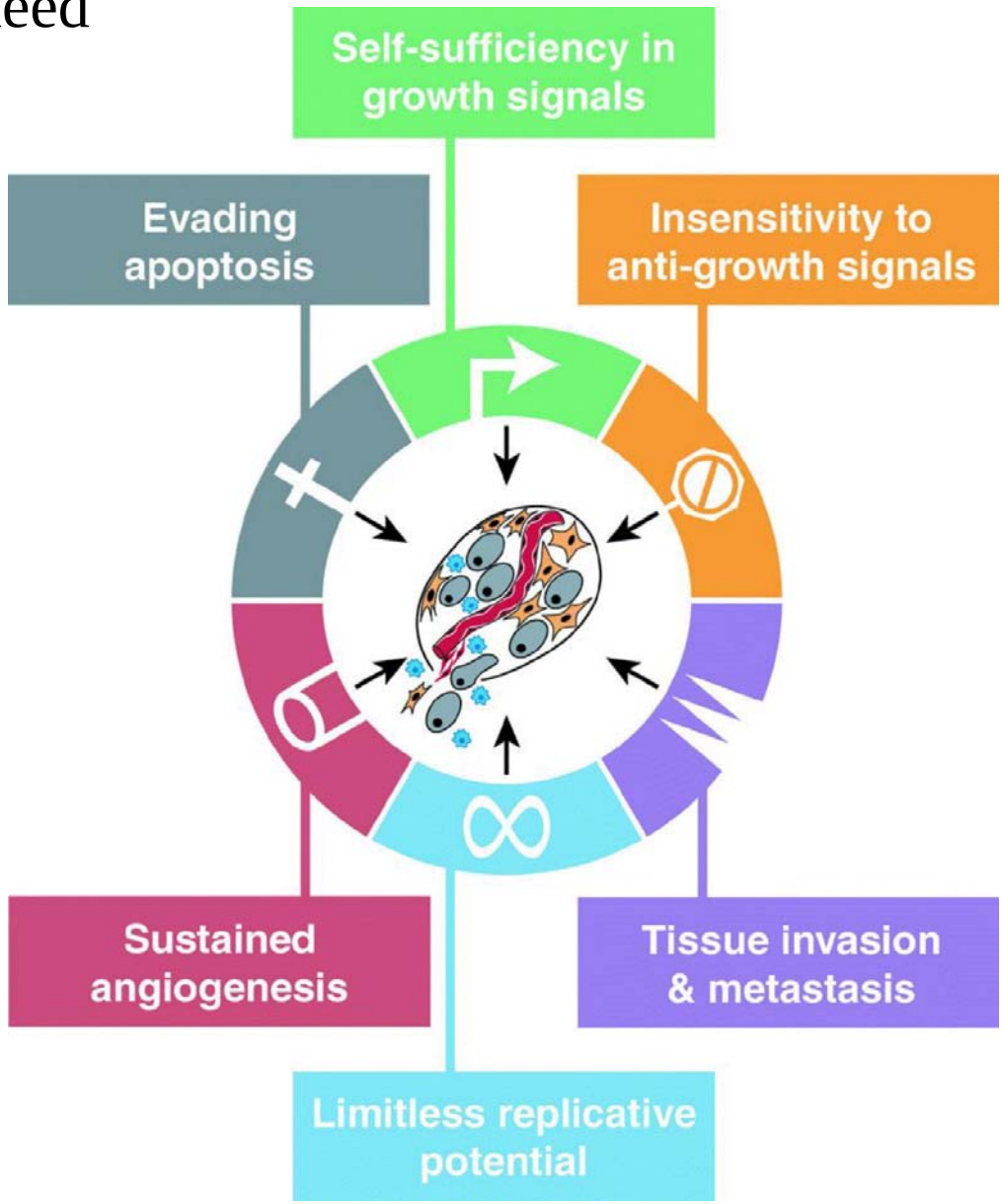


Normal cells in tissue culture growing attached to a culture dish; these cells lose their ability to divide when they become detached.



Cancer-forming cells have rounded up and lost their attachment, but, unlike most normal cells, they continue to divide when unattached.

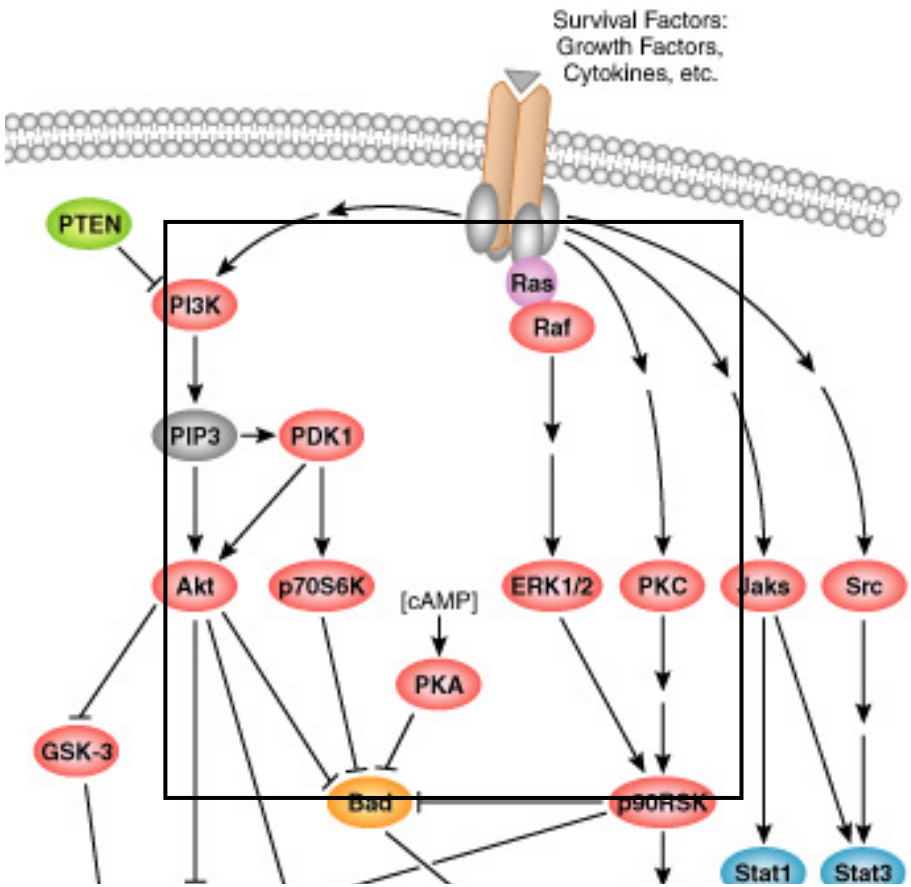
What qualifications do you need to be a cancer cell?

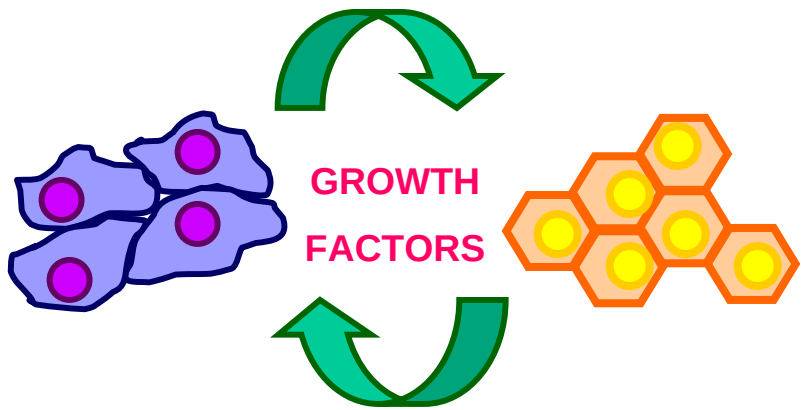


Cell 100:57 (2000)

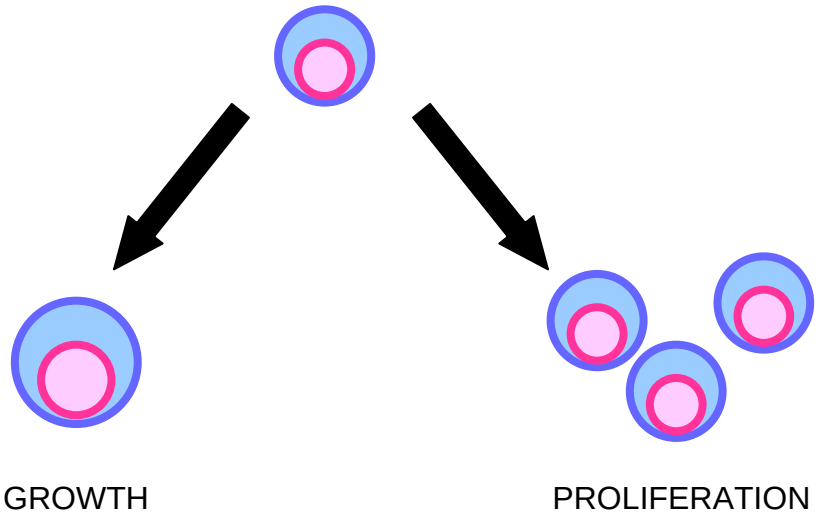
1. Self-sufficiency in growth signals

- All normal cells require extrinsic factors produced by other cells
- "Social control" model for cell growth





There is a difference between growth and proliferation



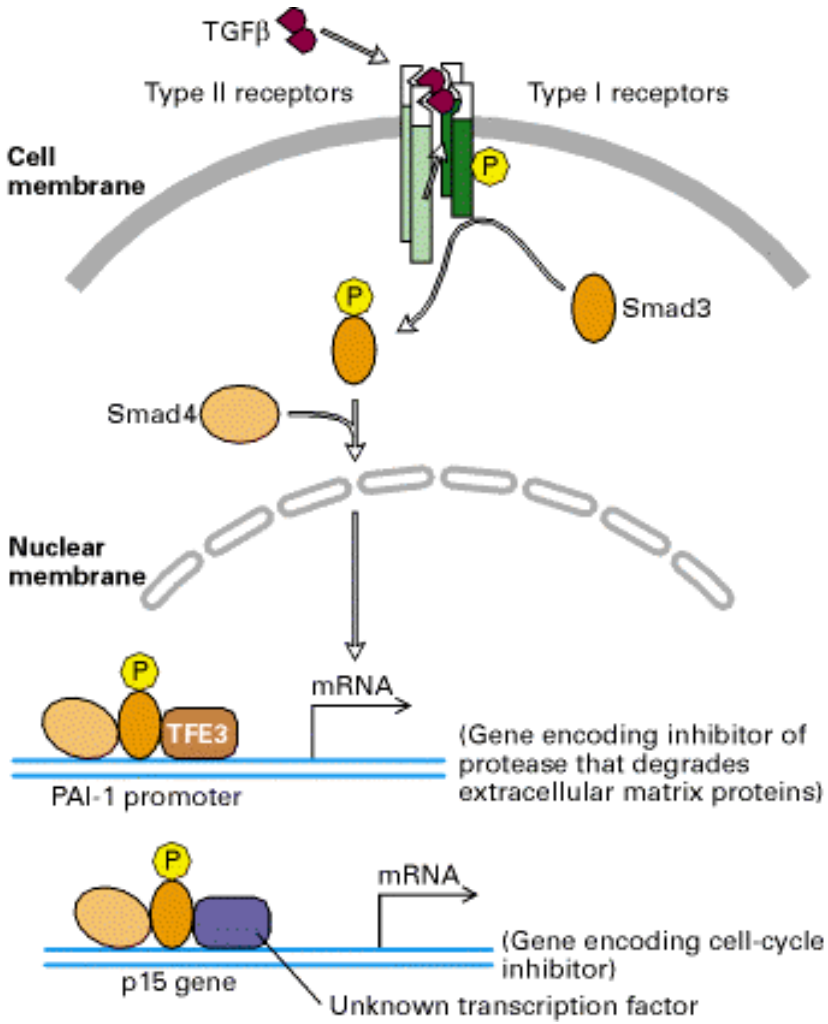
How do you achieve growth factor independence?

- Prolong ligand-induced signaling (decreased degradation, turn off negative regulator)
- Increase sensitivity (respond to lower ligand levels)
- Express new receptors (integrin signaling)
- Make your own growth factors
- Signal in the absence of ligand (upstream or downstream mutations)

2. Overcome growth-inhibitory signals

- Most cells in your body are sitting there happily in G0
- Are growth inhibitory proteins in the extracellular space
- Terminal differentiation inhibits further cell growth
- Oncogene expression can produce cell cycle arrest

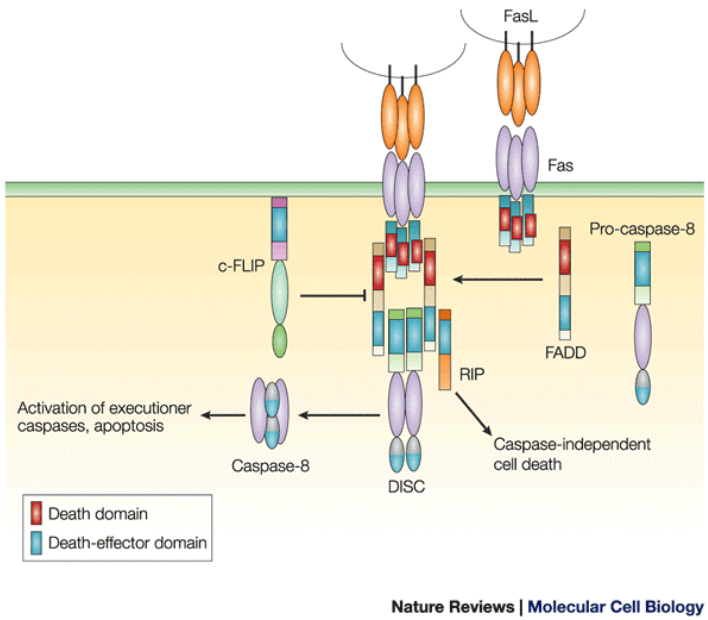
TGFb is a soluble growth inhibitor

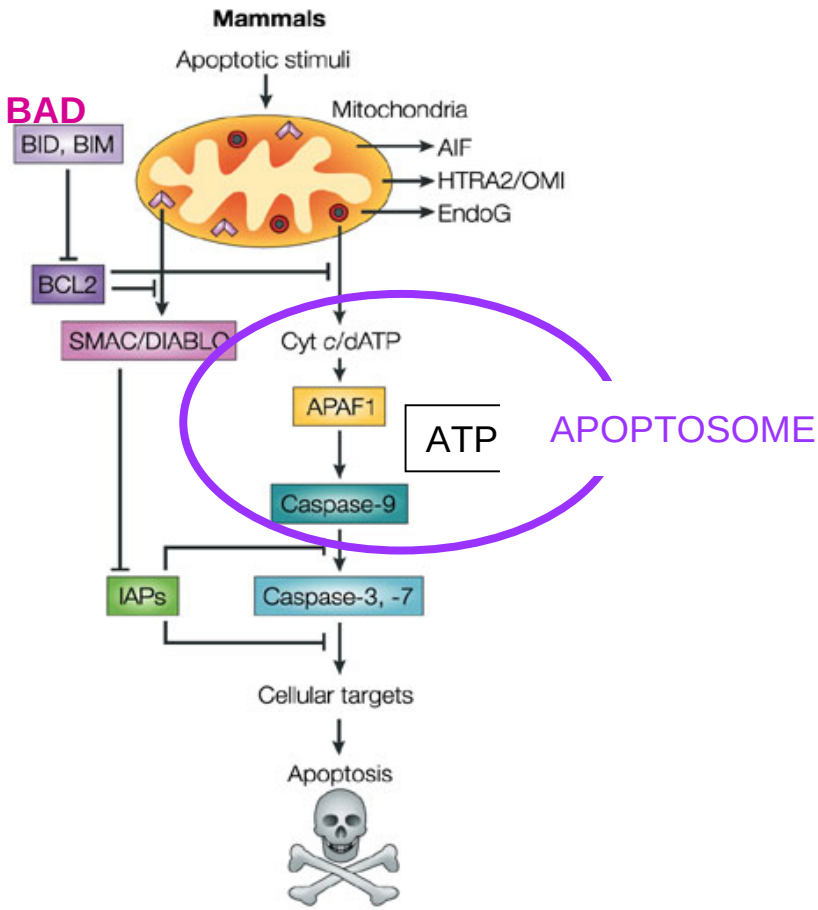


Molec. Cellular Biol. Fig. 24-20

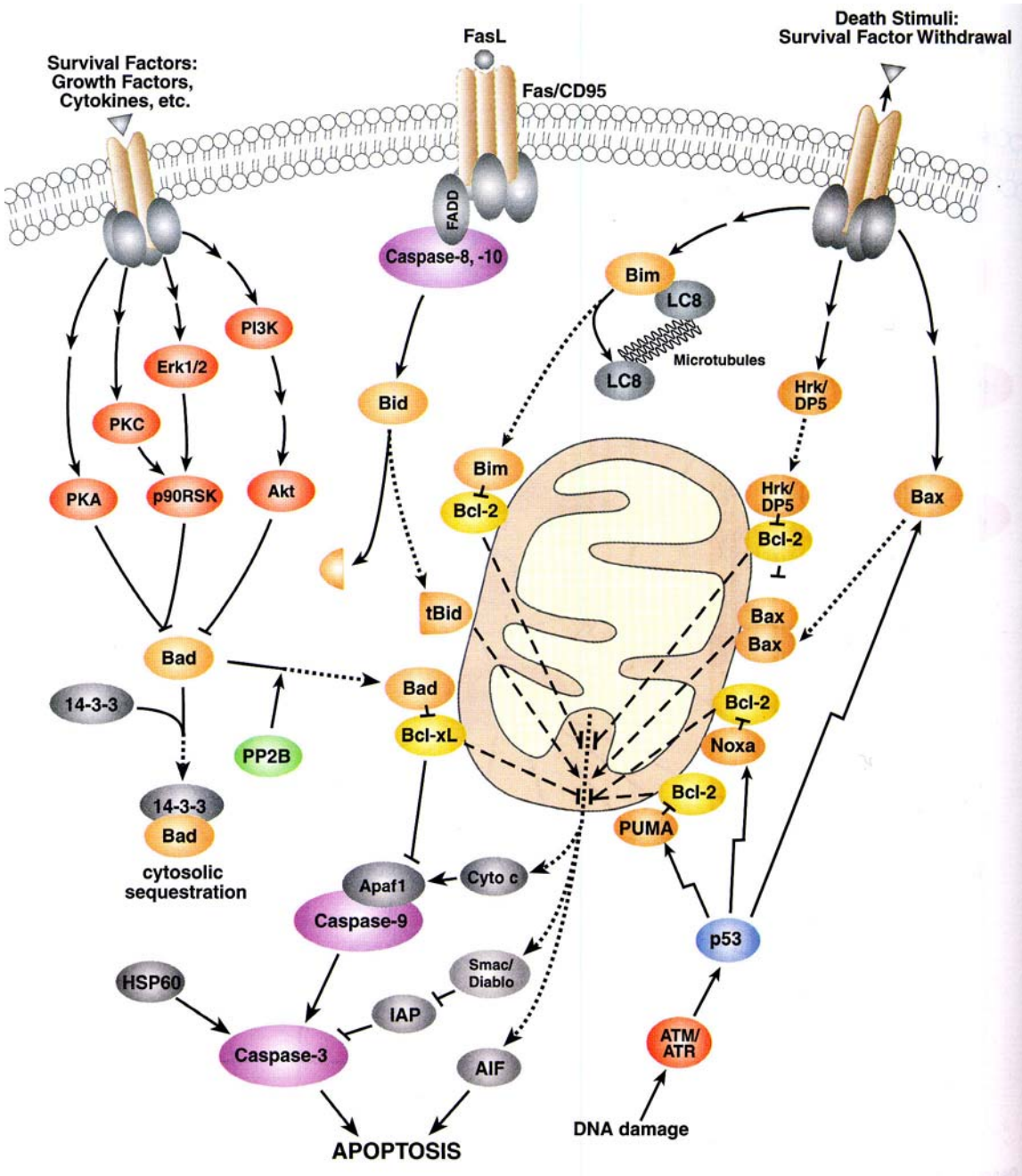
3. Evade apoptosis

- Fas/TNFa extrinsic pathway for apoptosis
- Mitochondrial intrinsic pathway
- Both pathways have caspases in common
- Ironically, oncogenes can also induce apoptosis

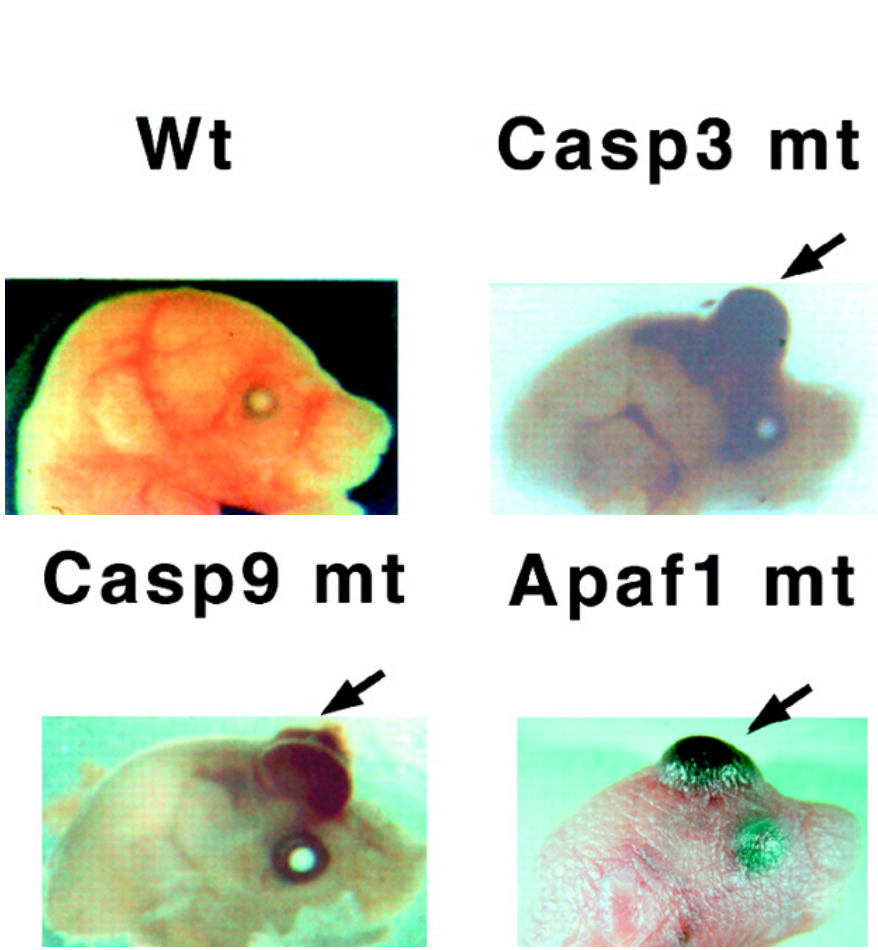


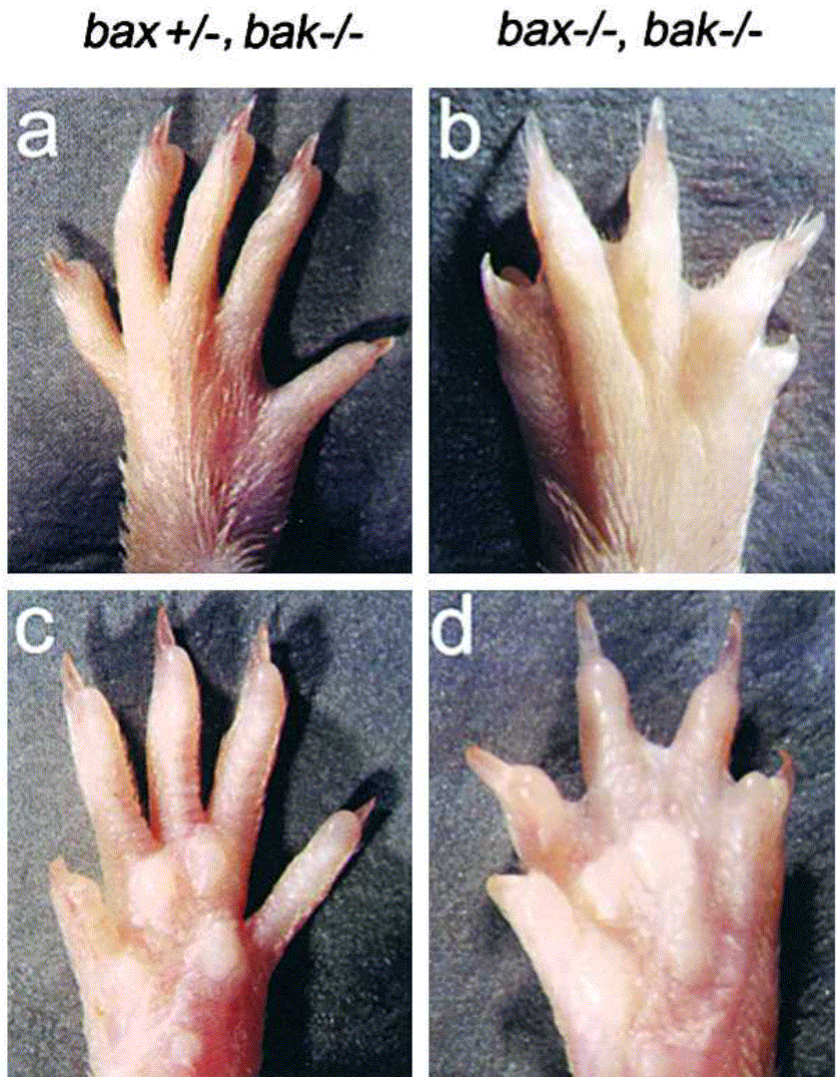


Growth & death signal



Phenotype of apoptosis deficient mice



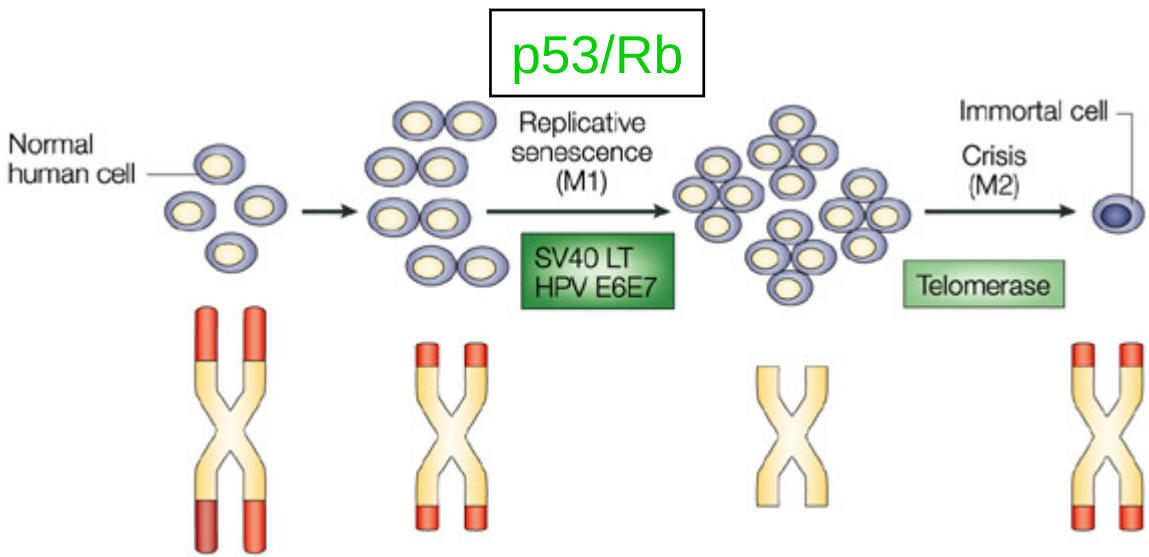


4.Limitless replicative potential

•Avoid replicative senescence: a non-dividing state from which cells do not recover (mutate p53/Rb)

•Avoid crisis: massive cell death and karyotypic disarray (activate telomerase)

Replicative senescence and crisis



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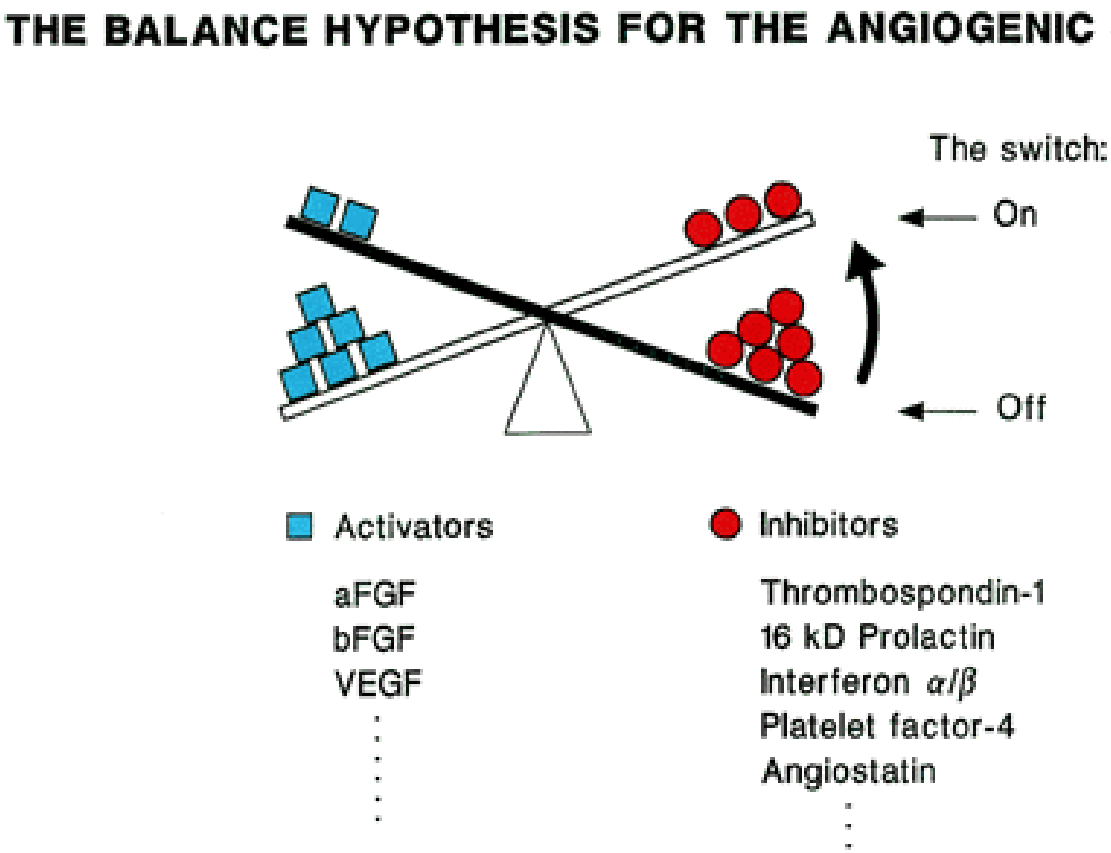
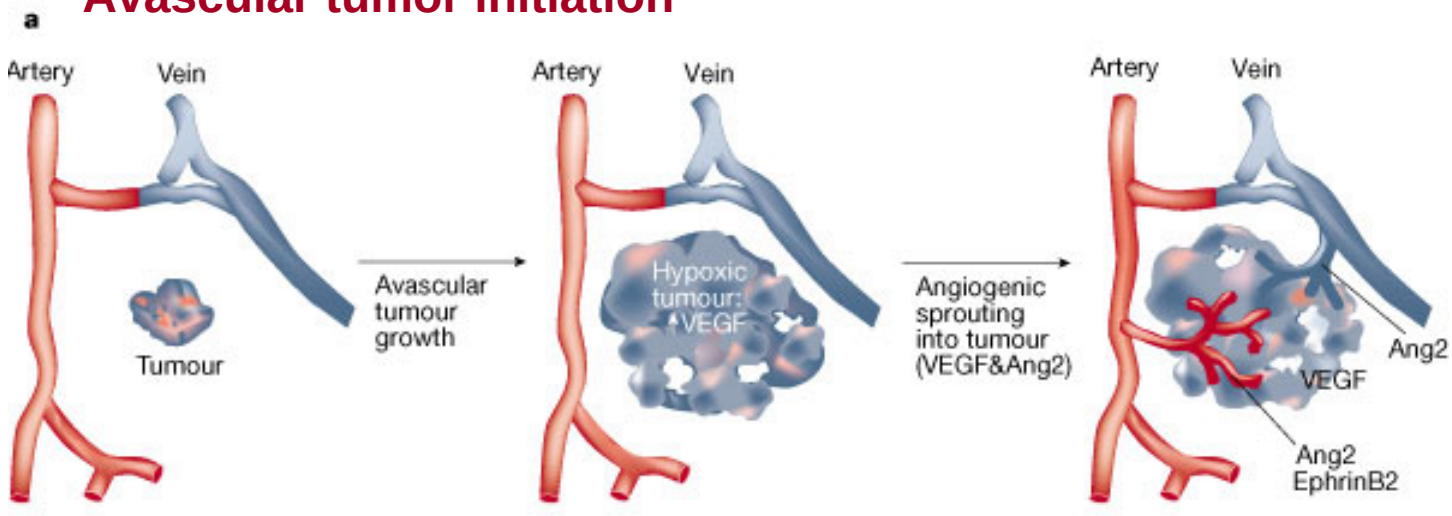
5. Tumors require angiogenesis

- Greater than 1-2 mm sphere needs a blood supply
- Tumors often have a necrotic center—angiogenesis does not keep up
- VHL/Hif/VEGF axis
- Angiogenesis inhibitors in clinical trials

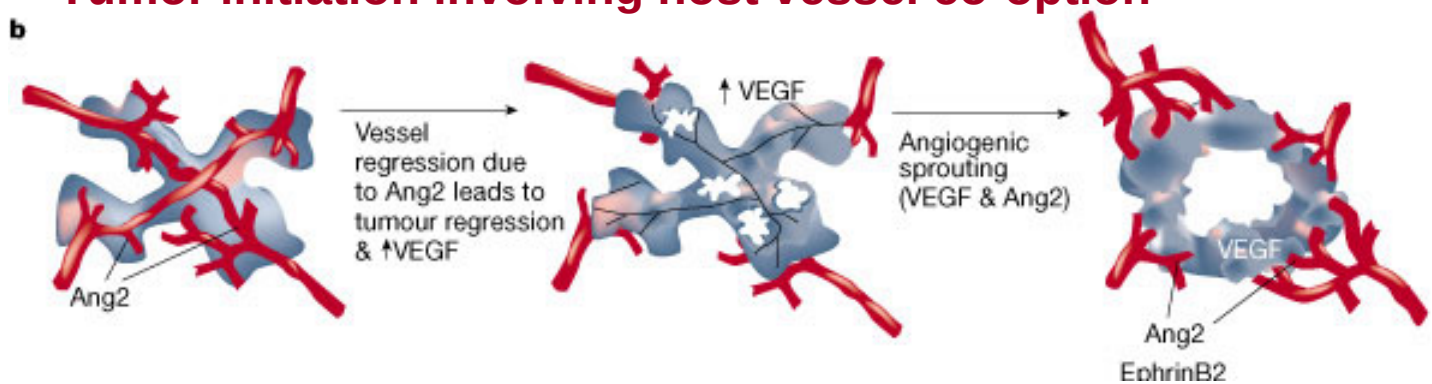


Models of tumour angiogenesis

Avascular tumor initiation



Tumor initiation involving host vessel co-option



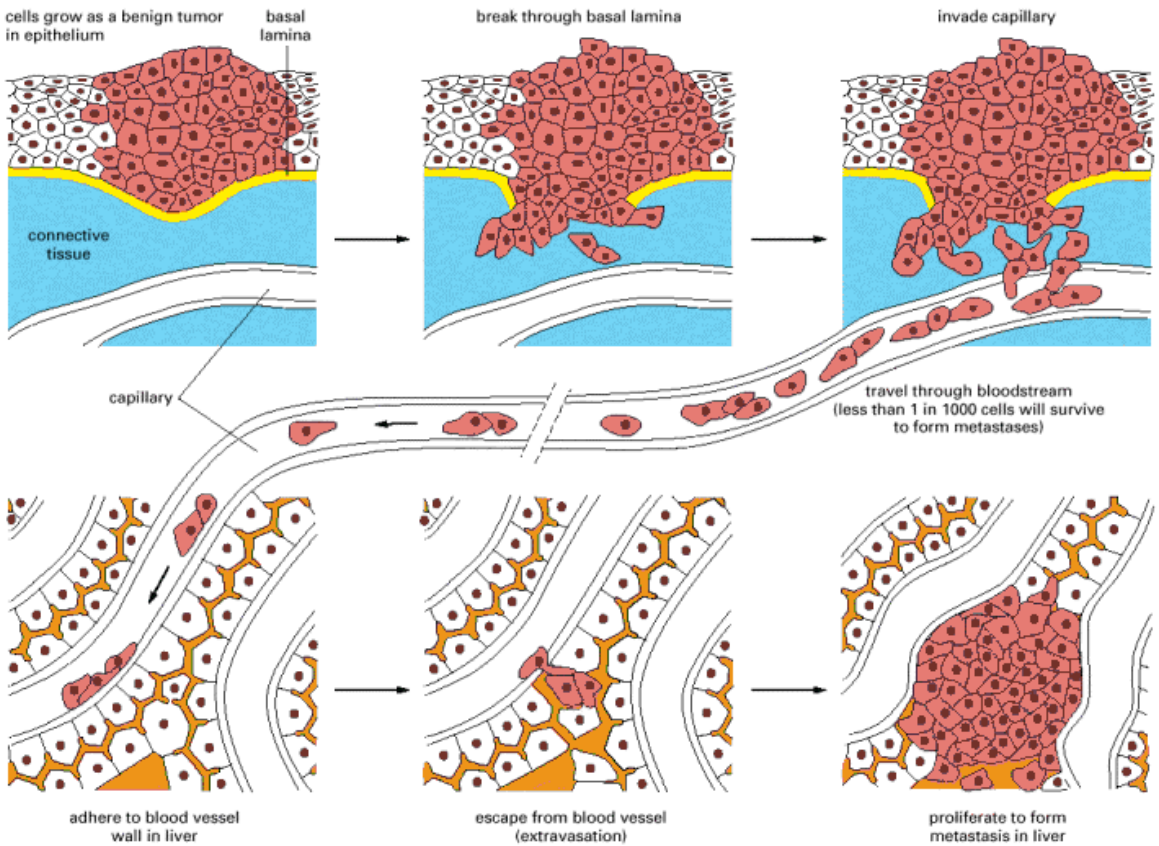
6. Invasive potential

•Metastases kill you, not the primary tumor

•Metastatic cells must be able to enter and leave bloodstream and to survive in an ectopic location

•Part of explanation of the role for Rho/Rac, integrins, and matrix metalloproteases in cancer

Steps in metastasis



Malignant tumors can invade other tissues and may kill the organism

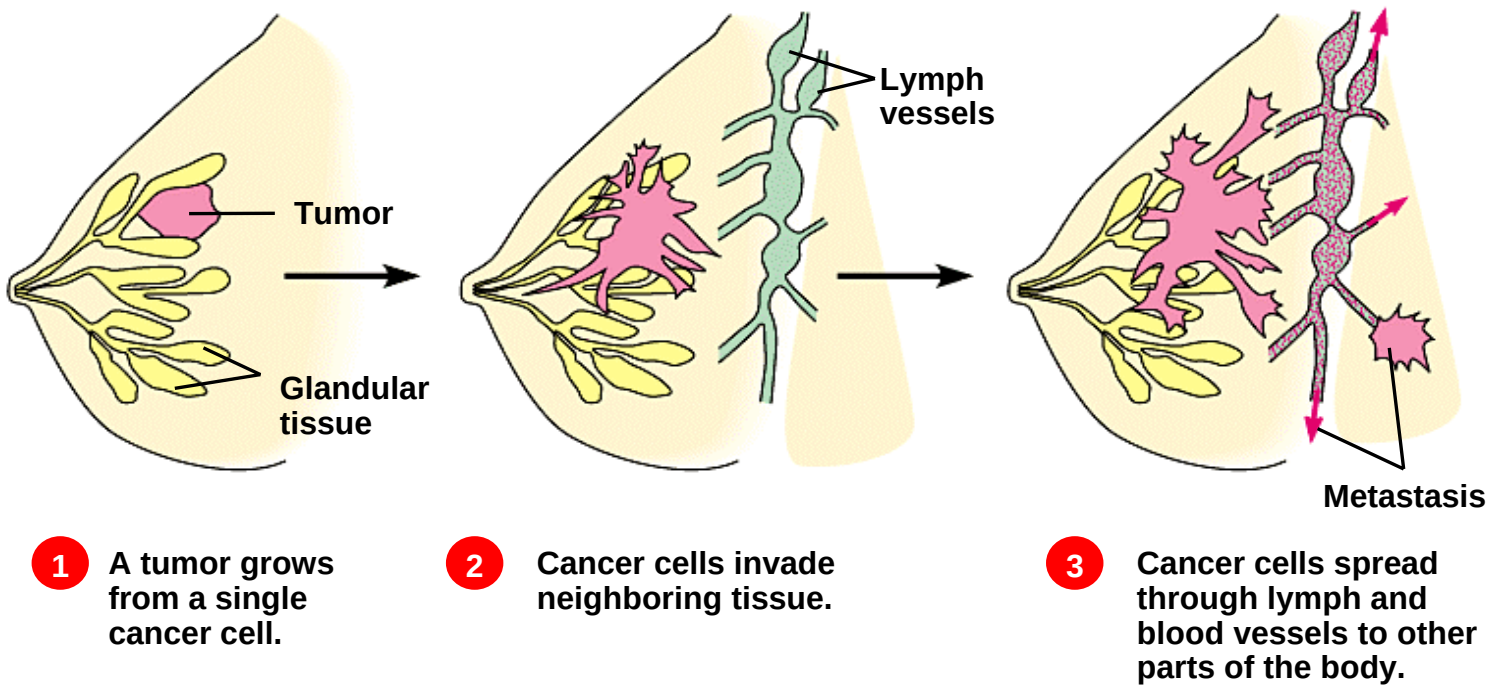
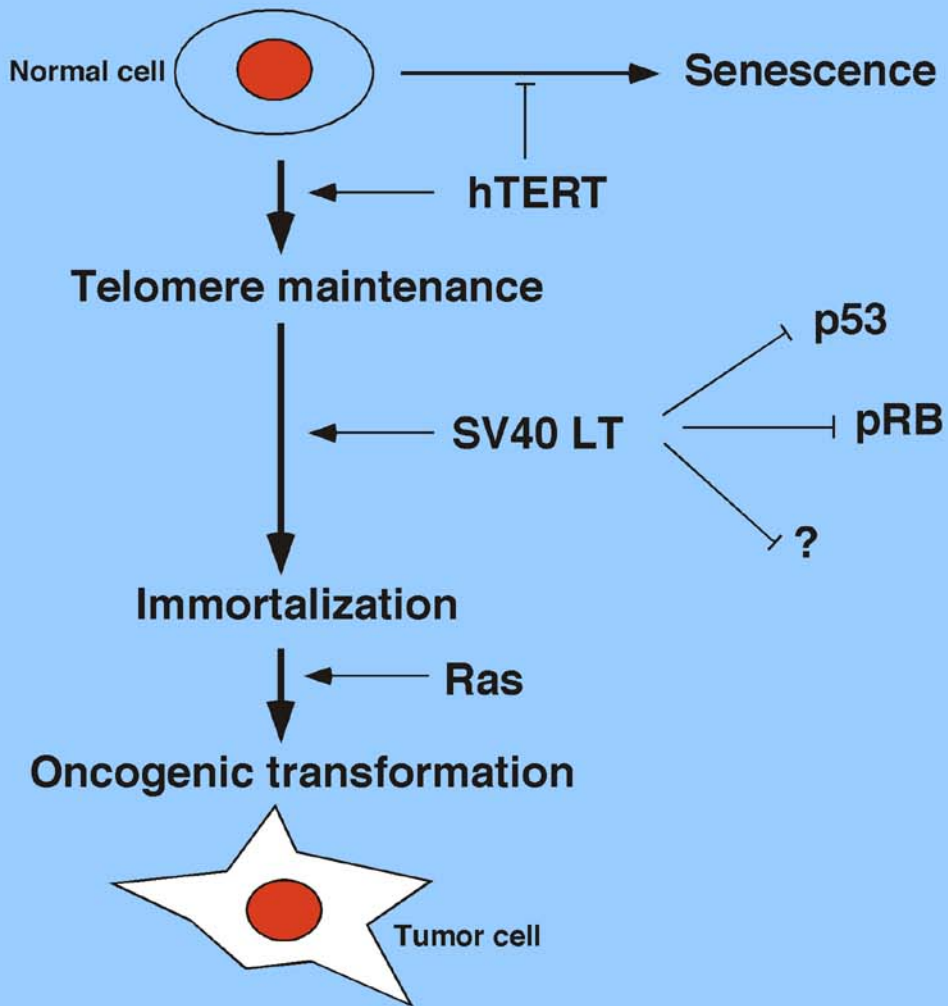
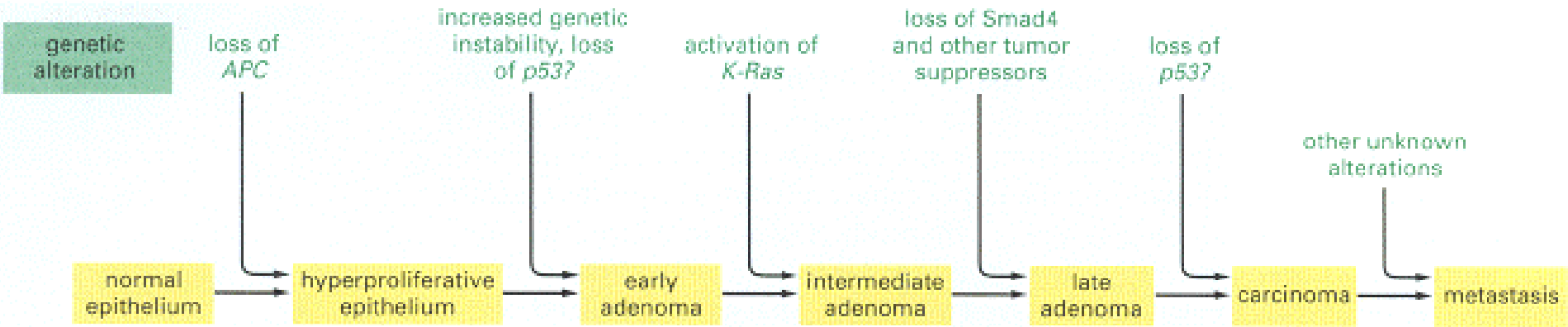


Figure 8.10

How Is a Normal Cell Converted into a Tumor Cell?



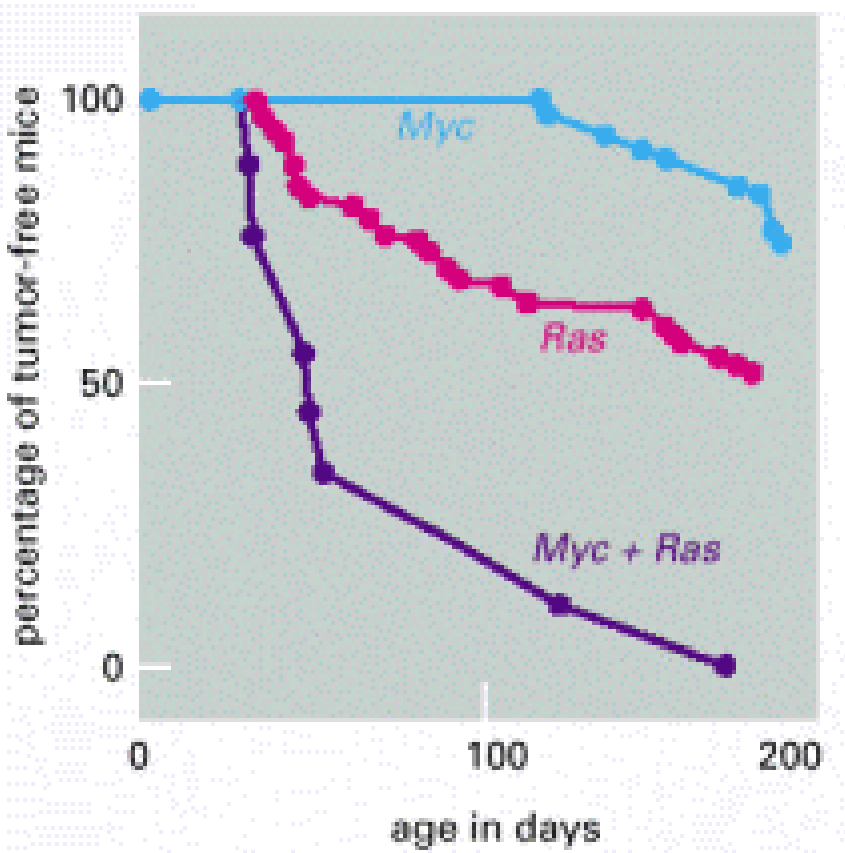
Cancer is a multistep process



Current view is that it probably takes mutations in 4 “pathways” in human cells to get cancer

Nature **400**, 464 - 468 (29 July 1999)

Cooperation between oncogenes



Oncogene vs. tumor suppressor gene

Oncogenes – cancer producing genes

-Have potential to induce cancer

-Mutated forms of normal genes

Proto-oncogene: when *activated*, promotes transformation

Types of Oncogenes

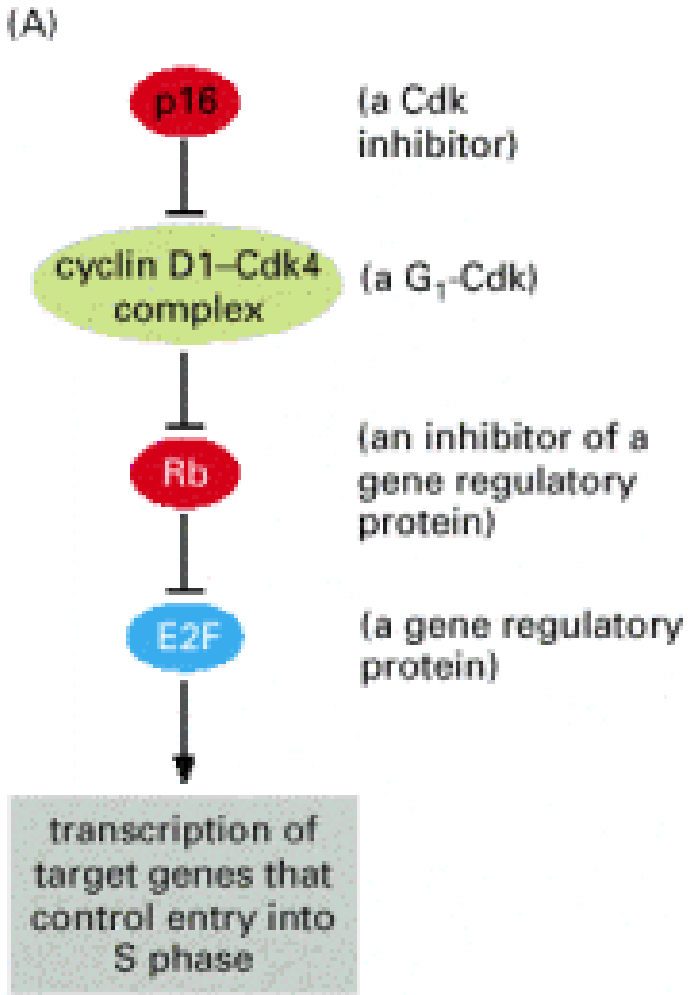
- Genes that specify proteins that induce cell proliferation
- Genes that inhibit cell proliferation
- Genes that suppress or trigger cell suicide

TSG: when *inactivated*, promotes transformation

4 Step Program to transformation:

1) Eliminate Rb

- Heterozygous loss of Rb results in Retinoblastoma
- Prevents the E2F transcription factor from transcribing genes required for cell cycle progression



4 Step Program to transformation:
2) Disable p53

- p53 is a transcription factor (tumor suppressor gene)
- "The Guardian of the Genome"; having an unstable genome is generally bad
- People heterozygous for p53 develop Li Fraumeni syndrome
- Mutated in many (most?) human tumors
- Inability to sense and repair damage makes tumor cells sensitive to chemotherapeutics

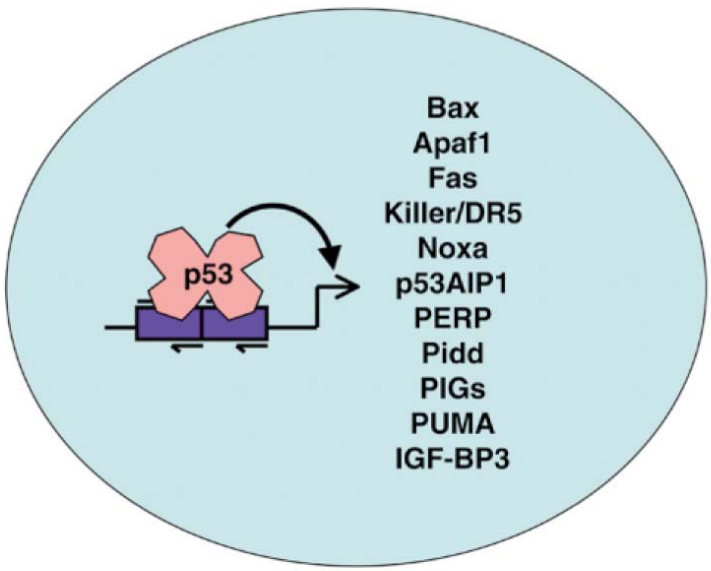
4 Step Program to transformation:
3) Activate Telomerase

- Without telomerase, cells eventually go through crisis
- Made up of proteins and RNA
- Rodent cells constitutively express telomerase and have long telomeres

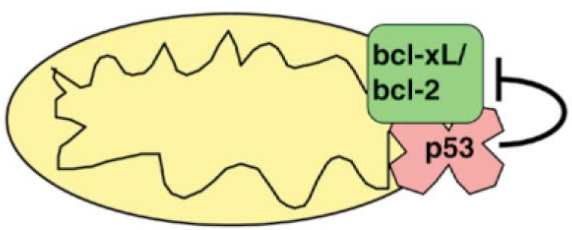
Roles of p53 in apoptosis

A common denominator in human cancer

- p53 induces apoptosis through transcriptional activation of proapoptotic genes, such as Puma, Noxa, p53AIP1, Bax, Apaf-1 etc.
- It can also directly induce apoptosis by localizing to mitochondria via interaction with Bcl-2 family protein Bcl-xL and facilitating Bax oligomerization

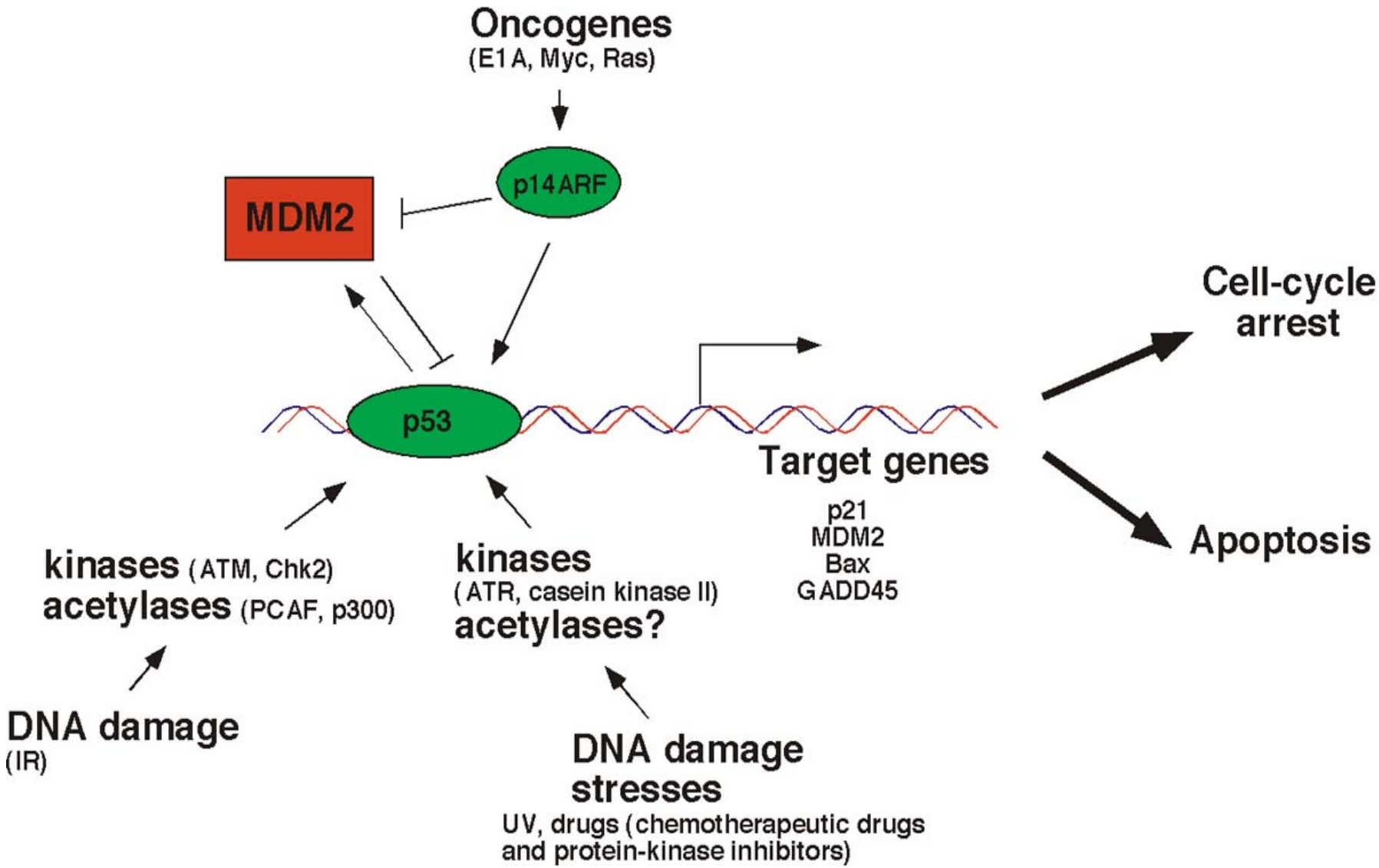


APOPTOSIS

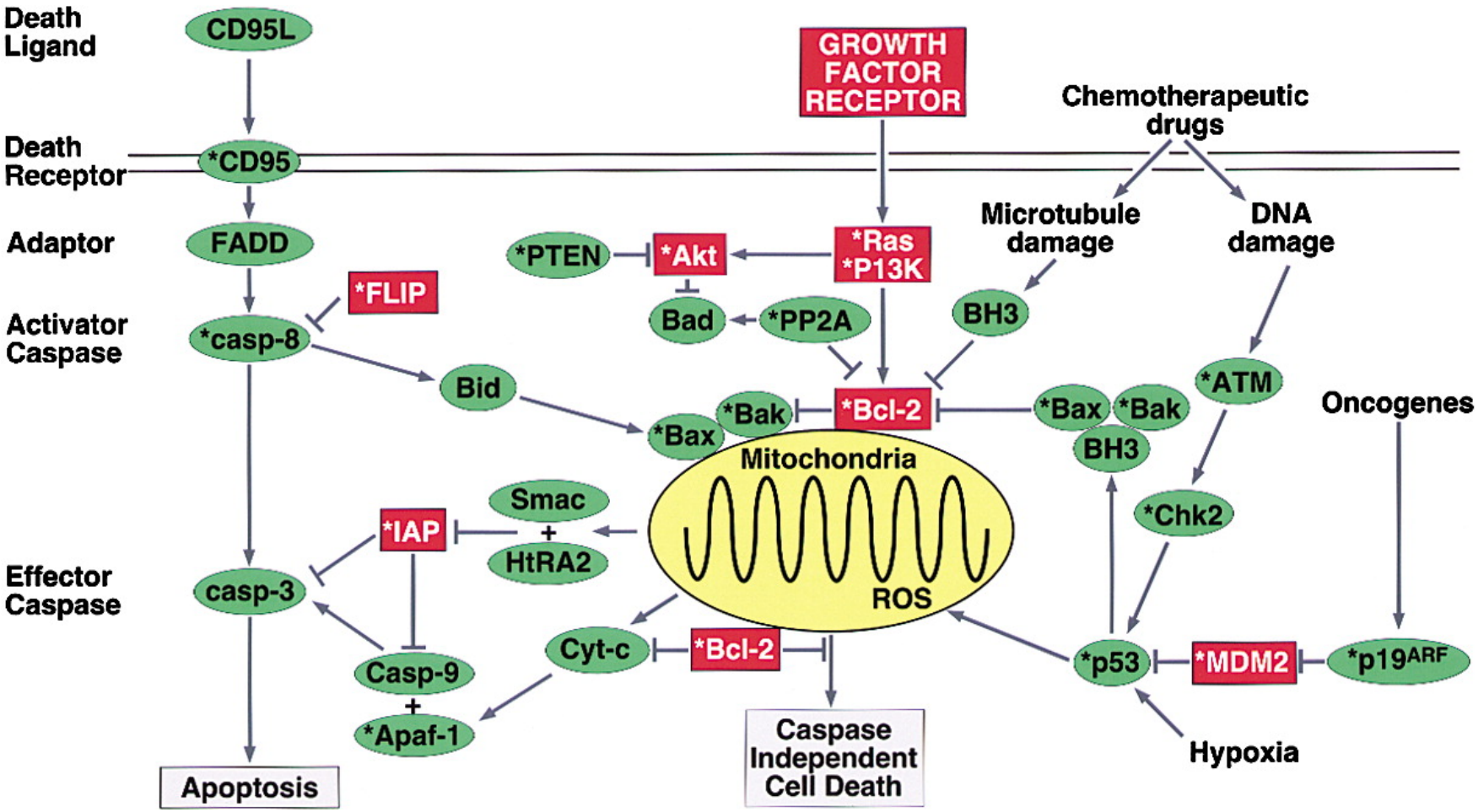


Ref: Mol. Cell, 2003, 11(3):552-4

The p53 pathways



p53 and apoptosis

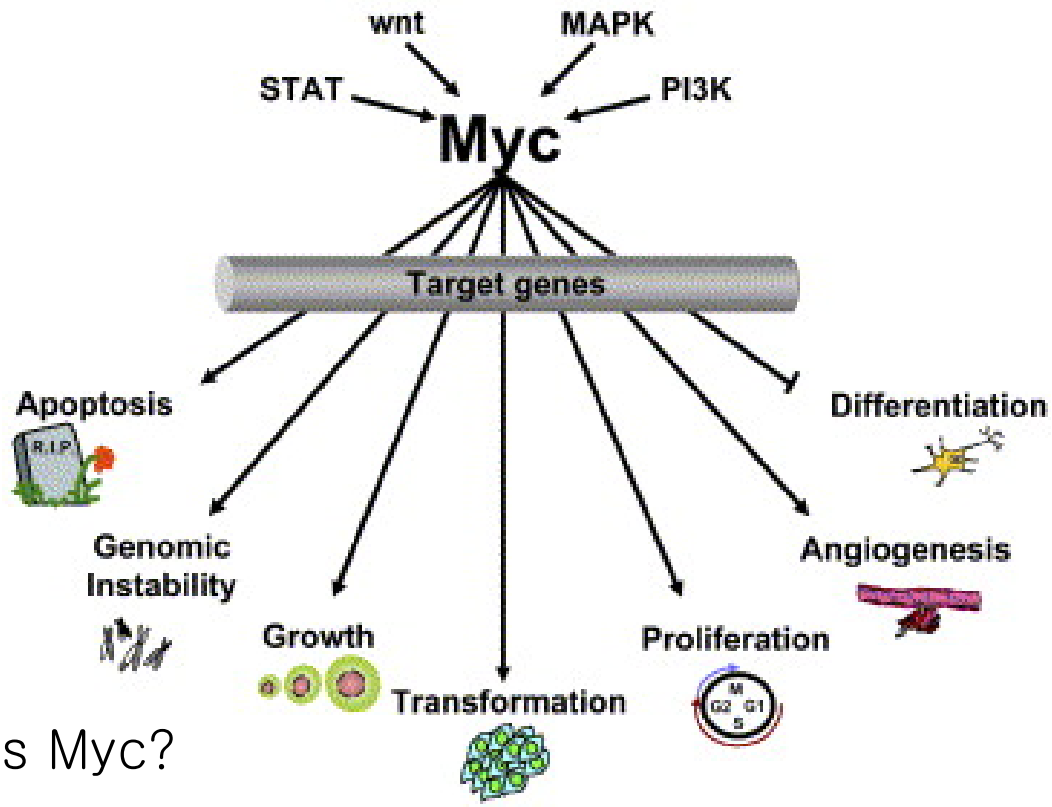


Ref: Cell, 2002, 108:153-164

4 Step Program to transformation:

4) Acquire a growth promoting mutation

- Lots of ways to do this—we started lecture by describing some
- PTEN/PI3kinase, Ras, myc
- Inactivation of PP2A (SV40 small T, okadaic acid)

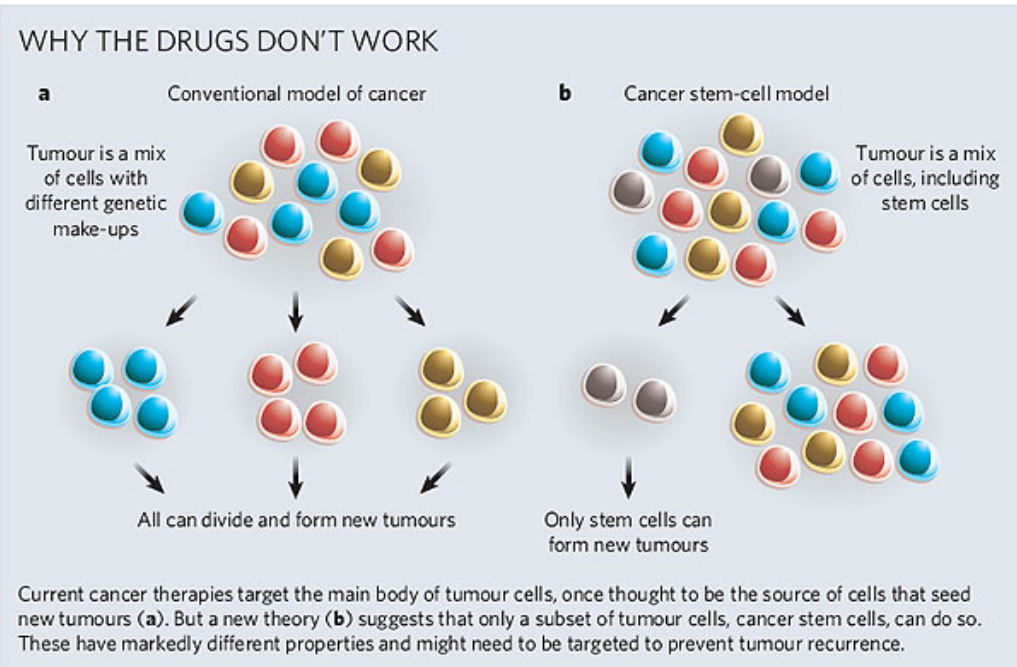


What is Myc?

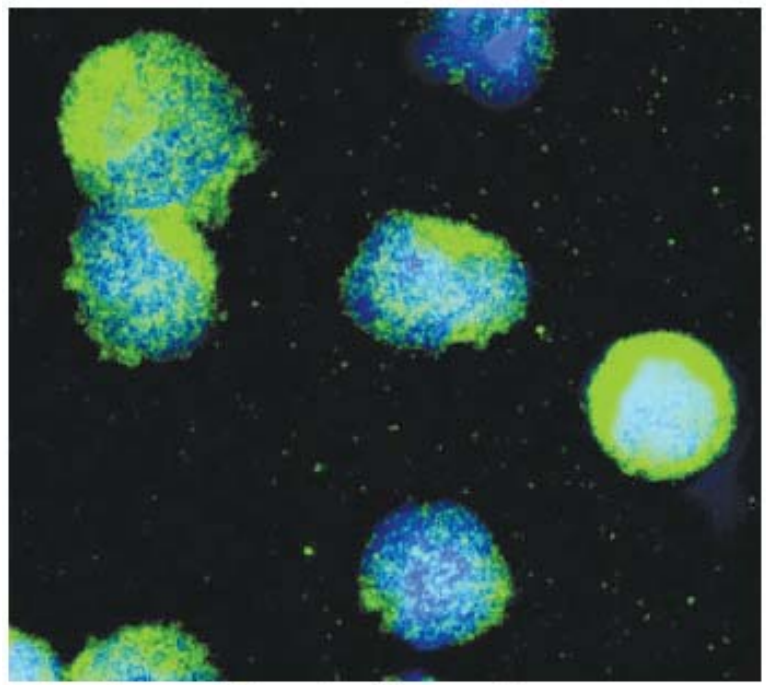
HOW MICE DIFFER FROM HUMANS

- Cancers tend to form in different types of tissue
- Tumours have fewer chromosomal abnormalities
- Ends of chromosomes (telomeres) are longer
- Telomere-repairing enzyme (telomerase) active in cells
- Short lifespan
- Fewer cell divisions (10^{11}) during life than humans (10^{16})
- Metabolic rate seven times higher than humans
- Lab mice highly inbred and genetically similar

Cancer stem cell



Current cancer therapies target the main body of tumour cells, once thought to be the source of cells that seed new tumours (**a**). But a new theory (**b**) suggests that only a subset of tumour cells, cancer stem cells, can do so. These have markedly different properties and might need to be targeted to prevent tumour recurrence.



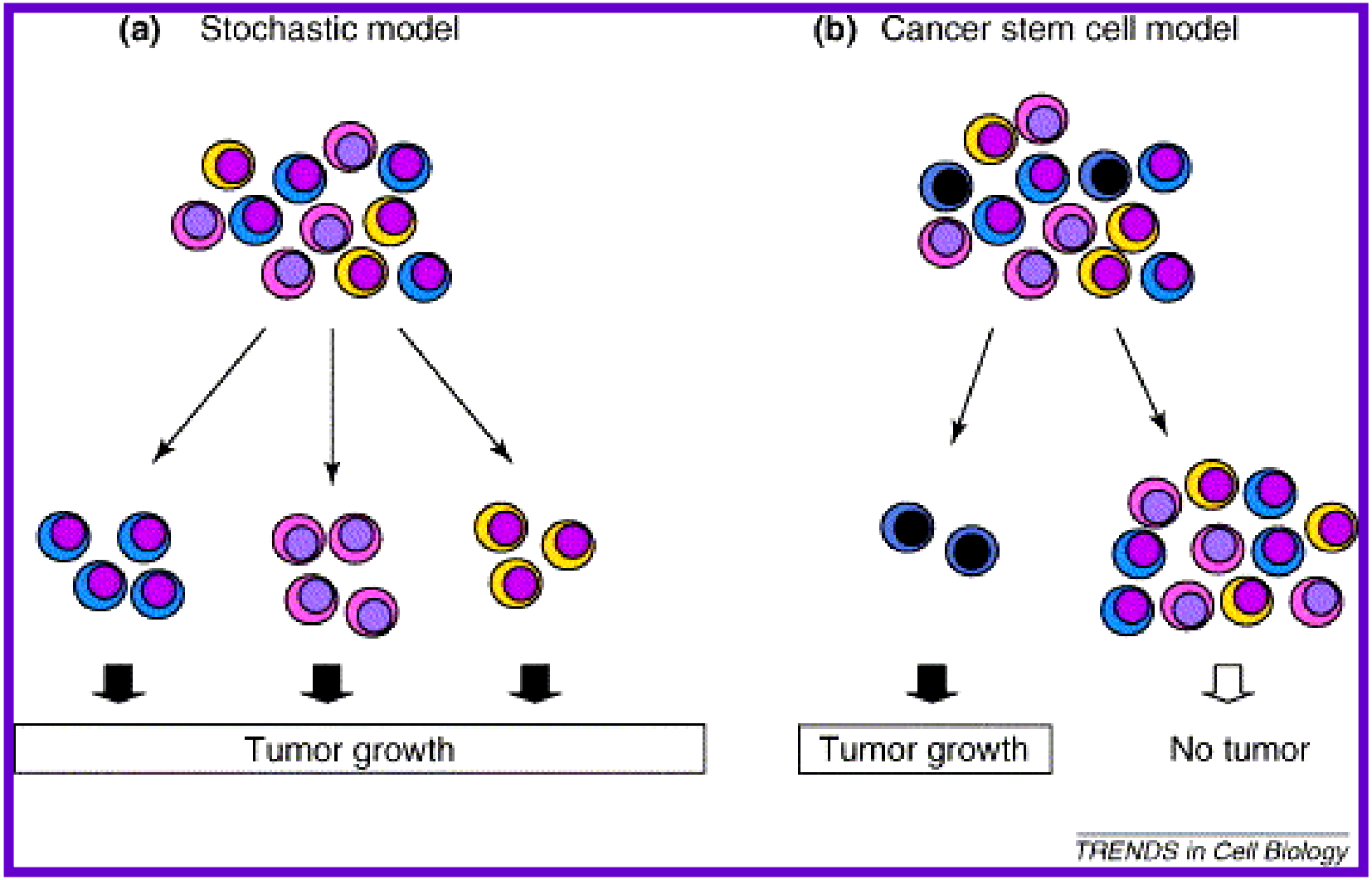
Leukaemia stem cells have the ability to seed new cancers.

Normal stem cells

Rare cells within organs with the ability to self-renew and give rise to all types of cells within the organ to drive organogenesis

Cancer stem cells

Rare cells within tumors with the ability to self-renew and give rise to the phenotypically diverse tumor cell population to drive tumorigenesis



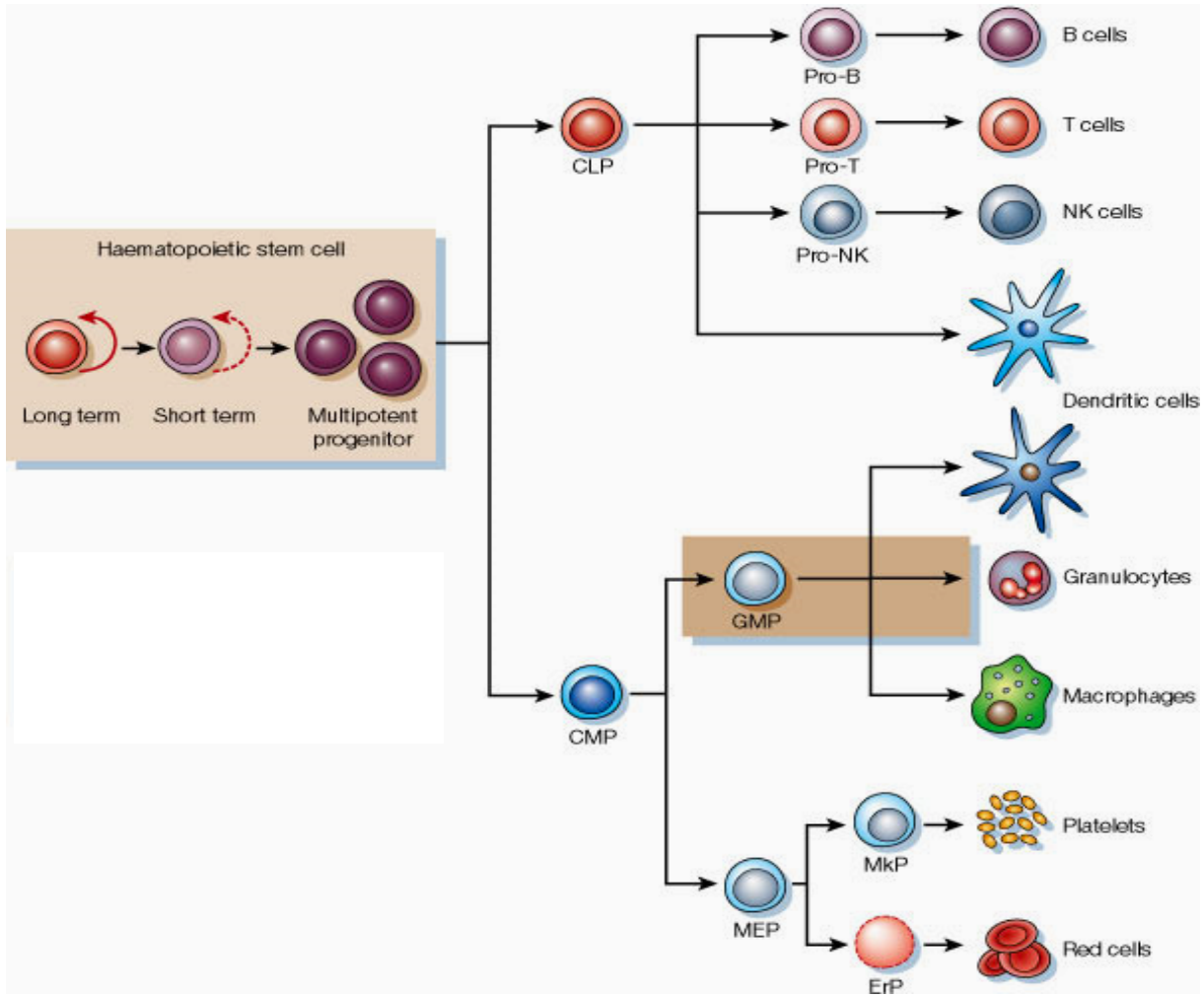
Self renewal and differentiation are random. All cells have equal but low probability of extensive proliferation. Only cells with self renewal capacity can sustain tumor growth.

Distinct classes of cells exist within a tumor. Only a small definable subset, the cancer stem cells can initiate tumor growth.

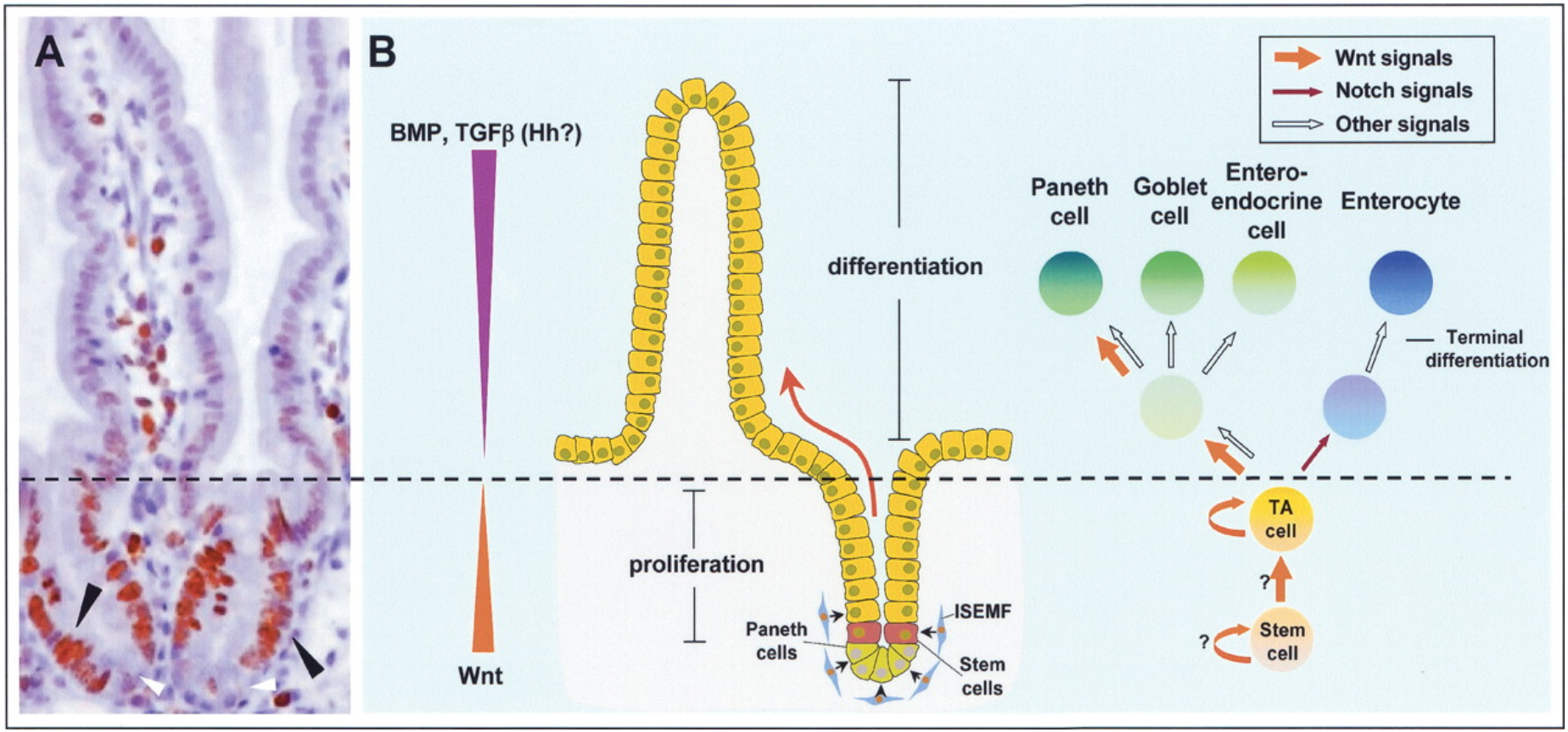
Development of Hematopoietic Stem Cells

Stem Cells → Multipotent Progenitors → Oligolineage Progenitors → Mature Cells

HSCs can be subdivided into long-term self-renewing HSCs, short-term self-renewing HSCs and multipotent progenitors (red arrows indicate self-renewal). They give rise to common lymphoid progenitors (CLPs; the precursors of all lymphoid cells) and common myeloid progenitors (CMPs; the precursors of all myeloid cells). Both CMPs/GMPs (granulocyte macrophage precursors) and CLPs can give rise to all known mouse dendritic cells. ErP, erythrocyte precursor; MEP, megakaryocyte erythrocyte precursor; MkP, megakaryocyte precursor; NK, natural killer.



Adult intestinal homeostasis



Schematic representation and section of the crypt-villus unit in the mature small intestine. Proliferative cells reside in the crypts, while differentiated cells occupy the villus. Crypt progenitors migrate up (red arrow) the crypt-villus axis before shedding into the lumen. The process of epithelial renewal takes 3-6 d and is ensured by a small number of asymmetrically dividing stem cells at the bottom of the crypts. Wnt signaling in the adult intestine promotes proliferation of progenitor or transit-amplifying (TA) cells, as well as commitment toward secretory lineages. Wnt signaling may also drive terminal differentiation of certain secretory lineages. Although it is commonly believed that Wnt signaling may promote proliferation and/or differentiation of intestinal stem cells, there is no evidence that formally proves this (see arrows with question marks). In panel *A*, black arrowheads indicate Ki67 positive transit-amplifying cells, while white arrowheads indicate the Paneth cell compartment.

Alex Gregorieff et al. Genes Dev. 2005; 19: 877-890