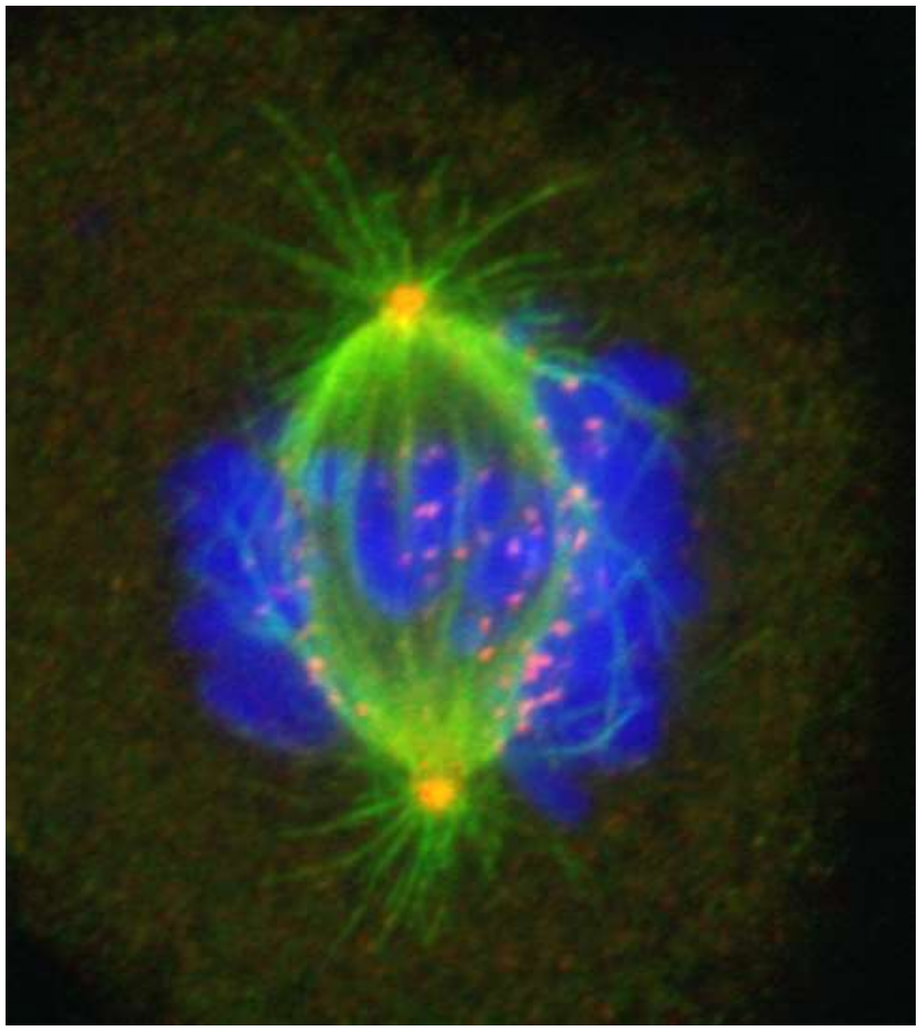
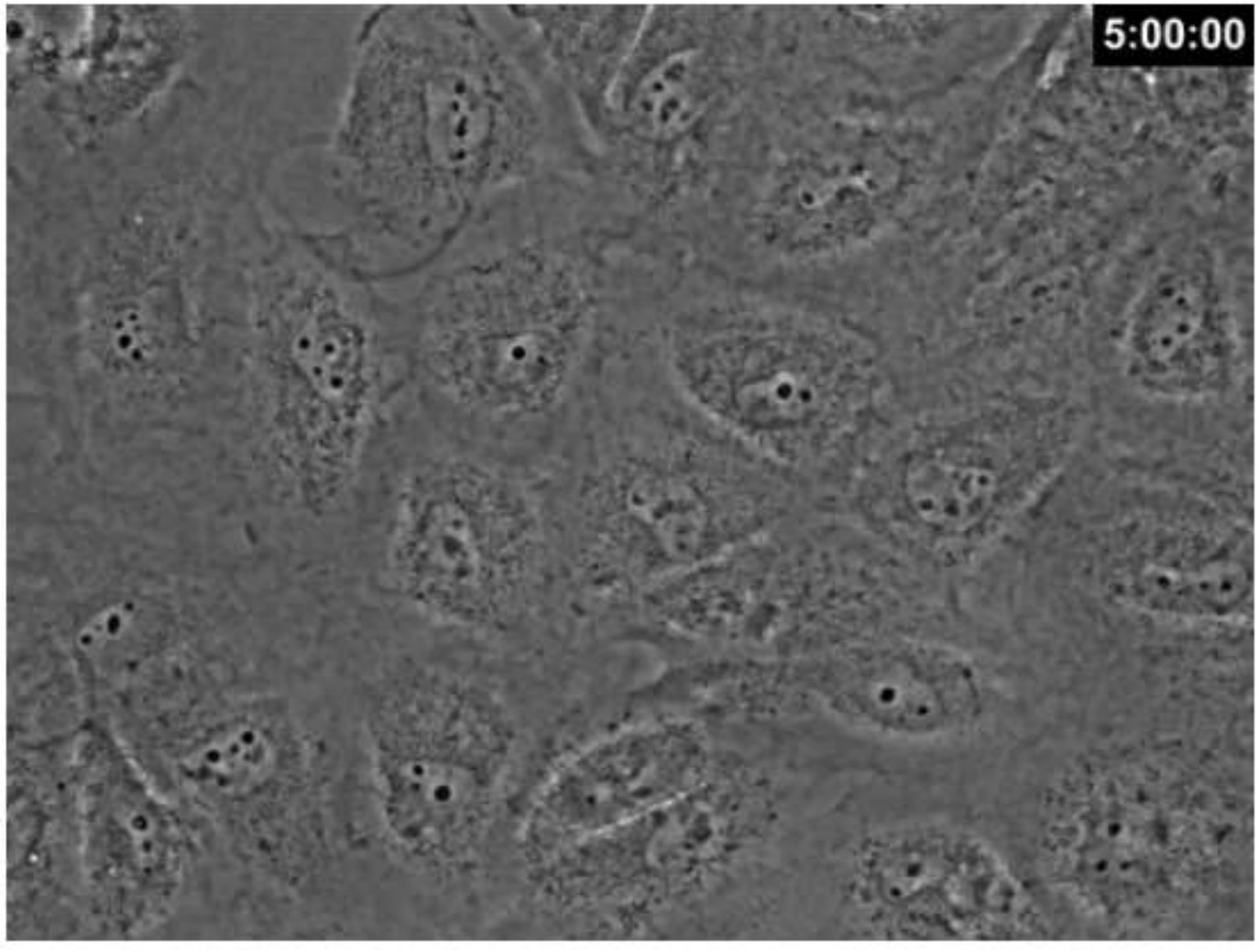
An introduction to cell biology, cancer, cell cycle, and mitosis





Dr. Lynne Cassimeris, Ph.D.
Biological Sciences
Lehigh University

Cells Replicate & Repair Themselves

- Bone marrow stem cells >1,000,000 divisions/min
- Skin stem cells
- Intestinal stem cells
- Muscle satellite cells
- Liver cells

Cells Work Together

25,000X

250X

Skin as an example of cells within a tissue

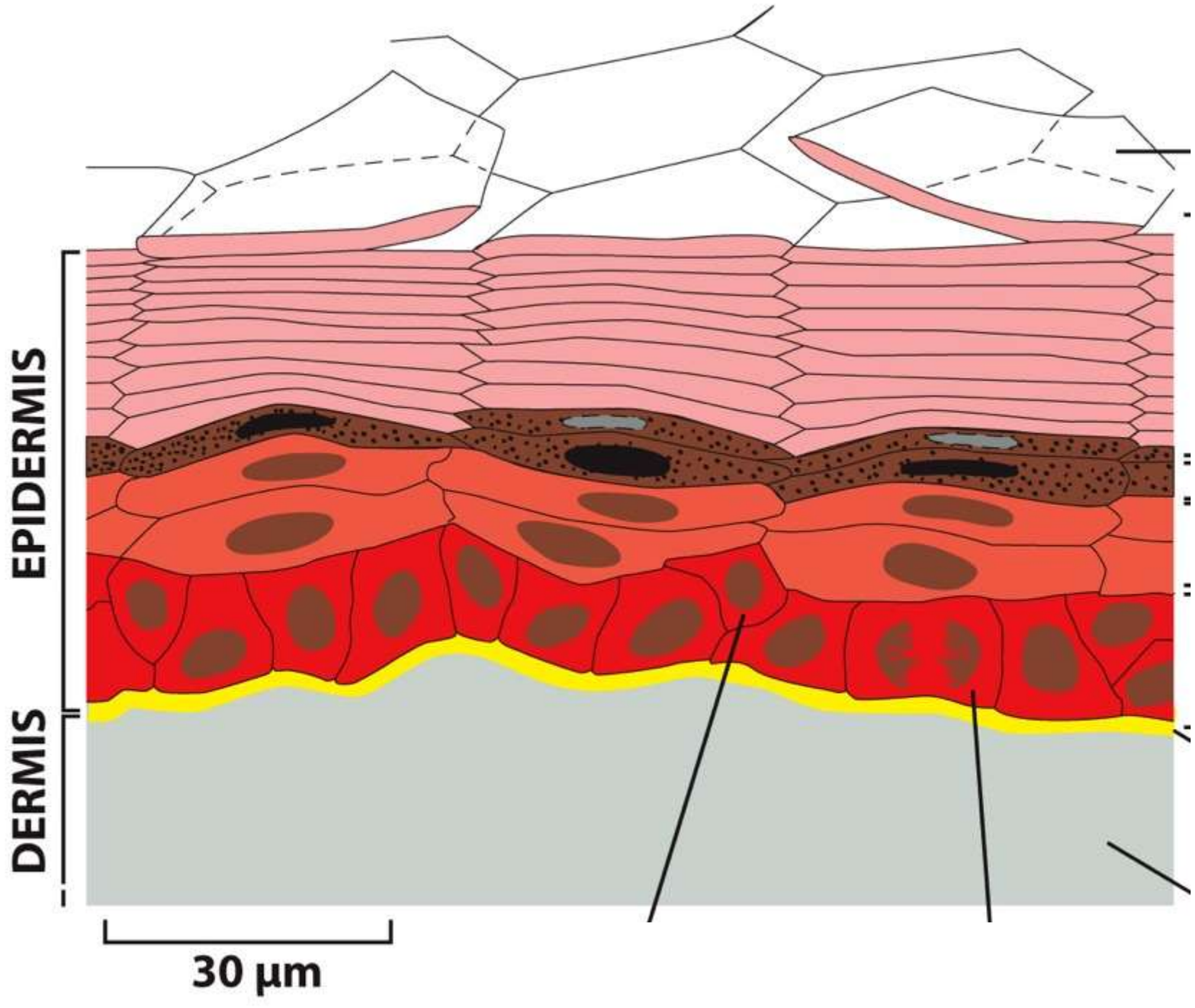


Figure 22-10a Molecular Biology of the Cell 6e (© Garland Science 2015)

Normal Skin

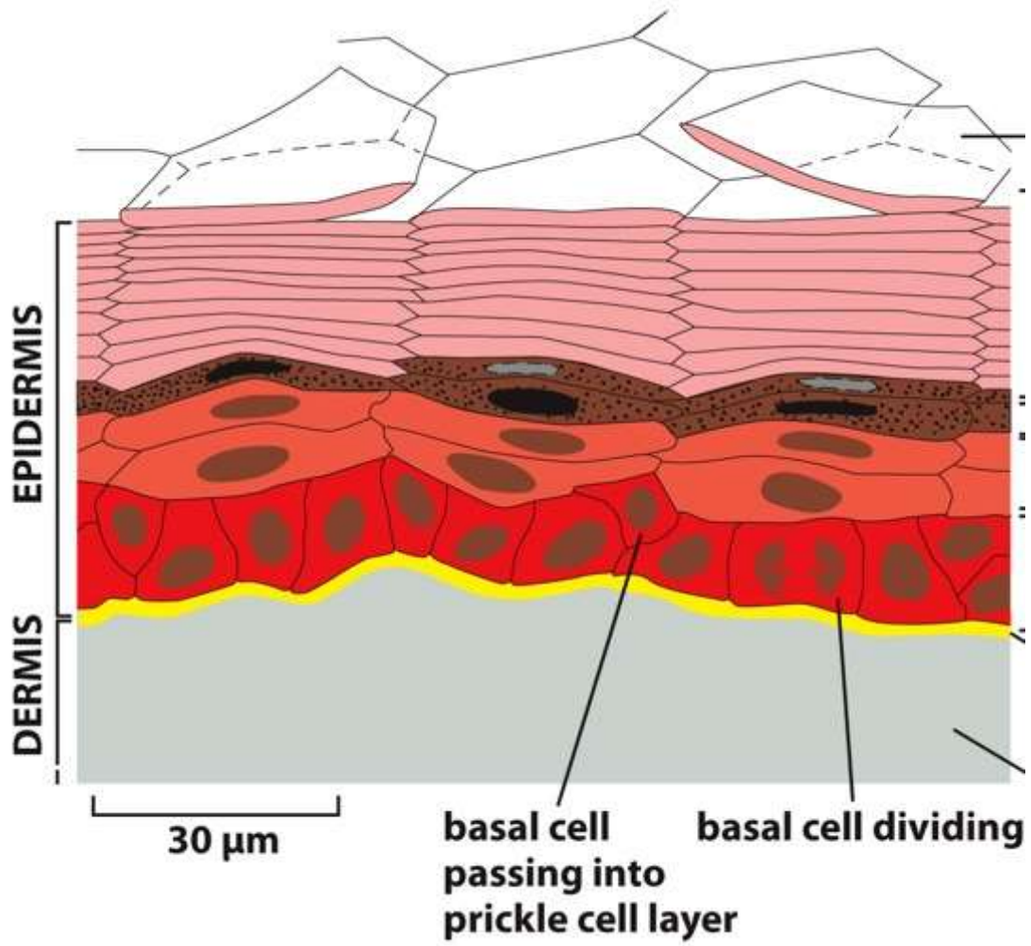
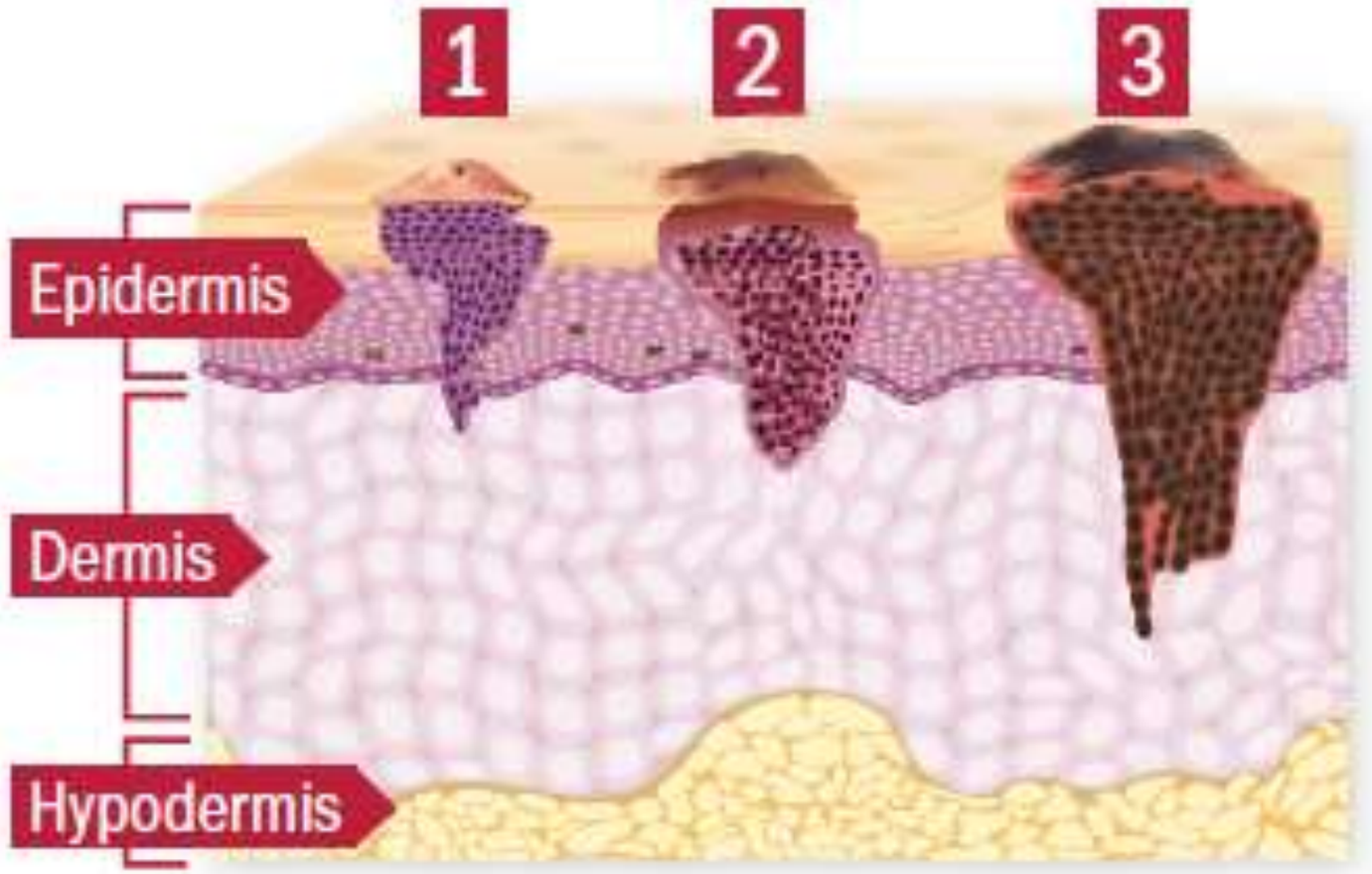


Figure 22-10a Molecular Biology of the Cell 6e (© Garland Science 2015)

Types of Skin Cancer



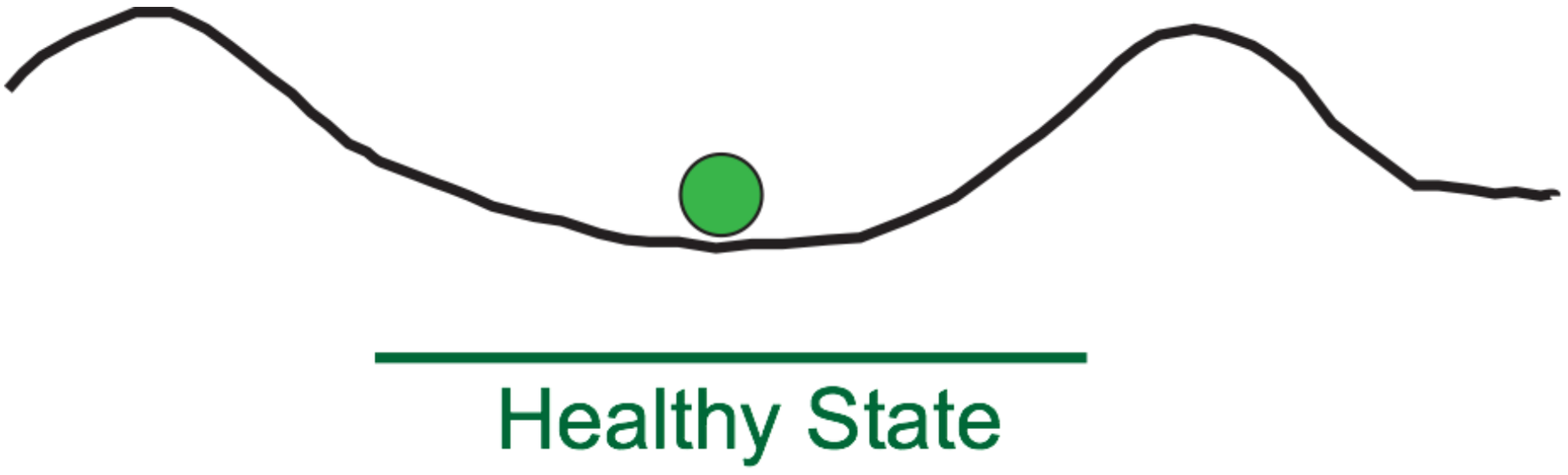
Squamous

Basal Cell

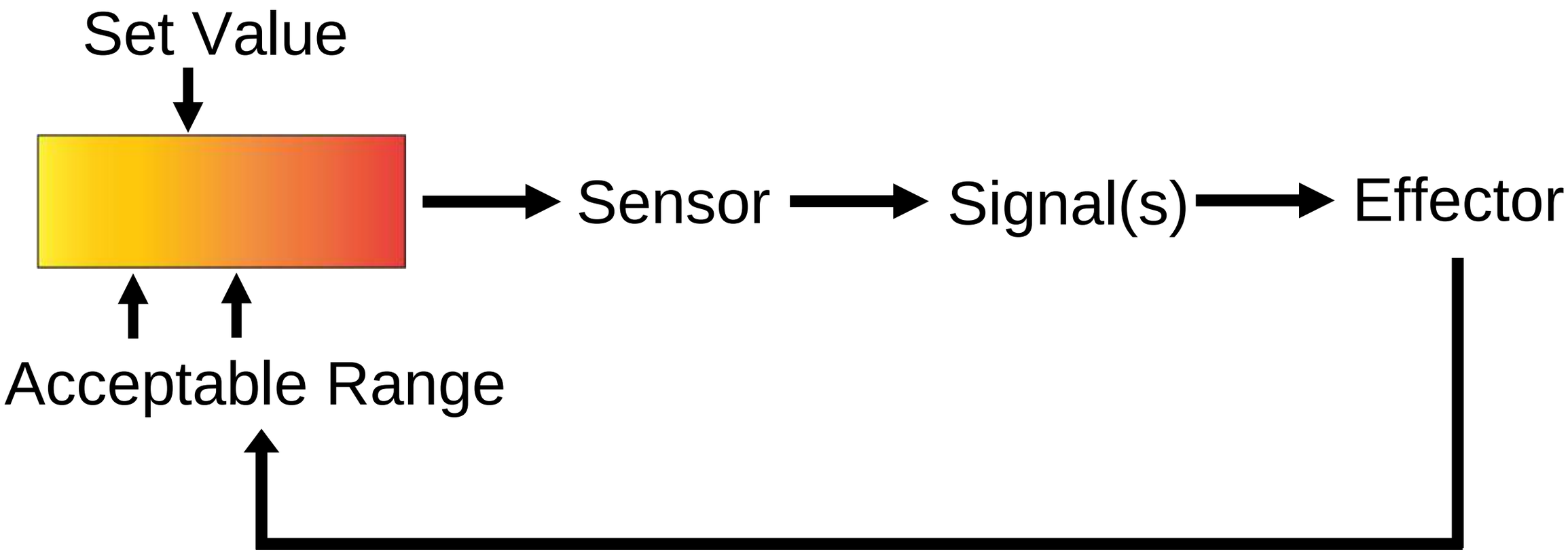
Melanoma

https://www.health.harvard.edu/cancer/save-your-skin-from-cancer

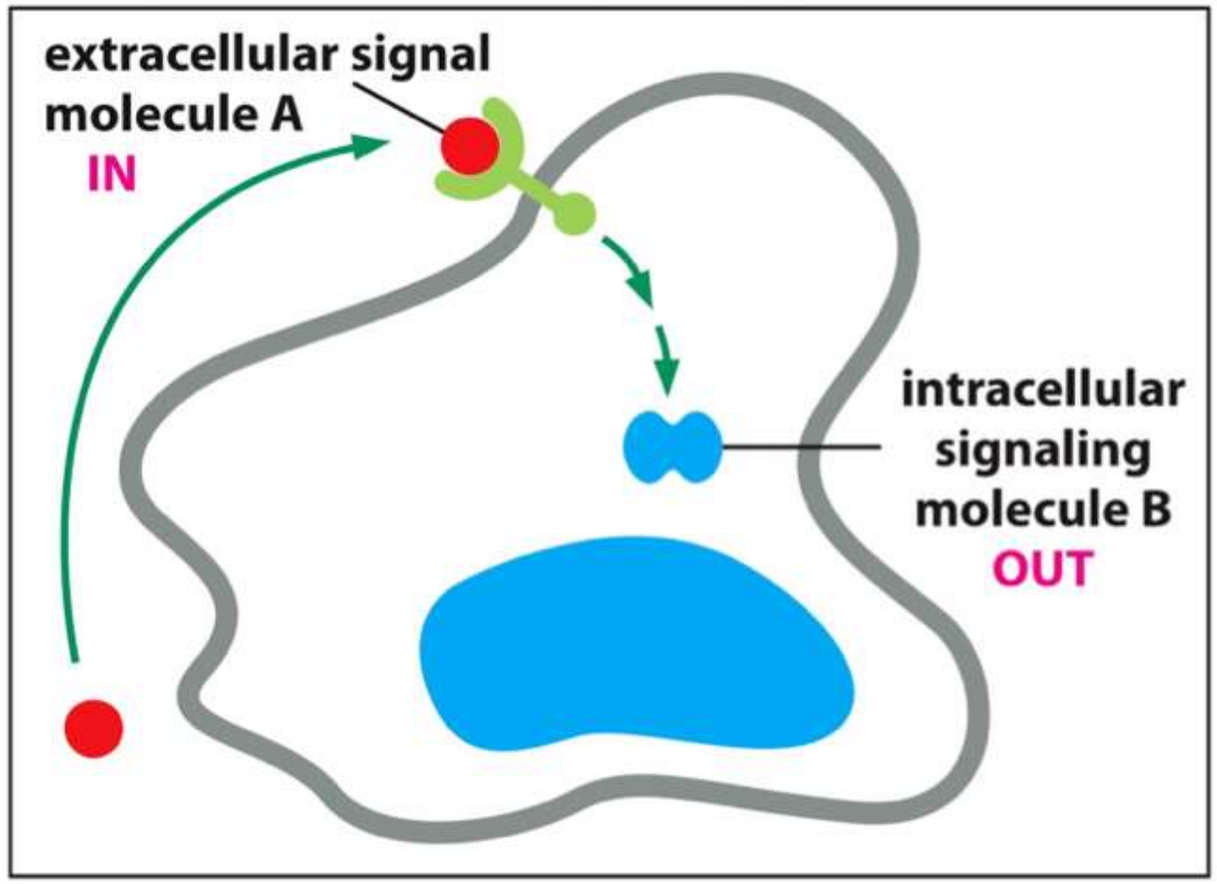
A healthy landscape



A simple homeostatic circuit

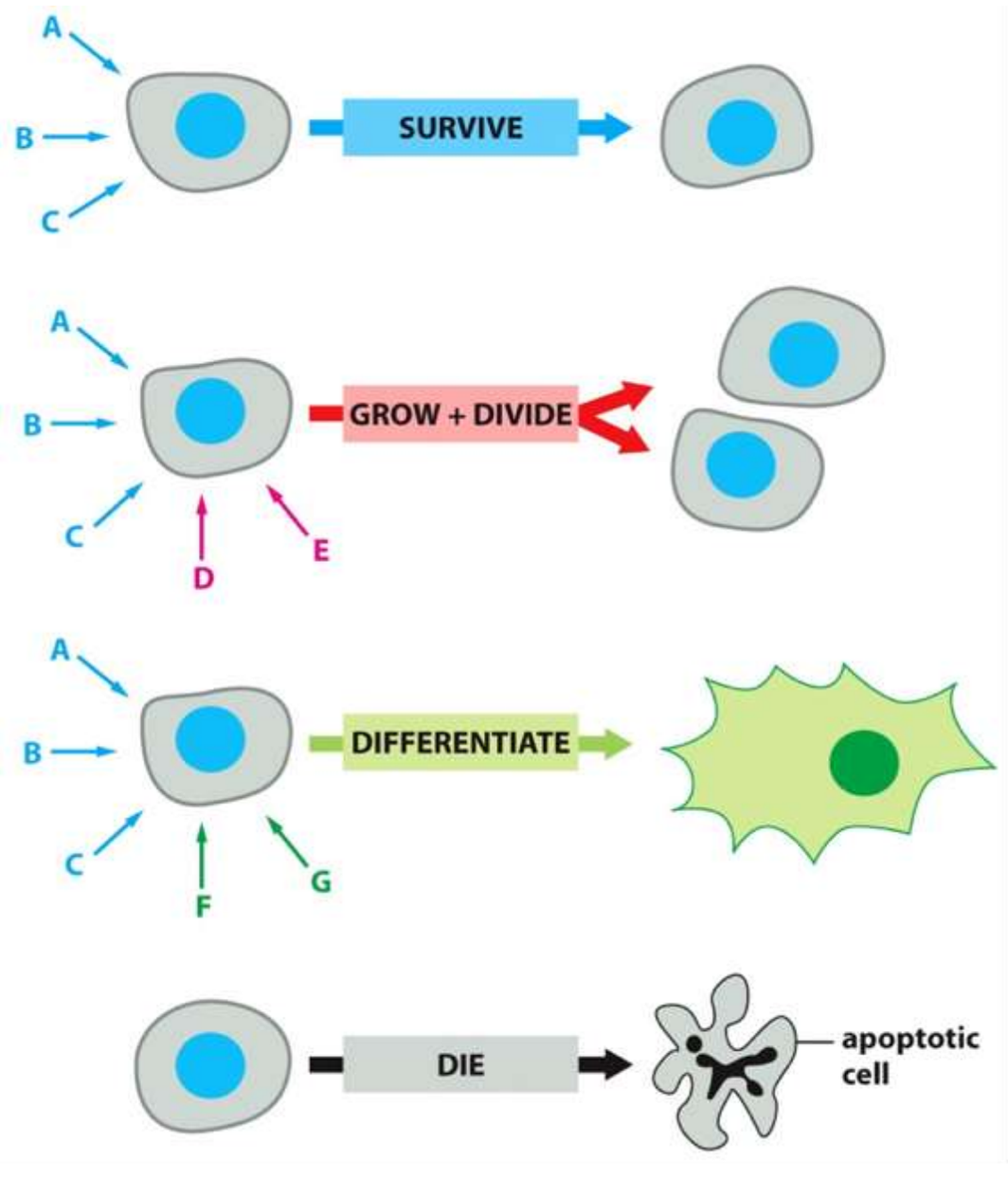


Cells constantly communicate with each other about how things are going

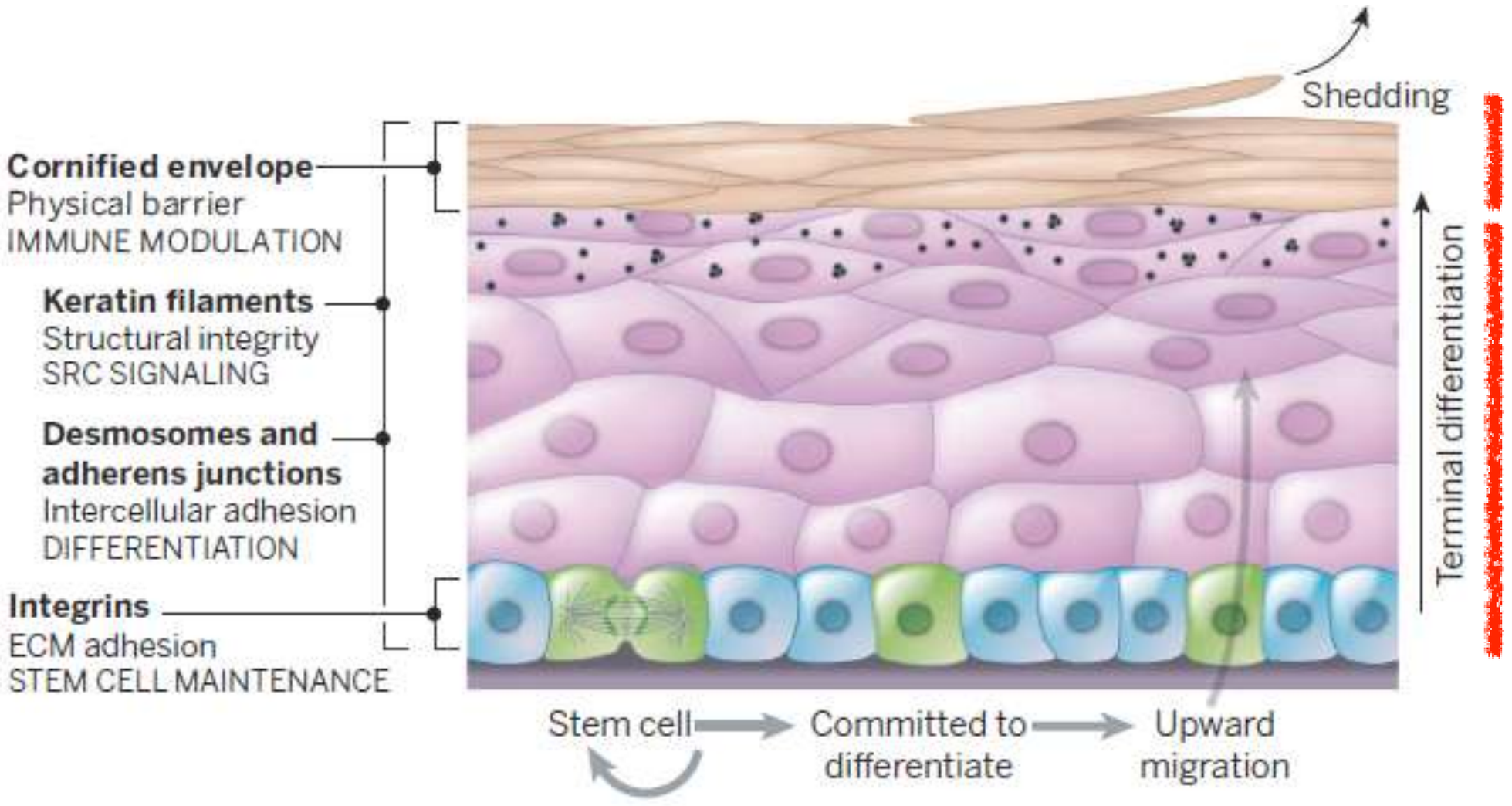


Essential Cell Biology. Garland Press

from all the signals in their environment: cells proliferate, specialize, interact, move, and sometimes they die



Normal, healthy cell turnover in skin tissue

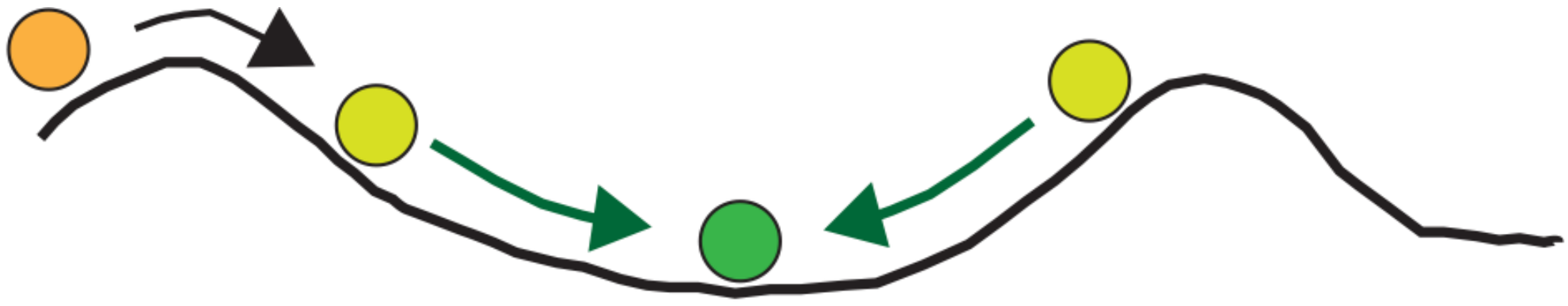


~ 14 days

~ 14 days

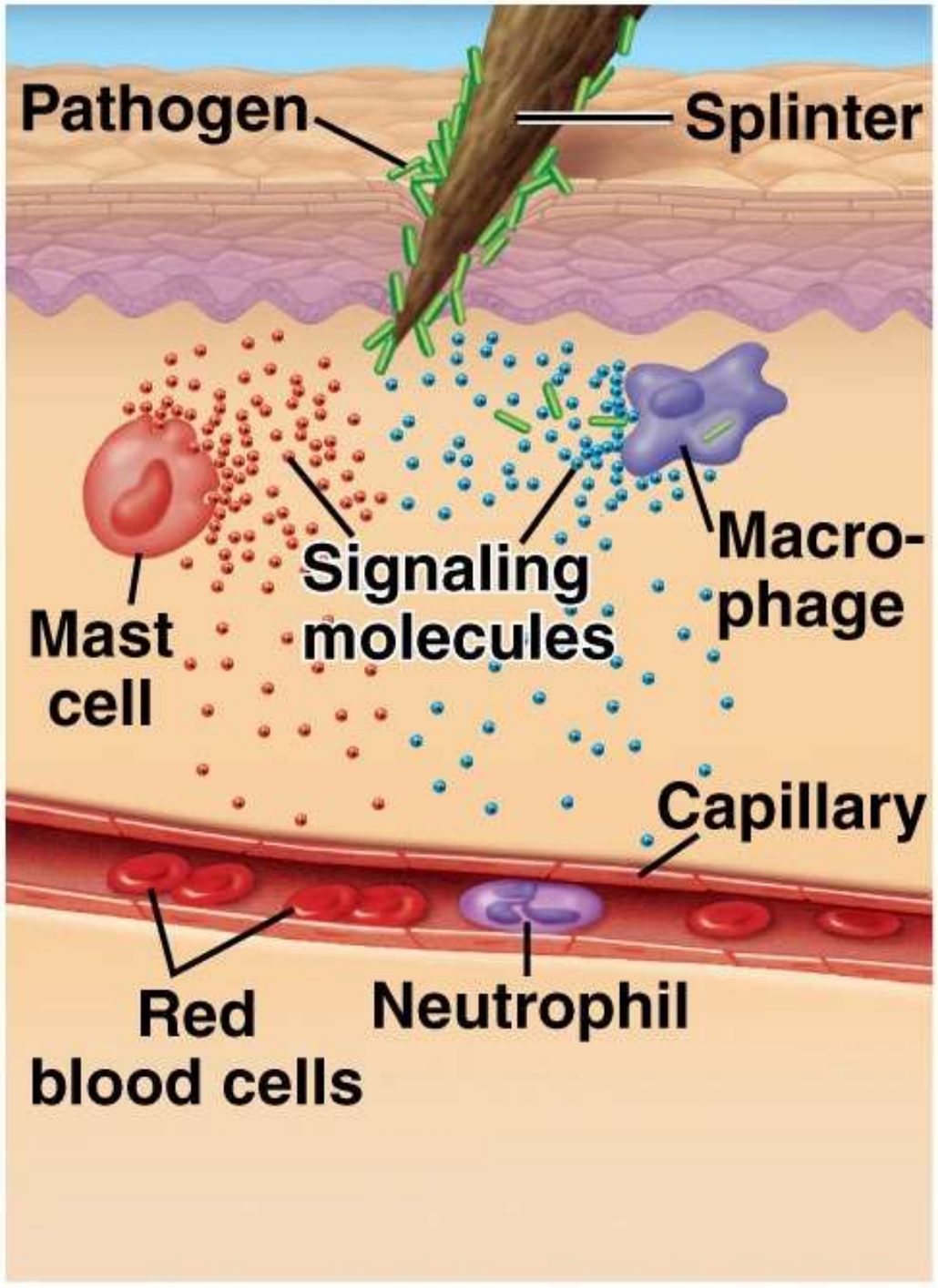
individual keratinocytes last for about a month and must be replaced

Healthy vs. Disease Landscapes

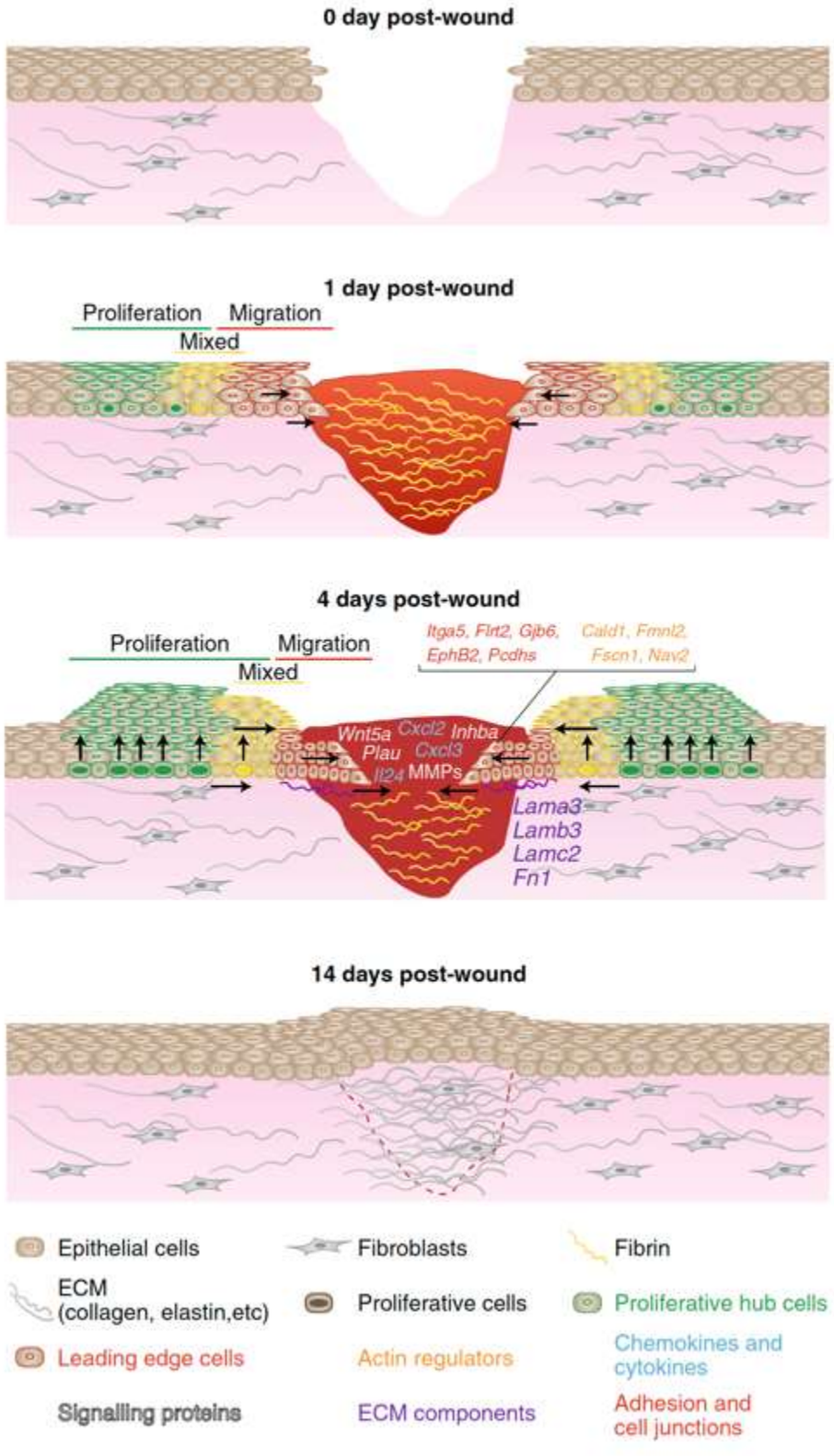


example: inflammation

Signals and responses to infection



Inflammation and repair at the wound



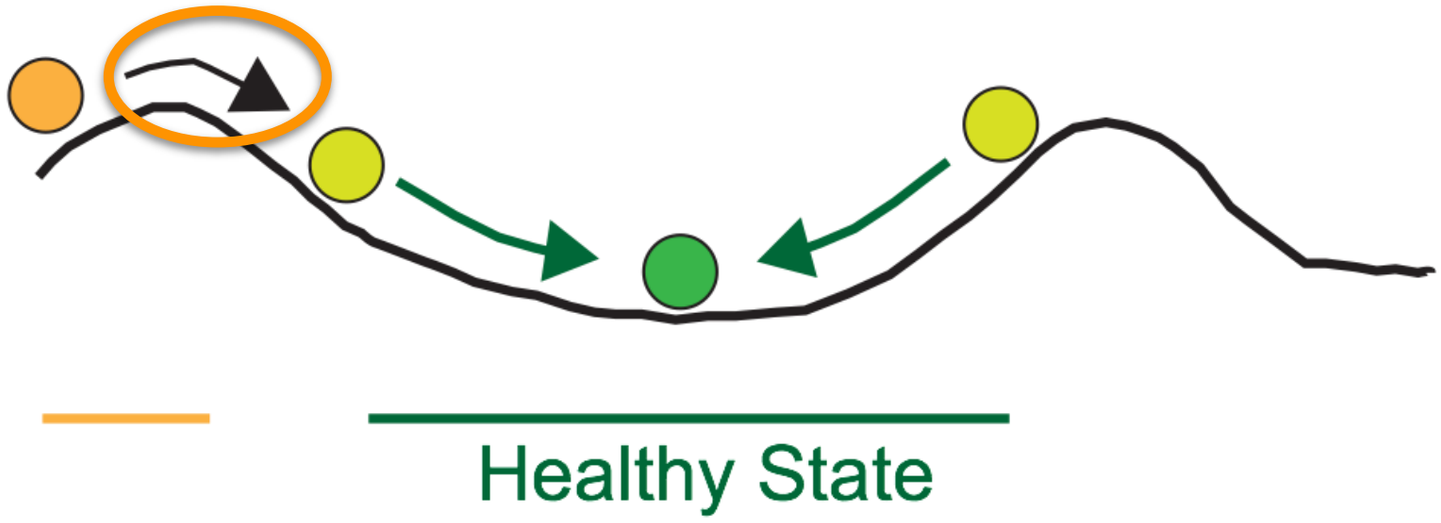
mechanical and chemical signals

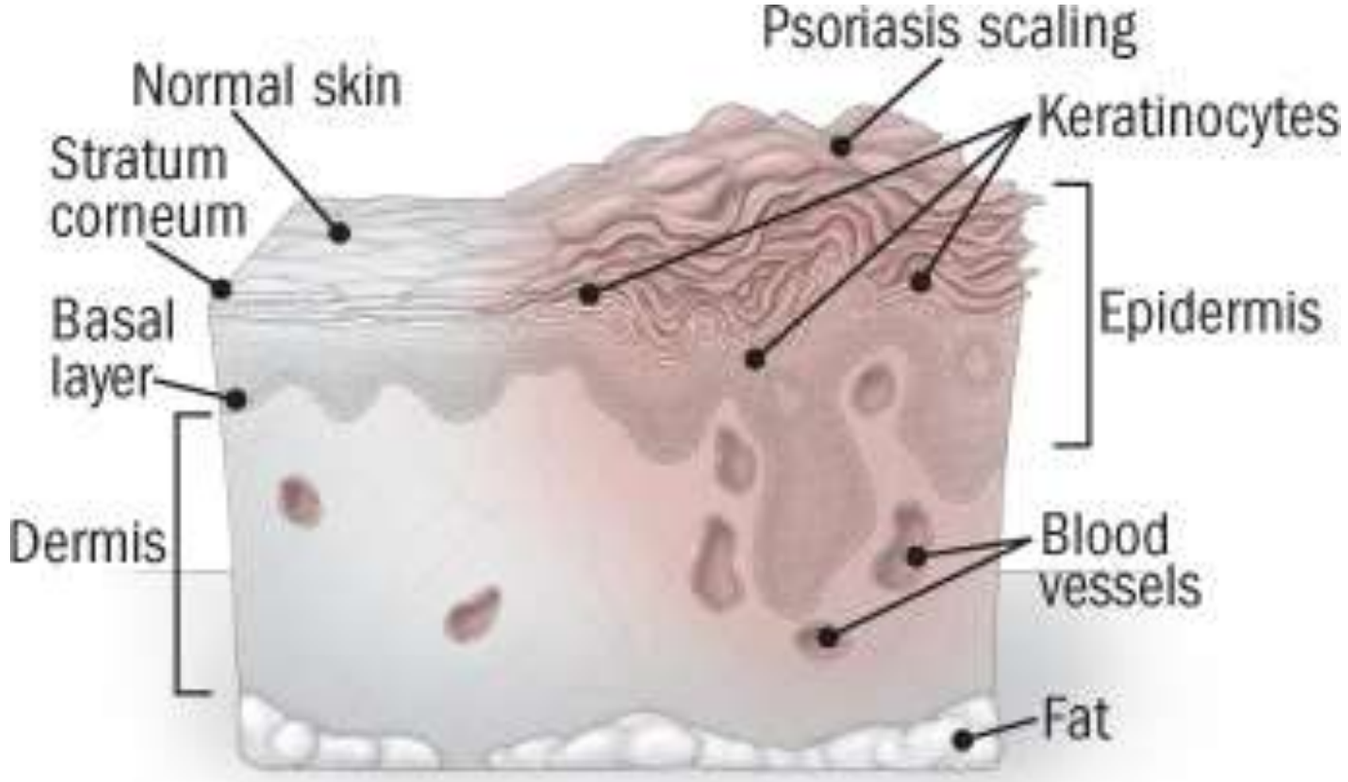
Some cells proliferate, others migrate,

eventually heal without a scar

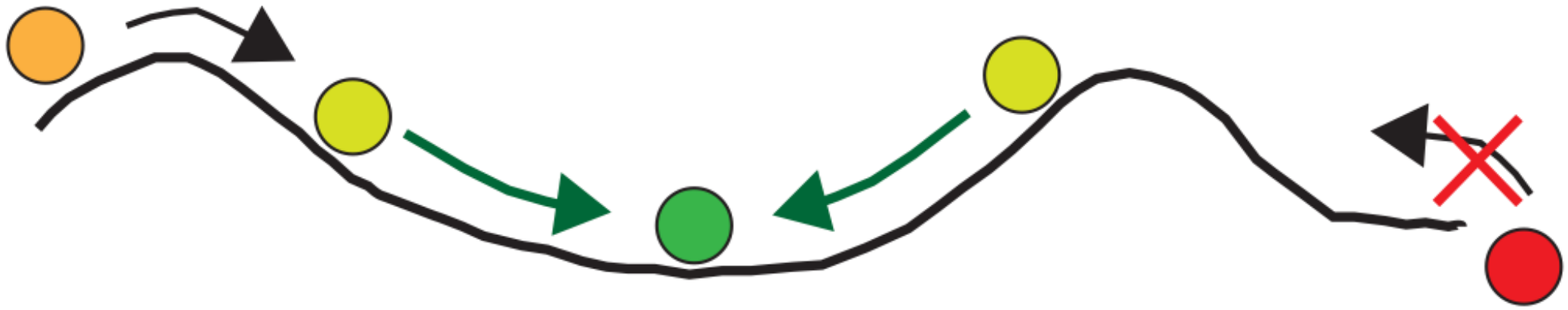
Nature Cell Biology. Volume 21, pages18–24 (2019)

Inflammation





https://www.health.harvard.edu/newsletter_article/bringing-psoriasis-under-control



Healthy State

Pathological State

Severe Disease

Cancer

Gene mutations

Normal Skin → **Skin Cancer**

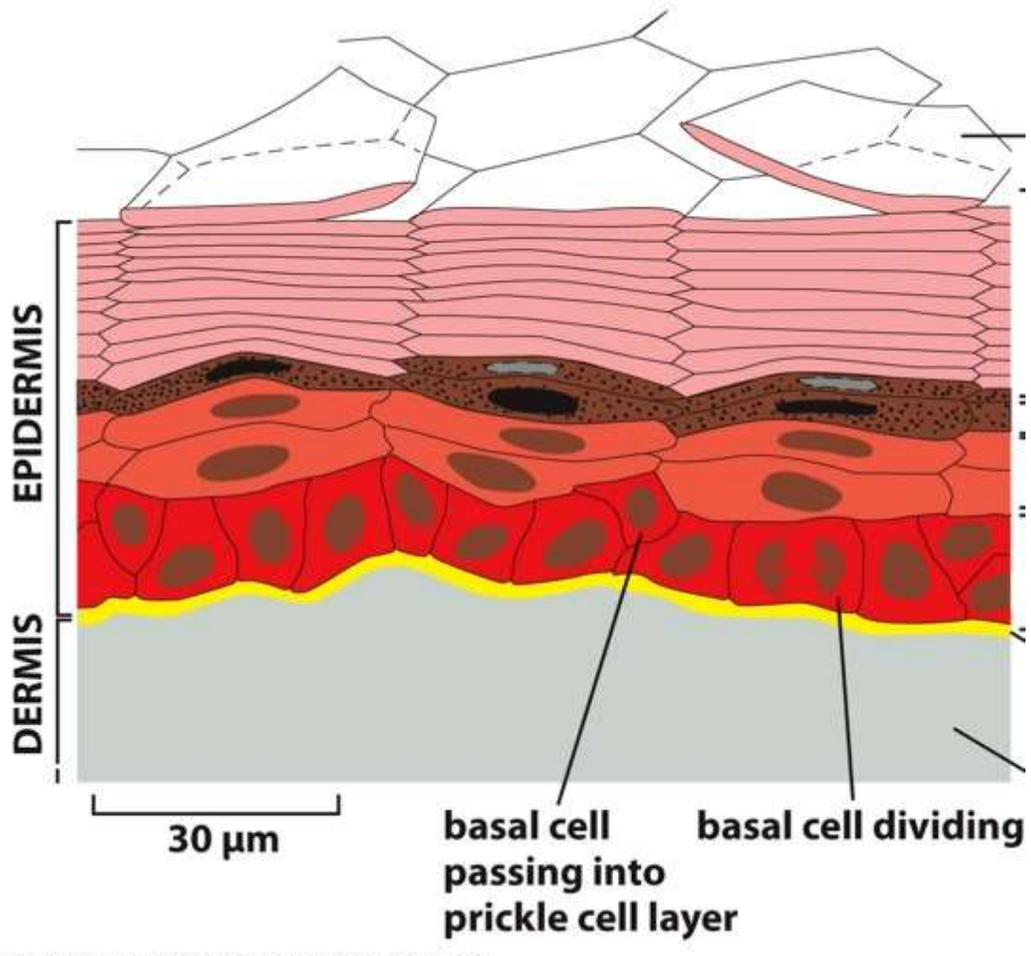
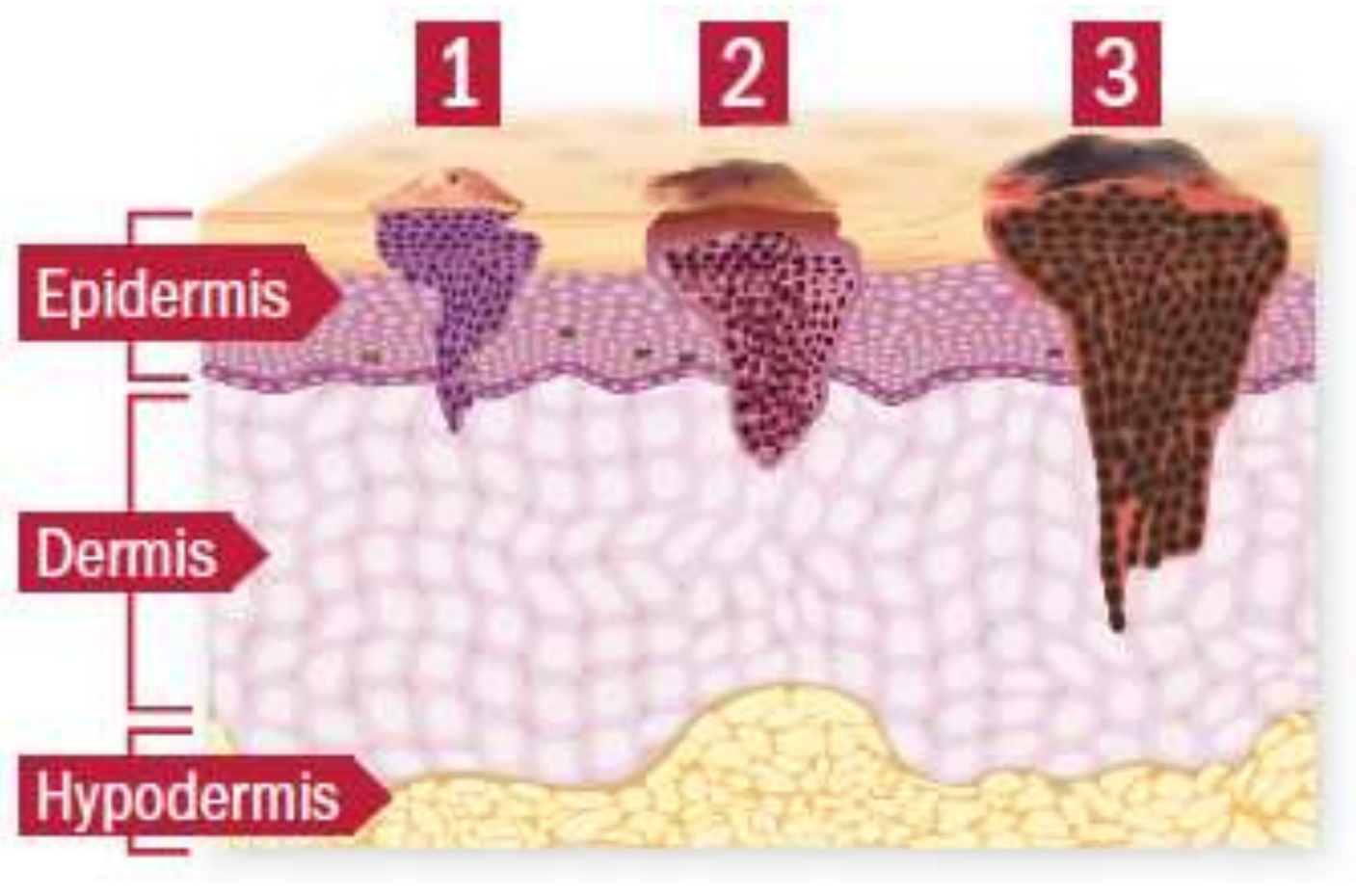


Figure 22-10a Molecular Biology of the Cell 6e (© Garland Science 2015)



Squamous

Basal Cell

Melanoma

https://www.health.harvard.edu/cancer/save-your-skin-from-cancer

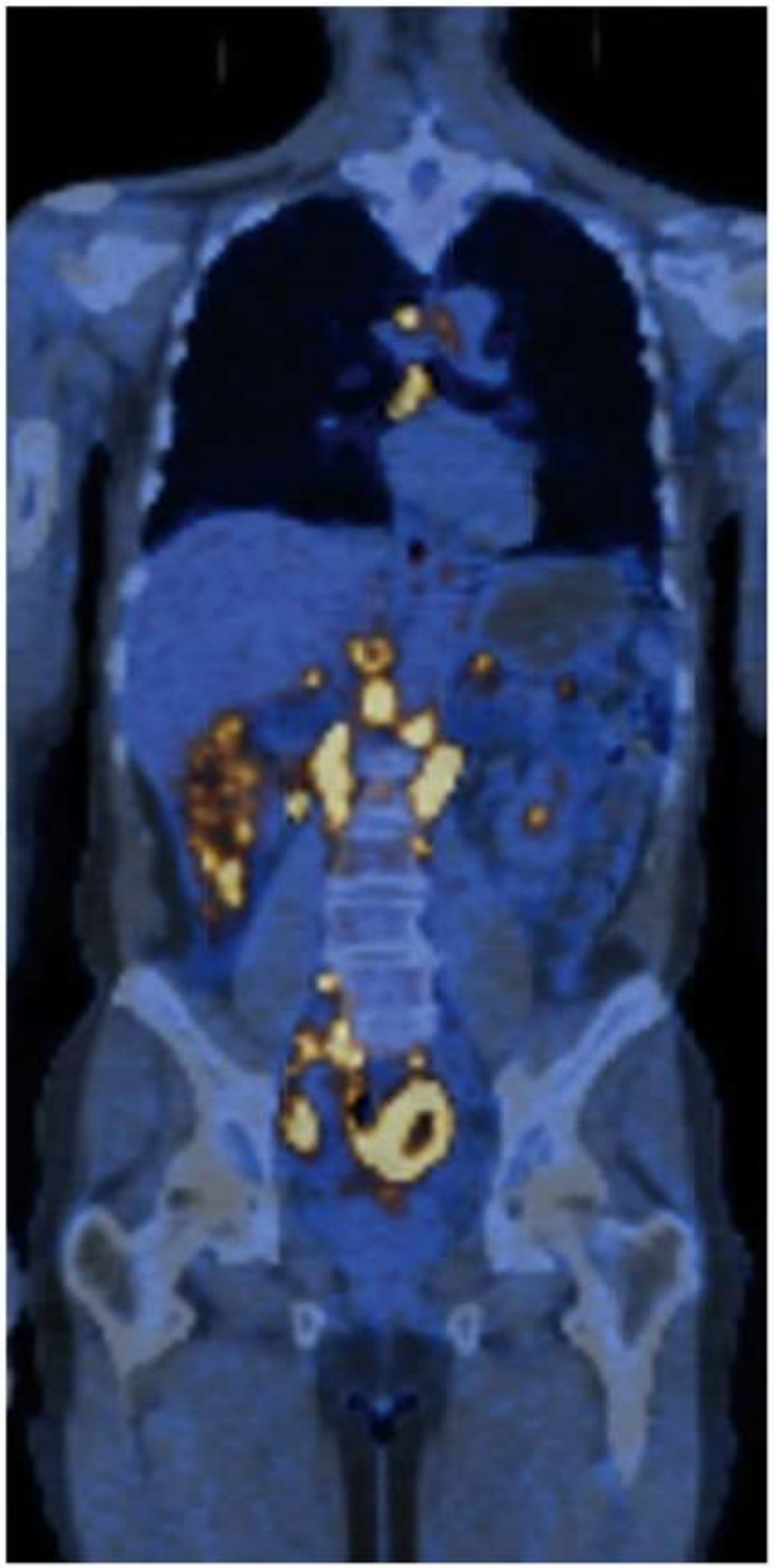


Figure 20-1 Molecular Biology of the Cell 6e (© Garland Science 2015)

yellow: metastasis

Cancer cells defined by:

reproduce without, or in defiance of, normal signals

invade and colonize areas reserved for other cells

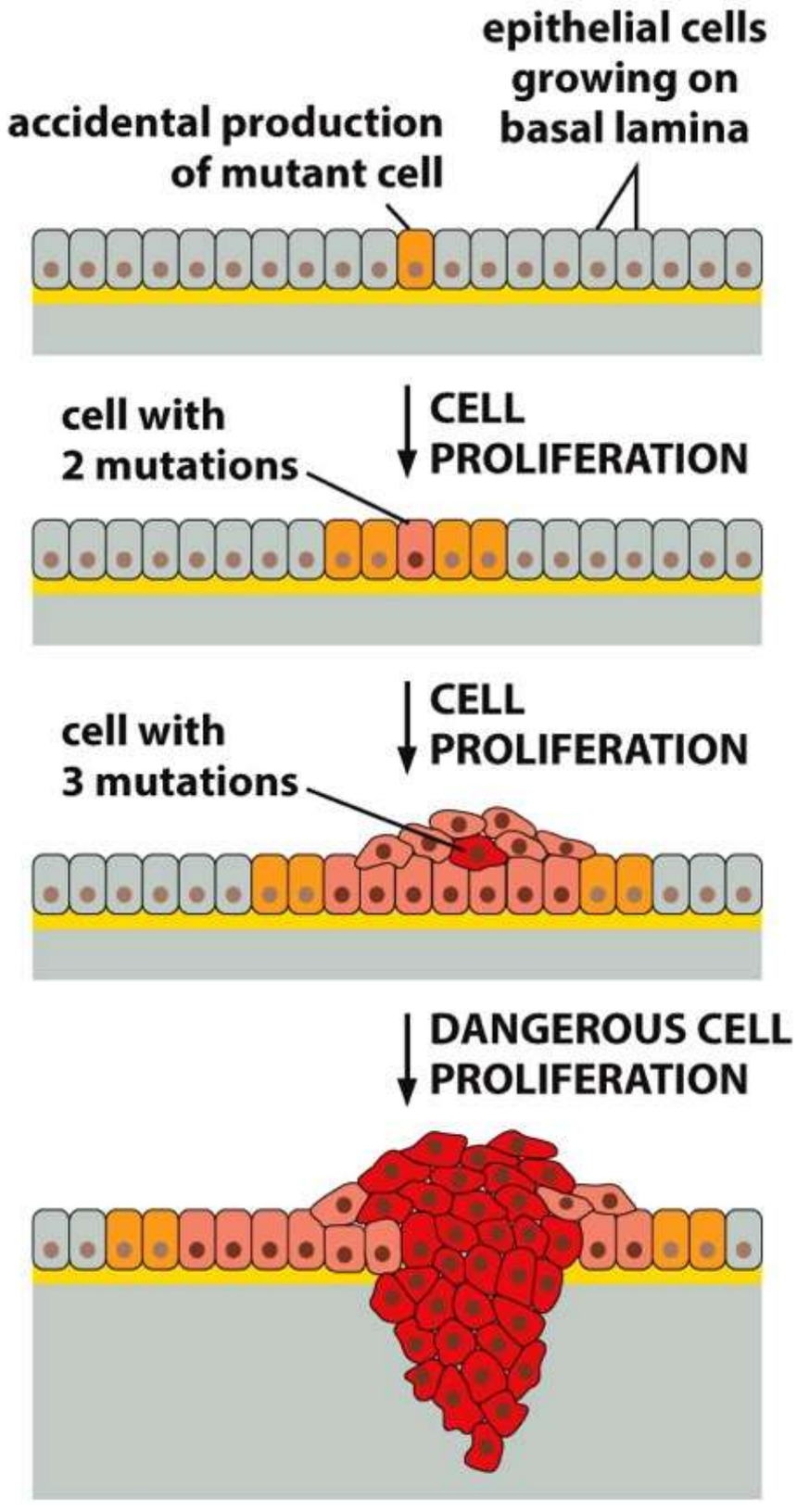
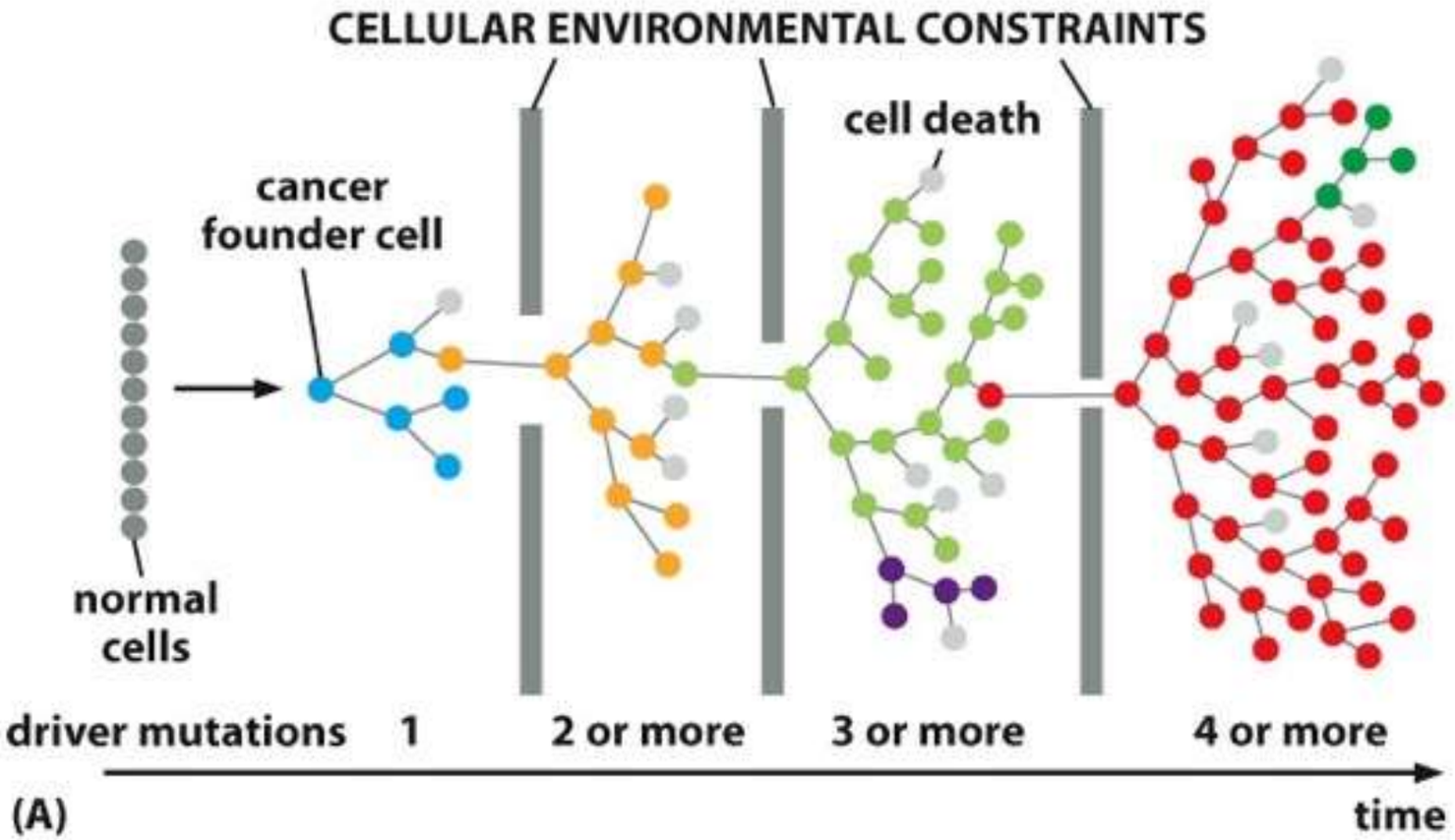


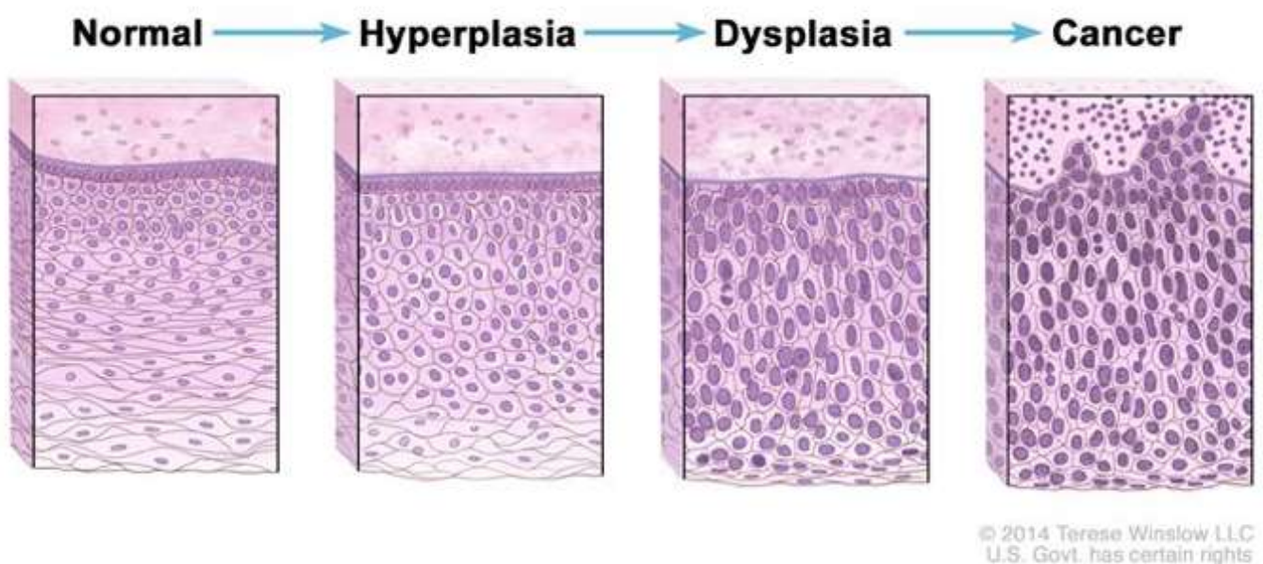
Figure 20-9 Molecular Biology of the Cell 6e (© Garland Science 2015)

Multiple mutations are required to overwhelm normal controls and drive cancer progression

Cancer cells evolve through a series of mutations



***hyperplasia**: increased cell numbers*



***dysplasia**: abnormal looking cells (may not be cancerous)*

Cancers can be defined by tissue of origin...

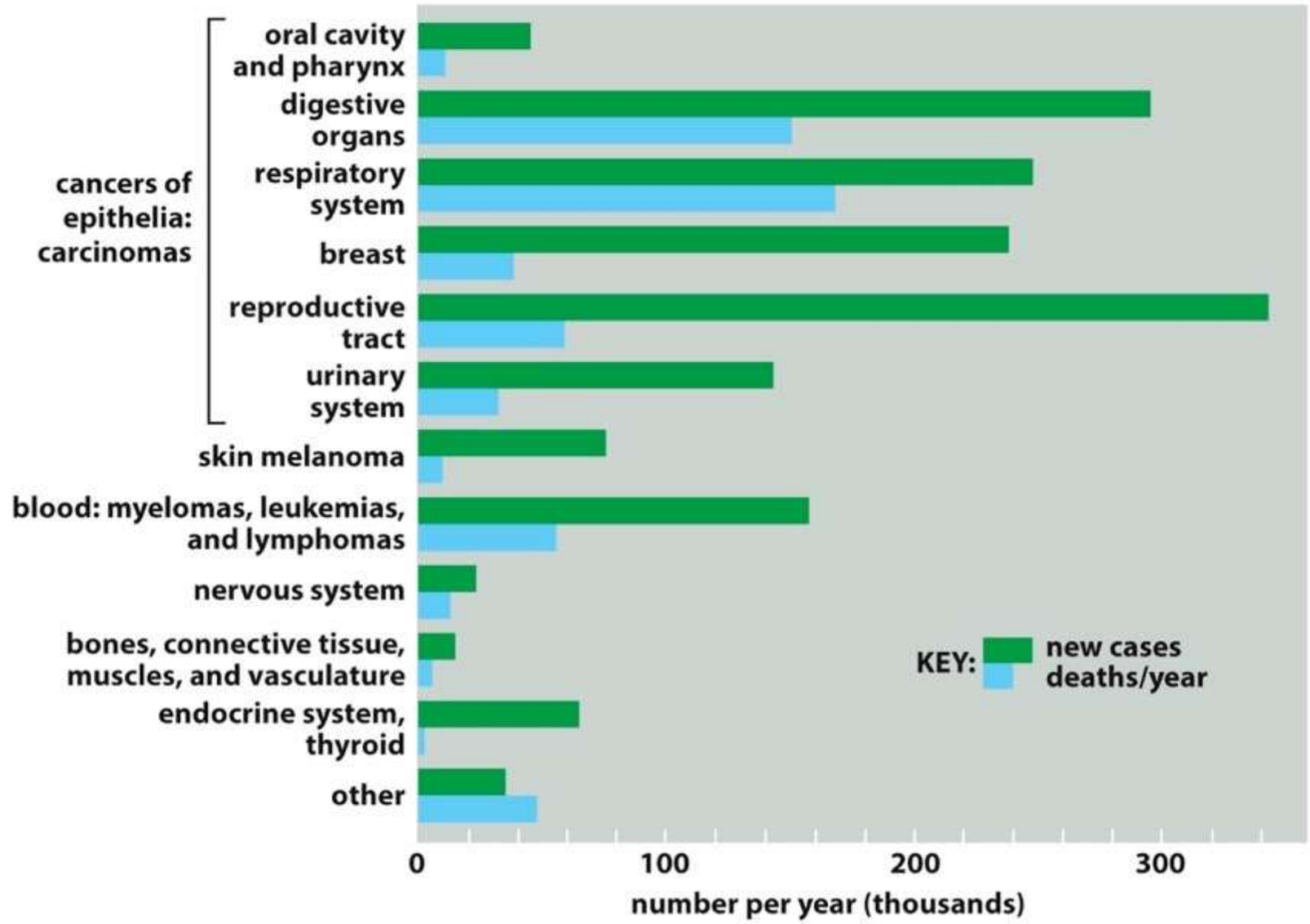


Figure 20-2 Molecular Biology of the Cell 6e (© Garland Science 2015)

carcinomas: epithelial cells
sarcomas: connective or muscle
leukemias and lymphomas: blood cells

....or by the driver mutations and the pathways they disrupt

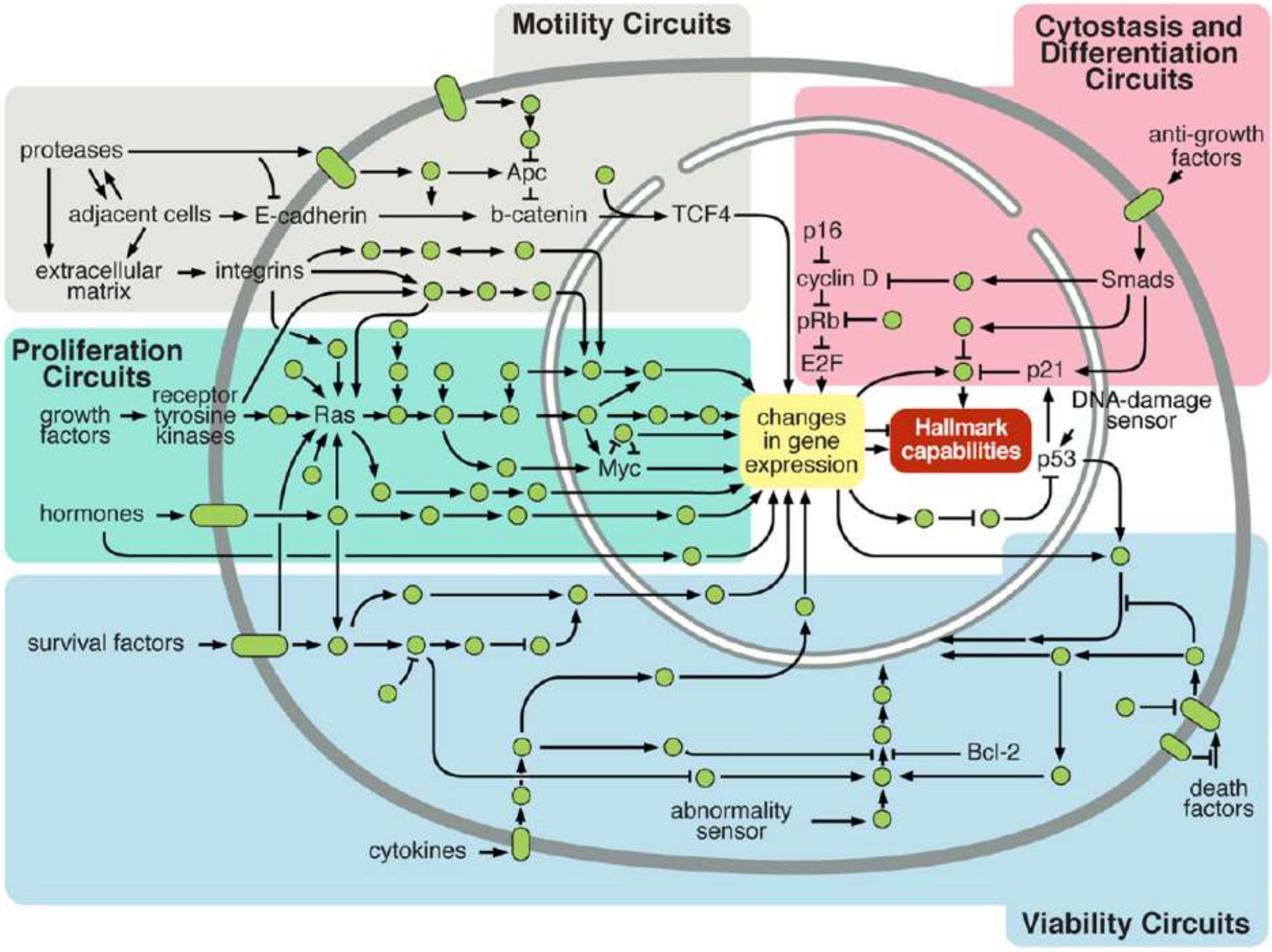
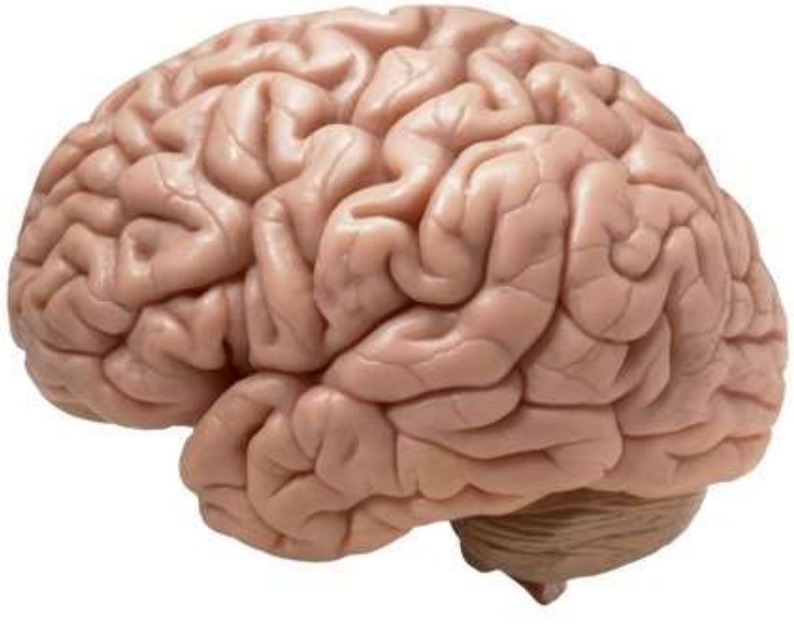


Figure 2. Intracellular Signaling Networks Regulate the Operations of the Cancer Cell

Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]
[1]The Swiss Institute for Experimental Cancer Research (ISREC), School of Life Sciences, EPFL, Lausanne CH-1015, Switzerland
[2]The Department of Biochemistry & Biophysics, UCSF, San Francisco, CA 94158, USA
[3]Whitehead Institute for Biomedical Research, Ludwig/MIT Center for Molecular Oncology, and MIT Department of Biology, Cambridge, MA 02142, USA
*Correspondence: dh@epfl.ch (D.H.), weinberg@wi.mit.edu (R.A.W.)
DOI 10.1016/j.cell.2011.02.013

Glioblastoma



Mutations in 3 circuits commonly hit (~75%)

Broadly, these control:

Cell Growth

Cell Division

Responses to Stress and DNA Damage

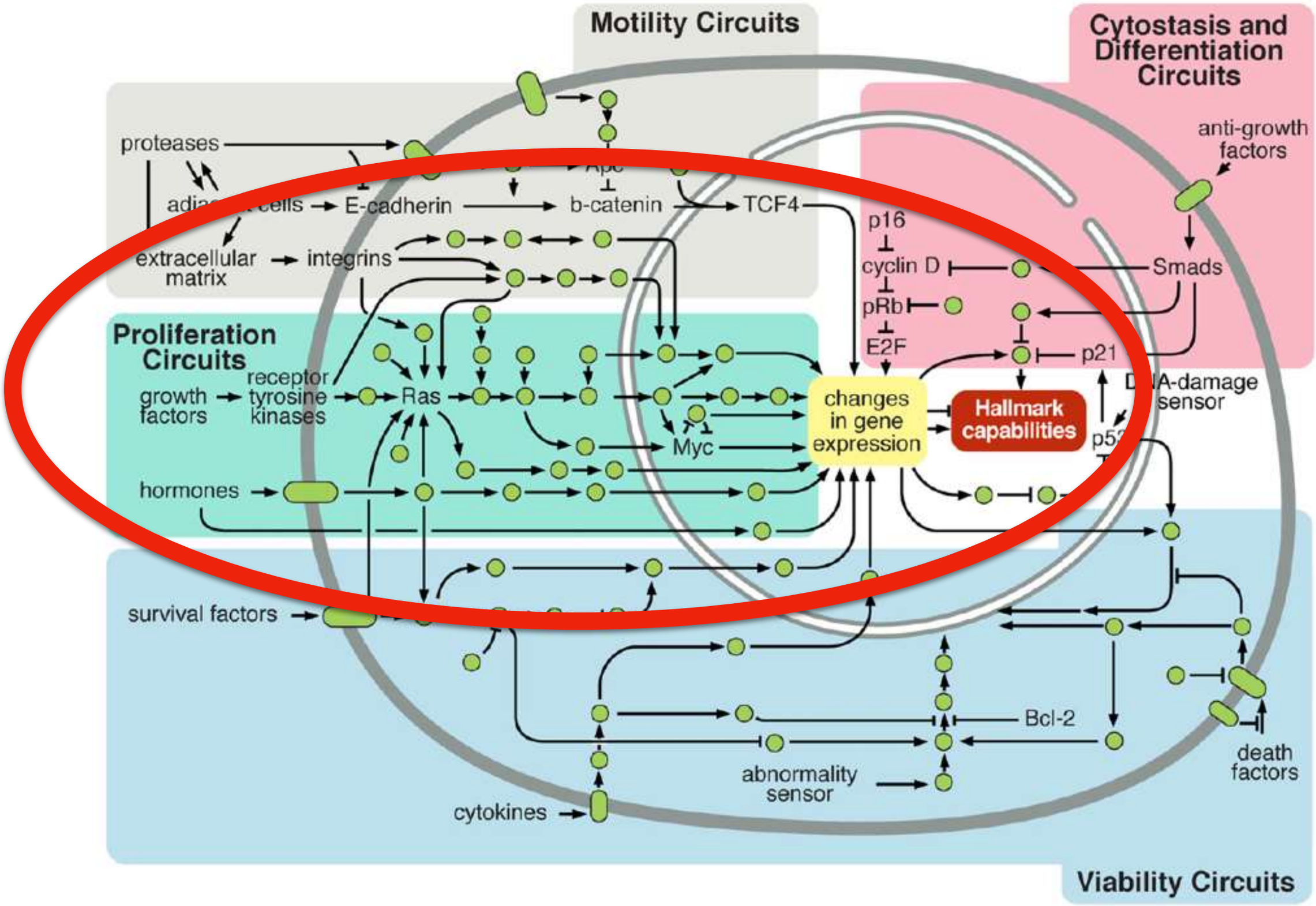


Figure 2. Intracellular Signaling Networks Regulate the Operations of the Cancer Cell

Cells multiply (proliferate) by dividing

Two views of the cell division cycle

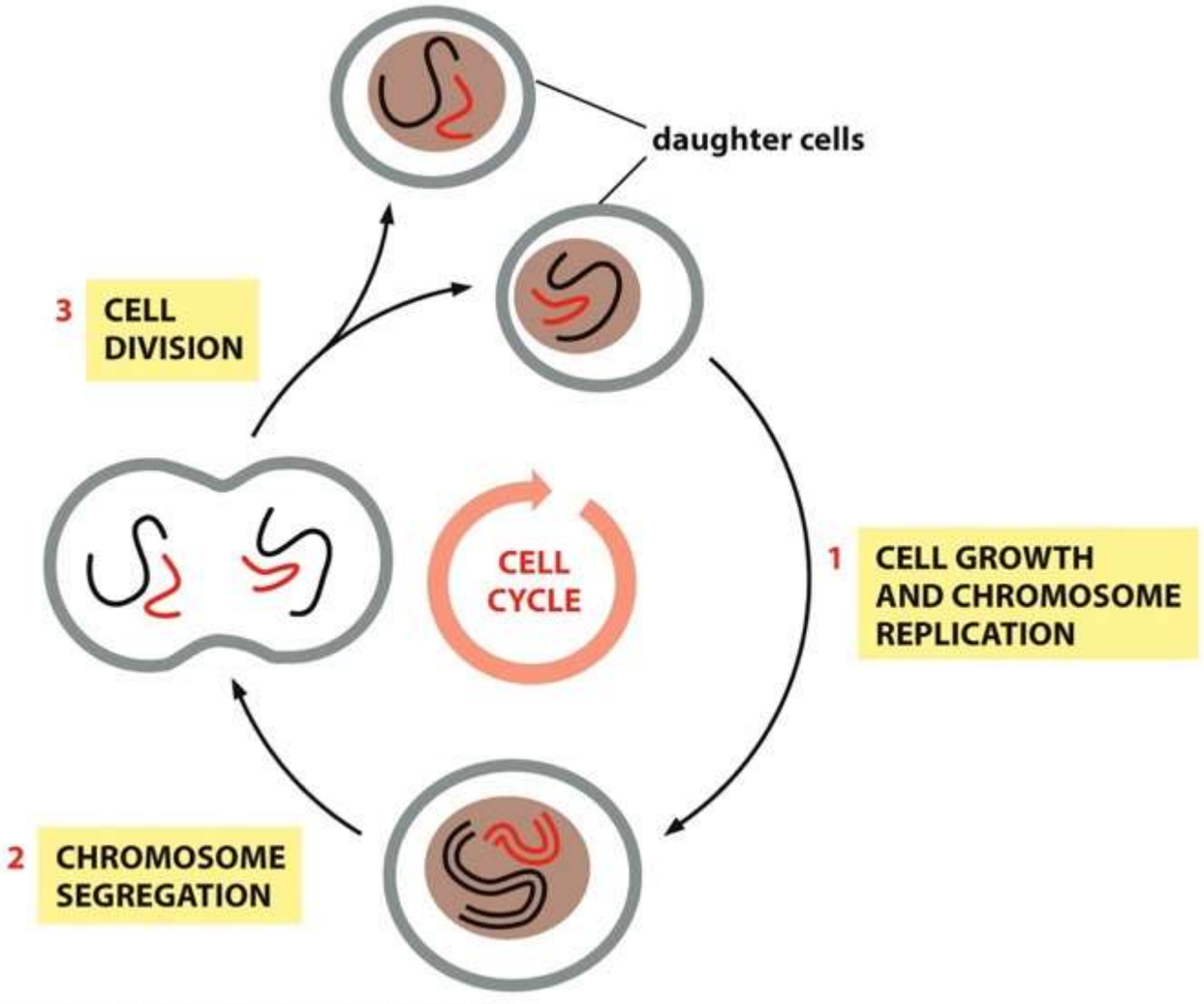


Figure 17-1 Molecular Biology of the Cell 6e (© Garland Science 2015)

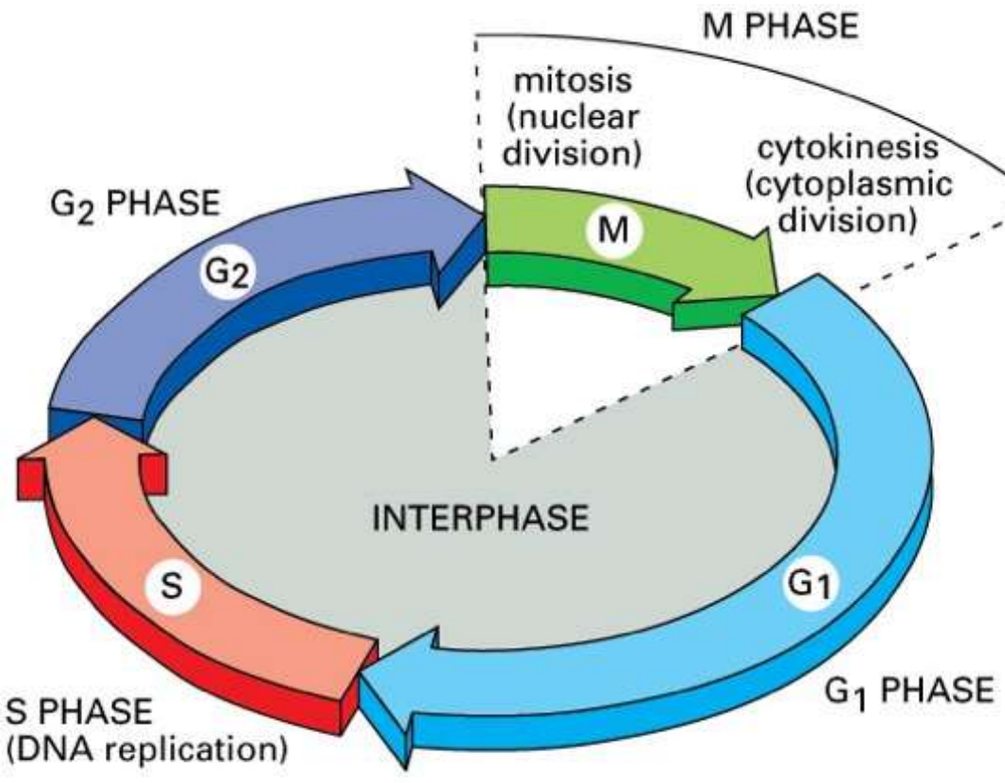


Figure 17–3. Molecular Biology of the Cell, 4th Edition.

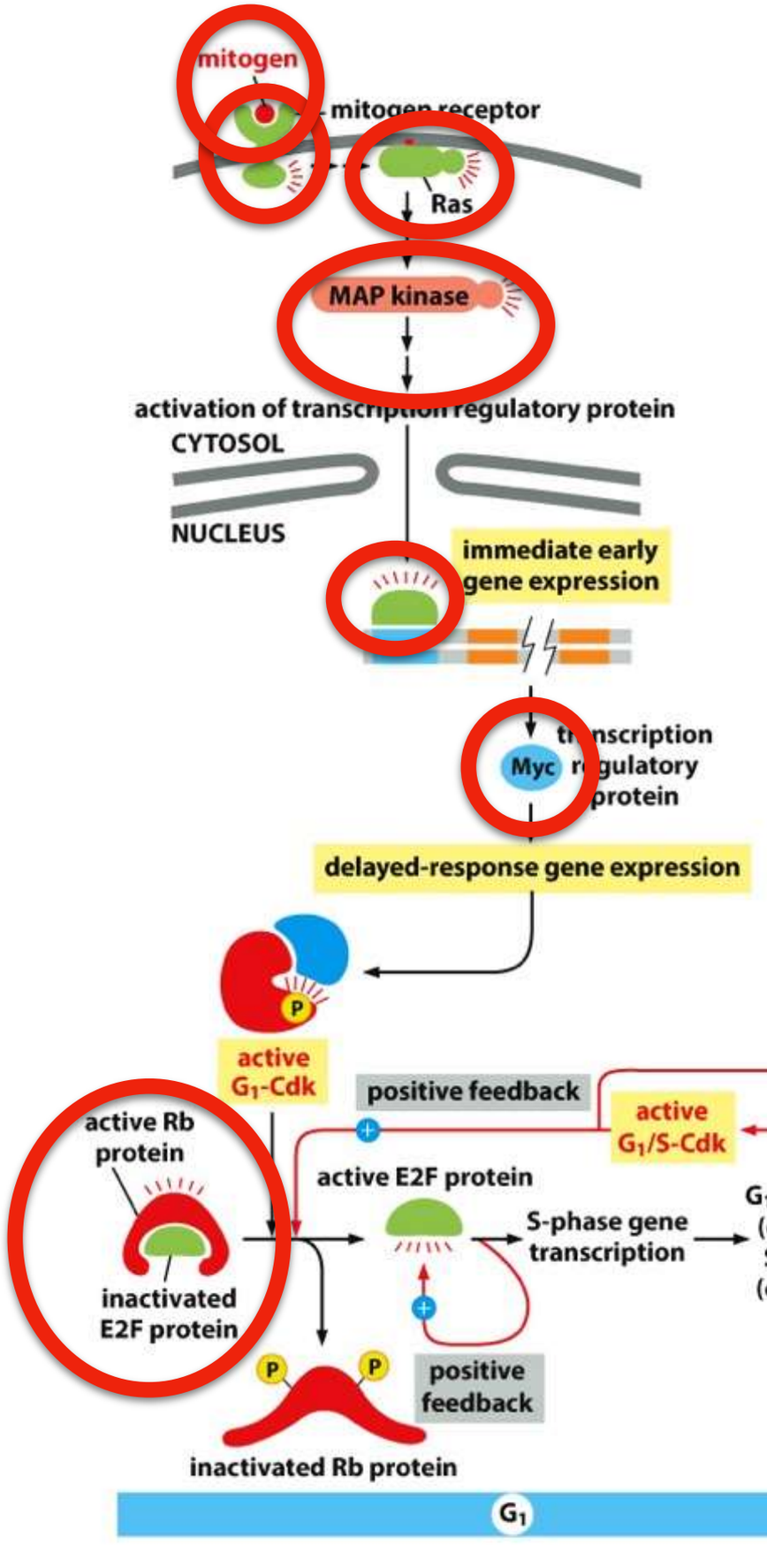


Figure 17-61 Molecular Biology of the Cell 6e (© Garland Science 2015)

A common pathway triggering entry into the cell cycle

and proteins frequently mutated in cancer cells

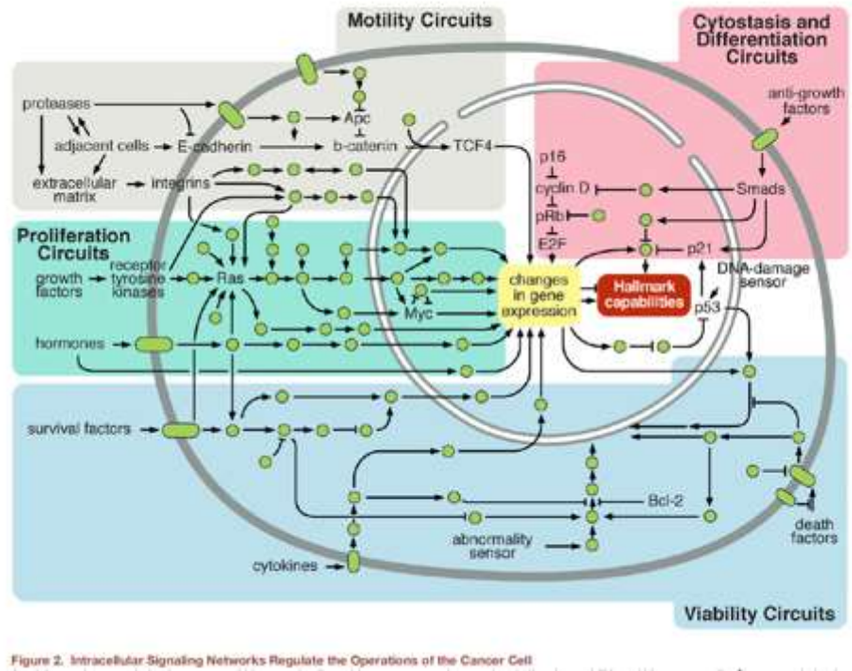


Figure 2. Intracellular Signaling Networks Regulate the Operations of the Cancer Cell

The actual cell division stage: mitosis and cytokinesis

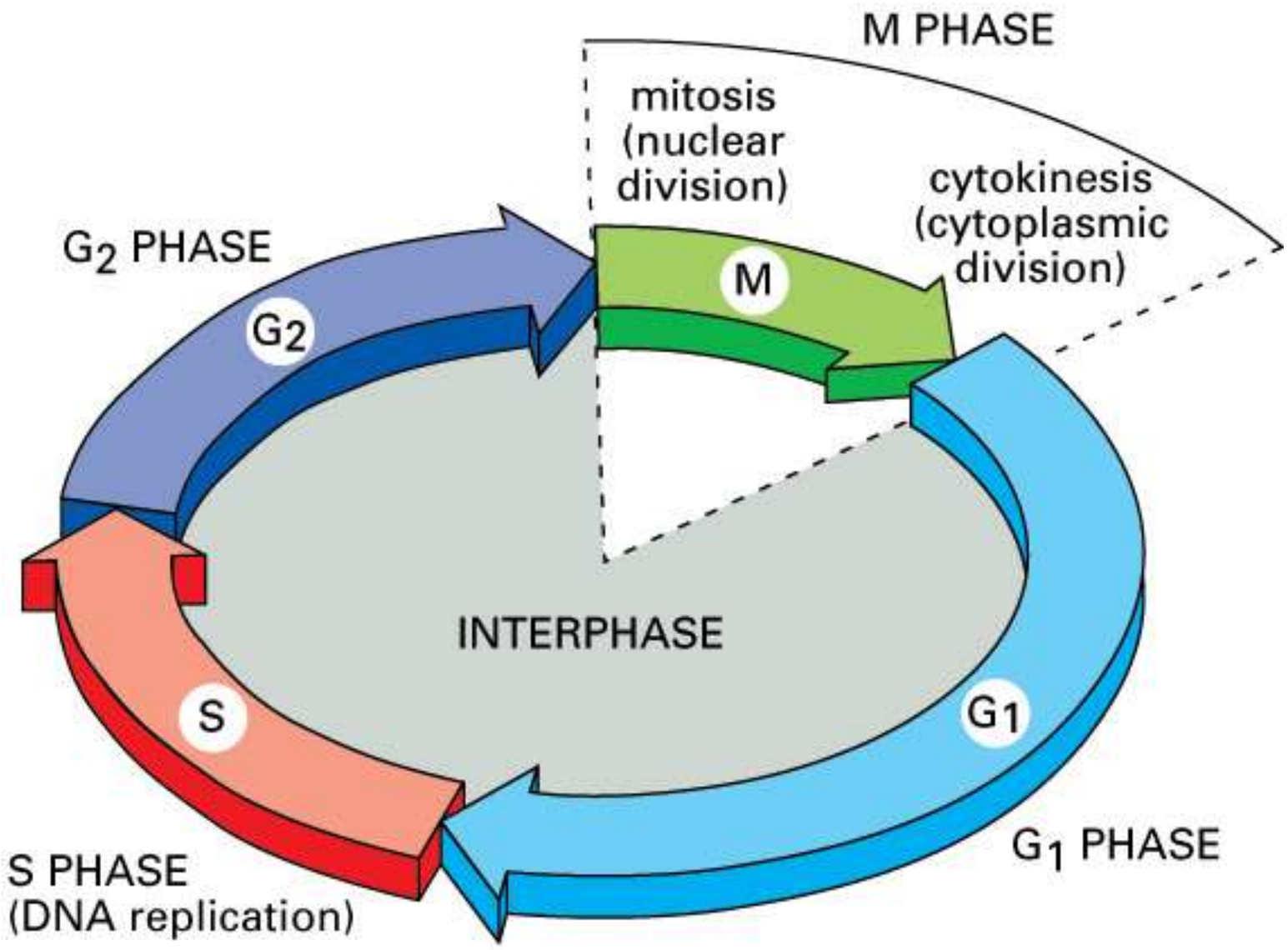
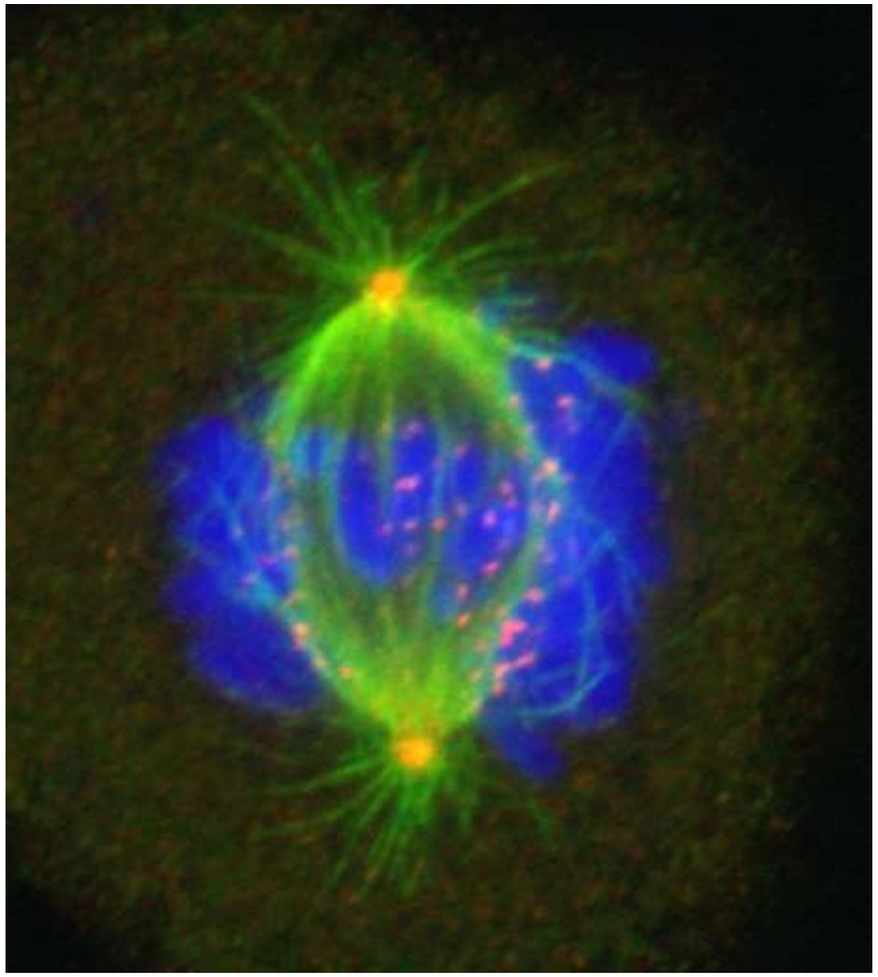
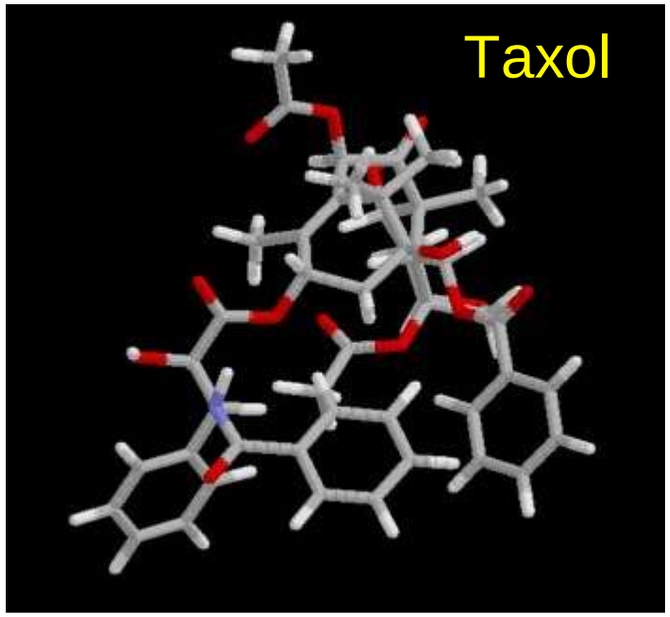


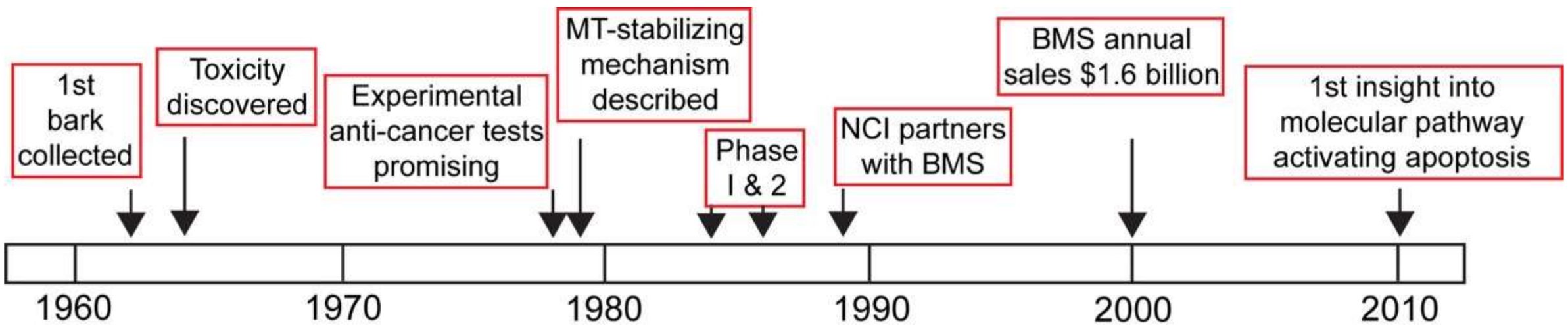
Figure 17–3. Molecular Biology of the Cell, 4th Edition.

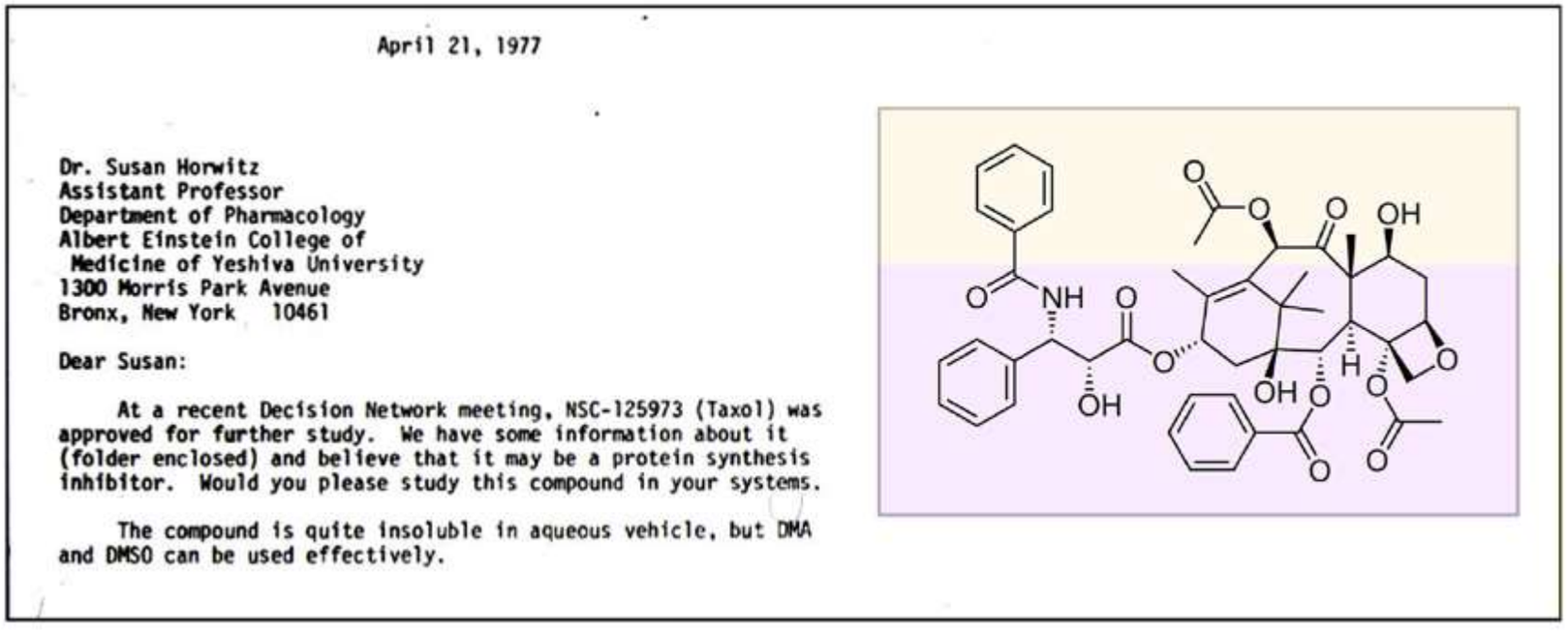
Some of the most successful chemotherapies target mitosis





A Brief History of Taxol as a Chemotherapy





April 21, 1977

Dr. Susan Horwitz
Assistant Professor
Department of Pharmacology
Albert Einstein College of
Medicine of Yeshiva University
1300 Morris Park Avenue
Bronx, New York 10461

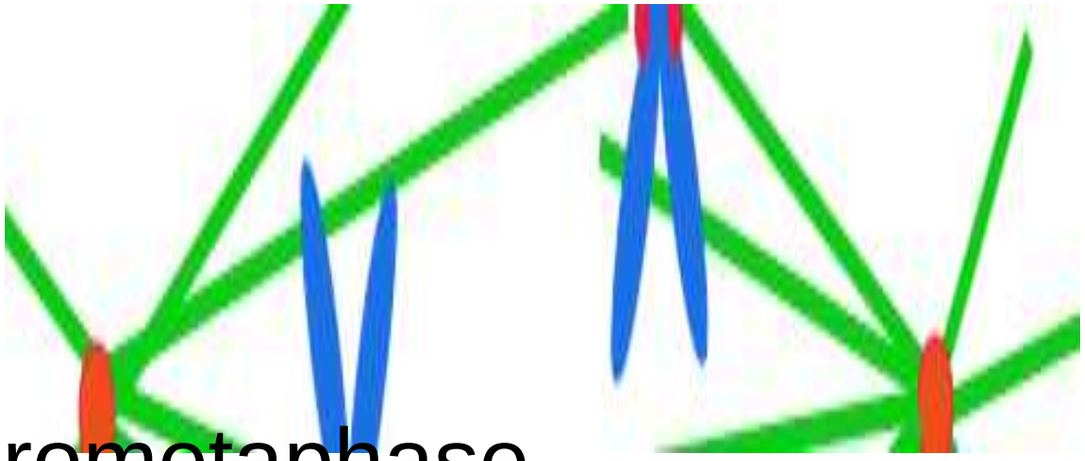
Dear Susan:

At a recent Decision Network meeting, NSC-125973 (Taxol) was approved for further study. We have some information about it (folder enclosed) and believe that it may be a protein synthesis inhibitor. Would you please study this compound in your systems.

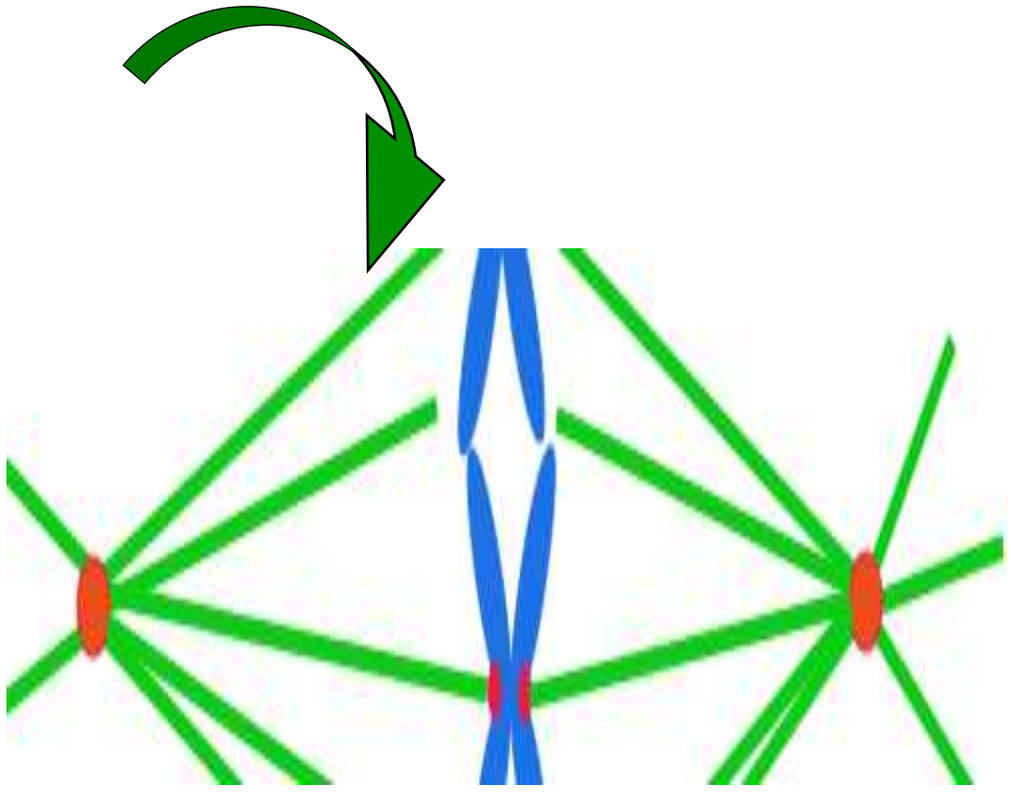
The compound is quite insoluble in aqueous vehicle, but DMA and DMSO can be used effectively.

Susan Horwitz. Reflections on my life with Taxol. Cell. 177: 502-505.

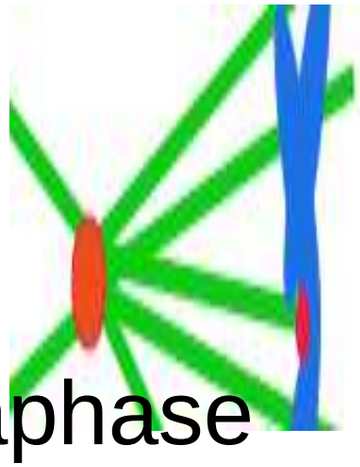
Mitosis Overview



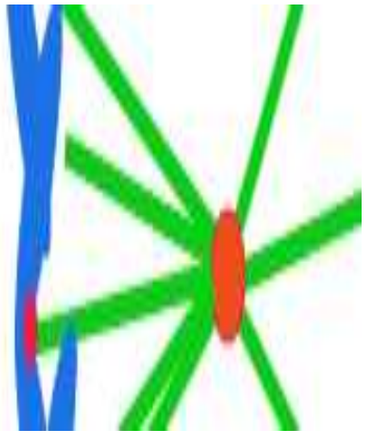
prometaphase



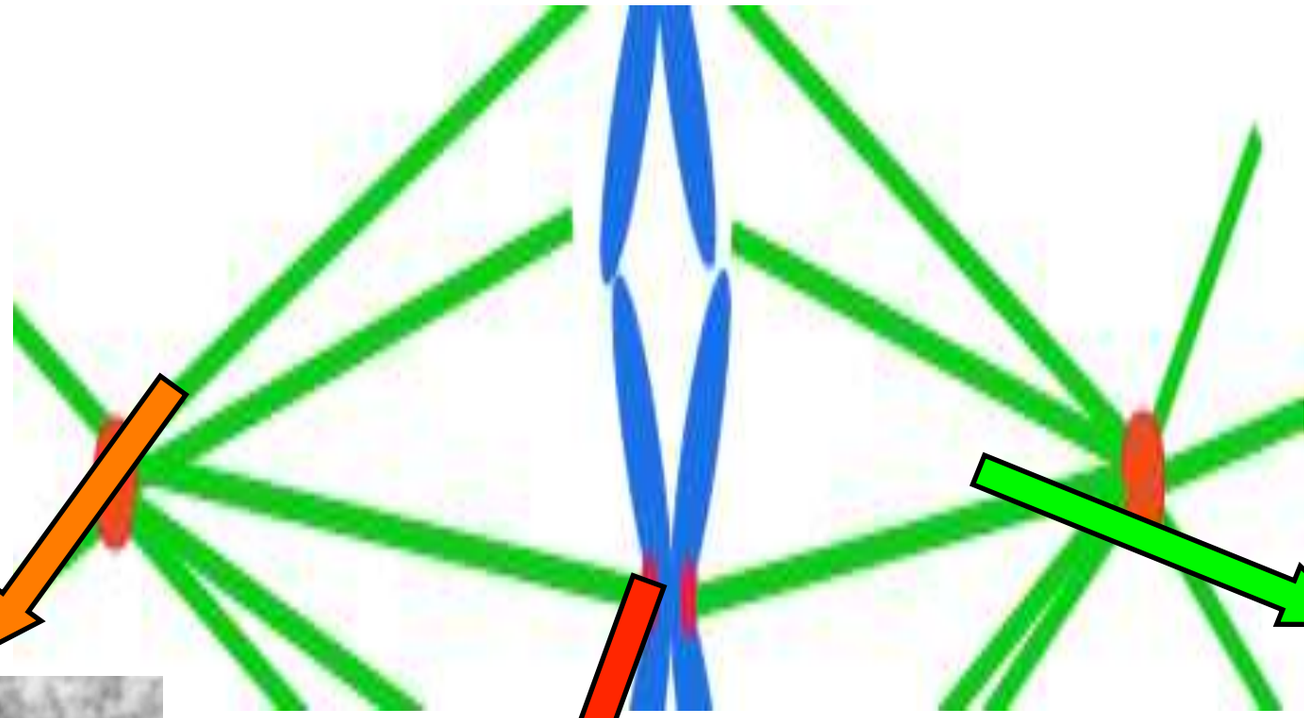
metaphase

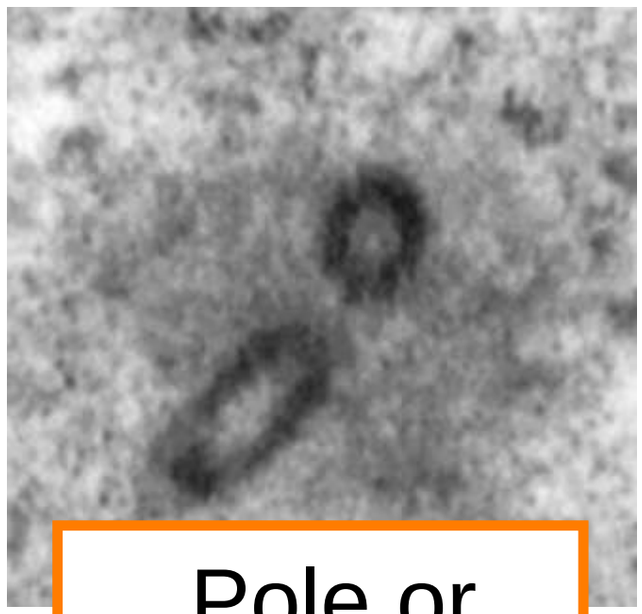


anaphase

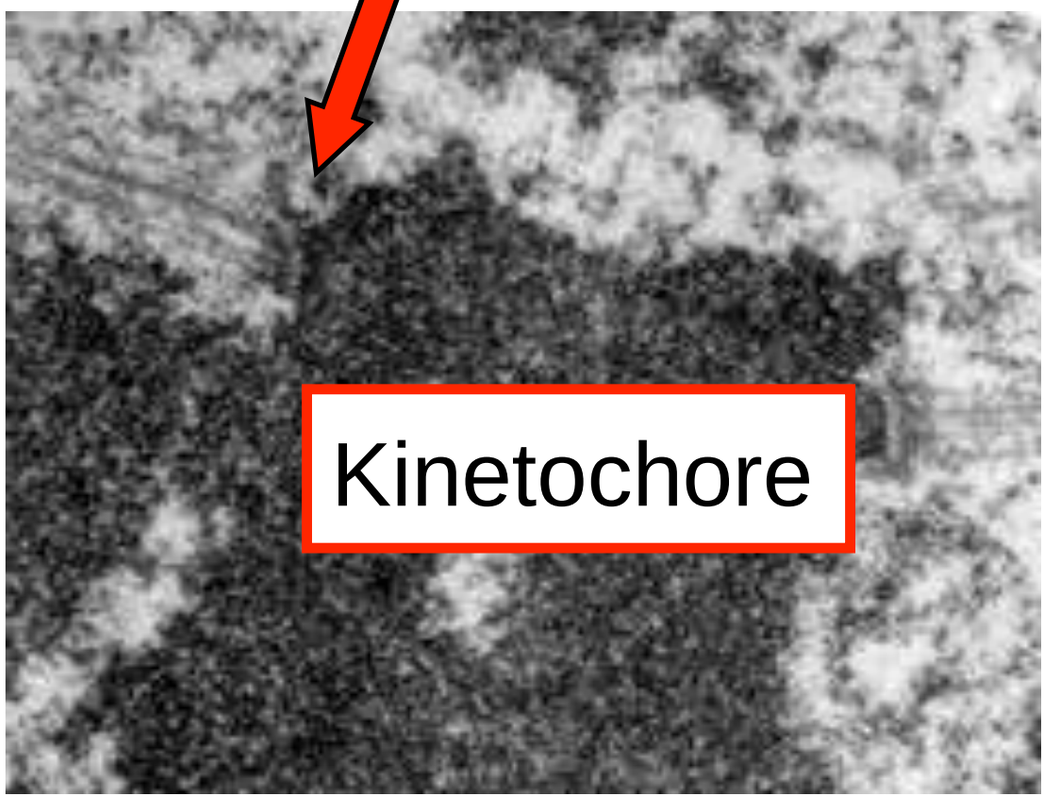


spindle structure

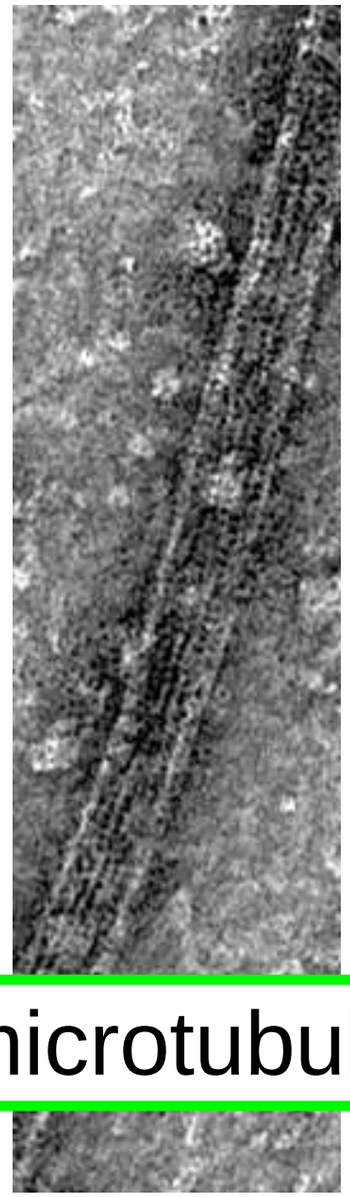




Pole or centrosome

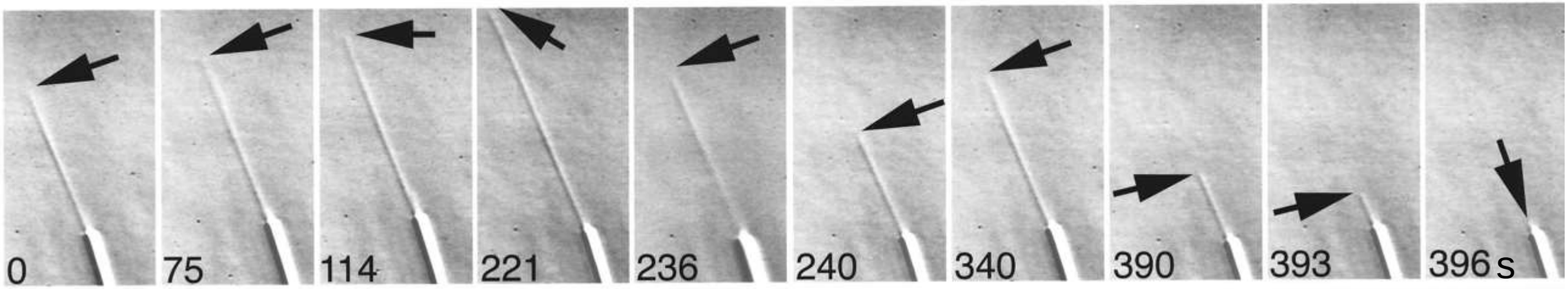


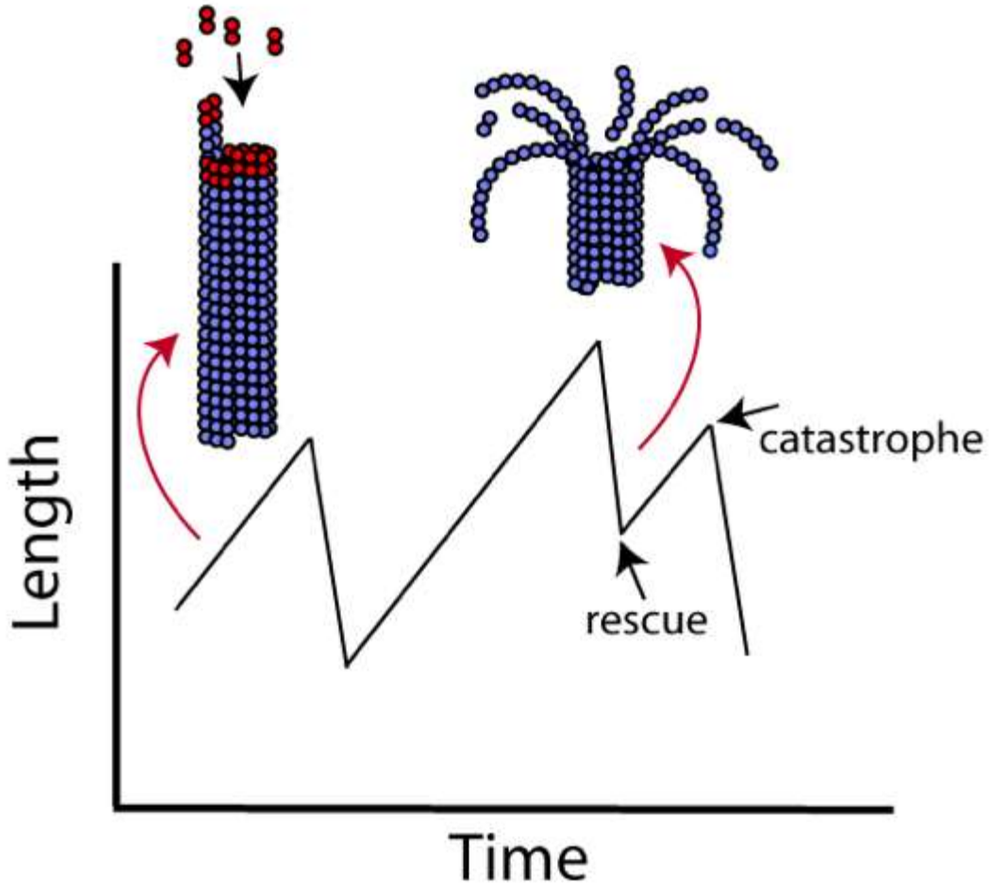
Kinetochore



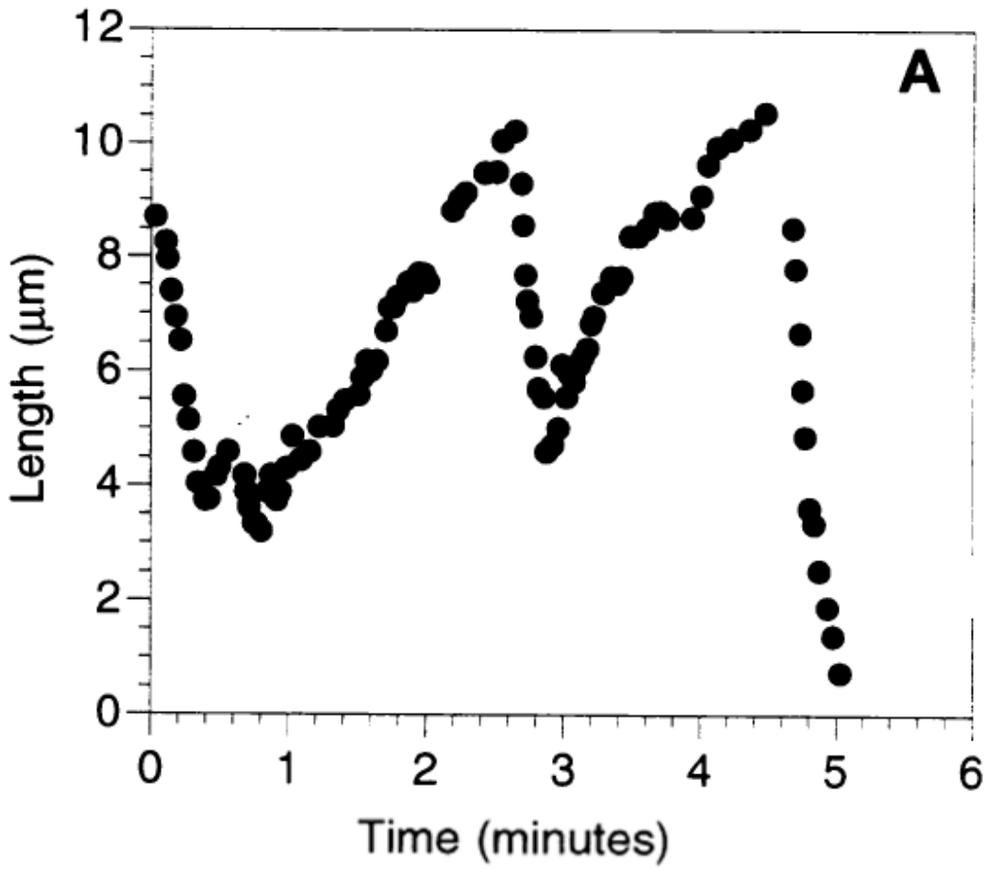
microtubule

Microtubules are dynamic protein polymers

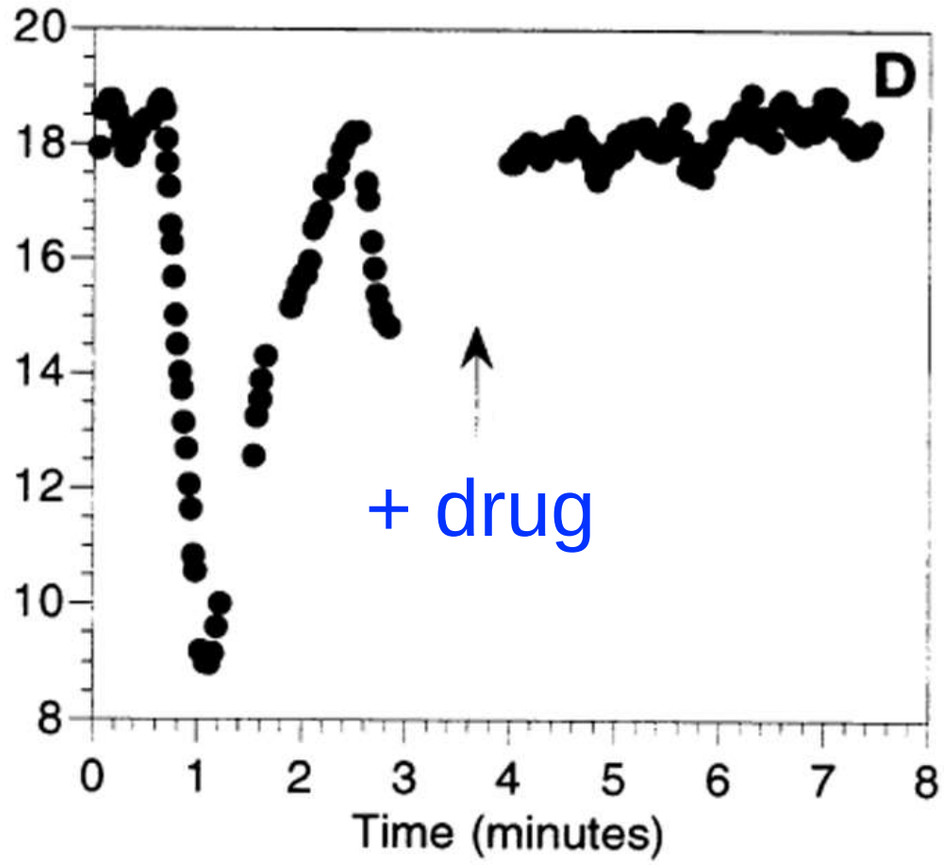




Taxol blocks microtubule disassembly

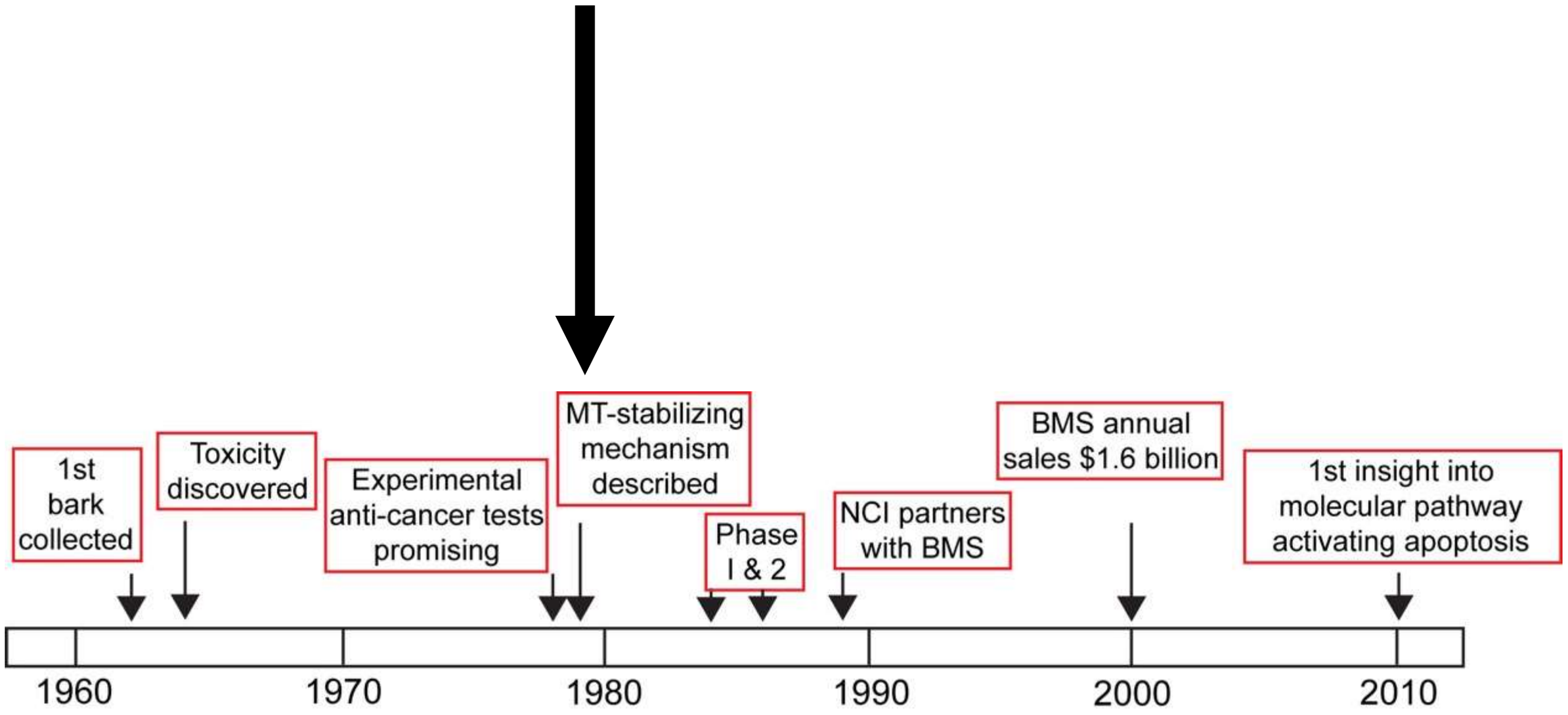


Untreated

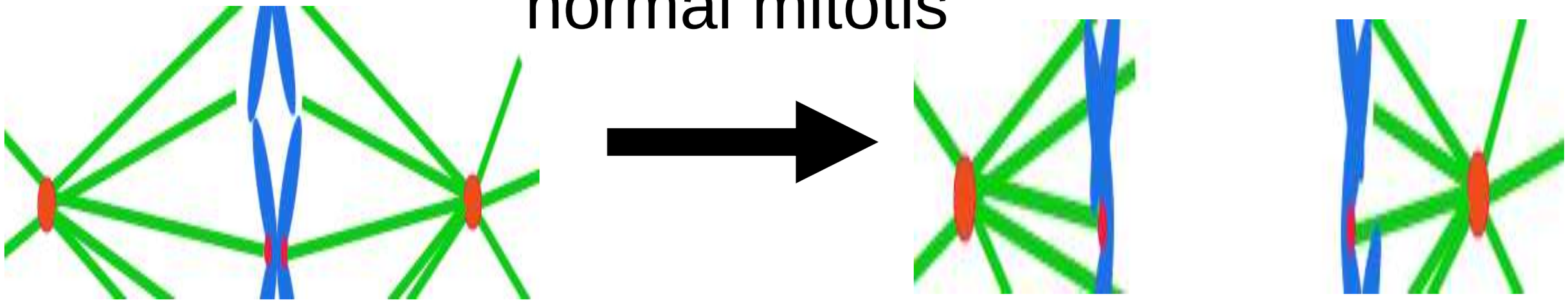


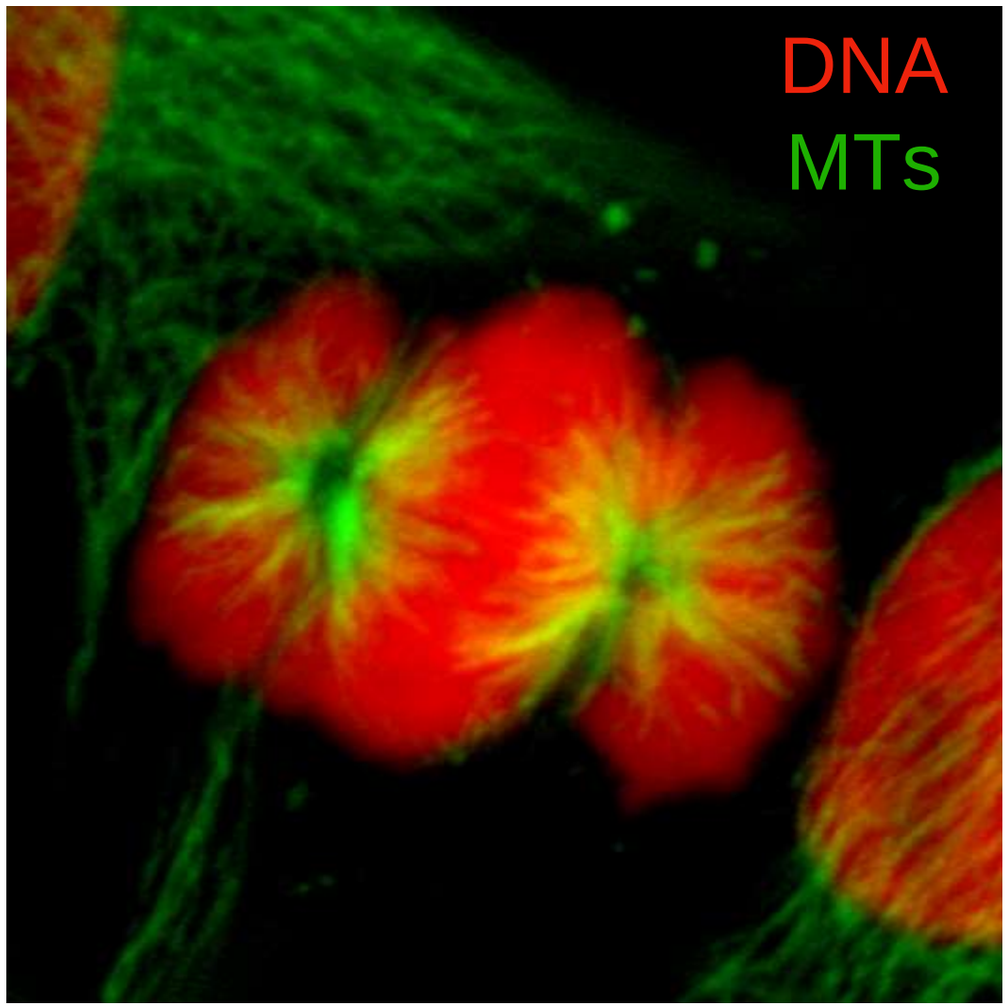
Vasquez et al., 1997.

Unique mode of action (at the time) led to highly successful clinical trials

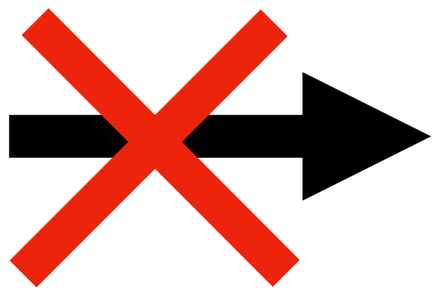


normal mitotis





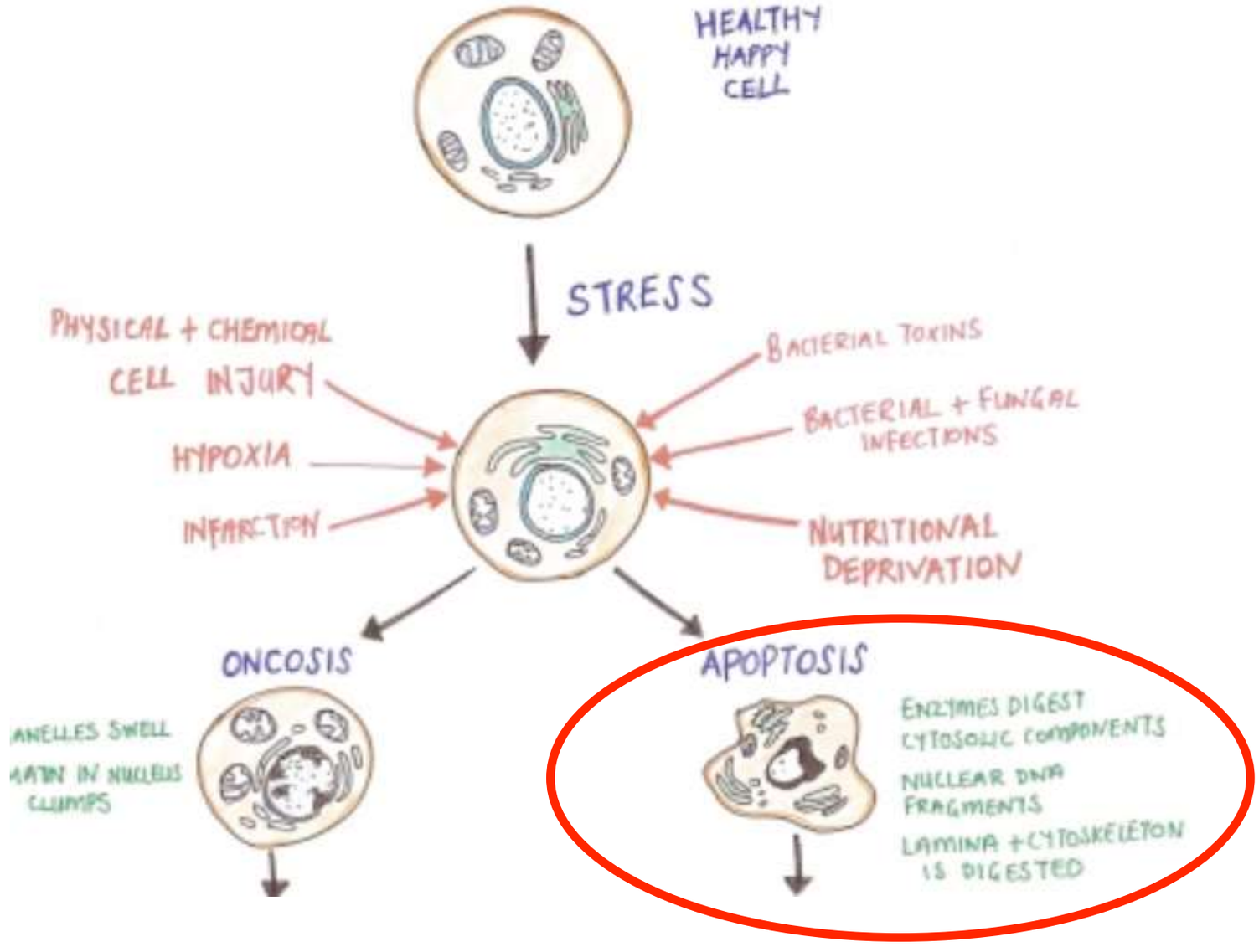
+ Taxol



prolonged
mitotic
block

Stuck in Mitosis: Activates Cell Death Pathway

prolonged mitotic block



Taxol and other chemotherapies come with major side effects

Cancer Cells

Normal Cells

<u>Newer approaches</u>

**combat side effects*

*new therapies that target only cancer cells

Avoid death of normal cells: Target something novel in cancer cells

chronic myeloid leukemia

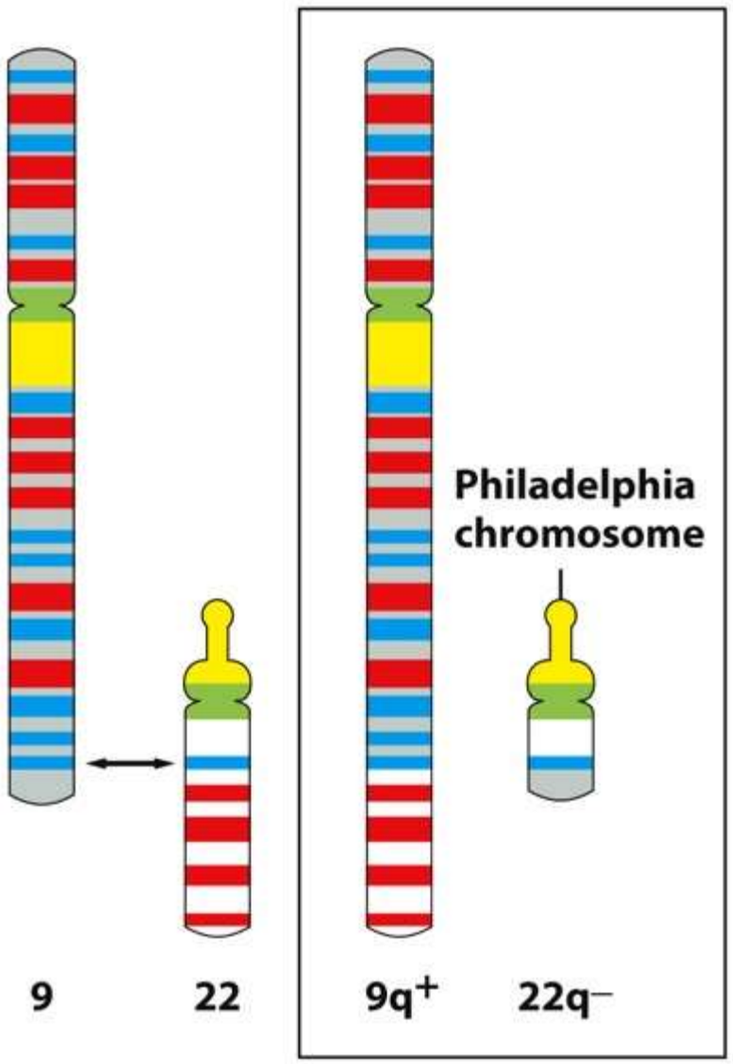


Figure 20-5 Molecular Biology of the Cell 6e (© Garland Science 2015)

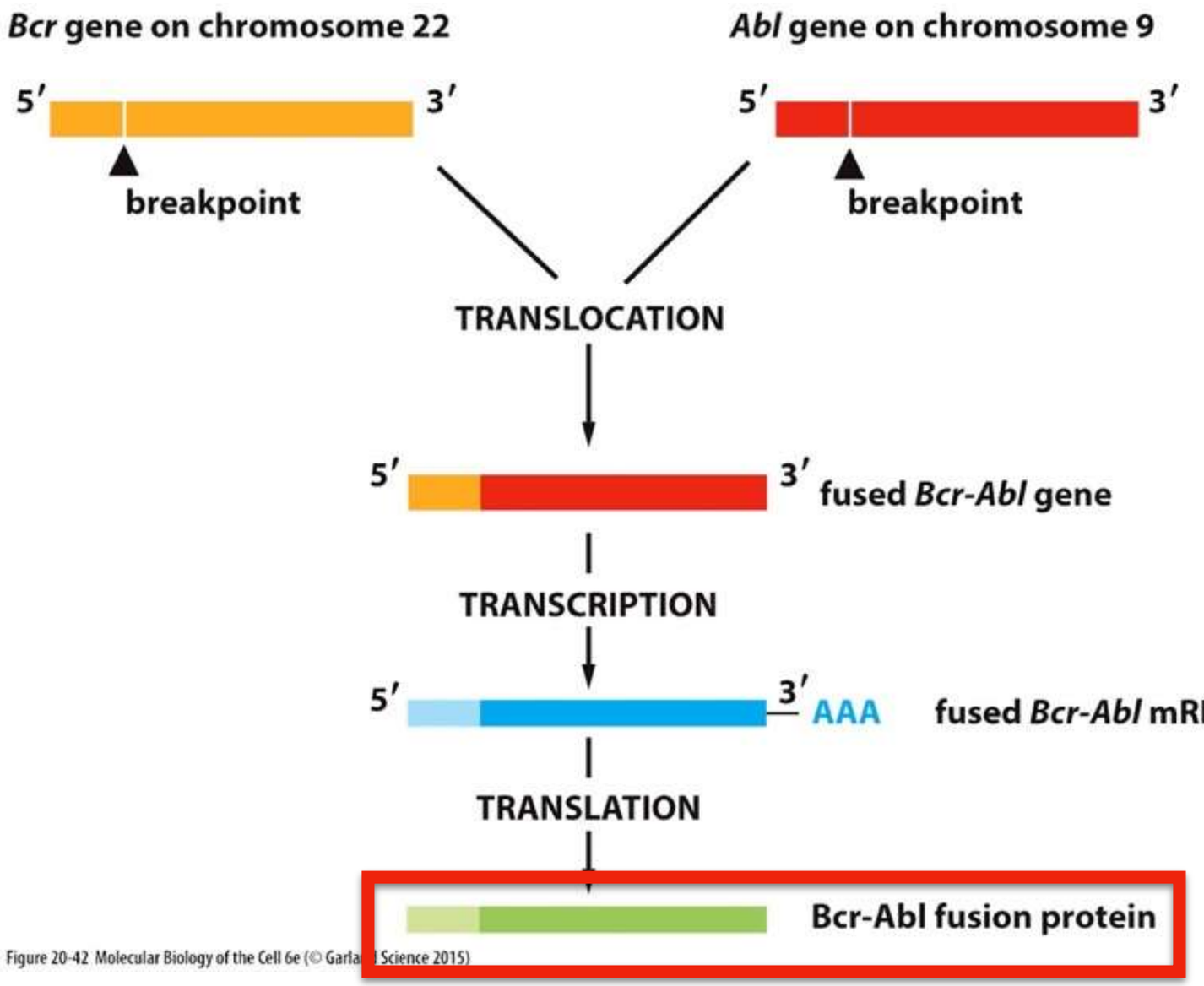


Figure 20-42 Molecular Biology of the Cell 6e (© Garland Science 2015)

Gleevec (drug) blocks Bcr-Abl fusion protein

Ras pathway is target for many inhibitors

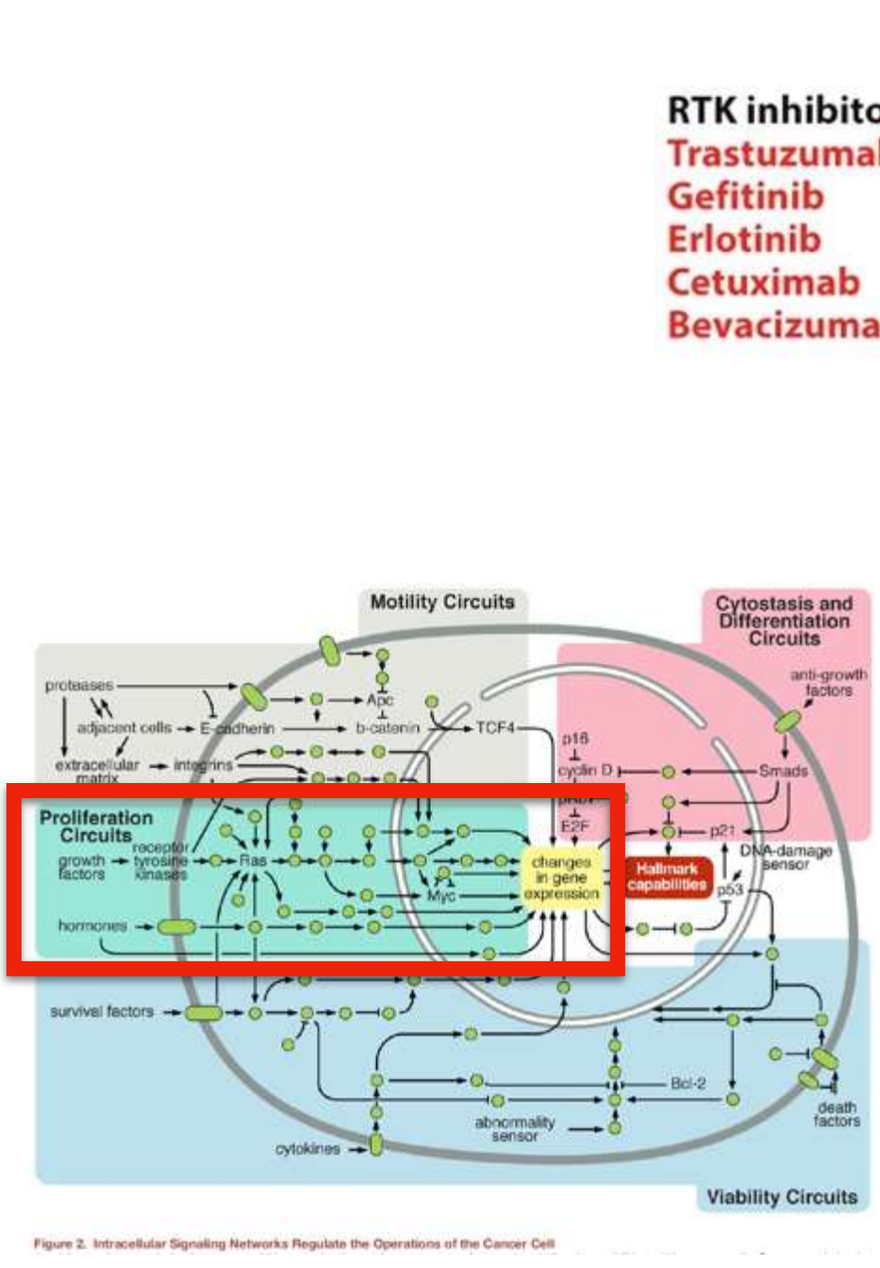


Figure 2. Intracellular Signaling Networks Regulate the Operations of the Cancer Cell

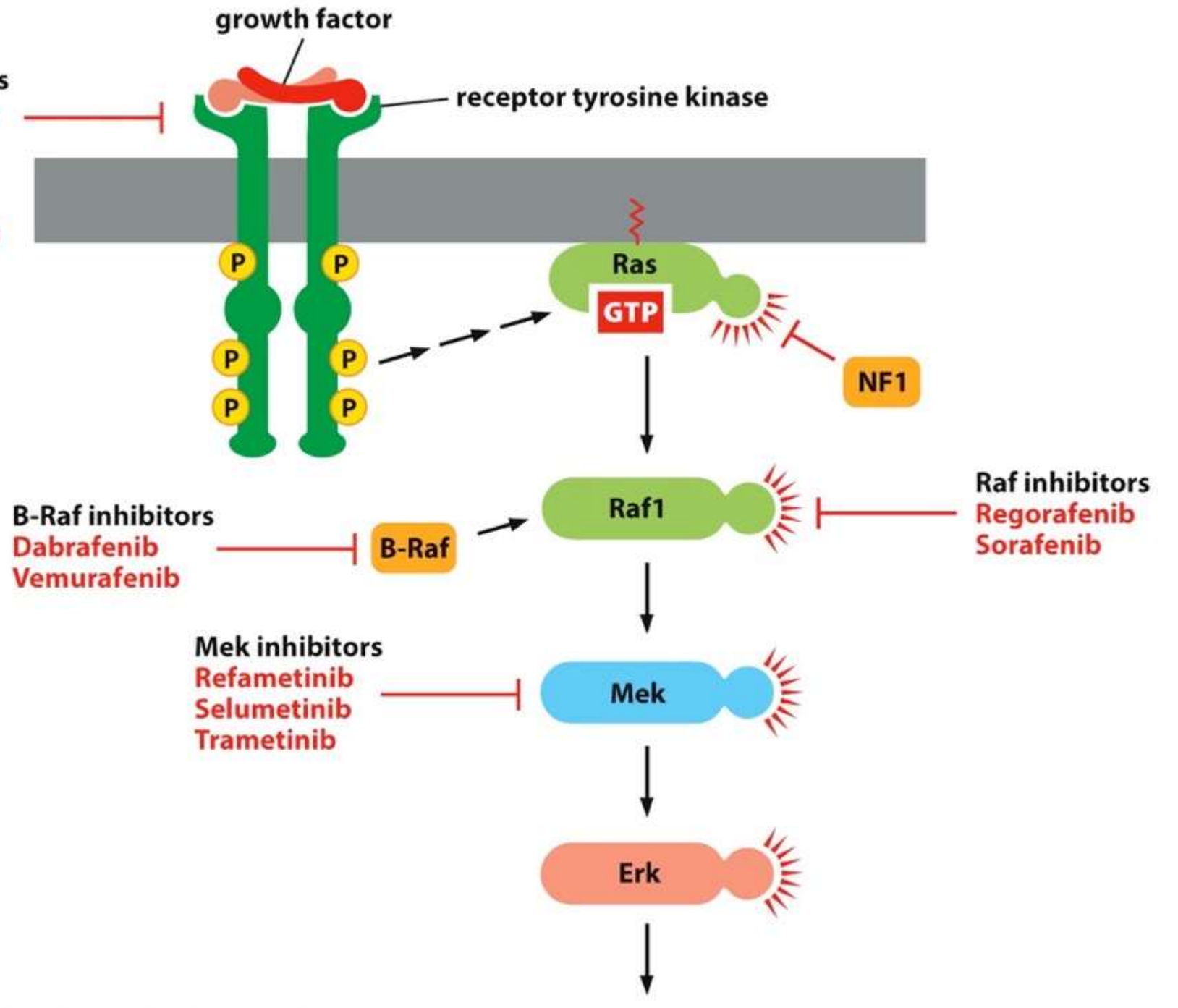
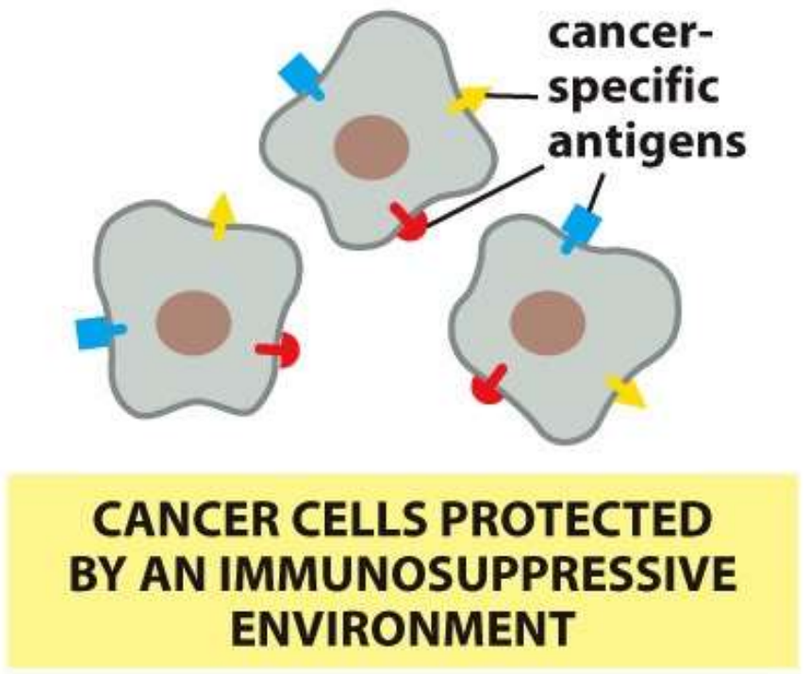


Figure 20-44 Molecular Biology of the Cell 6e (© Garland Science 2015)



Cancer cells protect themselves from detection by our immune system

Newer area for treatment - unmask cancer cells so immune system can attack

Mutations needed for metastasis are poorly understood

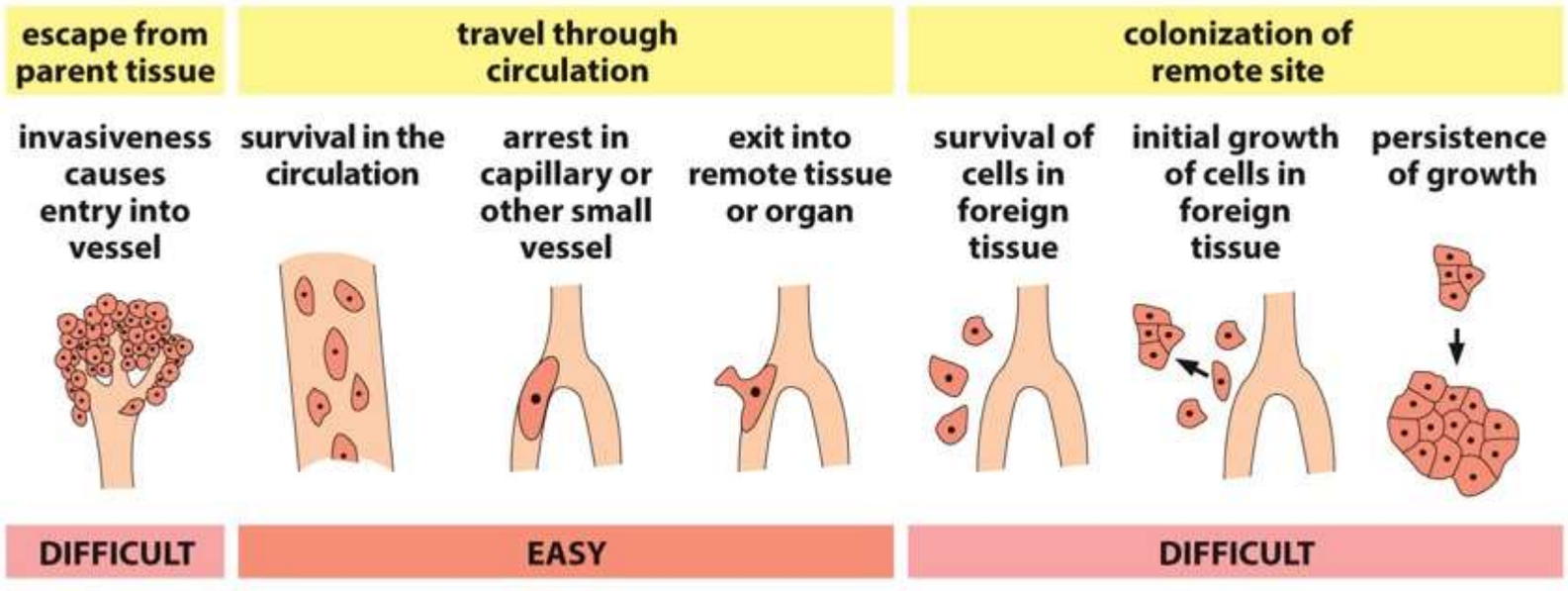
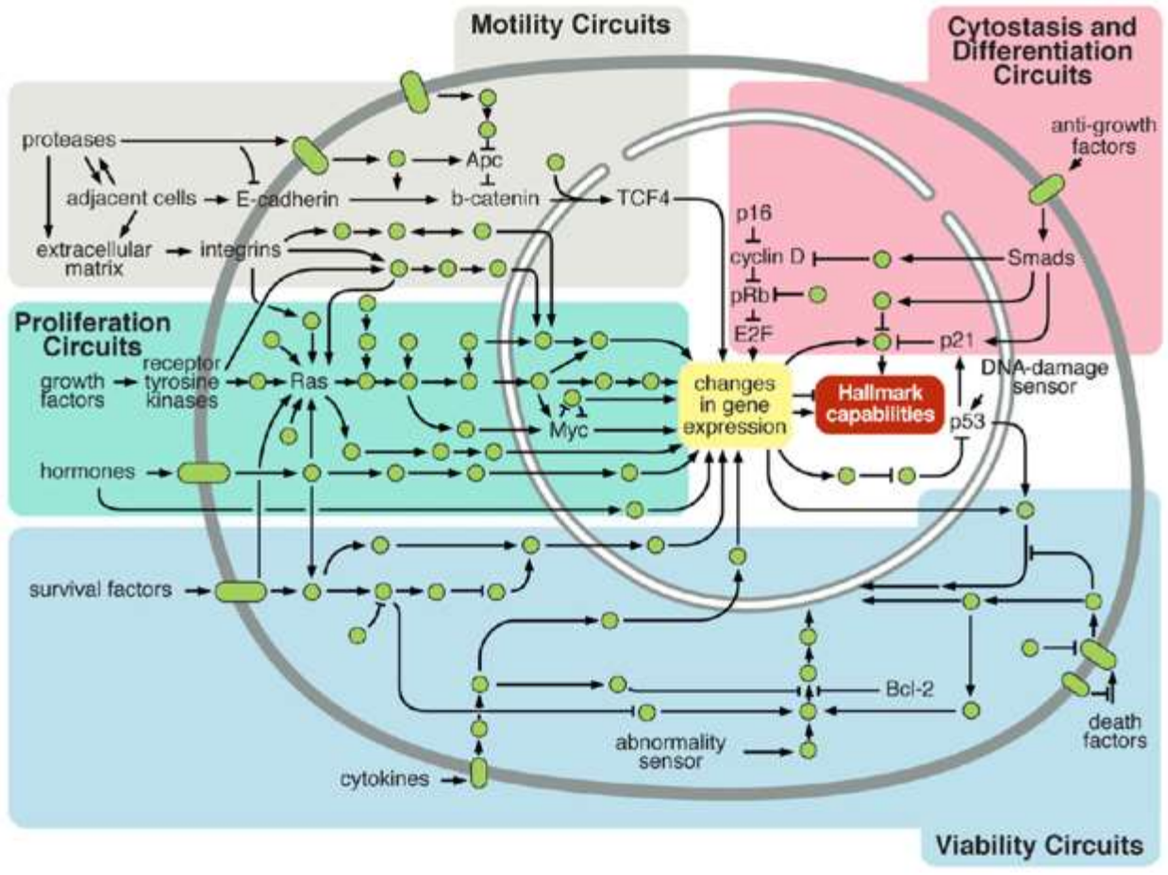
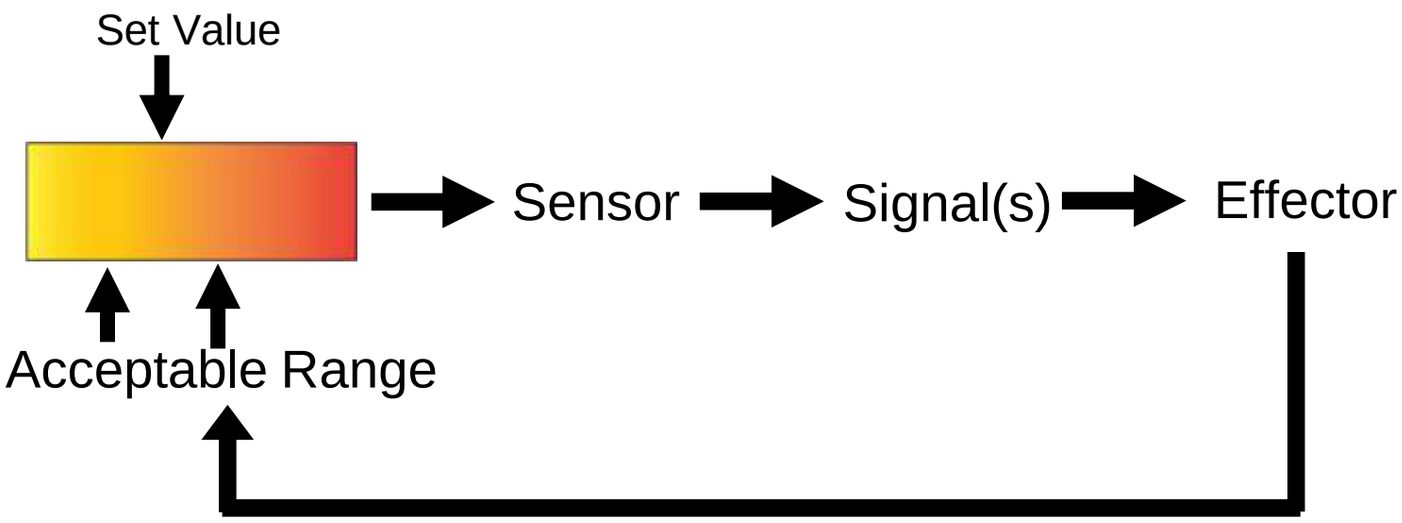


Figure 20-31 Molecular Biology of the Cell 6e (© Garland Science 2015)

predict these pathways necessary



Key points



Cells maintain a healthy state by constantly monitoring themselves and their environment

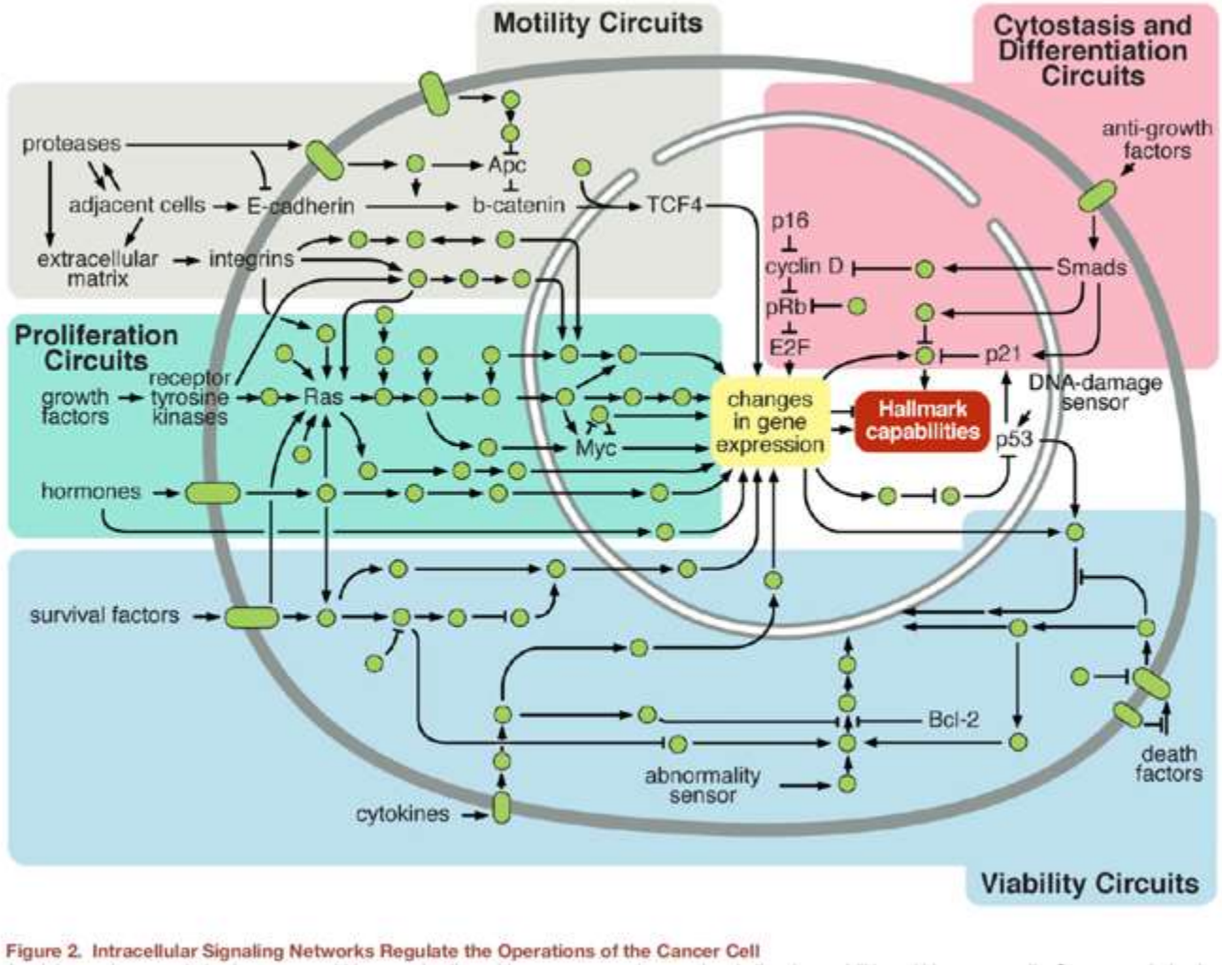


Figure 2. Intracellular Signaling Networks Regulate the Operations of the Cancer Cell

Mutations to the sensors and effectors drive cancer progression

Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,*] and Robert A. Weinberg[2,*]
[1]The Swiss Institute for Experimental Cancer Research (ISREC), School of Life Sciences, EPFL, Lausanne CH-1015, Switzerland
[2]The Department of Biochemistry & Biophysics, UCSF, San Francisco, CA 94158, USA
[2]Whitehead Institute for Biomedical Research, Ludwig/MIT Center for Molecular Oncology, and MIT Department of Biology, Cambridge, MA 02142, USA
[*]Correspondence: dh@epfl.ch (D.H.), weinberg@wi.mit.edu (R.A.W.)
DOI 10.1016/j.cell.2011.02.013