Introduction to Cancer
BCH 466

OBJECTIVES

- List the major hallmarks of cancer
- Relate specific genes/proteins to individual hallmarks
- Explain how hallmarks of cancer lead to cancer development

Cancer: overview

Cancer is a group of diseases characterized by unregulated cell growth and the invasion and spread of cells from the site of origin to other sites in the body. Cancer is considered to be a group of diseases. Over 100 types of cancer have been classified.

The tissue of origin gives the distinguishing characteristics of the cancer.

- **Carcinomas:** Cancers occur in epithelial cells **(**Approximately 85% of cancer).
- **Sarcomas:** Cancers derived from mesoderm cells (e.g. bone, muscle)
- **Adenocarcinomas:** Cancers of glandular tissue (e.g. breast).

Cancers of different origins have distinct features. For example, skin cancer has many characteristics that differ from lung cancer.
The major factor that causes cancer in each target tissue is different: ultraviolet (UV) radiation from the sun can easily target the skin, while inhalation of cigarette smoke can target the lungs.

On the basis of invasion and spread

Cancers can be benign tumor and a **malignant** tumor.

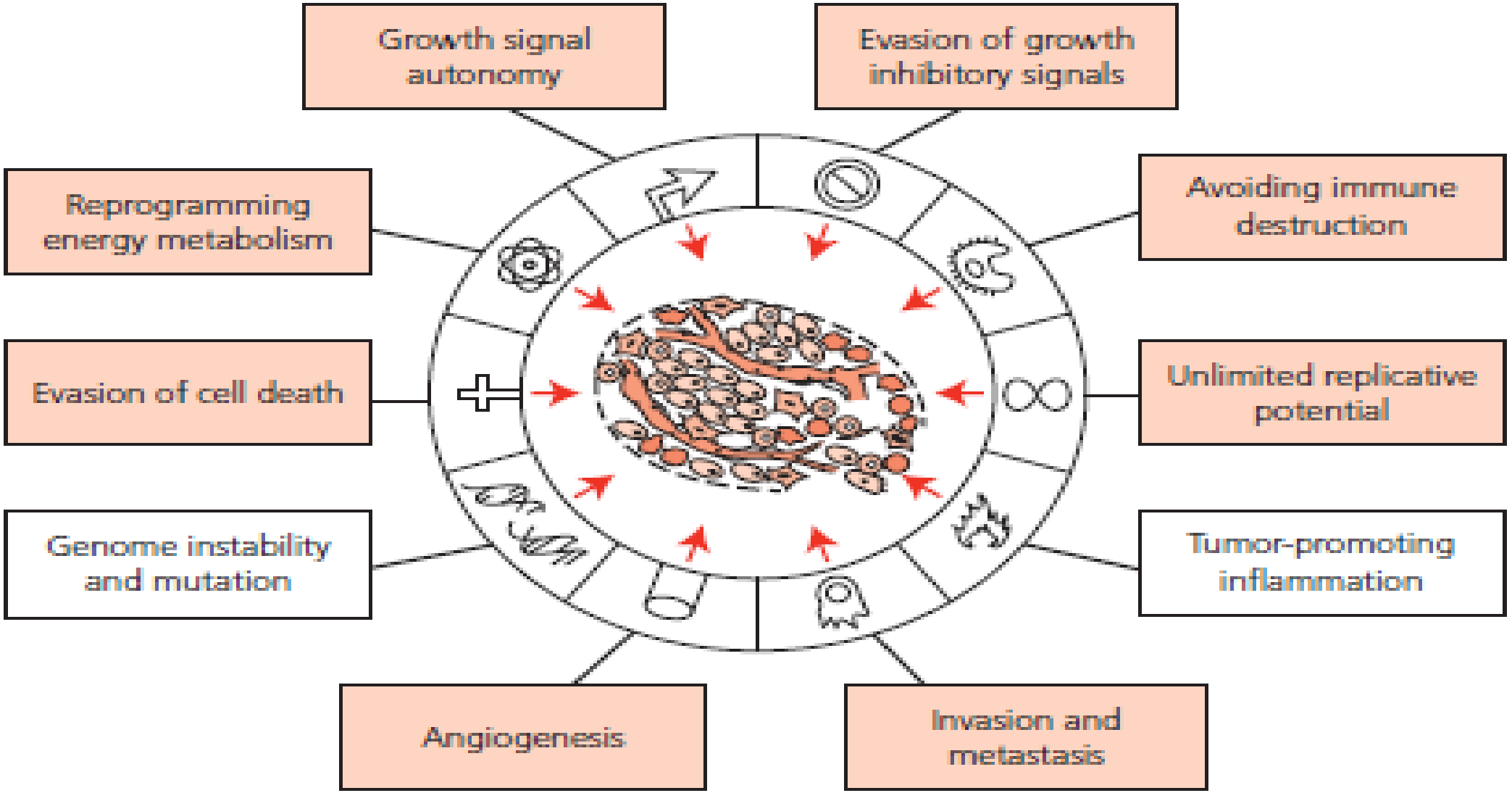
A benign tumor is not evidence of cancer. Benign tumors do not spread throughout the body (that is, they do not metastasize), although some can be life threatening because of their location (e.g. a benign brain tumor that may be difficult to remove).

Malignant tumors, on the other hand, do not remain encapsulated, show features of **invasion**, and metastasize.

Cancer cells can be distinguished from normal cells in cell culture conditions

- Normal cells grow as a single layer, or monolayer, in a Petri dish due to the so called contact inhibition; contact with neighboring cells inhibits growth.
- Transformed cells (cells that have become cancer cells) acquire the following **phenotypes**:
  - they fail to exhibit contact inhibition and instead grow as piles of cells or “foci” against a monolayer of normal cells
  - they can grow in conditions of low serum
  - they adopt a round **morphology** rather than a flat and extended one
  - they are able to grow without attaching to a substrate (e.g. the surface of a Petri dish), exhibiting “anchorage independence.”

Hallmarks of cancer



Case study

- 60 year old female
- Previously treated for breast cancer (5 years prior);
- no recurrence
- Presents with persistent cough, shortness of breath, fatigue
- X-ray reveals small mass in left lung
- A biopsy is performed

- A physician meets with this patient.
  - What is the first question she asks about the patient's lifestyle?

Brainstorming

- • A pathologist analyzes the biopsy sample. What does he look for?
- i.e. What information is gained from the analysis of the biopsy?
- • Biopsy results indicate that patient has a metastatic tumor of breast cancer origin in lung. Tumor is a carcinoma.
- • What changes occurred to a breast epithelial cell that led to the formation of a metastatic tumor in the lung?

What are the Hallmarks?

The hallmarks of cancer are the distinctive and complementary capabilities that enable tumor growth and metastatic dissemination.

In other words... The characteristics that make a cell, cancer cell.

The Characteristics of Cancer

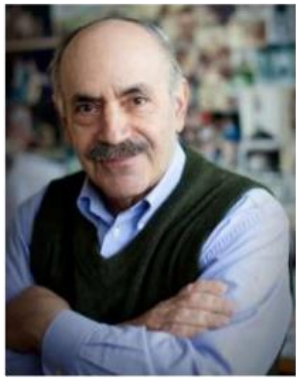
- Normally, as genes switch on and off, they determine when and how fast the cell will grow and divide, when it will stop dividing, and even when it will die.

- Cancer can result when controls over cell division are lost

Douglas Hanahan and Robert Weinberg

Six essential alterations in cell physiology that collectively dictate malignant growth:

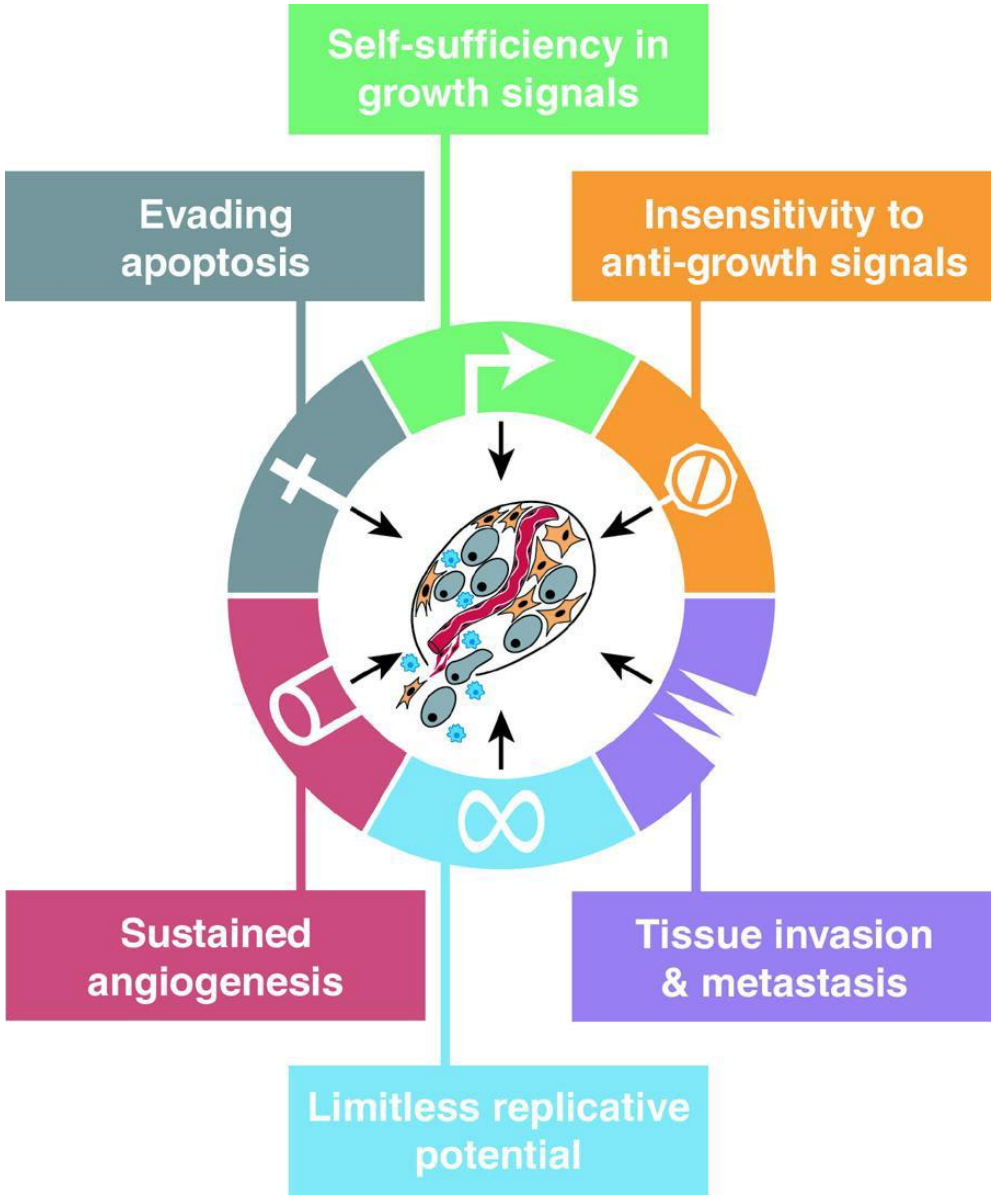
- self-sufficiency in growth signals,
- insensitivity to growth-inhibitory signals,
- evasion of programmed cell death (apoptosis),
- limitless replicative potential,
- sustained angiogenesis,
- tissue invasion and metastasis”



Weinberg

Hanahan

https://doi.org/10.1016/S0092-8674(00)81683-9

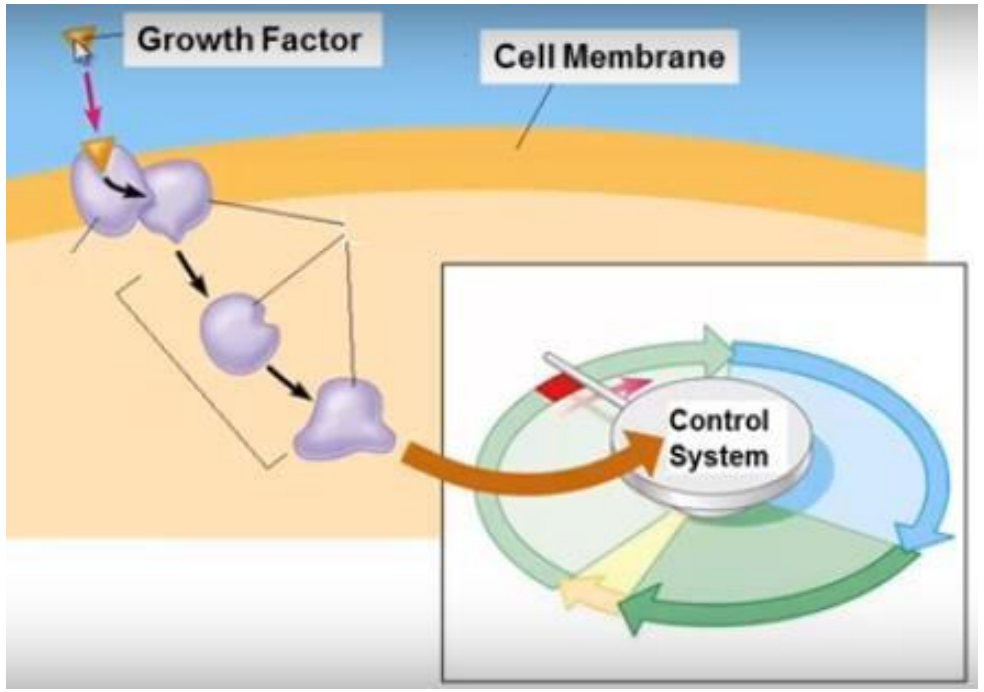


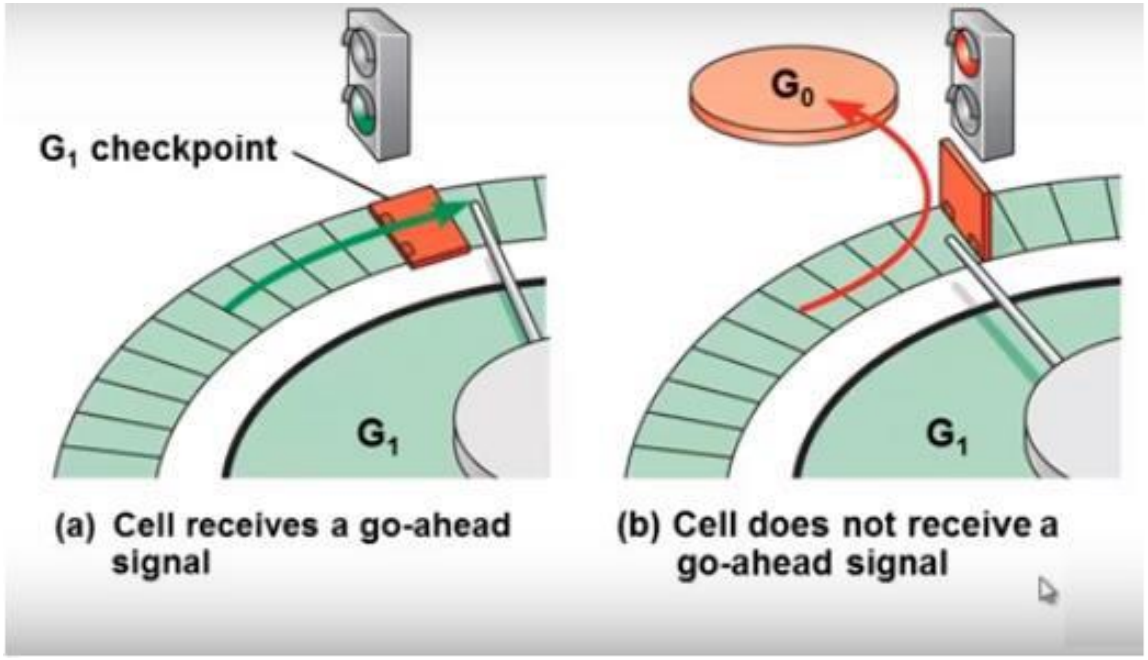
Hanahan and Weinberg (2000)

Cell, 100: 57- 70.

A Growth factor:
is a protein released by a cell that will stimulate another cell to grow and divide.

A Mitogen:
is a substance that induces or stimulates mitosis.





No type of normal cell can proliferate in the absence of stimulatory signals.

Many of the oncogenes in the cancer catalog act by mimicking normal growth signaling in one way or another.

Oncogene and Tumor Suppressor Genes

- **Oncogene:**

  mutated forms of normal cellular genes generally involved in promoting cell proliferation.

  These mutations result in dominant gain of function.

- **Tumor suppressor gene:**

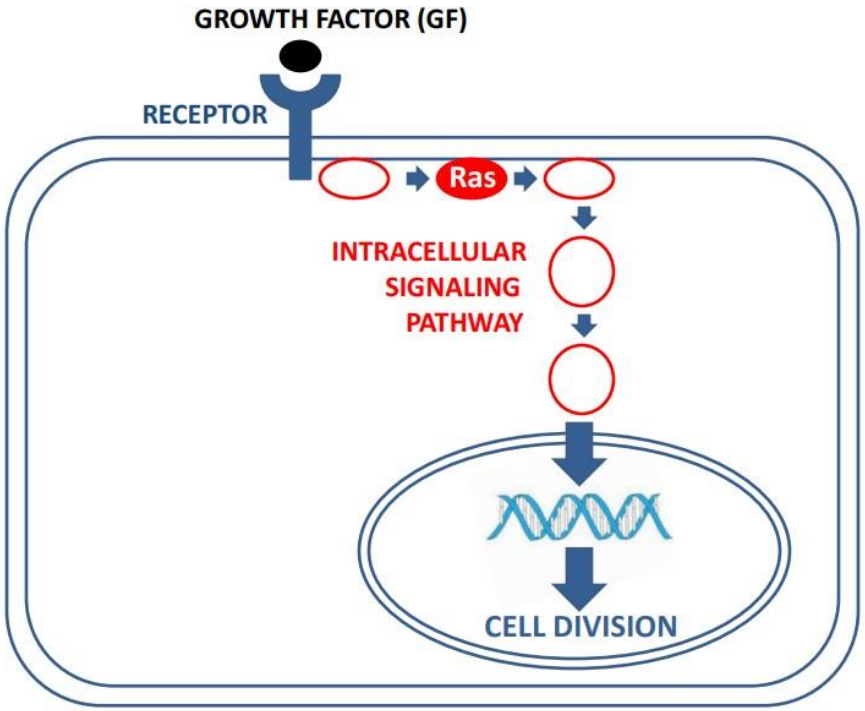
  whose normalfunction in regulating proliferation is to stop it.

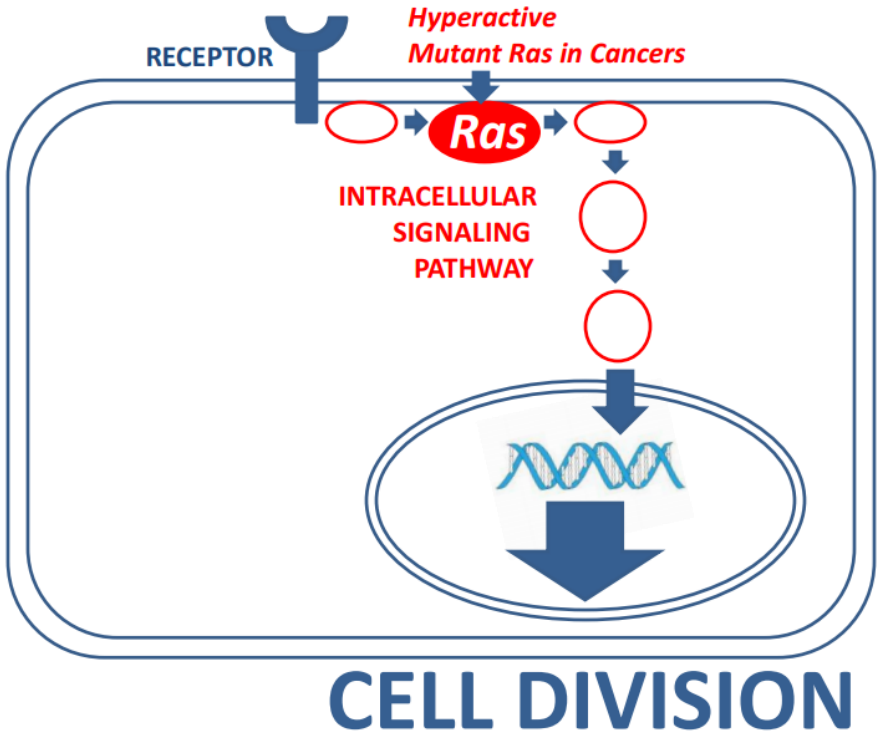
  These mutations result in recessive loss of function.

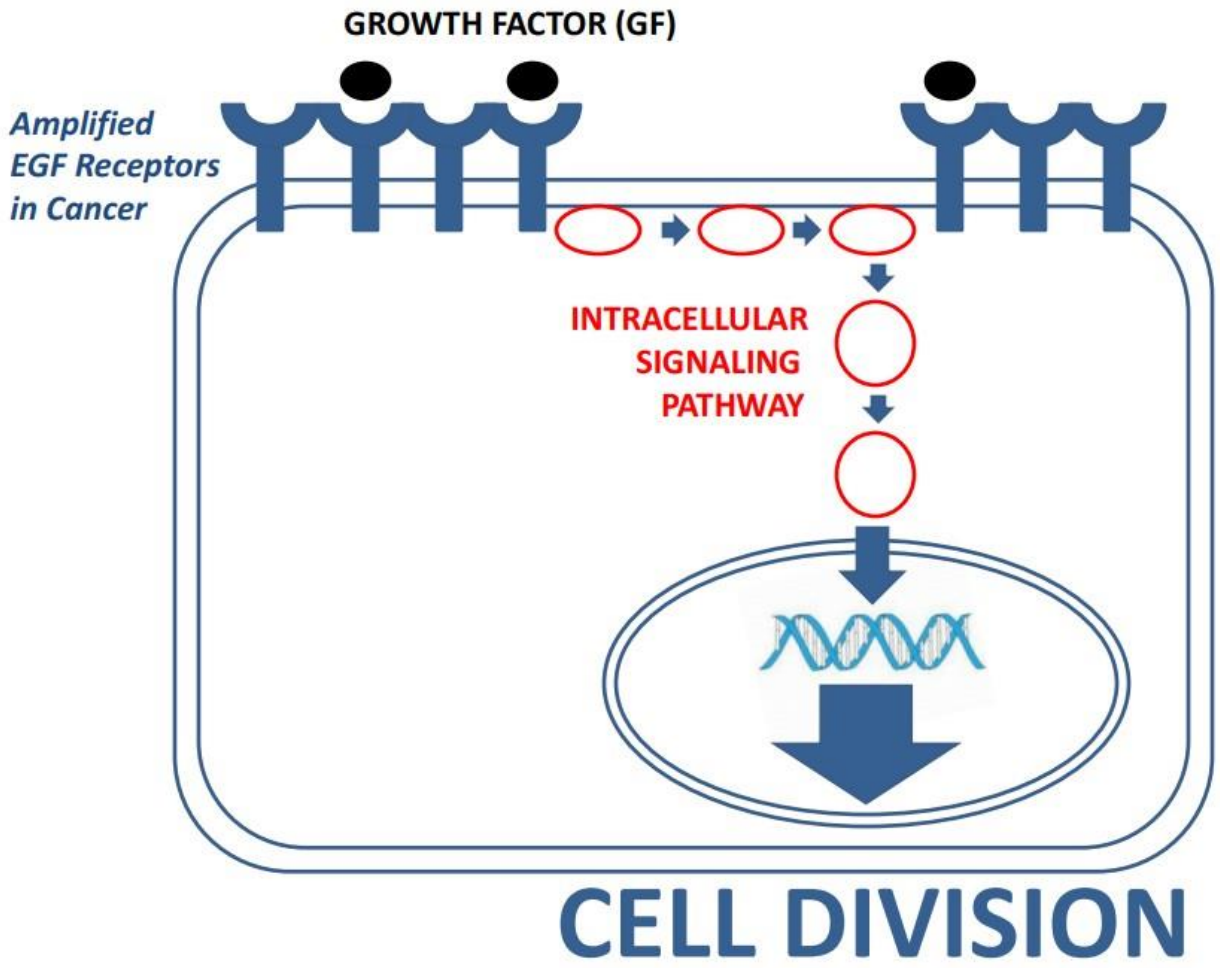
Hallmarks of cancer

1. Self-sufficiency in growth signals (Growth signal autonomy)

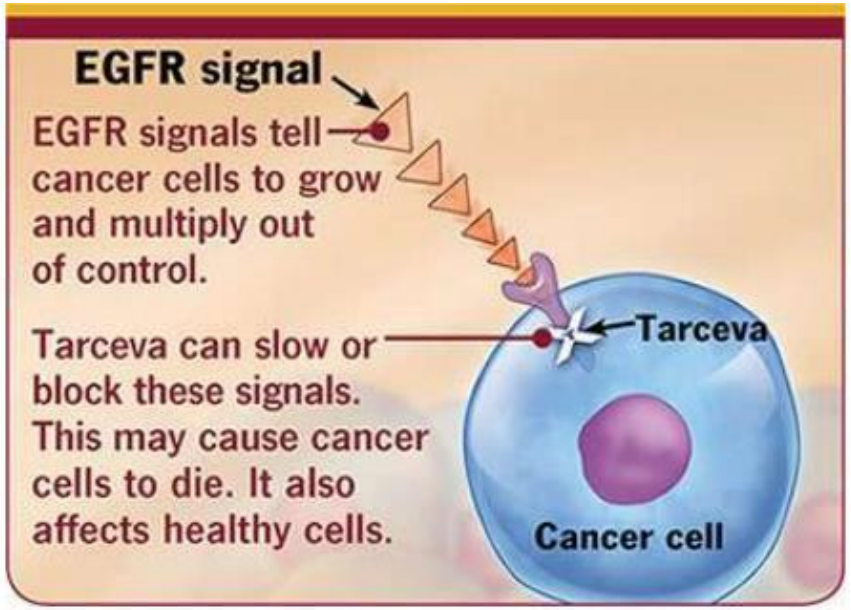
– Normal cells need external signals from growth factors to divide
– Cancer cells are NOT dependent on normal growth factor signaling
– Acquired **mutations** short-circuit growth factor pathways leading to unregulated growth.







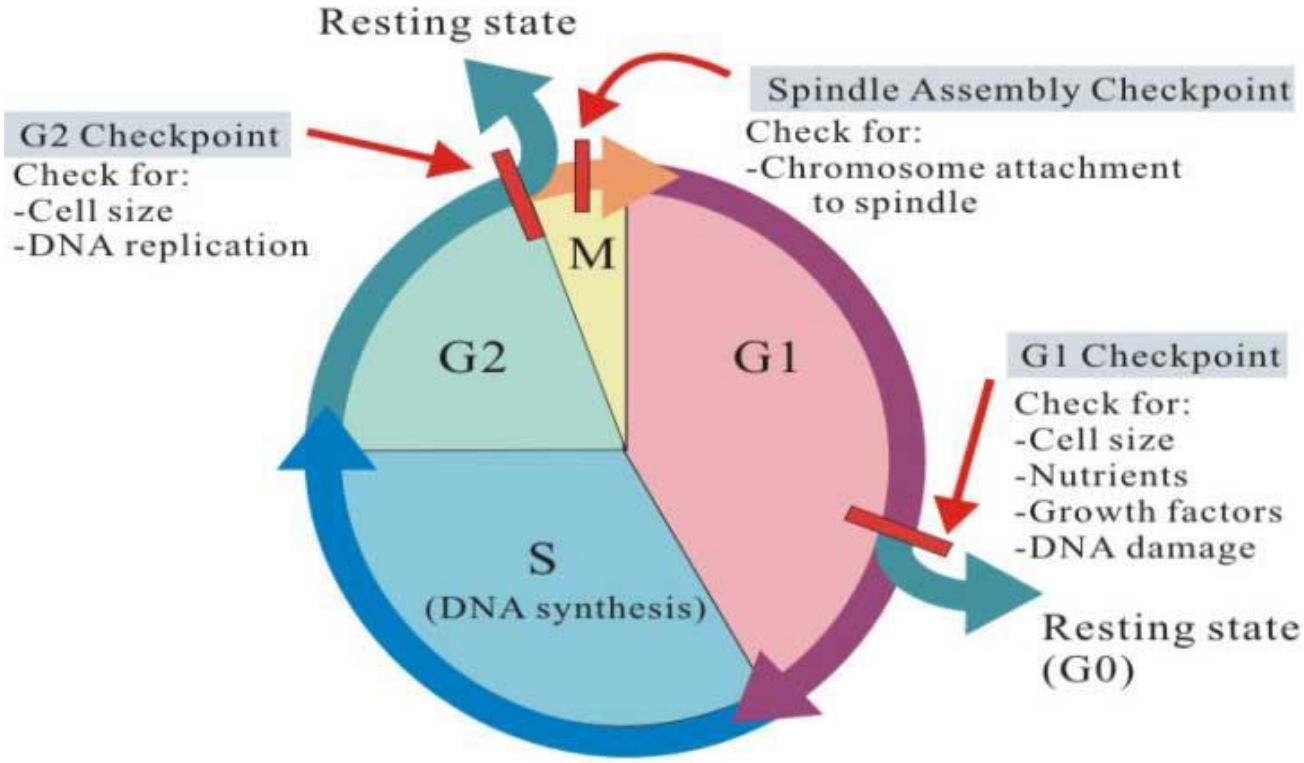
Tarceva – A Drug Which Targets
EGF Receptor In Lung Cancer

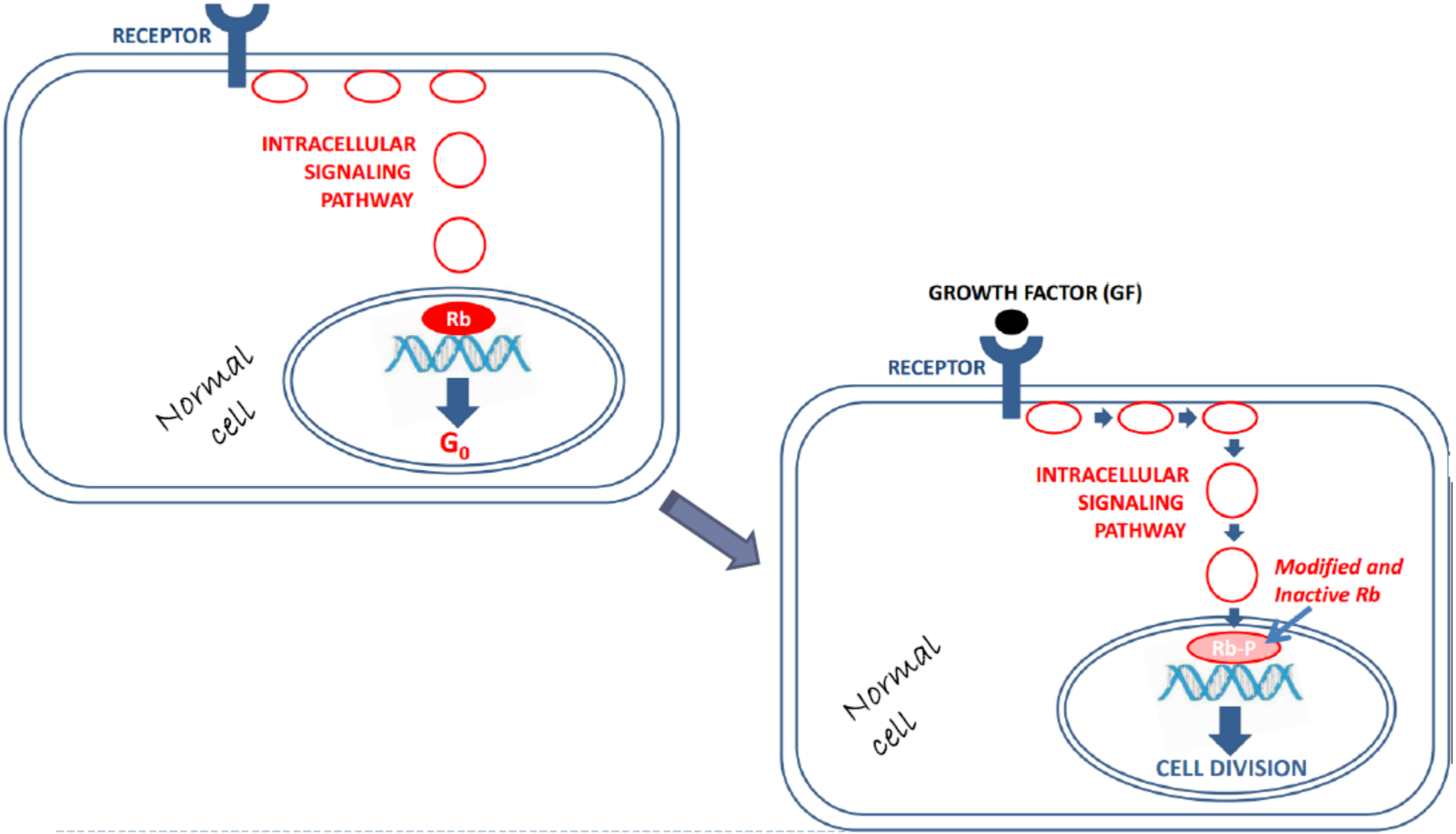


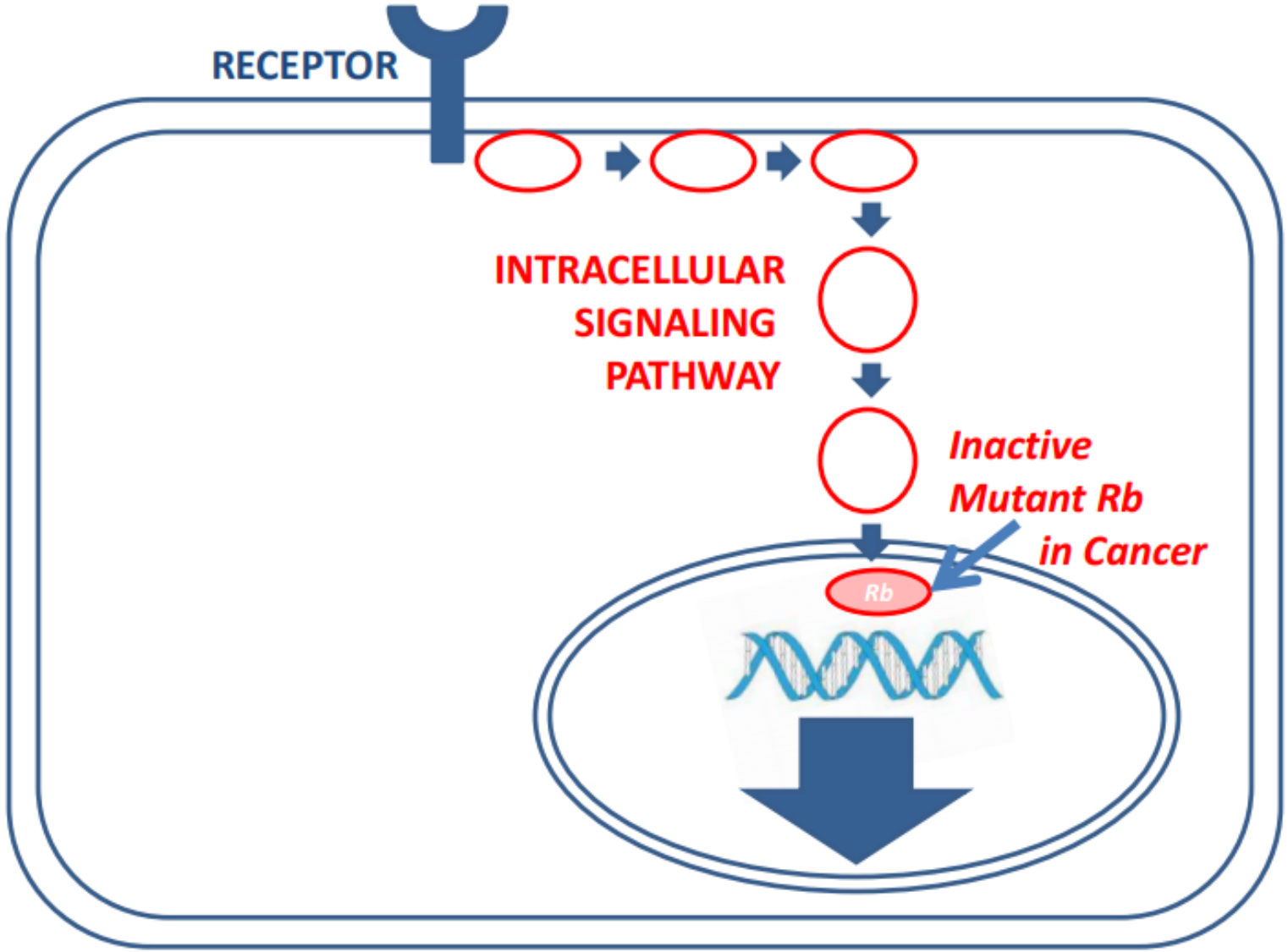
Hallmarks of cancer (Cont.1)

2. Insensitivity to anti-growth signals (Evasion of growth inhibitory signals)

– Normal cells respond to inhibitory signals to maintain homeostasis (most cells of the body are not actively dividing)
– Cancer cells do not respond to growth inhibitory signals
– Acquired mutations or gene silencing interfere with the inhibitory pathways.

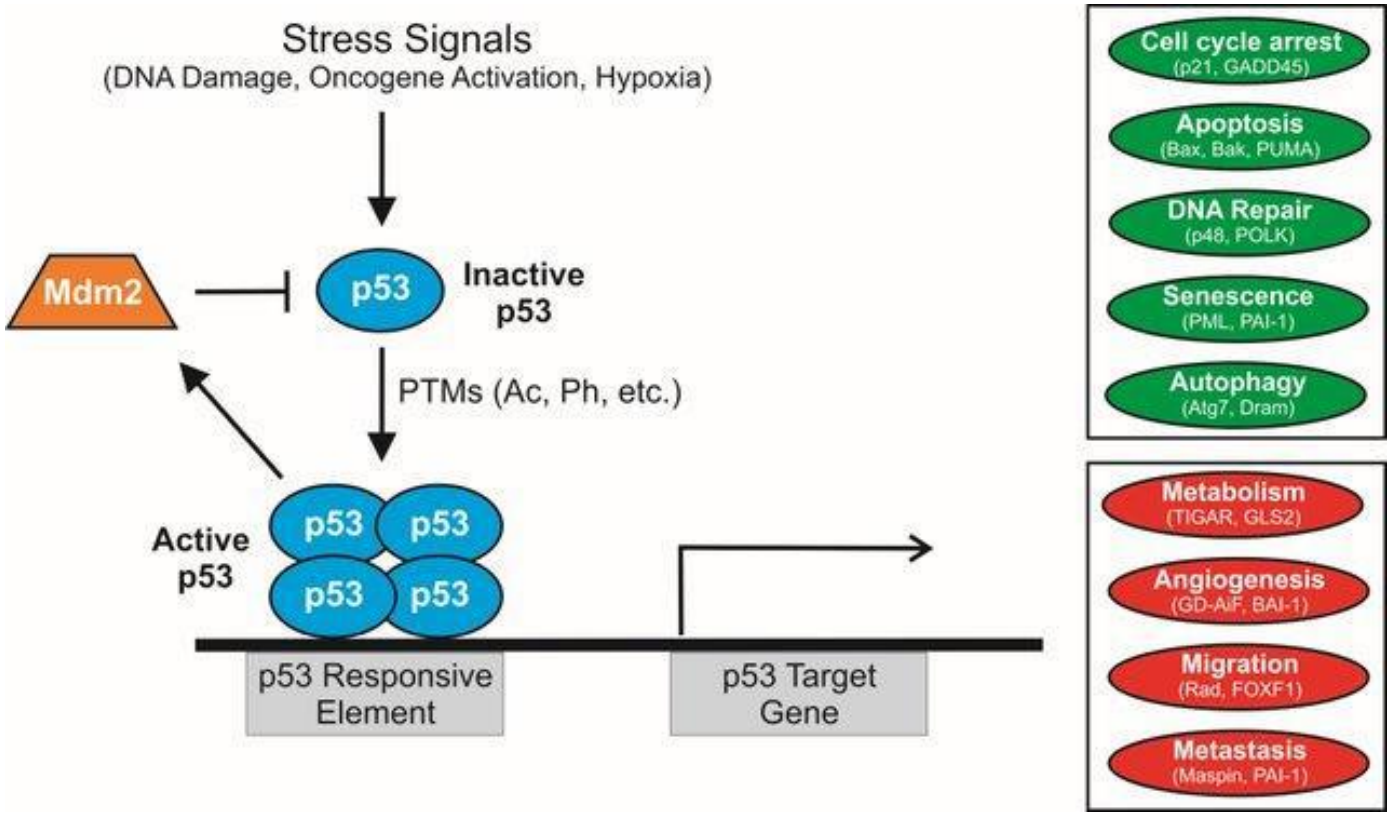



RECEPTOR
INTRACELLULAR SIGNALING PATHWAY
Rb
Normal cell
G_0
GROWTH FACTOR (GF)
RECEPTOR
INTRACELLULAR SIGNALING PATHWAY
Modified and Inactive Rb
Rb-P
Normal cell
CELL DIVISION



CELL DIVISION

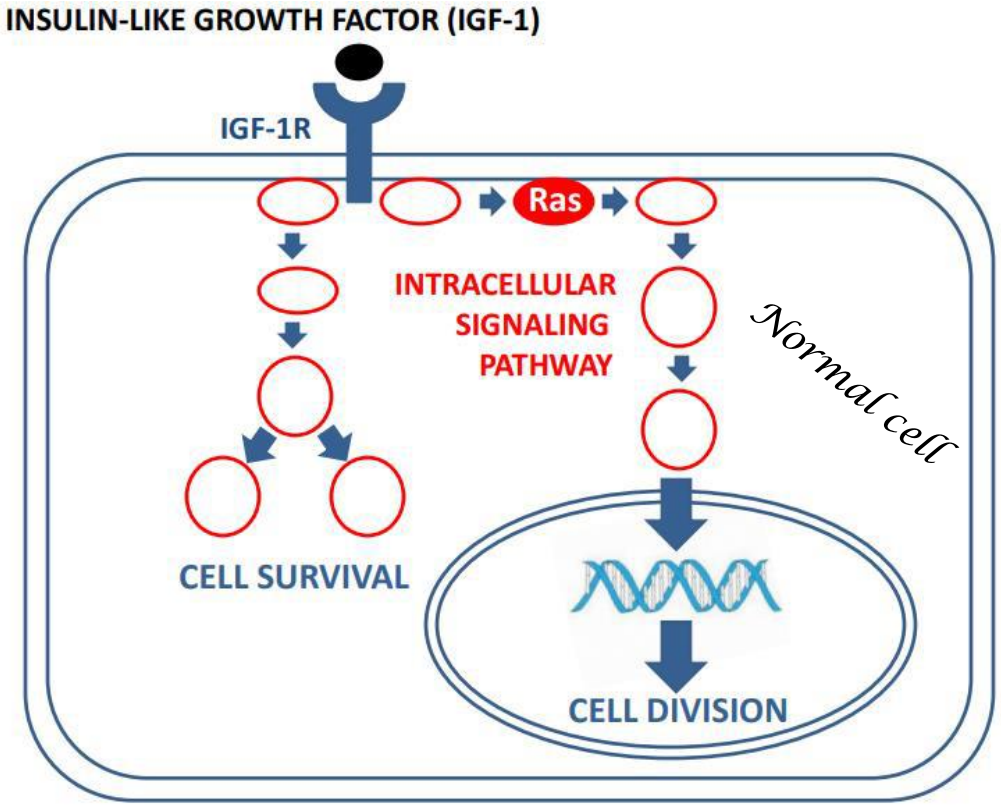
p53’S normal role is to inhibit cell division in response to cellular stresses.

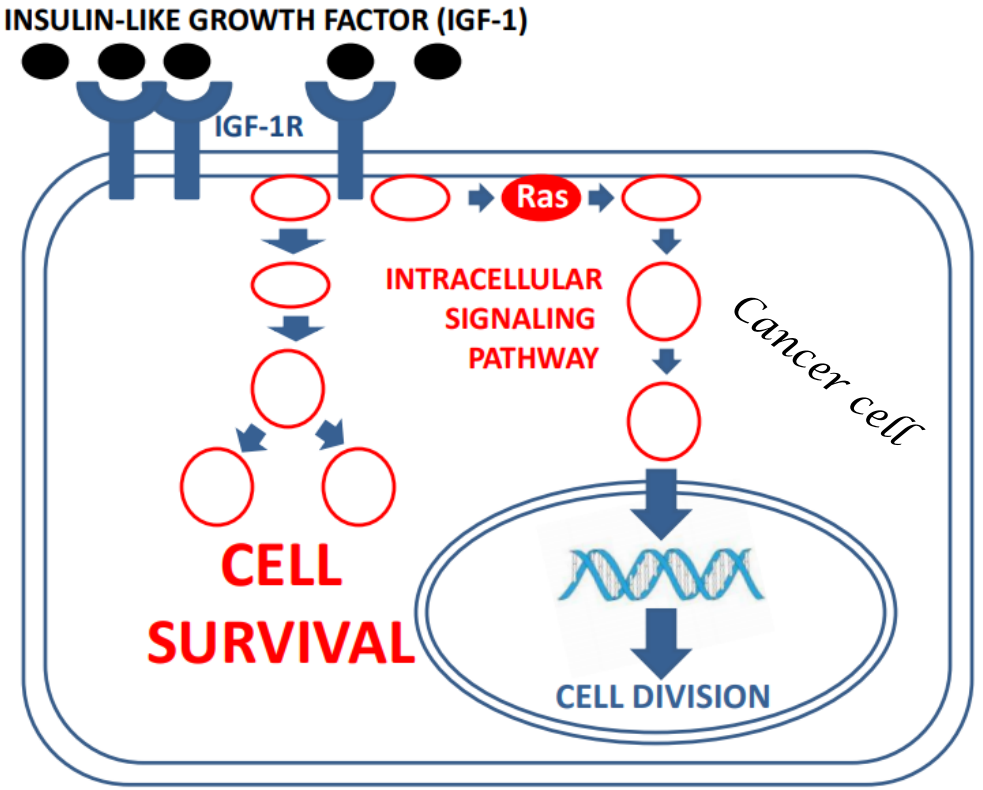


Cellular stress leads to p53 transcriptional activation of downstream targets. Normally, p53 levels are kept low by its major antagonist, Mdm2. Stress signals promote p53 stability and activity by inducing posttranslational modifications (PTMs). p53 functions as a transcription factor that binds to specific p53 response element supstream of its target genes. p53 affects many important cellular processes linked to tumor suppression, including the induction (green) of senescence, apoptosis, and DNA repair as well as inhibition (red) of metabolism, angiogenesis, and cell migration.

3. Evading Apoptosis (Evasion of cell death):

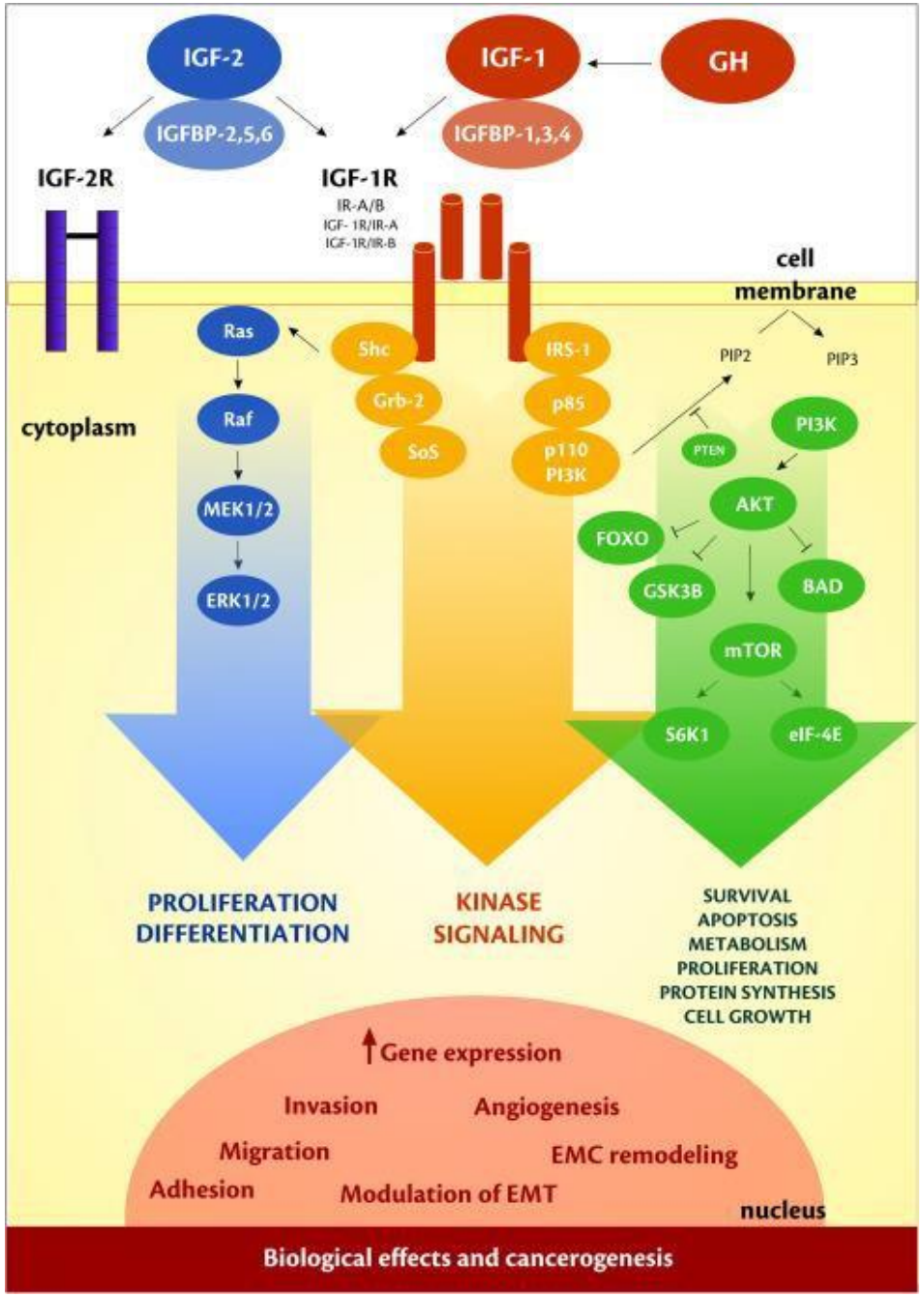
- Normal cells are removed by apoptosis, often in response to DNA damage
- Cancer cells evade apoptotic signals.





Some cancer cells upregulate cell survival pathways to evade apoptosis

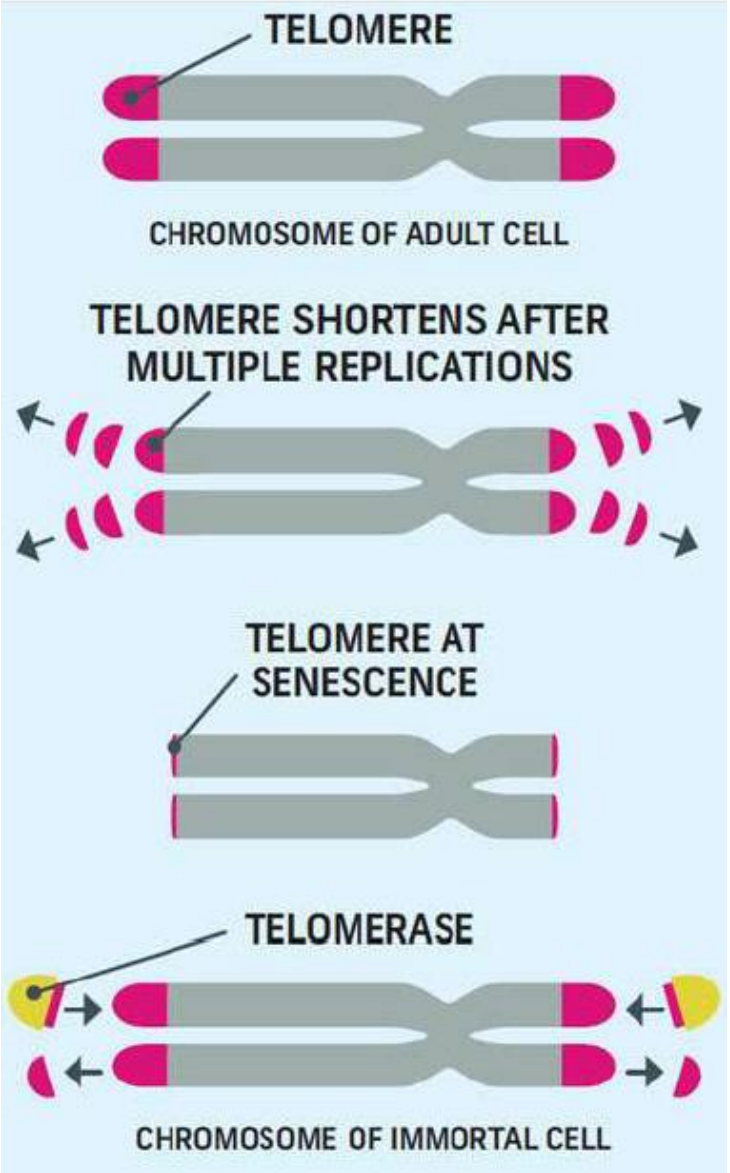
- The insulin-like GFs (IGFs) play a role in growth promotion involving various tissues and organs regulating cell proliferation, differentiation and apoptosis.
- IGFs exert their action by specific glycoproteins membrane receptors of :
  - type I (IGF-1R),
  - type II (IGF-2R) and other.
- Activity of this signaling pathway leads to an increased mitogenesis, cell cycle progression, and protection against different apoptotic stresses.
- Indirect effects of IGF axis depend on interactions between IGFs and other molecules important for cancer etiology (e.g. sex hormones, products of suppressor genes, viruses, other GFs) and the style of life (nutrition, physical activity).



4. Limitless replicative potential (Unlimited replicative potential)

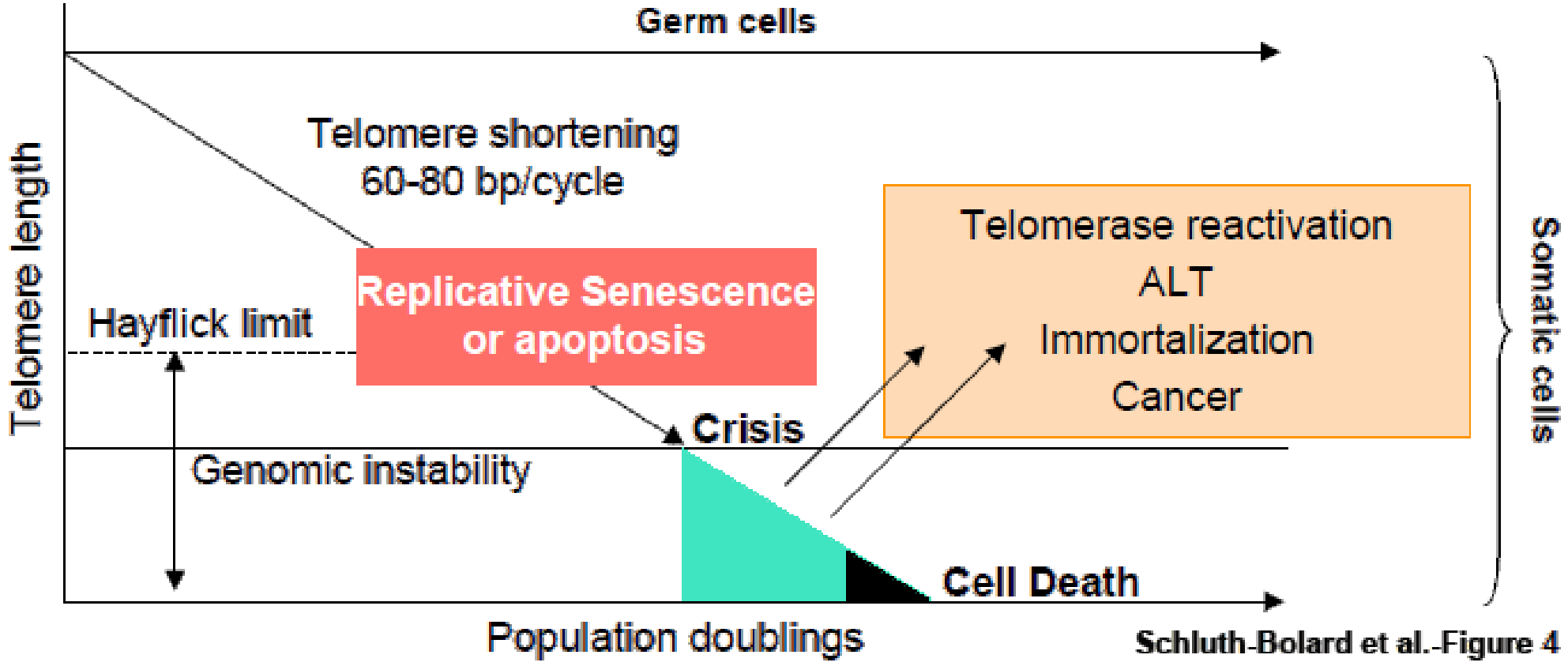
– Normal cells have an autonomous cellular counting device to define a finite number of cell doublings after which they become senescent.
- This cellular counting device is the shortening of chromosomal ends, **telomeres**, that occurs during every round of DNA replication
– Cancer cells maintain the length of their telomeres
– Altered regulation of telomere maintenance results in unlimited replicative potential.

Telomeres are chromosome ends.
Telomeres are made by telomerase early in development; then telomerase activity is normally turned off.
Telomeres shorten with each cell division, ultimately leading to senescence

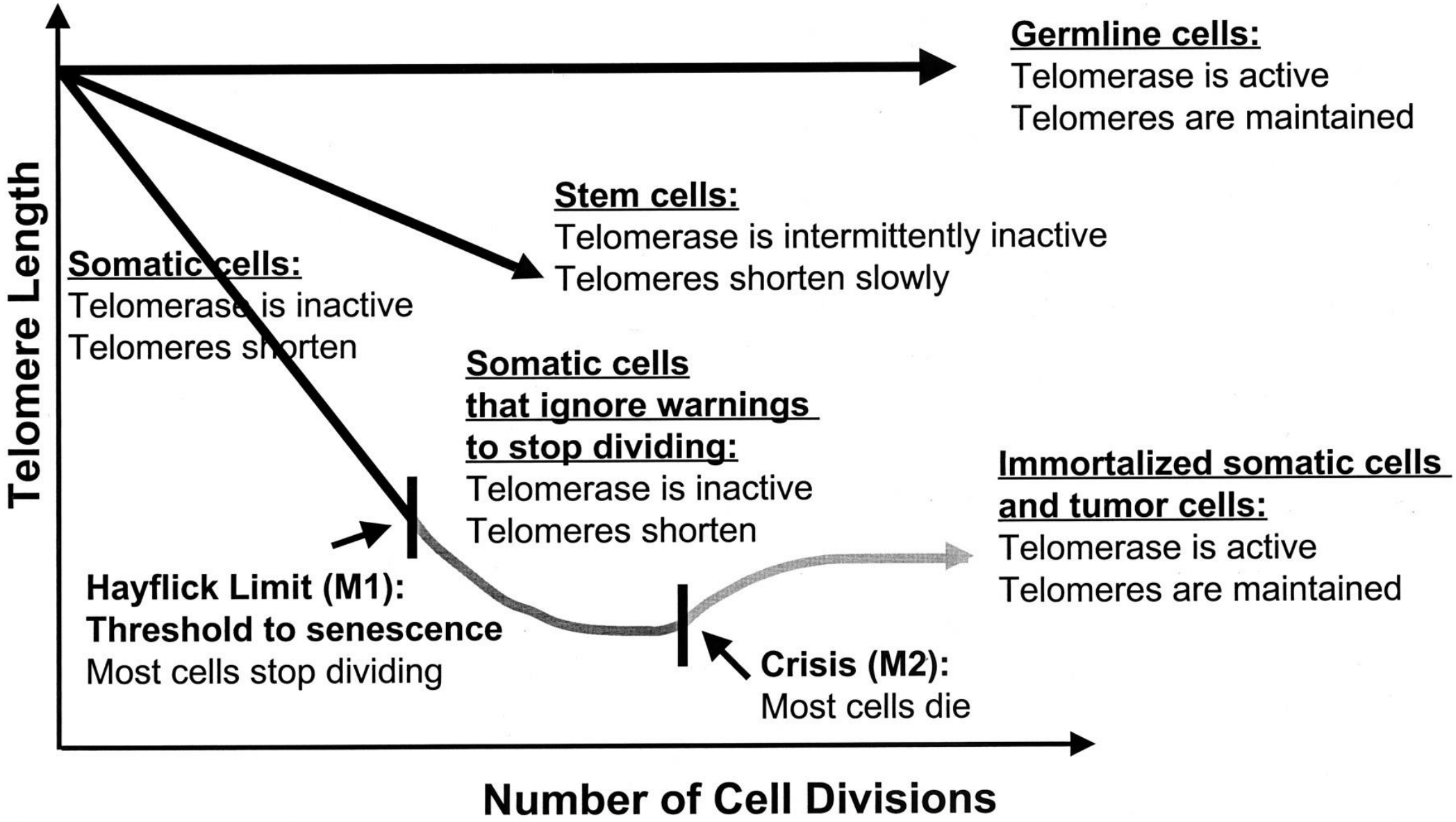


Cancer cells *reactivate* telomerase

Normal cells must overcome **senescence and crisis.**
The 'telomere hypothesis' proposes that activation of telomerase is necessary for cells to become immortal or capable of extended proliferation.

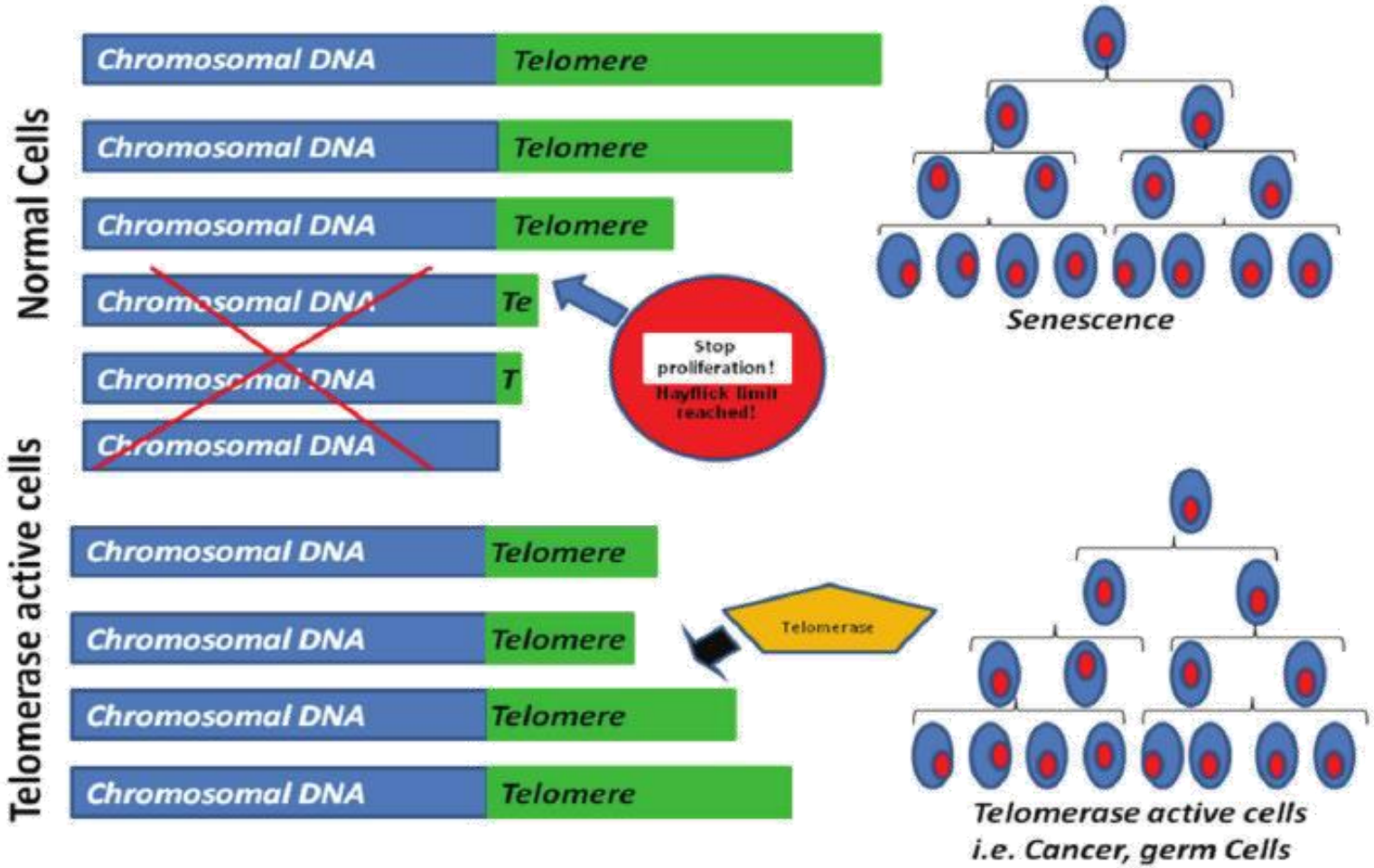


Schluth-Bolard et al.-Figure 4


Germline cells:
Telomerase is active
Telomeres are maintained
Stem cells:
Telomerase is intermittently inactive
Telomeres shorten slowly
Somatic cells:
Telomerase is inactive
Telomeres shorten
Somatic cells
that ignore warnings
to stop dividing:
Telomerase is inactive
Telomeres shorten
Immortalized somatic cells
and tumor cells:
Telomerase is active
Telomeres are maintained
Hayflick Limit (M1):
Threshold to senescence
Most cells stop dividing
Crisis (M2):
Most cells die
Telomere Length
Number of Cell Divisions

Telomere maintenance is regarded as an important mechanism by which tumor cells evade senescence, and in most cases, it is achieved by reactivating or up-regulating telomerase activity.

Telomerase is activated in ~85% of human carcinomas and also appears to be present in circulating cancer cells.



5. Sustained angiogenesis (formation of new blood vessels):

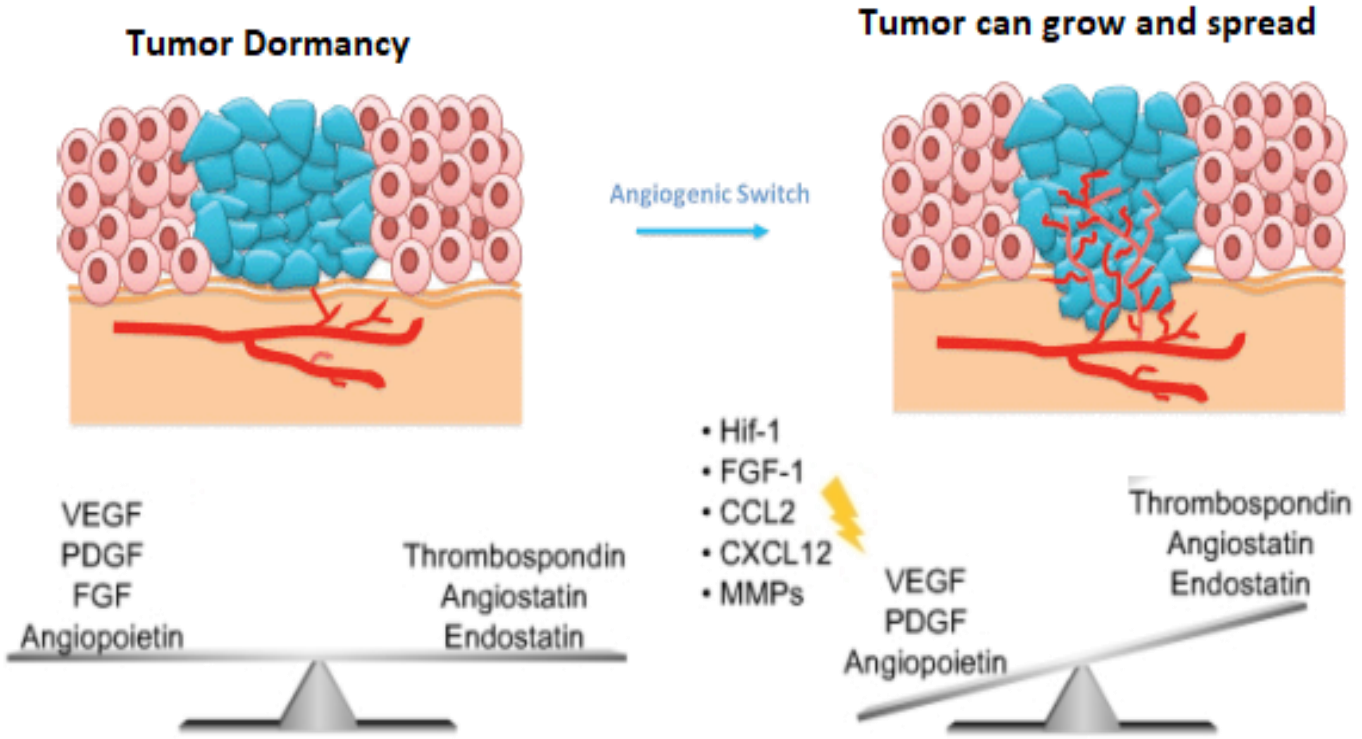
Angiogenesis from the Greek word *Angêion*, meaning vessel, the formation of blood vessels from existing vasculature.

- It occurs throughout life in both health and disease, beginning in utero and continuing on through old age.

– Normal cells depend on blood vessels to supply oxygen and nutrients but the vascular architecture is more or less constant in the adult.

– Cancer cells induce angiogenesis, the growth of new blood vessels, needed for tumor survival and expansion.

– Altering the balance between angiogenic inducers and inhibitors can activate the angiogenic switch.



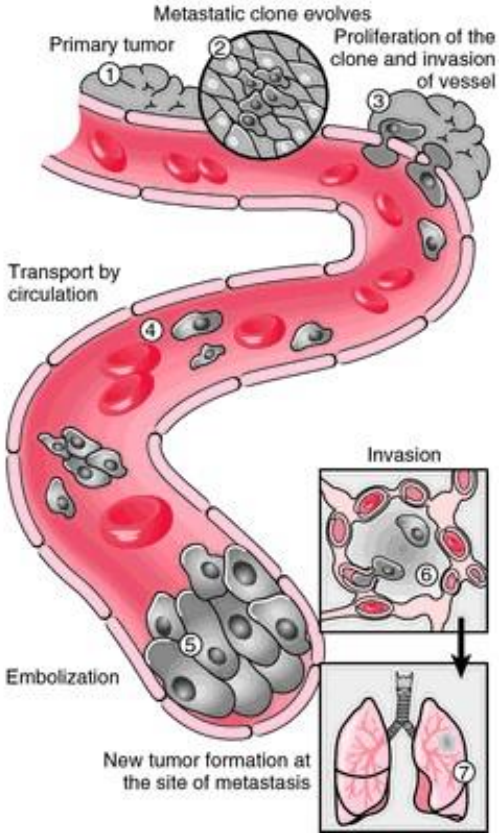
There is a balance between angiogenic and anti-angiogenic factors. When this equilibrium is destroyed by the prevalence of angiogenic factors, tumor can grow.

6. Invasion and metastasis:

– Normal cells maintain their location in the body and generally do not migrate.
– The movement of cancer cells to other parts of the body is a major cause of cancer deaths.
– Alterations of the genome may affect the activity and/or levels of enzymes involved in invasion or molecules involved in cell–cell or cellular–extracellular adhesion.

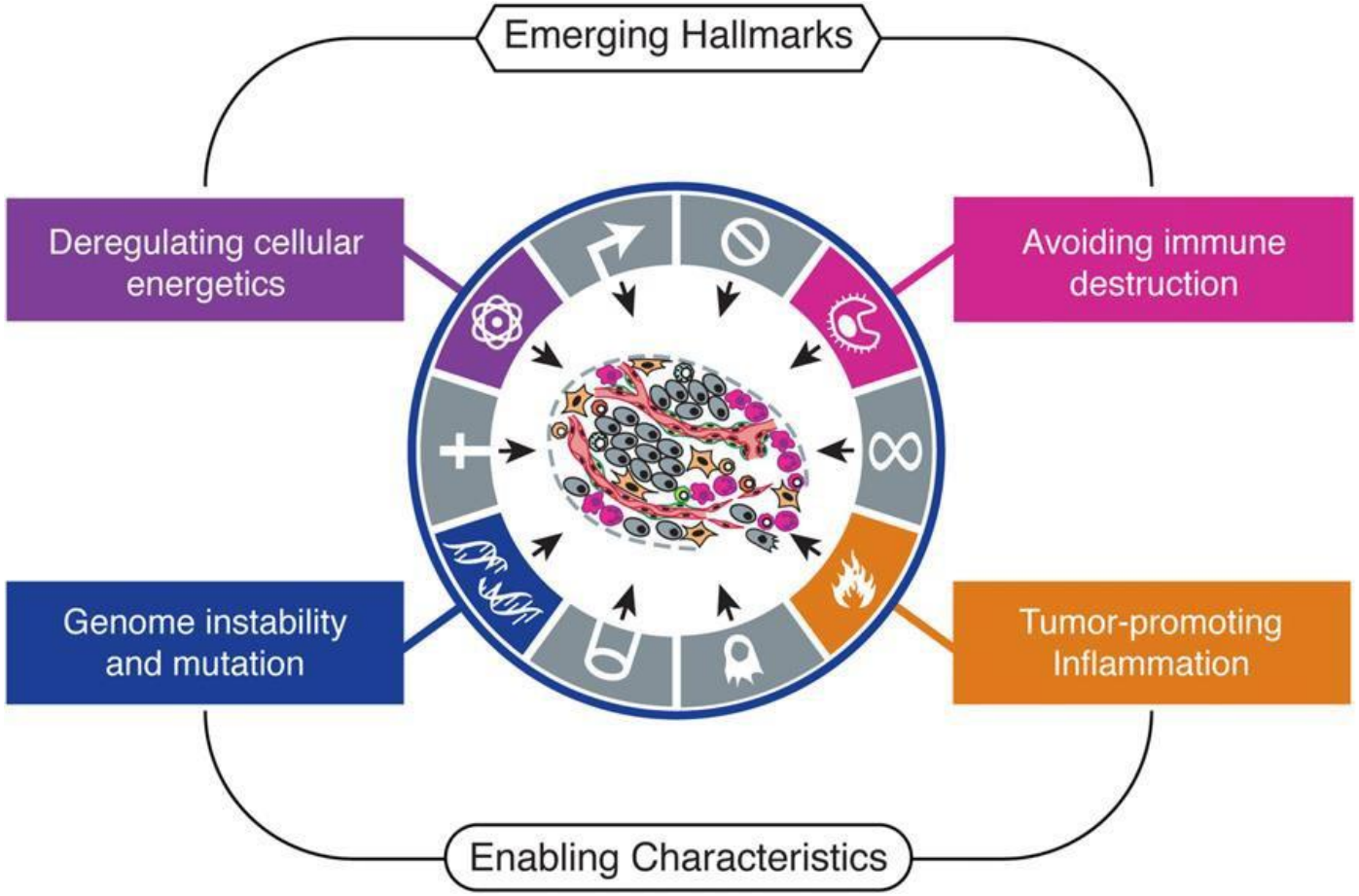
Step-1: Physical dissemination of cancer cells from primary tumor to distant tissues
Step 2: Adaptation of these cells to foreign tissue microenvironments, successful colonization.

Metastatic cancer is named based on the site where the cancer began. For example, if lung cancer spreads to the bones, it would not be called “bone cancer” but rather “lung cancer metastatic to the bones.” In this case, when the metastatic cells are looked at under the microscope they would be cancerous lung cells, not bone cells



Emerging Characteristics

More additional hallmarks of cancer are involved.



Emerging Characteristics

1- Tumor-promoting inflammation (an enabling characteristic):

– Virtually all tumors contain inflammatory immune cells.
– Inflammation is an immune response that can facilitate the ability of acquiring the core hallmarks of cancer. For example, inflammatory cells can provide growth factors and enzymes that promote angiogenesis and invasion
– In addition, inflammatory cells can release oxygen species that are mutagenic.

2- Reprogramming energy metabolism (emerging hallmark):

- Uncontrolled cell division demands increases in fuel and biosynthetic precursors that is obtained by adjusting energy metabolism

- Unlike normal cells, cancer cells carry out glycolysis even in the presence of oxygen. Glycolysis intermediates can be used in biosynthetic pathways.

3- Genome instability and mutation (an enabling characteristic):

– Acquiring the core hallmarks of cancer usually depends on genomic alterations
– Faulty DNA repair pathways can contribute to genomic instability.

4- Avoiding immune destruction (emerging hallmark):

– In normal conditions, there is evidence to support the theory of immune surveillance that states the immune system can recognize and eliminate cancer cells.
– Successful cancer cells may be those that do not stimulate an immune response or can interfere with the immune response so as to avoid immune destruction.