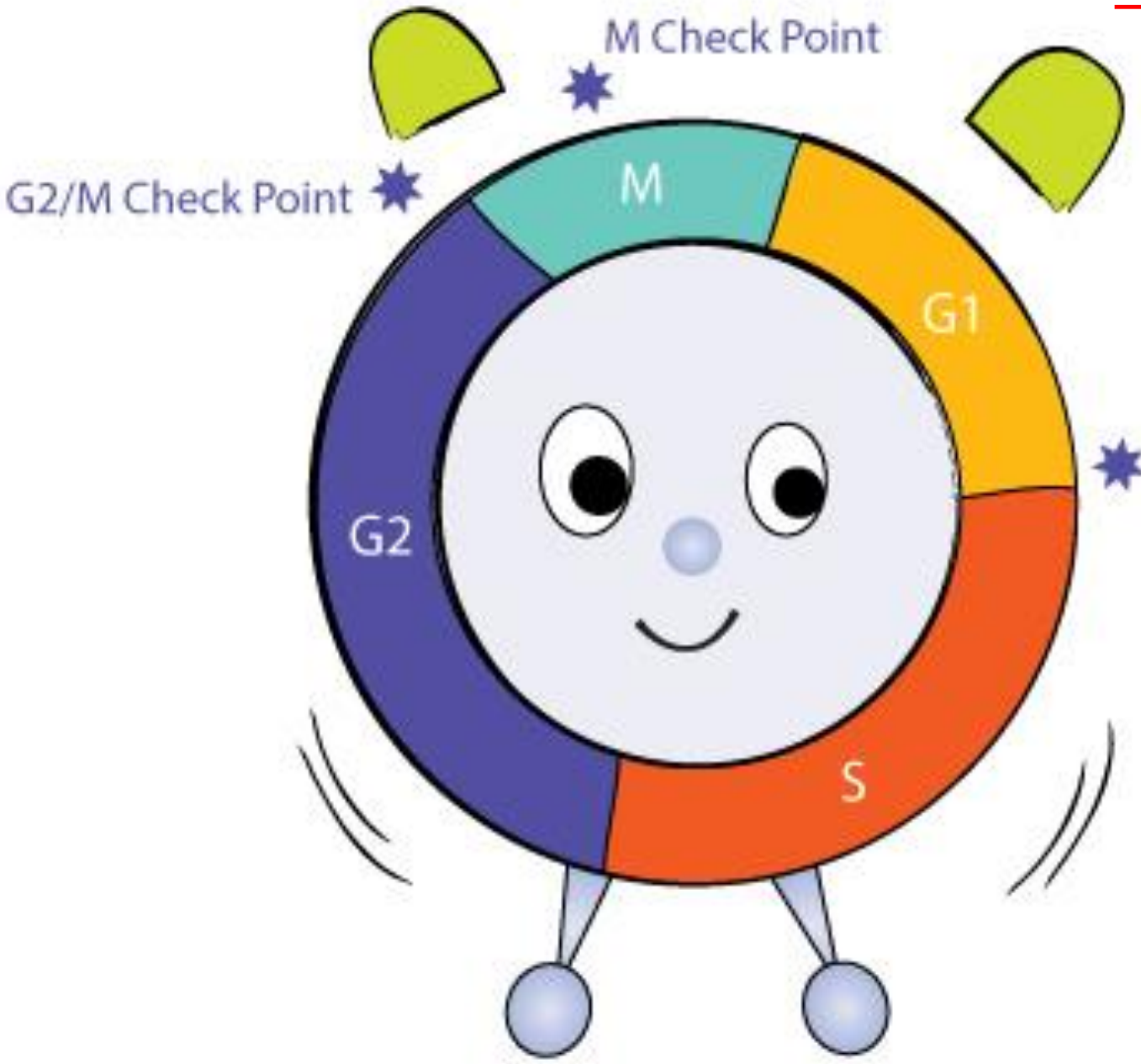
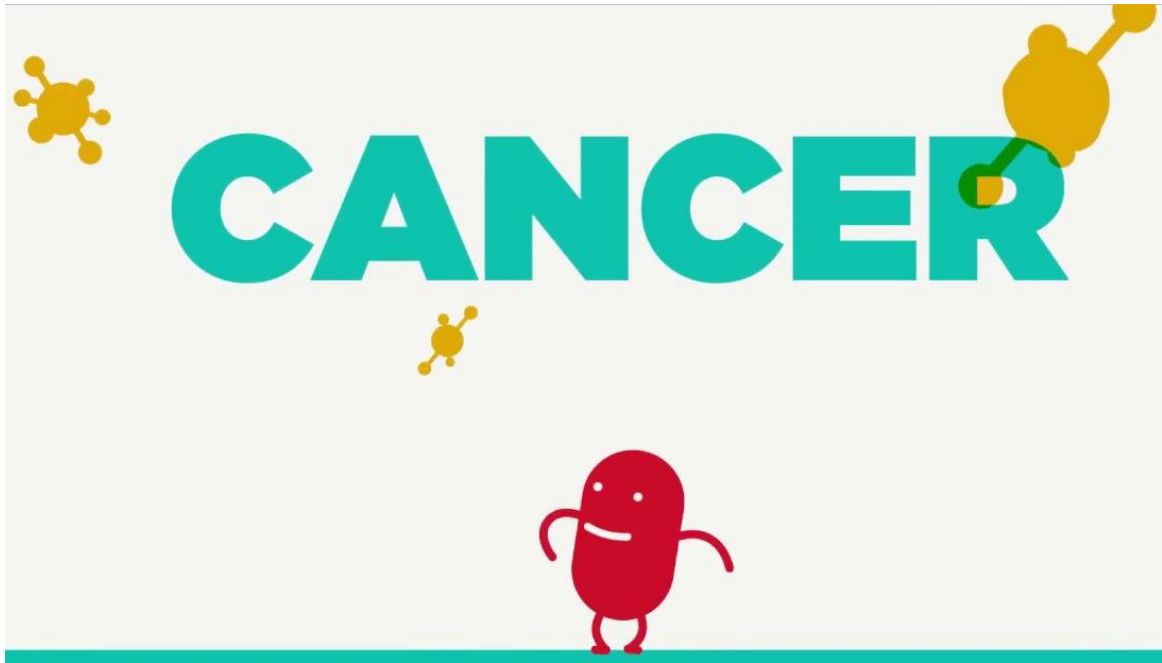
Cell Cycle Regulation and Basics of Cancer

Ms. Kirti Singh
Assistant Professor
Department of Zoology
Udai Pratap College, Varanasi

Regulation of cell cycle and Cancer



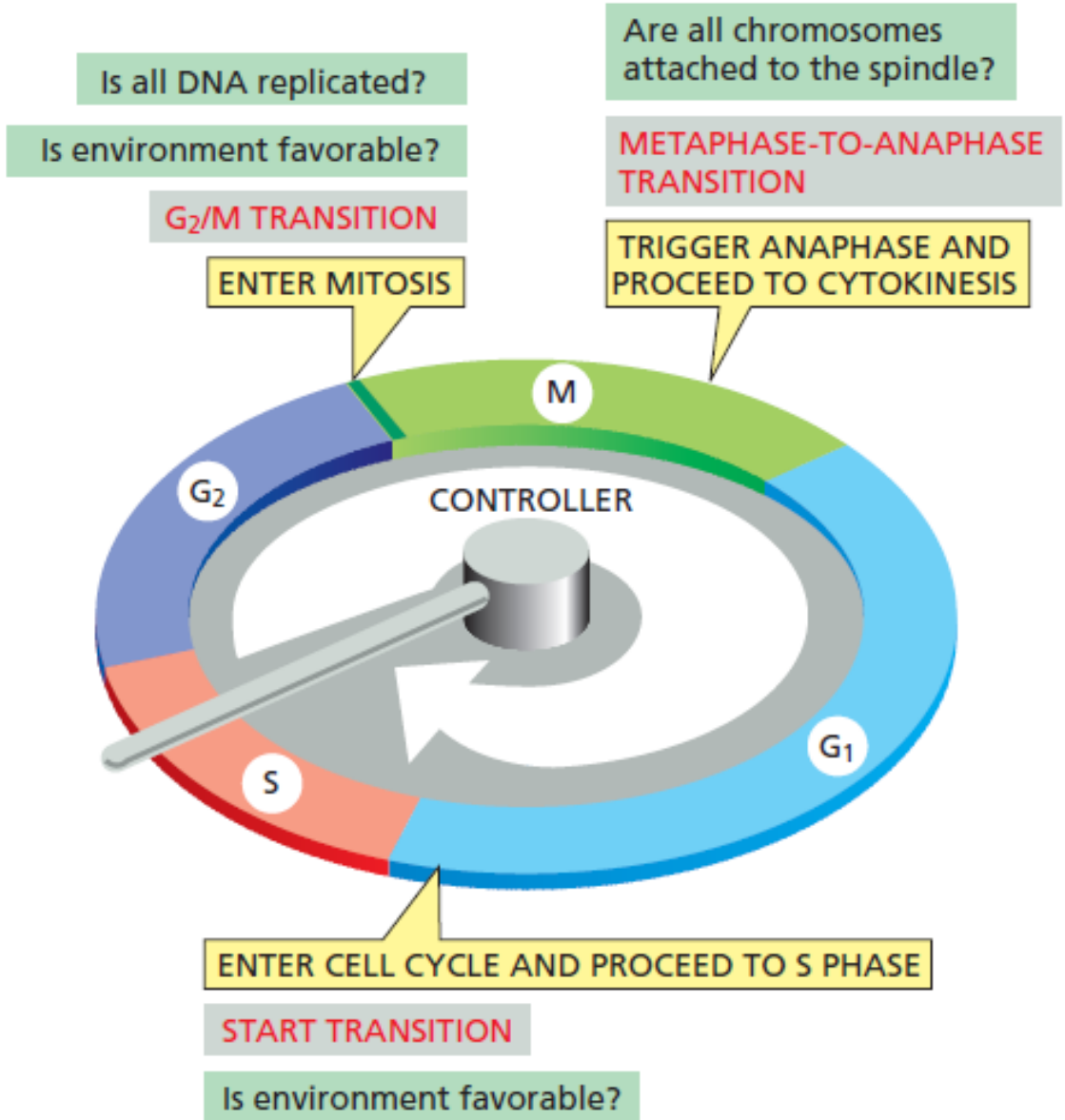


- The events in cell cycle operate with a precision so that cell can move from one stage to the next only if all the needs for the next stage have been completed.

- This regulation of transition from one stage to the next is used for maintaining the health of the cell and the system.

- These regulatory events are called as check points. There are 3 such check points:

1. G_1-S check point.
2. G_2-M check point.
3. M-check point.


Are all chromosomes attached to the spindle?
Is all DNA replicated?
METAPHASE-TO-ANAPHASE TRANSITION
Is environment favorable?
G_2/M TRANSITION
TRIGGER ANAPHASE AND PROCEED TO CYTOKINESIS
ENTER MITOSIS
M
G_2
CONTROLLER
G_1
S
ENTER CELL CYCLE AND PROCEED TO S PHASE
START TRANSITION
Is environment favorable?

- Each check point or restriction point serves particular function.

- The first is Start point in late G1, where the cell commits to cell-cycle entry and chromosome duplication.

- The second is the G2/M transition, where the control system triggers the early mitotic events that lead to chromosome alignment on the mitotic spindle in metaphase.

- The third is the metaphase-to-anaphase transition, where the control system stimulates sister-chromatid separation, leading to the completion of mitosis and cytokinesis.

- The control system blocks progression through each of these transitions if it detects problems inside or outside the cell.

- If the control system senses problems in the completion of DNA replication, it will hold the cell at the G2/M transition until those problems are solved.

- Similarly, if extracellular conditions are not appropriate for cell proliferation, the control system blocks progression through Start, thereby preventing cell division until conditions become favorable.

- Most cells in our body are in G_0, but the molecular basis and reversibility of this state vary in different cell types.

- Most of our neurons and skeletal muscle cells, for example, are in a *terminally differentiated* G_0 state, in which their cell-cycle control system is completely dismantled: the expression of the genes encoding various Cdks and cyclins is permanently turned off, and cell division rarely occurs.

- Some cell types withdraw from the cell cycle only temporarily and retain the ability to reassemble the cell-cycle control system quickly and re-enter the cycle.

- Most liver cells, for example, are in G_0, but they can be stimulated to divide if the liver is damaged.

- Other types of cells, including fibroblasts and some lymphocytes, withdraw from and re-enter the cell cycle repeatedly throughout their lifetime.

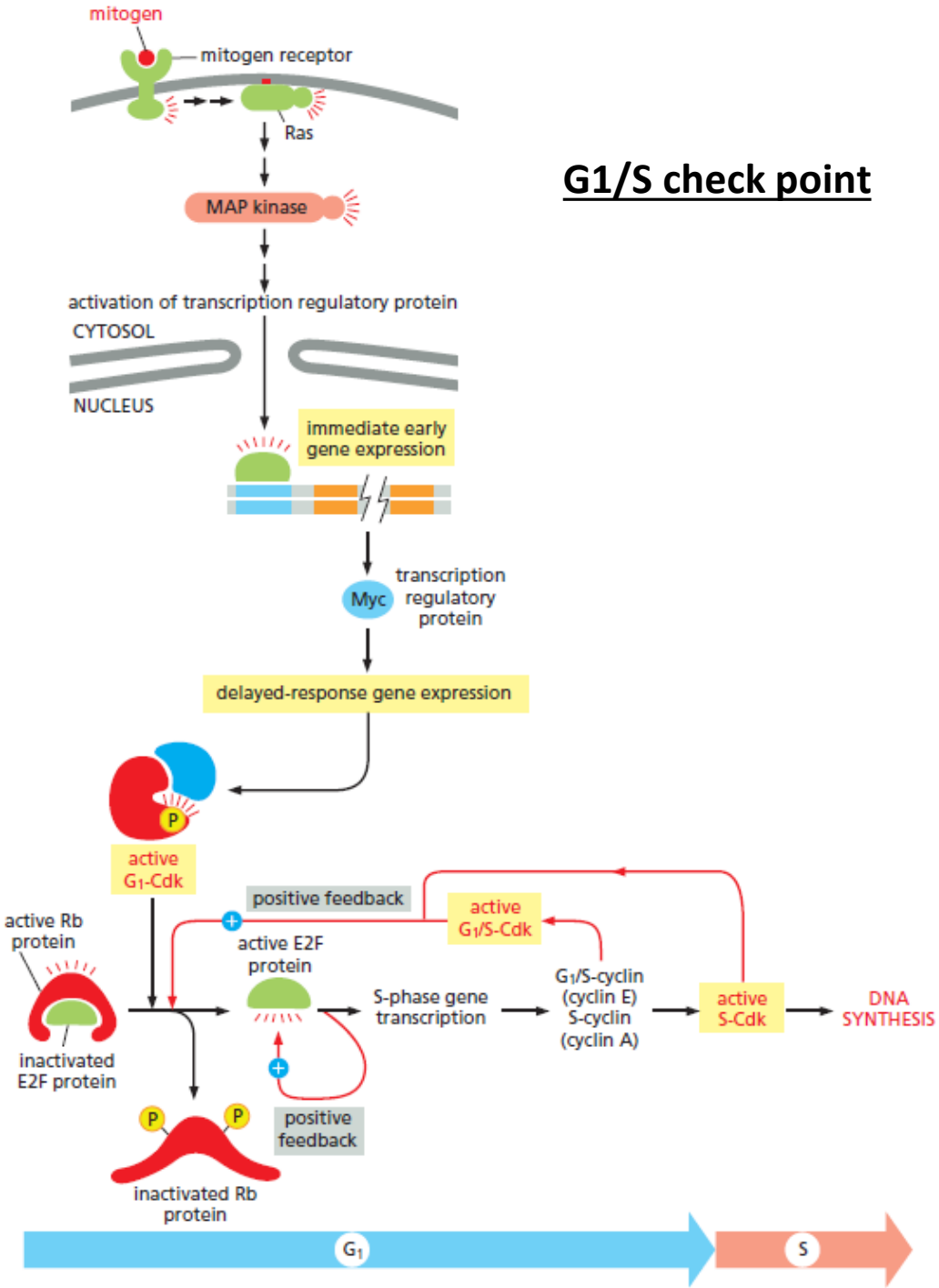
- **<u>How a cell gets the signal to cross G1 and start the process of division??</u>**

- These signals can be divided into 3 broad classes as shown below:

1. *Mitogens*, which stimulate cell division, primarily by triggering a wave of G1/S-Cdk activity. E.g. Platelet derived growth factor or PDGF.

2. *Growth factors*, which stimulate cell growth (an increase in cell mass) by promoting the synthesis of proteins and other macromolecules and by inhibiting their degradation. E.g. Growth hormone.

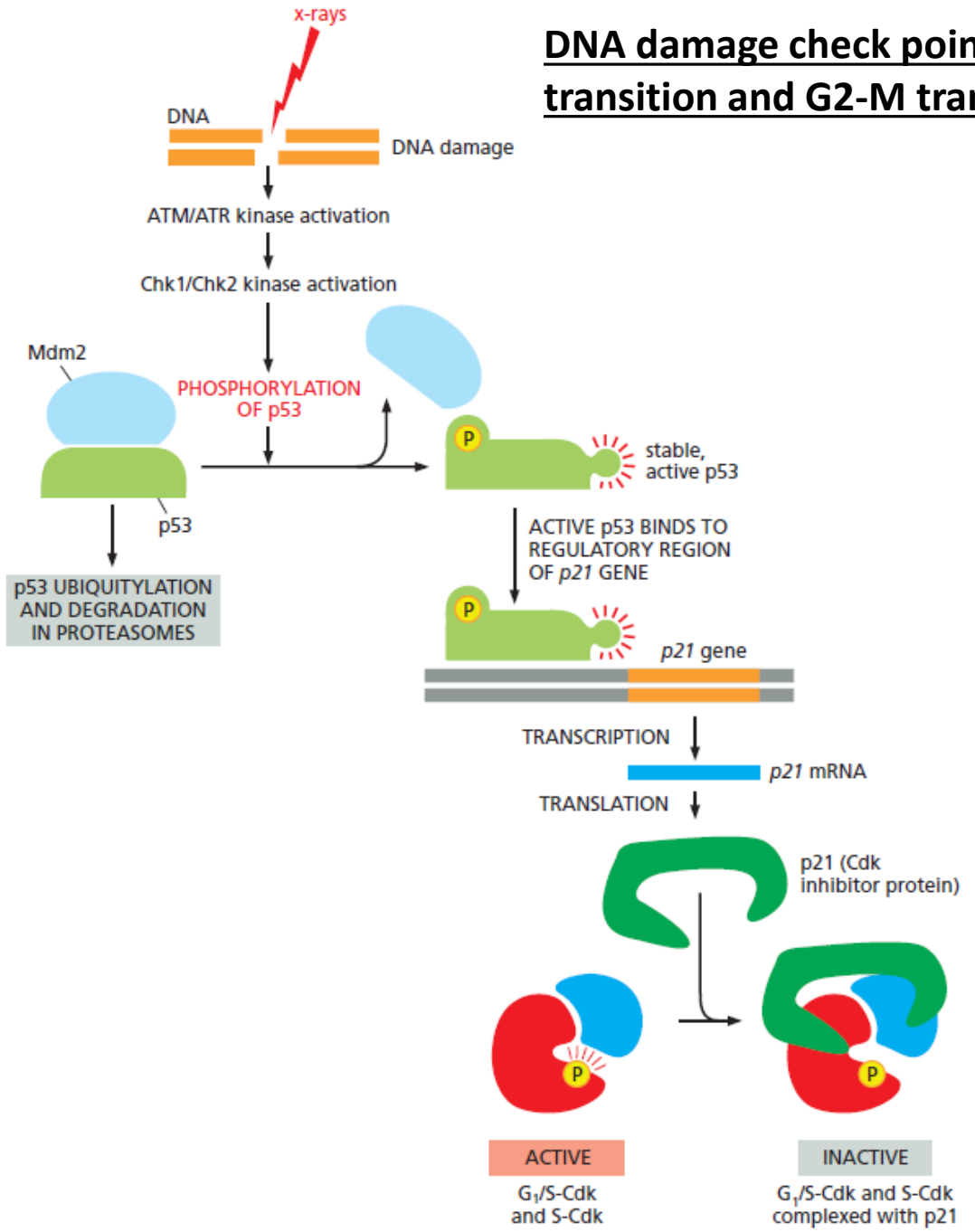
3. *Survival factors*, which promote cell survival by suppressing the form of programmed cell death known as *apoptosis*.



G1/S check point

- Mitogens activate the MAP kinase pathway.
- This pathway activates the expression of Myc gene.
- The myc protein acts to switch on the expression of G1 cyclins and proteins needed for cell growth.
- Now active G1 cyclin-Cdk complexes cause activation of E2F protein. This protein is bound to retinoblastoma protein (Rb) and is inactive.
- The active Cdk causes phosphorylation of Rb and inactivates it. Now, Rb dissociates from E2F and as a result E2F is now active.
- E2F will cause upregulation of proteins needed for the cell to enter S-phase.
- Rb protein was 1st identified in an inherited form of eye cancer in children.
- Loss of both the copies of Rb gene led to tumor in retina due to excessive and uncontrolled cell division.

DNA damage check point at G1-S transition and G2-M transition



- Cell can detect and respond to DNA damage in the cells at G1-S transition and at G2-M transition.
- DNA damage activates kinases ATM and ATR.
- Final effect of their activation is to make protein p53 stable and perform its function.
- p53 is transcriptional regulator for p21 gene.
- p53 causes expression of p21 gene.
- Now p21 protein formed binds to cyclin-cdk complexes and inactivates them.
- As a result, progression of cell cycle to next stage is blocked.
- Loss of function mutation in p53 is associated with half of the cancers. So, it is also called as guardian of genome.
- Mutations in ATM kinase lead to ataxia telangiectasia

- **Human fibroblasts and Hayflick limit:**

- Many human cells divide a limited number of times before they stop and undergo a permanent cell-cycle arrest.

- Fibroblasts taken from normal human tissue, for example, go through only about 25–50 population doublings when cultured in a standard mitogenic medium.

- Toward the end of this time, proliferation slows down and finally halts, and the cells enter a nondividing state from which they never recover.

- This phenomenon is called replicative cell senescence.

- This limit of cell division after which cells can no longer divide in culture is called as Hayflick limit.

- Replicative cell senescence in human fibroblasts seems to be caused by changes in the structure of the telomeres.

- When a cell divides, telomeric DNA sequences are not replicated in the same manner as the rest of the genome but instead are synthesized by the enzyme telomerase.

- Telomerase also promotes the formation of protein cap structures that protect the chromosome ends.

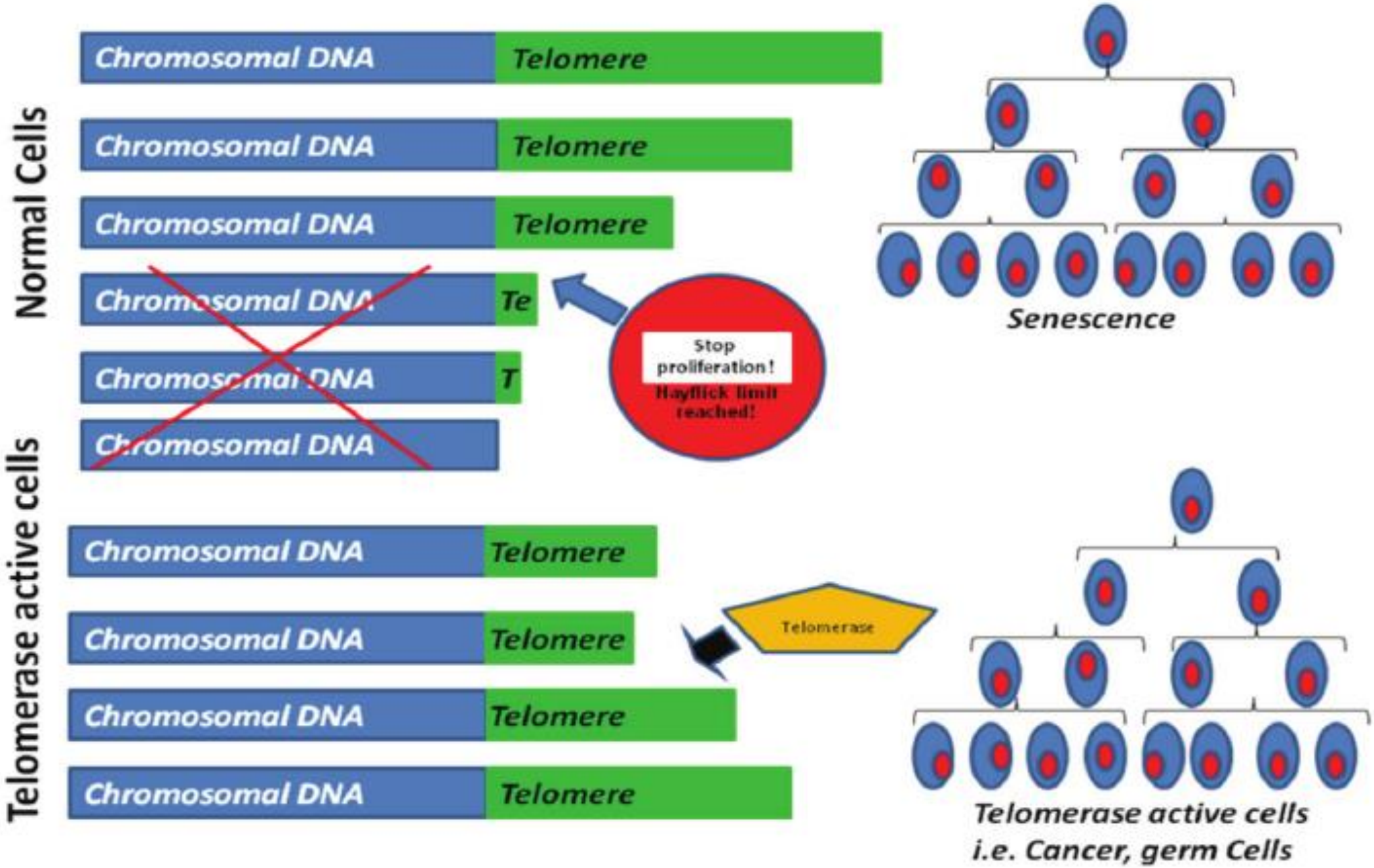
- Because human fibroblasts, and many other human somatic cells, do not produce telomerase, their telomeres become shorter with every cell division, and their protective protein caps progressively deteriorate.

- The exposed chromosome ends are sensed as DNA damage, which activates a p53-dependent cell-cycle arrest.

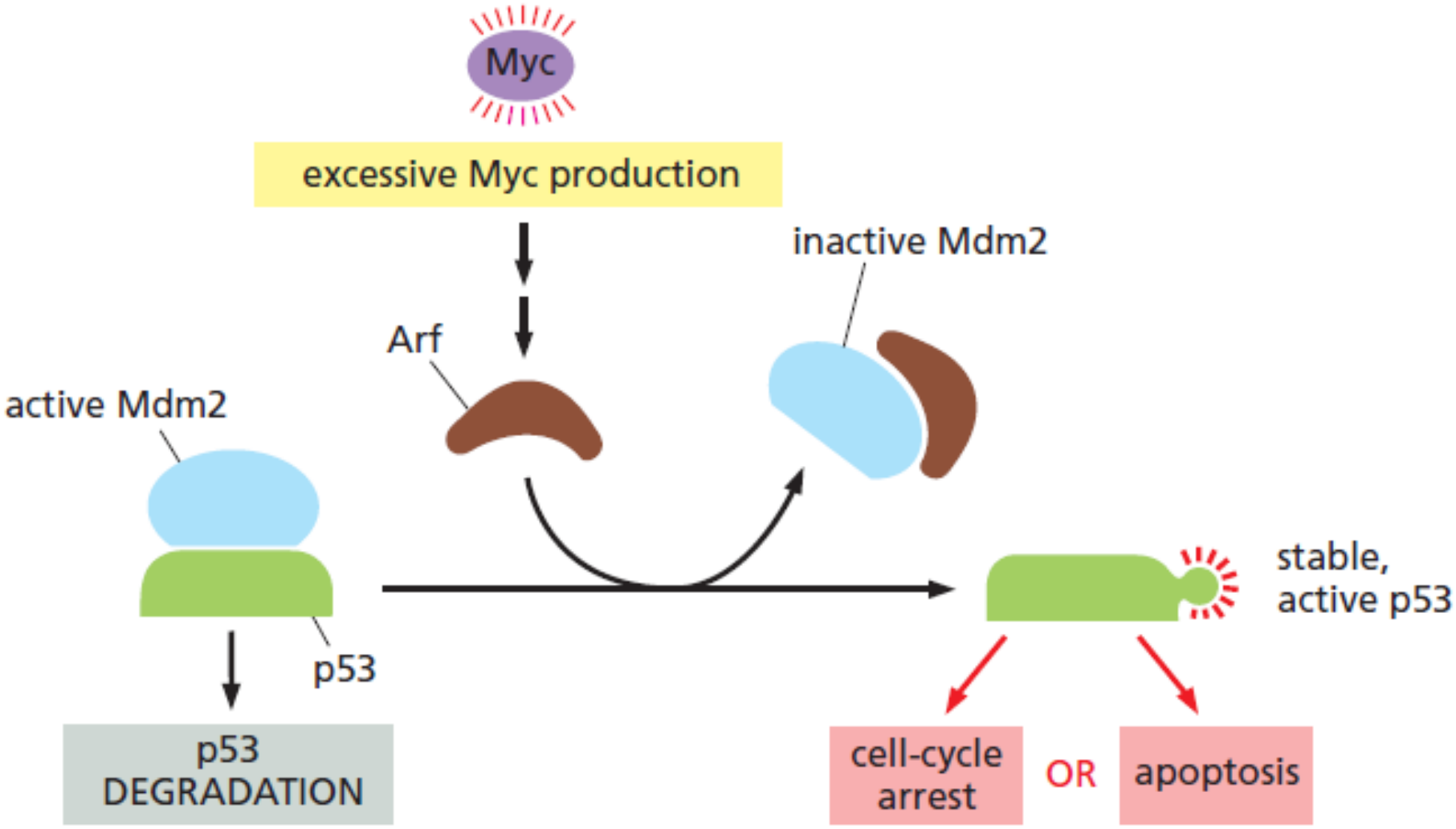
- The forced expression of telomerase in normal human fibroblasts, using genetic engineering techniques, blocks this form of senescence.

- Most cancer cells have regained the ability to produce telomerase and therefore maintain telomere function as they proliferate.

- As a result, they do not undergo replicative cell senescence.


Normal Cells
Chromosomal DNA
Telomere
Chromosomal DNA
Telomere
Chromosomal DNA
Telomere
Chromosomal DNA
Te
Chromosomal DNA
T
Chromosomal DNA
Stop proliferation!
Hayflick limit reached!
Senescence
Telomerase active cells
Chromosomal DNA
Telomere
Chromosomal DNA
Telomere
Chromosomal DNA
Telomere
Chromosomal DNA
Telomere
Telomerase
Telomerase active cells
i.e. Cancer, germ Cells

- Abnormal Proliferation Signals Cause Cell-Cycle Arrest or Apoptosis, except in Cancer Cells.



- **Cancer:** It refers to unregulated cell division and development of tumour due to the unregulated cell division.

- These tumours can be of two types

1. Benign, ones that are located at a place and cell are not metastatic yet.

2. Malignant, ones where cells have become metastatic and are able to spread to other parts from their site of origin.

- Malignant tumours are more difficult to treat.

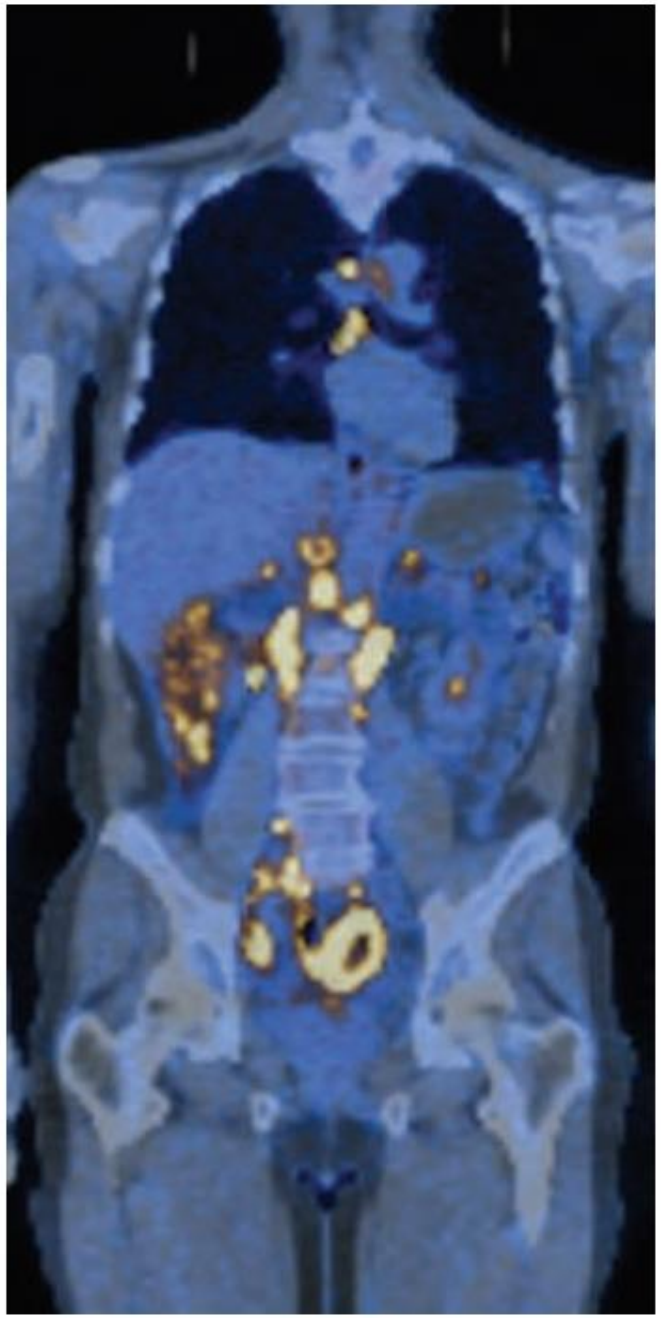


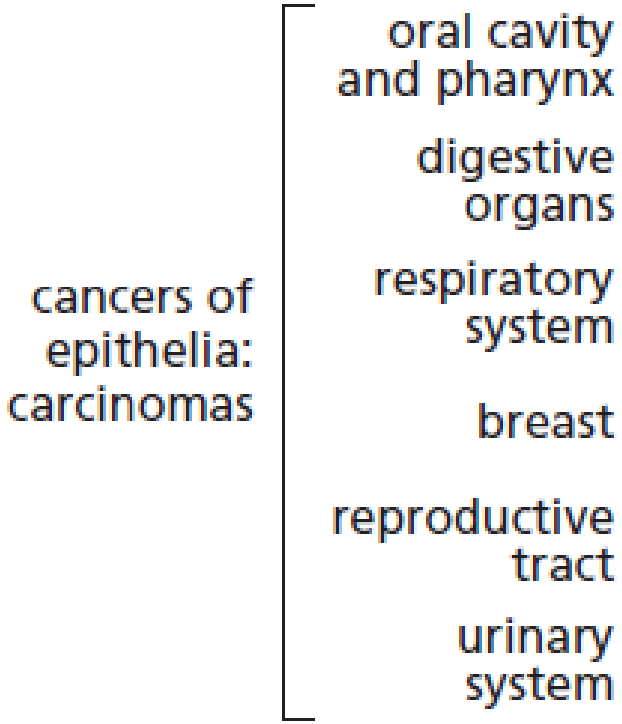
Figure: Metastatic tumour PET scan

- Cancers are defined as a microevolutionary process.

- Cancers are classified according to the tissue and cell type from which they arise.
- Carcinomas are cancers arising from epithelial cells, and they are most common cancers in humans. They account for about 80% of cases, perhaps because most of the cell proliferation in adults occurs in epithelia.

- Sarcomas arise from connective tissue or muscle cells.

- Cancers that do not fit in either of these two broad categories include the various leukemias and lymphomas, derived from white blood cells and their precursors (hemopoietic cells), as well as cancers derived from cells of the nervous system.



- Naming a cancer and reflection of benignness or malignancy in the name is given below.
- Name of a cancer shows its tissue of origin.
- names for benign tumors: an *adenoma*, for example, is a benign epithelial tumor with a glandular organization.
- the corresponding type of malignant tumor is an *adenocarcinoma.*
- Similarly, a *chondroma* and a *chondrosarcoma* are, respectively, benign and malignant tumors of cartilage.

- **Reasons for loss of cell cycle regulation:**

- *Infection by viruses*:

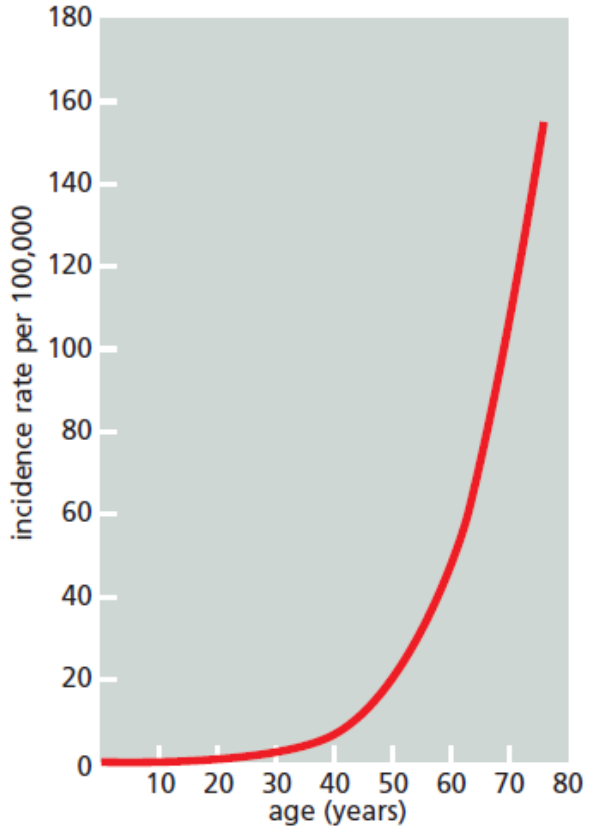
- These viruses are broadly divided into two large groups:**DNA tumor viruses** and **RNA tumor viruses**, depending on the type of nucleic acid found within the mature virus particles.

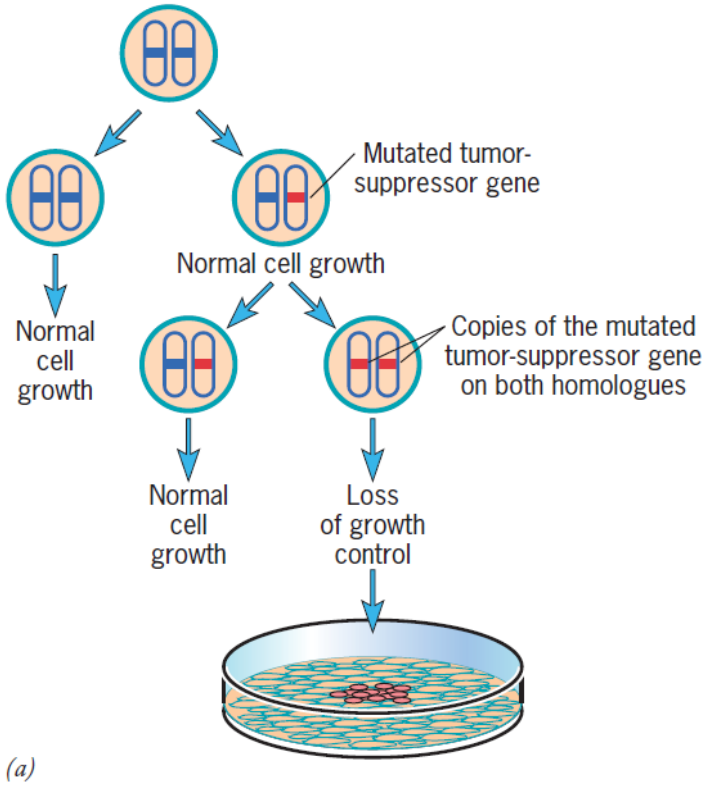
- Among the DNA viruses capable of transforming cells are polyoma virus, simian virus 40 (SV40), adenovirus, and herpes-like viruses.

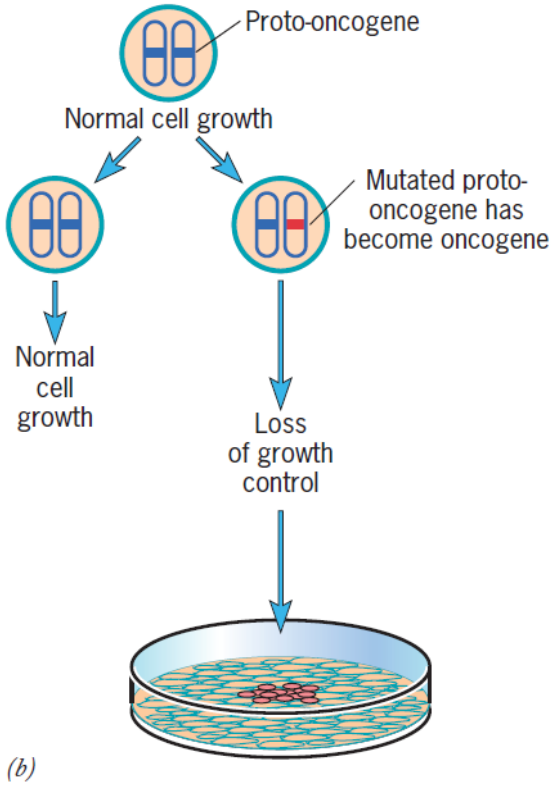
- RNA tumor viruses include Raus sarcoma virus, hairy cell leukemia virus.

- **Human Papilloma virus or HPV is a DNA virus and is associated with majority of the cases of cervical cancer.**

- *Accumulation of somatic mutations:*







- **Tumor-suppressor genes** act as a cell's brakes; they encode proteins that restrain cell growth and prevent cells from becoming malignant. E.g. p53

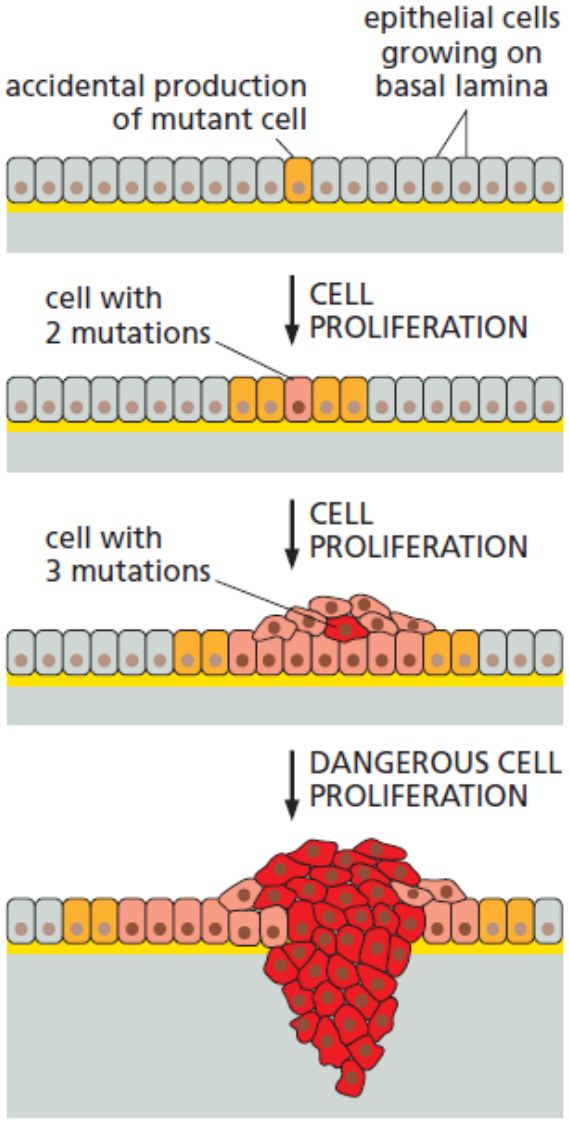
- **Oncogenes**, on the other hand, encode proteins that promote the loss of growth control and the conversion of a cell to a malignant state. E.g. myc, src etc.

- These oncogenes are not cancerous originally. It is the mutations in them that make them oncogenic.

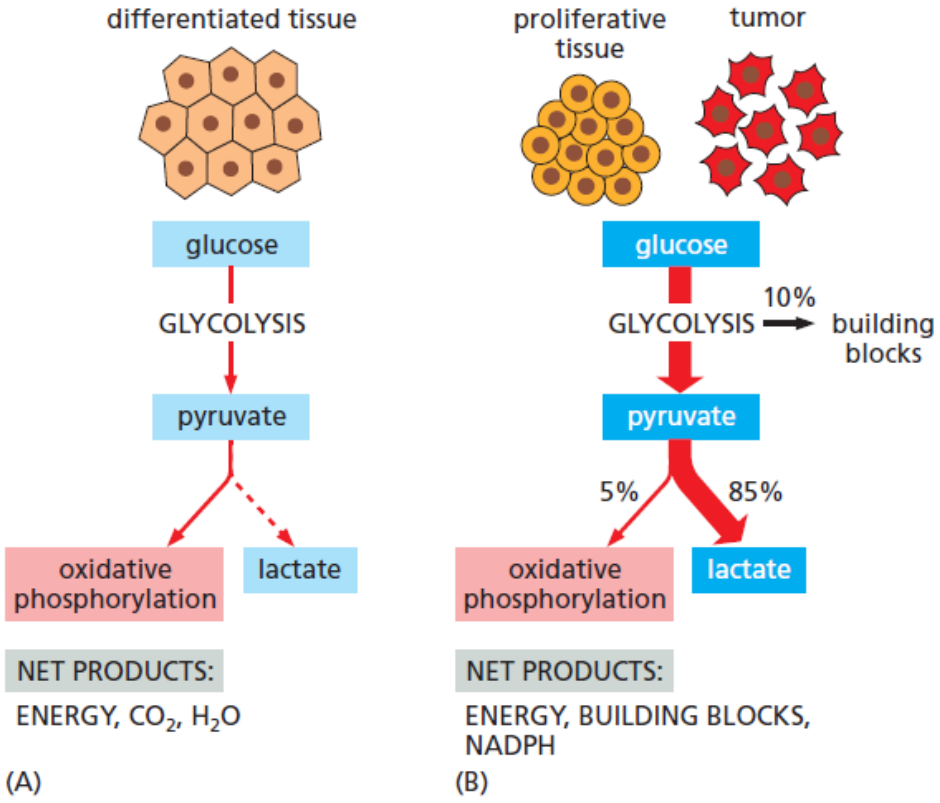
- Because most of the proto oncogenes have roles in the regulation or promotion of cell cycle, their mutations lead to aberrant cell cycle.

- *Properties of cancer cells:*

1. Cancer cells are monoclonal.



2. Cancer cells have abnormal metabolism.



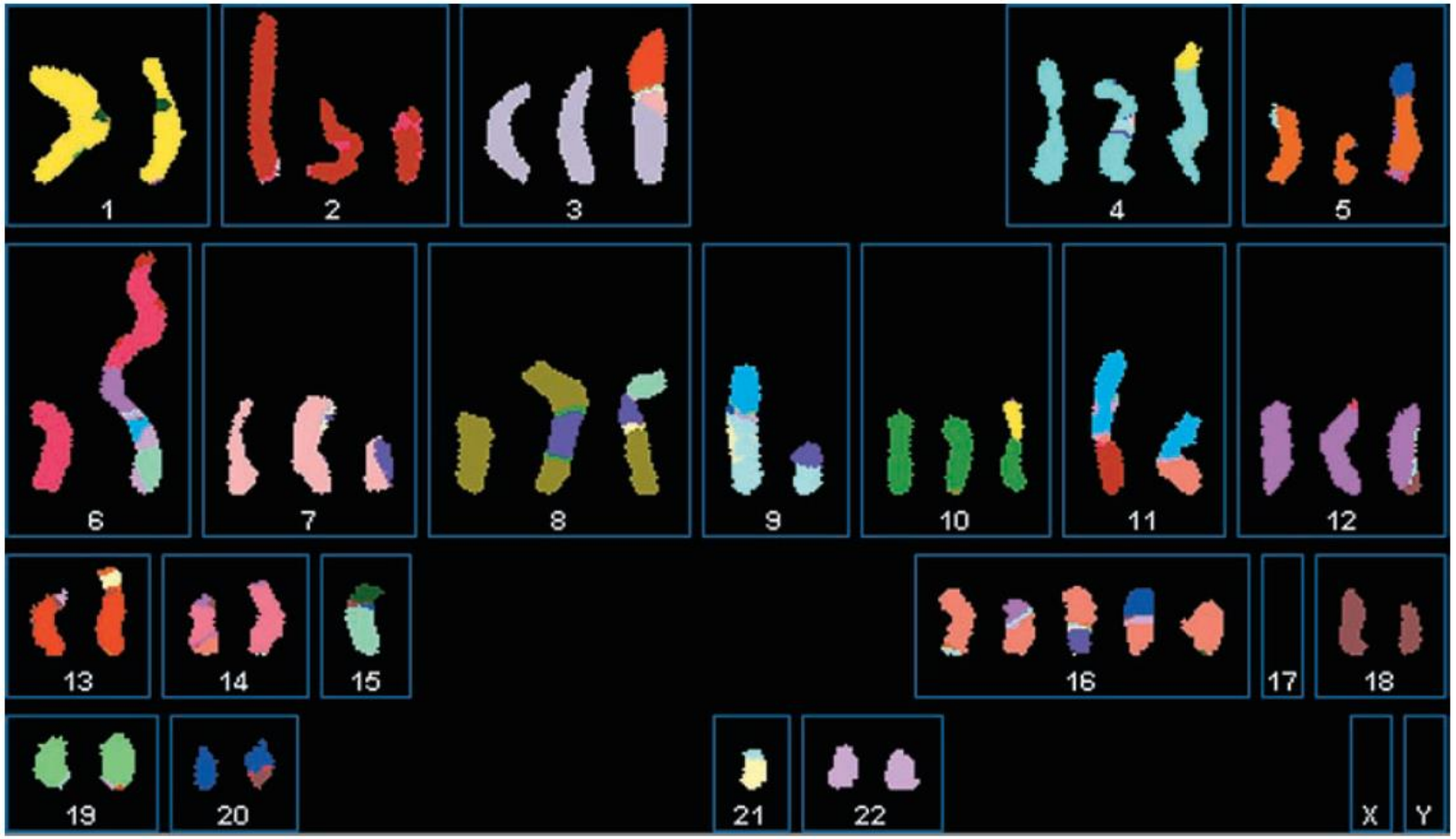
- A growing tumor needs nutrients in abundance to provide the building blocks to make new macromolecules.
- So, most tumors have a metabolism more similar to that of a growing embryo than to that of normal adult tissue.

- Tumor cells consume glucose avidly, importing it from the blood at a rate that can be as much as 100 times higher than neighboring normal cells.
- Moreover, only a small fraction of this imported glucose is used for production of ATP by oxidative phosphorylation.

- Instead, a great deal of lactate is produced, and many of the remaining carbon atoms derived from glucose are diverted for use as raw materials for synthesis of the proteins, nucleic acids, and lipids required for tumor growth.

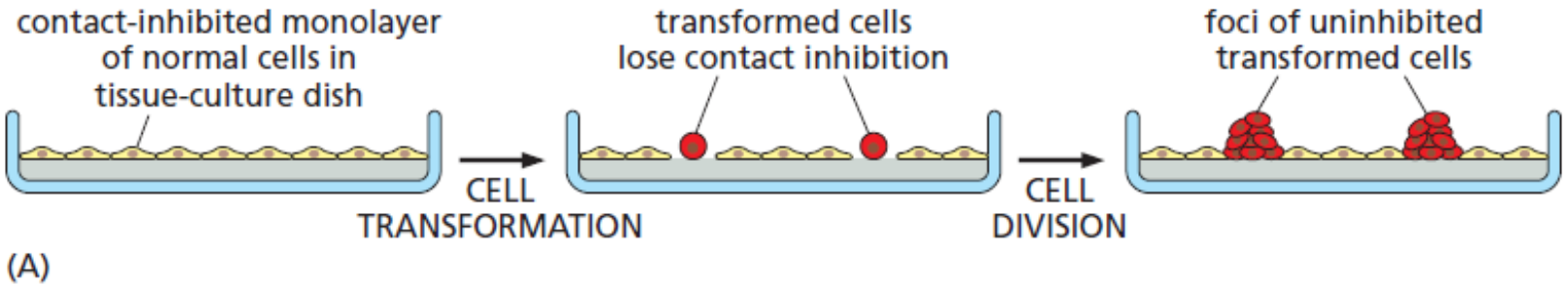
This tendency of tumor cells to de-emphasize oxidative phosphorylation even when oxygen is plentiful, while at the same time taking up large quantities of glucose, can be shown to promote cancer cell growth and is called the *Warburg effect.*

3. Cancer cells are genetically unstable.

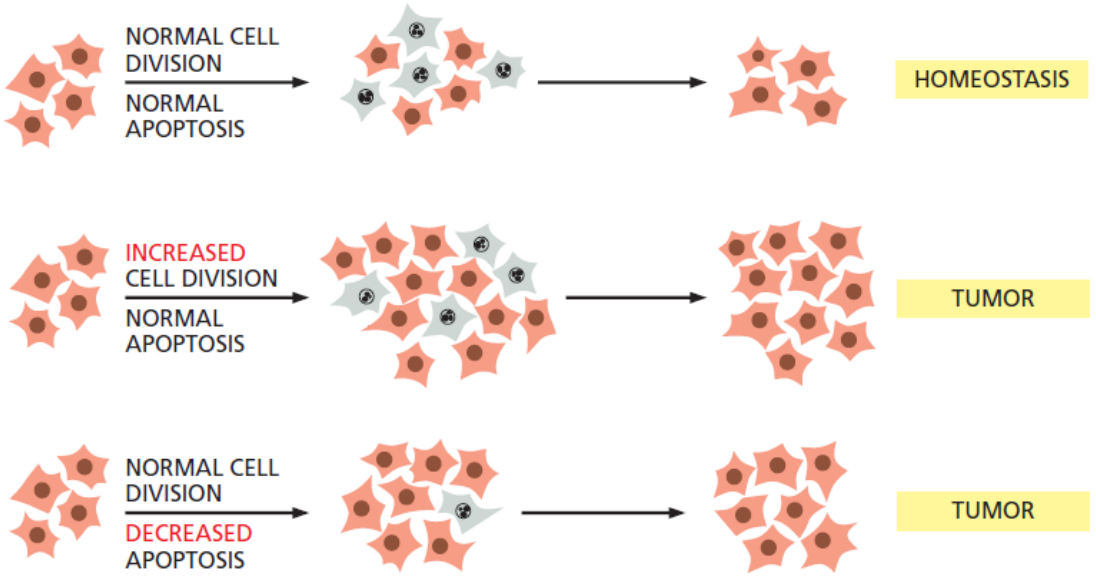


Karyotype of breast cancer cell

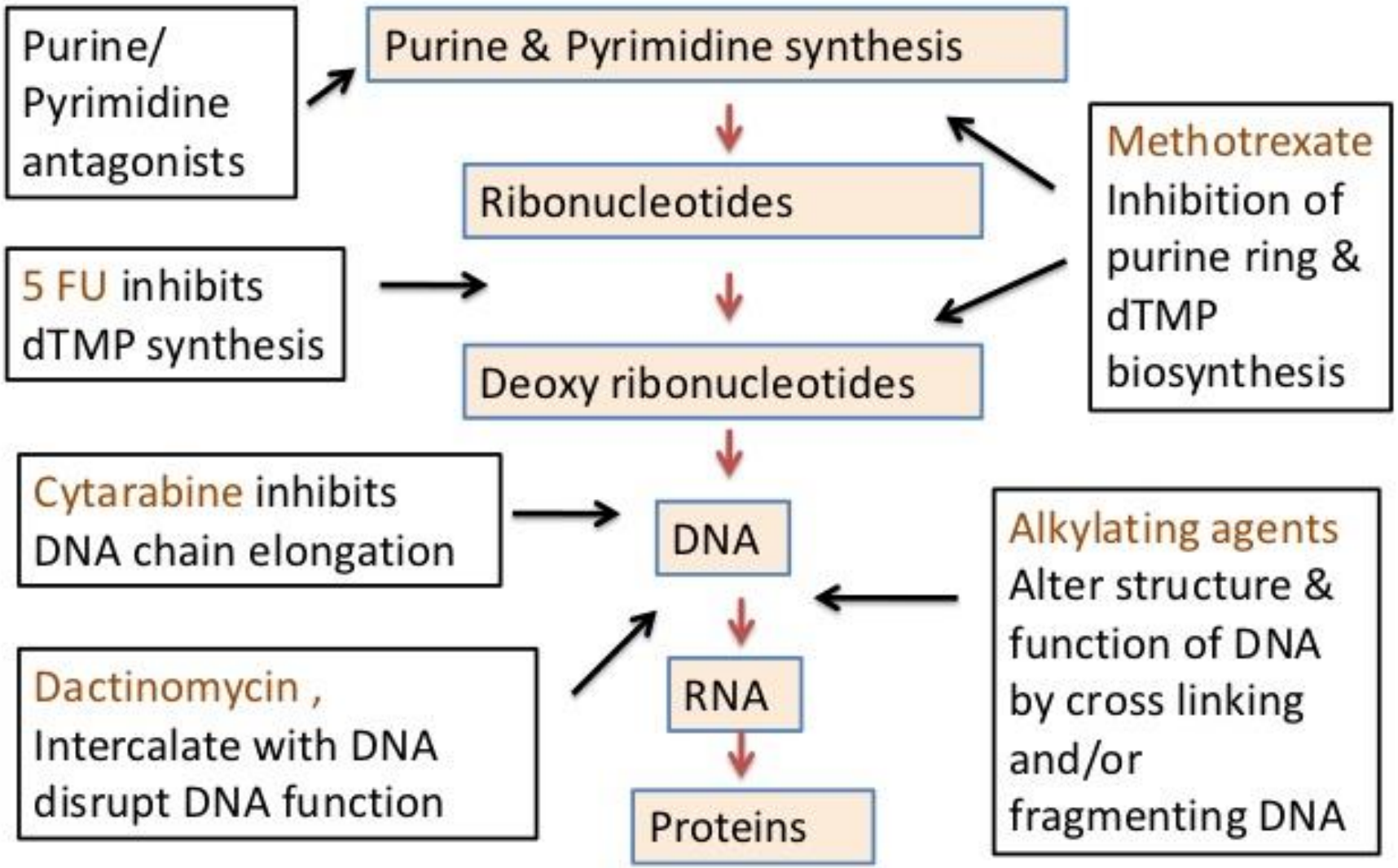
4. *Cancer cells lose contact inhibition and it helps them in metastasis.*



5. *Cancer cells have poor apoptosis regulation.*



MOA of some anticancer drugs



Thank you