BHARATHIDASAN UNIVERSITY

Tiruchirappalli- 620024

Tamil Nadu, India

Programme: M.Sc., Biochemistry

Course Title : Biochemistry of Signal Transduction

Course Code : BC203CR

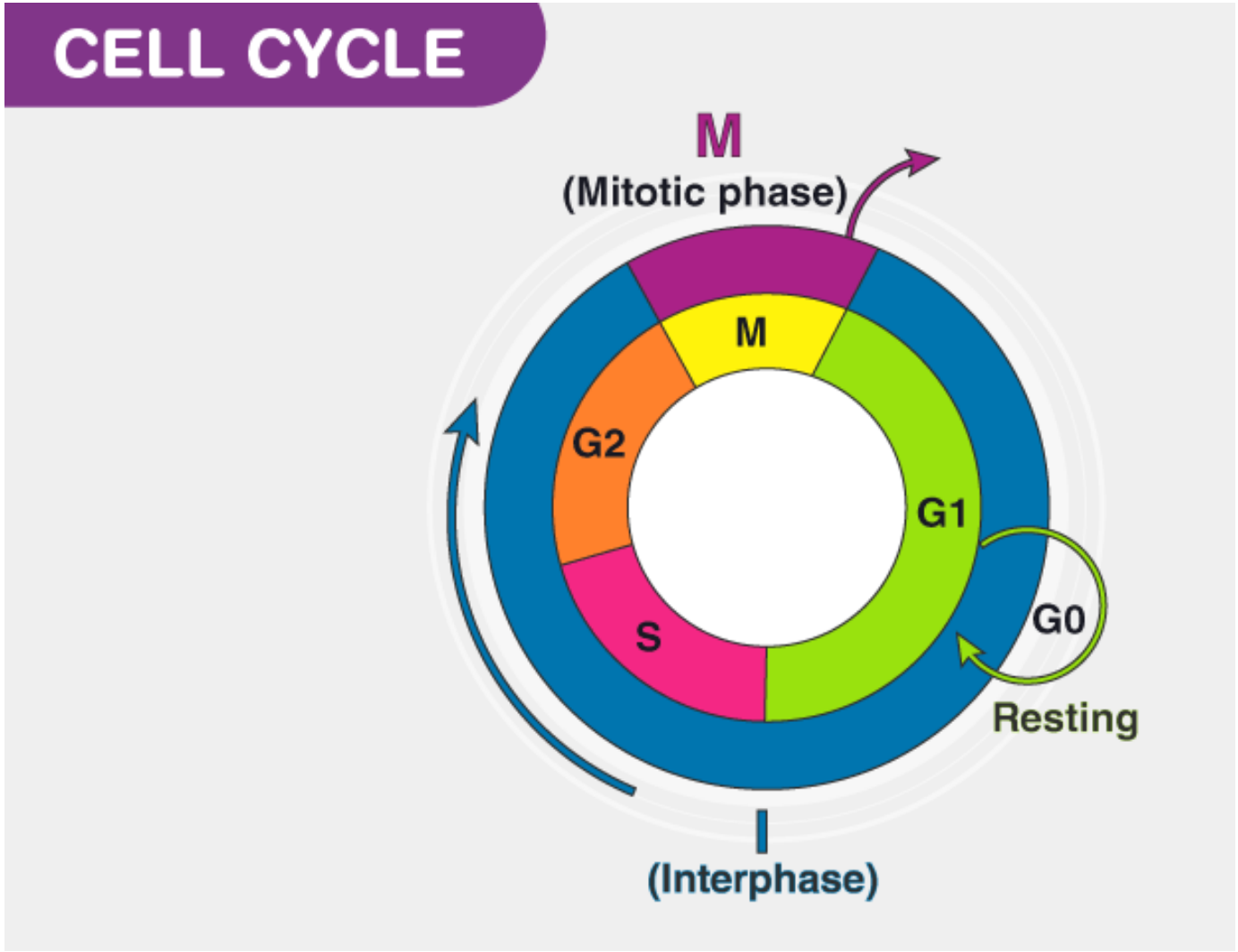
Unit-5

Cell Cycle and its Regulation

Dr. C. Prahalathan

Professor

Cell Cycle and its Regulation



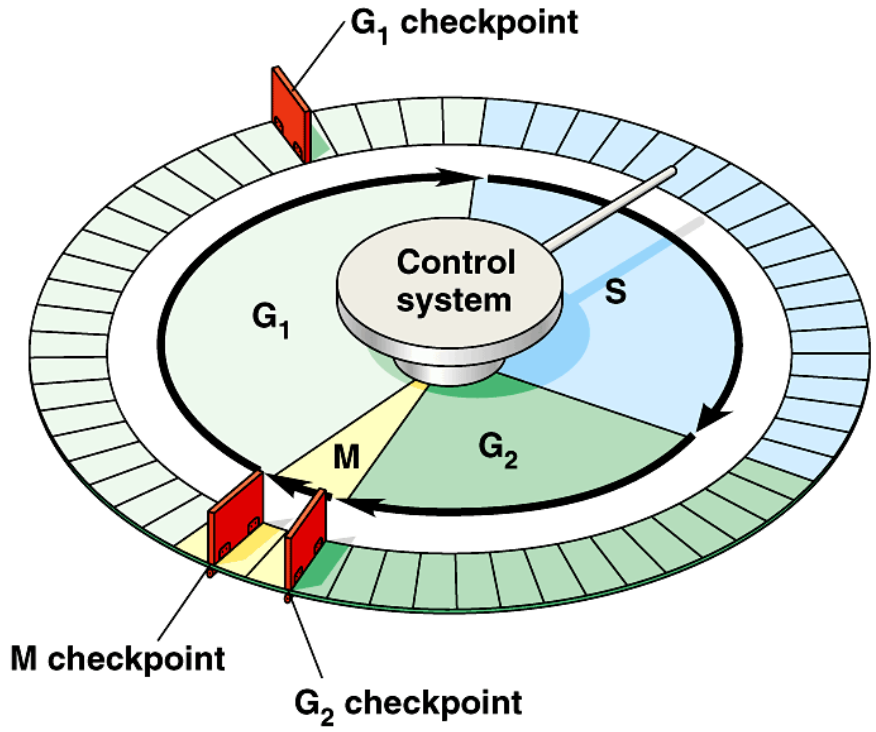
"Cell cycle refers to the series of events that take place in a cell, resulting in the duplication of DNA and division of cytoplasm and organelles to produce two daughter cells."

Cell Cycle Control

- Two irreversible points in cell cycle
  - replication of genetic material
  - separation of sister chromatids
- Cell can be put on hold at specific checkpoints

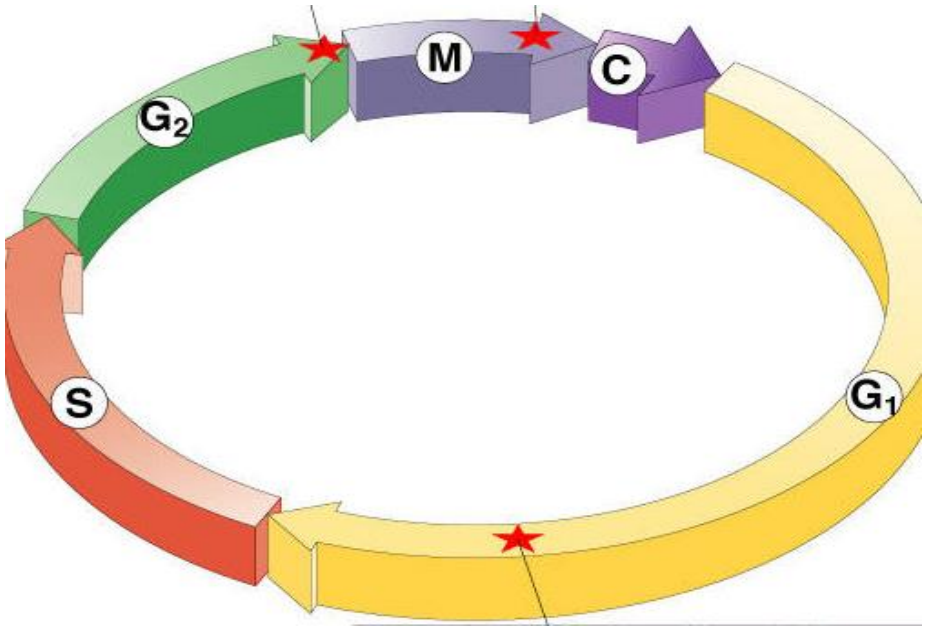
Checkpoint control system

- Checkpoints
  - cell cycle controlled by STOP & GO chemical signals at critical points
  - signals indicate if key cellular processes have been completed correctly



Checkpoint control system

- 3 major checkpoints:
  - G_1 checkpoint
    - can DNA synthesis begin?
  - G_2 checkpoint
    - has DNA been copied correctly?
    - commitment to mitosis
  - M checkpoint
    - AKA spindle checkpoint
    - Are chromosomes attaches to spindle properly allowing for sister chromatids to separate correctly?

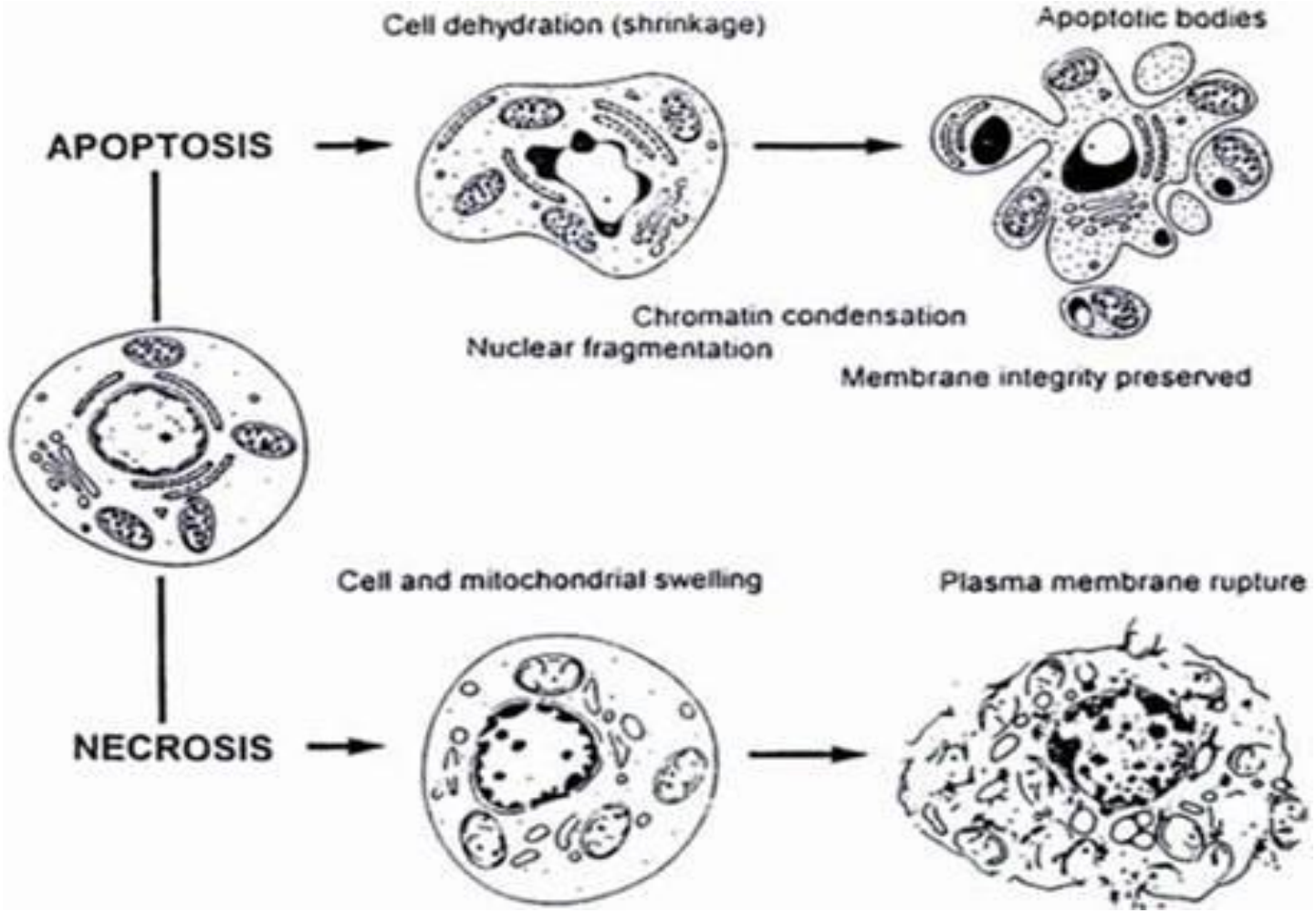


Apoptosis – Programmed Cell Death

- (True/False) In adult tissues cell death exactly balances cell division
- In apoptosis the cell destroys itself from within and avoids leakage of the cell contents into the extracellular space. Why do you think that this occurs via a different mechanism than in necrosis?
- What are some signals that indicate to a cell that apoptosis needs to occur? Where do these signals come from?
- What are some cellular components involved in the apoptotic pathway?
- What is the difference between a mitogen, a growth factor, and a survival factor?
- In what phase of the cell cycle do cells exit to undergo apoptosis?
- What effects do telomeres and telomerase have on cell aging and death? If you could turn on telomerase activity in all of our cells, would it prevent aging?
- Do the following types of cells exist in humans?
  - –Cells that do not grow and do not divide
  - –Cells that grow, but do not divide
  - –Cells that divide, but do not grow
  - –Cells that grow and divide

Death by Injury vs. Death by Suicide

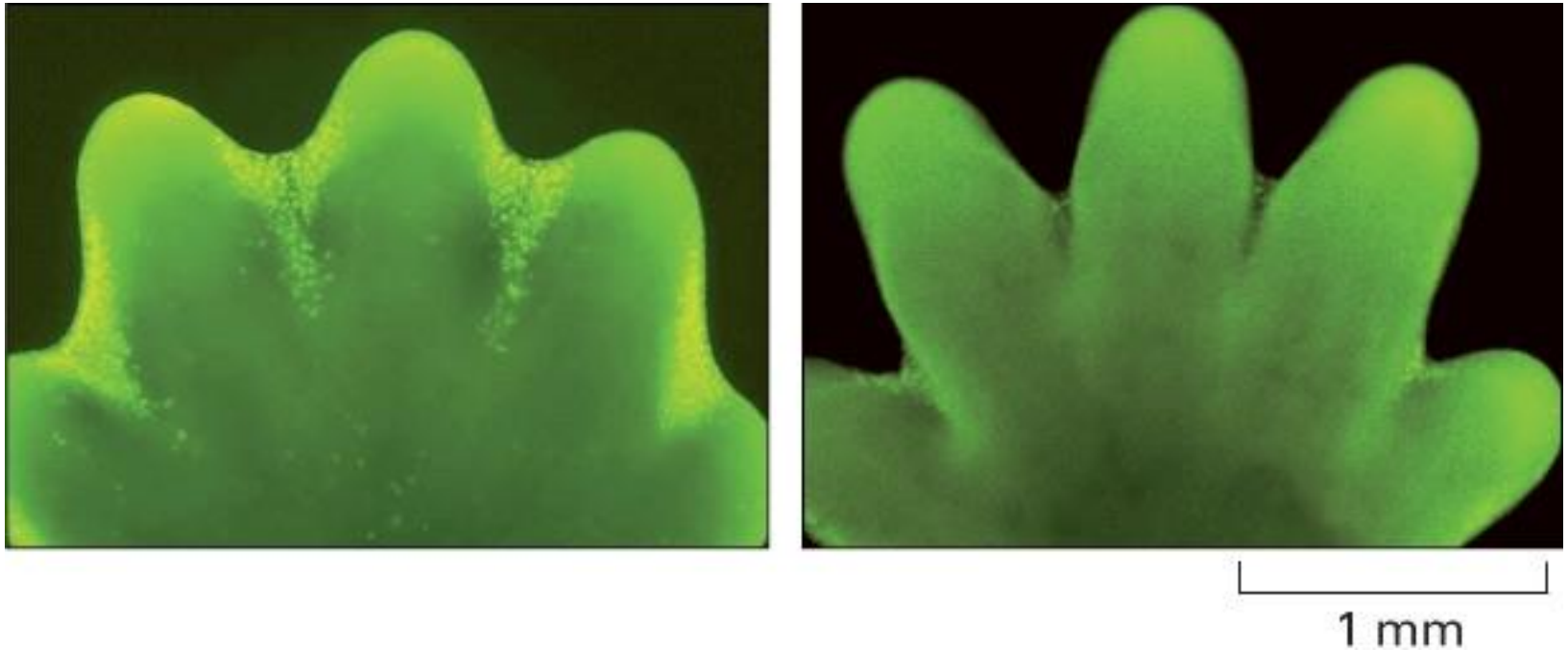
(Necrosis vs. Apoptosis)



Apoptosis – Programmed Cell Death

- Developmental
- Protective (destroy cells that are a threat)
- Infected with virus
- Turn off immune response
- DNA damaged cells
- Cancer

WHY?



What makes a cell commit suicide?

- ✓ Withdrawal of positive signals (growth factors, Il-2)
- ✓ Receipt of negative signals (increased levels of oxidants, DNA damage via X-ray or UV light, chemotherapeutic drugs, accumulation of improperly folded proteins, death activators such as: TNF-a, TNF-b, Fas / FasL)

Steps in apoptosis:

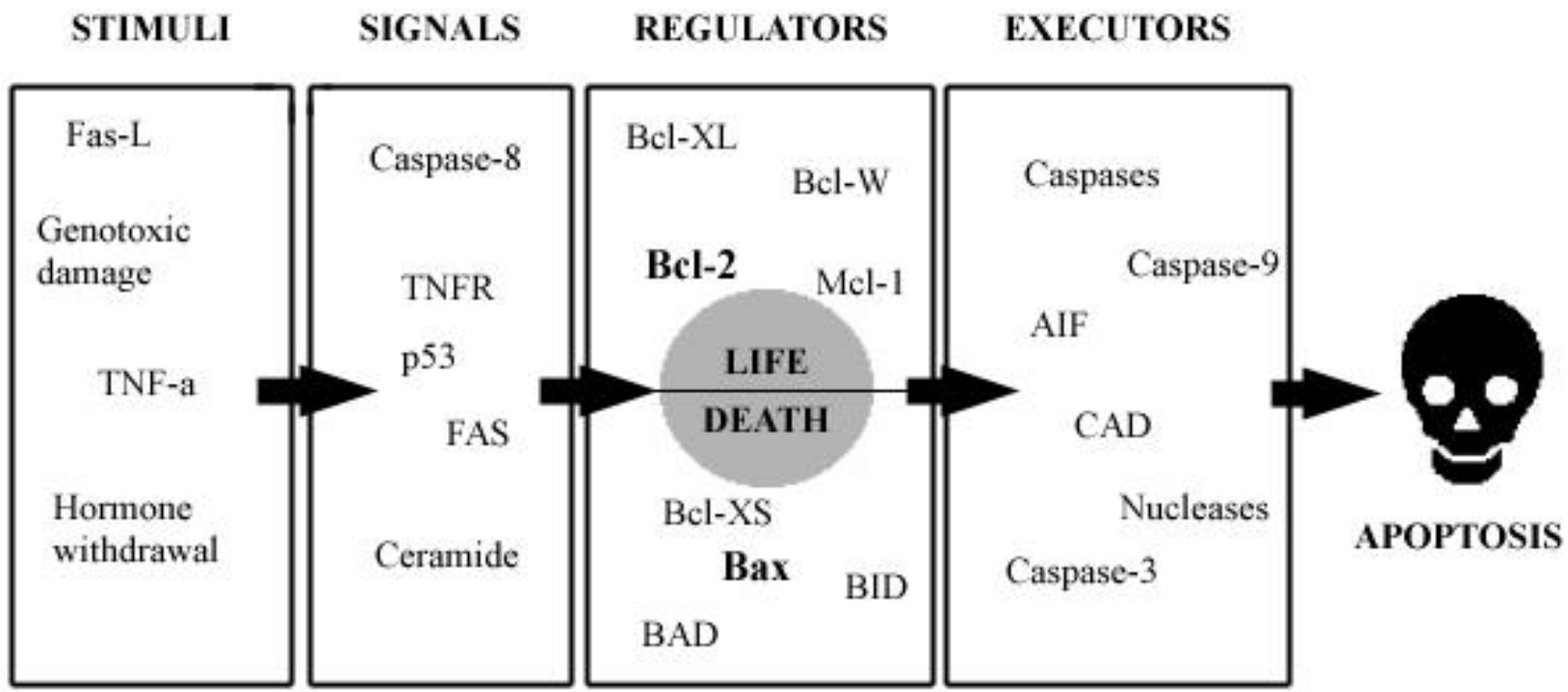
- ✓ The decision to activate the pathway;
- ✓ The actual "suicide" of the cell;
- ✓ Engulfment of the cell remains by specialized immune cells called phagocytes;
- ✓ Degradation of engulfed cell.

The actual steps in cell death require:

- ✓ Condensing of the cell nucleus and breaking it into pieces
- ✓ Condensing and fragmenting of cytoplasm into membrane bound apoptotic bodies;
- ✓ Breaking chromosomes into fragments containing multiple number of nucleosomes (a nucleosome ladder)

Apoptosis Triggered via Two Pathways

- ✓ Intrinsic or mitochondrial pathway
- ✓ Extrinsic or death receptor pathway

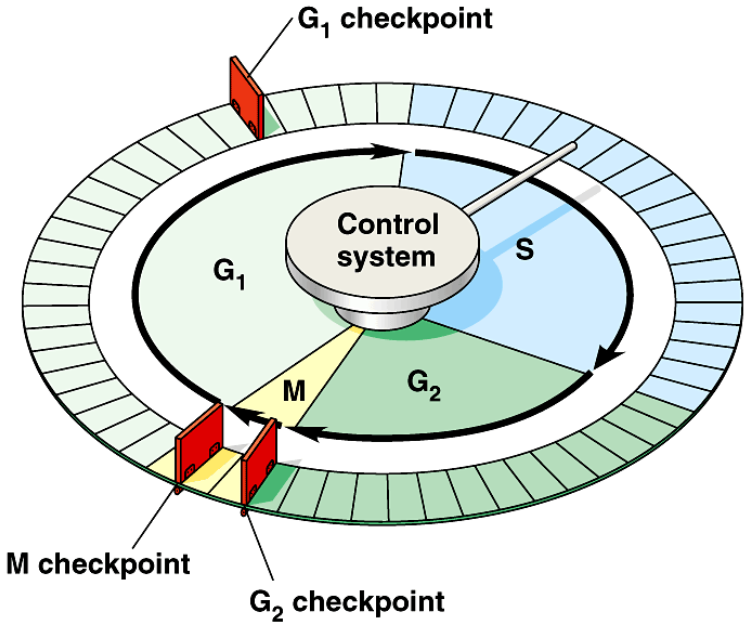

STIMULI
SIGNALS
REGULATORS
EXECUTORS
Fas-L
Genotoxic damage
TNF-a
Hormone withdrawal
Caspase-8
TNFR
p53
FAS
Ceramide
Bcl-XL
Bcl-W
Bcl-2
Mcl-1
LIFE
DEATH
Bcl-XS
Bax
BID
BAD
Caspases
Caspase-9
AIF
CAD
Nucleases
Caspase-3
APOPTOSIS

Cancer

- Uncontrolled cell growth
  - Why??
  - Checkpoints in cell cycle break down
    - Due to mutations in genes that produce proteins that control the checkpoints
  - Can cause tumors (mass of cells)
    - Malignant tumor – cancerous tumor that may spread to other areas of the body
    - Benign tumor – non-cancerous tumor
    - Biopsy- sample tissue is taken from tumor to determine if it is cancerous or not
  - Metastasis- the spreading of cancer from one part of the body to another

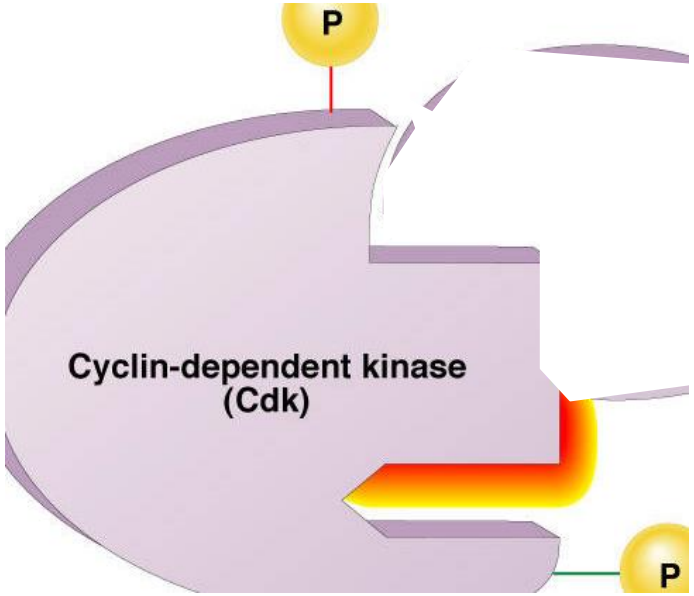
G_1 checkpoint

- G_1 checkpoint is most critical
  - primary decision point
  - if cell receives "go" signal, it divides!
  - if does not receive "go" signal, cell exits cycle & switches to G_0 phase or apoptosis occurs



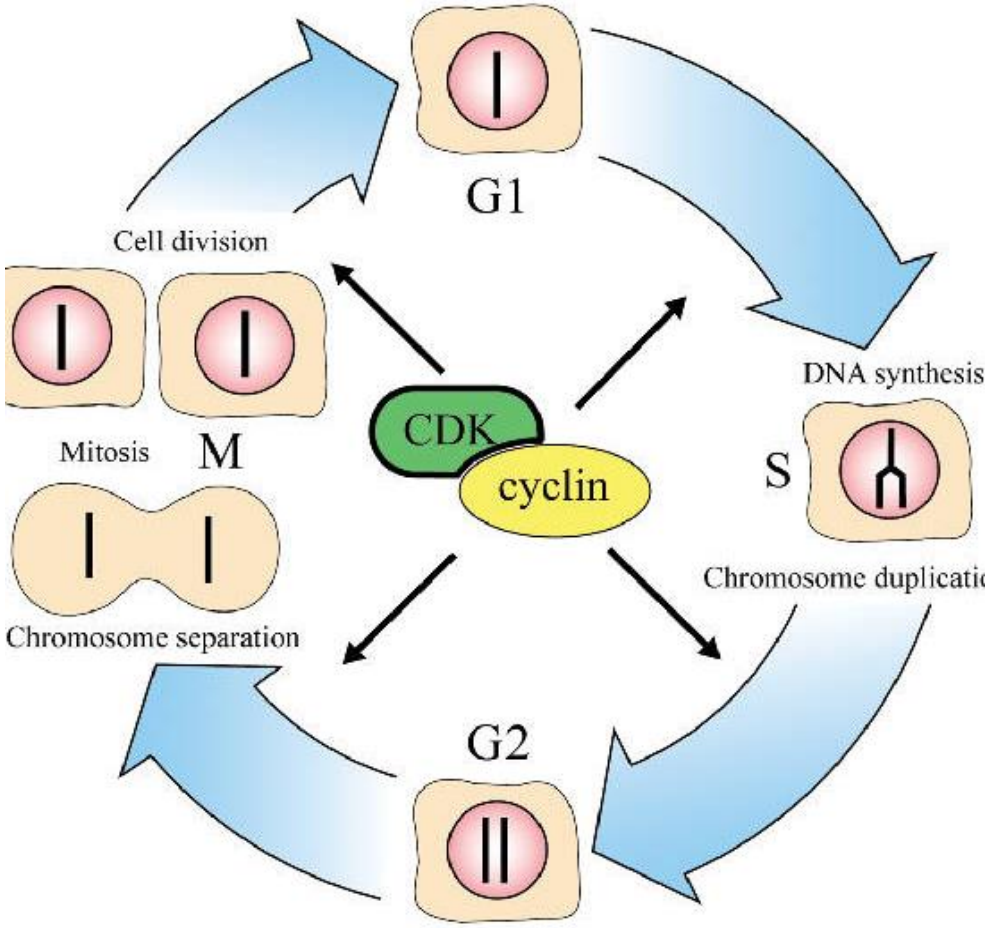
“Go-ahead” signals

- Signals that promote cell growth & division
  - proteins
  - internal signals
    - “promoting factors”
  - external signals
    - “growth factors”
- Primary mechanism of control
  - phosphorylation
    - kinase enzymes



Cyclin & Cyclin dependent kinases

- CDKs & cyclin drive cell from one phase to next in cell cycle



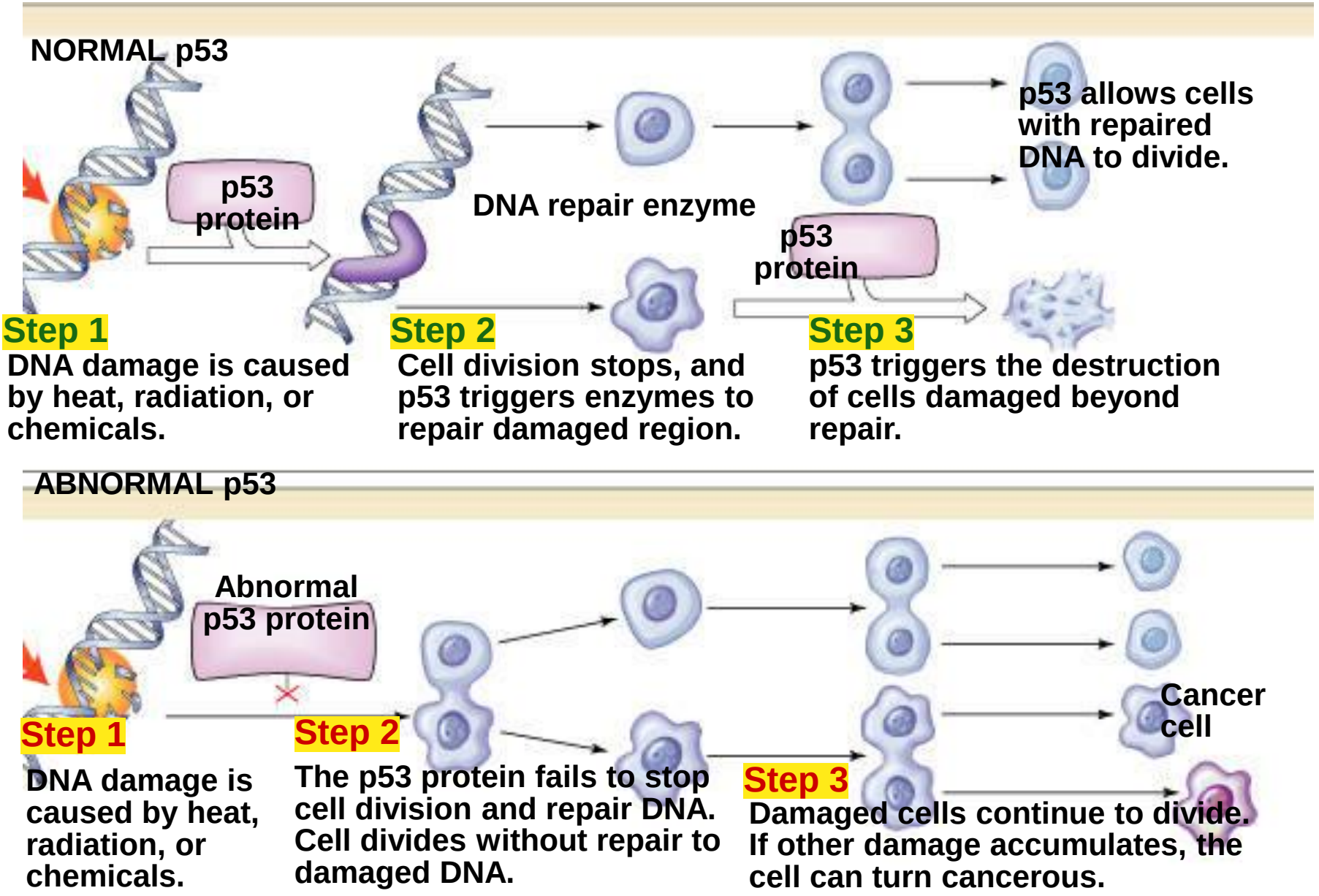
Growth Factors and Cancer

- Growth factors influence cell cycle
  - proto-oncogenes
    - normal genes that become oncogenes (cancer-causing) when mutated
    - stimulates cell growth
    - if switched on can cause cancer
    - example: RAS (activates cyclins)
  - tumor-suppressor genes
    - inhibits cell division
    - if switched off can cause cancer
    - example: p53

Cancer & Cell Growth

- Cancer is essentially a failure of cell division control
  - unrestrained, uncontrolled cell growth
- What control is lost?
  - checkpoint stops
  - gene p53 plays a key role in G_1 checkpoint
    - p53 protein halts cell division if it detects damaged DNA
      - stimulates repair enzymes to fix DNA
      - forces cell into G_0 resting stage
      - keeps cell in G_1 arrest
      - causes apoptosis of damaged cell
    - ALL cancers have to shut down p53 activity

p53 — master regulator gene



Development of Cancer

- Cancer develops only after a cell experiences
  - unlimited growth
    - turn on growth promoter genes
  - ignore checkpoints
    - turn off tumor suppressor genes
  - escape apoptosis
    - turn off suicide genes
  - immortality = unlimited divisions
  - promotes blood vessel growth

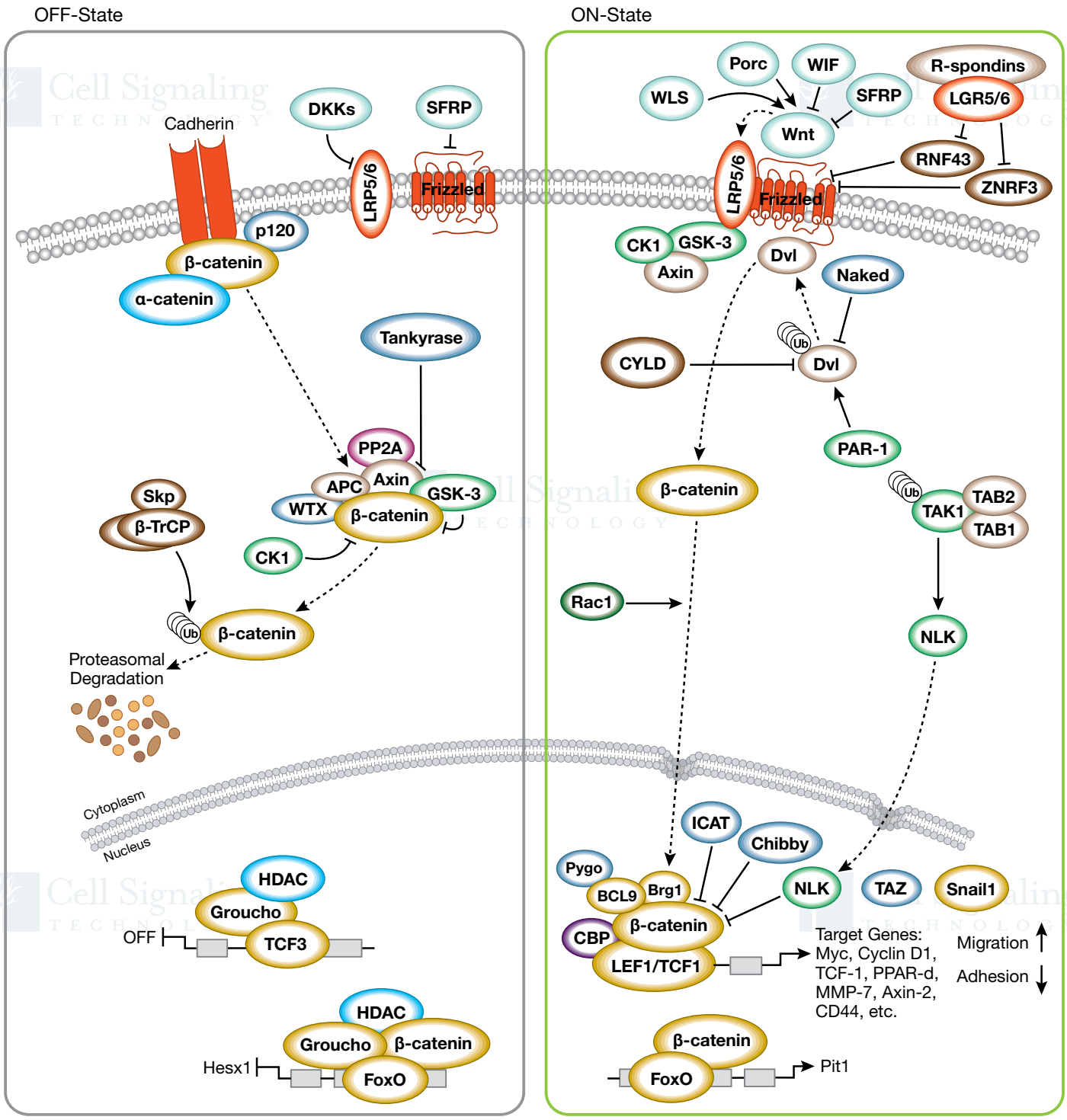
What causes these “hits”?

- Mutations in cells can be triggered by
  - **UV radiation**
  - **chemical exposure**
  - **radiation exposure**
  - **heat**
  - **cigarette smoke**
  - **pollution**
  - **age**
  - **genetics**

Tumors

- Mass of abnormal cells
  - Benign tumor
    - abnormal cells remain at original site as a lump
      - p53 has halted cell divisions
    - most do not cause serious problems & can be removed by surgery
  - Malignant tumors
    - cells leave original site
      - lose attachment to nearby cells
      - carried by blood & lymph system to other tissues
      - start more tumors = metastasis
    - impair functions of organs throughout body

Wnt / β-Catenin Signaling



rev. 01/22/20

Pathway Diagram Key

Acetylase · Adaptor · Apoptosis/Autophagy Regulator · Cell Cycle Regulator · Deacetylase or Cytoskeletal Protein · Growth Factor/Cytokine/Development Protein · GTPase/GAP/GEF · Kinase · Metabolic Enzyme · Methyltransferase or G-protein · Phosphatase · Protein Complex · Ubiquitin/SUMO Ligase or Deubiquitinase · Transcription Factor or Translation Factor · Receptor · Other

Direct Process · Tentative Process · Translocation Process · Stimulatory Modification · Inhibitory Modification · Transcriptional Modification