Pathobiochemistry of tumorigenesis

Pathobiochemistry of malignant transformation

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Cancer intro:

Malignant cancer – the genetic disease

Normal tissue

malignant transformation

Affection of genomic DNA by various pathogenetic events

MaLigNant tumor formation

Cancer intro:

Malignant cancer – the genetic disease

Normal tissue

malignant transformation

WHICH GENES?

Affection of genomic DNA by various

WHICH PROCESSES?

pathogenetic events

WHICH CELLS?

MaLigNant tumor formation

A few introductory remarks:

- cells in multicellular organism
- known facts about malignant transformation
- cell renewal

Growth control in multicellular organism:

Considered hierarchical building plan

Organism → Organs → Tissues → Tissue clusters → Cells

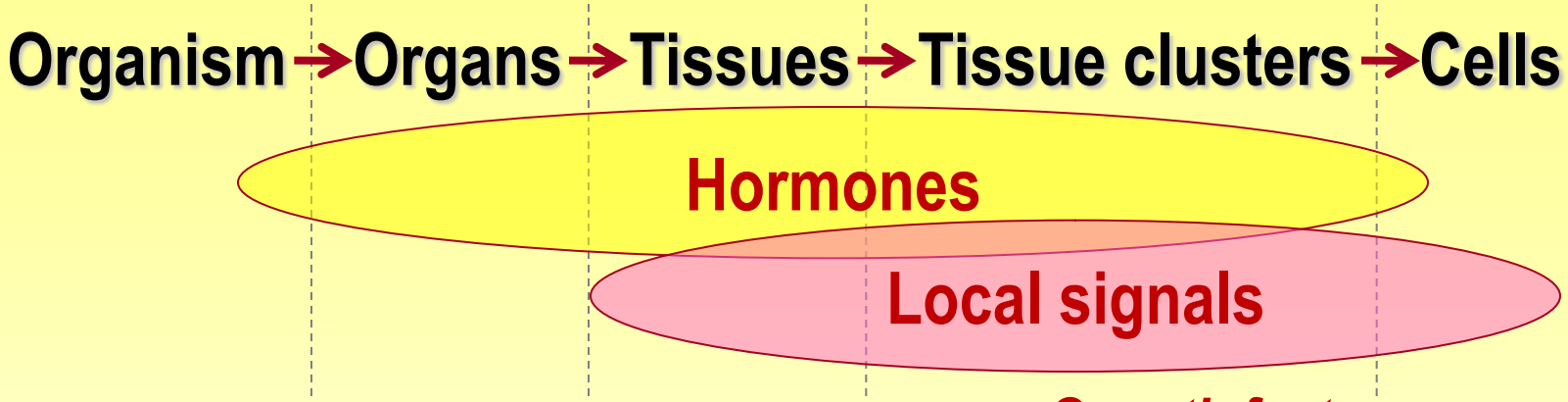
1 → 10^2 → 10^3 → 10^8 → 10^{14}

[entities]

10^7 x  population

Growth control in multicellular organism:

Regulated by hierarchical chemical signalling



- *Growth factors*
- *Cytokines*
- *Apoptotic regulators*
- *Etc.*

Growth control in multicellular organism:

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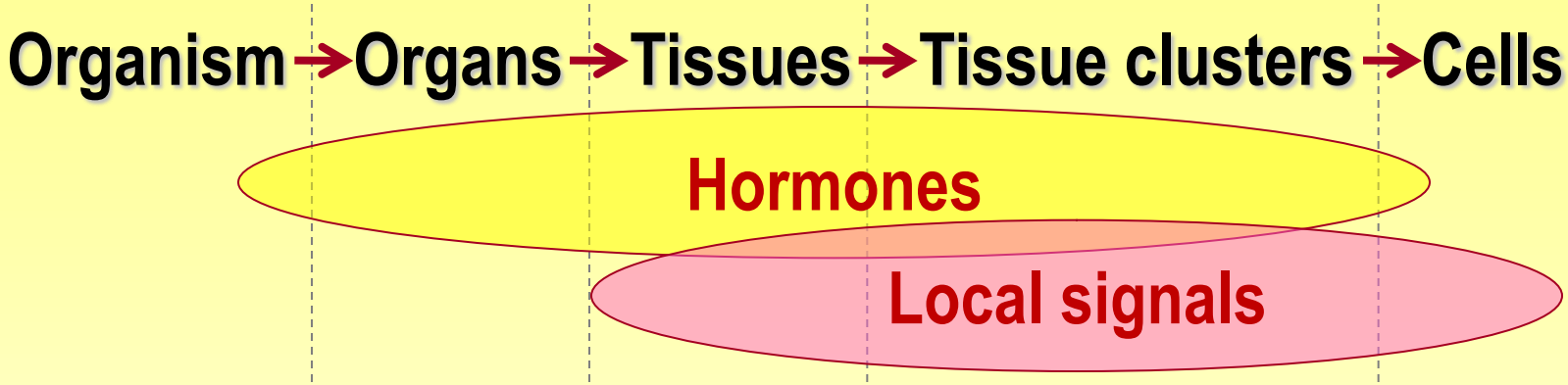
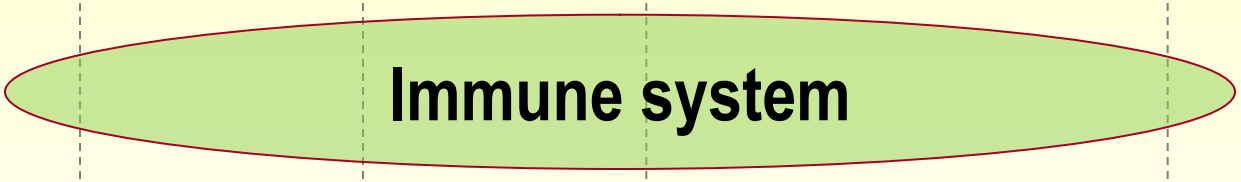


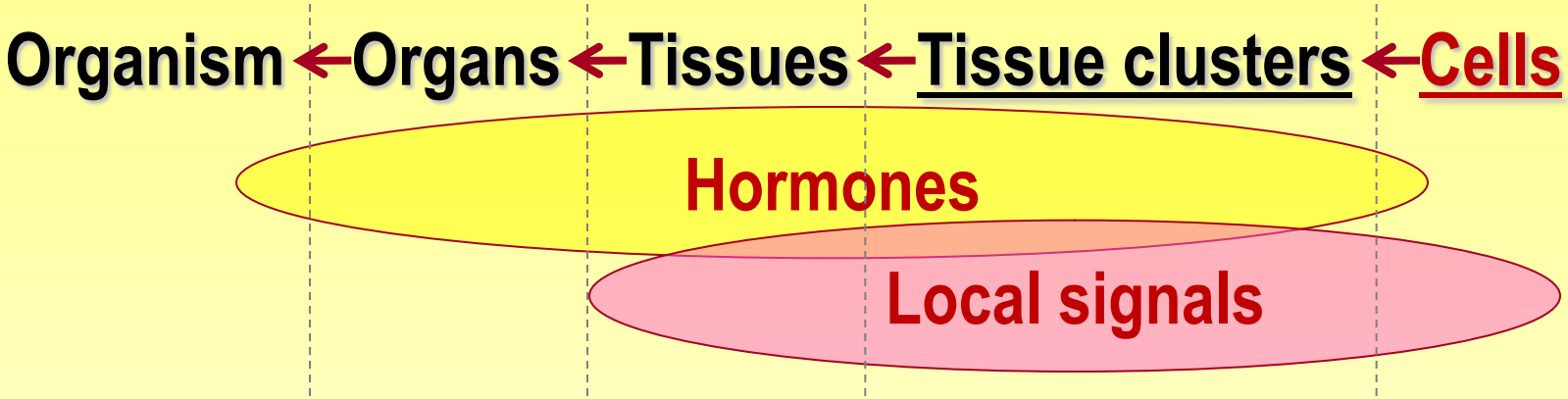
Surveillance by continuous control



- *Self?*
- *Proper?*
- *Controlled?*

Growth control in multicellular organism:

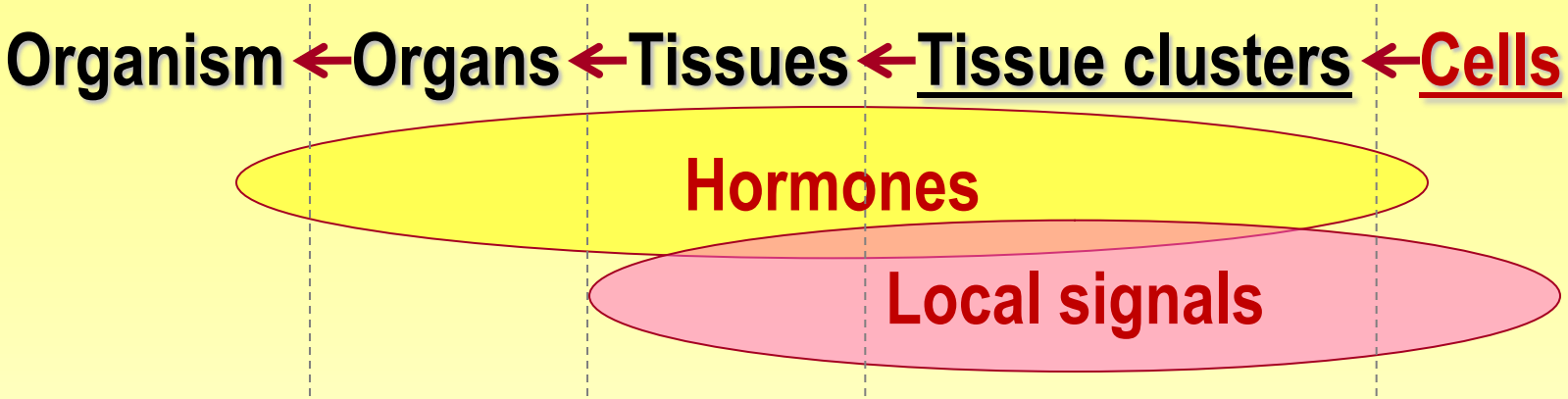
Regulated by chemical signalling at the cellular level



Considering the intracellular conditions and local environment in a tissue cluster

Growth control in multicellular organism:

Regulated by chemical signalling at the cellular level



Considering the intracellular conditions and local environment in tissue cluster

Cells (not the organism) autonomously regulate the absolute amount of entities in a tissue clusters

Cellular growth control:

Interactions of local and distant factors

chemical signalling	&	*intracellular conditions*	&	*local environment in tissue cluster*
▪ Hormones ▪ Local signals ▪ „Immune“ signals		▪ Cell integrity ▪ DNA integrity ▪ Energetics		▪ Resources ▪ Space, contacts ▪ Stromal interaction

Cellular growth control:

Represented by biochemical interactions

chemical signalling	&	*intracellular conditions*	&	*local environment in tissue cluster*
▪ Hormones ▪ Local signals ▪ „Immune“ signals		▪ Cell integrity ▪ DNA integrity ▪ Energetics		▪ Resources ▪ Space, contacts ▪ Stromal interaction
▪ signal ligands ▪ receptors ▪ signal transducers ▪ IC signaling networks ▪ transcription factors ▪ executive proteins		▪ cell membrane ▪ mitochondrion ▪ damage sensors ▪ transducers ▪ DNA repair ▪ telomere maintenance ▪ ATP production		▪ nutrients ▪ oxygen ▪ integrins ▪ cell-cell interaction molecules

A few introductory remarks:

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Cellular growth control:

Represented by biochemical interactions regulating

chemical signalling	&	*intracellular conditions*	&	*local environment in tissue cluster*

- Hormones
- Local signals
- „Immune“ signals

- Cell integrity
- DNA integrity
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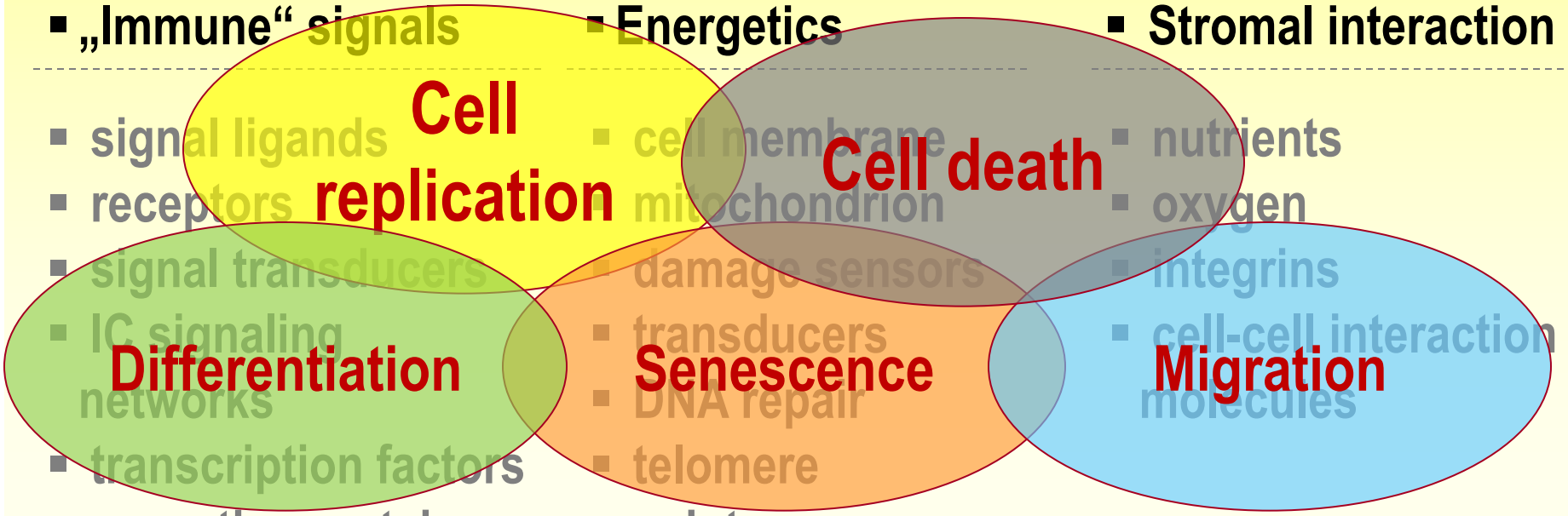

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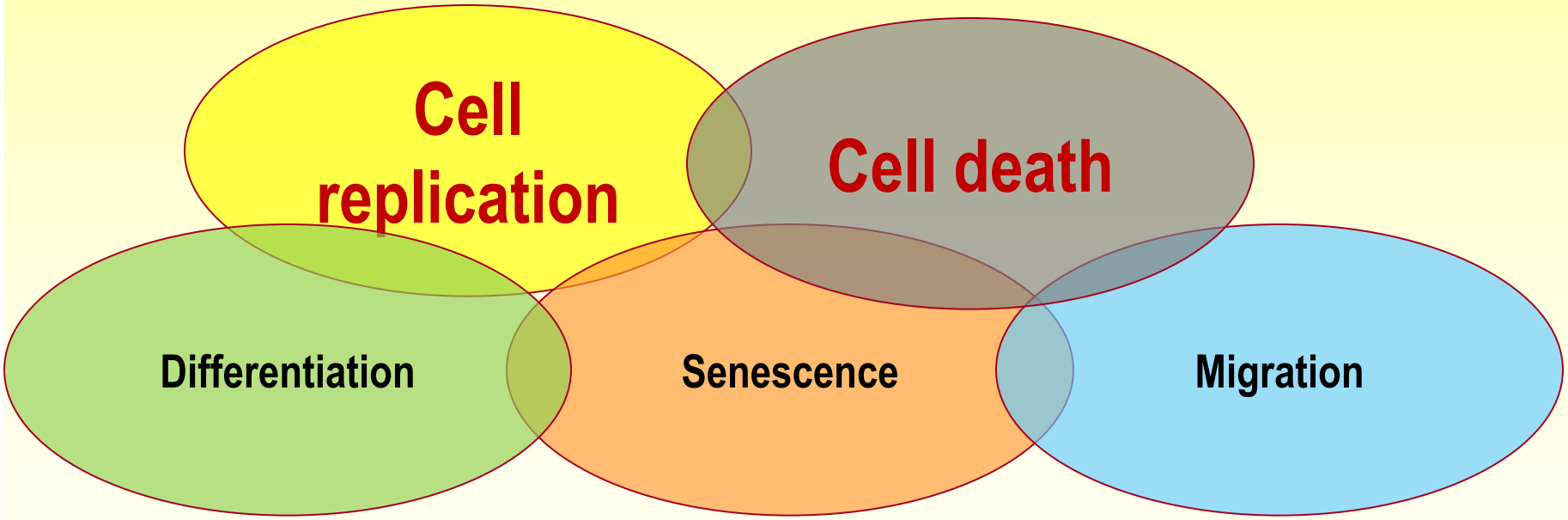
- cell-cell interaction molecules

Cellular growth control:

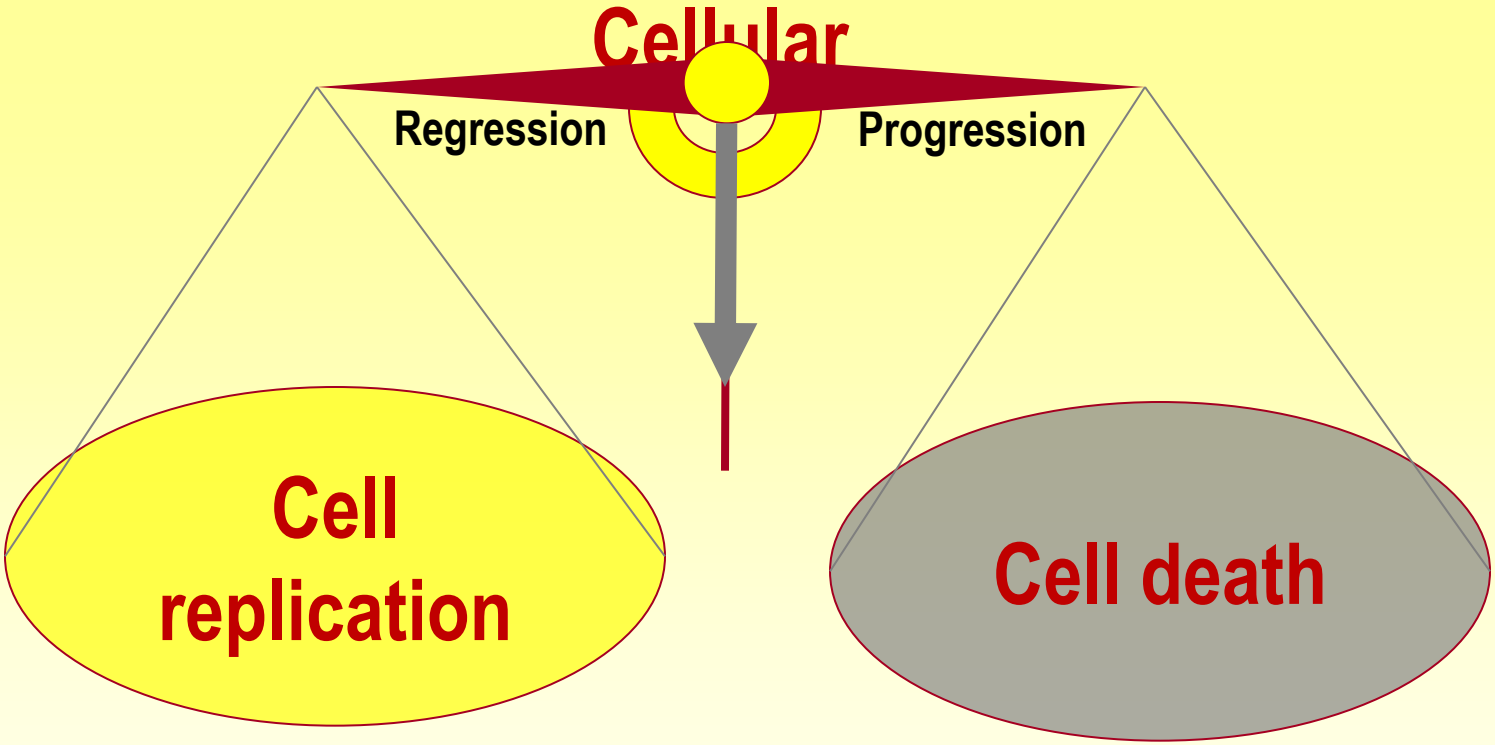
***Physiologically* - balanced state in tissues**

Tissue homeostasis



Cellular growth control:

Critical events for tissue homeostasis maintenance



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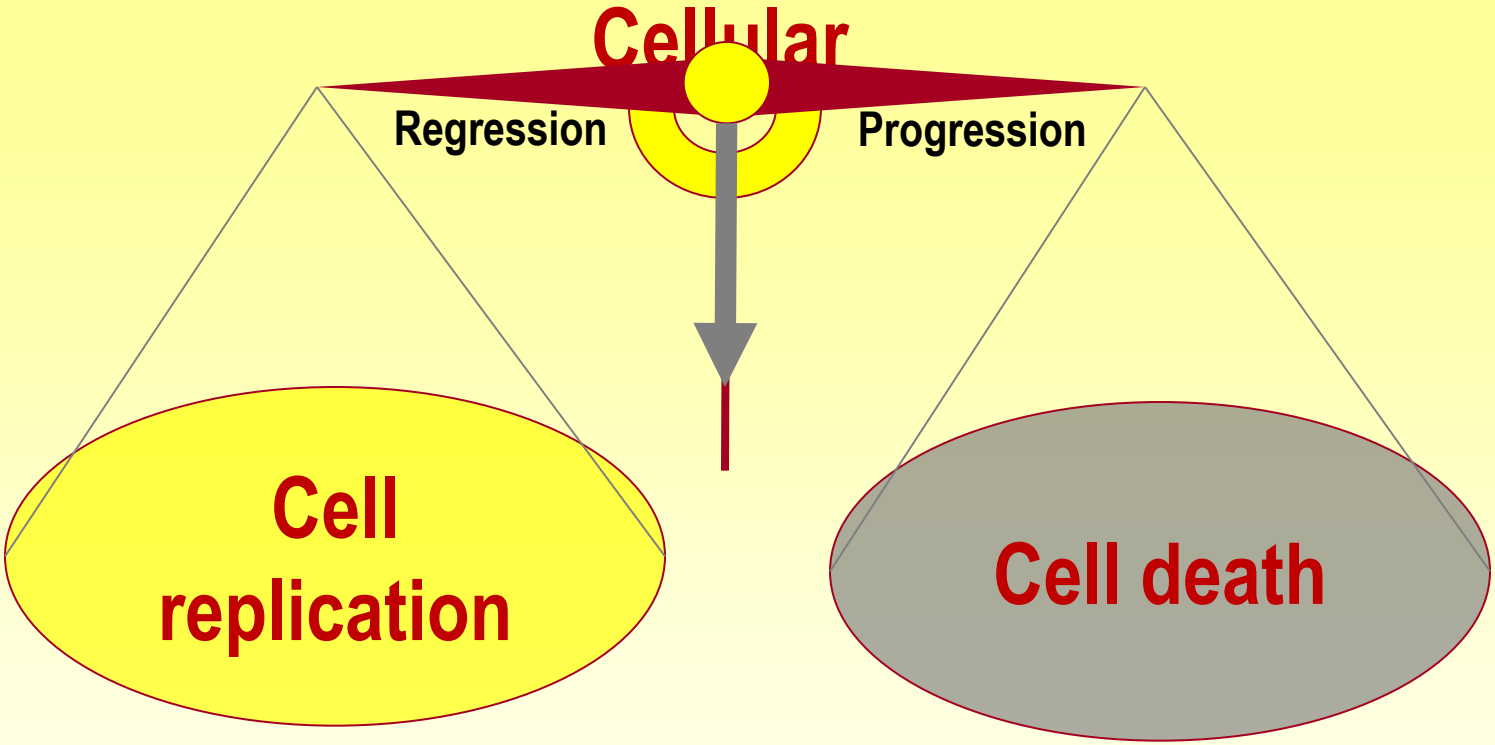
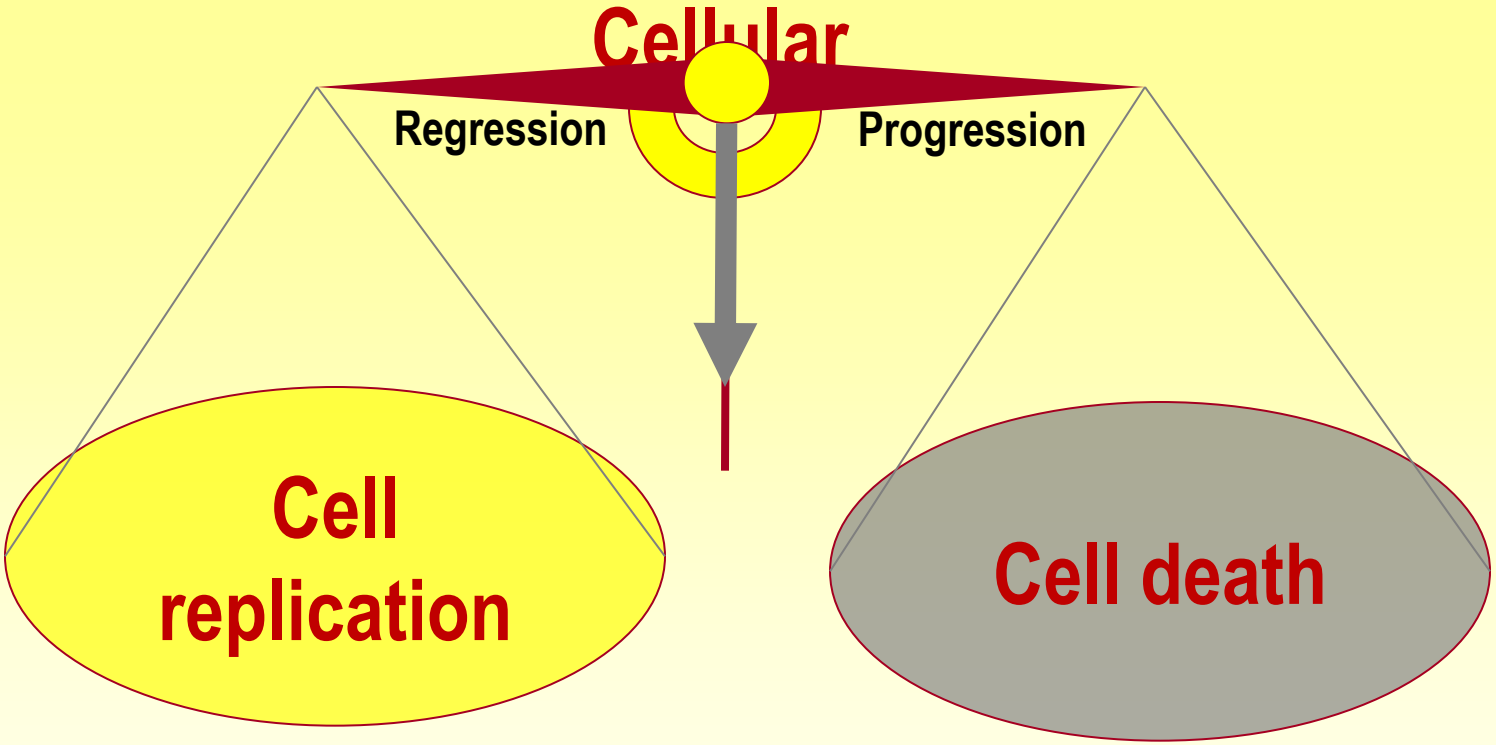


- Mitotic signaling pathways
- Cell cycle regulation

- Apoptotic pathways

Cellular growth control:

***Critical events* for tissue homeostasis maintenance**

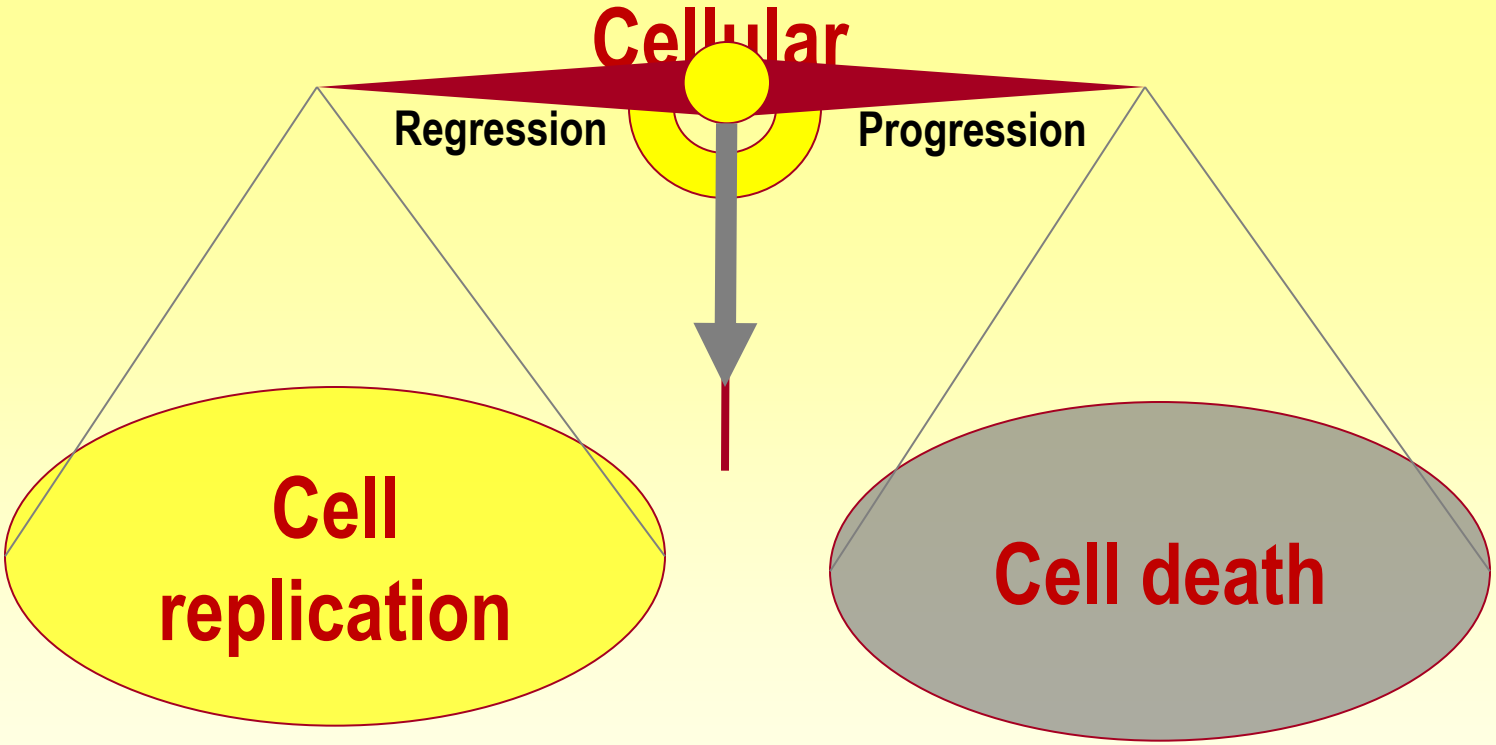


***Critical conditions*:**

- ***healthy (intact) DNA***
- ***competent immunity system***

Cellular growth control:

Critical events for tissue homeostasis maintenance



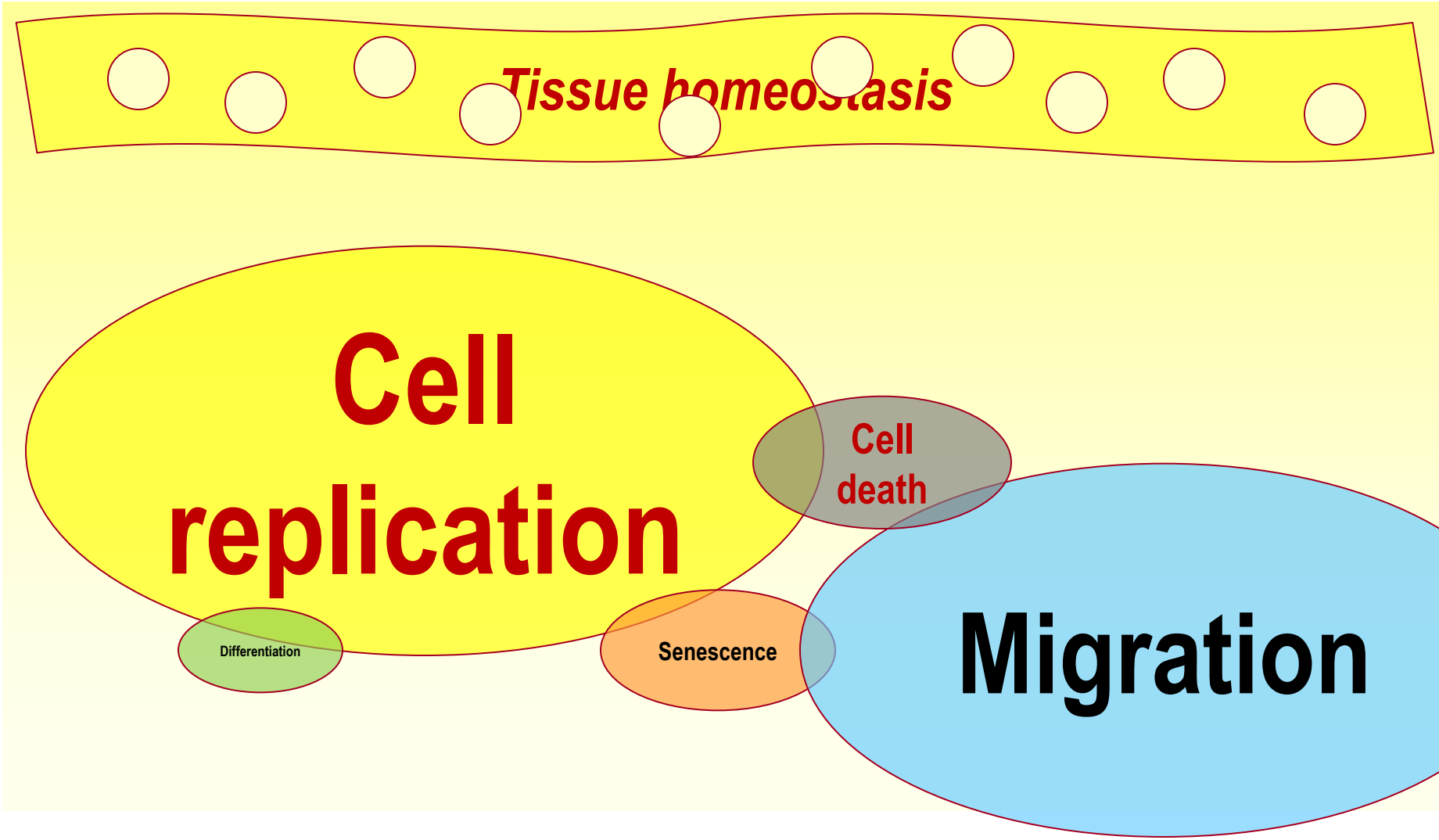
Critical conditions:

- *healthy (intact) DNA*
- *competent immunity system*

- DNA repair mechanisms
- Cell cycle checkpoints
- Differentiation

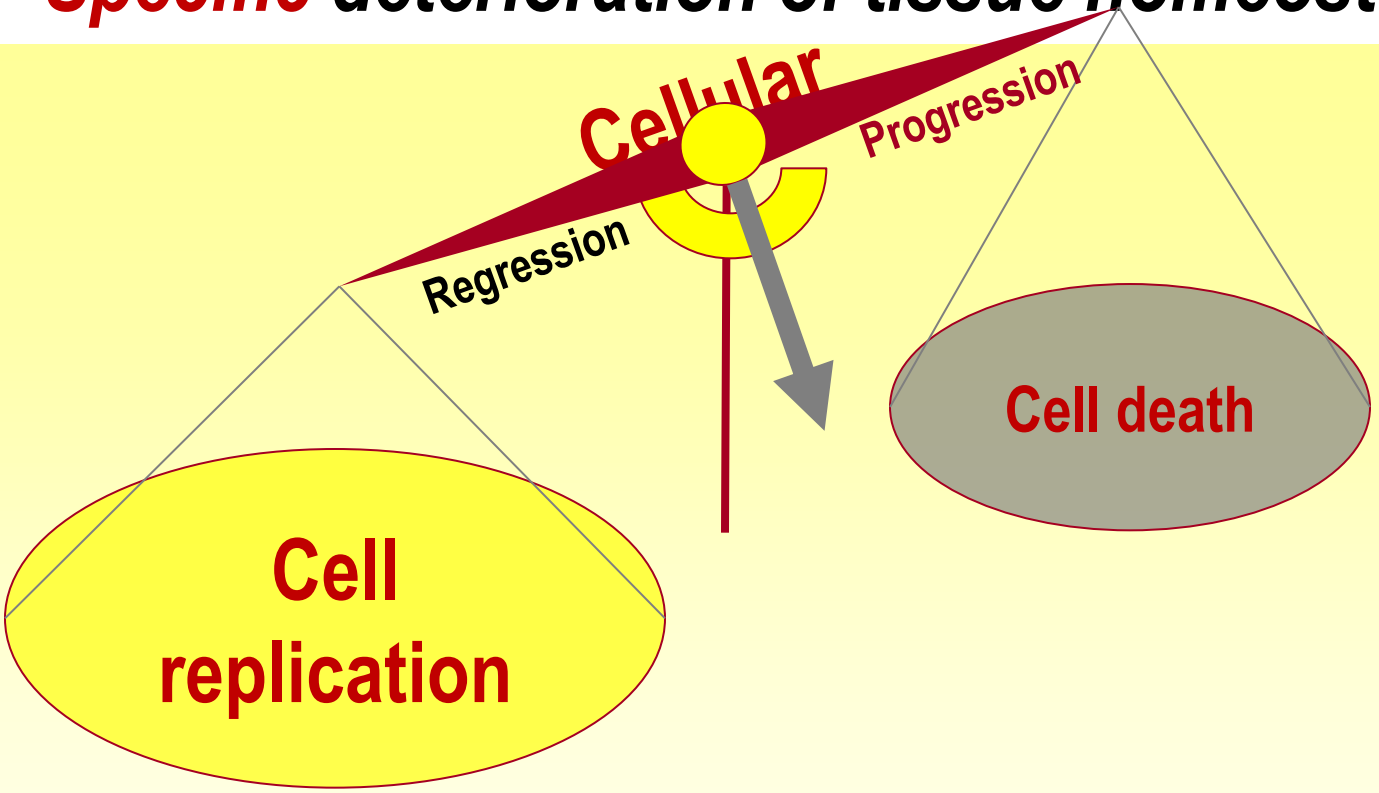
Cellular growth control:

***Pathologically* – deterioration of tissue homeostasis**



Cancer:

Specific deterioration of tissue homeostasis

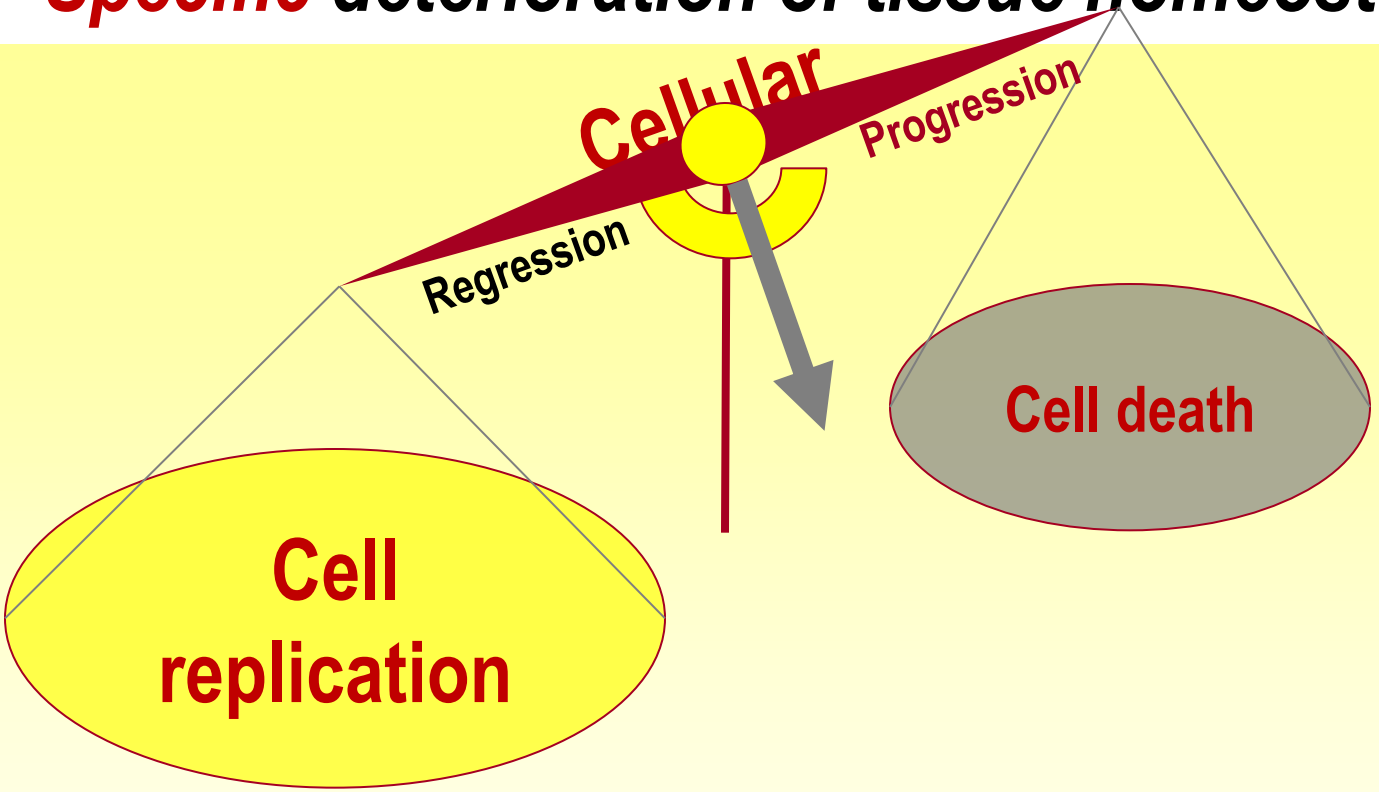


↑Mitotic signaling pathways
↑Cell cycle regulation

↓Apoptotic pathways

Cancer:

***Specific* deterioration of tissue homeostasis**



***Enabled by*:**

- ***Damaged DNA***
- ***Uncompetent* immunity system**

☒DNA repair mechanisms
☒Cell cycle checkpoints
☒ Differentiation

Malignant transformation:

Specific deterioration of tissue homeostasis

Mitotic hyperstimulation

Cell cycle upregulation

Evasion of apoptosis

Deterioration of DNA repair

Impaired differentiation

- Growth of malignant tissue
- Insensitivity to local and systemic growth control
- Growth across the tissue architecture
- Immortalization
- Toleration of genetic alterations
- Clonal variability
- Immature phenotype
- Metastatic potential
- Escape from immune surveillance

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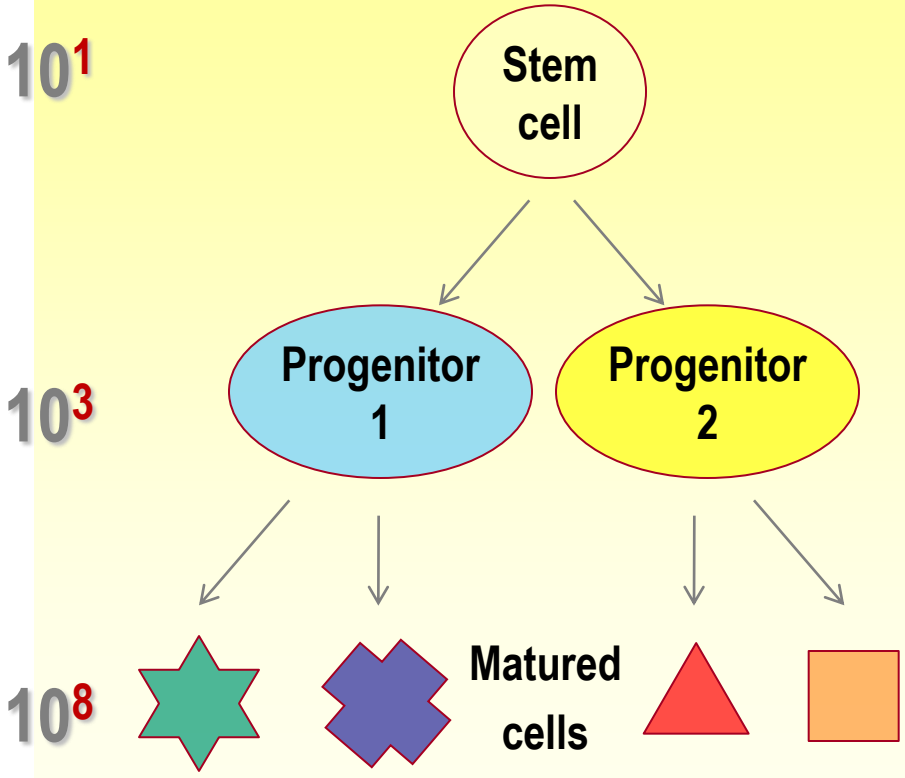
Cell growth control in tissues:

Majority of tissues have self renewal capacity

provided by gradual maturation from tissue stem/progenitor cells



[entities in hypothetical tissue]

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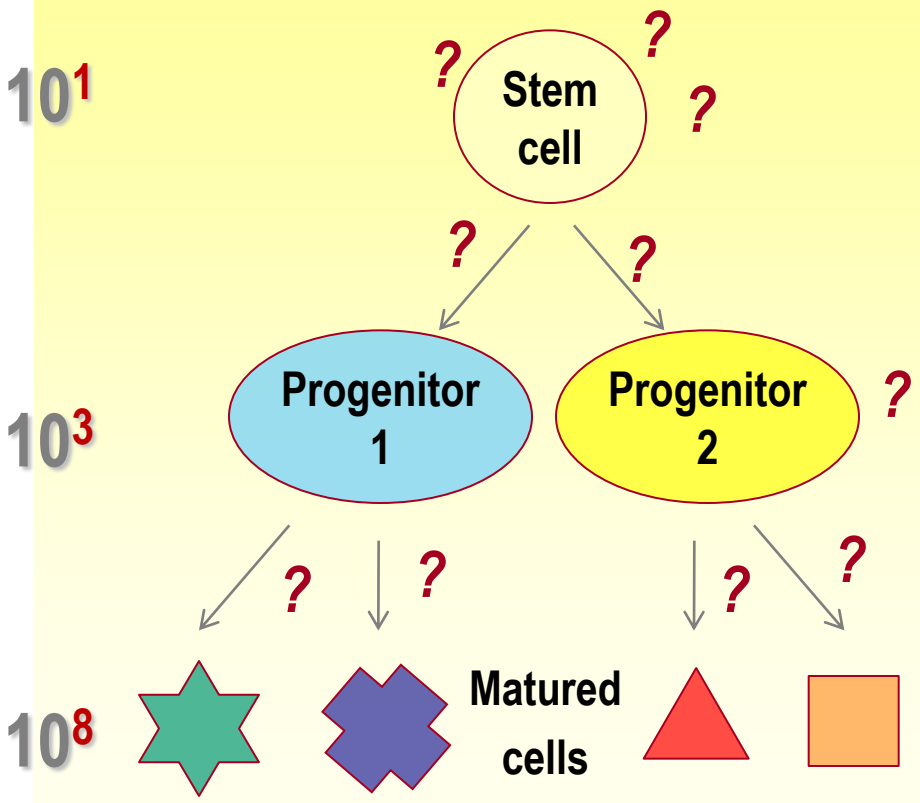

Stimulated by many (?),

mainly local, ***factors***

[entities in hypothetical tissue]

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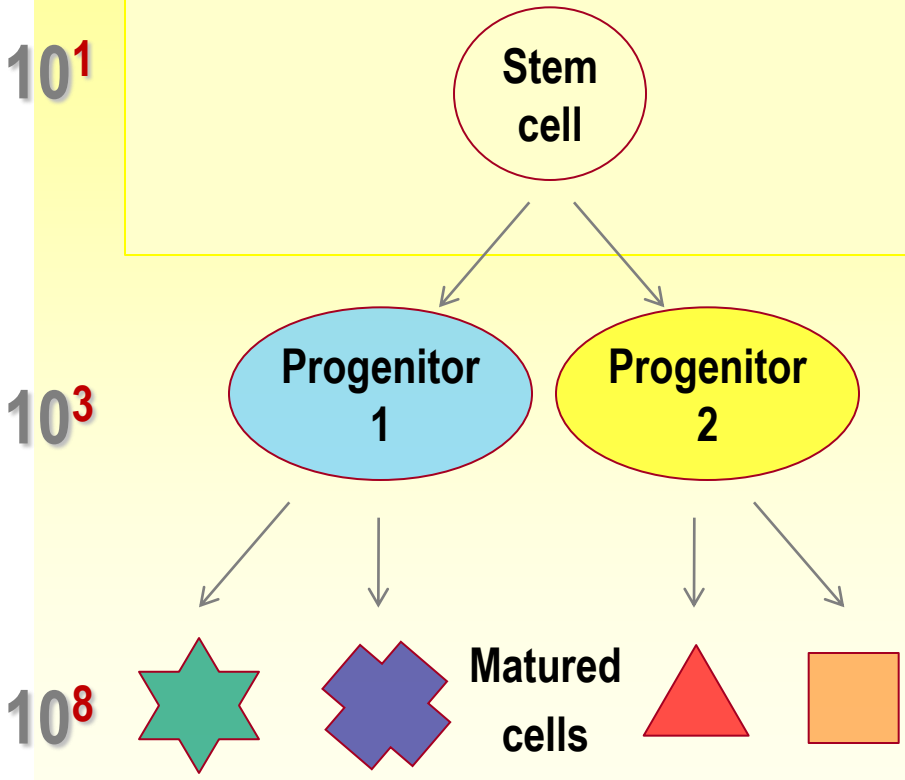

: Supplementation of progenitors

-Divisions: unlimited

-Mitotic activity: low

-Phenotype: unmaturated

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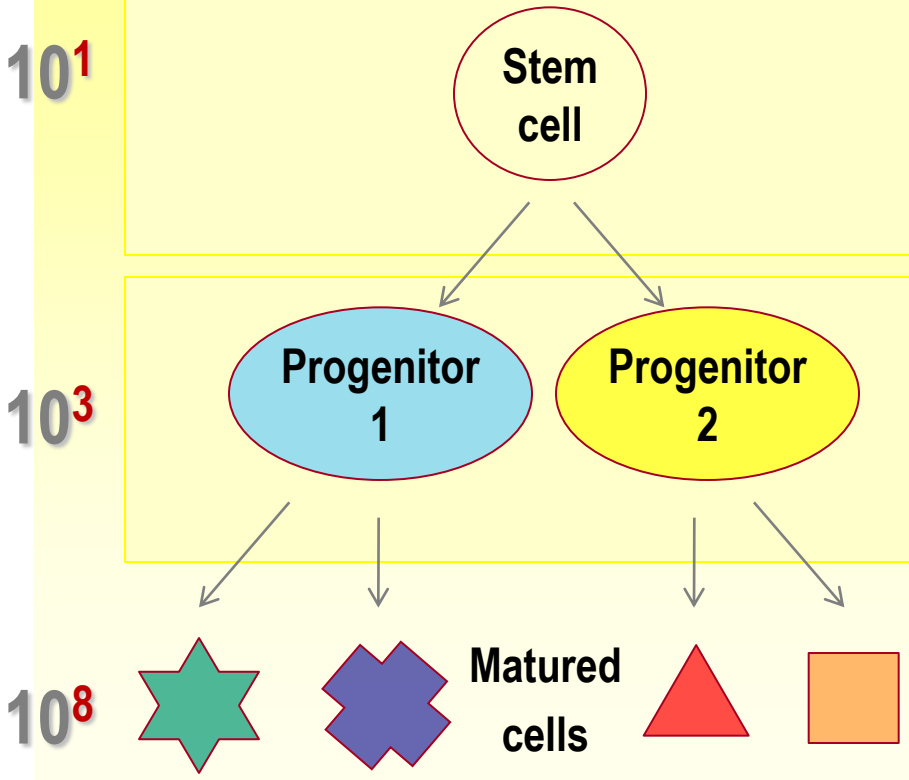

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: Supplement desired cell types

-Divisions: limited (100x)

-Mitotic activity: high

-Phenotype: partialy maturated

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Cell growth control in tissues:

Majority of tissues have self renewal capacity

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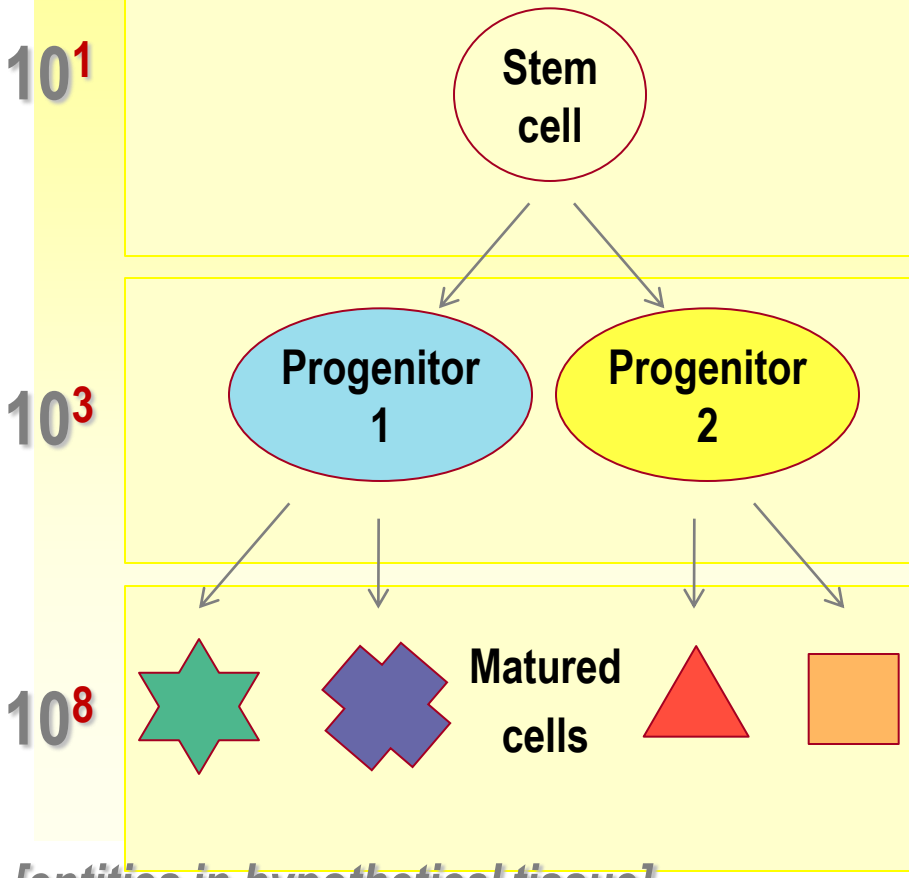

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: Supplement desired cell types
-Divisions: limited (100x)
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-Phenotype: partialy maturated

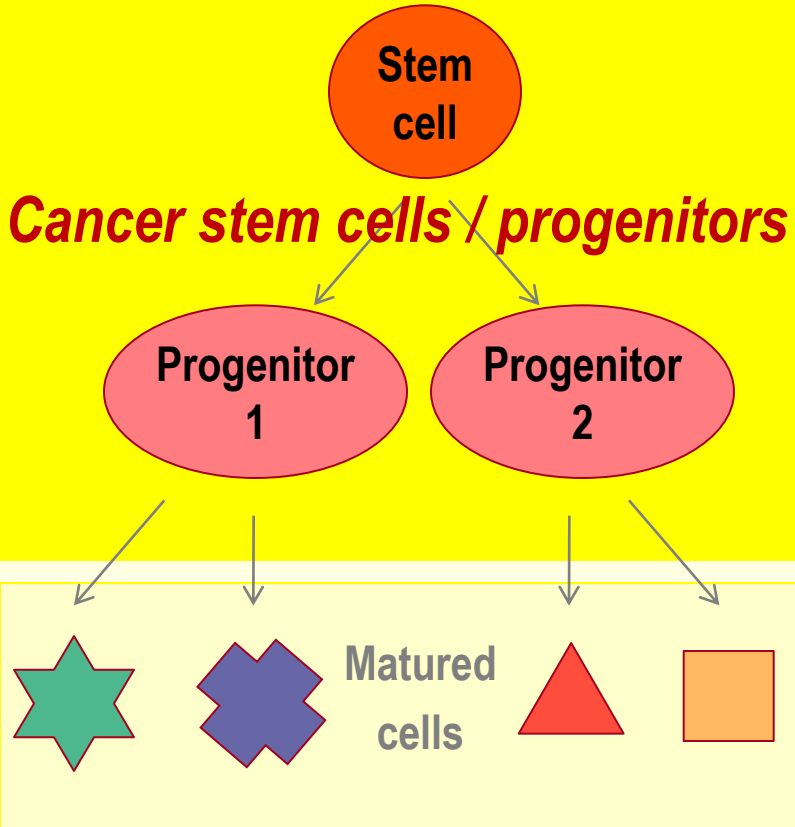
: Providing specific tissue functions
-Divisions: very limited (10x)
-Mitotic activity: variable
-Phenotype: maturated

[entities in hypothetical tissue]

Origin of cancer cells:

Genetic abberations in stem /progenitor cells

provide propagation of cancer-prone mutations to downstream cells



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Part 2: Signaling pathways failure in oncogenesis

Examples of:

- **mitotic hyperstimulation**
- **defects of DNA repair mechanisms**
- **evasion of apoptosis**

Signals of cascades pathways for mitotic stimulation

Growth factors
cytokines+ lipophilic hormones

Mitotic signal

↓

Their receptors

Signal recognition and its transport accross cell membrane

↓

Signal transducers

Transmission of mitogenic signal from receptors to intracelular transducers

Intracytoplasmic kinases

↓

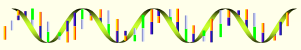
Amplification and propagation of the signal toward the cell nucleus

↓

Nuclear receptors and transcription factors

Transmission of mitotic signals to the nucleus

↓

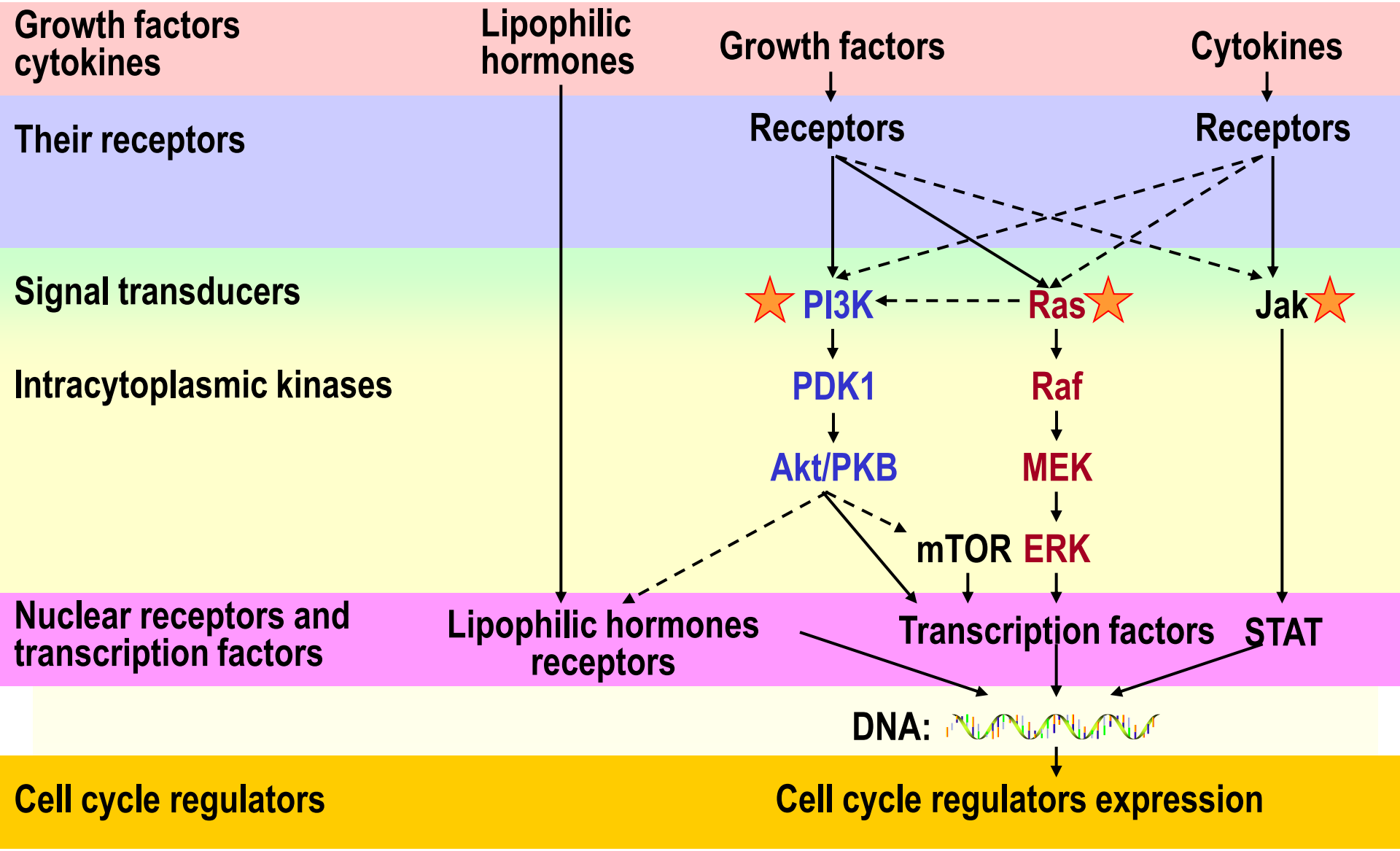
DNA: 

↓

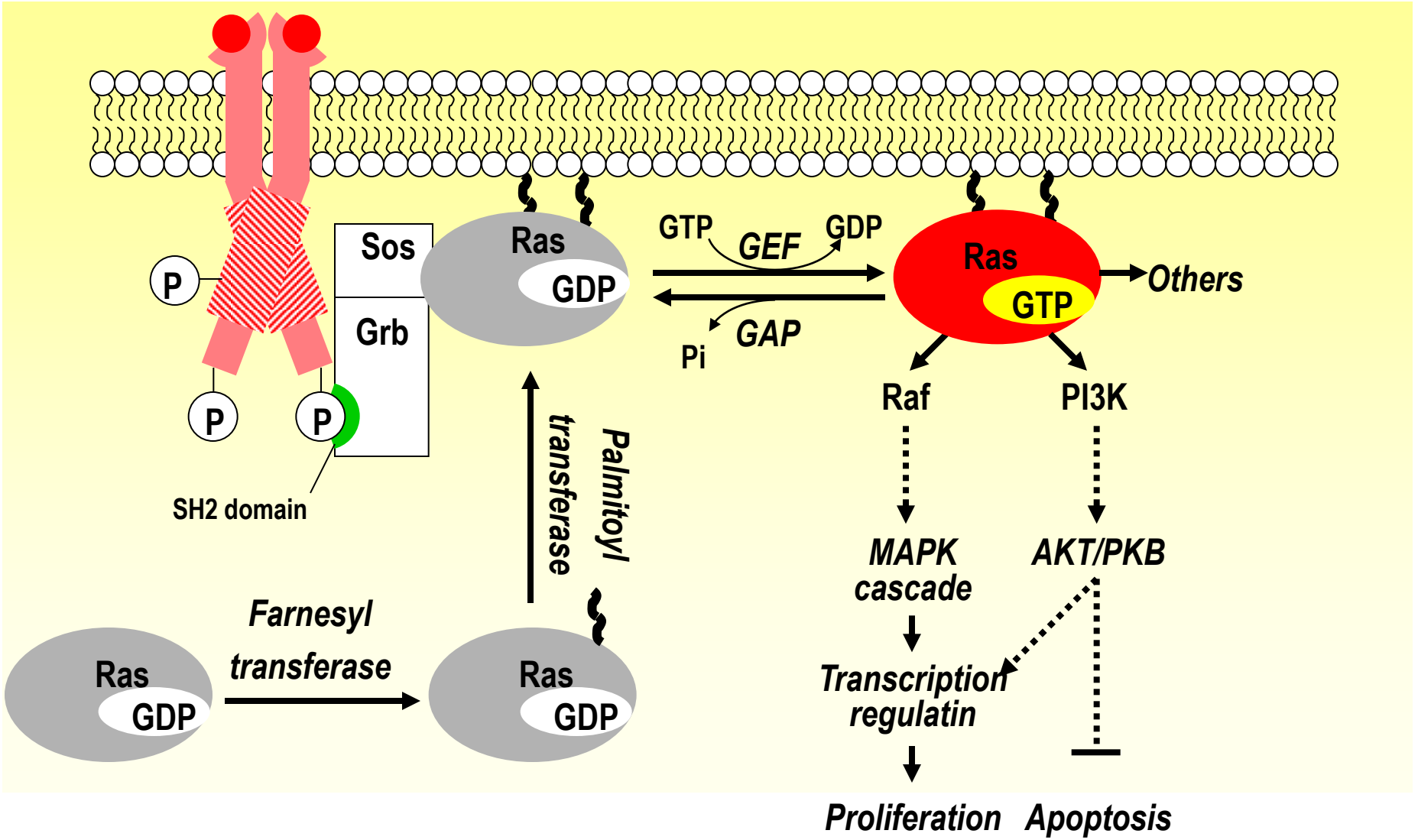
Cell cycle regulators

Gene expression changes

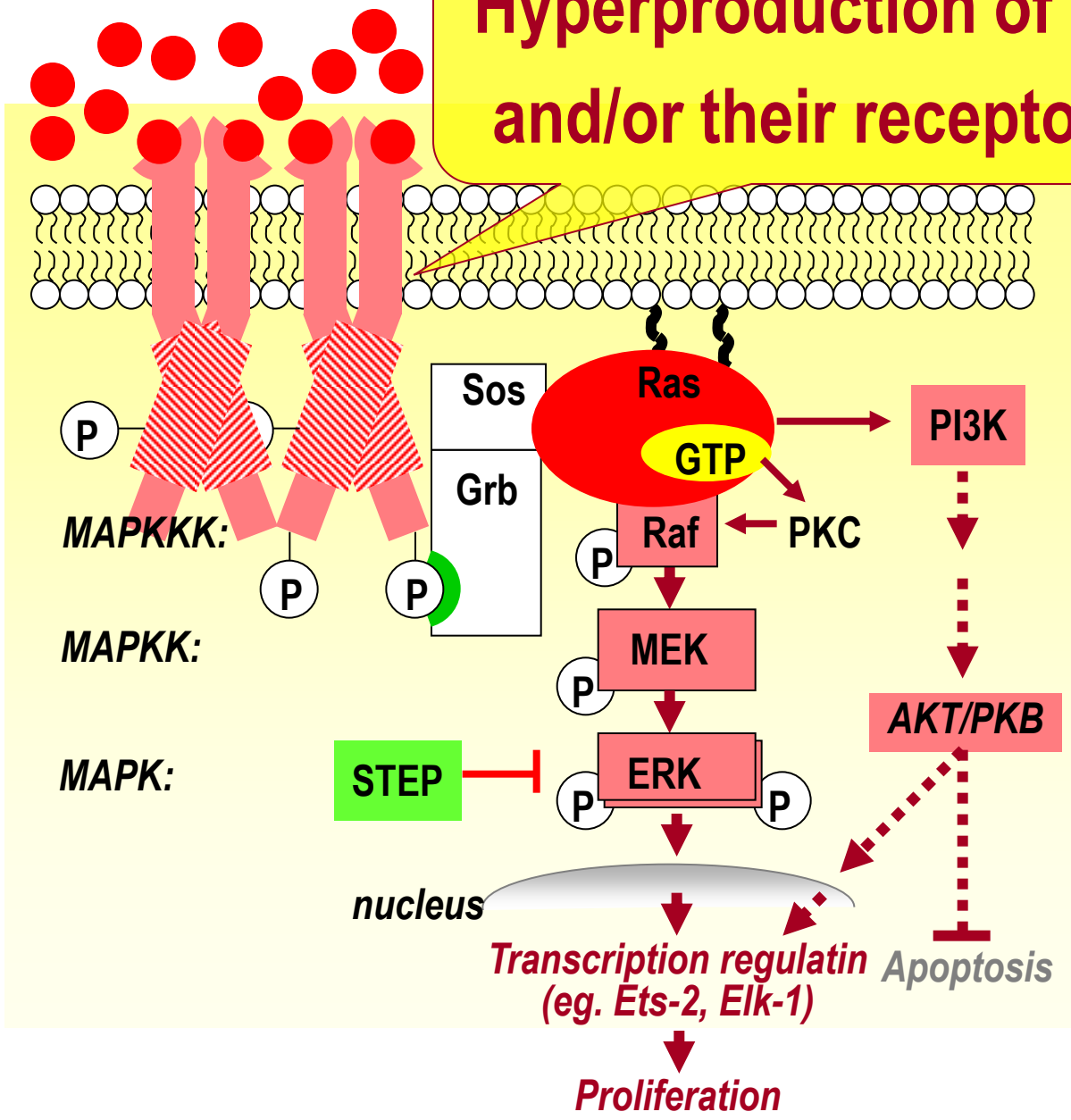
Signals of cascades pathways for mitotic stimulation



Signaling of receptor tyrosine kinases

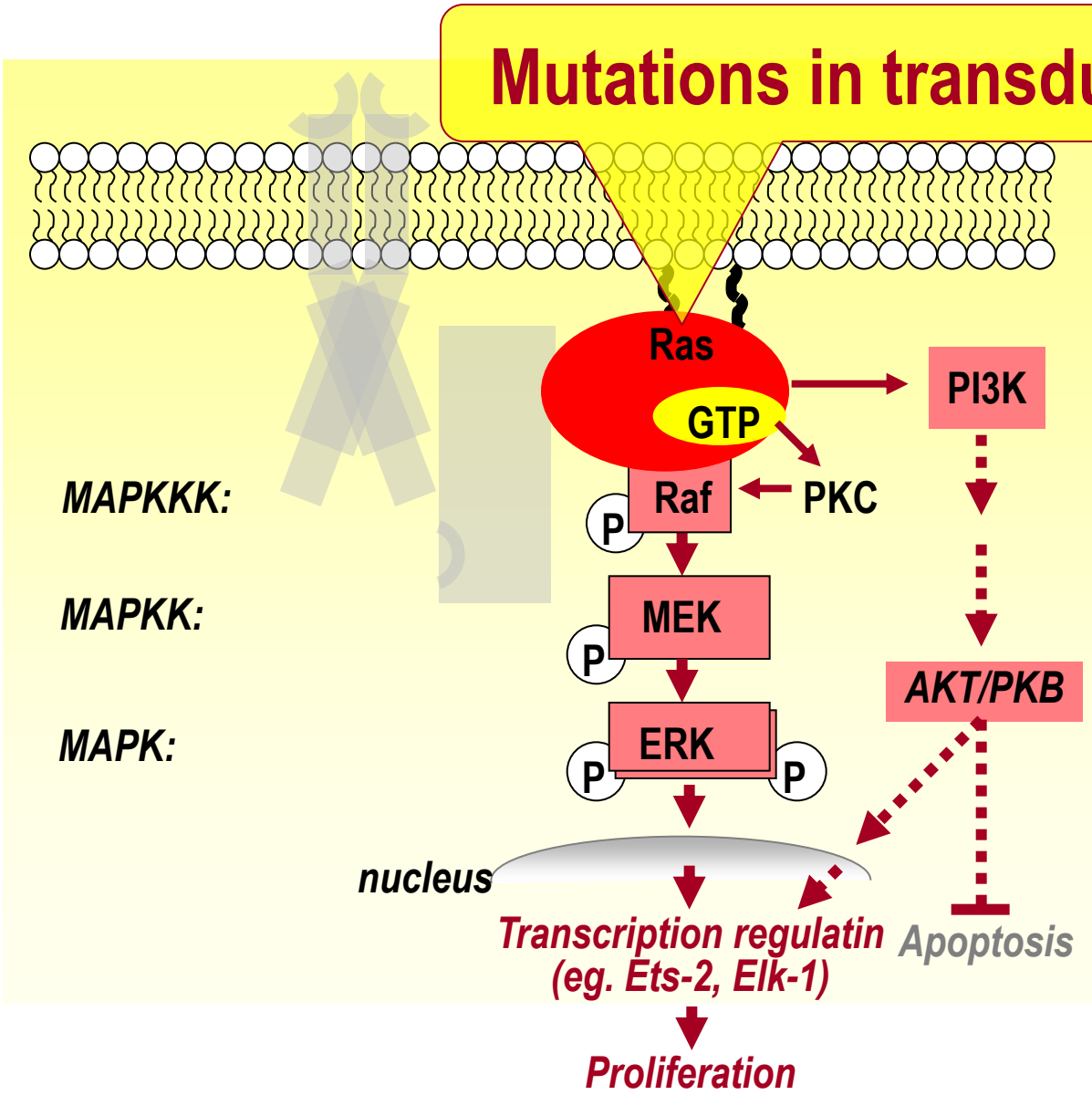


Defects of receptor tyrosine kinases signaling



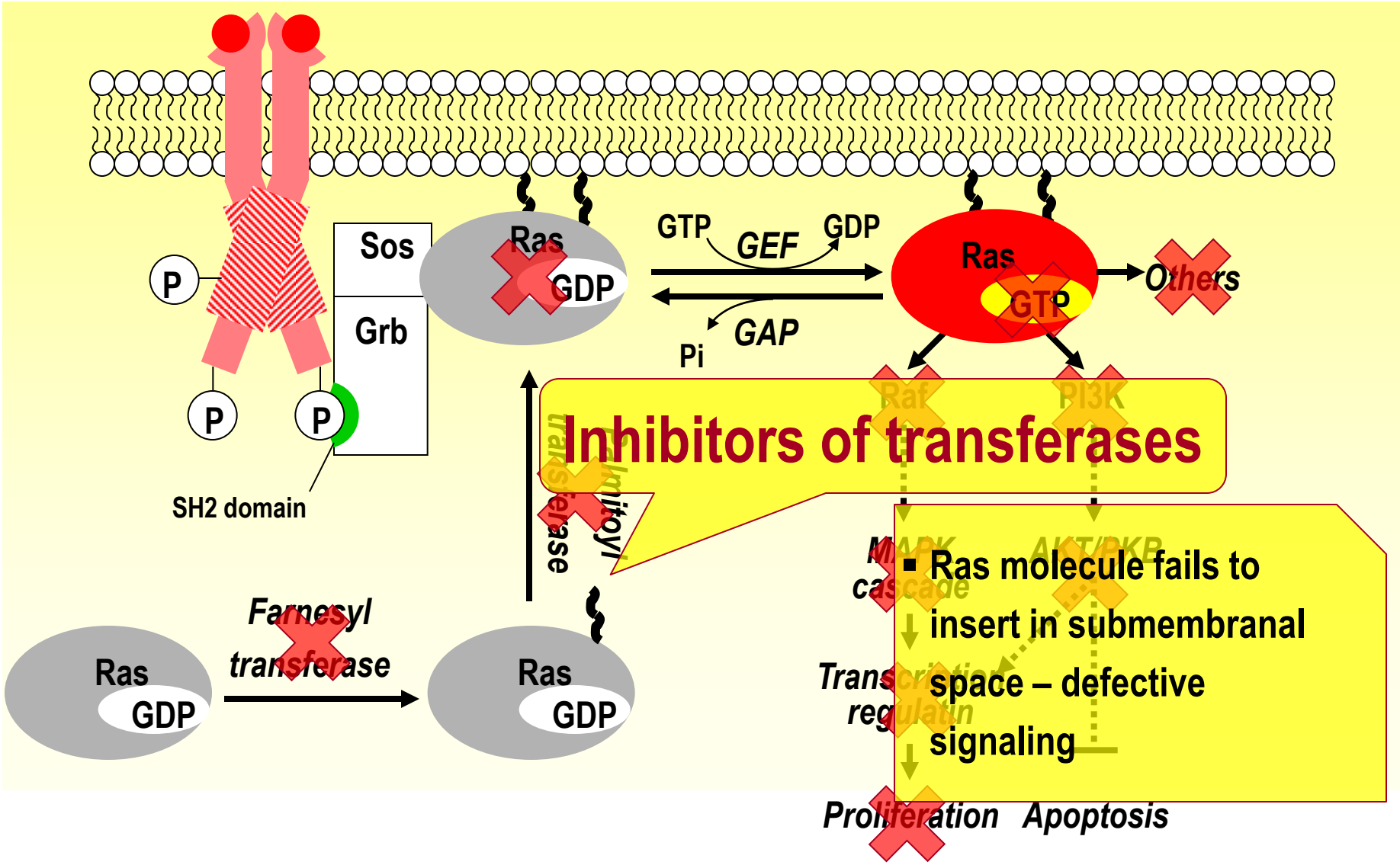
- Many cancer cells overexpress production of growth factors
- ErbB-2 (EGFR member) overexpressed (by gene amplification) in ~25% breast cancers
- ErbB-2 (her2/neu) could be targeted by specific Ig (Herceptin)

Defects of receptor tyrosine kinases signaling



- Mutation in *k-ras* oncogene: one of the most frequent event in solid cancers (~30%).
- Mostly pancreatic (~80%) and lung (~40%) cancers.
- Triggering the down-stream pathways independent on presence of upstream stimulatory events

Ras - directed therapy



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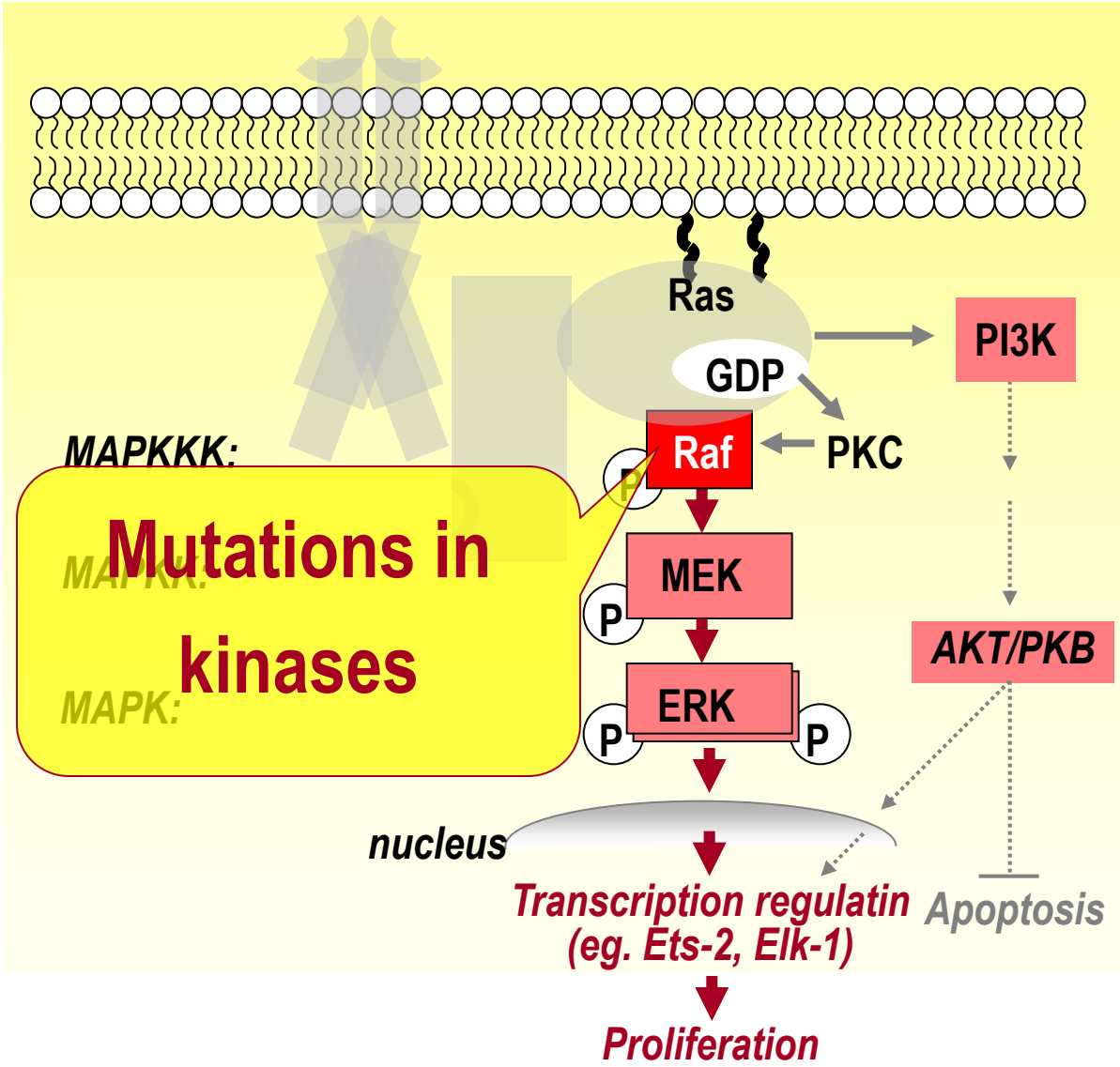
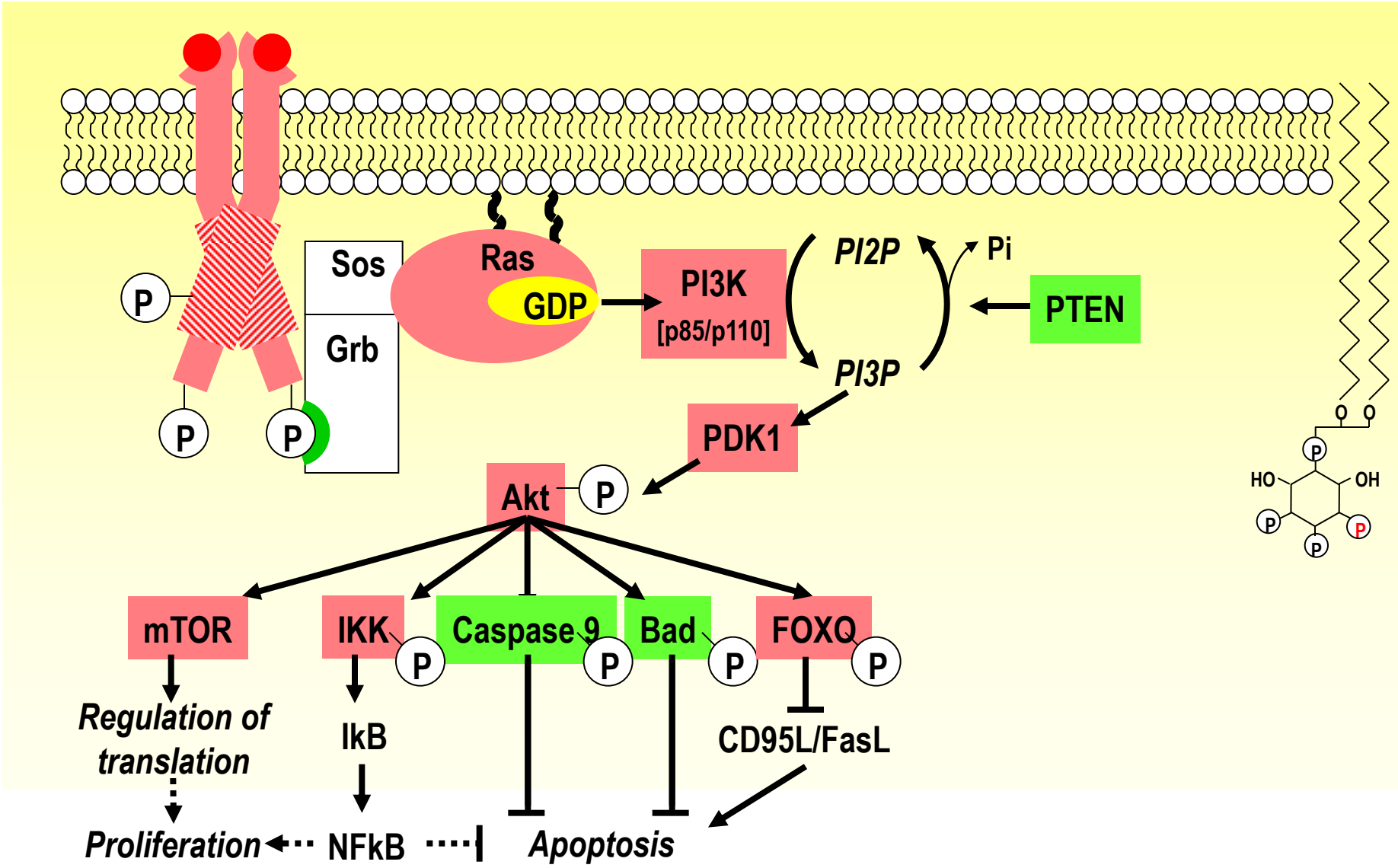
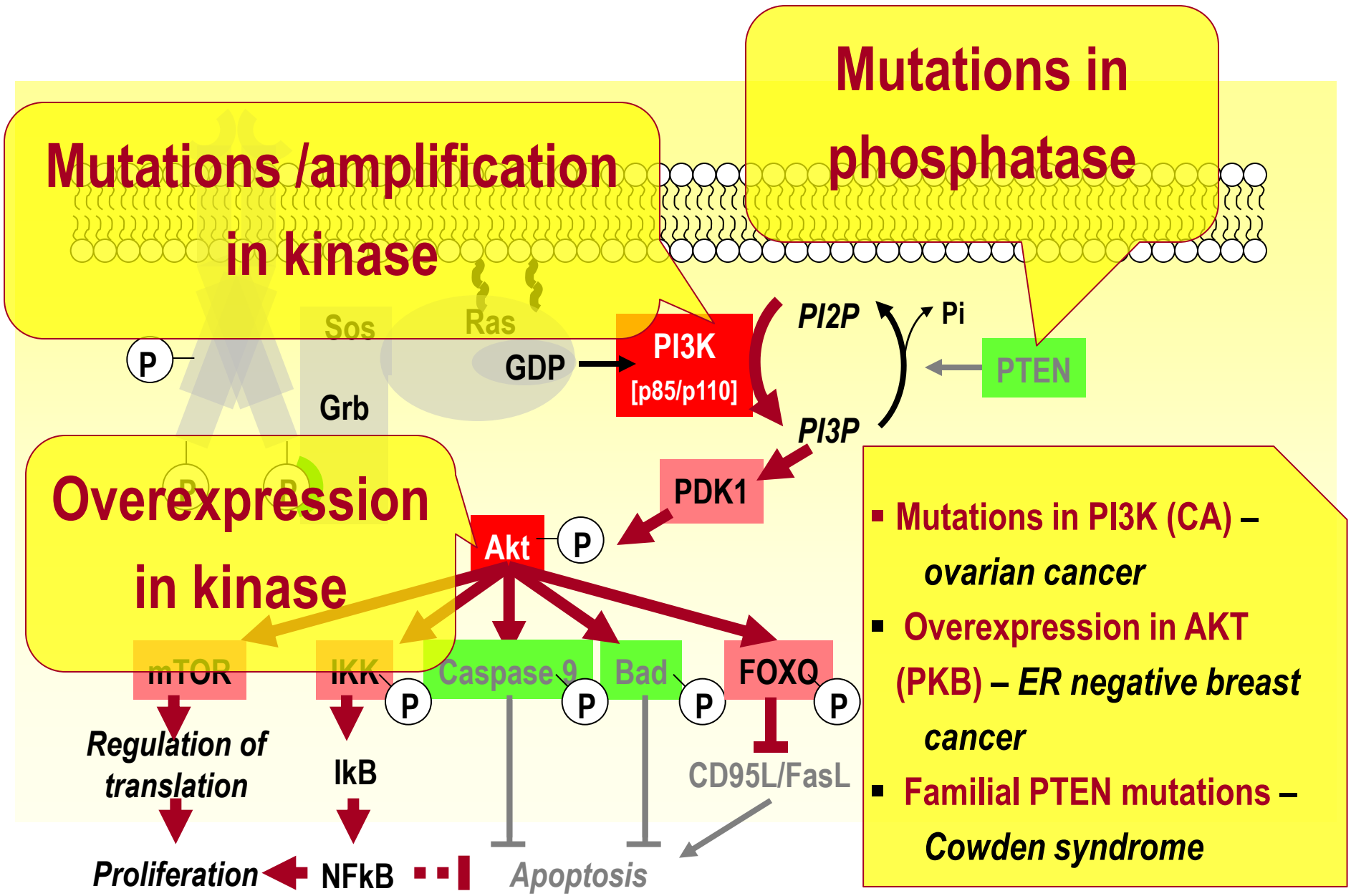


- Mutation in *B-raf* oncogene: melanoma (~70%), papillary thyroideal cancer (~50%) and colorectal (~40%) cancers.
- Specific therapy: antisense oligos and specific inhibitors of kinase activity

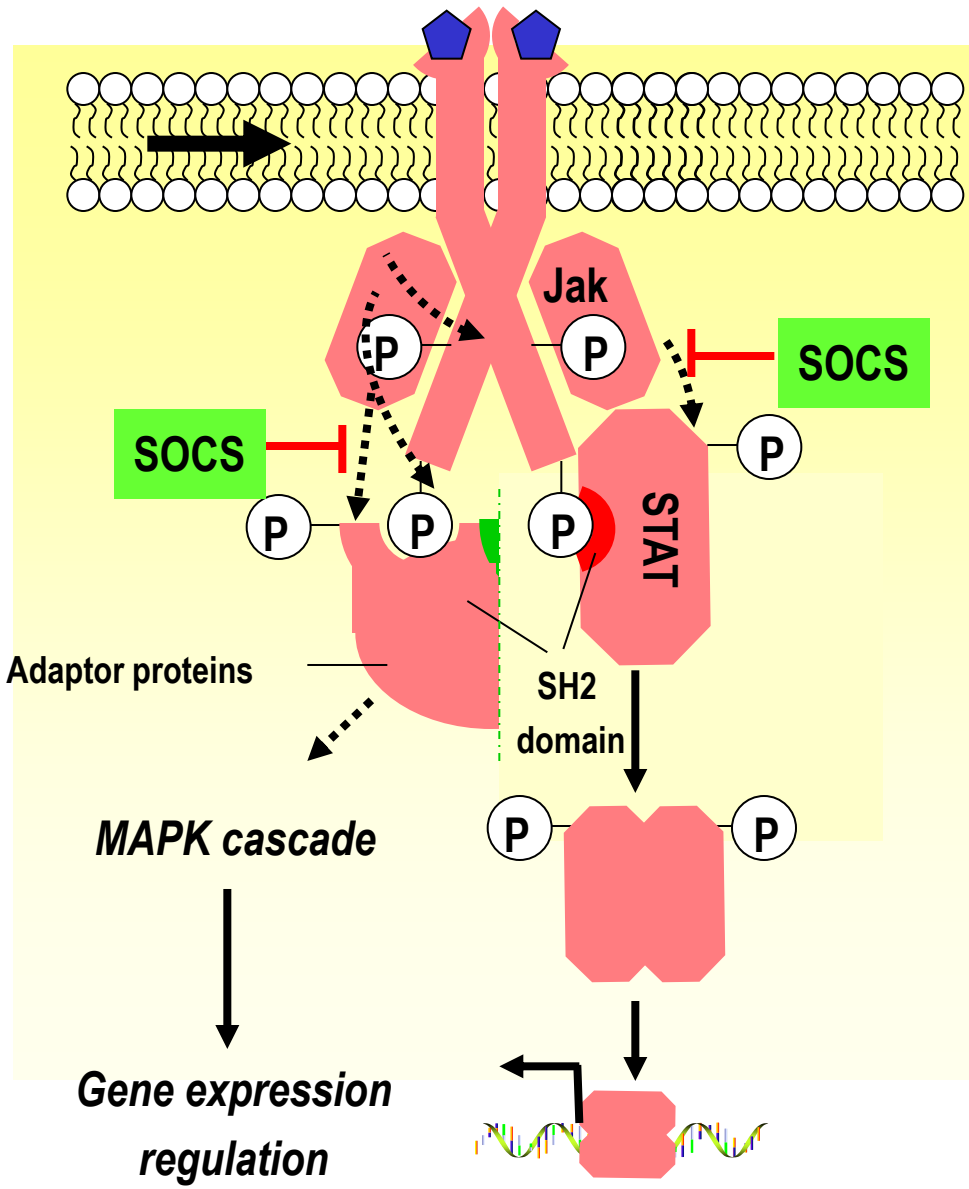
PI3K signaling



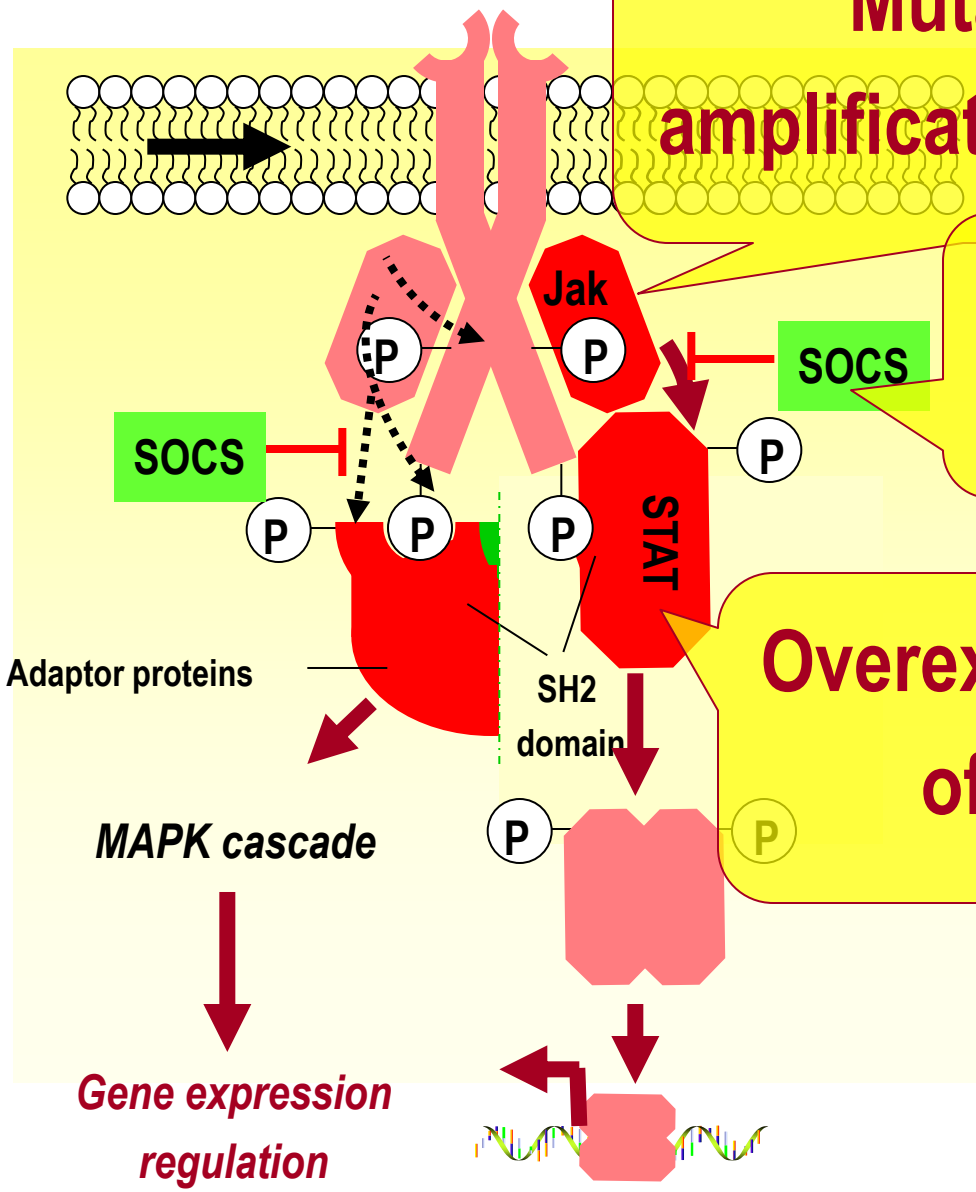
Defects of PI3K signaling



Cytokine signaling canonnical pathway



Defects of cytokine signaling



Mutations / amplification in kinase

Down-regulation / hyper-methylation of SOCS

Overexpression of TFs

- **Upregulation of JAK/STAT pathways – hallmark of many lymphoproliferative diseases**

Results of aberrant signaling pathways?

- Autonomous hyperstimulation of cellular growth potential
- Immaturity
- Enhanced migration potential

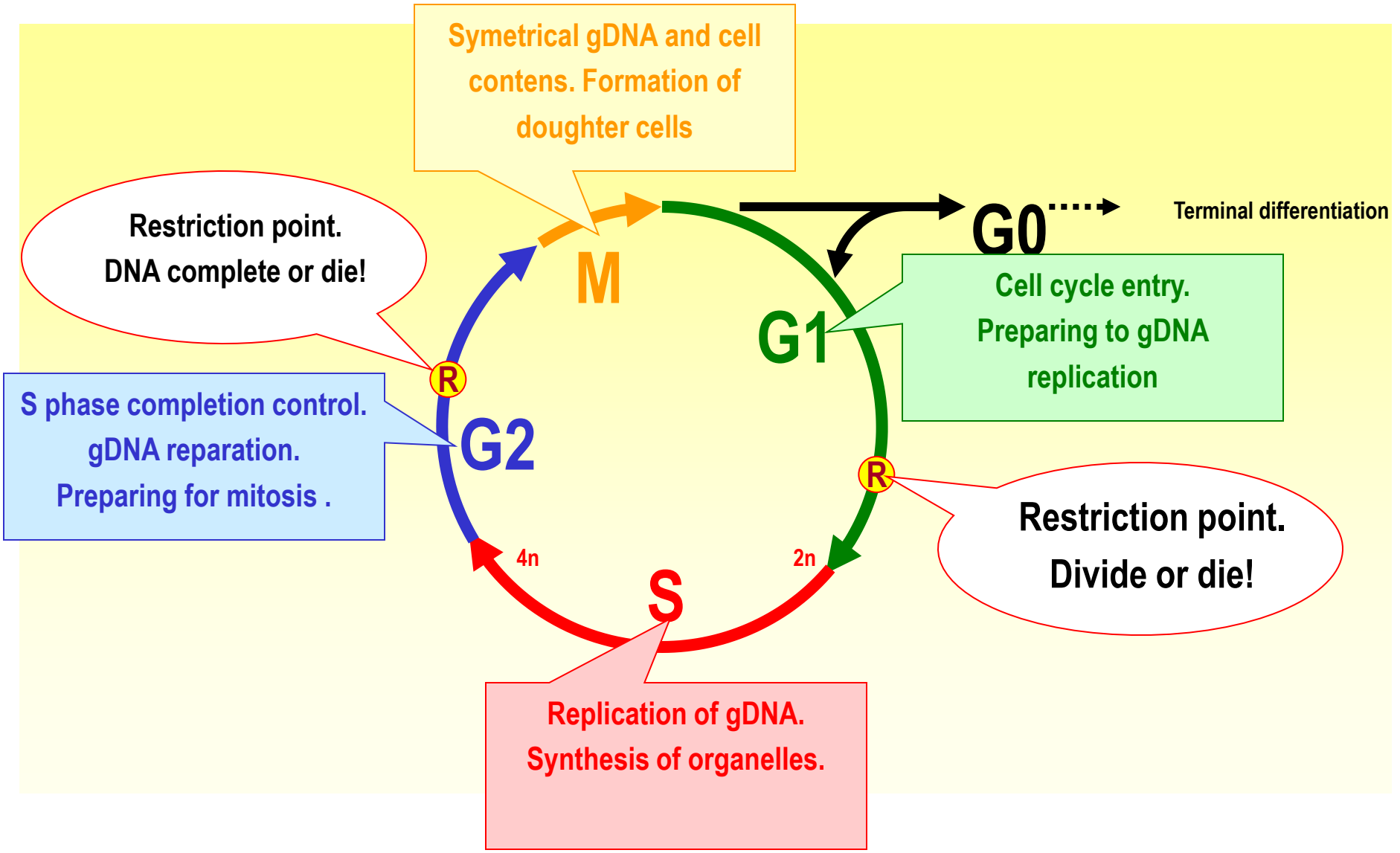
Cell cycle (CC): aims

Cell cycle – the sequence of consecutive biochemical events leading to cell replication

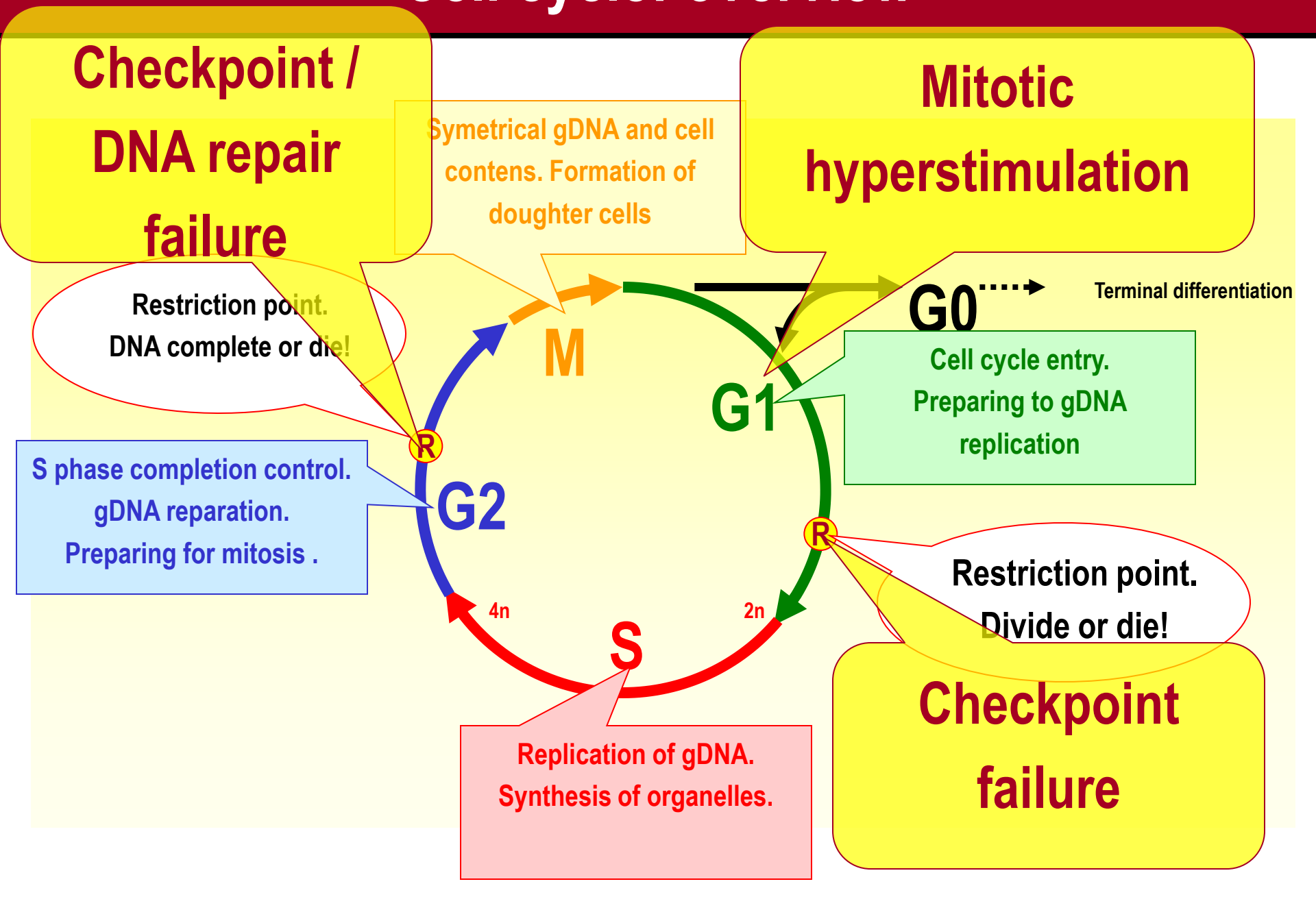
The aims of CC:

- **Highly precise copying and even distribution of genetic material between the new daughter cells**
- **Creation of two identical daughter cells from mother cell**
- Cell differentiation in some cases

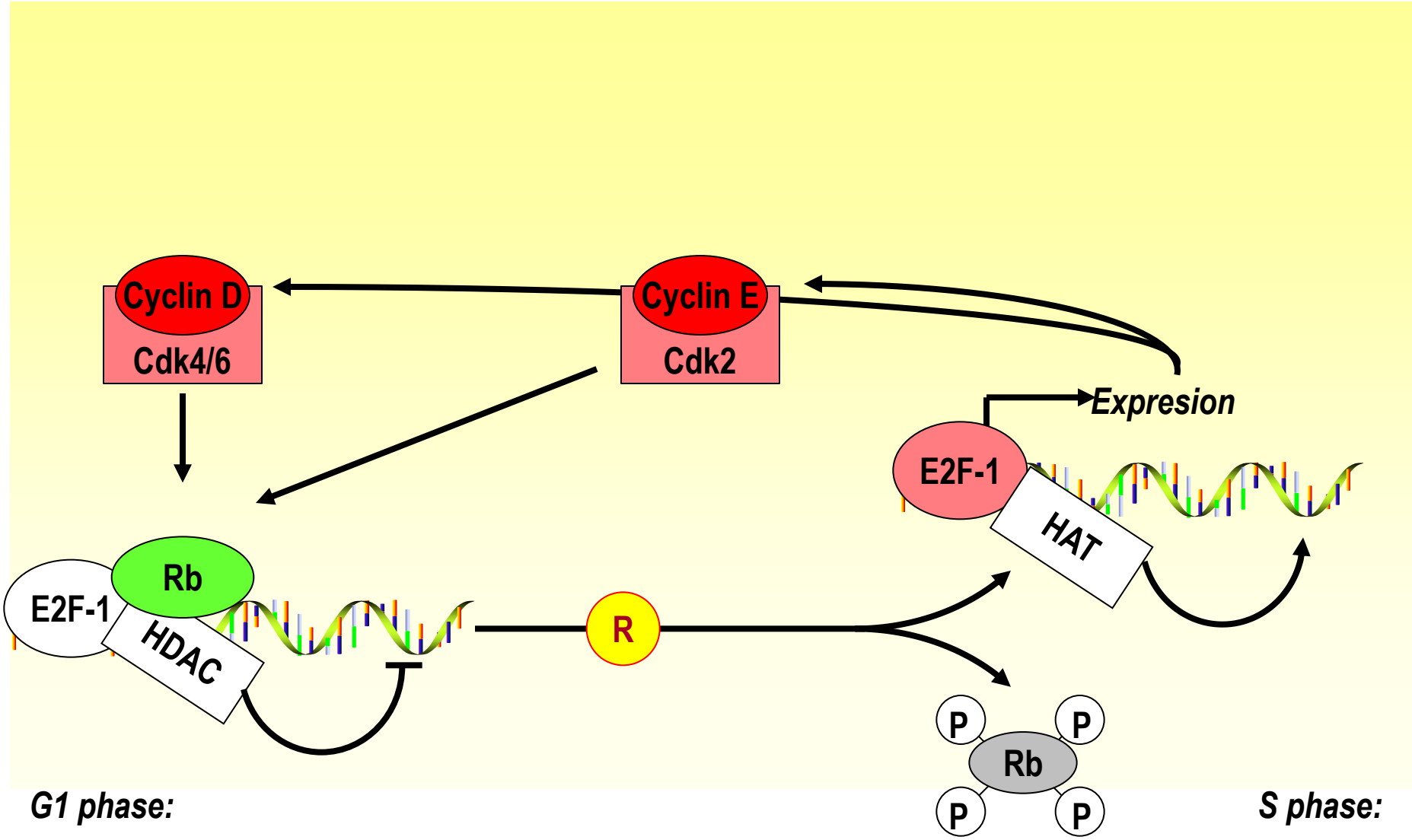
Cell cycle: overview



Cell cycle: overview



Regulation of cell cycle entry



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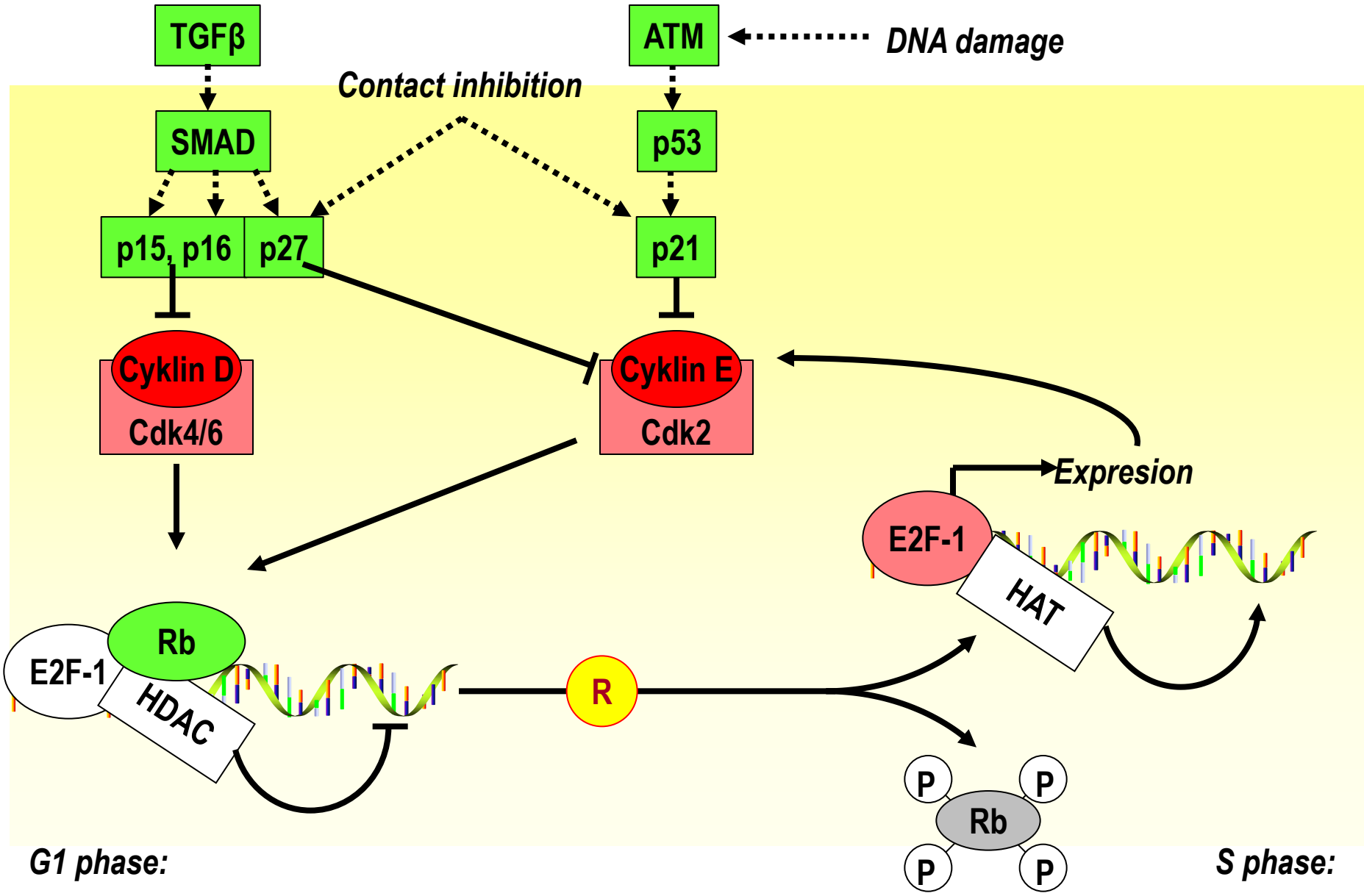
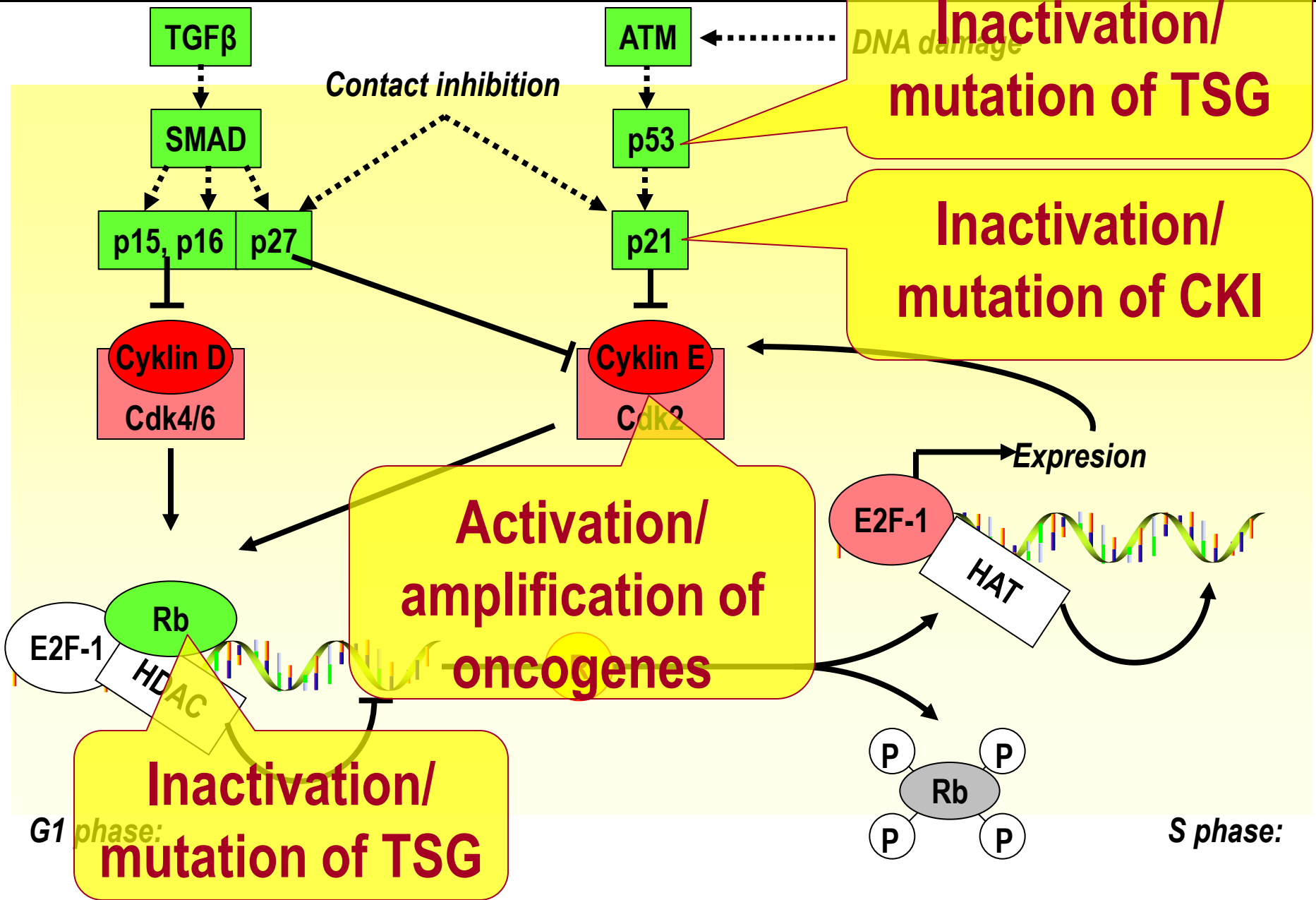
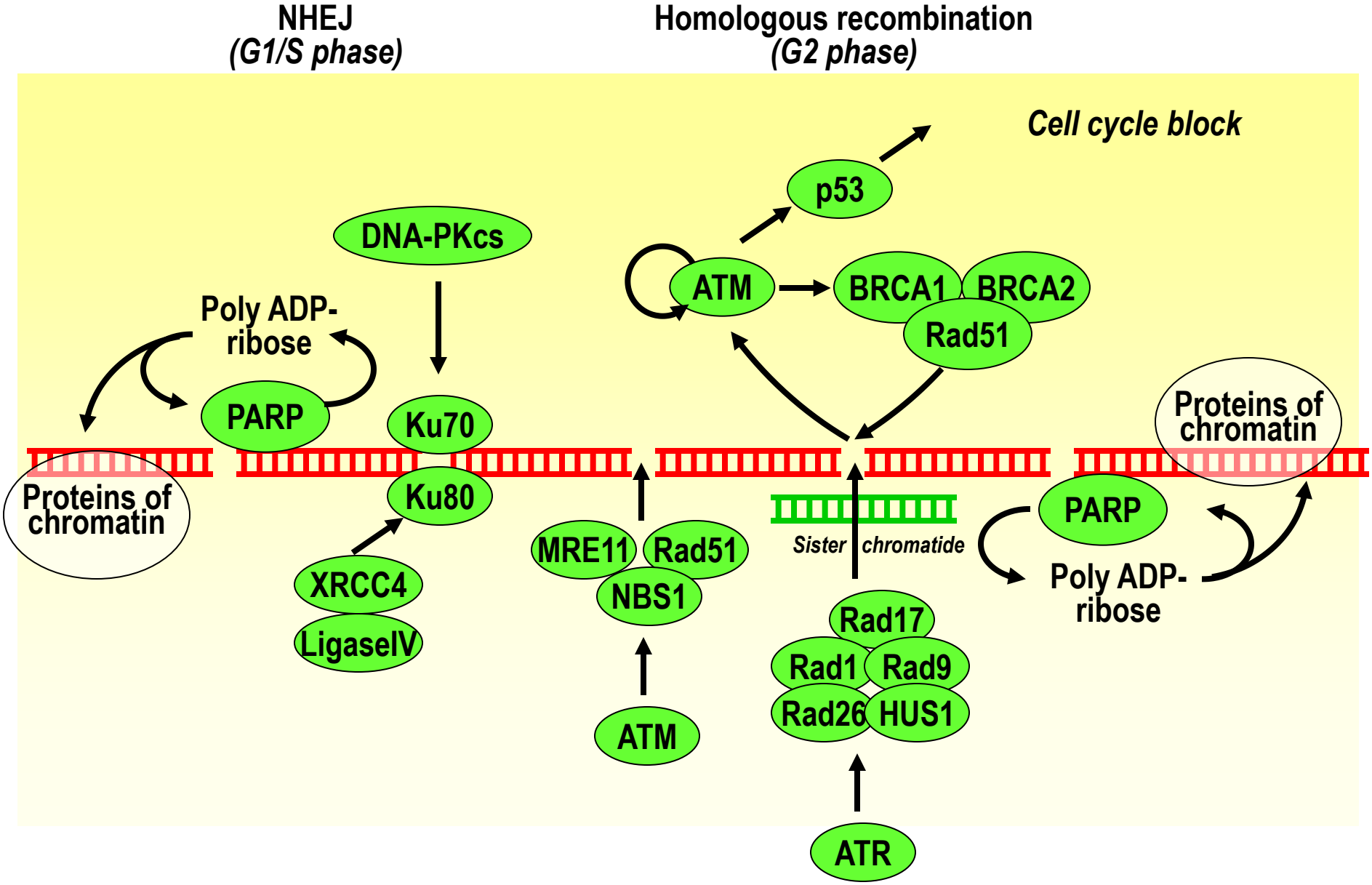


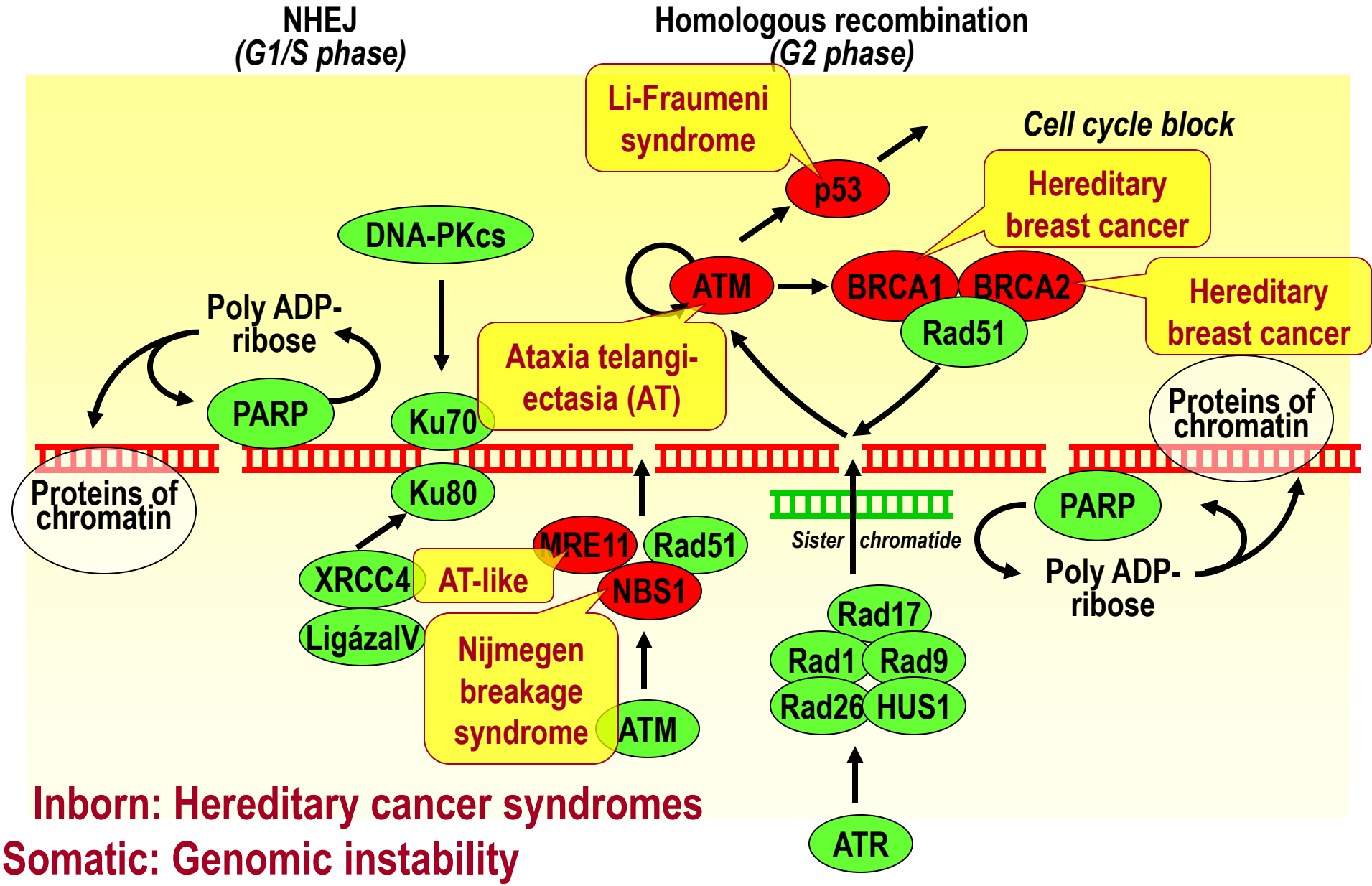
Perturbances of proper cell cycle entry



Core DNA repair pathways (DSBR)



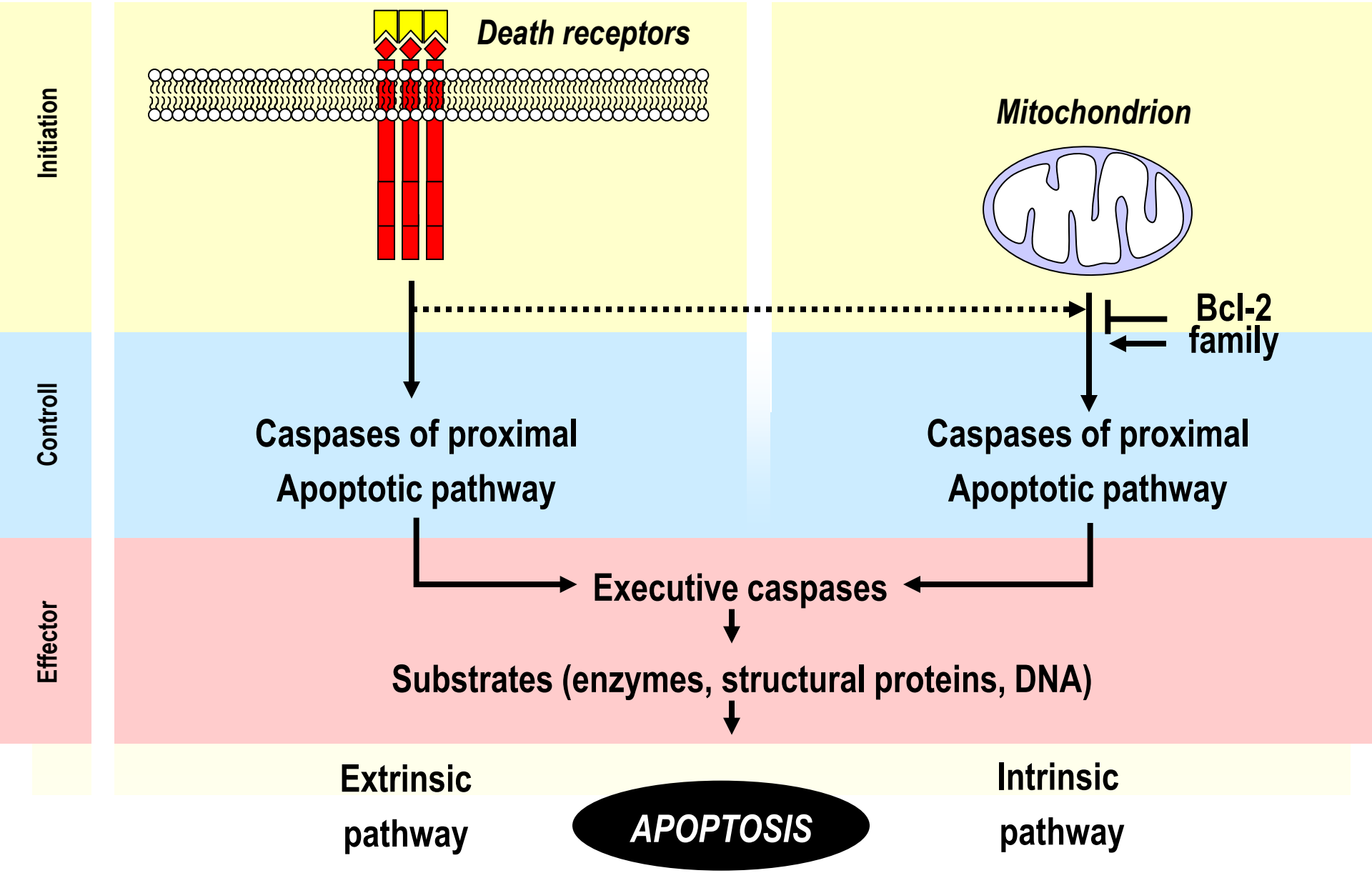
Deterioration of DNA repair pathways (DSBR)



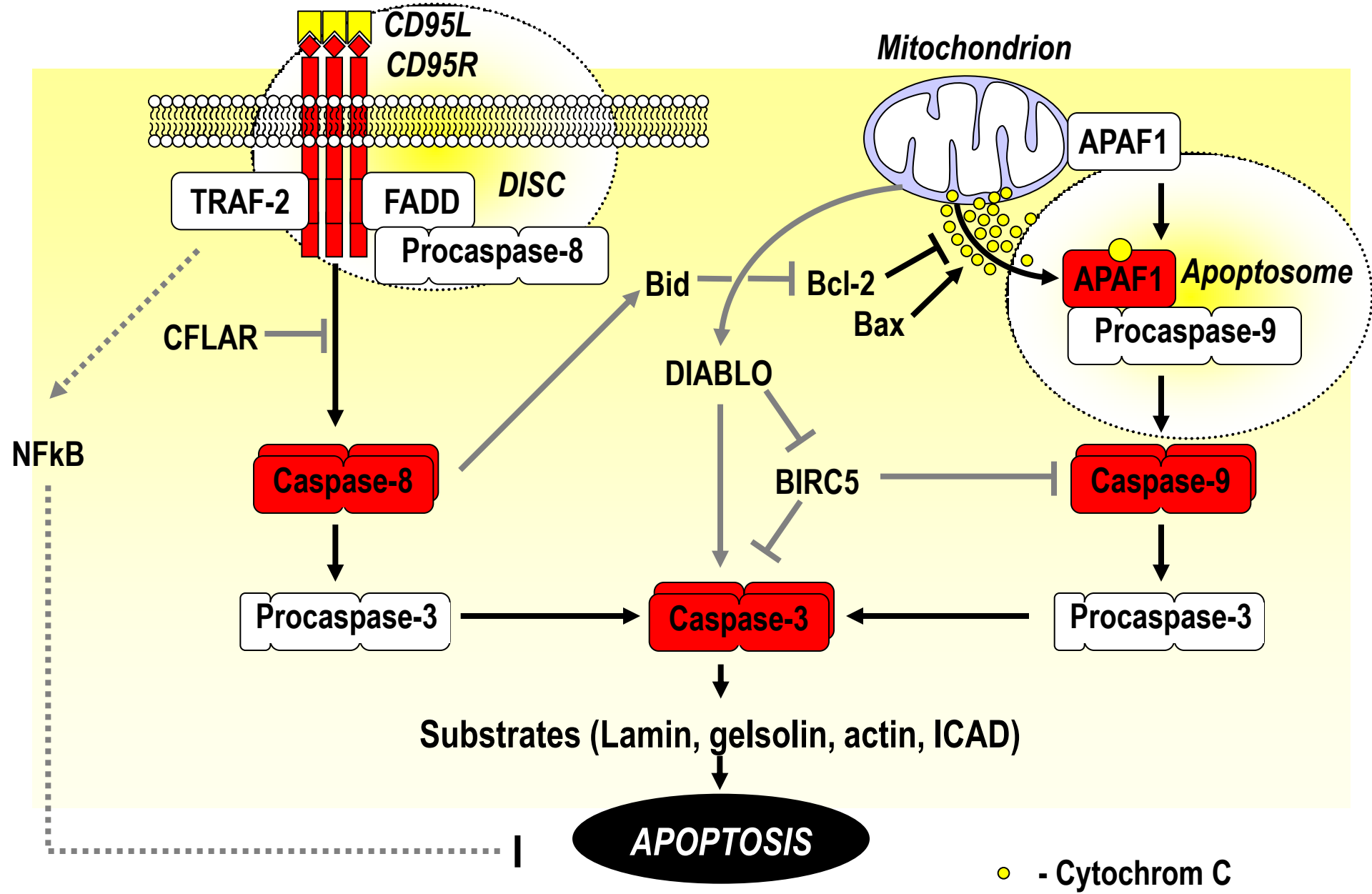
Inborn: Hereditary cancer syndromes

Somatic: Genomic instability

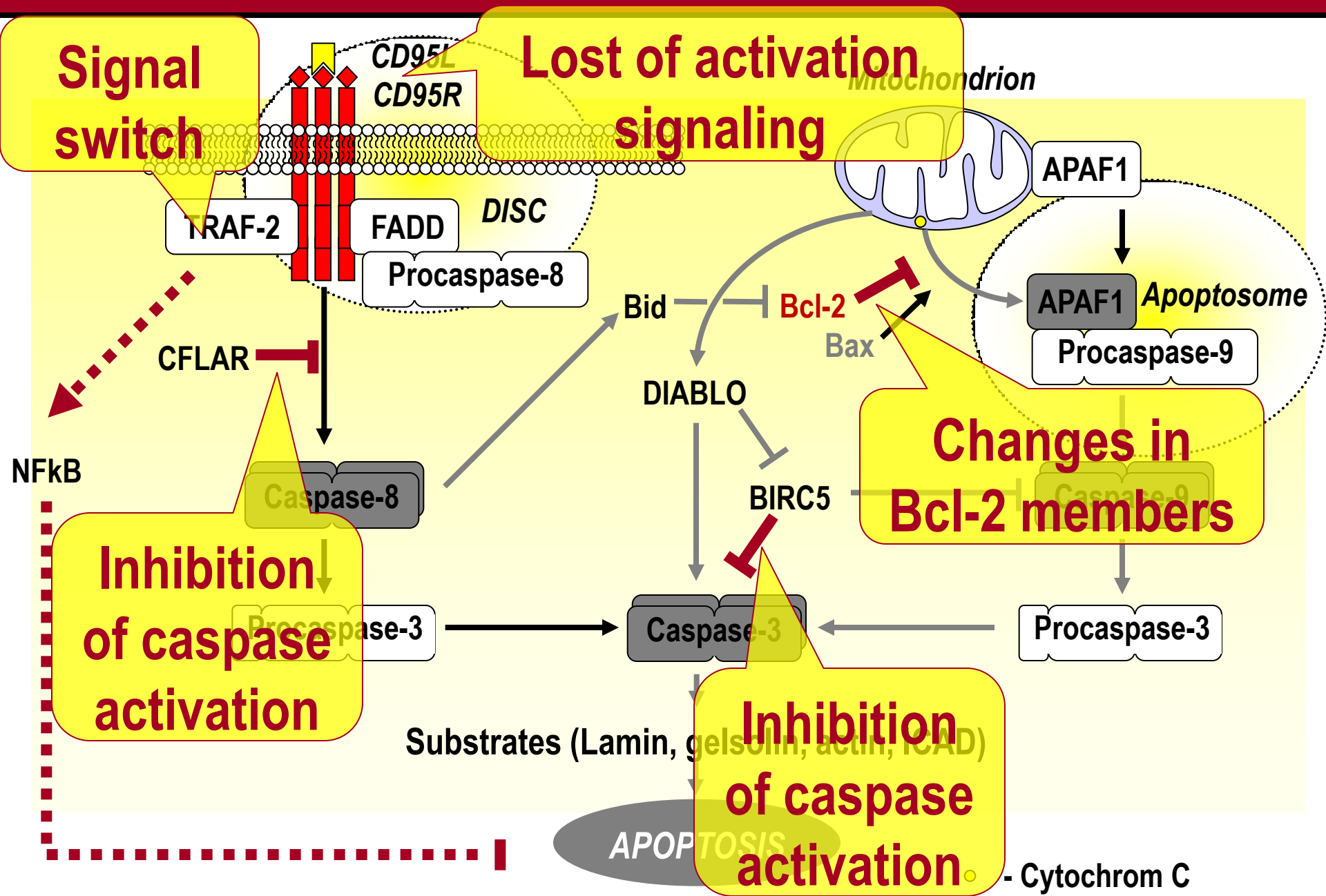
Apoptosis pathways: overview



Apoptosis pathways: players

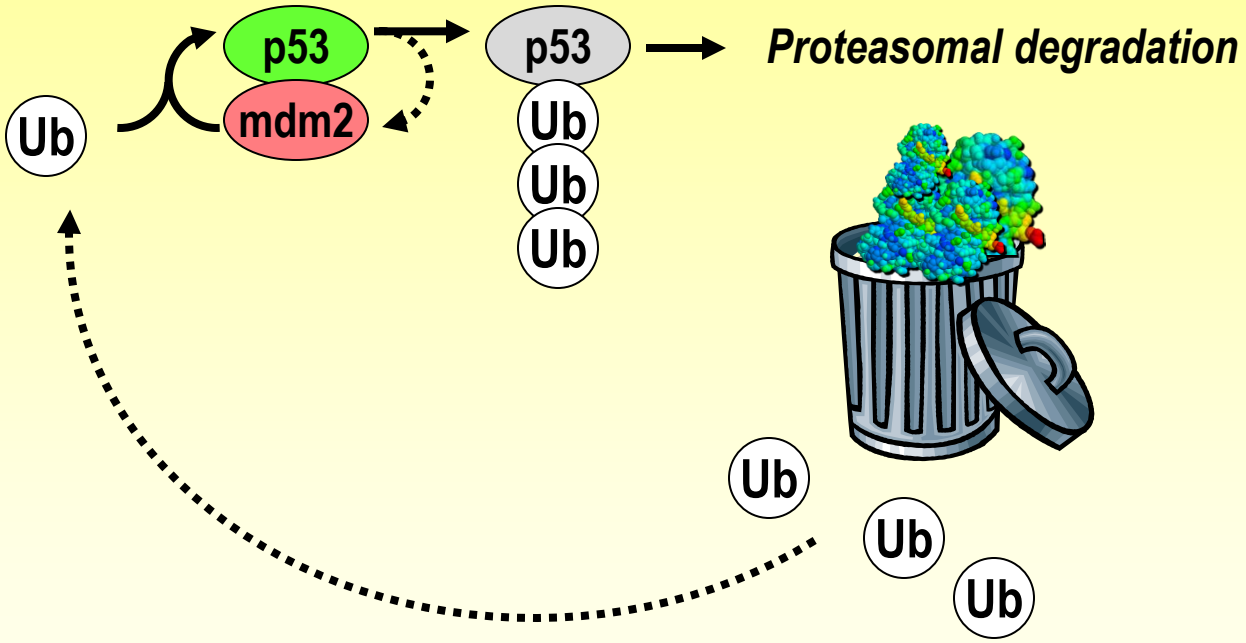


Apoptosis pathways: defects



p53 – the most frequently mutated TSG

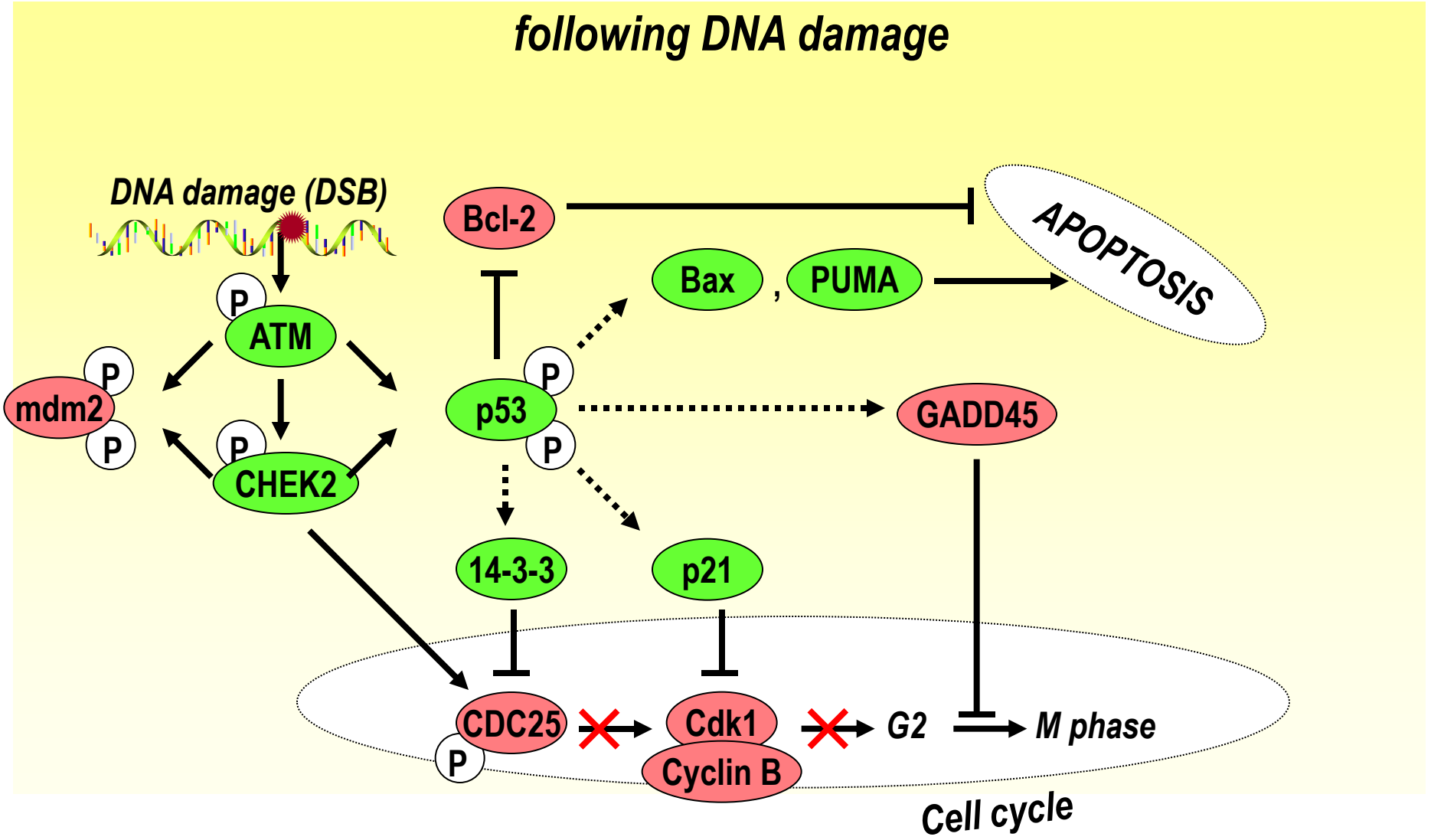
TP53 stably expressed under physiological conditions



Low IC concentration of p53 maintained by its targeting for ubiquitin mediated proteasomal degradation my mdm2 E3 activity

p53 – the most frequently mutated TSG

p53 – transcriptional regulation of CC & apoptosis



Malignant transformation: summary

Malignant cancer – the genetic disease

Normal tissue

malignant transformation

WHICH GENES?

Affection of genomic DNA by various

WHICH PROCESSES?

pathogenetic events

WHICH CELLS?

MaLigNant tumor formation

Malignant transformation: summary

Malignant cancer – the genetic disease

Normal tissue

- **Up-regulation of oncogenes** (genes promoting cell cycle or inhibiting apoptosis)
- **Downregulation / silencing of tumor supressor genes** (genes halting cell cycle or facilitating apoptosis)
- **Inactivation of genes coding for DNA repair proteins** main-taining DNA integrity

WHICH GENES?

Affection of genomic DNA by various pathogenetic events

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WHICH MUTATIONS?

WHICH GENES?

Affection of genomic DNA by various pathogenetic events

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Malignant transformation: summary

Malignant cancer – the genetic disease

- **Drivers**

  - mutations „driving“ malignant transformations

- Passengers

  - mutations that arise from disordered DNA repair processes that are NOT involved in tumorigenesis

Normal tissue

WHICH MUTATIONS?

WHICH GENES?

Affection of genomic DNA by various pathogenetic events

WHICH PROCESSES?

WHICH CELLS?

MaLigNant tumor formation

Malignant transformation: summary

Malignant cancer – the genetic disease

Normal tissue

- **Activation of cell cycle** (including the promitotic pathways)
- **Evasion of apoptosis**
- **Impairment of DNA repair mechanisms**
- Decreased maturation and senescence

WHICH GENES?

Affection of genomic DNA by various pathogenetic events

WHICH PROCESSES?

WHICH CELLS?

MaLigNant tumor formation

Malignant transformation: summary

Malignant cancer – the genetic disease

Normal tissue

- **Stem / progenitor cells** rather than **matured cells in tissues**

WHICH GENES?

Affection of genomic DNA by various pathogenetic events

WHICH PROCESSES?

WHICH CELLS?

MaLigNant tumor formation

Cancer pathways:

Why we should know them?

- ***Classification of tumors***
  - **Identification of cancer genes and „driving“ mutations**
- ***Improved, optimized treatment***
  - **Targeting of tumor cells – not somatic cells**
  - **Individualization of therapy based on molecular cancer profile**