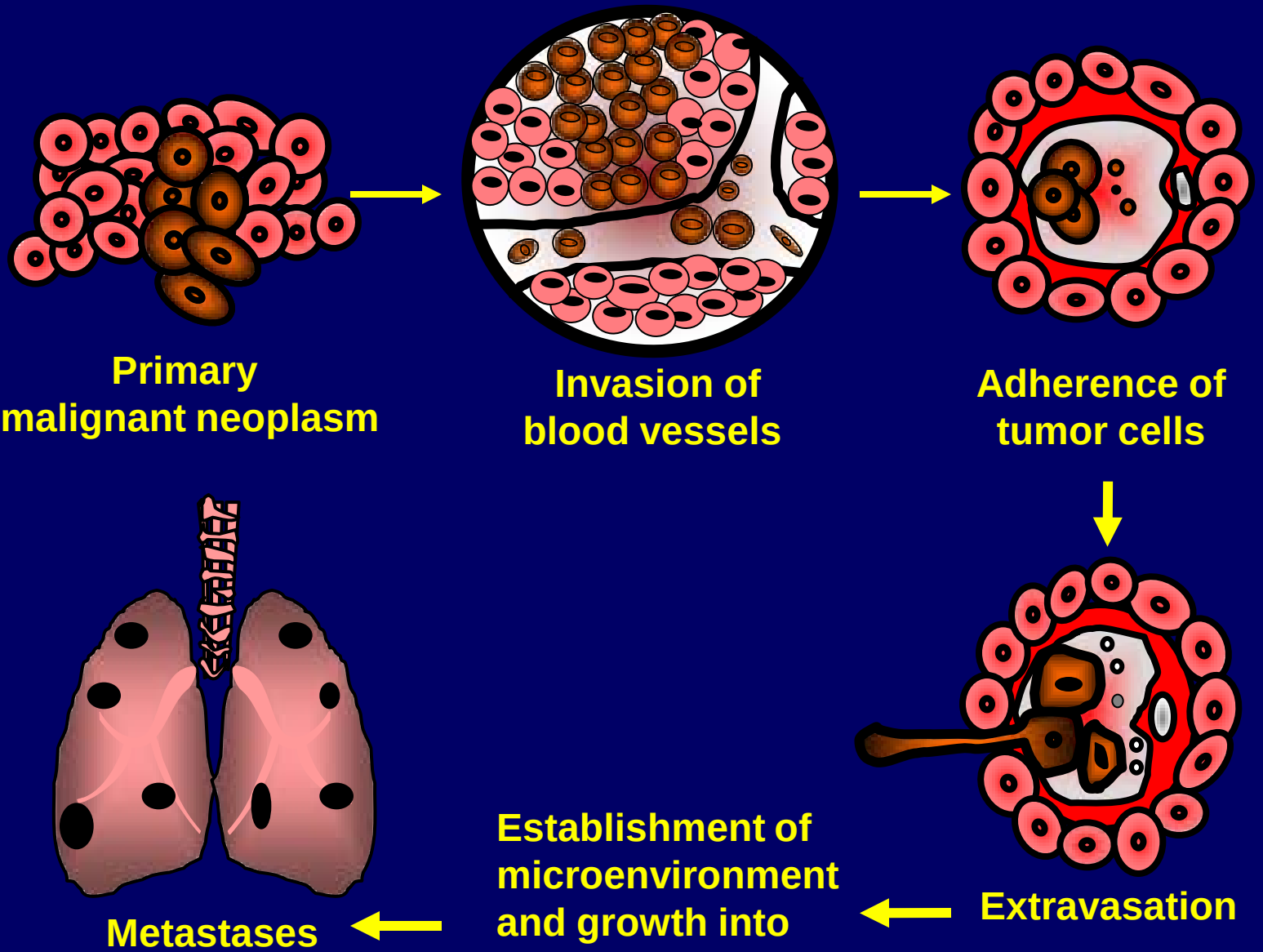
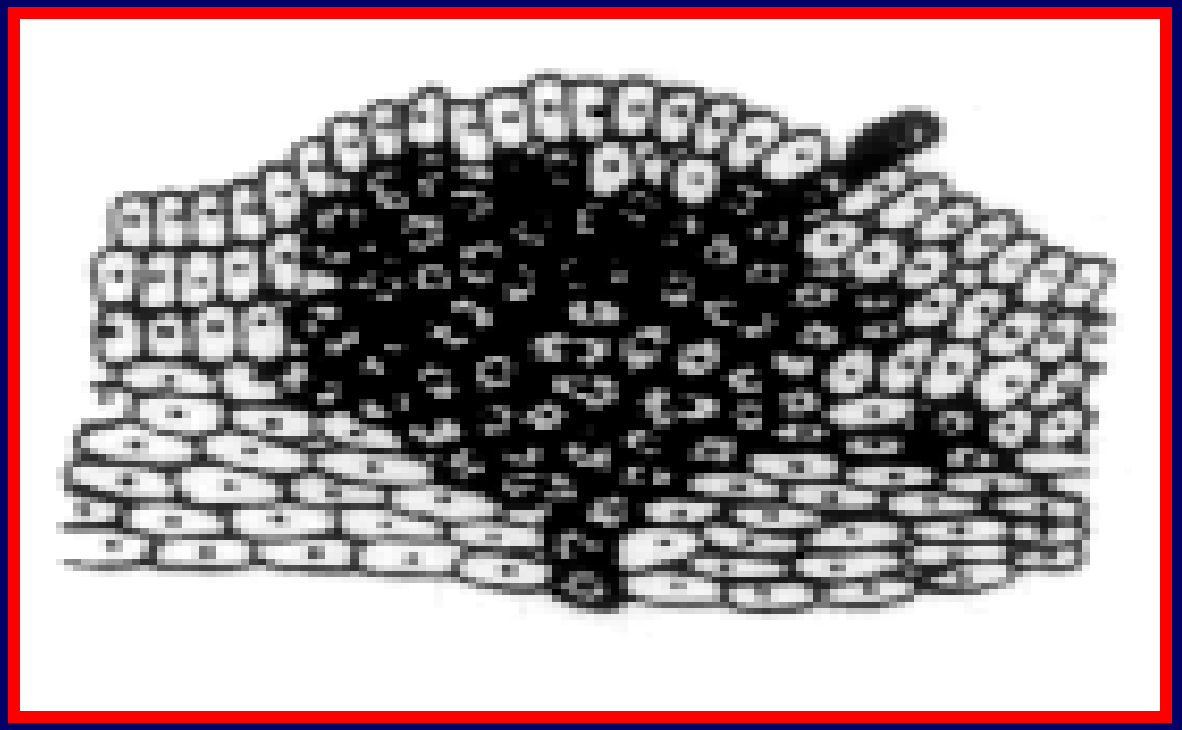
Cancer formation and metastasis

The Pathogenesis of a Metastasis



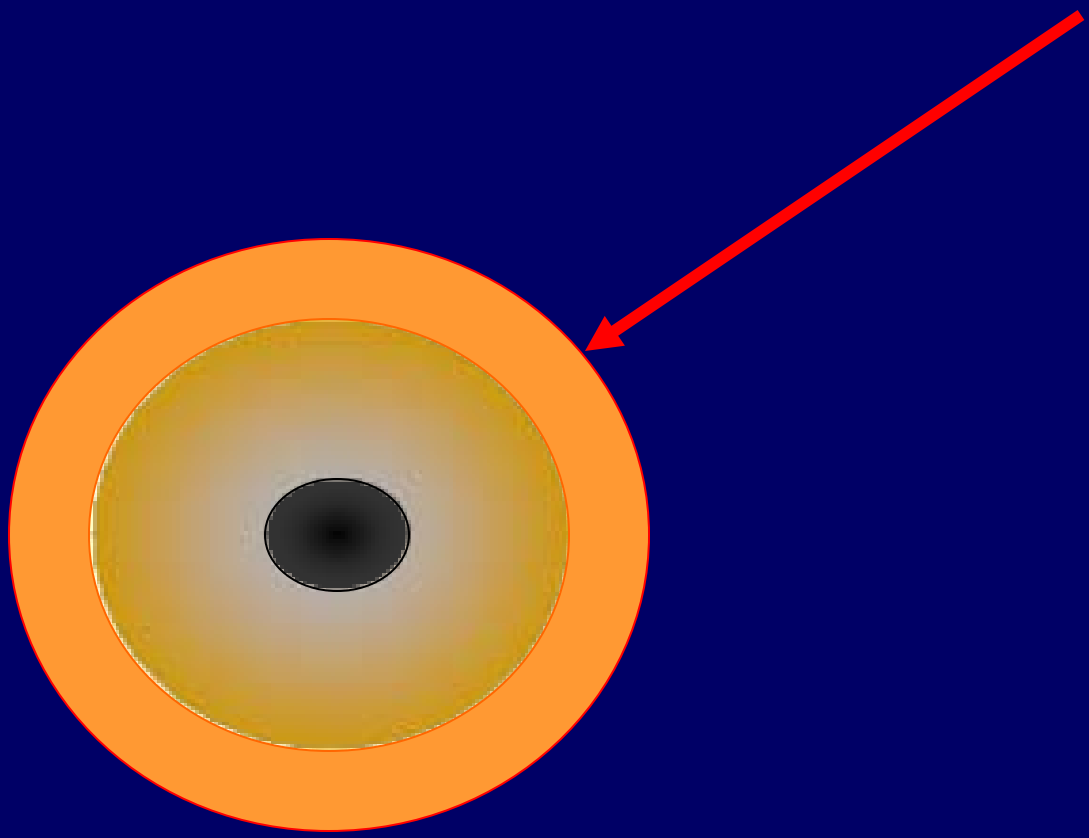
The Pathogenesis of a Metastasis

Primary malignant neoplasm



Cancer is a disease involving dynamic changes in the genome

- Mutations that produce oncogenes with dominant gain of function
- Mutations that produce tumor supressor genes with recessive loss of function



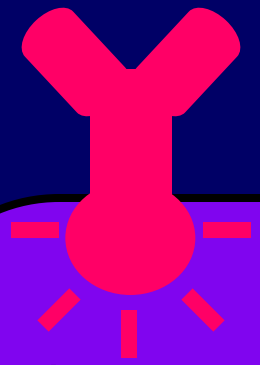
(Proto)-oncogenes

- Genes whose protein products stimulate or enhance the division and viability of cells.
- The normal versions of these genes are called proto-oncogenes.
- The mutated or otherwise damaged versions of these genes are called oncogenes.
- A single altered copy of an oncogene leads to unregulated growth.

(Proto)-oncogenes

- Growth factors (*c-sis*)
- Protein kinases (*c-abl*, *c-src*, *c-fms*)
- GTP binding proteins (*ras*)
- Transcription factors (*c-myc*, *c-fos*, *c-jun)*

PDGF receptor
EGF receptor [*erb*B]
M-CSF receptor [*fms*]

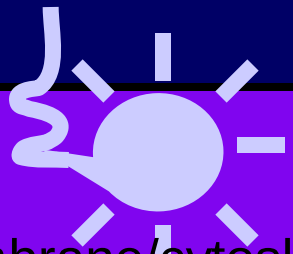


growth-factor receptors acting via tyrosine-specific protein-kinase activity

Ras proteins
[H-*ras*]
[N-*ras*]
[K-*ras*]

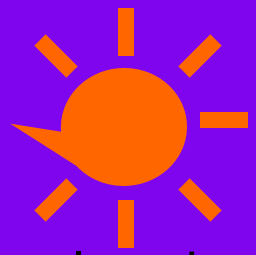
GTP-binding proteins

Src protein kinase
[*src*]



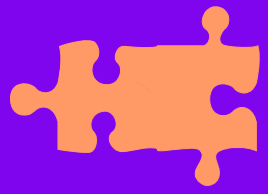
membrane/cytoskeleton-associated tyrosine-specific protein kinases

[*fes*]



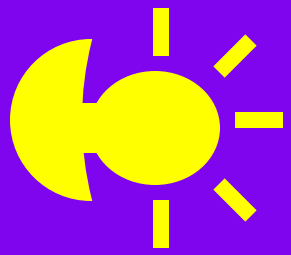
cytoplasmic tyrosine-specific protein kinases

Thyroid hormone receptor [*erb*A]



steroid-type growth-factor receptors

[*raf*]



serine/threonine-specific protein kinases

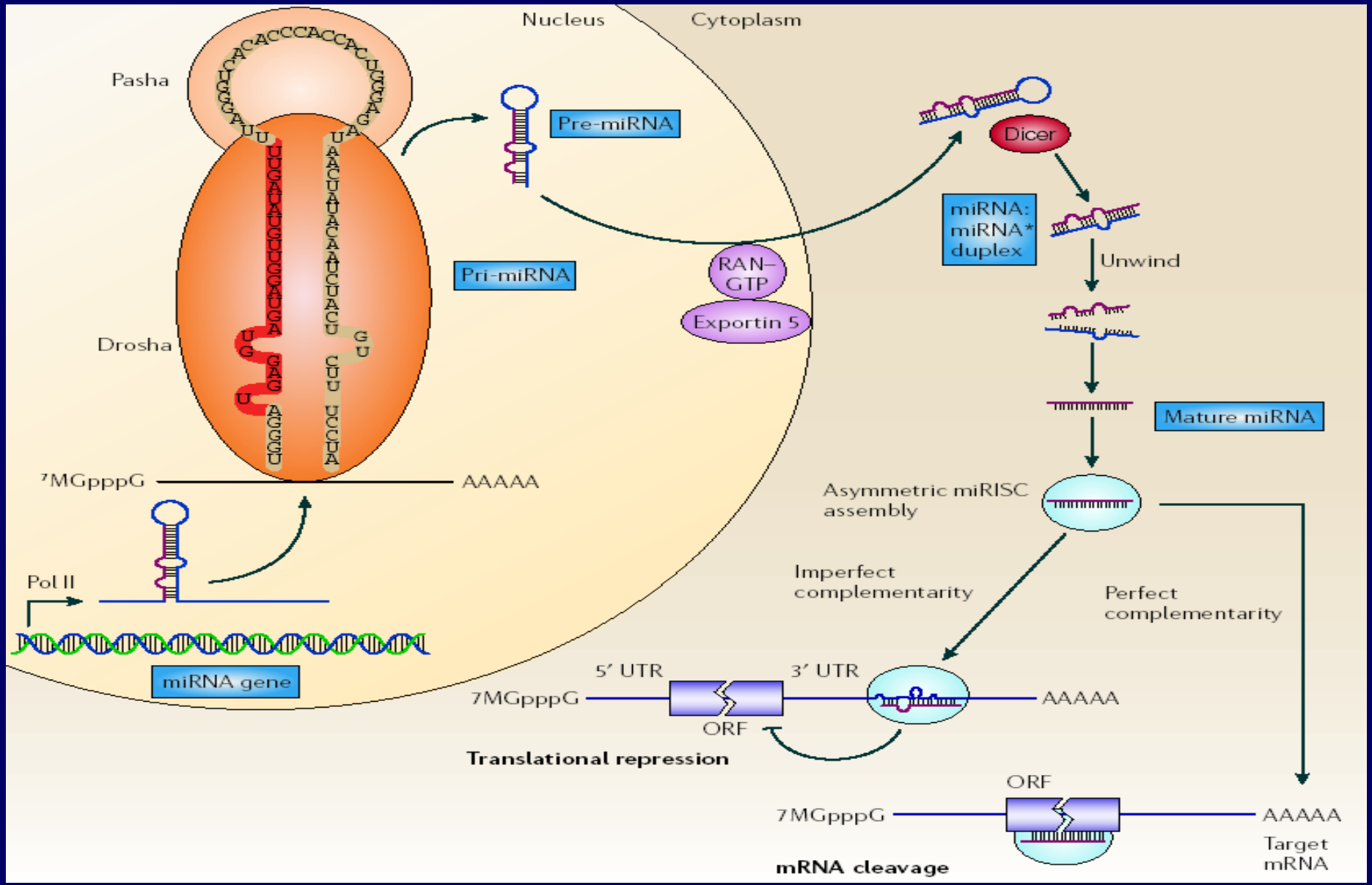
[*myc*]
[*fos*]
[*jun*]

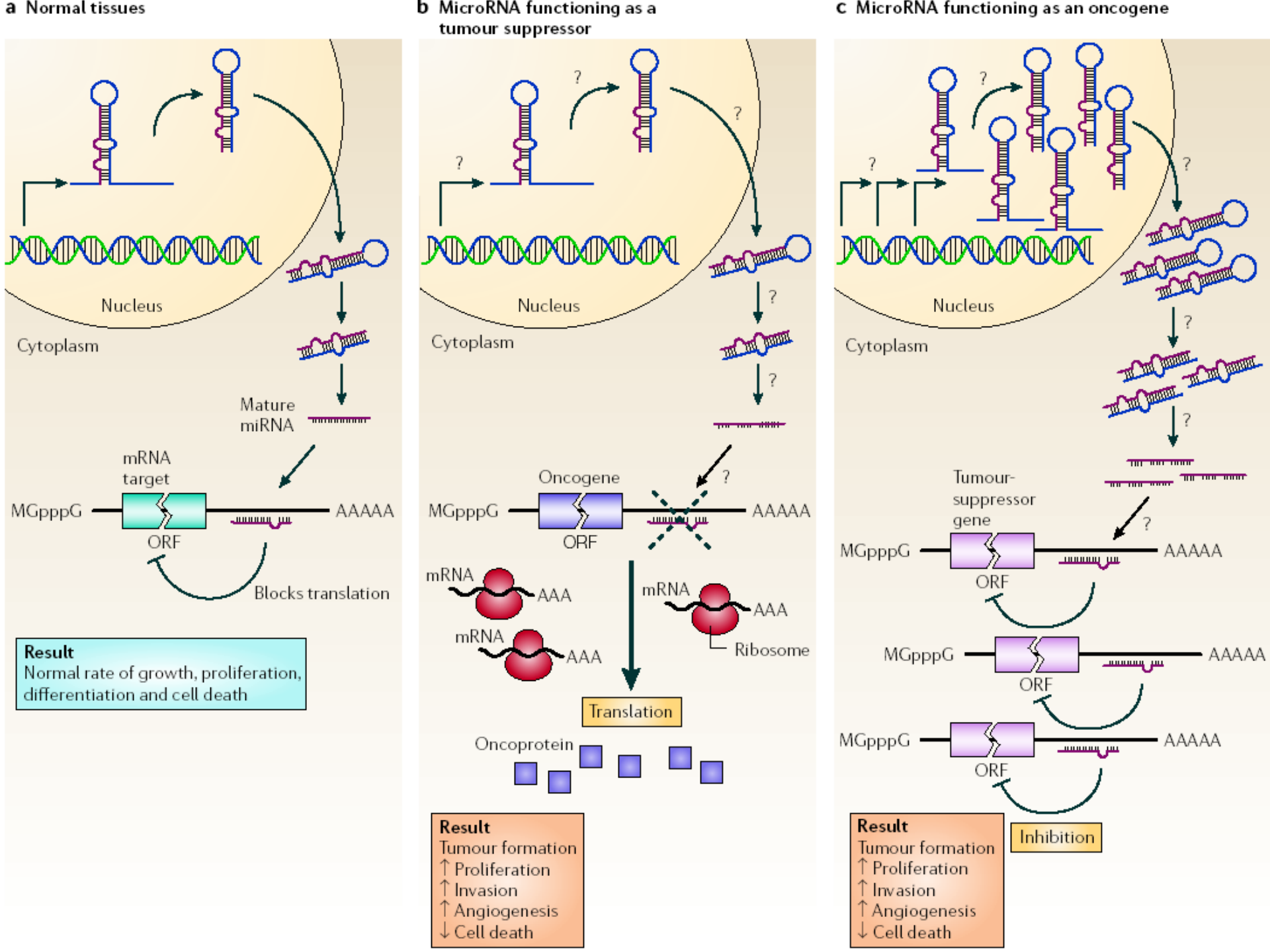
Nuclear proteins

Tumor suppresors

- Genes whose protein products can directly or indirectly prevent cell division or lead to cell death
- Rb
- p53
- Both copies of tumor supressor genes must be defective to lead to abnormal cell division

The biogenesis of microRNA




a Normal tissues
Nucleus
Cytoplasm
Mature miRNA
mRNA target
MGpppG
AAAAA
ORF
Blocks translation
Result
Normal rate of growth, proliferation, differentiation and cell death
b MicroRNA functioning as a tumour suppressor
Nucleus
Cytoplasm
Oncogene
MGpppG
AAAAA
ORF
mRNA
AAA
Ribosome
Translation
Oncoprotein
Result
Tumour formation
↑ Proliferation
↑ Invasion
↑ Angiogenesis
↓ Cell death
c MicroRNA functioning as an oncogene
Nucleus
Cytoplasm
Tumour-suppressor gene
MGpppG
AAAAA
ORF
Inhibition
Result
Tumour formation
↑ Proliferation
↑ Invasion
↑ Angiogenesis
↓ Cell death

Role of miRNAs in cancer

- Half of the human miRNA map within fragile regions of chromosomes, which are areas of the genome associated with various human cancers
- miRNAs can function as tumor suppressors or oncogenes
- Factors that are required for the biogenesis of miRNA have been associated with various cancers

Cell transformed with oncogenic viruses

- Alterations in cell membrane
- Alterations in cell adhesion
- Alterations in growth rate

Cancer cell genotypes are a manifestation of several essential alterations in cell physiology

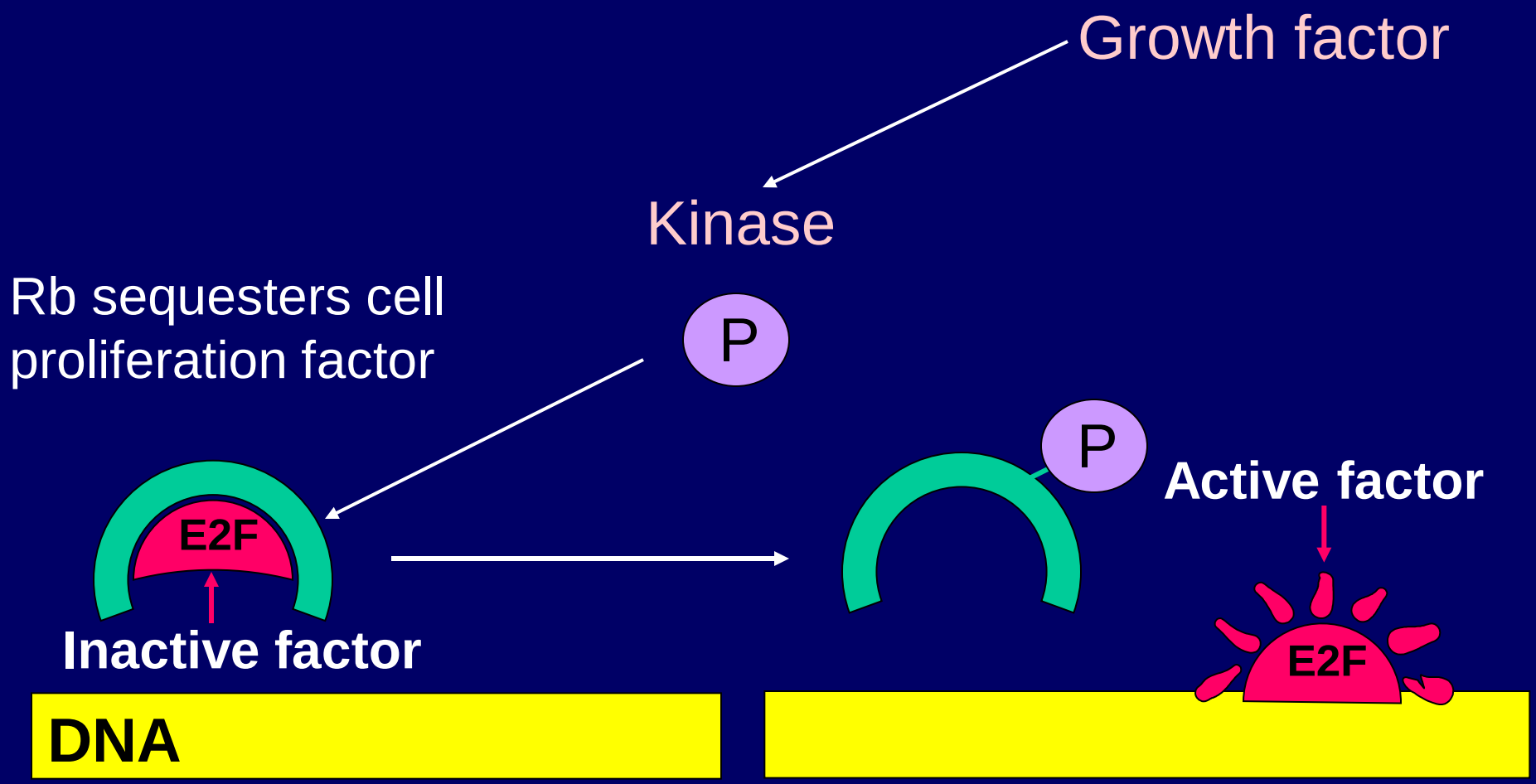
- Self-sufficiency in growth signals
- Insensitivity to growth-inhibitory (antigrowth) signals
- Evasion of apoptosis
- Limitless replicative potential

Self-sufficiency in growth signals

- Production of growth factors by cancer cells (PDGF, TGFα)
- Overexpression or structural alterations of growth factor receptors (EGF-R/*erbB*)
- Alterations in components of signaling pathways (*ras*)
- Expression of integrins that transmit progrowth signals

Insensitivity to antigrowth signals

At the molecular level, most antiproliferative signals are funneled through the retinoblastoma protein Rb


Growth factor
Kinase
Rb sequesters cell proliferation factor
P
P
E2F
Active factor
Inactive factor
E2F
DNA
PROLIFERATION BLOCKED
PROLIFERATION ACTIVATED

Evasion of programmed cell death

The ability of tumor cell populations to expand in number is determined not only by the rate of cell proliferation but also by the rate of cell elimination

Apoptosis

- Sensors-responsible for monitoring the extracellular and intracellular environment for conditions of normality and abnormality
- IGF/IGF-R, IL-3/IL3R (survival signals)
- FAS ligand/FAS receptor, TNFα/TNFα-R1 (apoptosis)
- Effectors Bcl-2 family (Bax proapoptotic, Bcl-2 antiapoptotic)

Apoptosis

Death pathway is activated in response to cell abnormalities including;

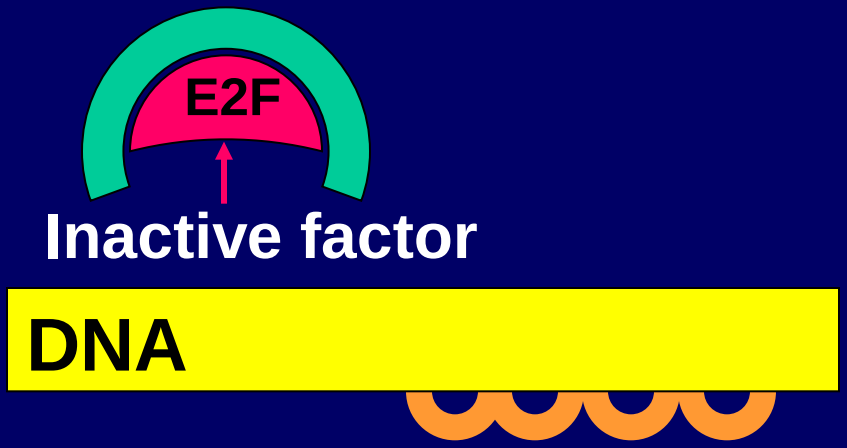
- DNA damage
- signaling imbalance provoked by oncogene action
- survival factor insufficiency
- hypoxia
- abrogation of cell-cell and cell-matrix interactions

Evading Apoptosis

At the molecular level, most proapoptotic signals are regulated by p53

Activation of cell proliferation by the SV40 DNA tumor virus

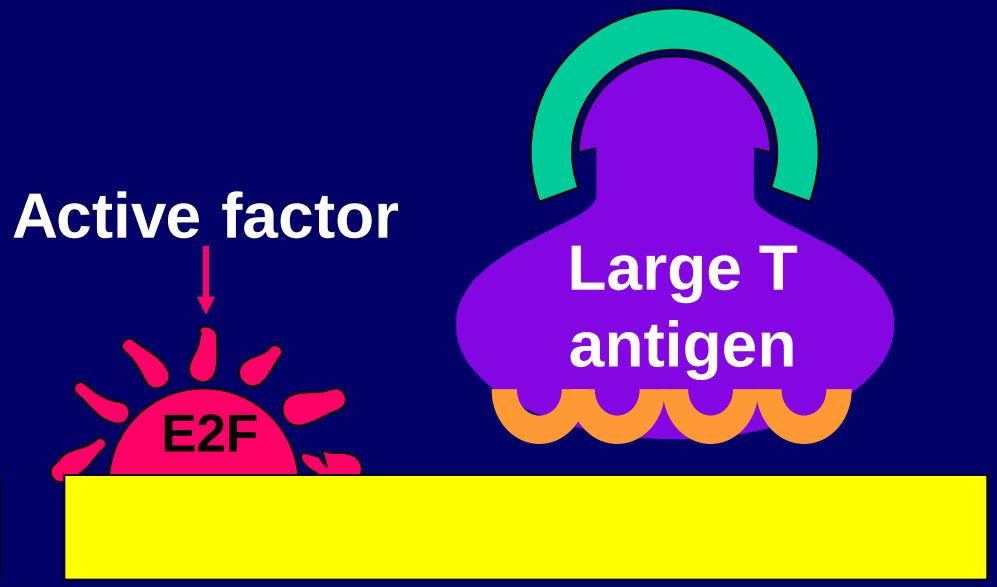
Rb sequesters cell proliferation factor



p53 activates safety brake on proliferation

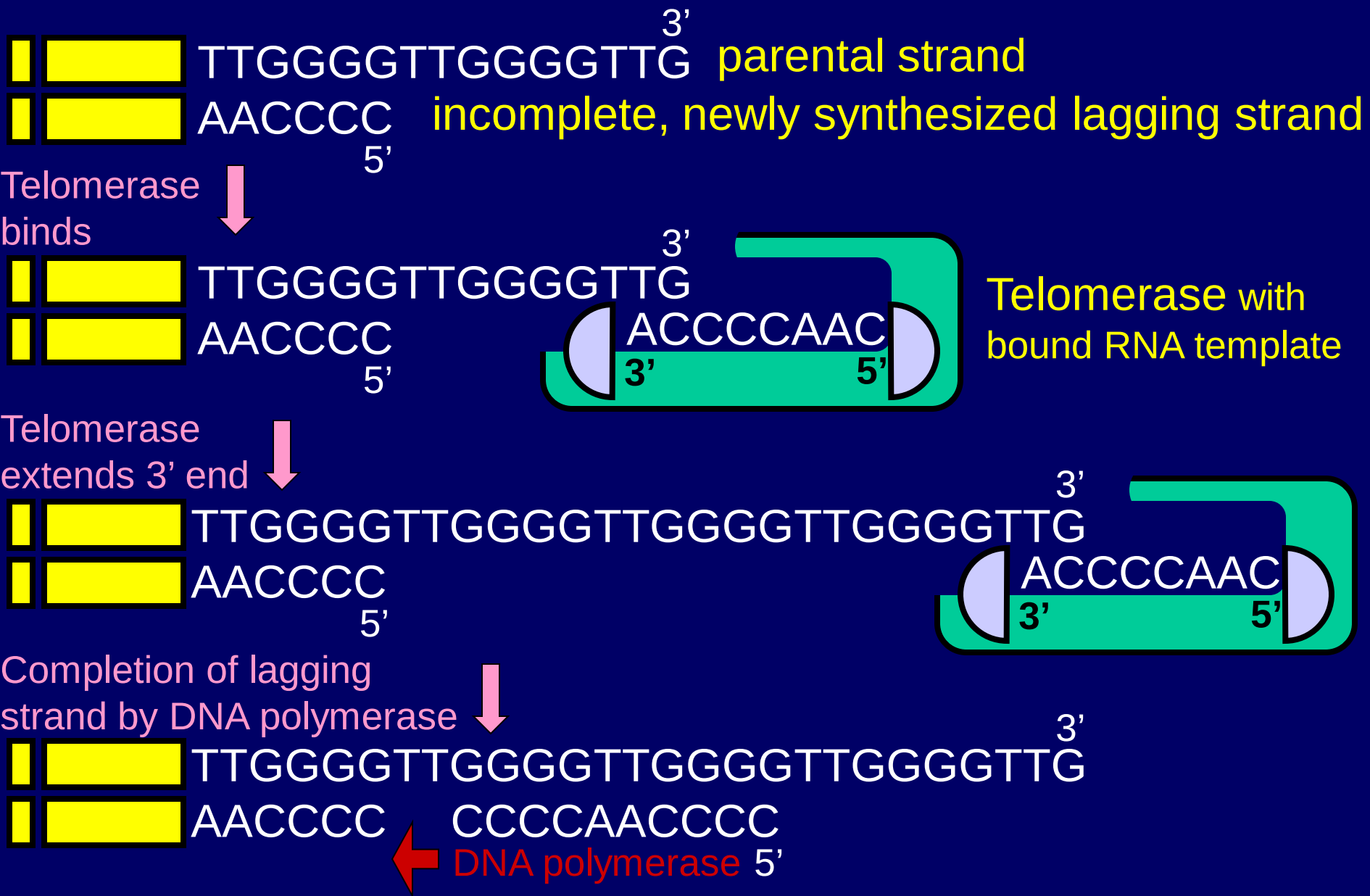
PROLIFERATION BLOCKED

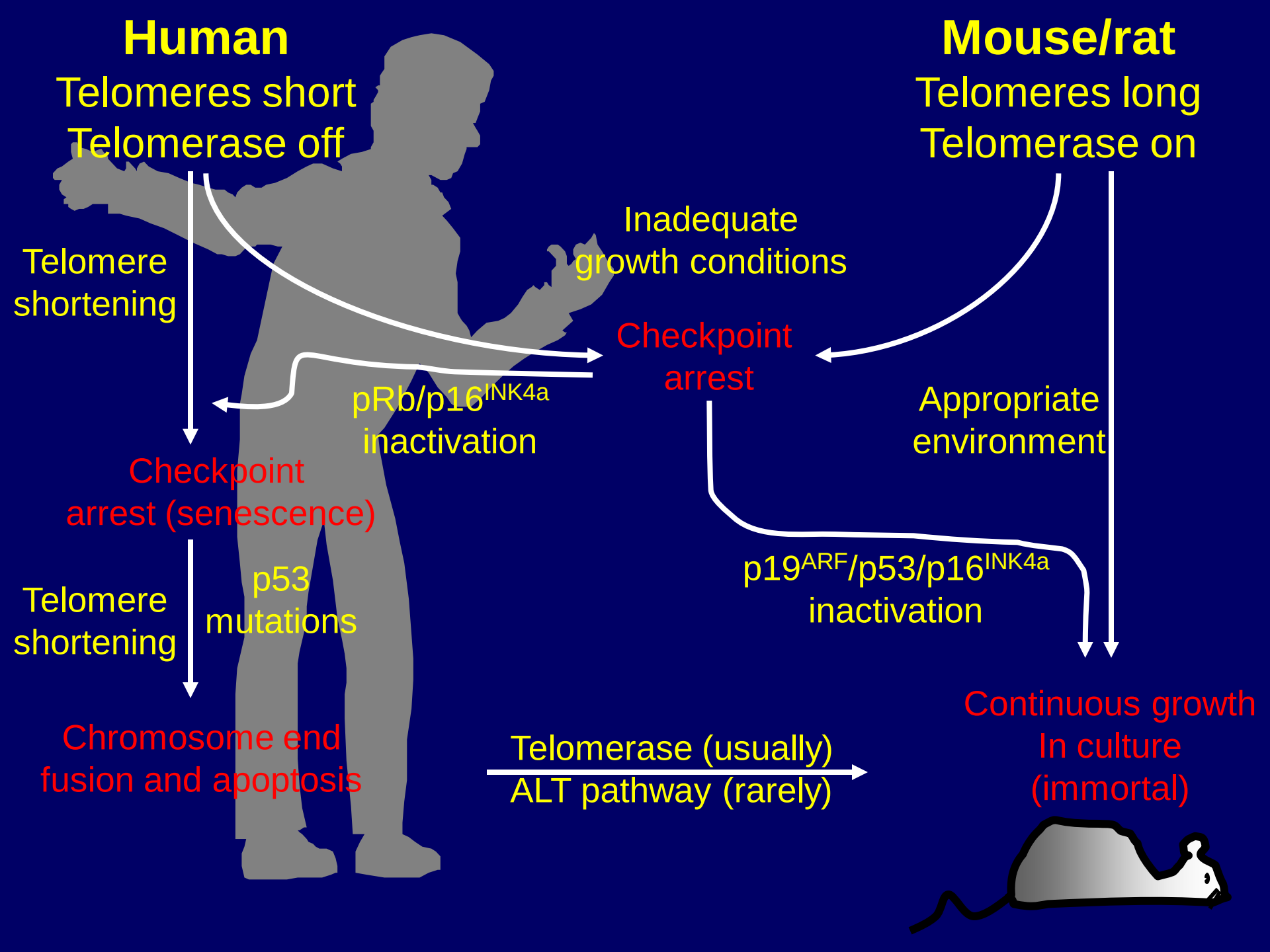
Viral protein sequesters Rb and p53



PROLIFERATION ACTIVATED

Replication of telomers




Human
Telomeres short
Telomerase off
Mouse/rat
Telomeres long
Telomerase on
Telomere shortening
Inadequate growth conditions
Checkpoint arrest
pRb/p16INK4a inactivation
Appropriate environment
Checkpoint arrest (senescence)
p19ARF/p53/p16INK4a inactivation
Telomere shortening
p53 mutations
Chromosome end fusion and apoptosis
Telomerase (usually)
ALT pathway (rarely)
Continuous growth In culture (immortal)