

Genetics of Cancer

Lecture 34

Alterations in different kinds of Genes cause Cancer

Oncogenes

dominant gain-of-function mutations
promote cell transformation

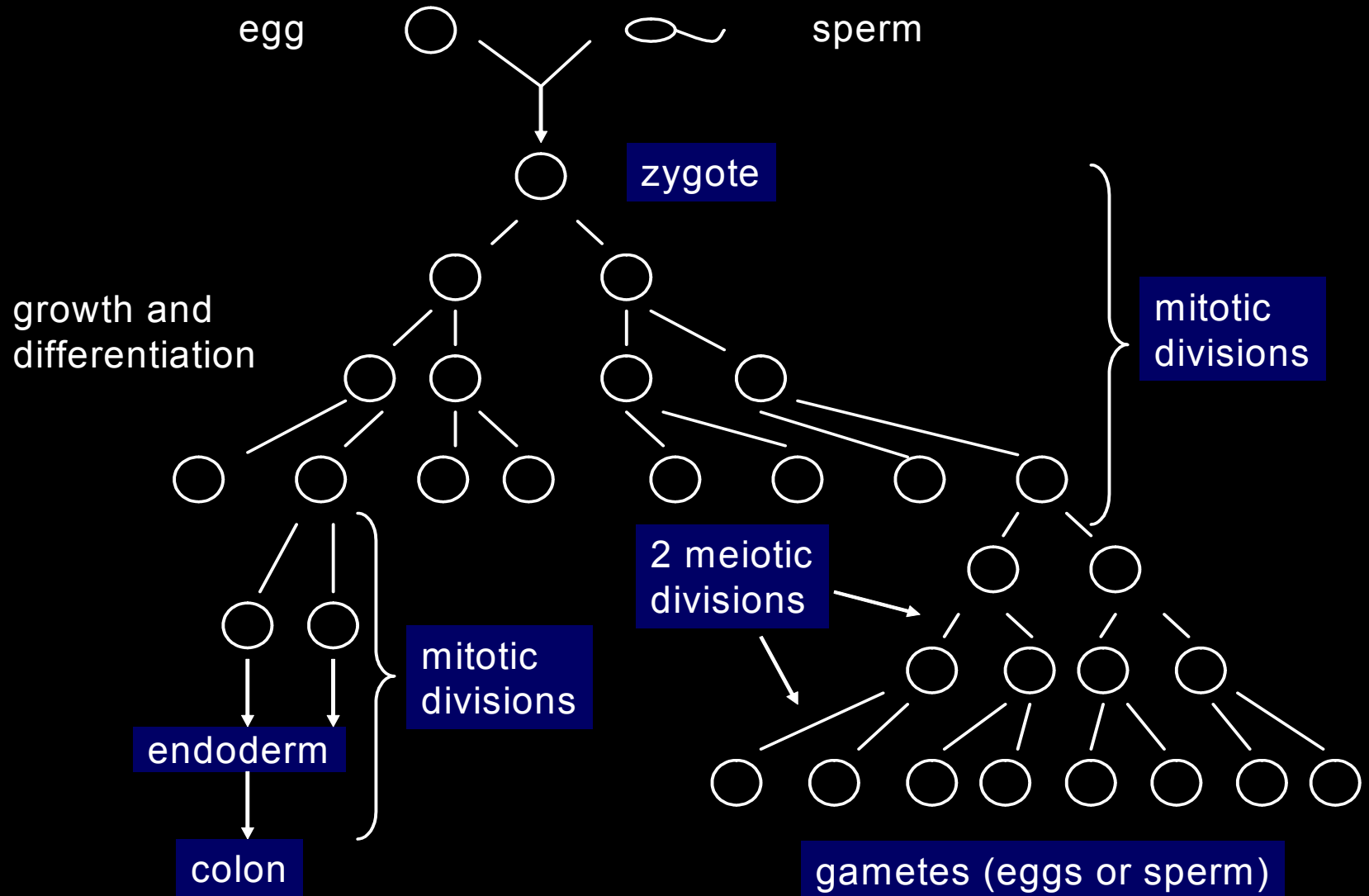
Tumor suppressor genes

recessive, loss-of-function mutations
promote cell transformation

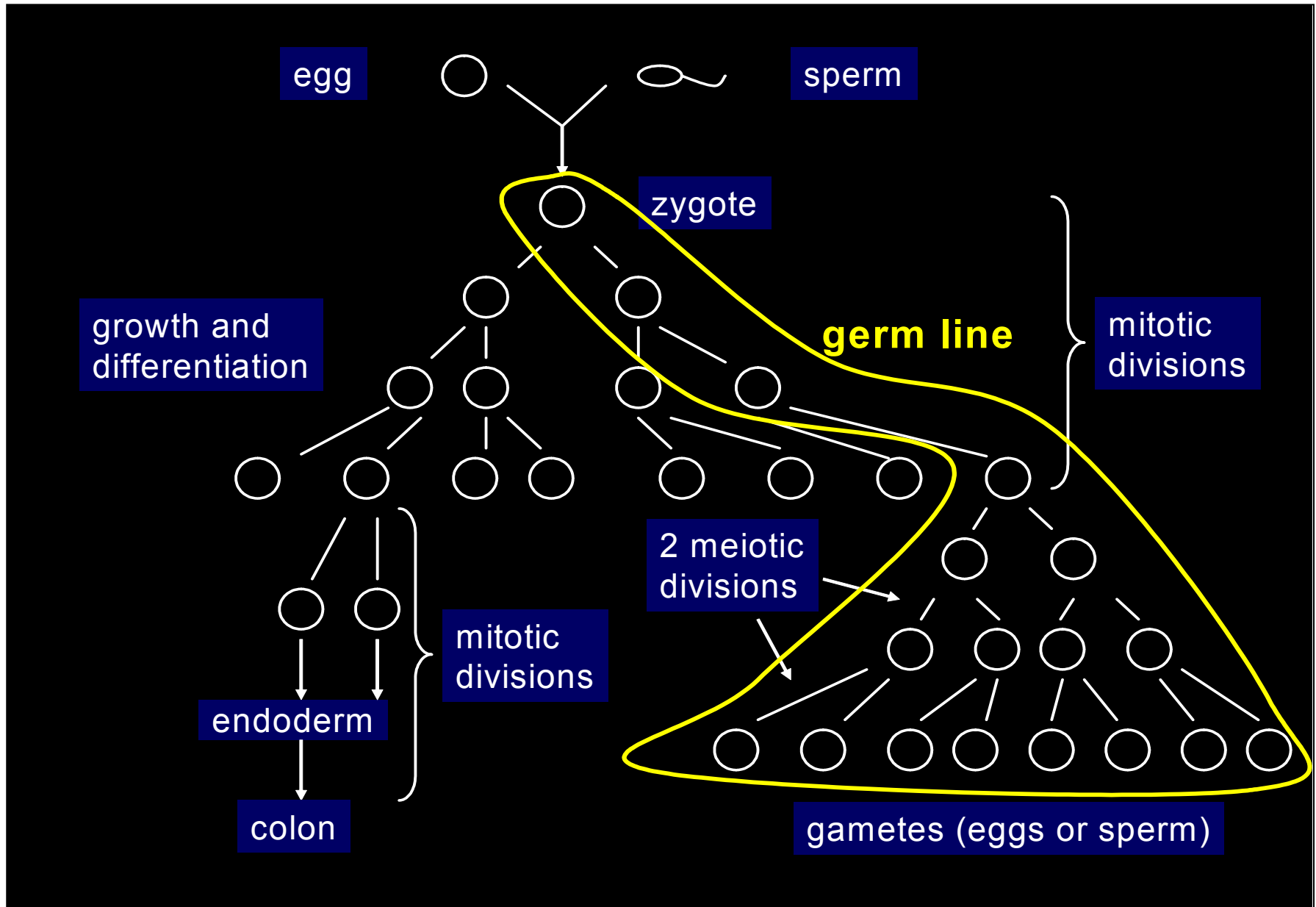
Mutator genes

Usually recessive, loss-of-function mutations
that increase spontaneous and environmentally
induced mutation rates

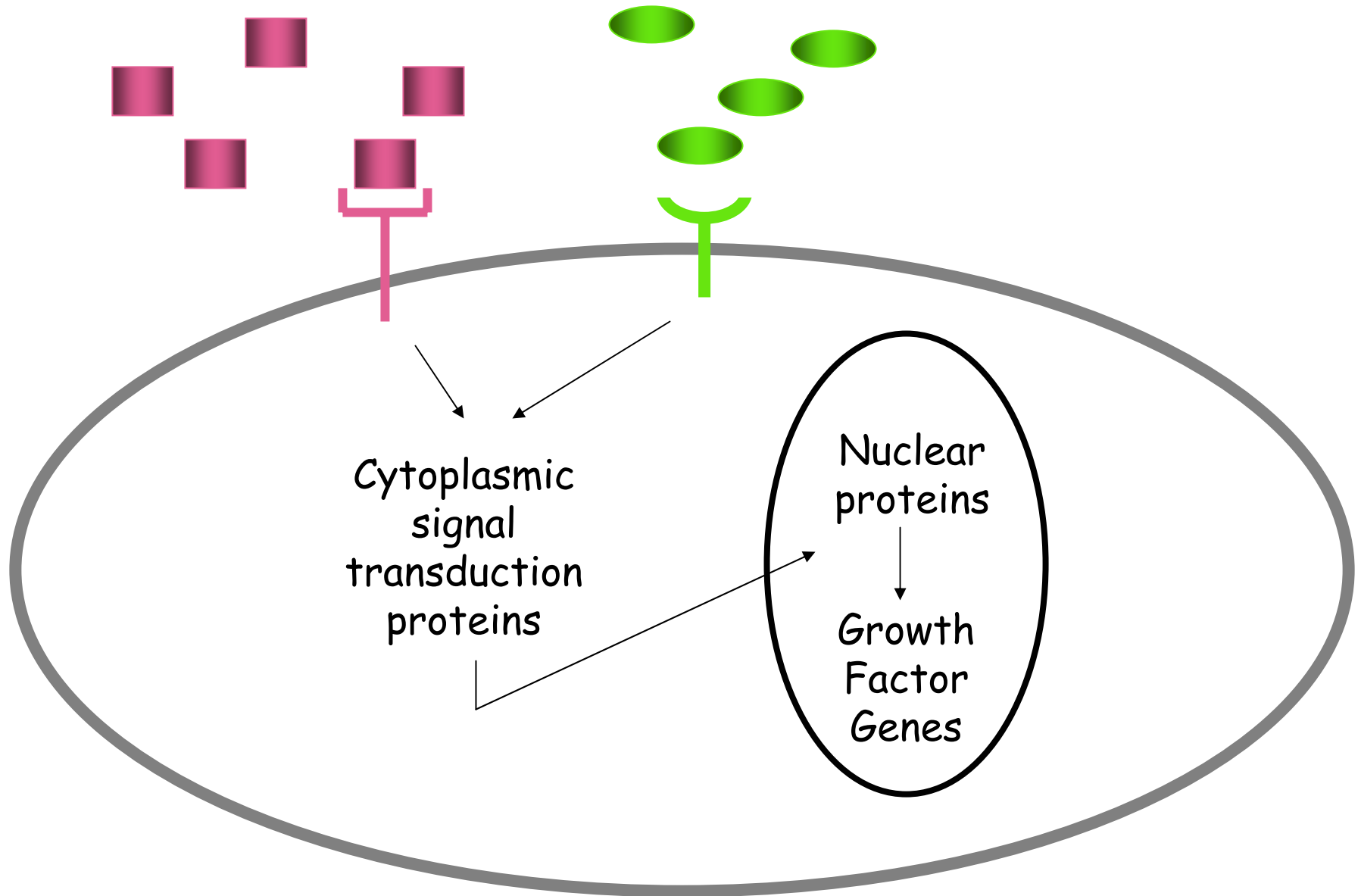
Most of the mutations that contribute to cancer occur in somatic cells - but germ line mutations can also contribute



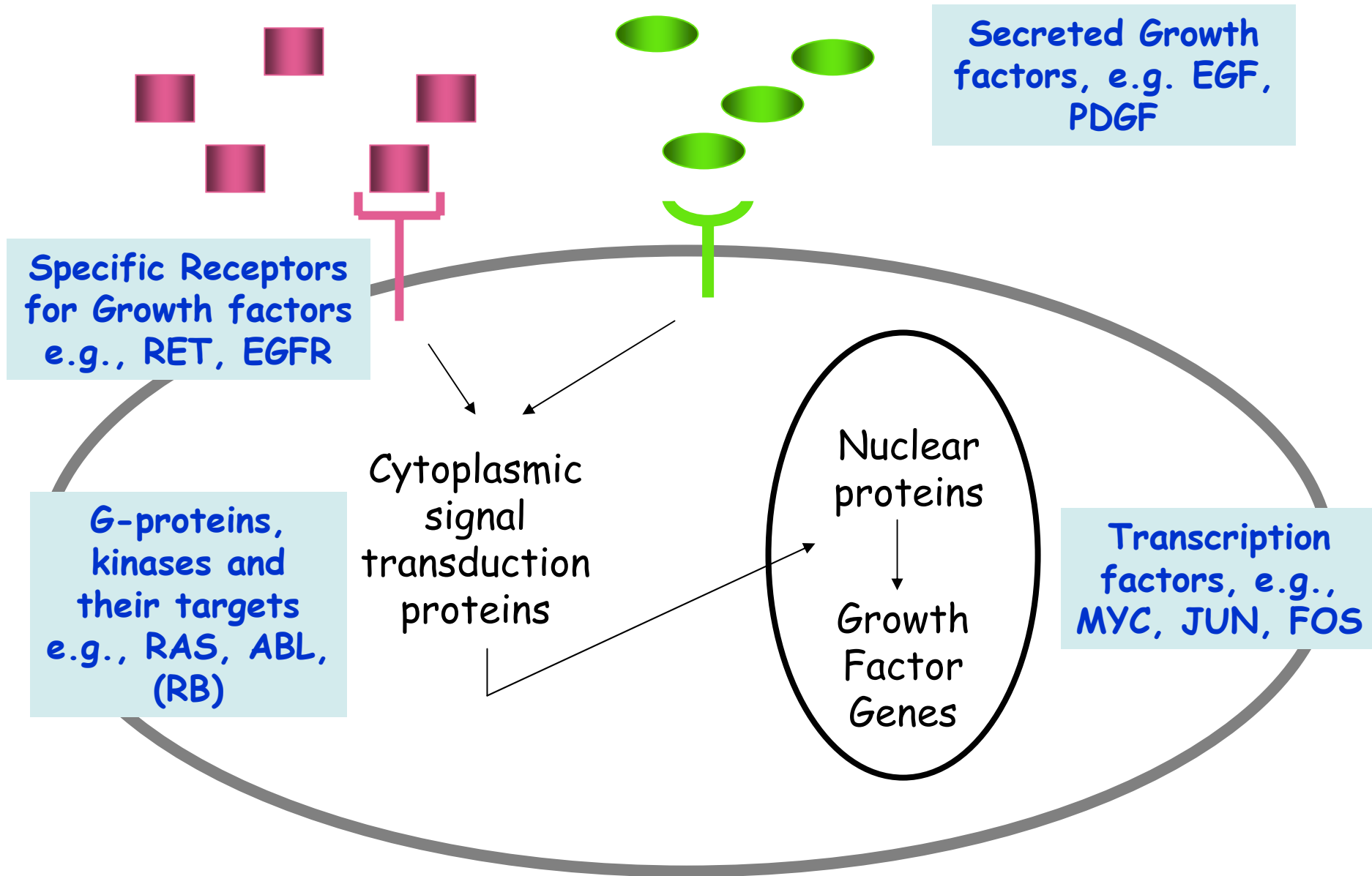
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Signal Transduction and Growth Regulation



Great Targets for Dominant Acting Oncogenes



Receptor Tyrosine Kinases (RTKs)

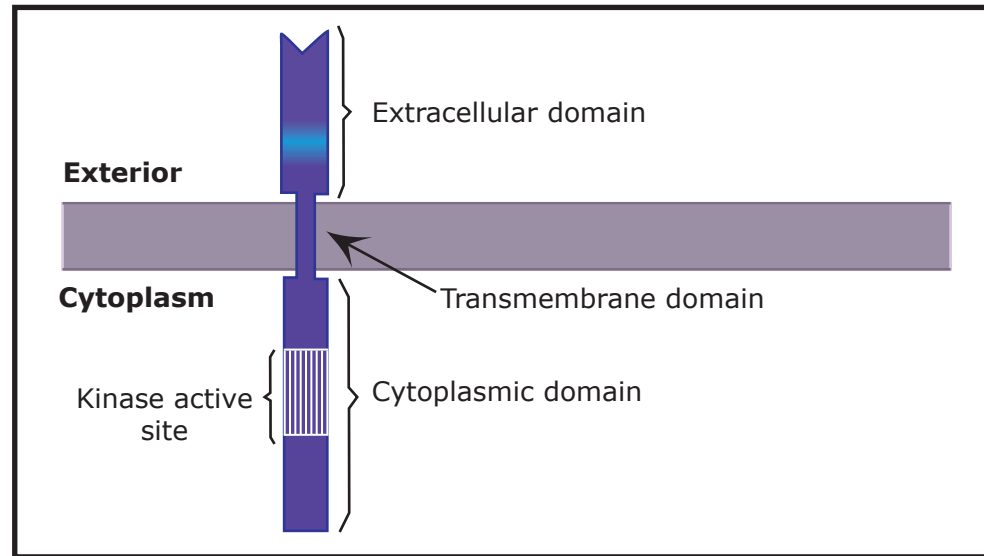


Figure by MIT OCW.

Receptor Tyrosine Kinases (RTKs)

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Extracellular Growth
factor



Engages with and
dimerizes specific
receptors on cell surface



Dimerized Receptor
activates cascade of
molecular events



Machinery for increased
cell proliferation is
mobilized

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Please see Figure 1 in Zwick, E., J. Bange and A. Ullrich.

"Receptor Tyrosine Kinases as Targets for Anticancer Drugs."

Trends Mol Med. 8, no.1 (Jan 2002): 17-23.

Receptor Tyrosine Kinases (RTKs)

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Kinases

Trans-
cription
Factors

Constitutive Activation converts RTKs to Dominant Acting Oncogenes

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Please see Figure 2 in Zwick, E., J. Bange and A. Ullrich.

"Receptor Tyrosine Kinases as Targets for Anticancer Drugs."

Trends Mol Med. 8, no. 1 (Jan 2002):17-23.

Genetic alterations leading to Constitutive Activation of RTKs

- Deletion of extracellular domain
- Mutations that stimulate dimerization without ligand binding
- Mutations of Kinase domain
- Overexpression of Ligand
- Overexpression of Receptor

Two Classic Examples

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Please see Lodish, Harvey, et. al. *Molecular Cell Biology*.

5th ed. New York : W.H. Freeman and Company, 2004.

Her2
receptor

EGF
receptor

Her2 = Human Epidermal
growth factor receptor 2

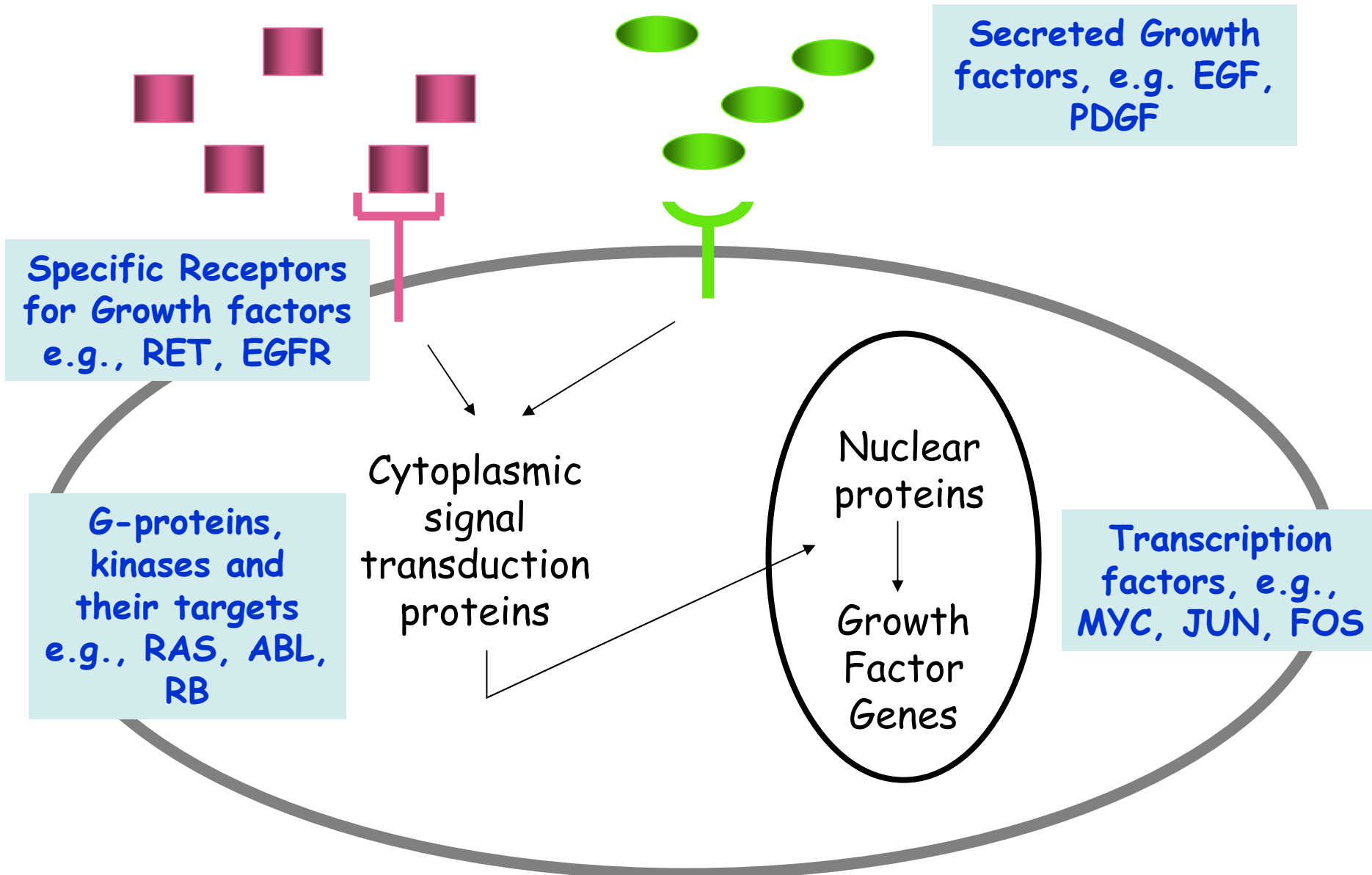
EGFR = Epidermal growth
factor receptor

EGF Receptors signal through the RAS G-protein

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Signal Transduction and Growth Regulation



cABL - A **non-receptor**, cytoplasmic tyrosine kinase that can be converted into an oncoprotein

- cABL proto-oncogene product signals to many of the same molecules as the RTKs
- Signals cell cycle progression and cell proliferation

The Philadelphia Chromosome and Chronic Myeloid Leukemia

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Human Chromosome Spread - G-banding Karyotype

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Human Chromosome Spread - G-banding Karyotype

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The Philadelphia Chromosome created by a Translocation between Chrs 9 and 22 Chronic Myeloid Leukemia

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The Philadelphia Chromosome and Chronic Myeloid Leukemia

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Fusion Protein

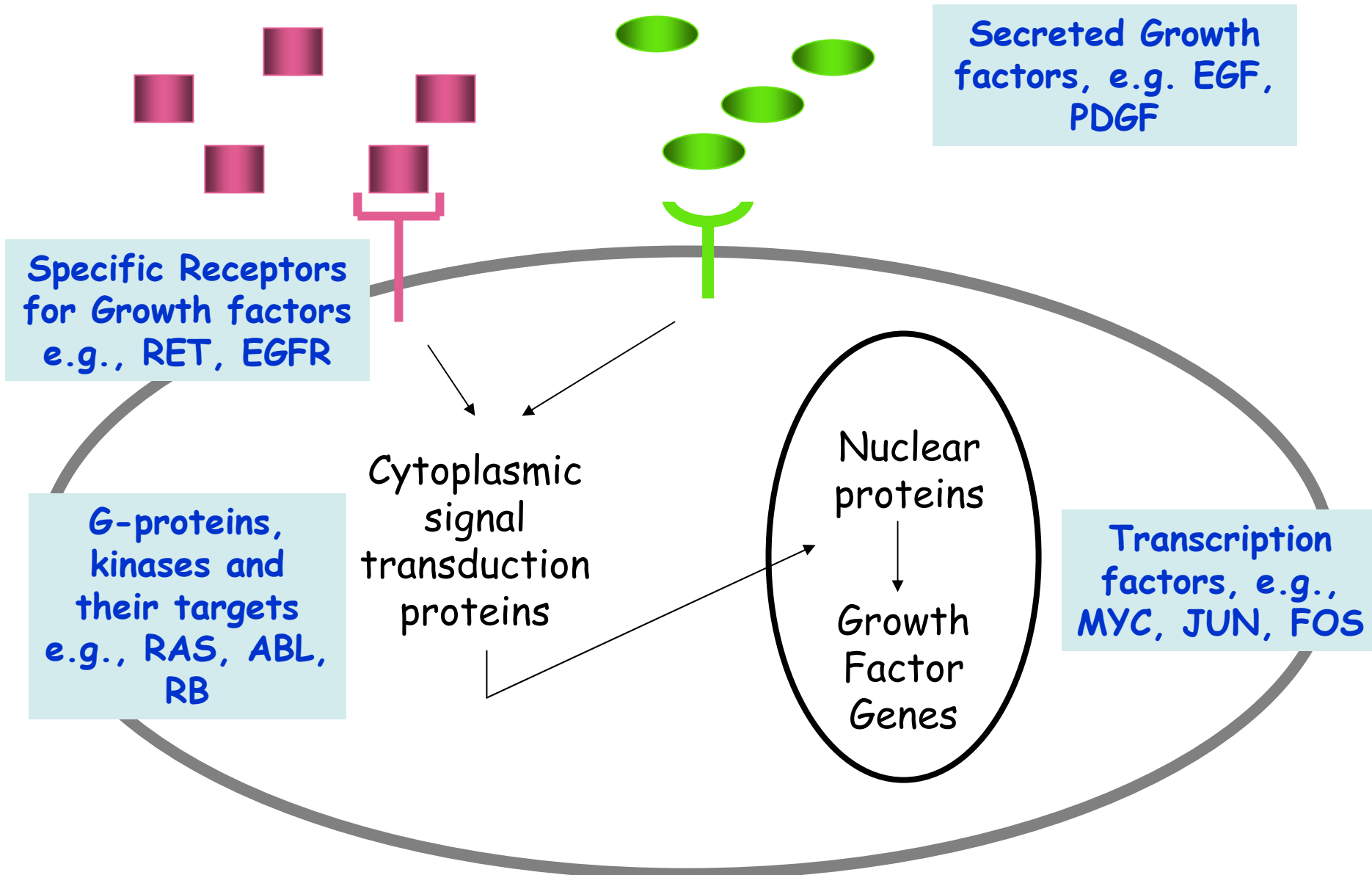
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Uncontrolled ABL Kinase Activity
and Signal Transduction

Chronic Myeloid Leukemia

Signal Transduction and Growth Regulation



Burkitt's Lymphoma: A chromosome translocation

→ cMYC to be expressed inappropriately in B-cells

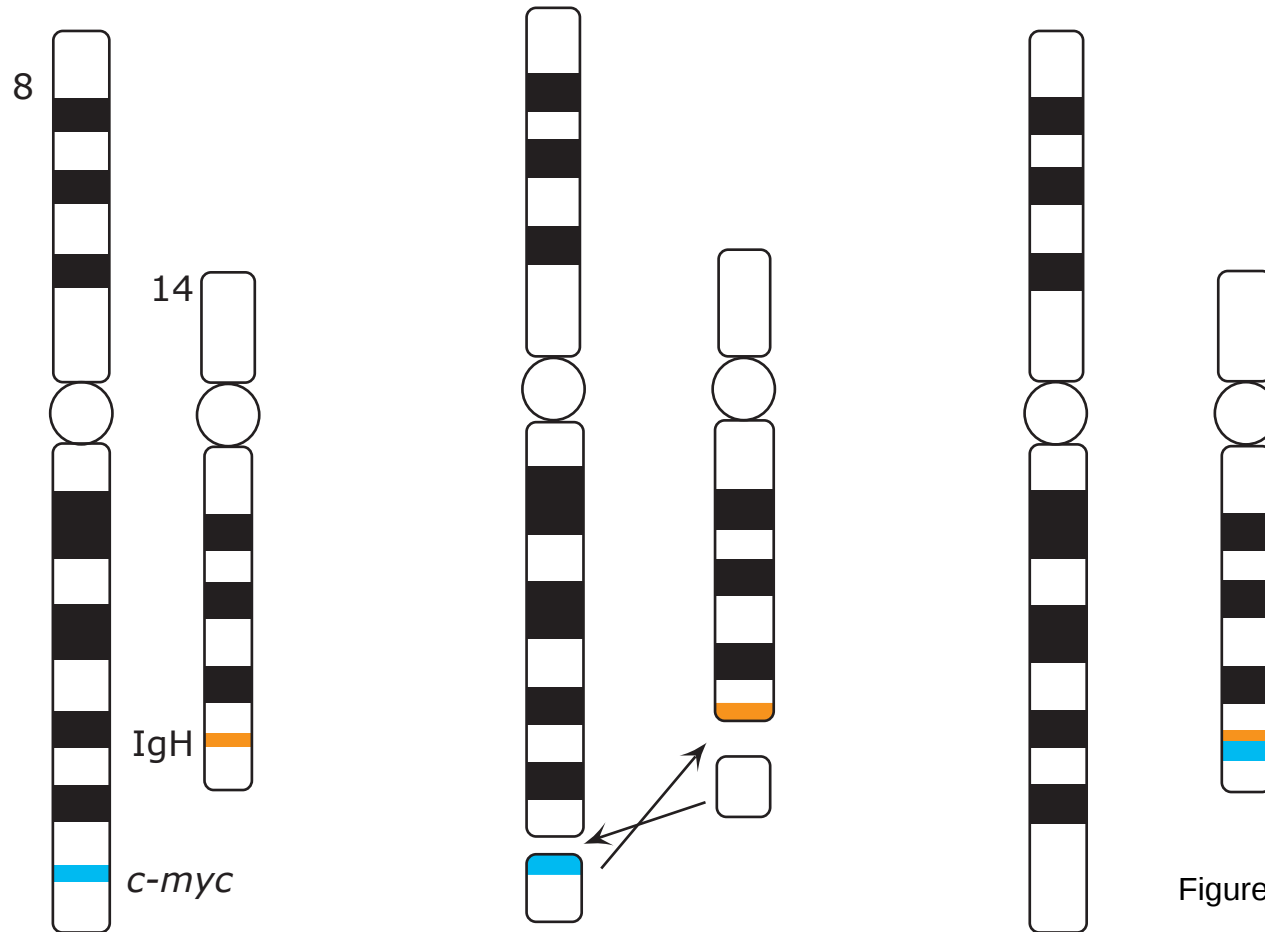


Figure by MIT OCW.

cMYC drives cells from G1 to S

Another way that oncogenic transcription factors can be up-regulated: **Gene Amplification**

Chromosome from a TUMOR

Blue - staining of all chromosomes

Red - staining of chromosome 4

Green - staining of the N-MYC gene

(N-MYC and cMYC share many similar properties)

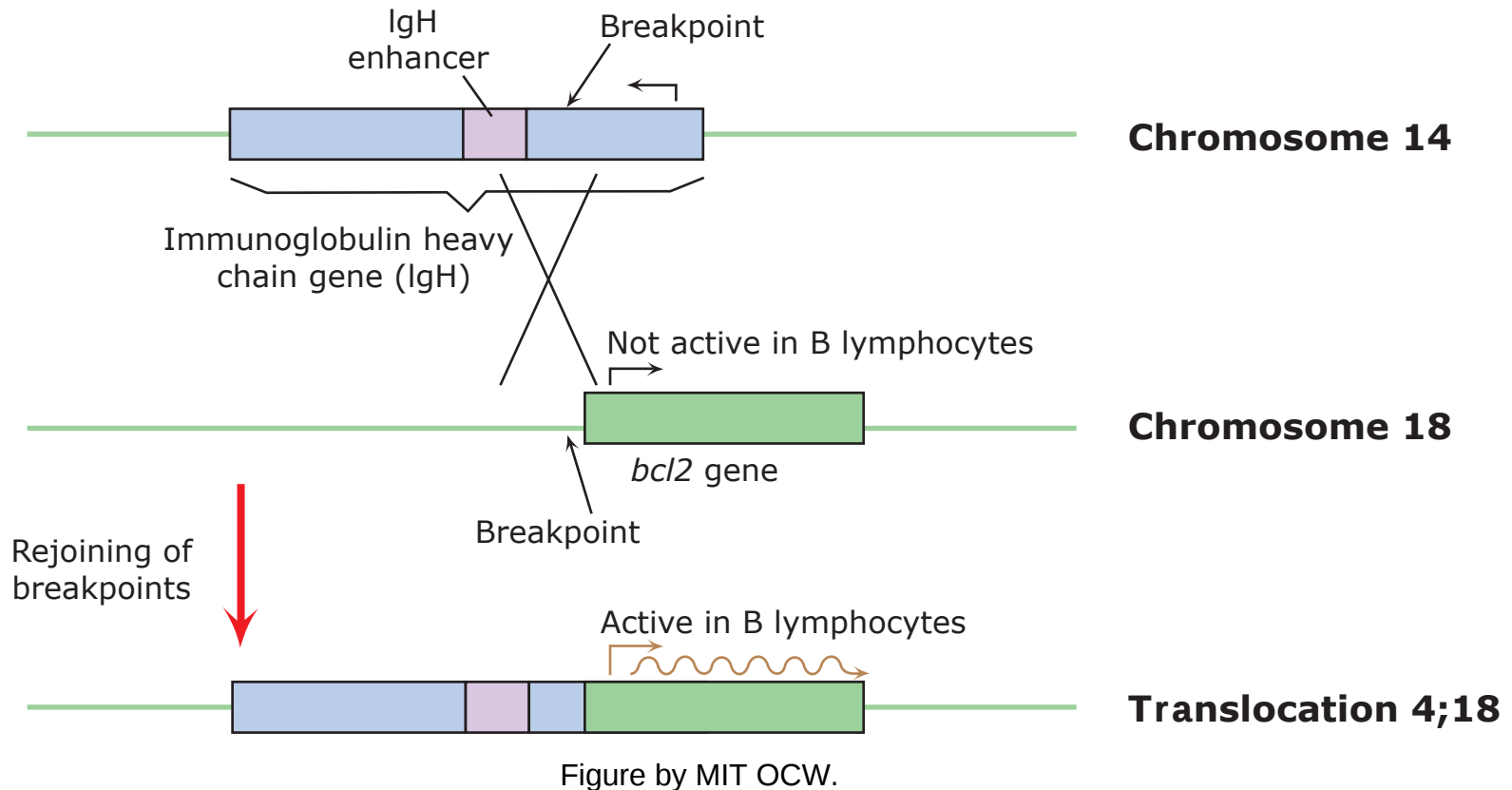
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5th ed. New York : W.H. Freeman and Company, 2004.

One more example - **with an interesting twist**

A translocation between Chr 14 and Chr 18 to put the BCL2 gene under the strong IgH promoter

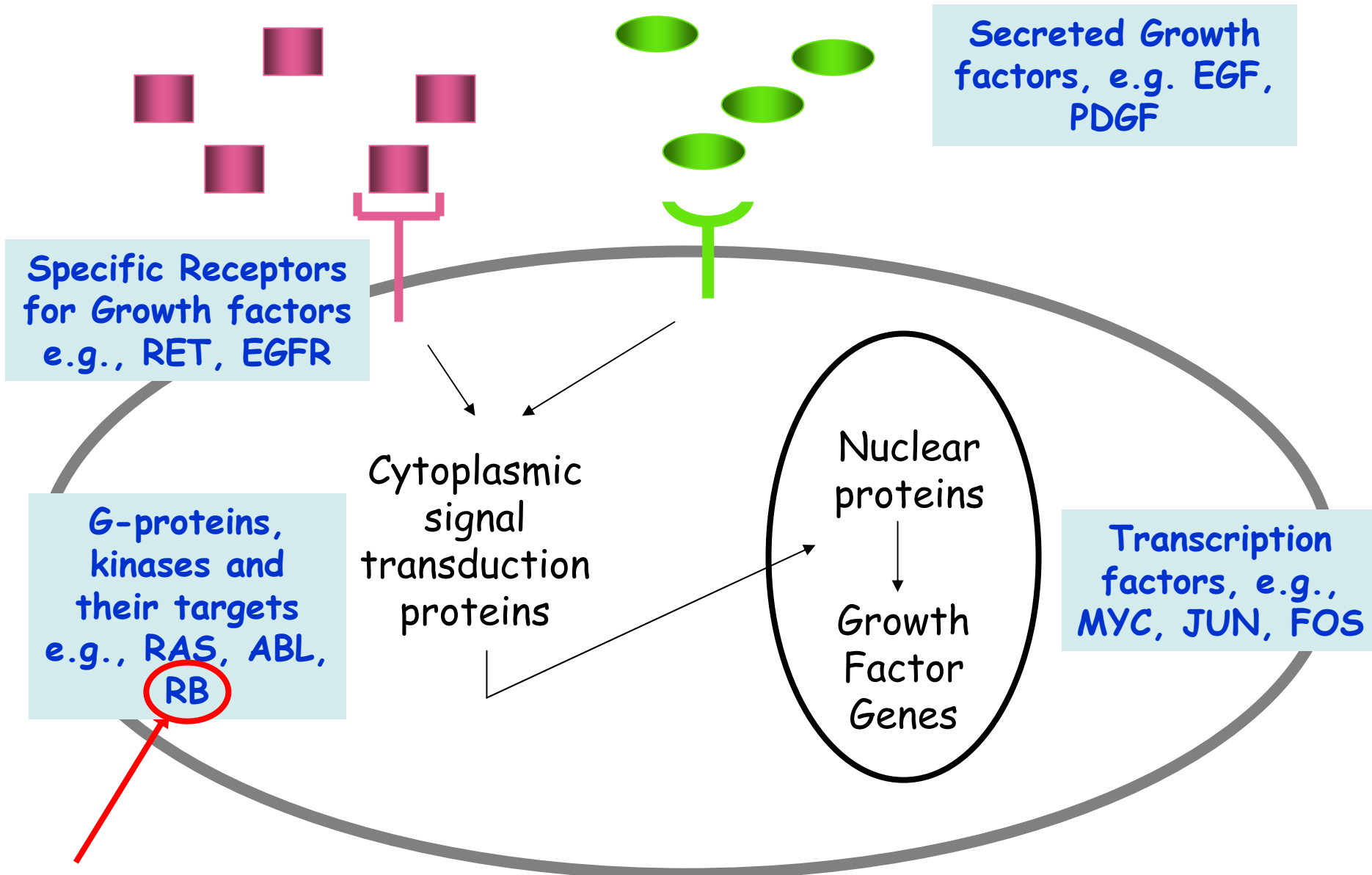


The BCL2 protein **PREVENTS** programmed cell death, B cells live longer than normal leading to B-cell Lymphomas

What chromosomal events convert proto-oncogenes to dominantly acting oncogenes

- Point mutations (e.g., RAS)
- Deletion mutations (e.g., RTKs)
- Chromosomal translocations that produce novel fusion proteins (e.g., Bcr-Abl)
- Chromosomal translocation to juxtapose a strong promoter upstream and the proto-oncogene such that it is inappropriately expressed (e.g., Bcl2)
- Gene amplification resulting in overexpression (e.g., N-Myc)

Signal Transduction and Growth Regulation



RB - the **Retinoblastoma** Gene - was the first example of a Tumor Repressor Gene (aka a Recessive Oncogene)

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Loss of Function Mutations in both RB genes lead to malignant tumors of the retina during the first few years of life

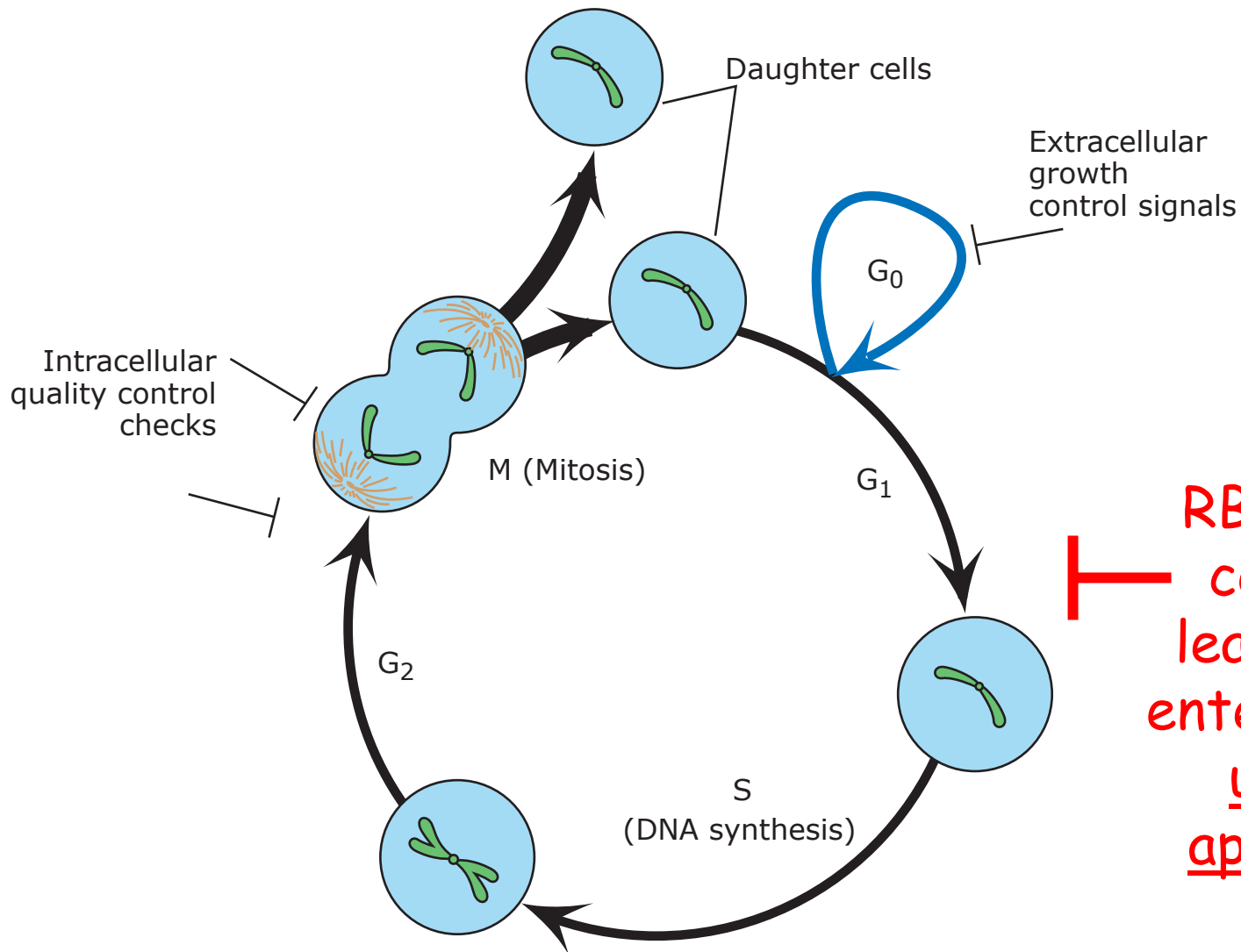
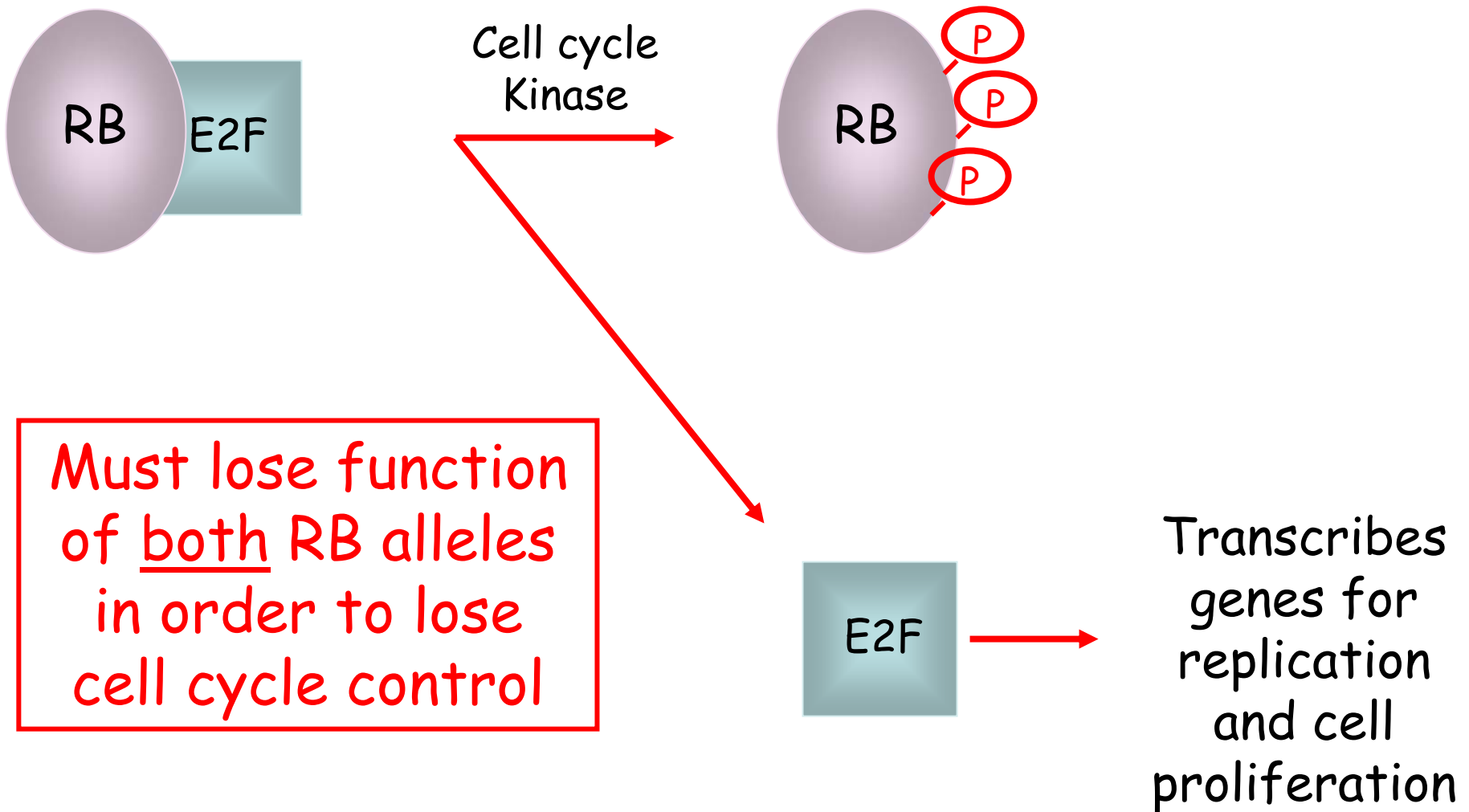


Figure by MIT OCW.

Phosphorylation of RB at the **appropriate** time in G1 allows release of the E2F Transcription Factor



Two ways to get retinal tumors due to loss of RB function

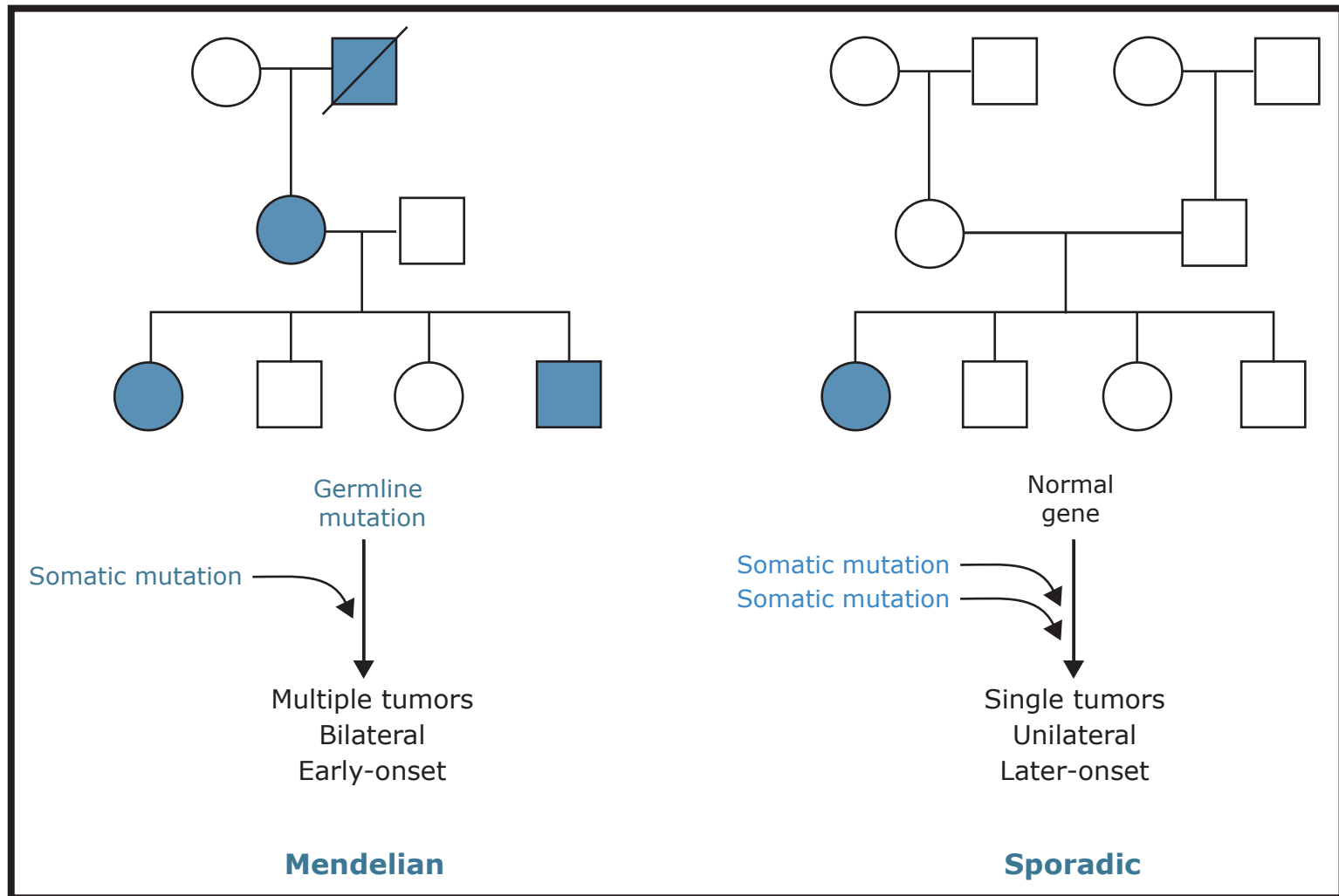


Figure by MIT OCW.

The Retinoblastoma disease behaves as an autosomal **dominant** mutation

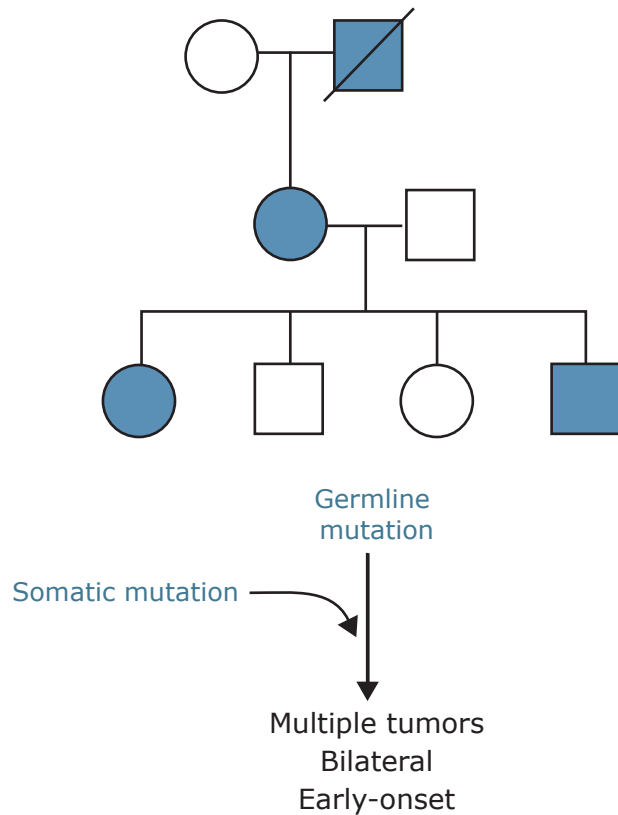
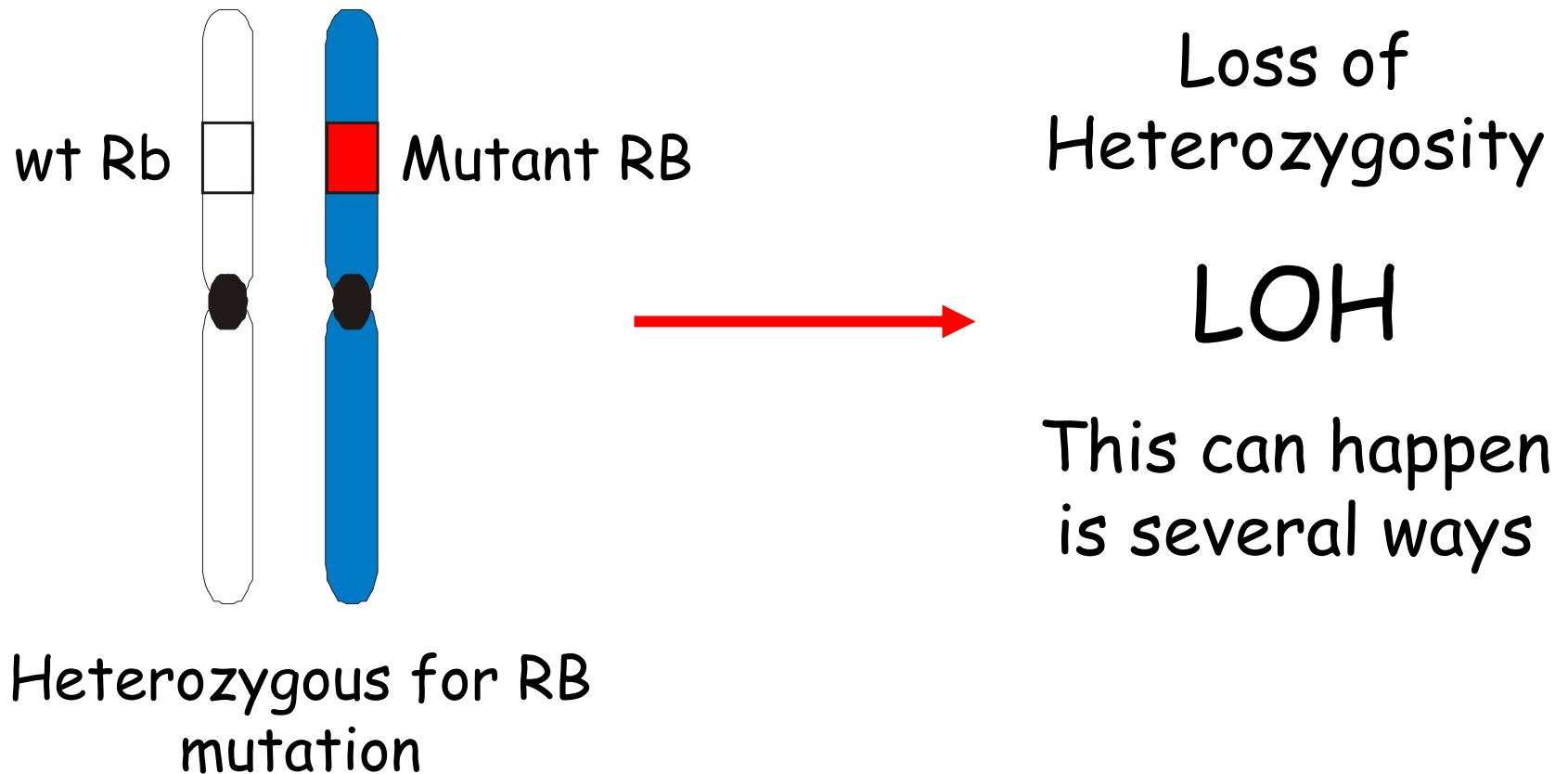


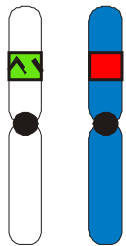
Figure by MIT OCW.

- In order to lose cell cycle control **MUST** lose function of both alleles
- But, for Mendelian inheritance of RB, children need only inherit only one non-functional allele
- To explain this the "TWO HIT" hypothesis was proposed
- During development of the retina a second mutation is almost certain to occur
- RB is one of the very few cancers that seems to require defects in only one gene (but in both alleles)

How is the second RB allele rendered non-functional?



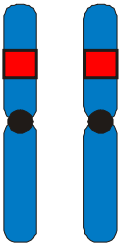
Point Mutation



Non-Disjunction

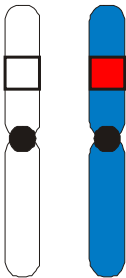


Chromosome loss



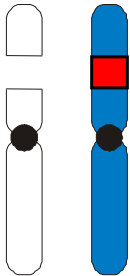
Chromosome loss & duplication

wt Rb

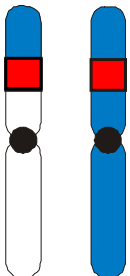


Mutant Rb

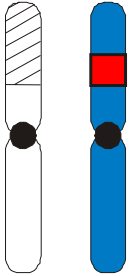
Recombination



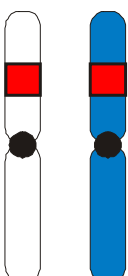
Deletion



Interchromosomal Recombination

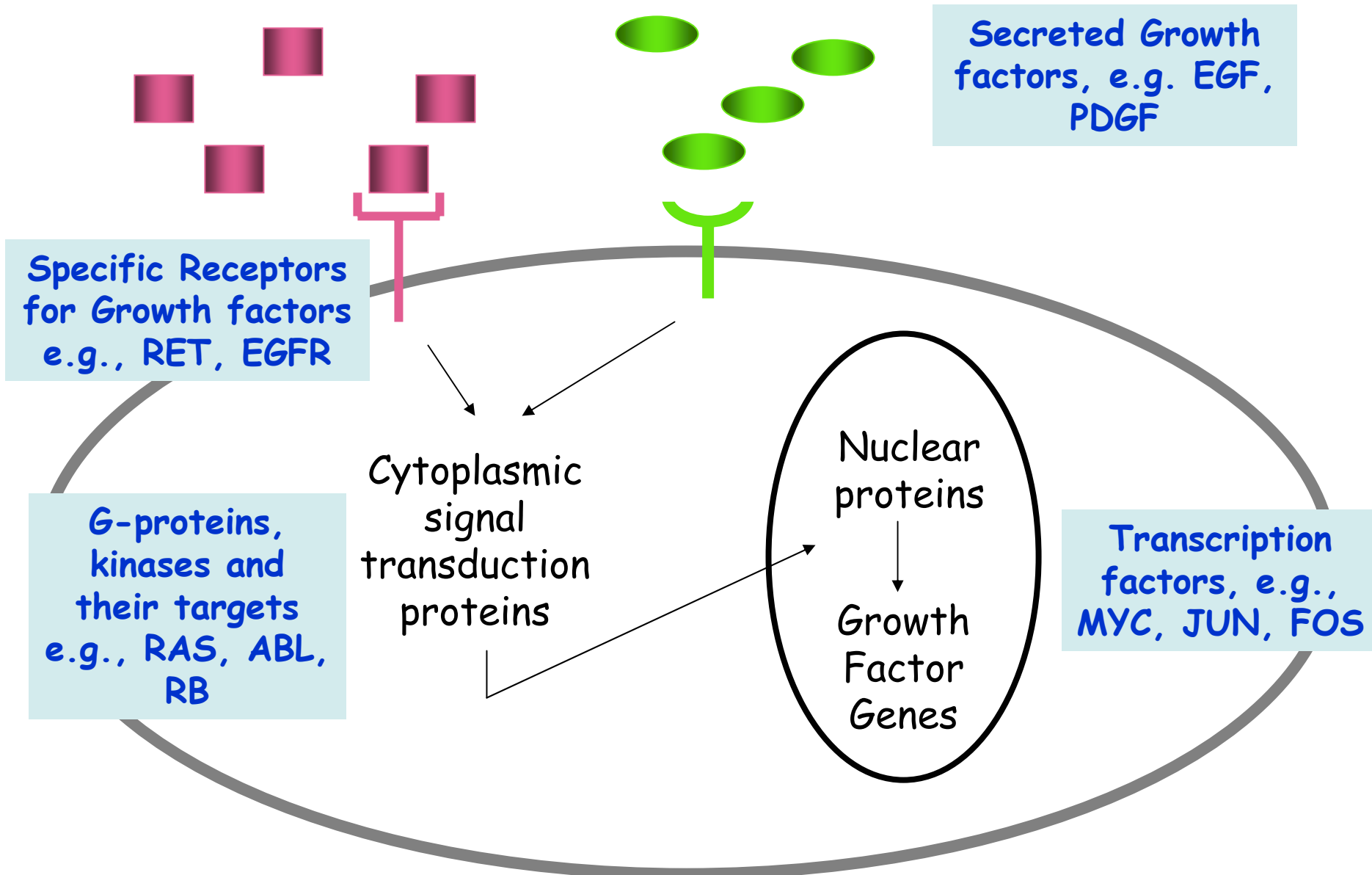


Translocation



Gene Conversion

Signal Transduction and Growth Regulation



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