Genetics of Cancer

Lecture 34

Alterations in different kinds of Genes cause Cancer

Oncogenes

dominant gain-of-function mutations
promote cell transformation

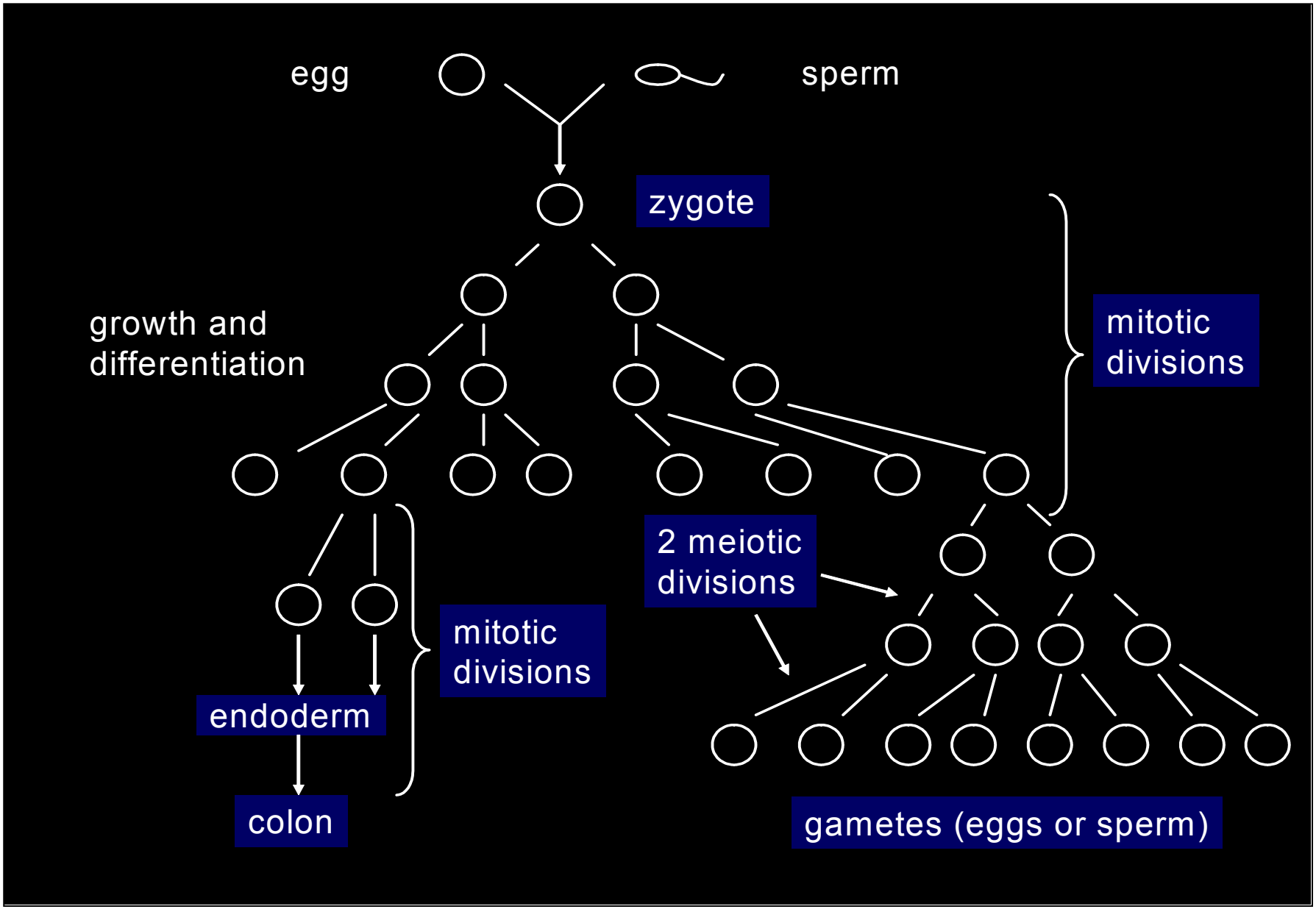
Tumor suppressor genes

recessive, loss-of-function mutations
promote cell transformation

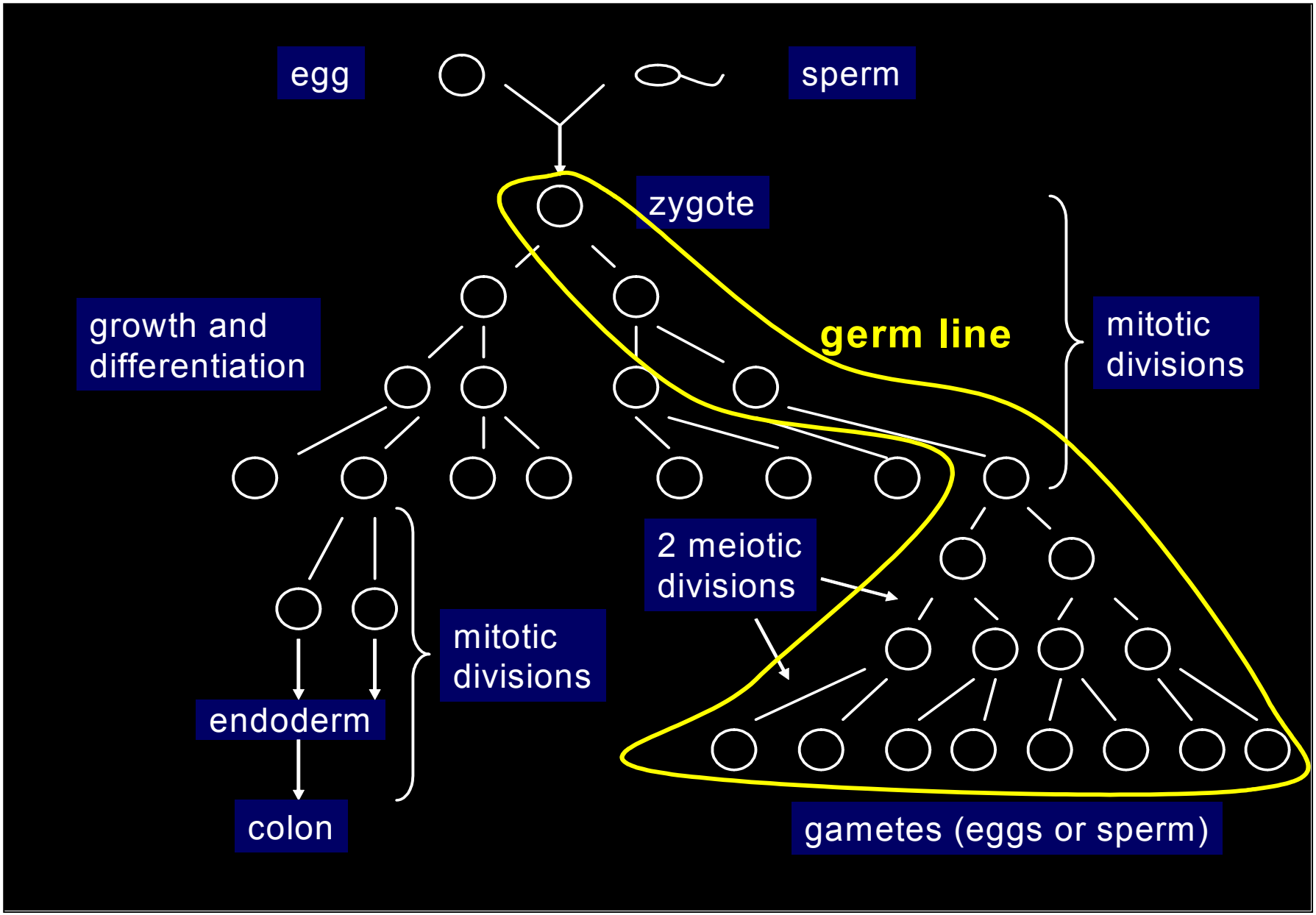
Mutator genes

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

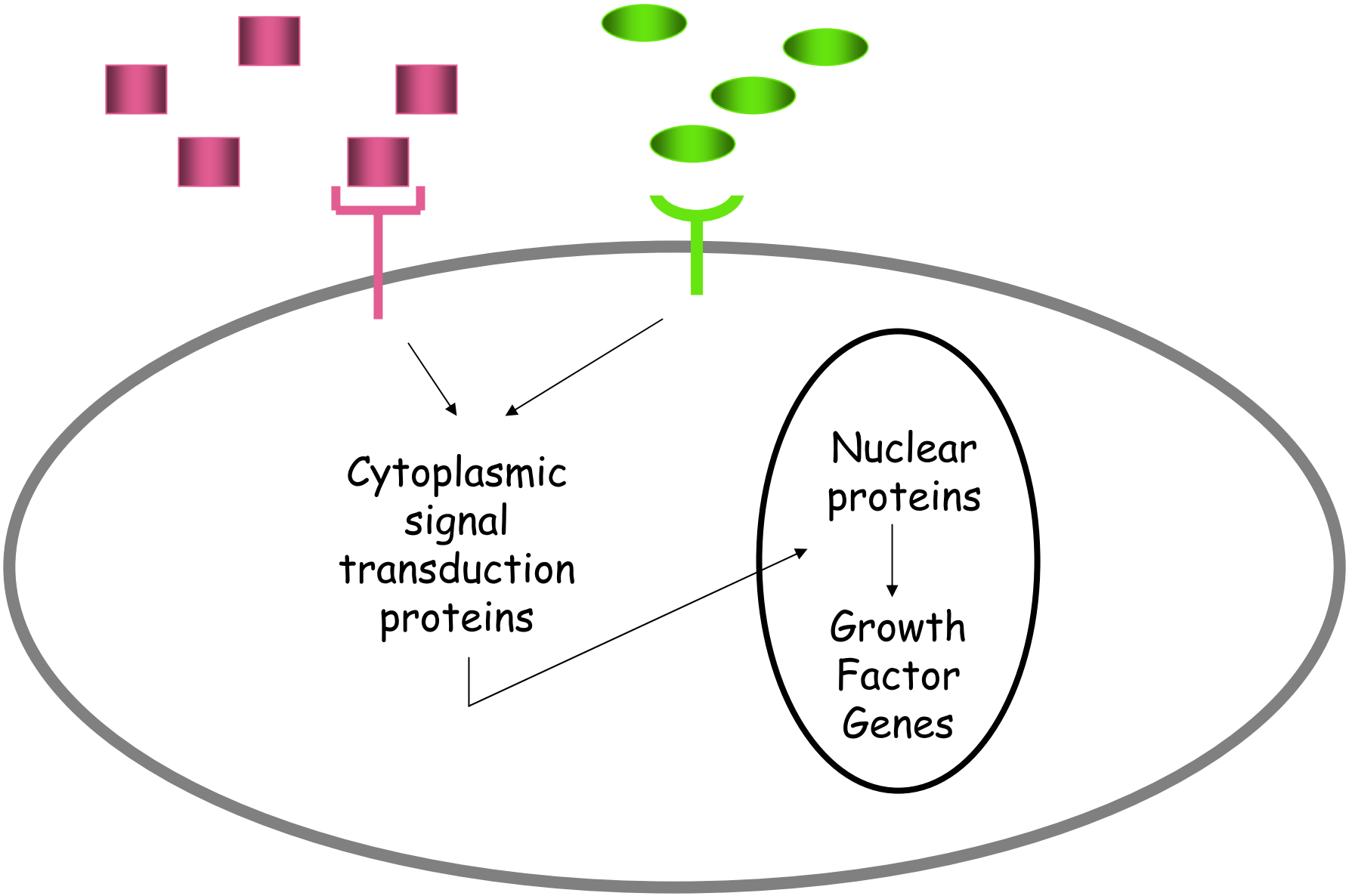
Most of the mutations that contribute to cancer occur in somatic cells – but germ line mutations can also contribute



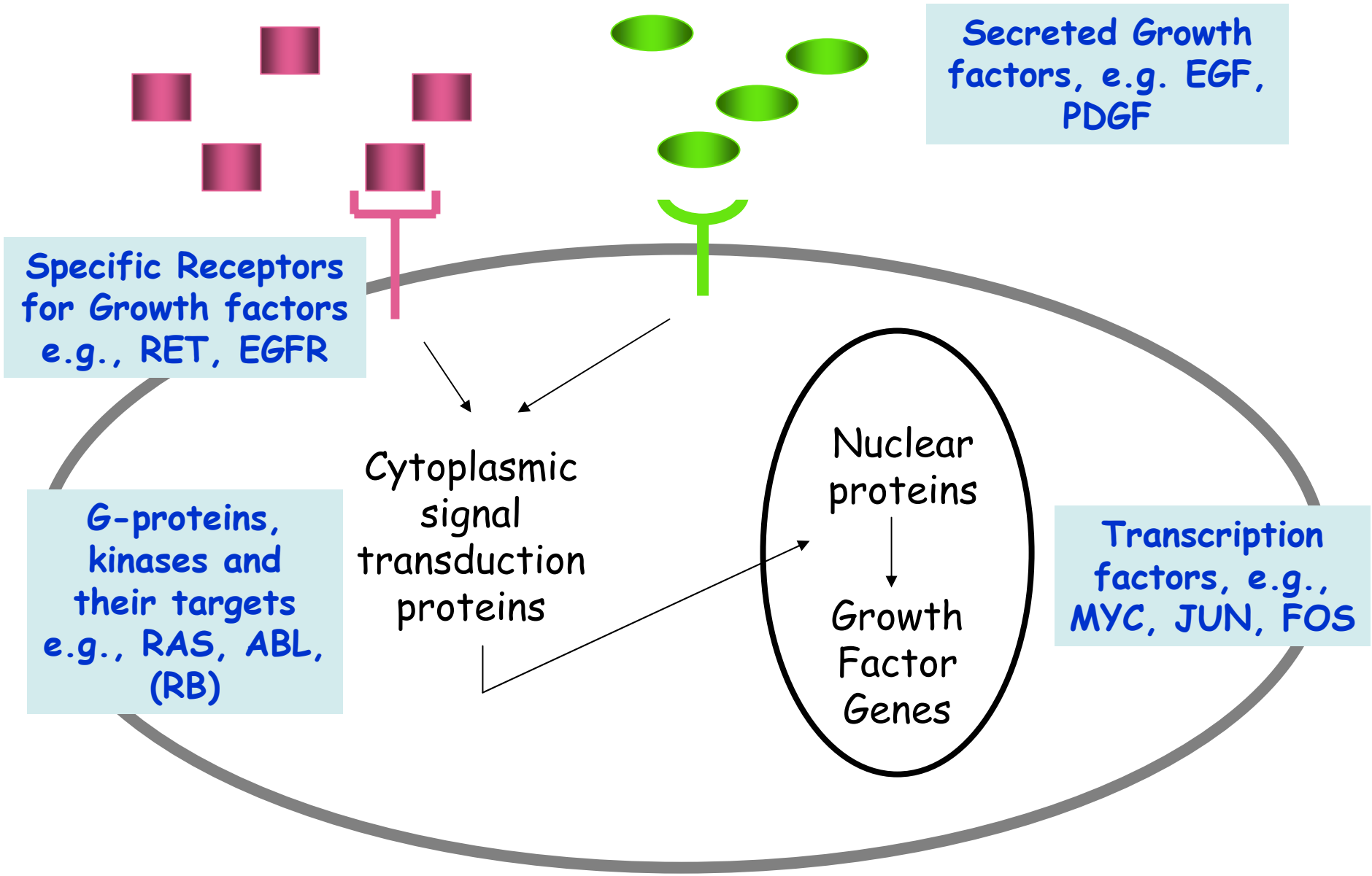
Most of the mutations that contribute to cancer occur in somatic cells – but germ line mutations can also contribute



Signal Transduction and Growth Regulation



Great Targets for Dominant Acting Oncogenes



Receptor Tyrosine Kinases (RTKs)

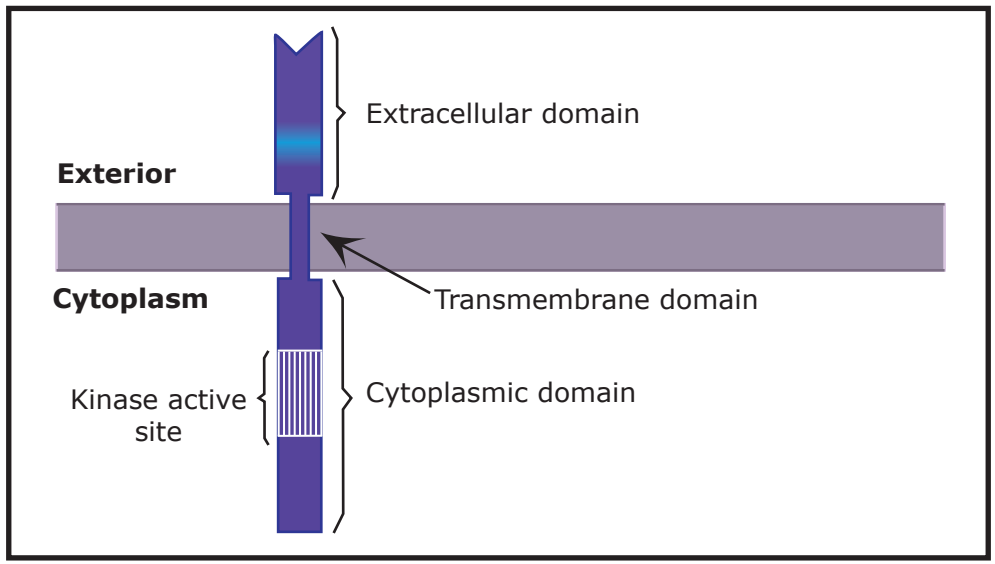


Figure by MIT OCW.

Receptor Tyrosine Kinases (RTKs)

Images removed due to copyright reasons.

Images removed due to copyright reasons.
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.

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

Receptor Tyrosine Kinases (RTKs)

Images removed due to copyright reasons.

Kinases

Trans-
cription
Factors

Constitutive Activation converts RTKs to Dominant Acting Oncogenes

Images removed due to copyright reasons.

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

Her2 receptor

EGF receptor

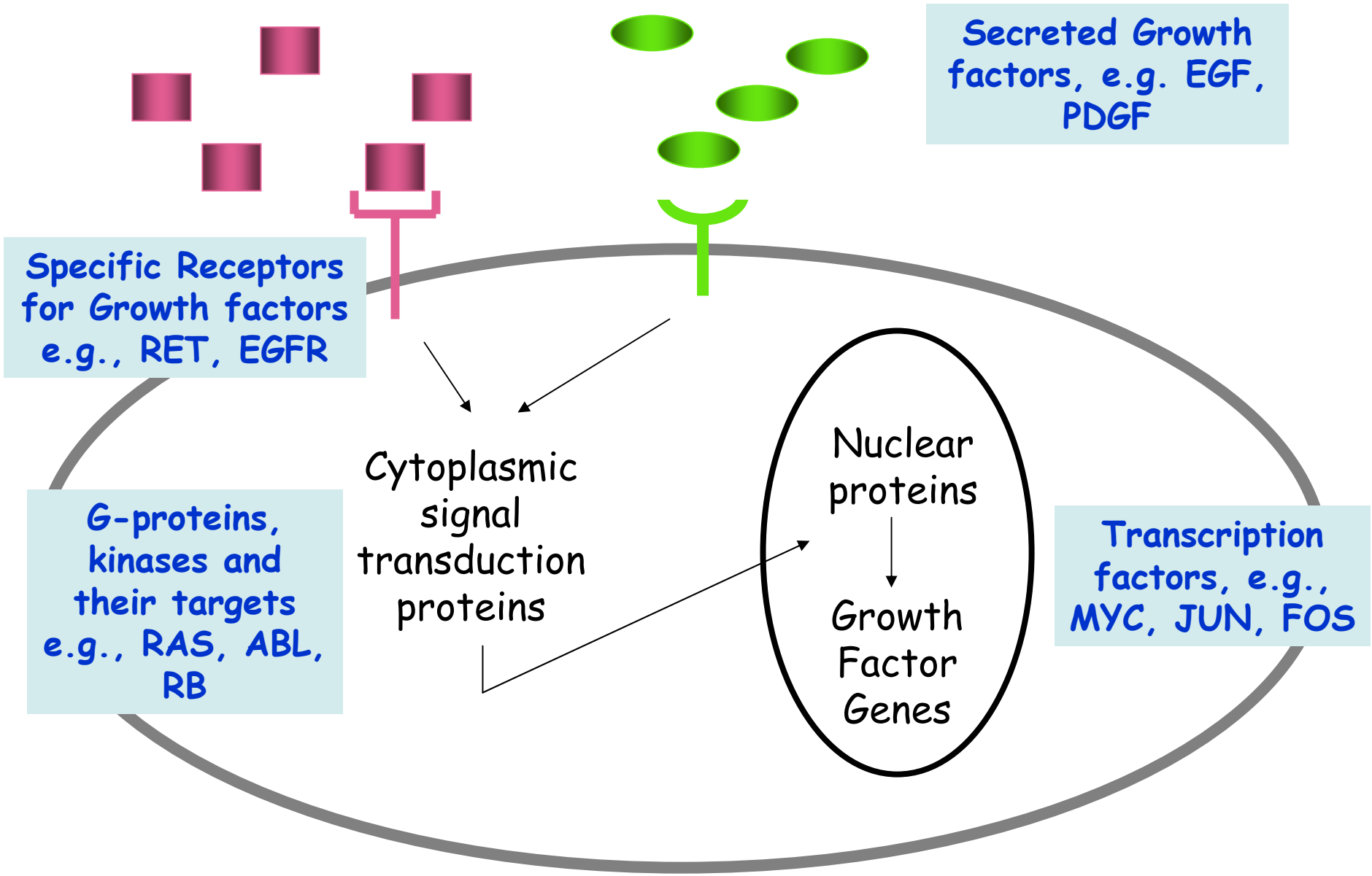
Her2 = Human Epidermal growth factor receptor 2

EGFR = Epidermal growth factor receptor

EGF Receptors signal through the RAS G-protein

Images removed due to copyright reasons.
Please see Lodish, Harvey, et. al. *Molecular Cell Biology.*
5th ed. New York : W.H. Freeman and Company, 2004.

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

Images removed due to copyright reasons.

Human Chromosome Spread – G-banding Karyotype

Images removed due to copyright reasons.

Human Chromosome Spread – G-banding Karyotype

Images removed due to copyright reasons.

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

Images removed due to copyright reasons.

The Philadelphia Chromosome and Chronic Myeloid Leukemia

Images removed due to copyright reasons.

The Philadelphia Chromosome and Chronic Myeloid Leukemia

Images removed due to copyright reasons.
Please see Lodish, Harvey, et. al. *Molecular Cell Biology.*
5th ed. New York : W.H. Freeman and Company, 2004.

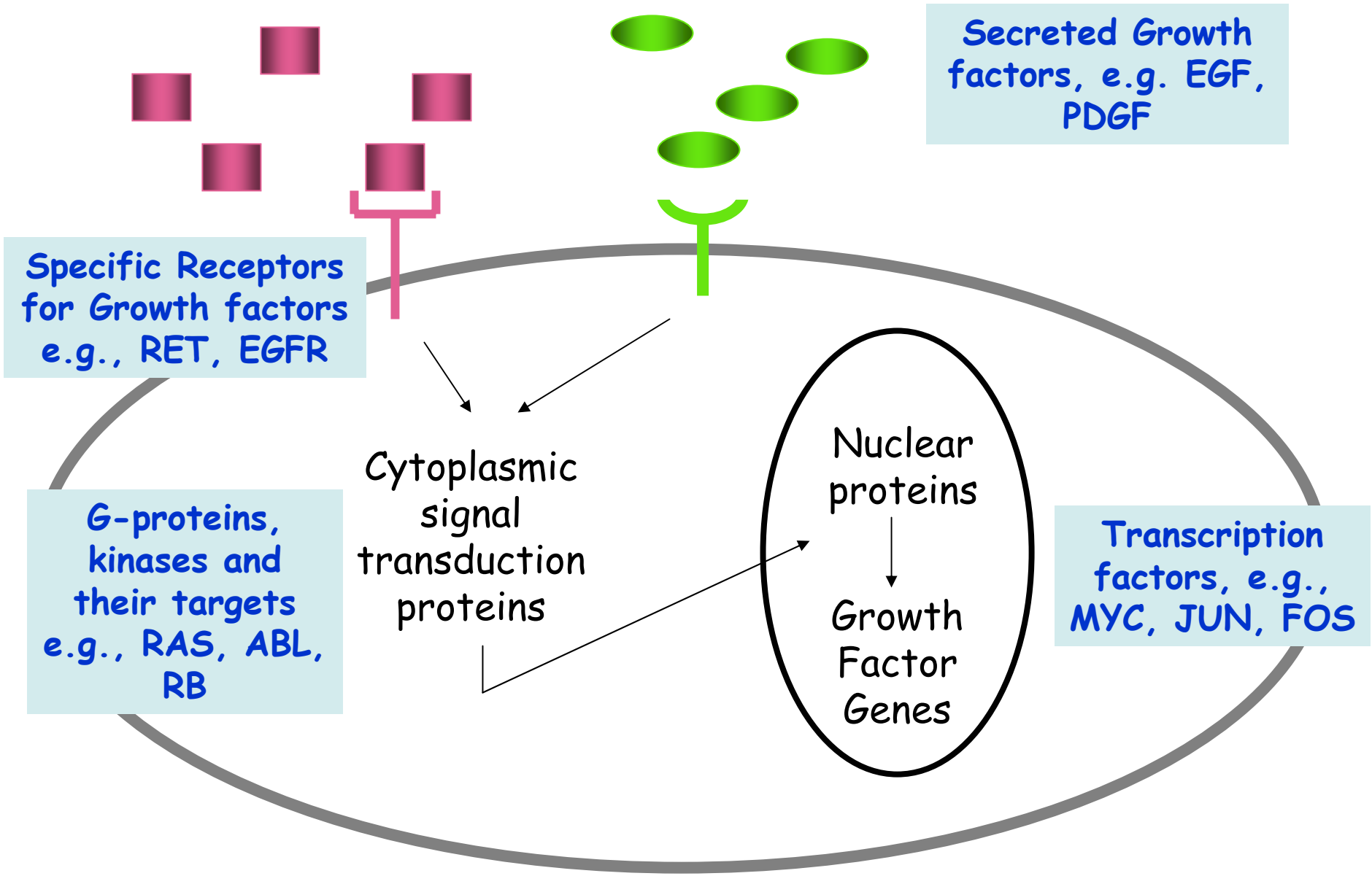
Fusion Protein

Images removed due to copyright reasons.
Please see Lodish, Harvey, et. al. *Molecular Cell Biology.*
5th ed. New York : W.H. Freeman and Company, 2004.

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

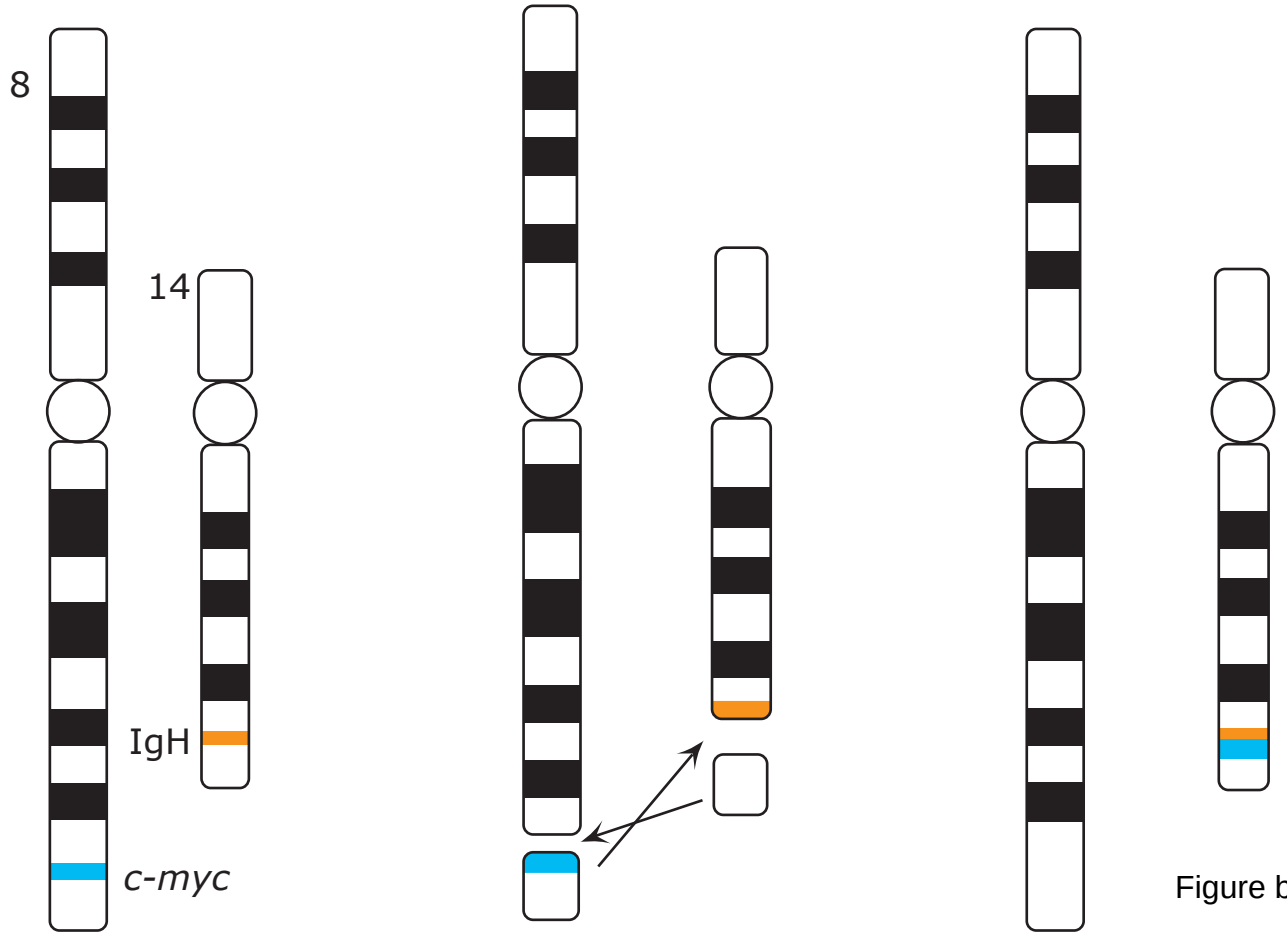


Figure by MIT OCW.

cMYC drives cells from G1 to S

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

Chromosome from a TUMOR

Images removed due to copyright reasons.
Please see Lodish, Harvey, et. al. *Molecular Cell Biology.* 5th ed. New York : W.H. Freeman and Company, 2004.

Blue – staining of all chromosomes

Red – staining of chromosome 4

Green – staining of the N-MYC gene

(N-MYC and cMYC share many similar proerties)

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

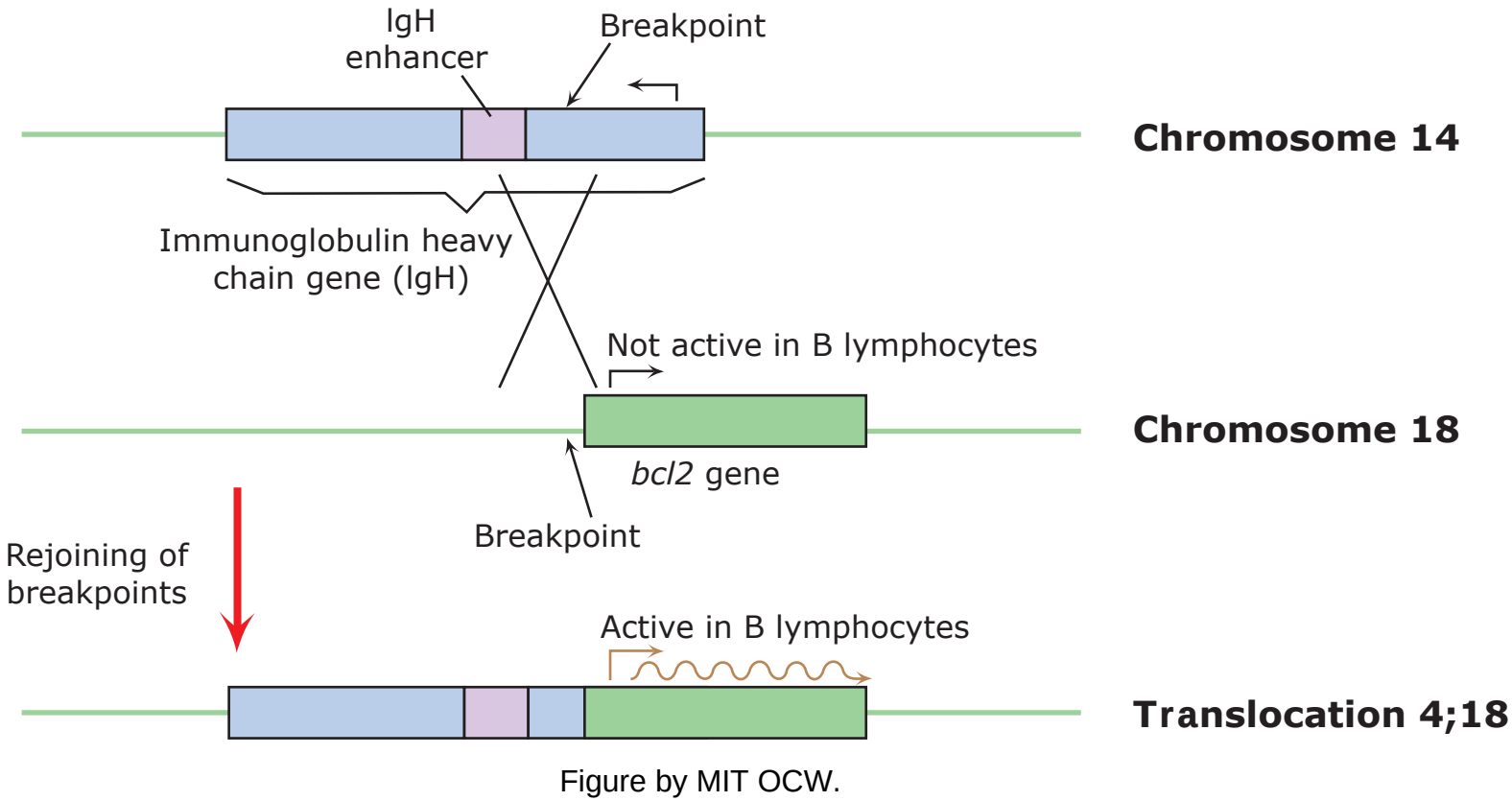


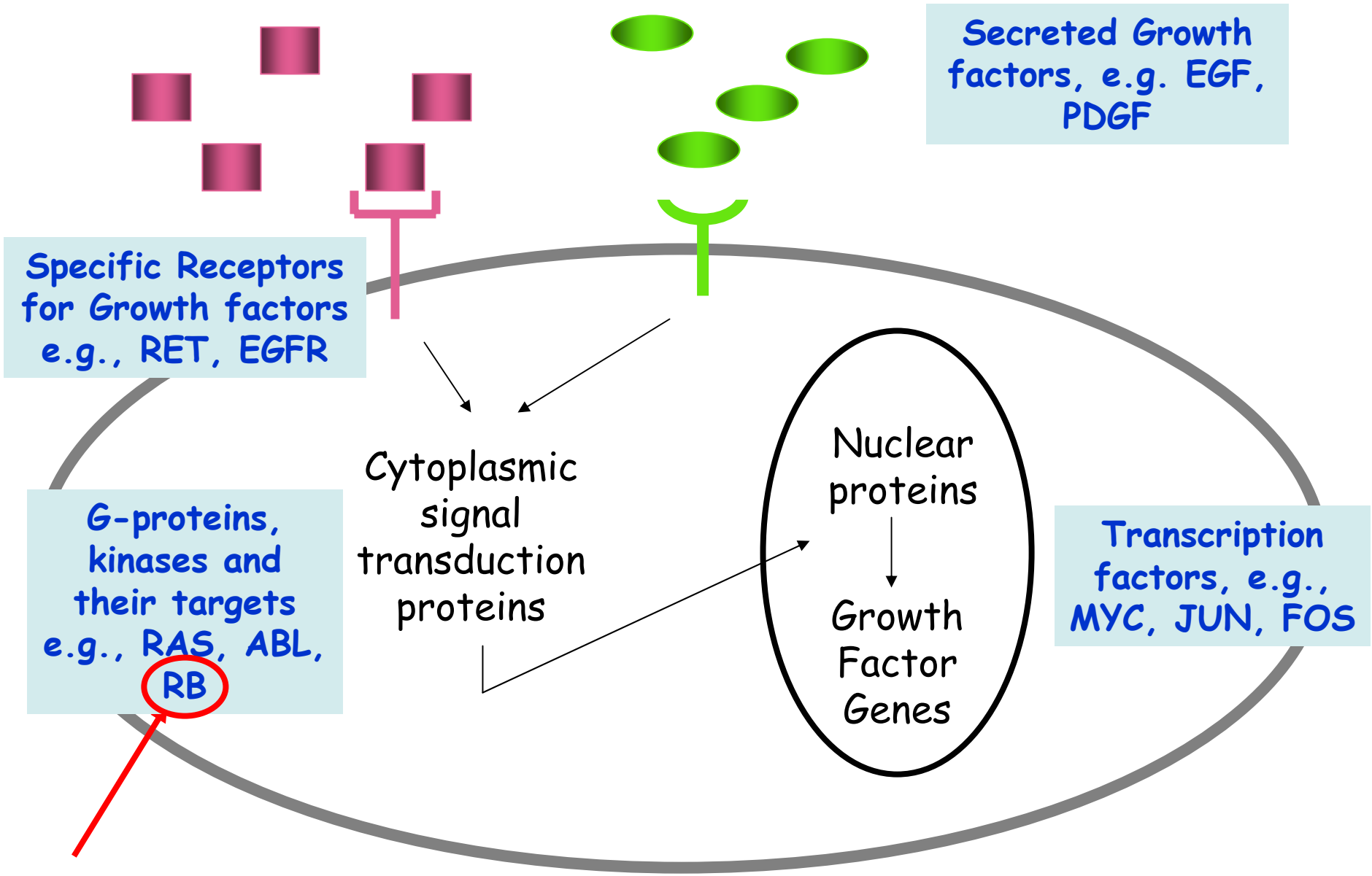
Figure by MIT OCW.

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)

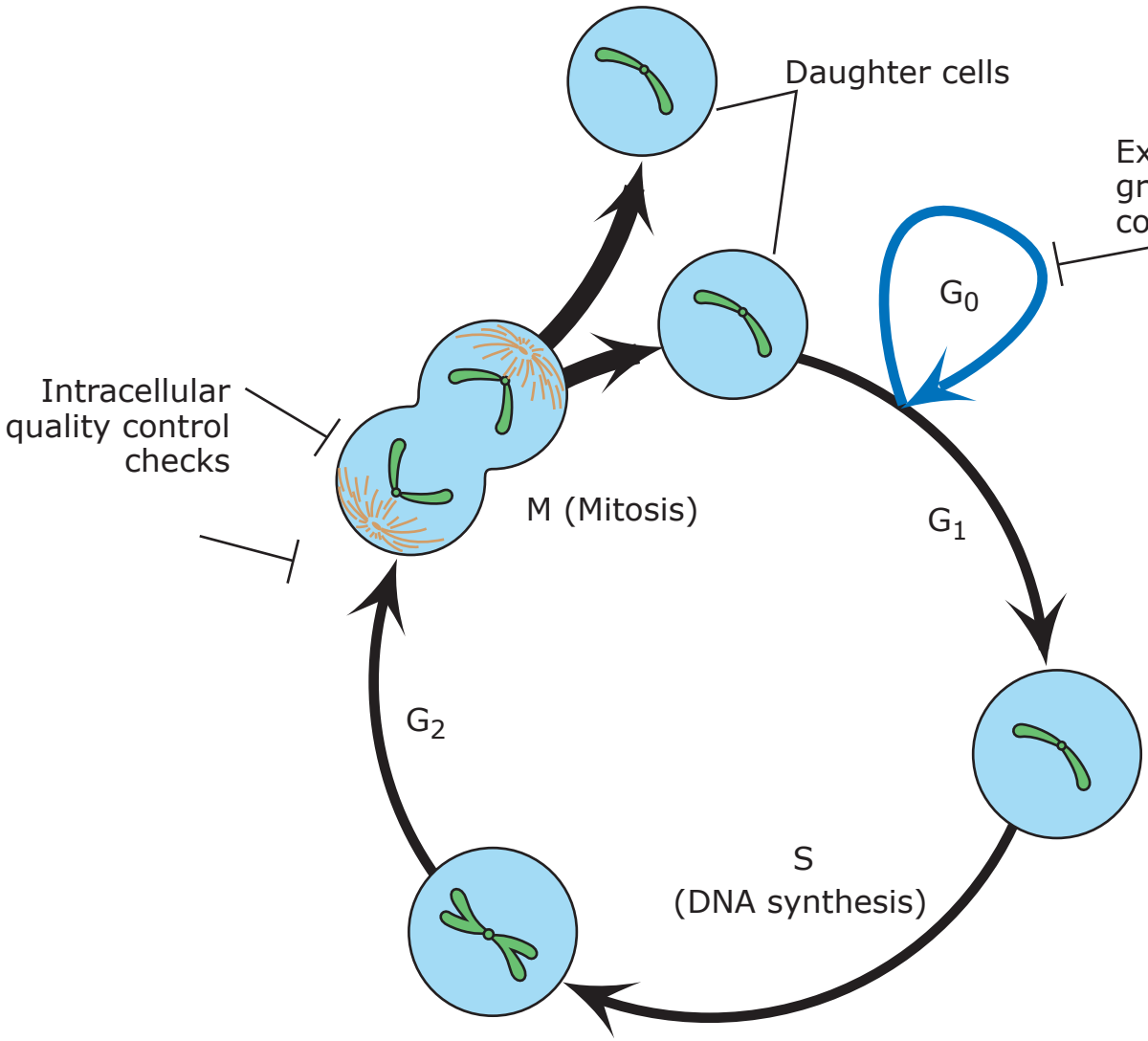
Signal Transduction and Growth Regulation



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

Images removed due to copyright reasons.

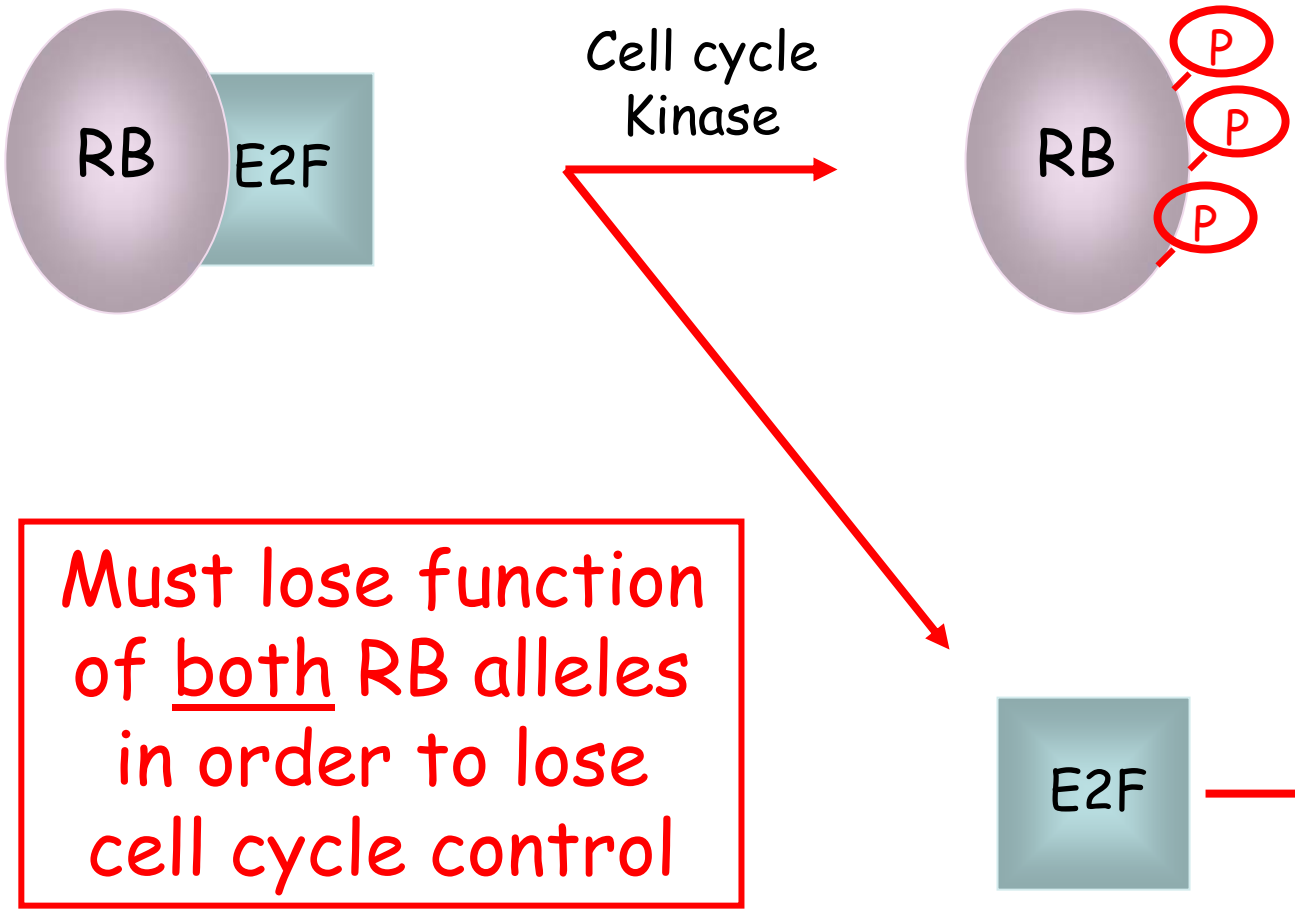
Loss of Function Mutations in both RB genes lead to malignant tumors of the retina during the first few years of life



RB prevents cells from leaving G1 to enter S-phase, until the appropriate time

Figure by MIT OCW.

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



Must lose function of <u>both</u> RB alleles in order to lose cell cycle control

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

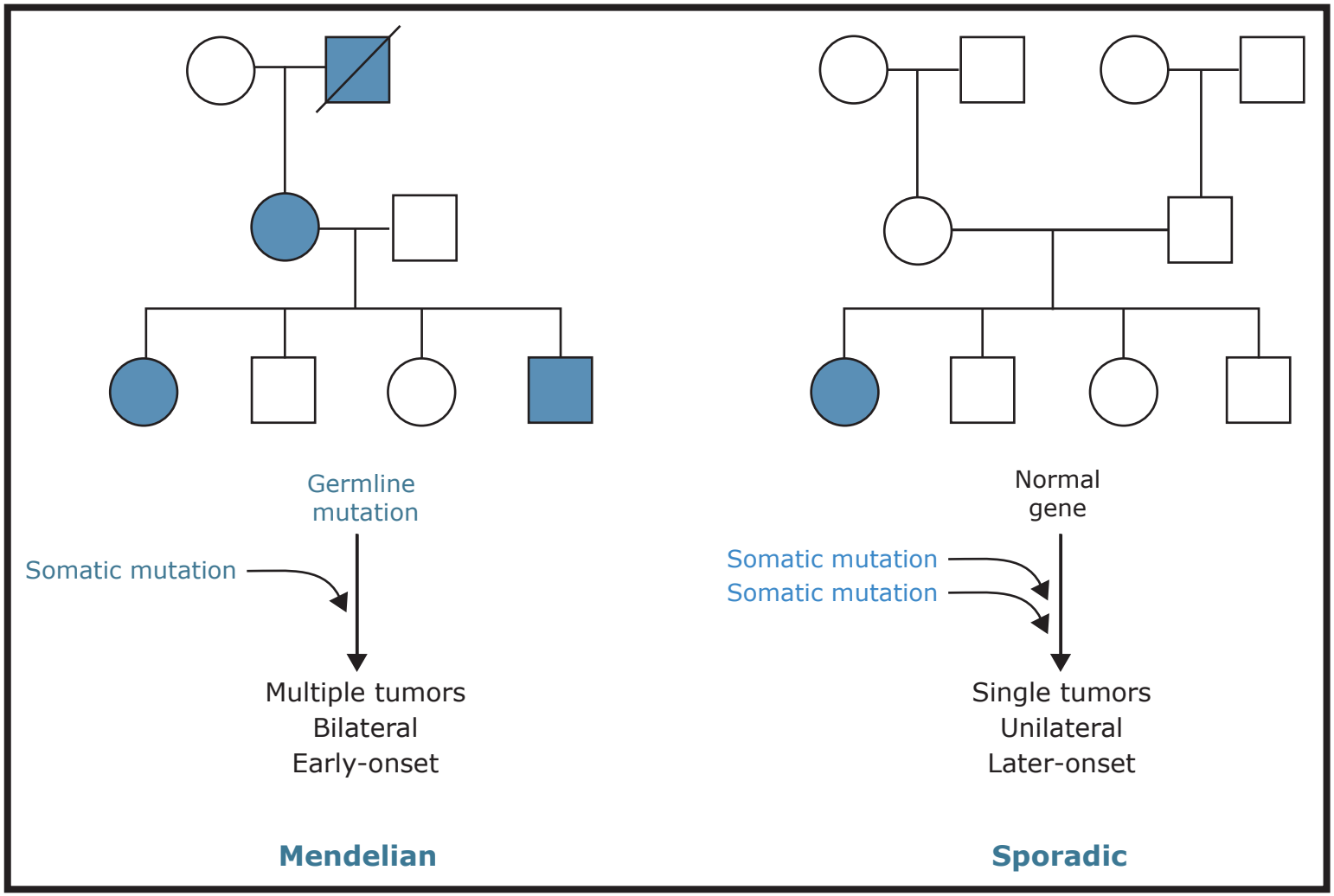


Figure by MIT OCW.

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

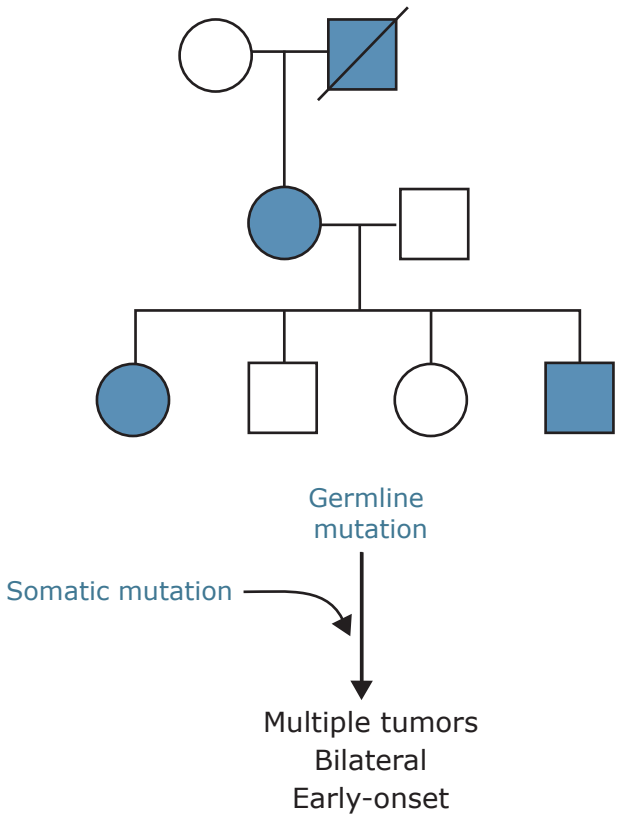
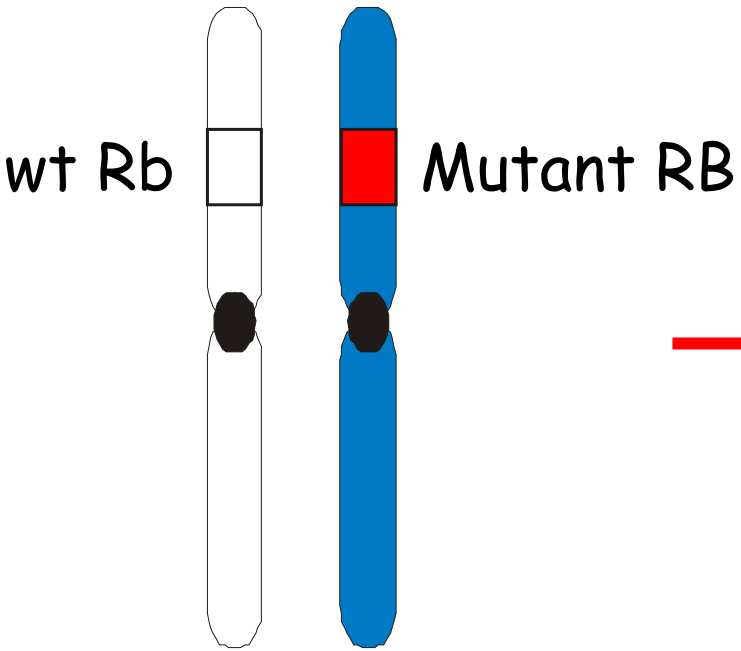


Figure by MIT OCW.

- 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" hypthesis 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?

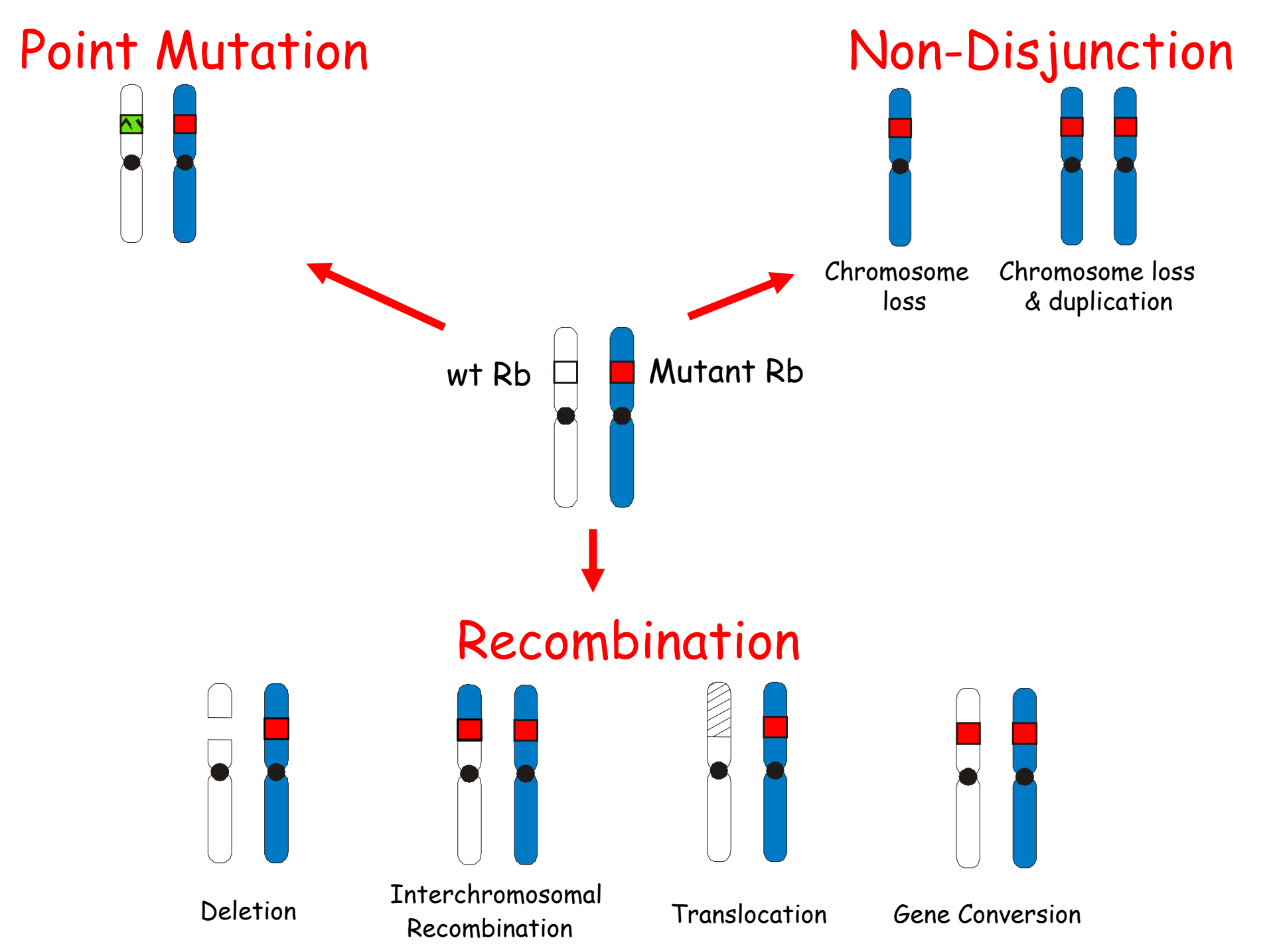


Heterozygous for RB mutation

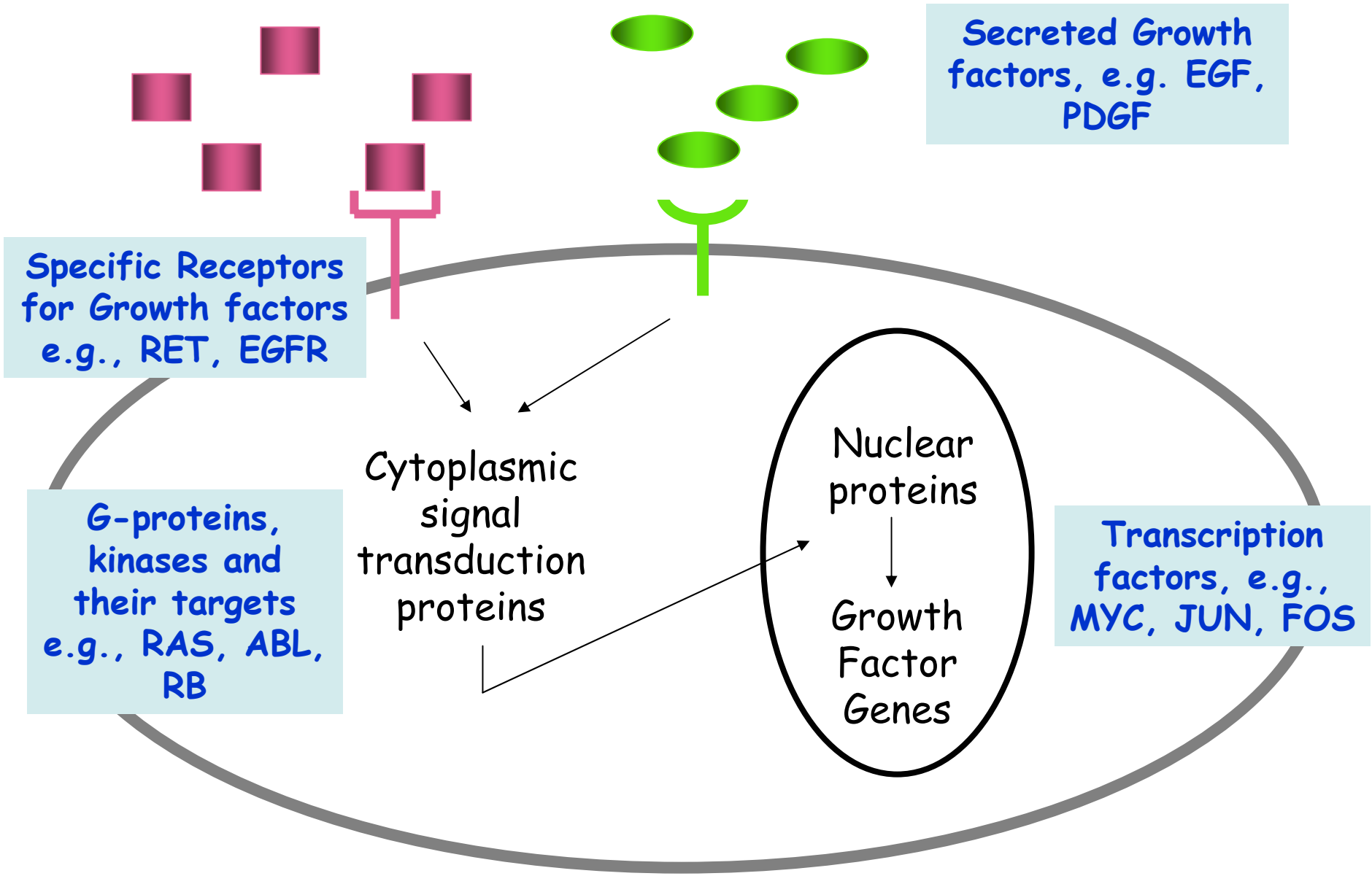
Loss of Heterozygosity

LOH

This can happen is several ways


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



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