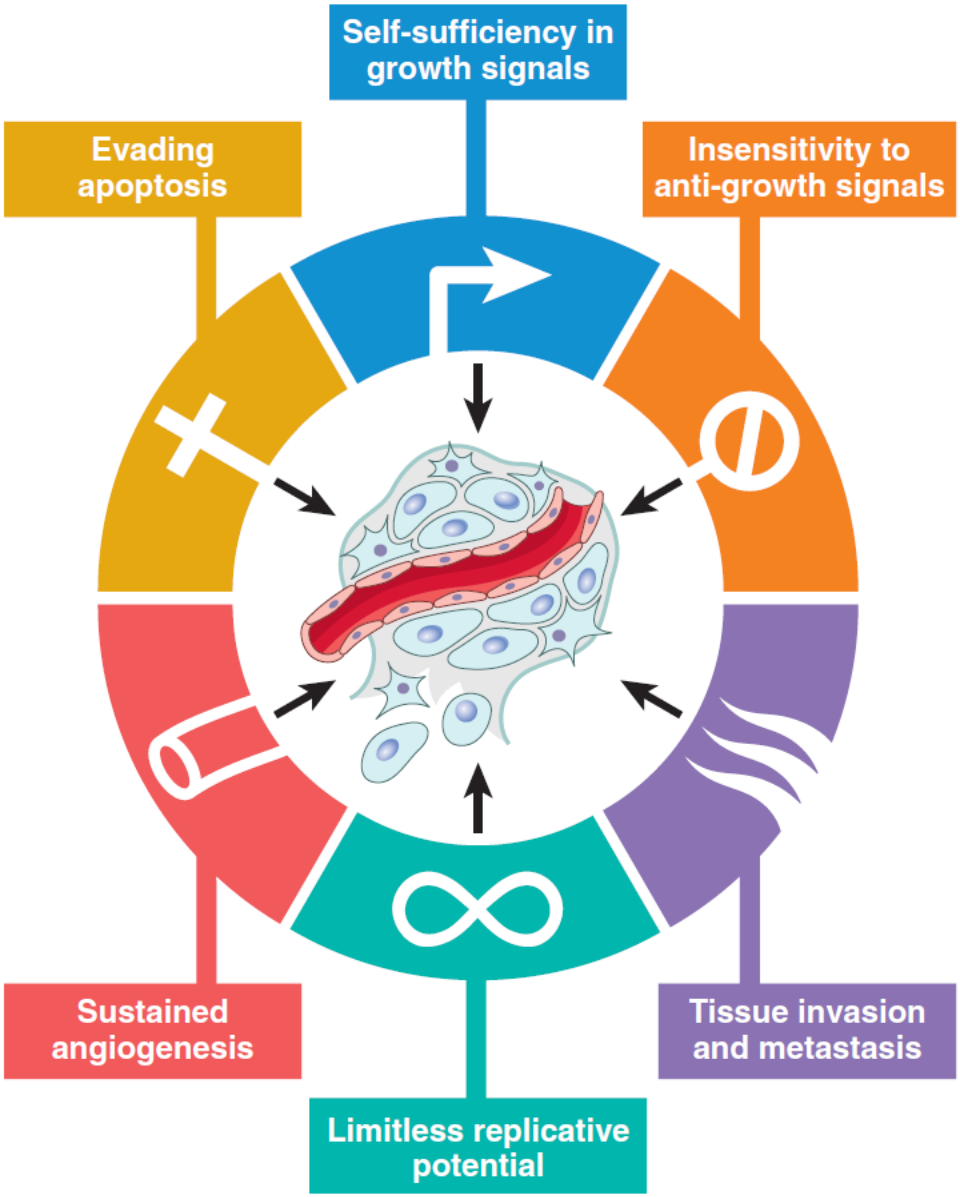
# Hallmarks of Cancer



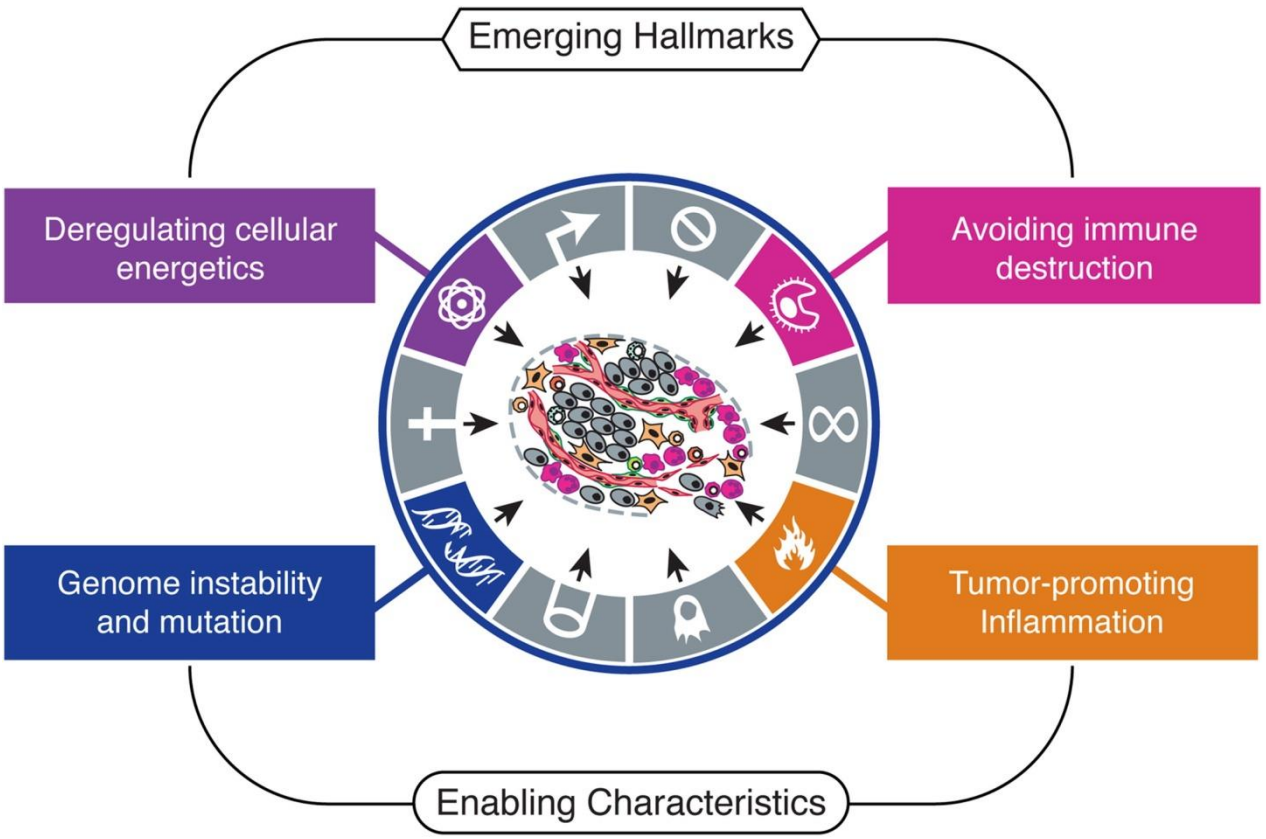

## Original Hallmarks

Fundamental changes in cellular physiology compared to non-cancerous cells

Based in a large part on the SMT although some stromal interaction for angiogenesis

*Hanahan D, Weinberg RA: The hallmarks of cancer. Cell 100:57, 2000.*

## New Hallmarks

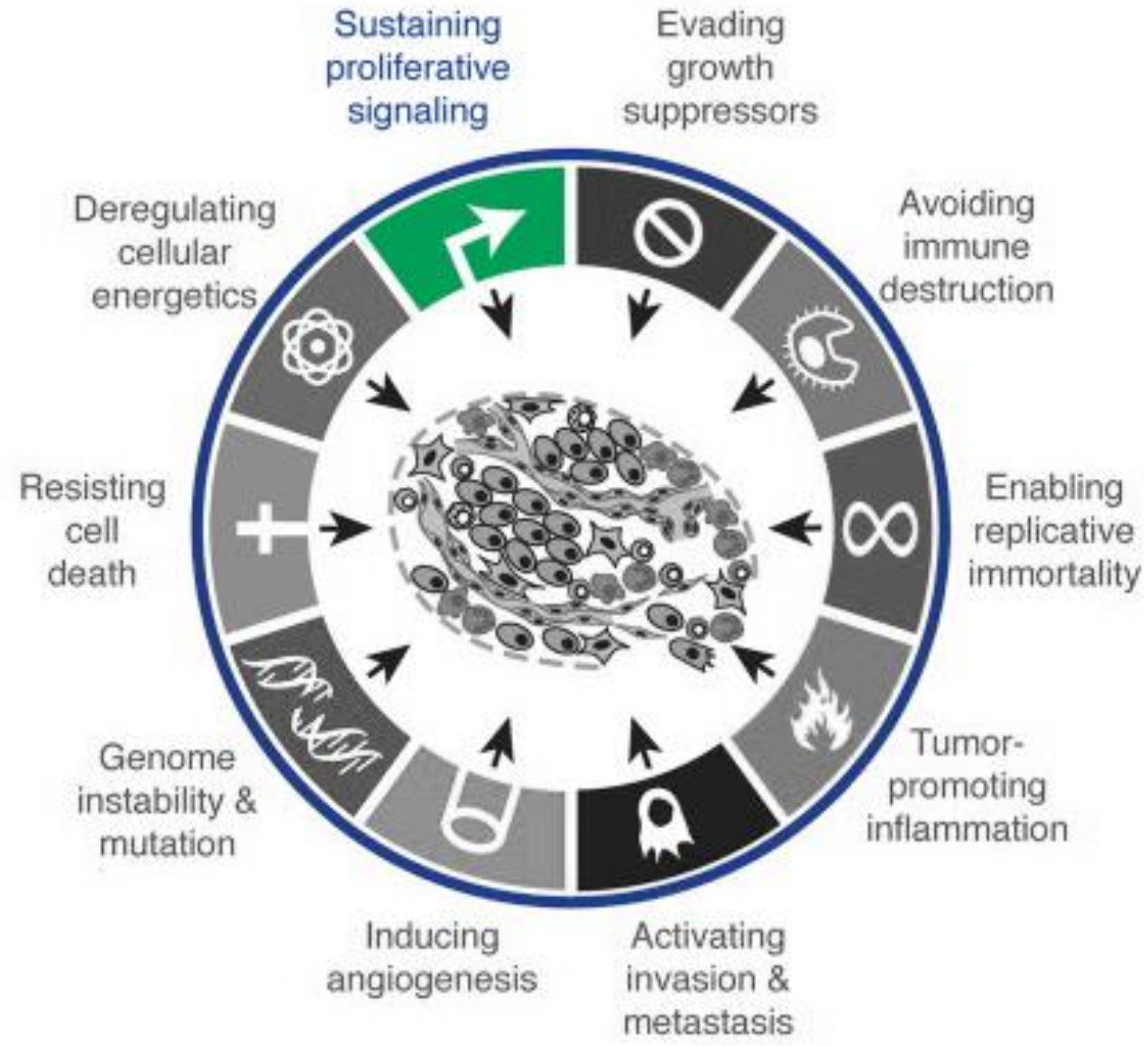



A better understanding that there is a two way conversation between the tumor parenchymal cells and the surrounding stroma

*Hanahan D, Weinberg RA: The hallmarks of cancer: the next generation. Cell 144:646, 2011.*

# Hallmarks of Cancer
## *Growth*


Sustaining proliferative signaling
Evading growth suppressors
Avoiding immune destruction
Enabling replicative immortality
Tumor-promoting inflammation
Activating invasion & metastasis
Inducing angiogenesis
Genome instability & mutation
Resisting cell death
Deregulating cellular energetics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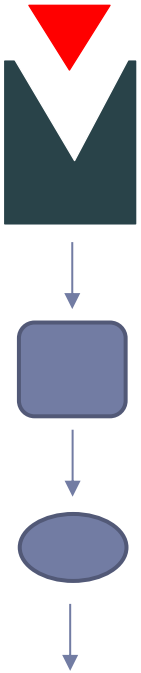
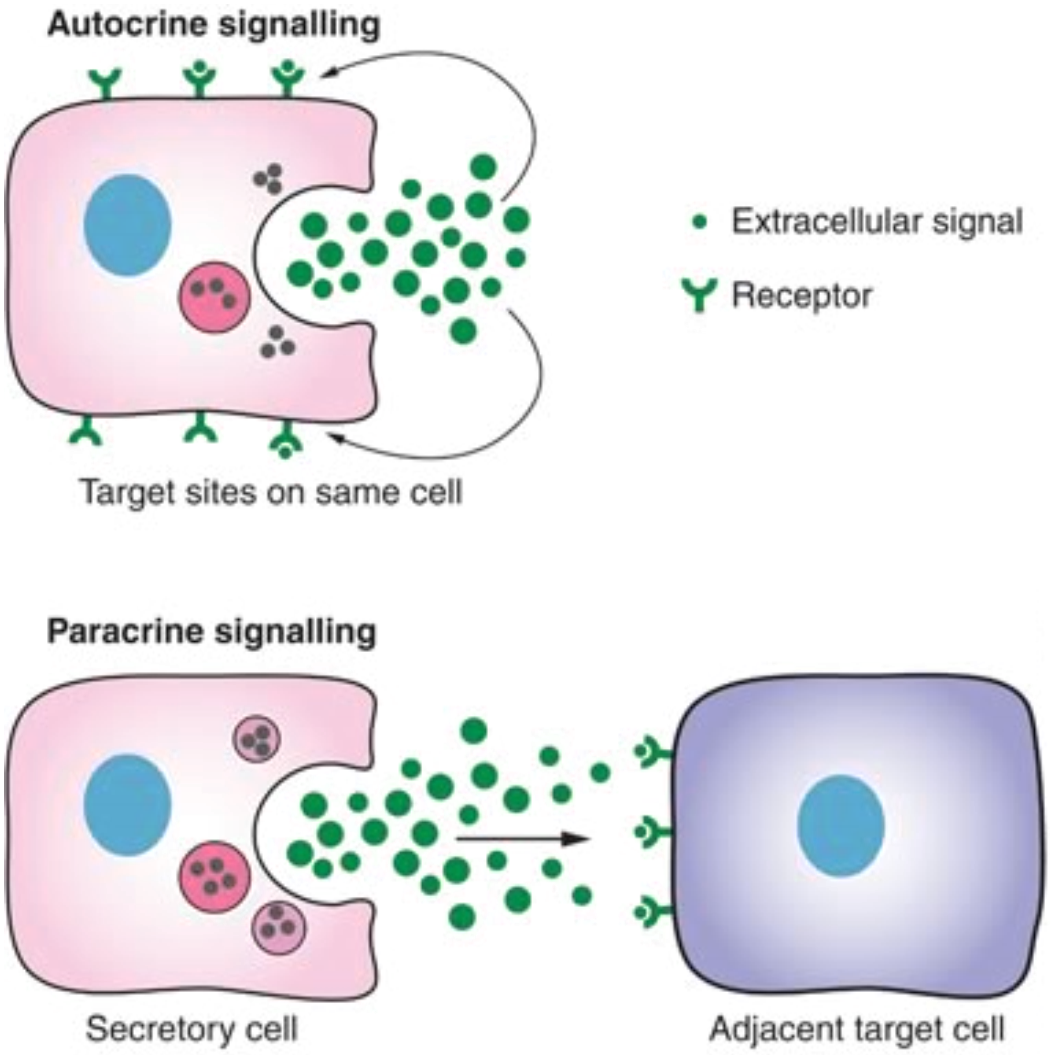


## Cell signalling

1. Growth factor binding
2. Transient activation of the growth factor receptor
3. Signal transduction
4. Transcription regulation
5. Cell cycle entry & progression

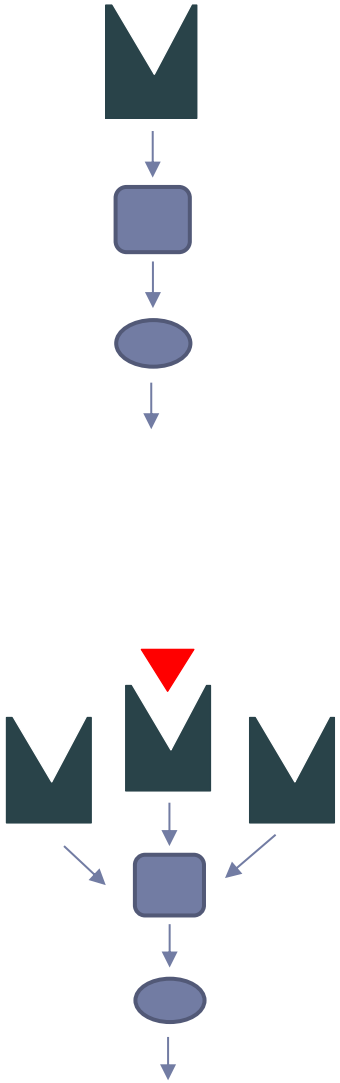



## Growth factors

Typically paracrine
Subverted by abnormal stromal interaction

Autocrine = +ve feedback loop

e.g. Glioblastoma - PDGF
Sarcomas - TGFα



## Receptors

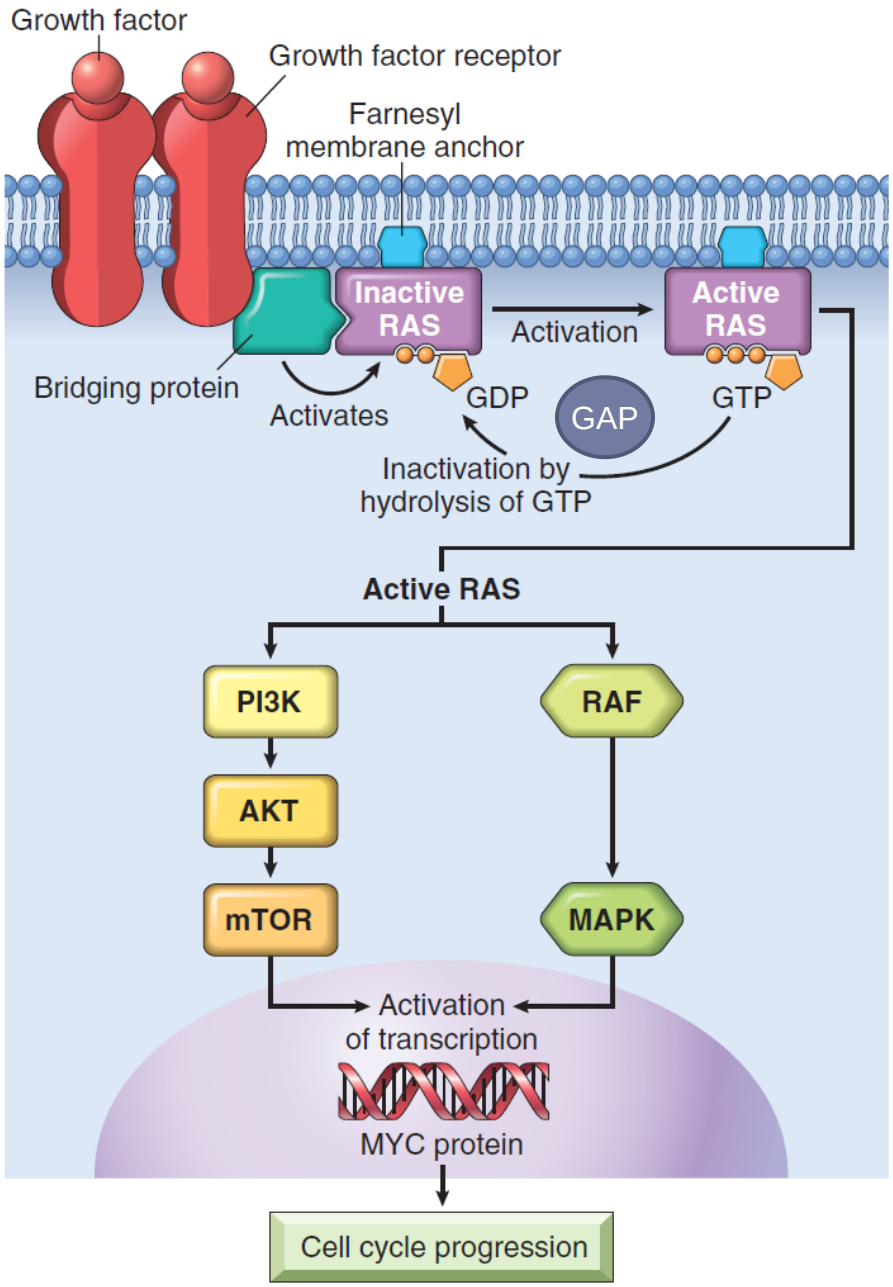
Receptor mutations leading to constitutive activation

e.g. EGFR mutations in colon/lung cancer

Receptor over-expression

e.g. EGFR Lung SCC
HER2/NEU breast

e.g. EGF
PDGF



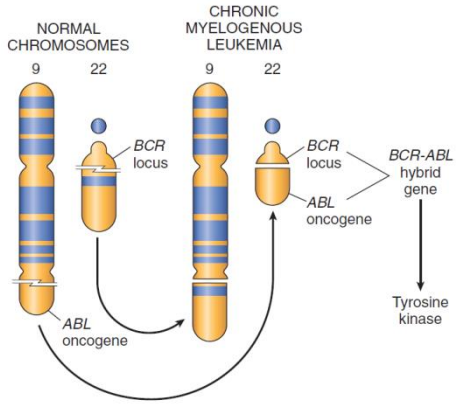

## Signal transducers

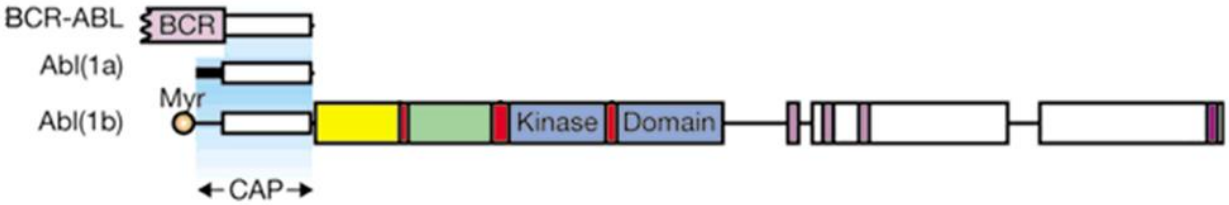
### RAS

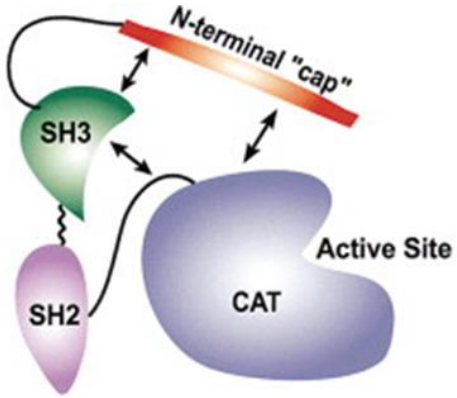
Small G protein

Most commonly mutated proto-oncogene in human tumors

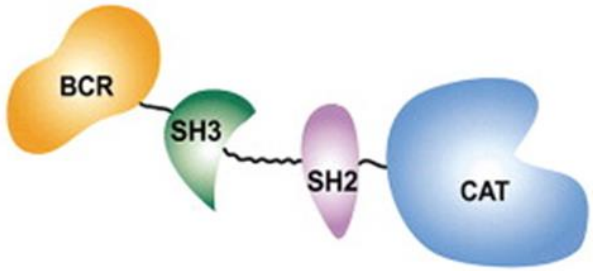
Point mutations within the GTP-binding pocket or in the enzymatic region essential for GTP hydrolysis.




INACTIVE C-ABL




ACTIVE BCR-ABL

## Signal transducers

### ABL

Non-receptor associated tyrosine kinase (TK)

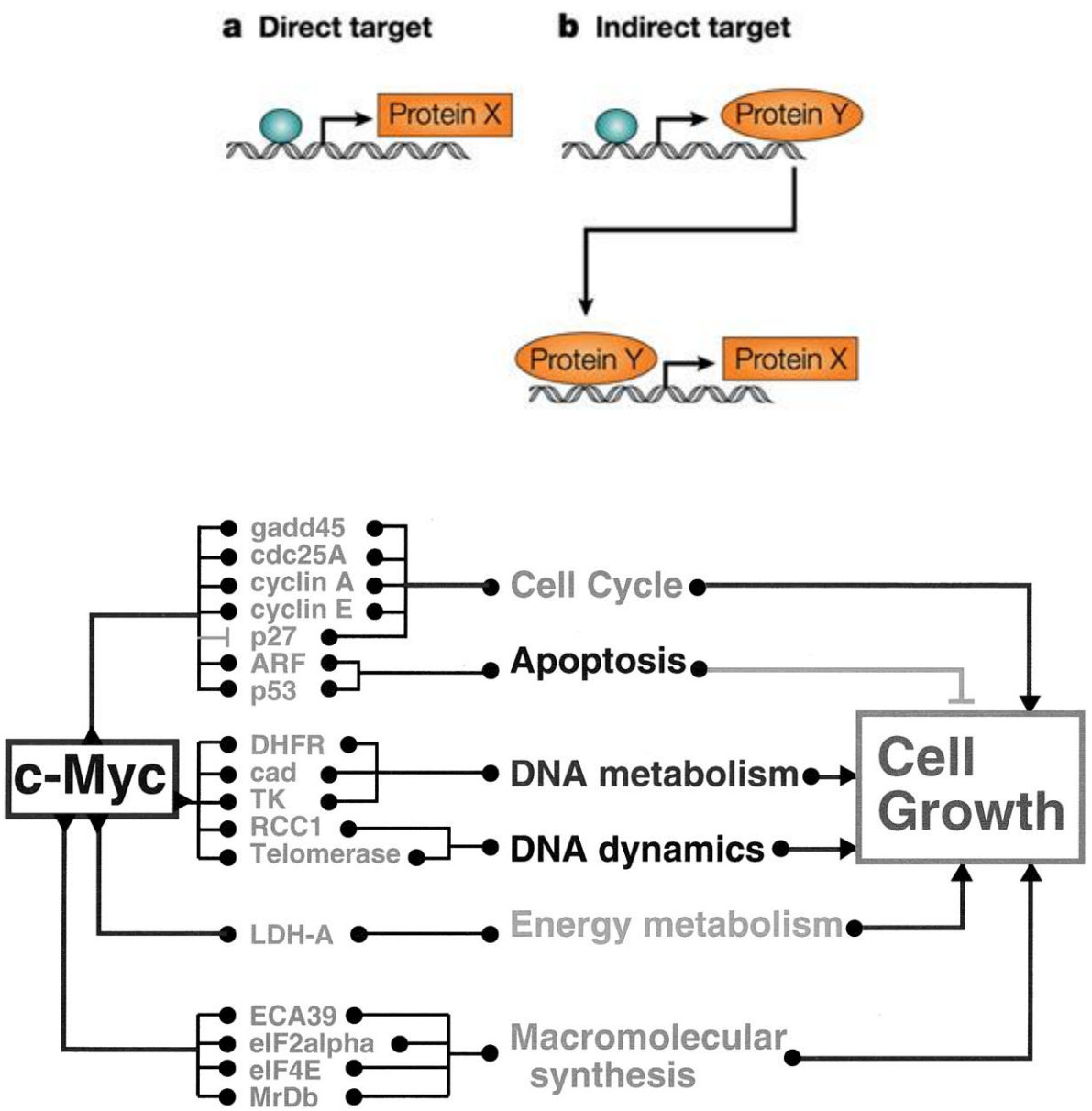
Internal ABL regulatory mechanism disrupted

Constitutive TK activity

Downstream RAS pathway activation

Oncogene addiction

Imatinib (Gleevec)




## Transcription factors

**MYC**

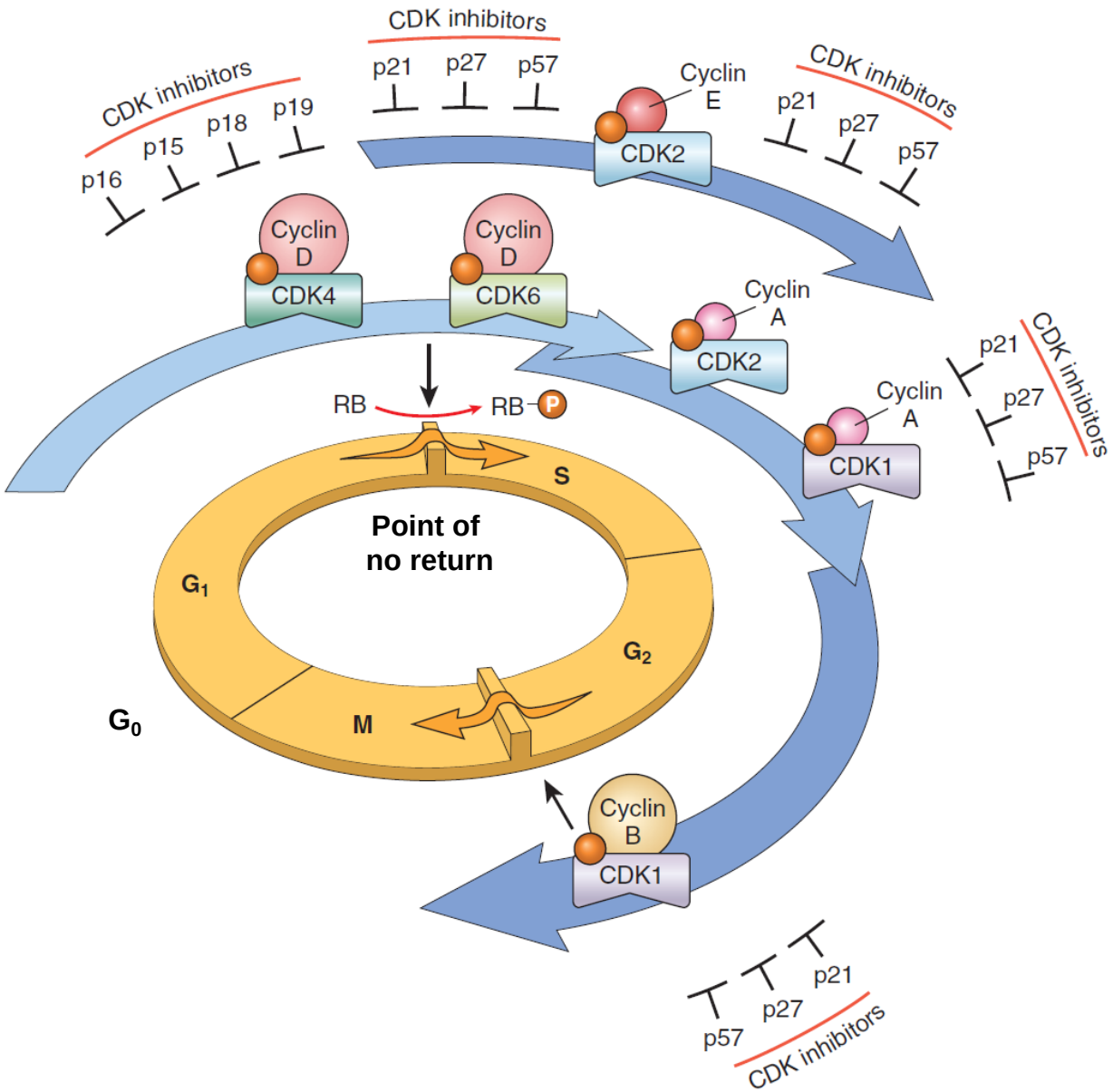
Activate/repress transcription

+CDK
-CDKI

t(8;14) *MYC* in Burkitt lymphoma

Amplification in breast, colon, & lung cancers

*NMYC* neuroblastoma
*LMYC* small cell lung cancer




## Cyclins & CDKs

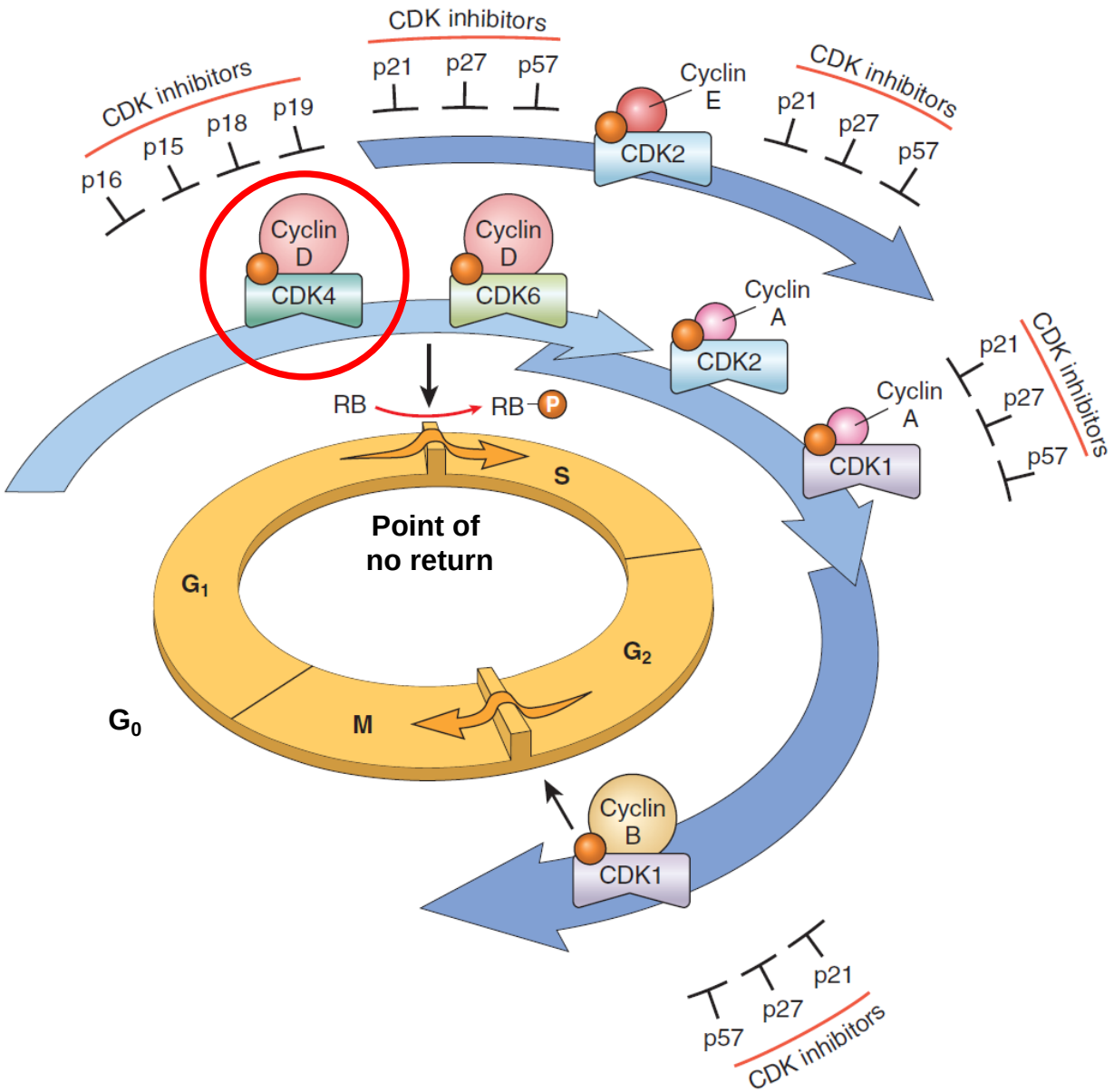
Quiescent cells $G_0$ induced to enter the cell cycle by GF & ECM integrin signalling

Cyclin+CDK=active CDK

Regulation by CDKI

Checkpoints:

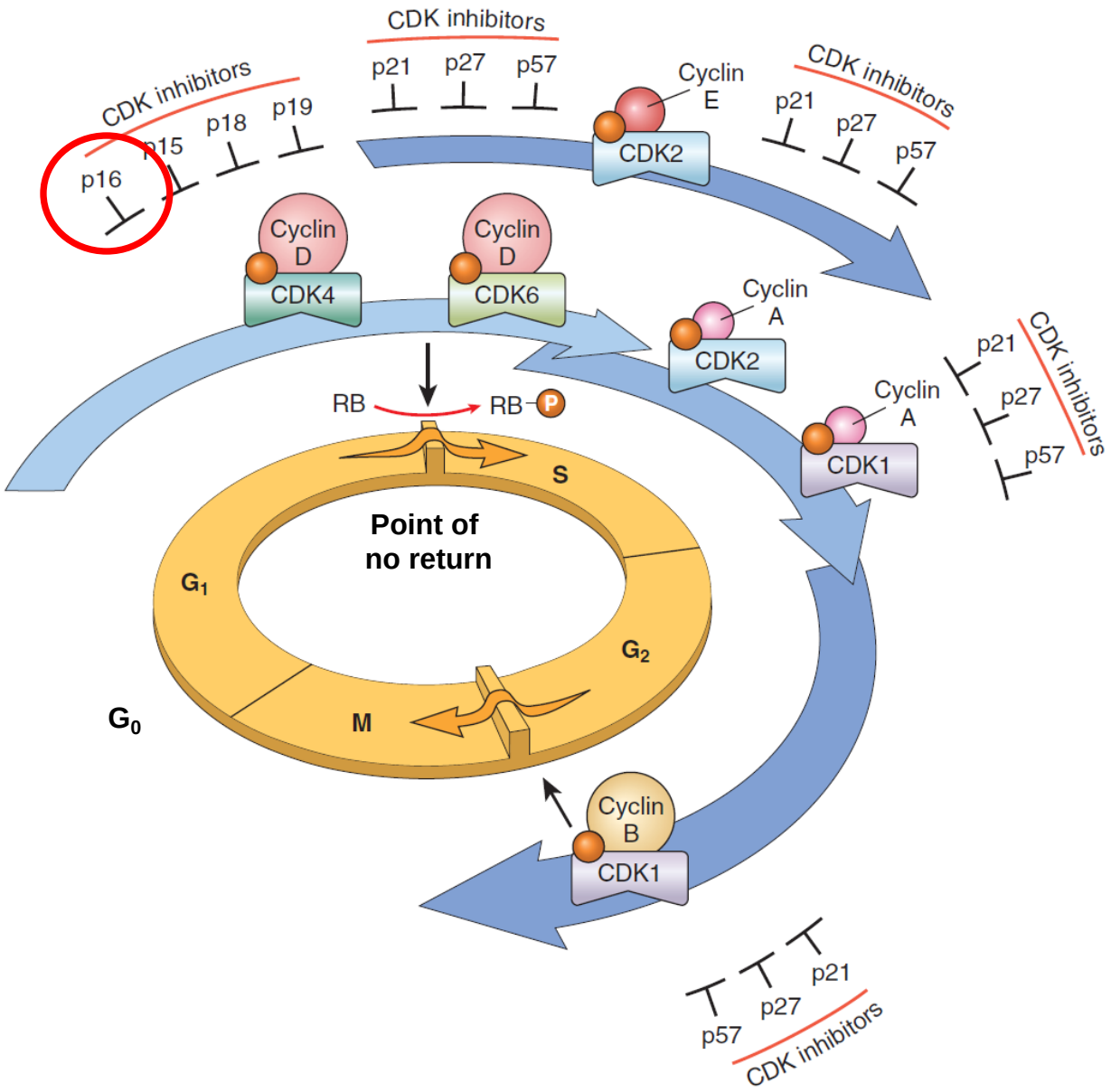
- $G_1$-S
- $G_2$-M
- Metaphase




## Cyclins & CDKs

Cyclin D over-expression:
breast
esophagus
liver
lymphomas
plasma cell tumors

*CDK4* amplification:
melanomas
sarcomas
glioblastomas

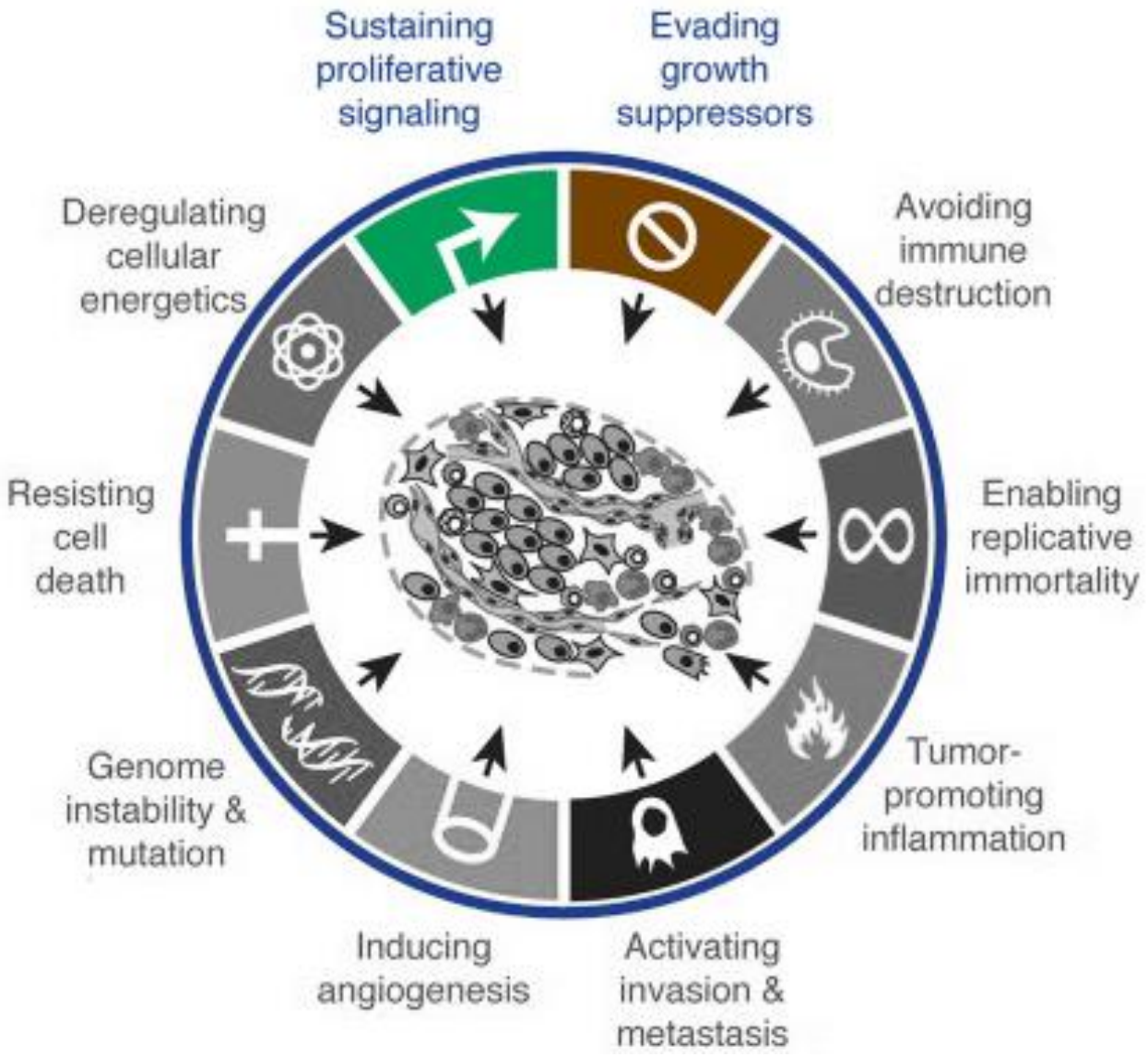



## Cyclins & CDKs

*CDKN2A* germline mutations:
25% of melanoma-prone kindreds

*CDKN2A somatic deletion/inactivation:*
pancreatic carcinomas
glioblastomas
esophageal cancers
non–small cell lung carcinomas
soft tissue sarcomas
bladder cancers

# Hallmarks of Cancer
## *Evading Growth Inhibition*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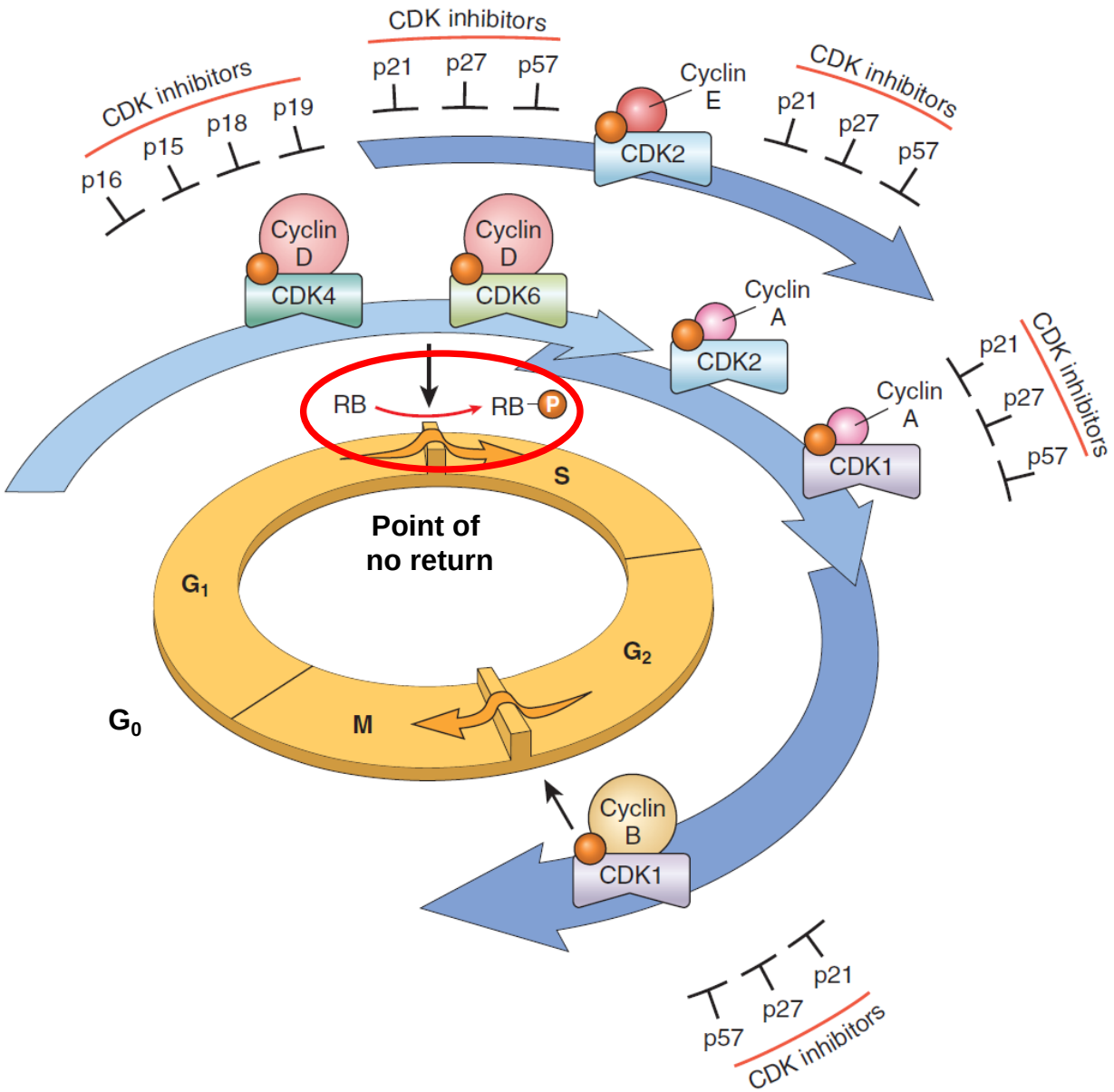


## *RB* : Governor of the Cell Cycle

First tumor suppressor gene to be discovered

Identified in retinoblastoma patients

Chromosome 13q14

Rare disease but mechanisms learned apply to a wide range of tumors

60% sporadic
rest famillial AD

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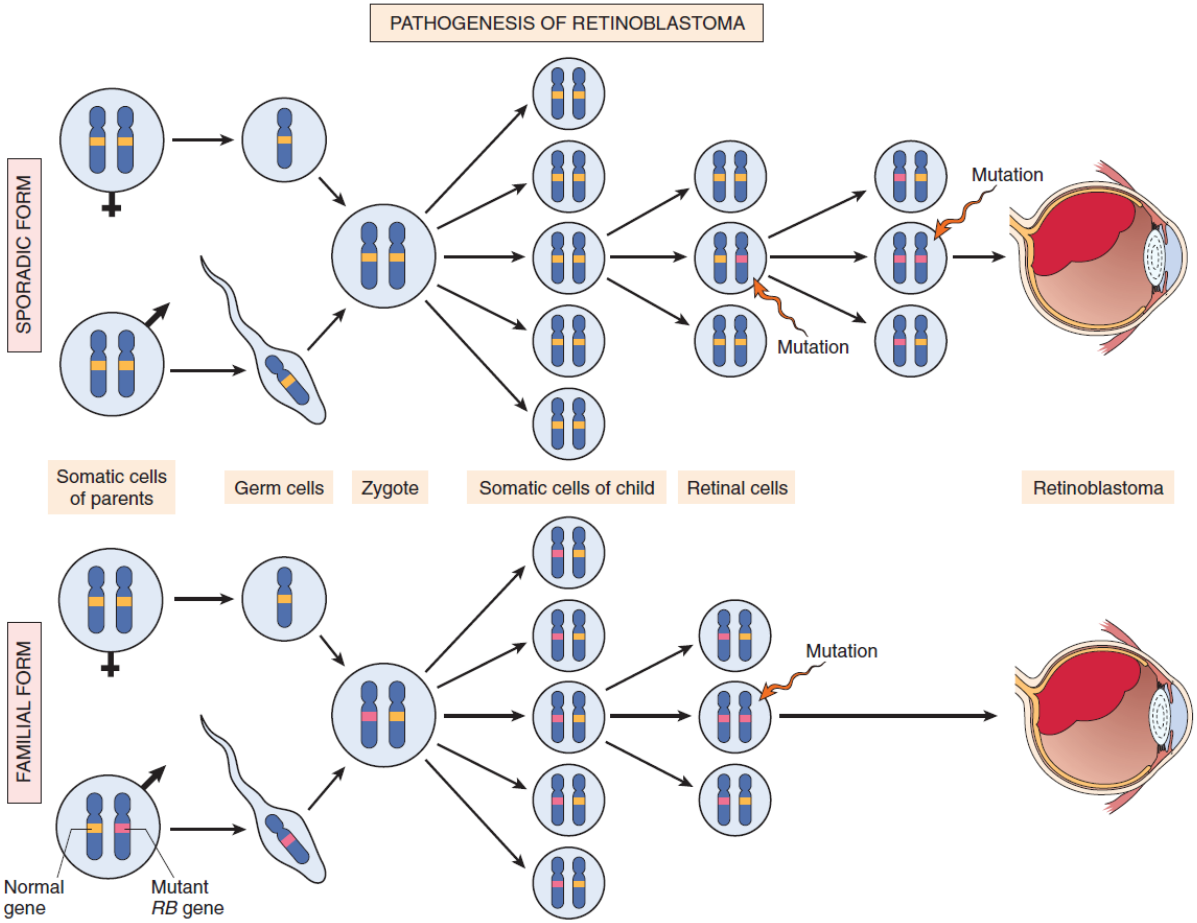
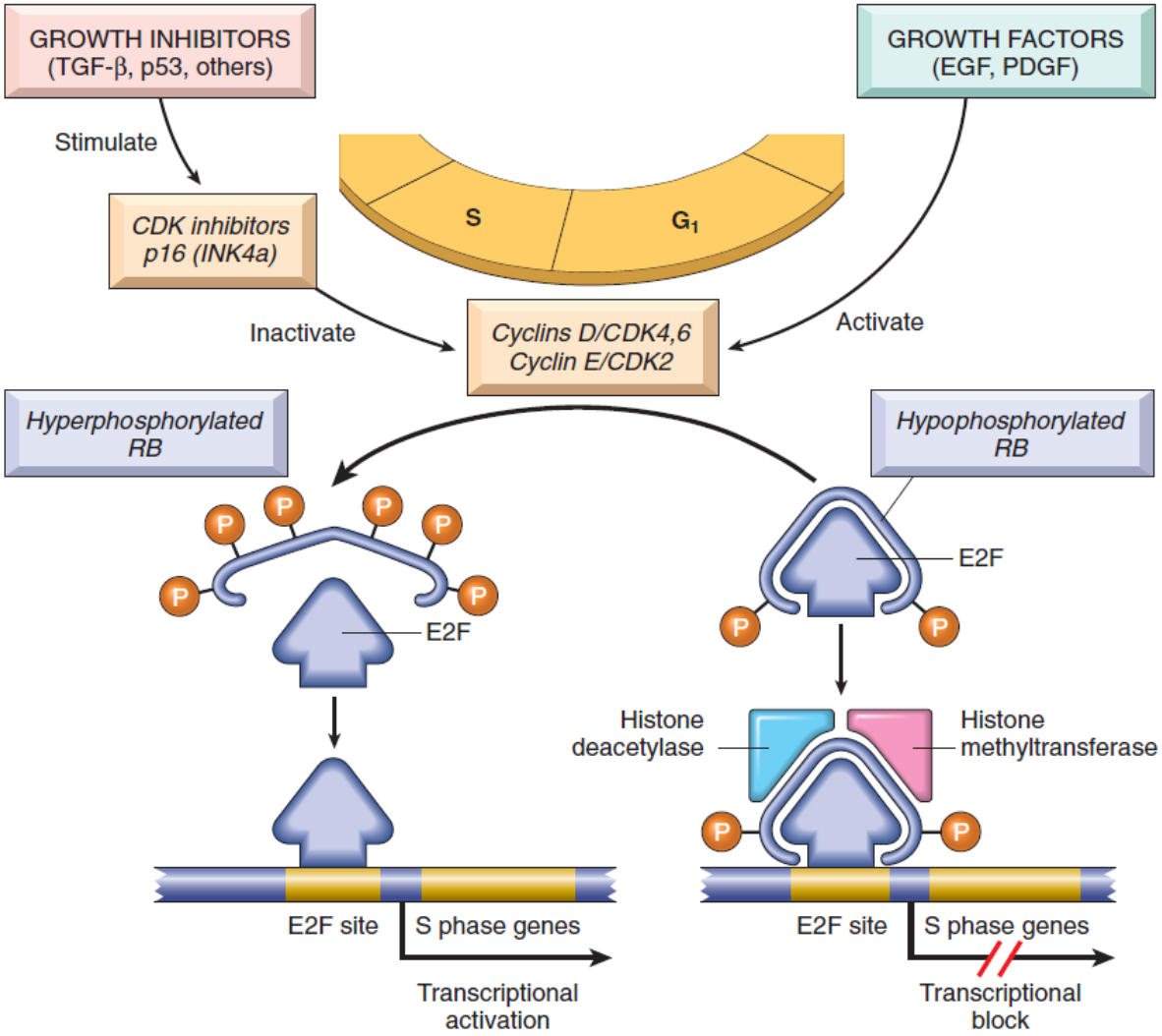



Knudson “two-hit” hypothesis

Two defective copies needed

Familial: -inherited
-somatic mutation

Sporadic: 2 somatic mutations




## *RB* : Governor of the Cell Cycle

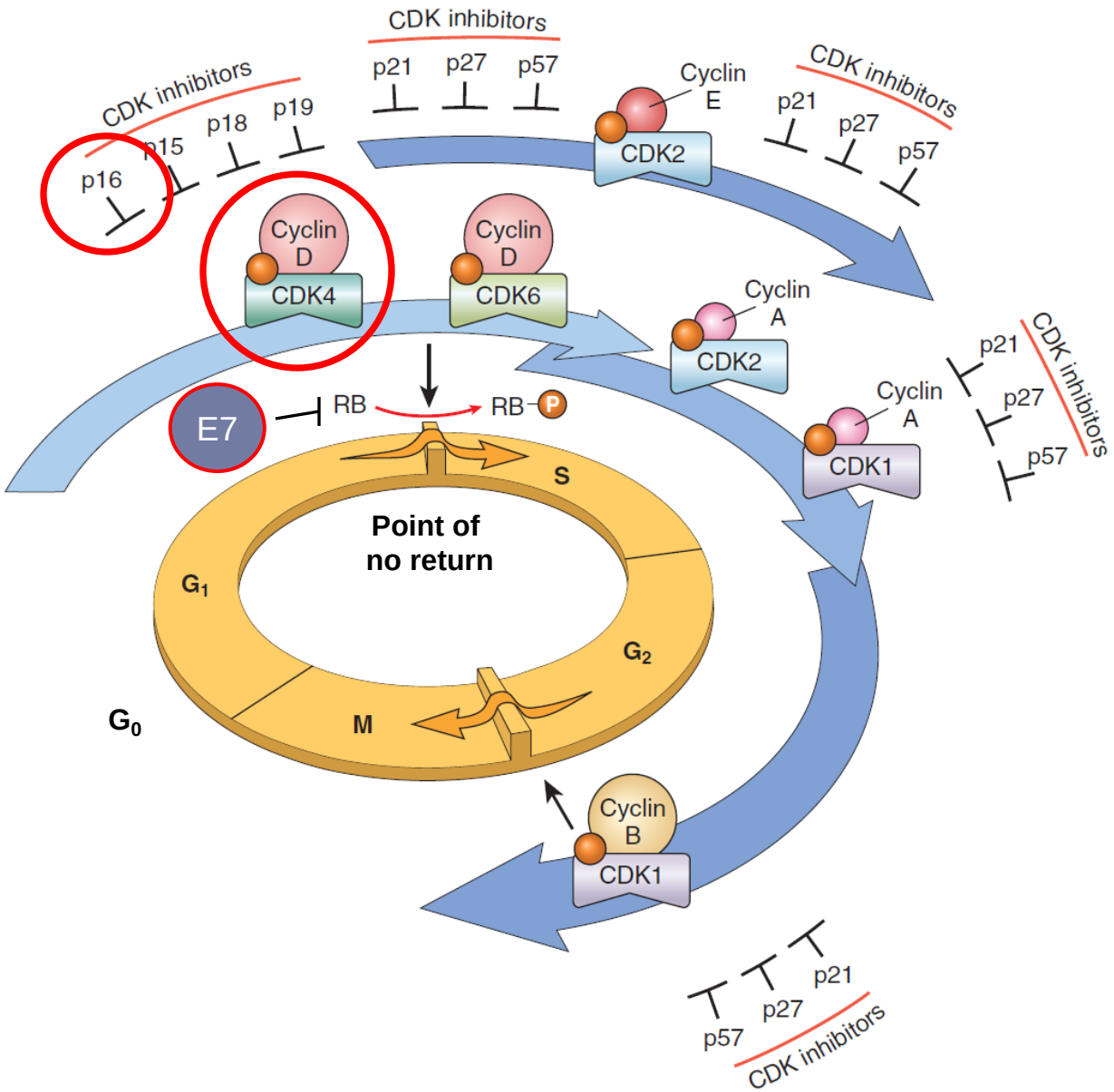
**G1-S transition**

Cyclin E expression control:

- E2F sequestration
- Chromatin remodelling

Rb phosphorylation control:

- Cyclin D/CDK4,6
- Phosphatases




## *RB* mutation mimicking

Activation of CDK4 *(mutation)*

Over-expression of cyclin D *(translocation/ amplification)*

Inactivation of CDKI (e.g. CDKN2A) *(mutation/ deletion/epigenetics)*

Oncogenic viruses (e.g. HPV E7 protein binds to Rb preventing E2F binding)