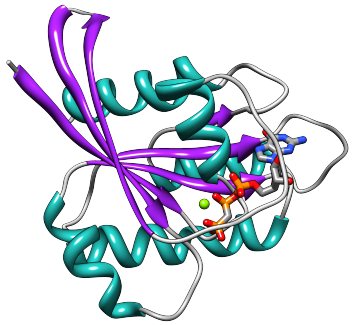
L:6 Signaling via small G-proteins

Objectives:

- Understand fundamental properties of small G-proteins
- Understand the role of GEF and GAP in small G-protein signaling
- Describe cellular signaling pathways mediated by Ras GTPases : MAP kinases and PI3 kinase
- Describe physiological roles of Ras/Raf/MEK/ERK and Ras/PI3K/Akt/mTOR signaling

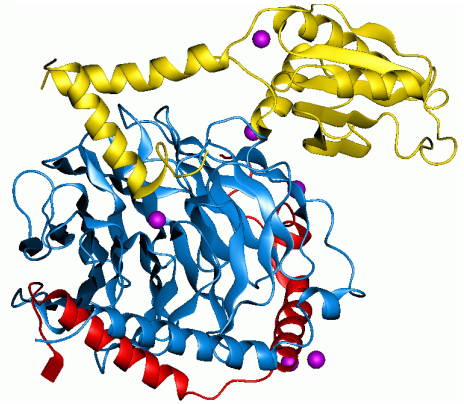
Small G-protein (Monomeric G-protein)

Small G-protein



https://en.wikipedia.org/wiki/Ras_subfamily#/media/File:Hras_secondary_structure_ribbon.png

Heterotrimeric G-protein



https://en.wikipedia.org/wiki/G_protein#/media/File:1b9x_opm.png

- Small G-proteins are typically between 20-25 kDa (about one half of the average size of the α subunits of heterotrimeric G-proteins).
- Serve as a molecular switch by cycling between the inactive GDP-bound form and active GTP-bound form.

Monomeric GTPases

Family	members	Functions
Ras	K-Ras, H-Ras, N-Ras	Relay signals from RTKs
	Rheb	mTOR signaling
	Rap1	Activate cAMP-dependent GEF: cell adhesion
Rho	Rho, Rac, Cdc42	Relay signals from surface receptor to cytoskeleton
Rab	Rab1-60	Regulate intracellular vesicle traffic
Ran	Ran	Regulates mitotic spindle assembly and nuclear transport
ARF	ARF1-ARF6	Regulate assembly of protein coats on intracellular vesicles

Ras oncogenes

Table 1 | **Activation of RAS signalling pathways in different tumours**

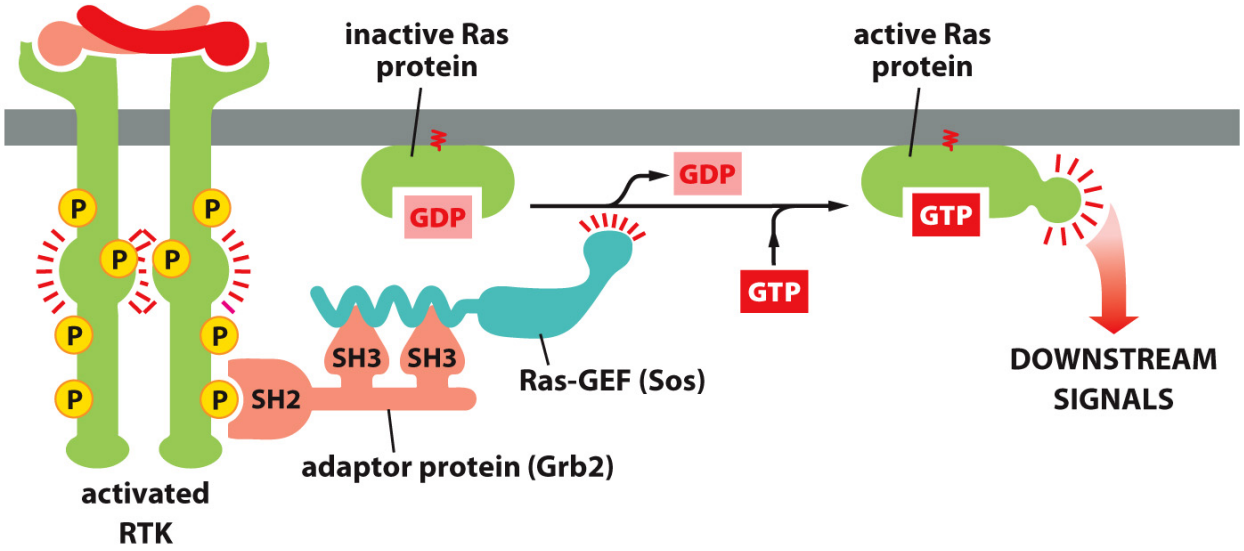
Defect or mutation	Tumour type	Frequency (%)
RAS mutation	Pancreas	90 (K)
	Lung adenocarcinoma (non-small-cell)	35 (K)
	Colorectal	45 (K)
	Thyroid (Follicular)	55 (H, K, N)
	Thyroid (Undifferentiated papillary)	60 (H, K, N)
	Seminoma	45 (K, N)
	Melanoma	15 (N)
	Bladder	10 (H)
	Liver	30 (N)
	Kidney	10 (H)
	Myelodysplastic syndrome	40 (N, K)
	Acute myelogenous leukaemia	30 (N)
BRAF mutation	Melanoma	66
	Colorectal	12
EGFR overexpression	Most carcinomas	>50
ERBB2 amplification	Breast	30
PTEN loss	Glioblastoma multiforme	20–30
	Prostate	20
	Pancreas	40
AKT2 amplification	Ovarian	12
	Pancreas	10
PI3K amplification	Ovarian	40

EGFR, epidermal-growth-factor receptor; PI3K, phosphatidylinositol 3-kinase. H, K and N refer to *HRAS*, *KRAS* and *NRAS*, respectively.

Nature Reviews Cancer 3, 11-22 (January 2003)

RTK signaling via Ras: Grb2 (Ras-GEF)

(2): Sos (Ras-GEF) promotes disassociation of GDP from Ras; GTP binds and Sos dissociates from active Ras



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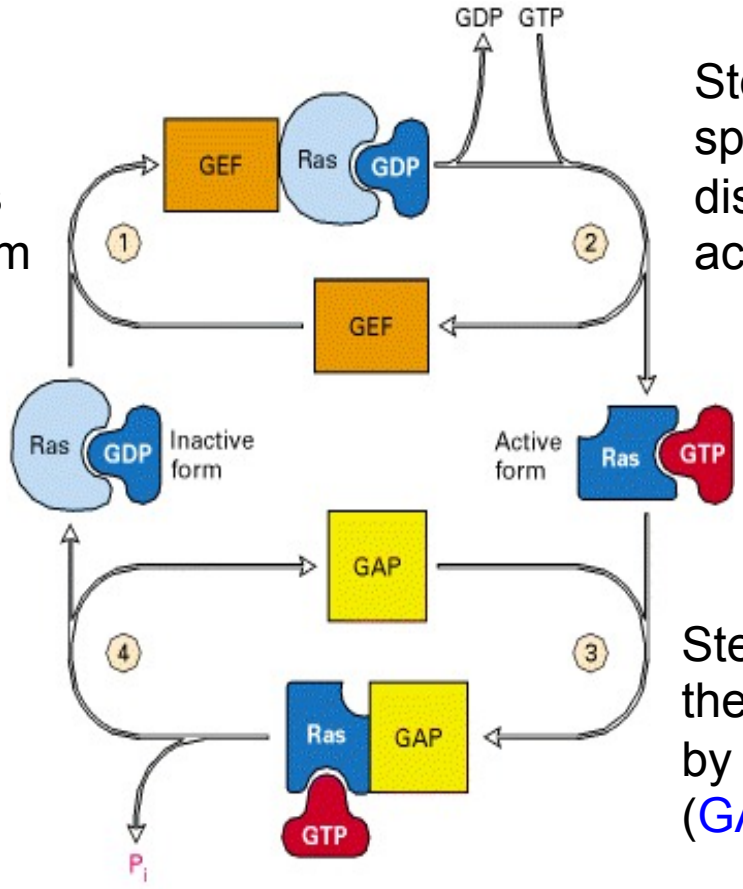
(1) Grb2 (Growth factor receptor-bound protein 2) binds to a specific phosphorylated tyrosine by mean of SH2 domain (Src homology domain 2) and recruits Sos (Son of Sevenless) by mean of SH3 domains (Src homology domain 3)

Cycling of Ras proteins

Step **1**: Guanine nucleotide- exchange factors (GEF) facilitates dissociation of GDP from Ras.



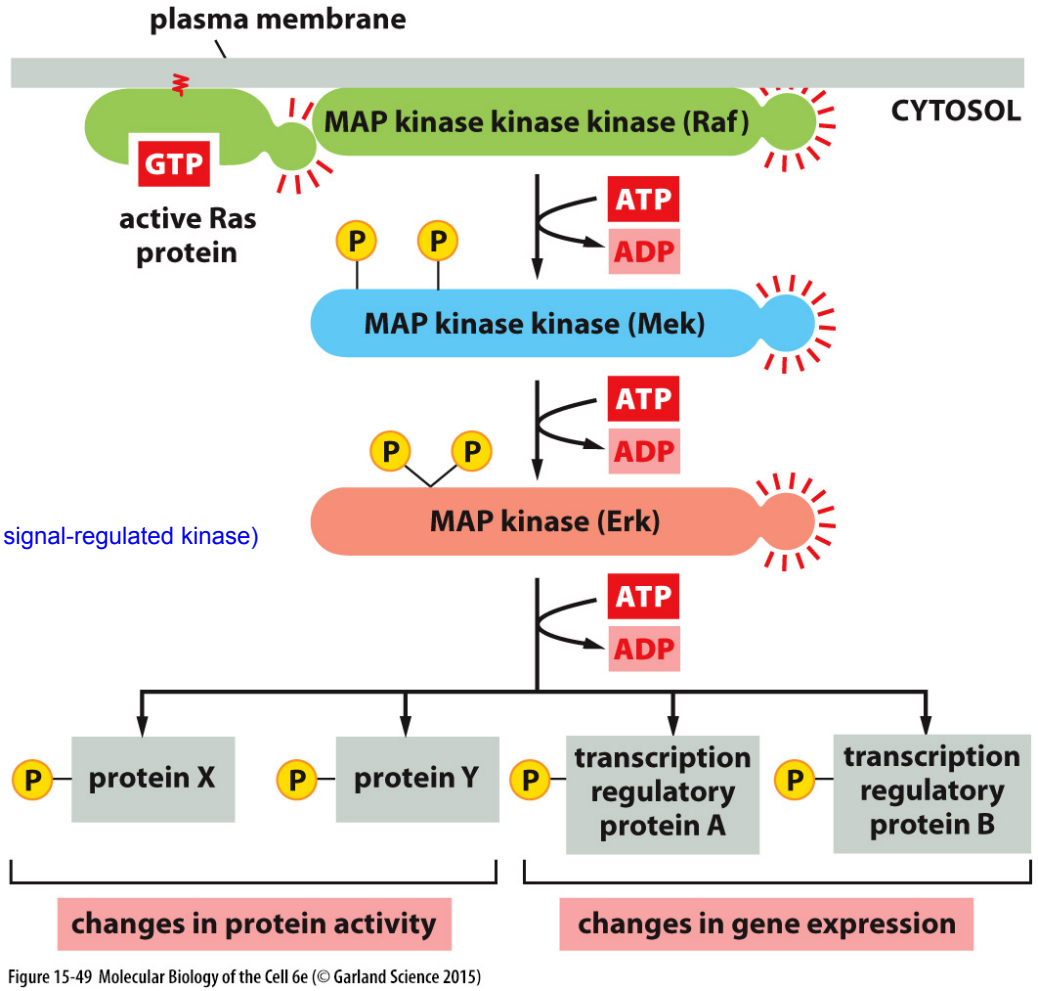
Step **2**: GTP binds spontaneously, and GEF dissociates yielding the active Ras .

ONWARD TRANSMISSION OF SIGNAL

Steps **3**and **4**: Hydrolysis of the bound GTP is accelerated by GTPase-activating proteins (GAP).

http://www.ncbi.nlm.nih.gov/books/NBK21720/figure/A5807/?report=objectonly

Ras/Raf/Mek/Erk signaling pathways Mitogen-Activated Protein Kinase (MAPK)



(Erk =Extracellular signal-regulated kinase)

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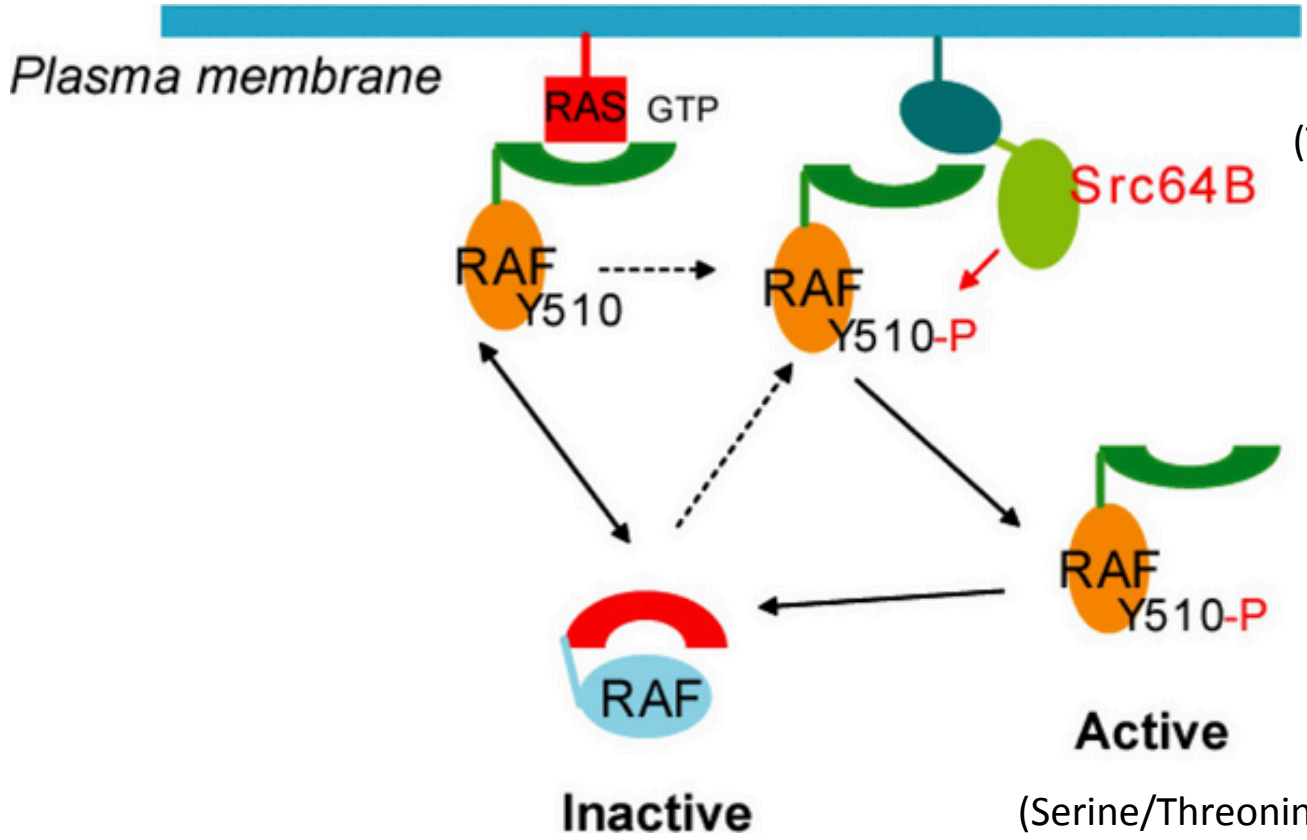
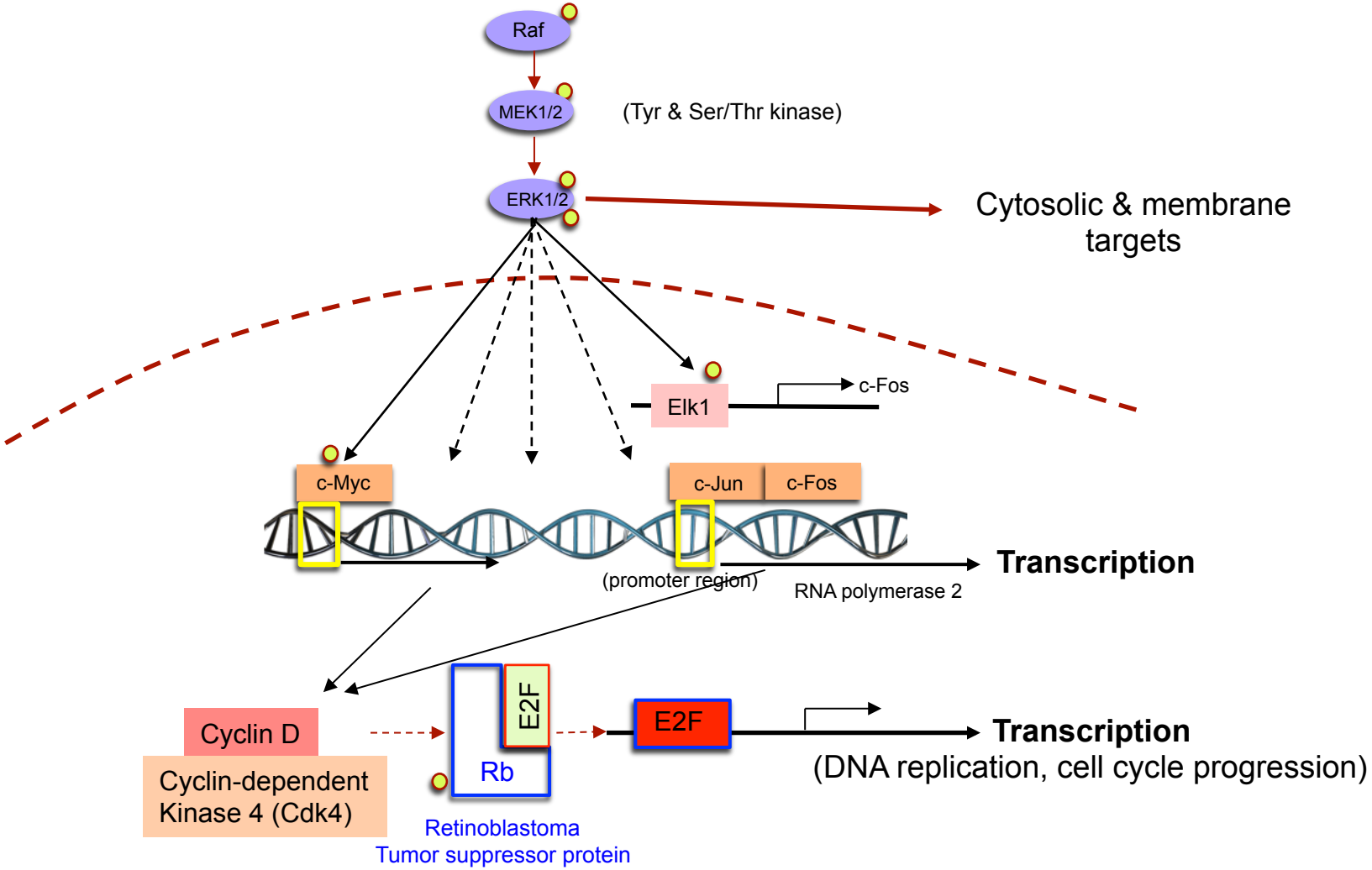
Raf (MAP3K) activation

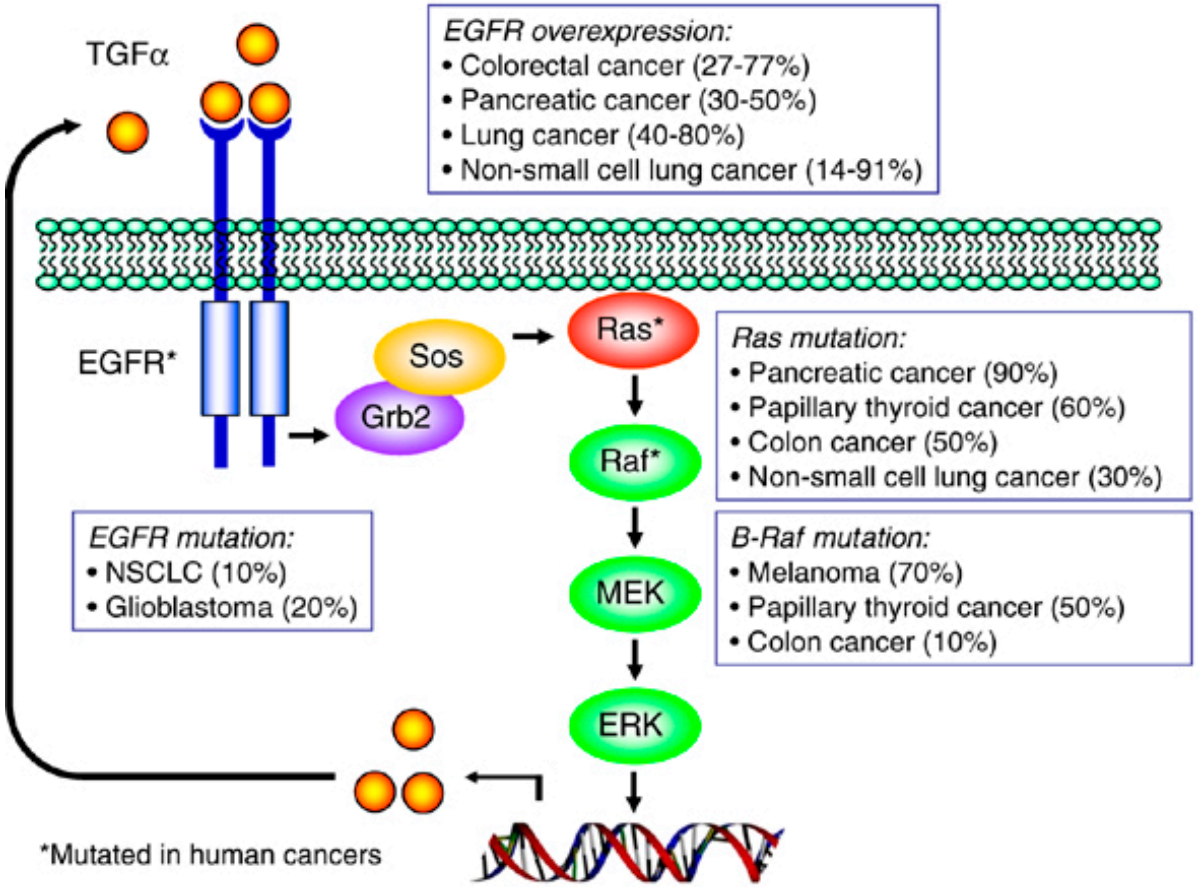


Modified from: Xia et al. (2008) PLOS Biology 6(5): e128. doi:10.1371/journal.pbio.0060128

ERK increases gene transcription



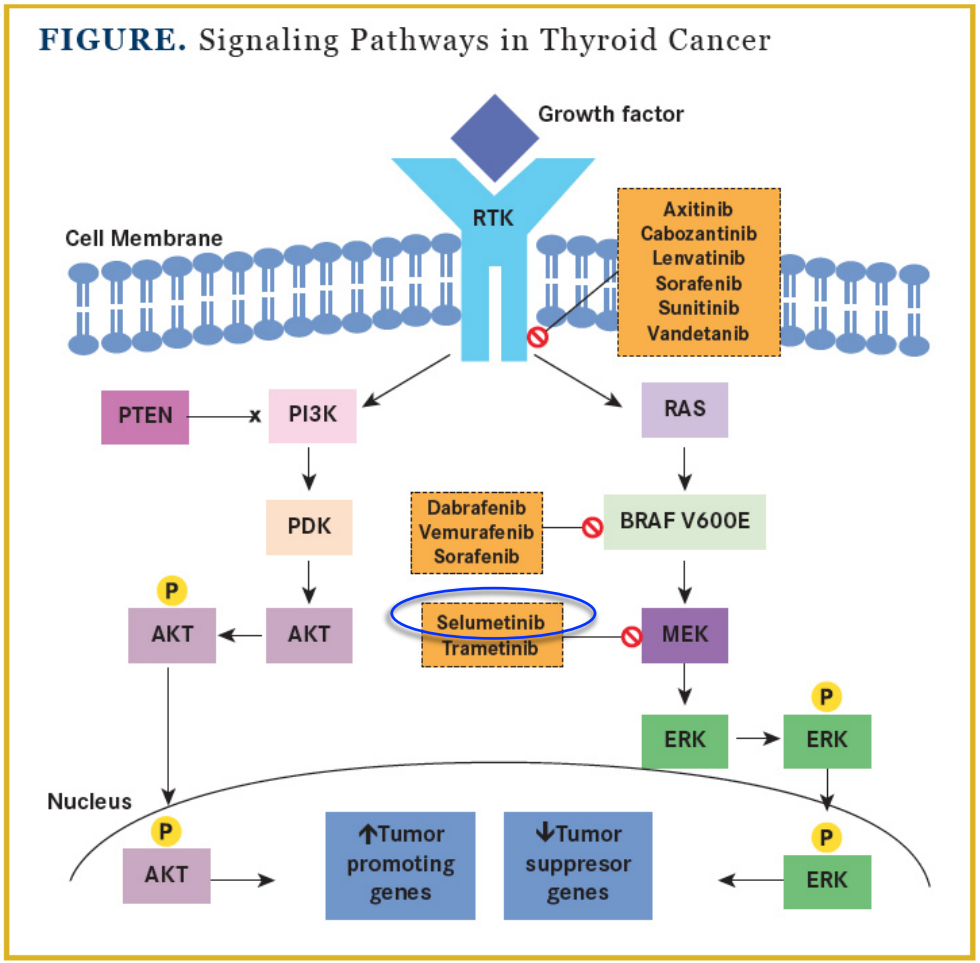
Ras/MAPK cascade and cancer



Oncogene (2007) 26, 3291–3310. doi:10.1038/sj.onc.1210422

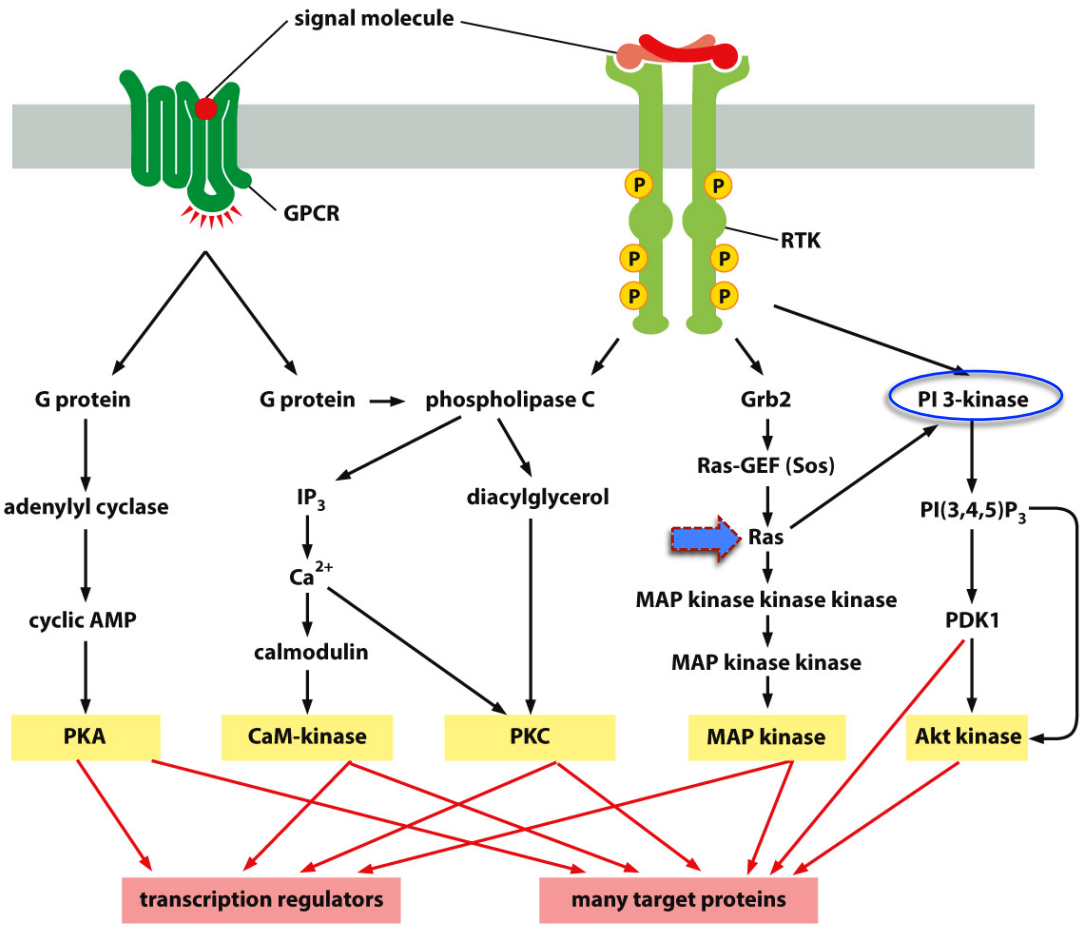
Targeting Ras/MAPK pathway in cancer treatment

AstraZeneca



Tanaka etal (2015) Am J Hemato Onco

Phosphoinosotide 3-kinase (PI3K) signaling



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PI3K : Lipid kinase

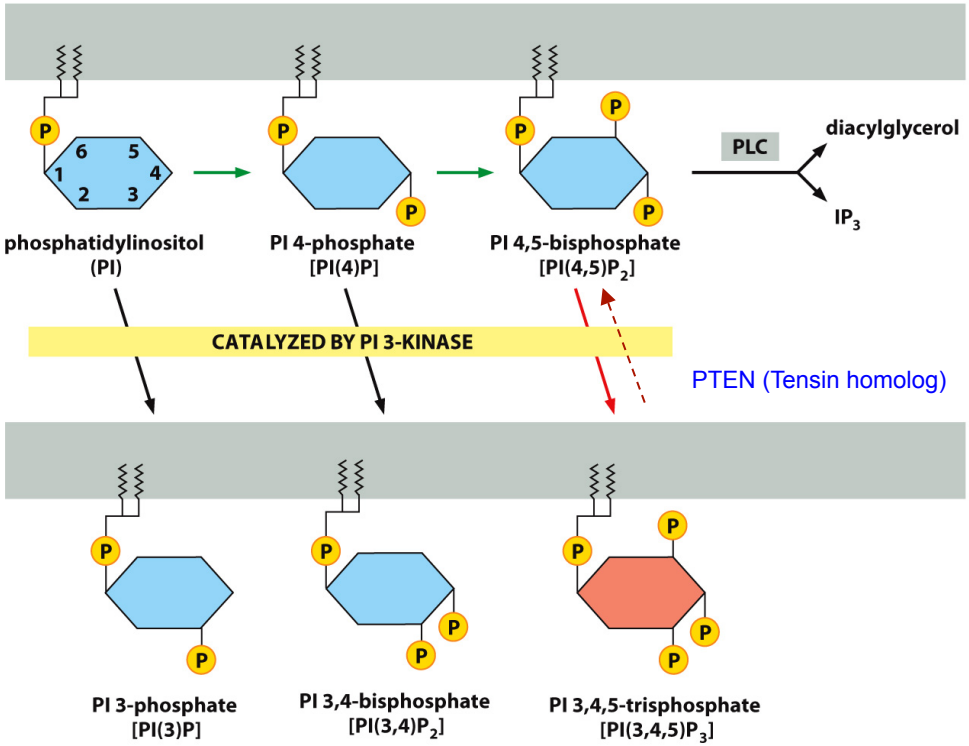
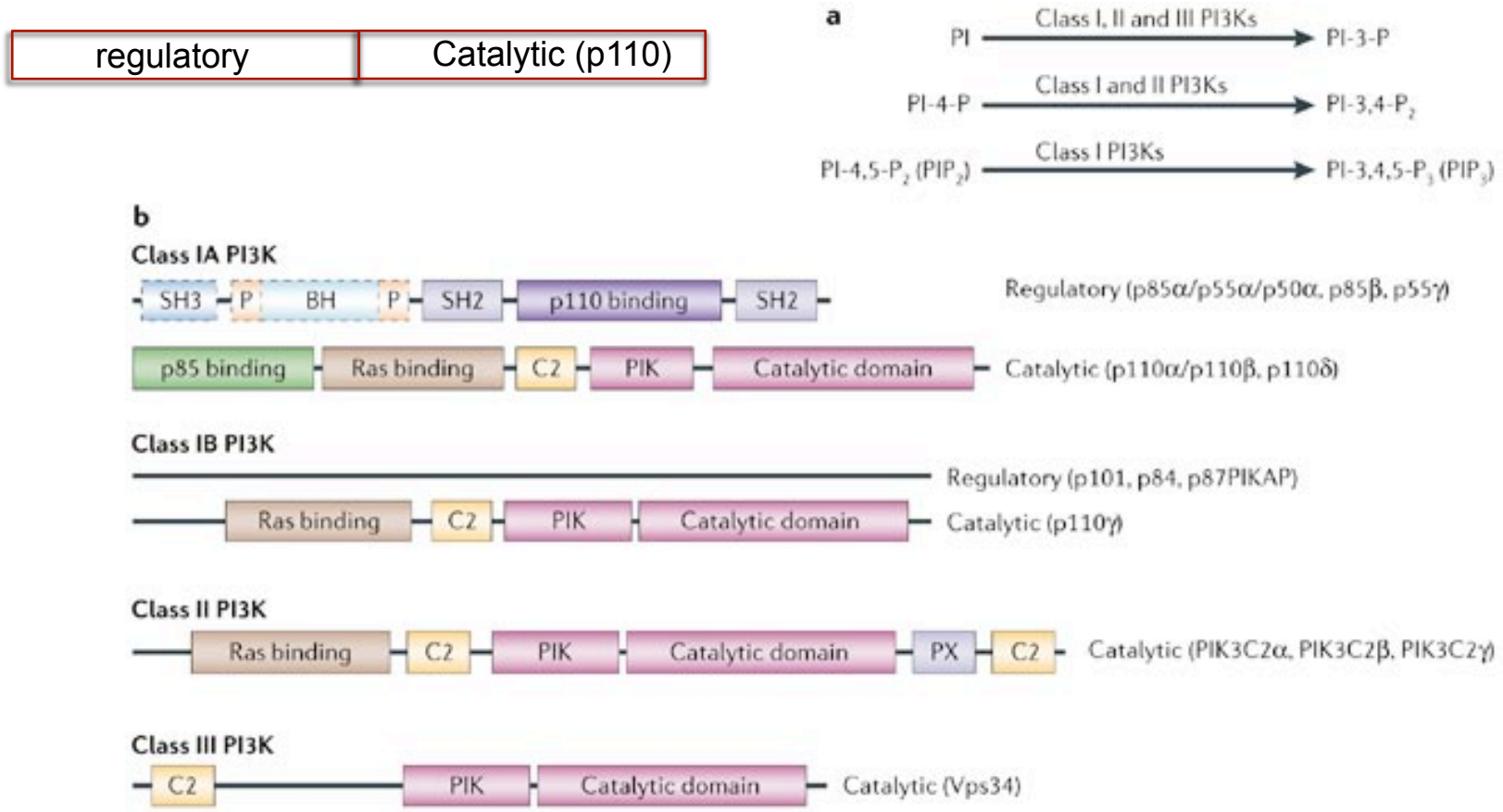


Figure 15-52 Molecular Biology of the Cell 6e (© Garland Science 2015)

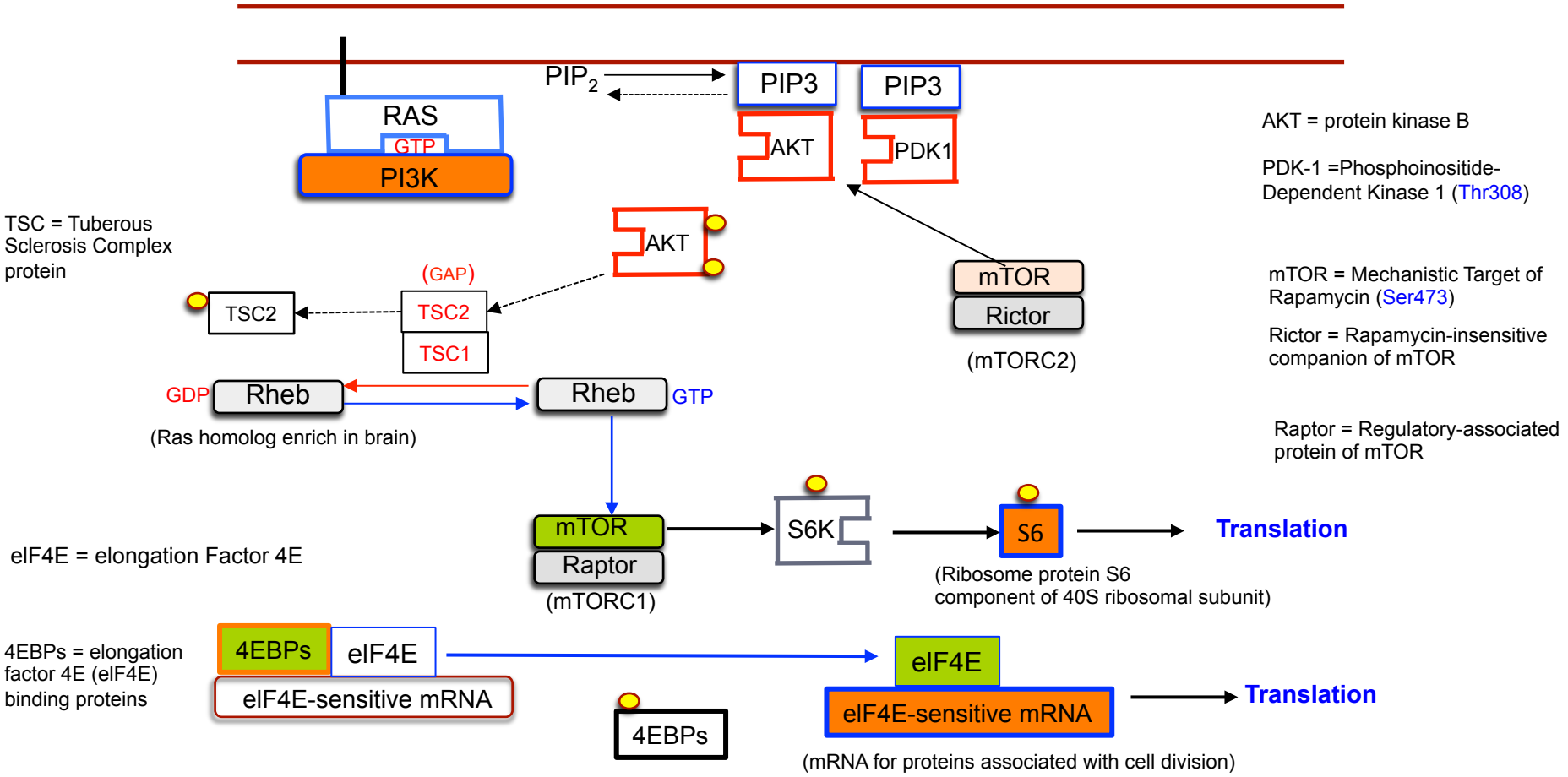
Djordjevic & Driscol (2002) DOI: http://dx.doi.org/10.1016/S0968-0004(02)02136-9

PI3K



Engelman et al (2006) doi:10.1038/nrg1879

Ras/PI3K/mTOR pathway



PI 3K/mTOR signaling promotes cell survival

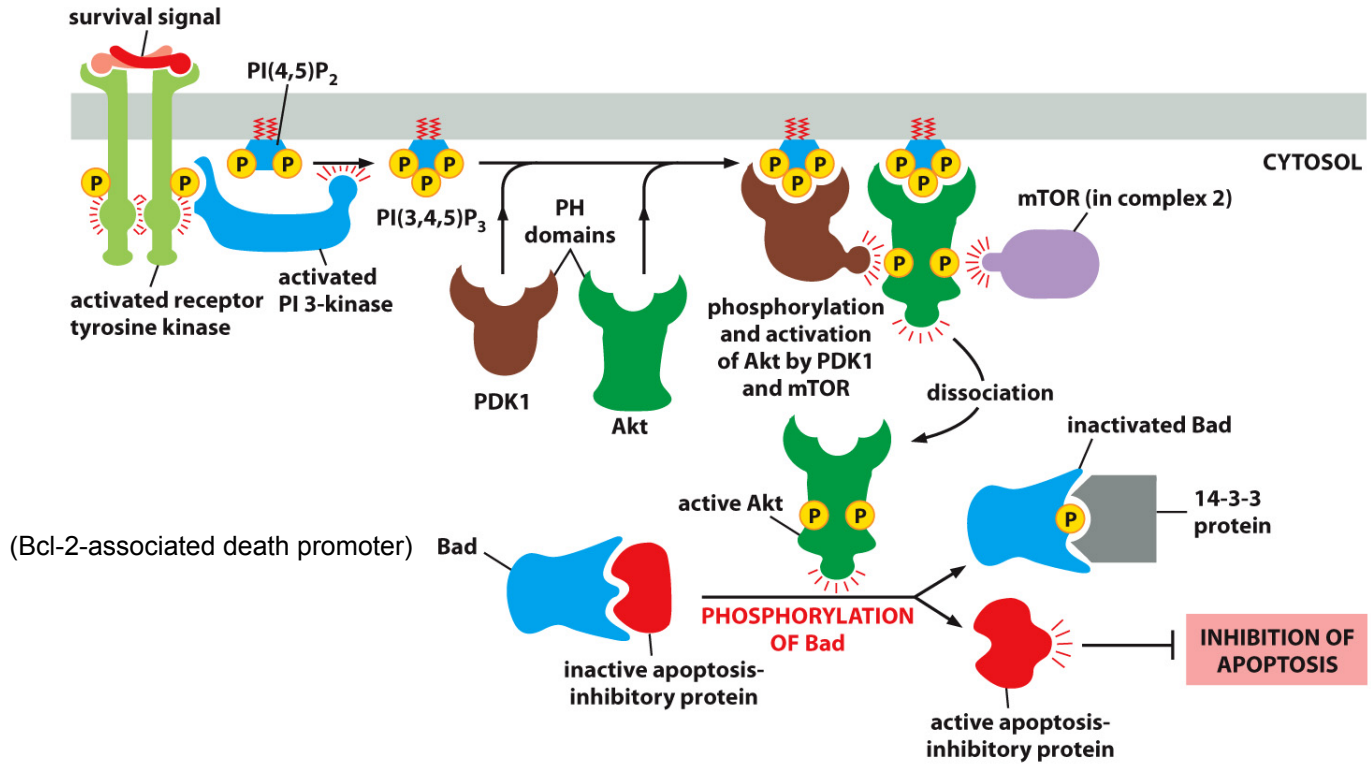
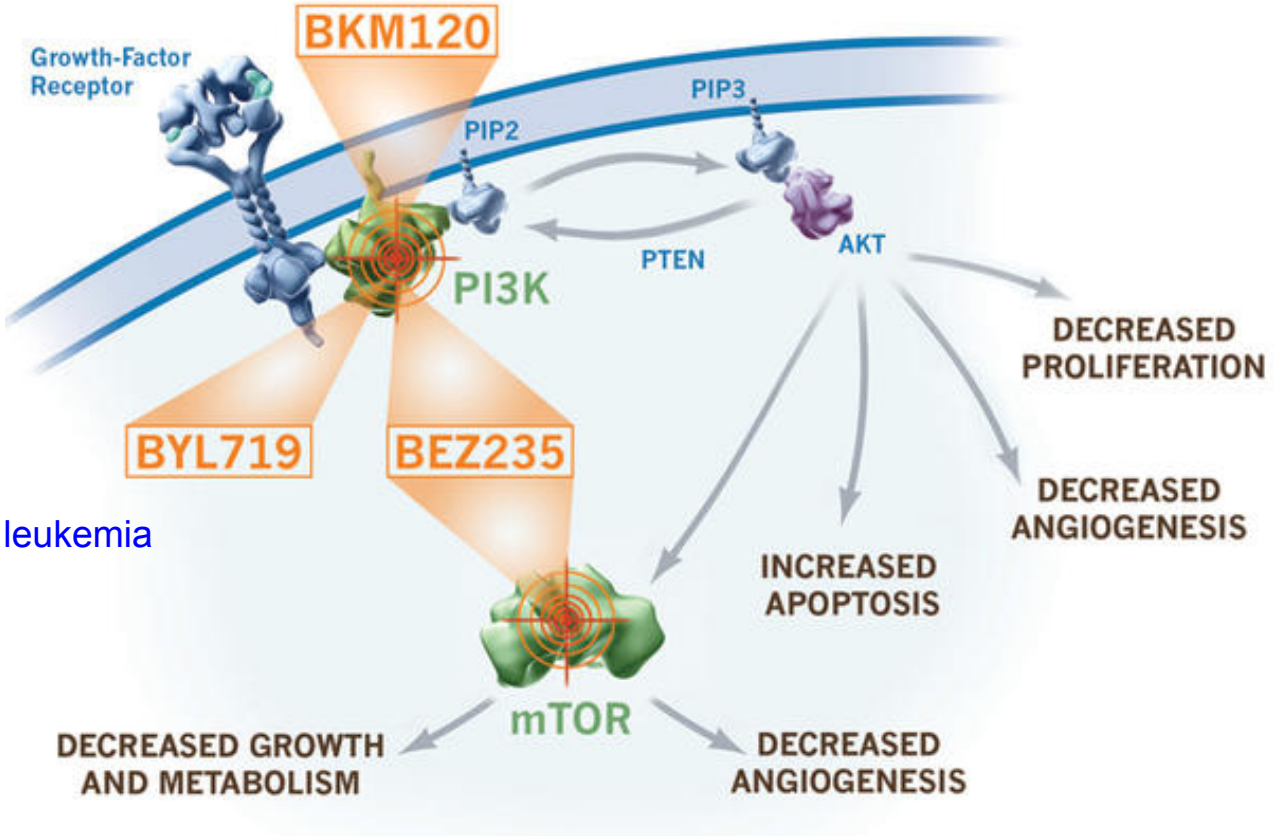


Figure 15-53 Molecular Biology of the Cell 6e (© Garland Science 2015)

Targeting PI3K in lung and breast cancers



Idelalisib (Zydelig)
P110δ inhibitor
chronic lymphocytic leukemia

http://www.dddmag.com/articles/2012/06/targeting-pi3k-key-survival-gene-solid-tumor-cancers