SEASON 2

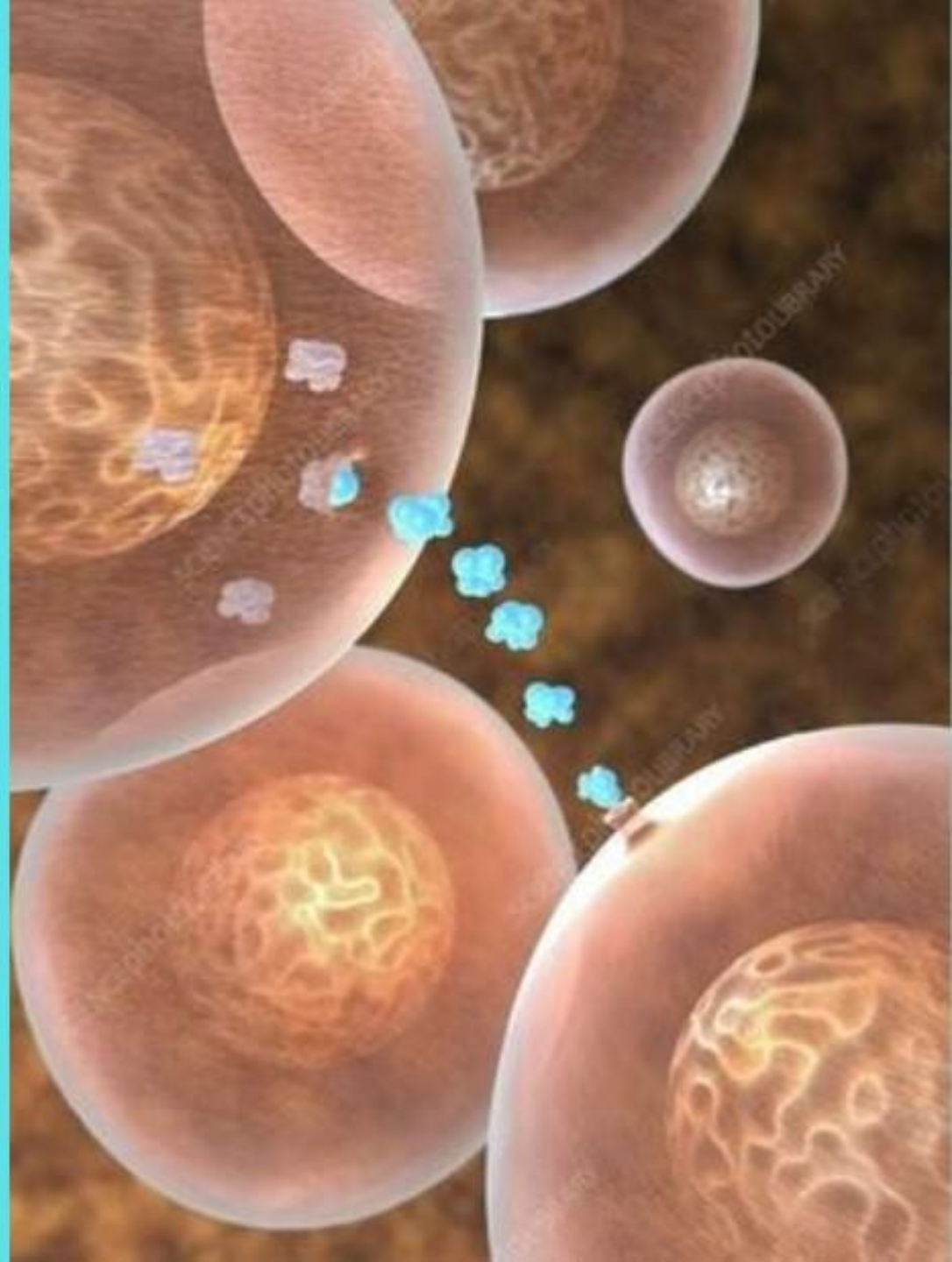
Understanding Cancer

Lecture 8

Types of signalling pathway: normal and dysregulated PI3K-AKT-mTOR

DR HAFSA WASEELA ABBAS

www.hafsaabbas.com



RECAP:

What you hopefully should understand so far from Lecture 7

- **The EGF ligand binds with EGFR receptor. This leads to dimerization of the receptor and autophosphorylation of the cytoplasmic domains.**
- **There are 7 effector proteins activated in signal transduction:**
  GRB2 → Sos → Ras → Raf-1
  This begins a protein kinase cascade with MEK→ERK 1/2 → MAPK.
- **Overexpression of genes/increased gene amplification and mutated proteins of the ligand, receptor, adaptors and effectors are implicated in various cancers.**
- **Cross-talk between GPCR and EGFR targets is via the members of the RAS family of proteins Rap-1 and 2 which are targets of PKA.**
  One of cAMP targets, Epac also stimulates Rap-1

What will we learn today?

- *The structure of Phosphatidylinositol 3-Kinases (PI3Ks)*
- *The structure of AKT*
- *The structure of mTOR*
- *Types of mTORs*
- *How is mTOR regulated?*
- *Normal PI3K/Akt/mTOR signalling pathway: Receptor activation*
- *Normal PI3K/Akt/mTOR signalling pathway: Signal transduction*
- *Normal PI3K/Akt/mTOR signalling pathway: Cellular response*
- *The link between EGFR and PI3K/Akt/mTOR signalling pathways*
- *Causes of dysregulated PI3K/Akt/mTOR signalling pathway in cancer*

GENTLE REMINDER
An ideal way of learning:

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday

Mini-lectures.

Approximate total time: 1 hour

Divide over 7 days at your **own pace**.

Challenge yourself with a quiz!

HN

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RECAP: How to support your learning?

- **Key facts with diagrams by HN designs presented in a simplified way.**
- **Glossary to help understand what key words mean.**
- **Summary doodle revision posters by HN designs.**
- **Quizzes to test your knowledge and reflect.**
- **Reference list for further reading.**

Acknowledgements: Special thanks to my parents, family, friends and colleagues for their support and the respected teachers and health professions who taught me and installed the passion of cancer/oncology.

The structure of Phosphatidylinositol 3-Kinases (PI3Ks)

The structure of Phosphatidylinositol 3-Kinases (PI3Ks)

There are **eight mammalian Phosphatidylinositol 3-Kinases (PI3Ks) enzymes**.

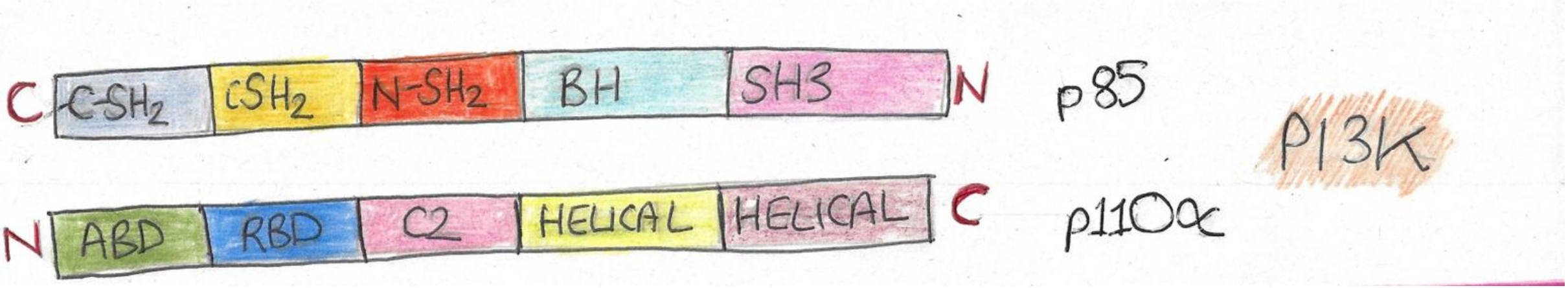
They are heterodimers with two subunits:

Catalytic p110

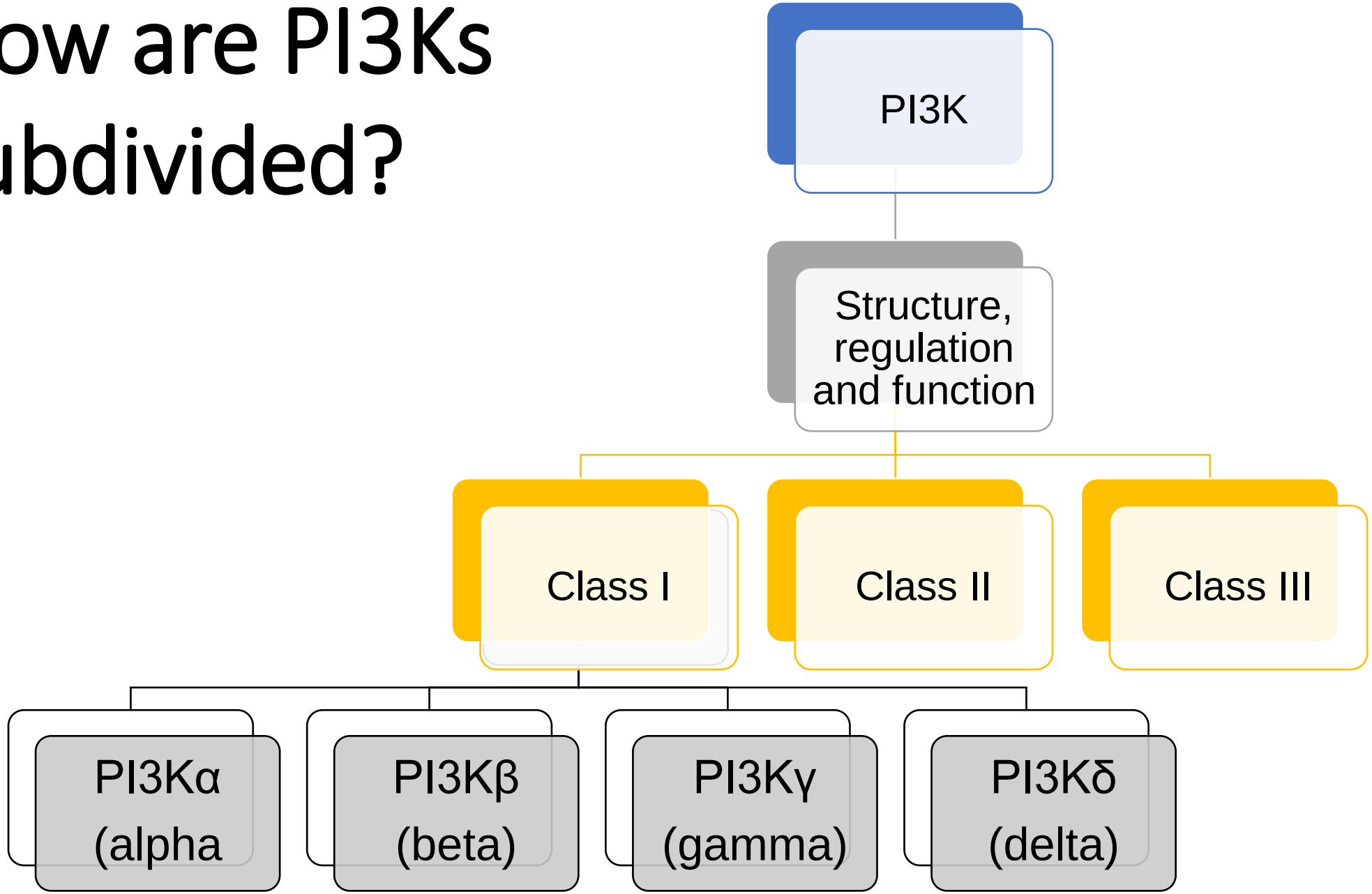
Regulatory p85

The structure of Phosphatidylinositol 3-Kinases (PI3Ks)

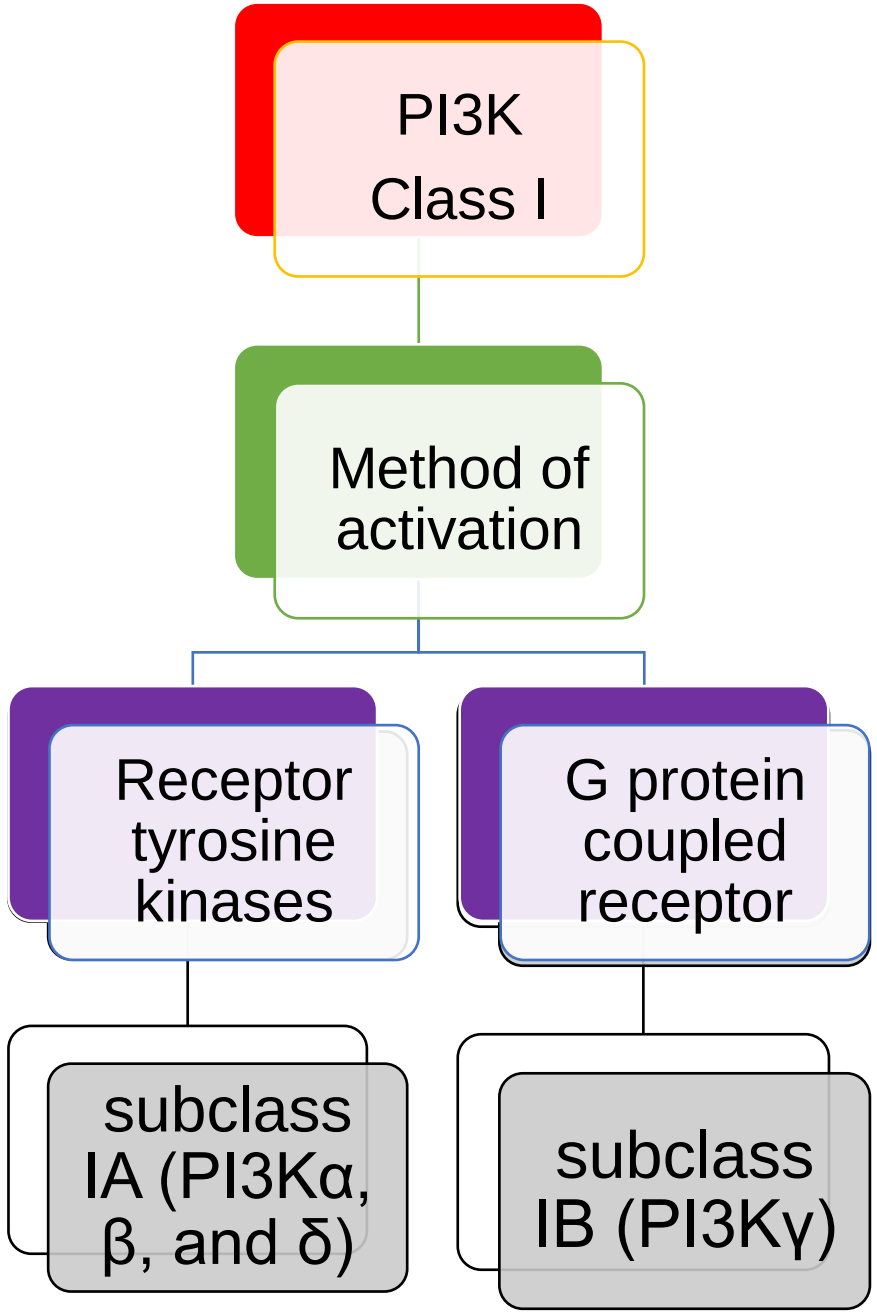
Name of domain	Sub-domain
p110	Adaptor binding domain (ABD)
	Ras-binding domain (RBD)
	C2
	Helical
	Catalytic kinase (CAT)
p85	N-terminal
	SH3
	Rho-GAP
	nSH2
	iSH2
	cSH2


C
C-SH2
cSH2
N-SH2
BH
SH3
N
p85
N
ABD
RBD
C2
HELICAL
HELICAL
C
p110α
PI3K

How are PI3Ks subdivided?

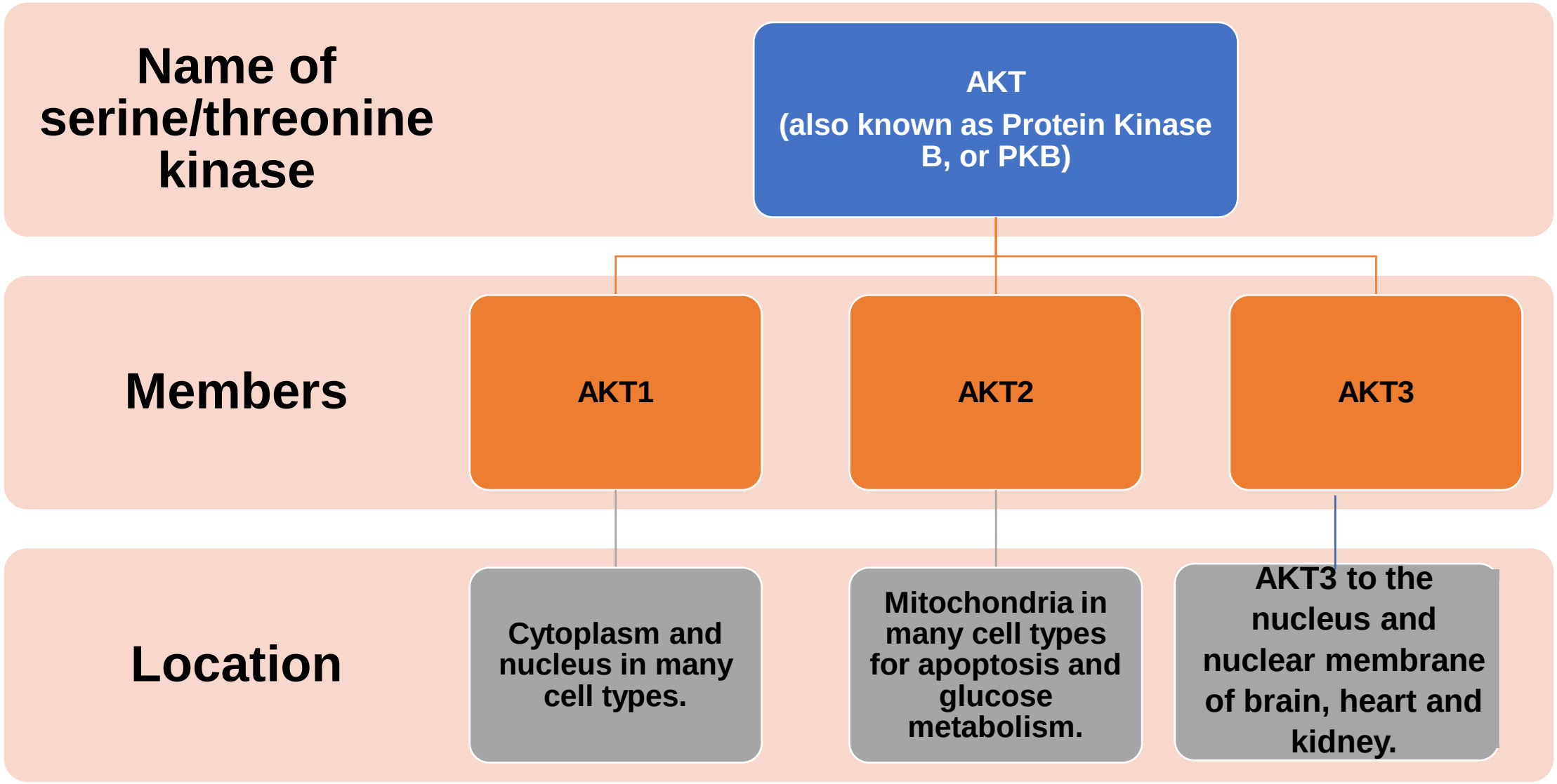


How are PI3Ks subdivided?



The structure of AKT

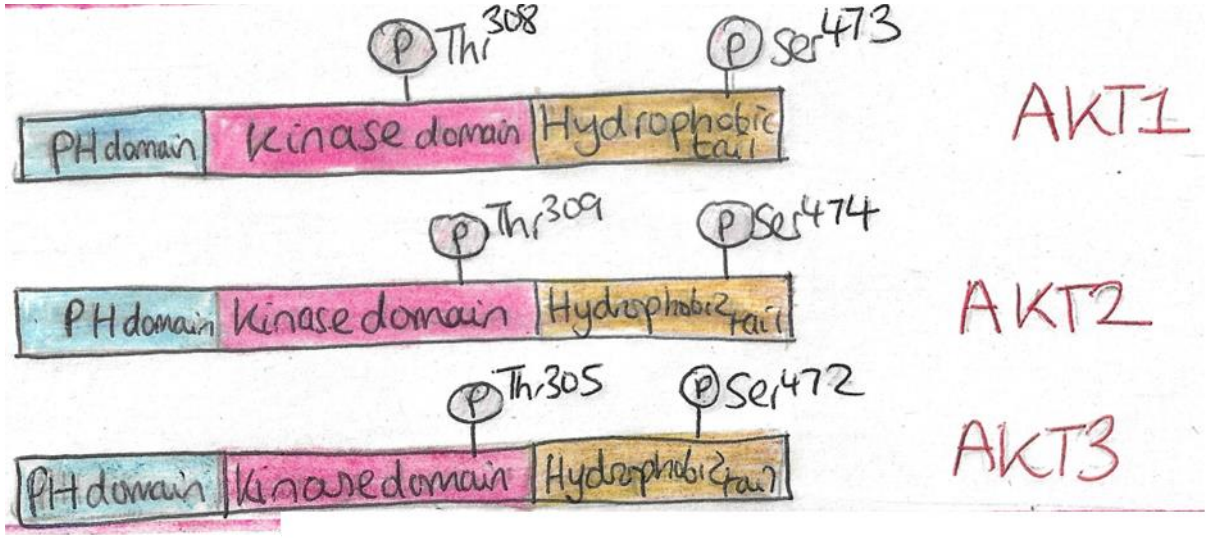
The structure of AKT



The structure of AKT

There are three member of AKT:

AKT1, AKT2 and AKT3



Each type of AKT has:

- **N-terminal pleckstrin homology (PH) domain.**
- **Central kinase catalytic (CAT) domain**
- **C-terminal extension (EXT)** containing a **regulatory hydrophobic motif (HM).**

AKT2 have 81% amino acid homology to AKT1.

AKT3 have 83% amino acid homology to AKT1.

There is a linker region (LINK) between PH and CAT that have no homology to other protein kinases.

The structure of mTOR

The mTOR

mTOR (the mammalian target of rapamycin) is an important AKT target. It is also known as:

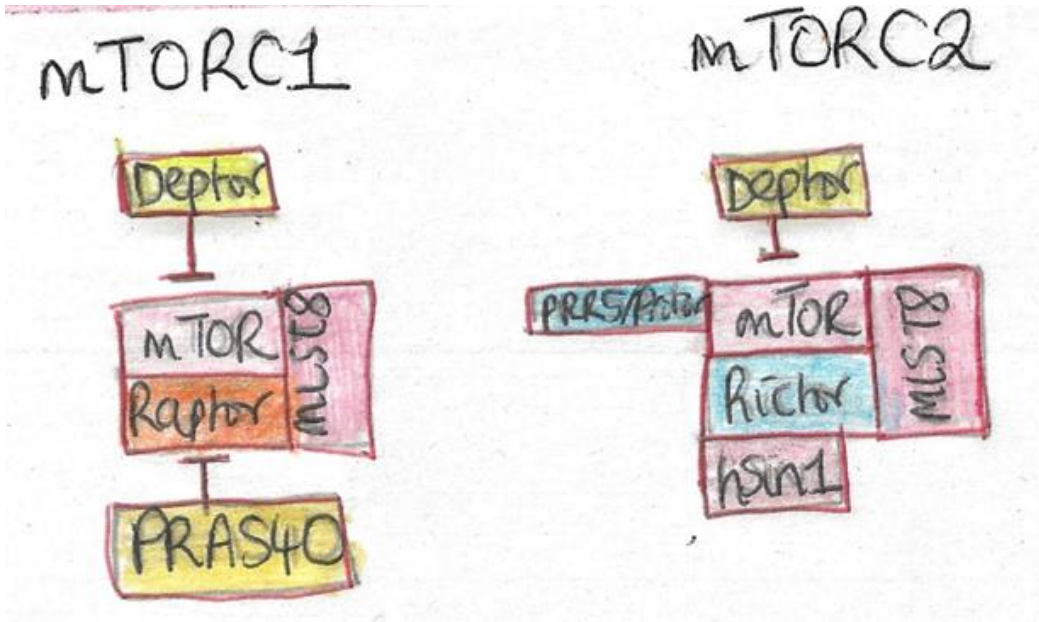
- FRAP (FKBP12-rapamcyin-associated protein)
- RAFT1 (rapamycin and FKBP12 target)
- RAPT 1 (rapamycin target 1)
- SEP (sirolimus effector protein)

The structure of mTOR

mTOR is a **289 kDa serine/threonine kinase**.

It belongs to the **PI3K-related protein kinase (PIKKs) family** and the **C-terminus has a high percentage of being similar to the catalytic domain of PI3K**.

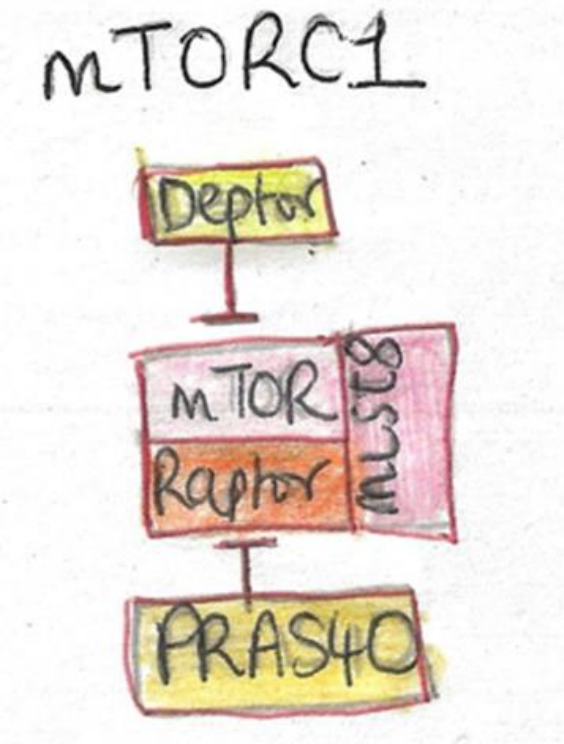
There are **two types of mTOR: 1 and 2.**



Types of mTORs

Structure of mTOR1

The mTORC1 **(mammalian target of rapamycin complex 1 or mechanistic target of rapamycin complex 1)** consists of:



- ***mTOR***
- ***Raptor:*** **Regulates mTOR activity** via **phosphorylation** and **facilitate the recruitment of substrates for mTORC1**.
- ***mLST8:*** It **binds to kinase domain of mTOR** to **maintain interaction between raptor and mTOR.**
- ***PRAS40 and DEPTOR: Negatively regulate mTORC1 activty***

Structure of mTOR2

The mTORC2 **(mammalian target of rapamycin complex 1 or mechanistic target of rapamycin complex 2).** It consists of:

- ***mTOR***
- ***Rictor:*** A **protein associated with mTOR.**
- ***mLST8:*** It **binds to kinase domain of mTOR** and **forms a complex between two mTOR.**
- ***mSin1:*** It **facilitates mTOR activity to phosphorylate AKT**.
- ***Protor-1 (protein observed with rictor-1):*** It **interacts with rictor.**
- ***Hsp70*** **heat shock protein** under **standard conditions and after heat shock effect** to form **mTORC2 and maintain kinase activity**.
- ***DEPTOR***: It **negatively regulates mTORC1 and mTORC2**.

It phosphorylates AKT at serine residues (Ser473) and other kinases.

Regulatory function of mTORC1	Regulatory function of mTORC2
Growth factors	Growth factors
Cellular metabolism ornithine decarboxylase), glycogen synthase	Cell adhesion to extracellular matrix e.g. paxillin (focal adhesion-associated adaptor protein)
Cell growth e.g. STAT3 (signal transducer and activator of transcription 3) and Protein kinase C-δ (PKCδ) PP2A (protein phosphatase 2A). Growth is negatively regulated by p21Cip1 and p27Kip1 cyclin-dependent kinase inhibitors. Rb (retinoblastoma) protein is a tumour suppressor that normally helps to regulate cell cycle progression and differentiation.	GTPases Rac and Rho cell involved in cell survival, migration and regulation of the actin cytoskeleton. Protein kinase C-α negatively regulates cell cycle progression in some cells but most cells there is proliferation and differentiation
Cellular stress e.g. HIF-1 α (hypoxia-inducible factor 1α).	PKC alpha e.g. inflammation.
Protein synthesis e.g. translation in ribosomes. It negatively regulated by eEF2 (eukaryotic elongation factor 2) kinase	
Cell death e.g. autophagy and apoptosis (Protein kinase C-δ PKCδ and protein kinase C-ε)	Cell death e.g. apoptosis (Protein kinase C-α)
Lipid synthesis e.g. lipin	
Production of nucleotides	
Cell migration cytoplasm linker protein-170	Motility e.g. Protein kinase C-α

How is mTOR regulated?

How is mTOR regulated?

POSITIVE

PI3K/AKT

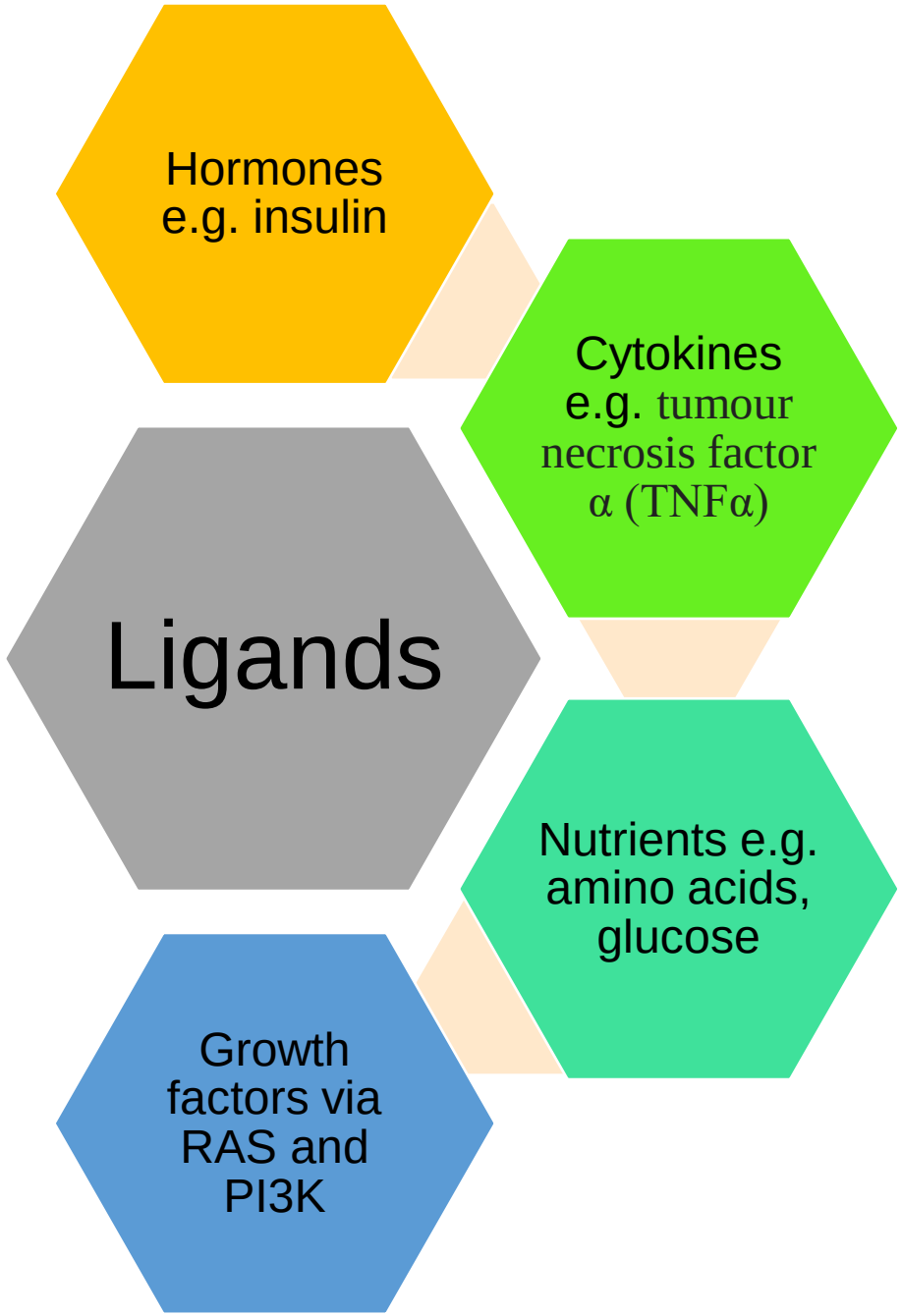
- **AKT inhibits TSC complex on mTORC1 to increase activity.**

NEGATIVE

TSC complex

- **The complex consists of TSC1, TSC2 and TBC1D7 proteins.**
- **Liver kinase B1 (LKB1) phosphorylates AMP-activated protein kinase (AMPK).**
- **AMPK phosphorylates TSC2 protein.**

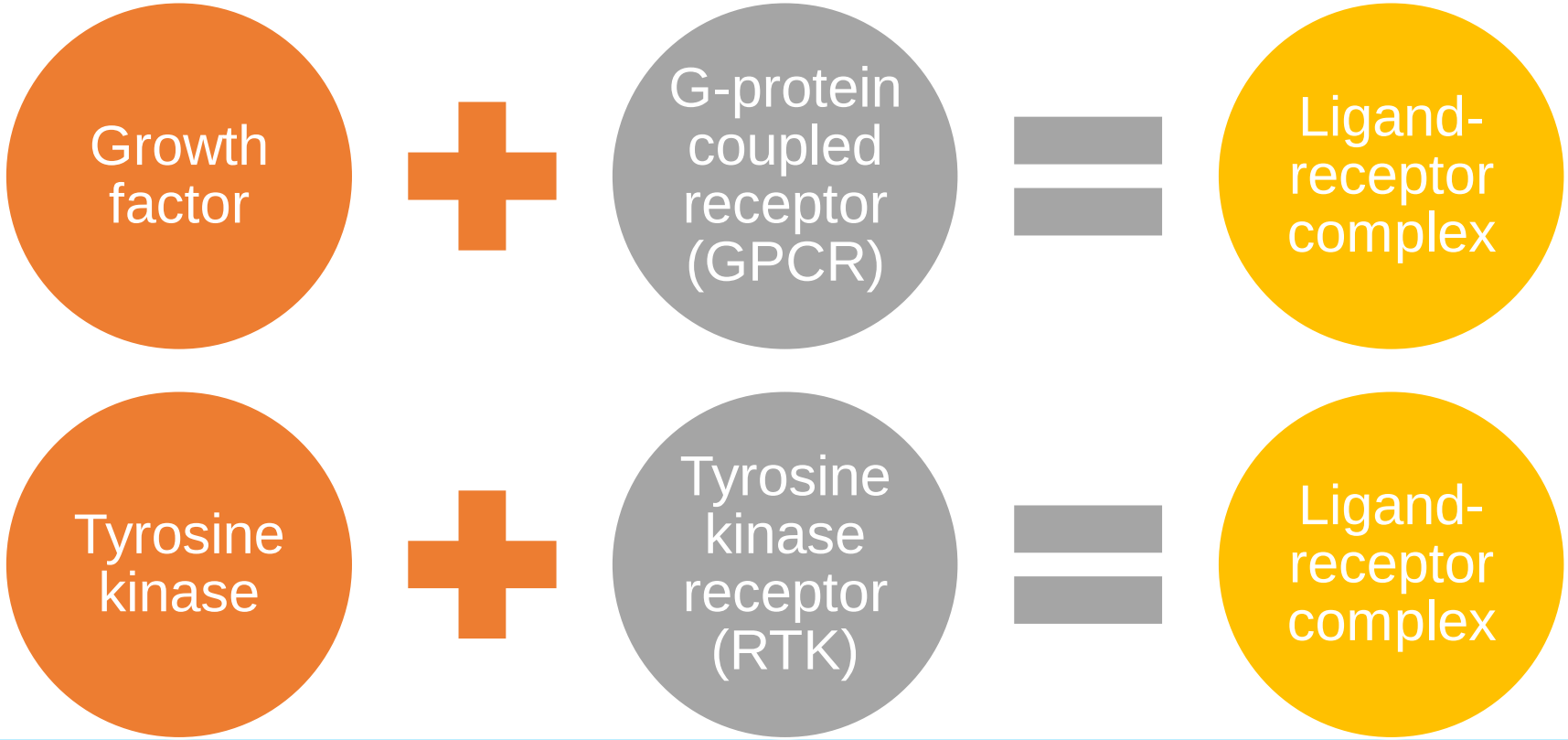
Normal PI3K/Akt/mTOR signalling pathway:
Receptor activation

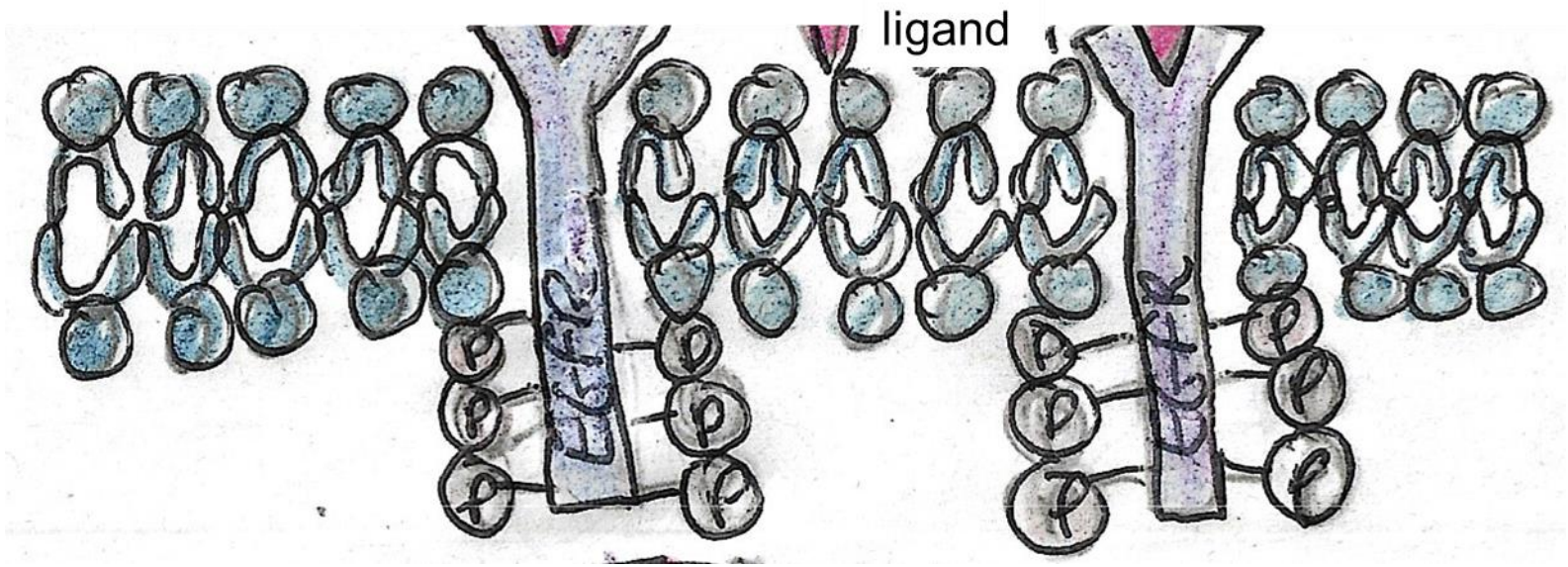

Hormones e.g. insulin
Cytokines e.g. tumour necrosis factor α (TNFα)
Ligands
Nutrients e.g. amino acids, glucose
Growth factors via RAS and PI3K

Normal PI3K/Akt/mTOR signalling: Receptor activation

Step 1.

The **ligand binds to its specific receptor.**




ligand
EGFR
EGFR
P
P
P
P
P
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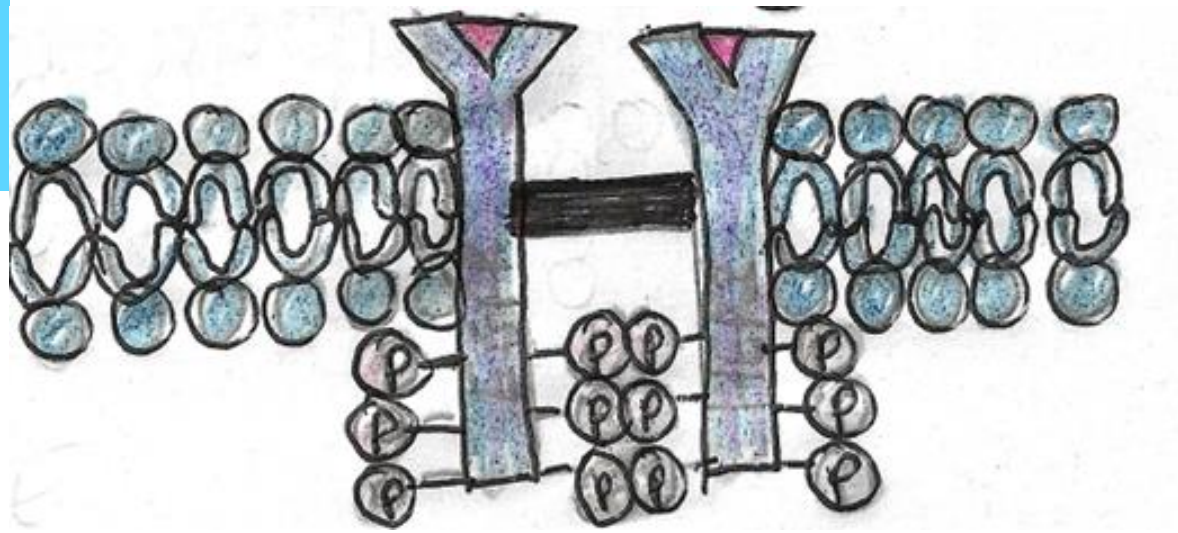
P
P

Normal PI3K/Akt/mTOR signalling: Receptor activation

Step 2.

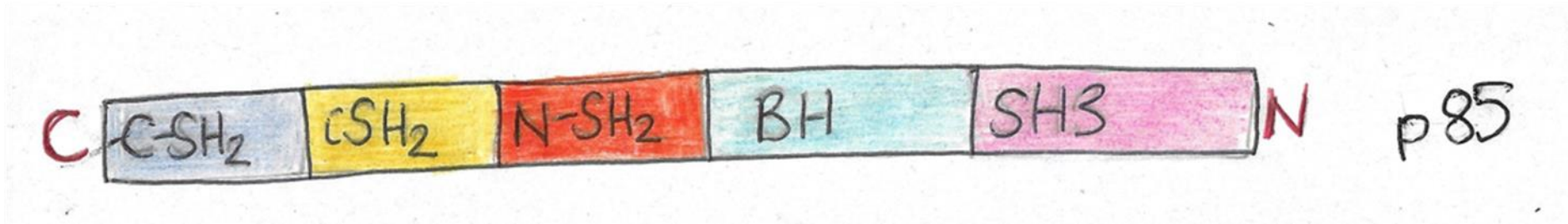
Dimerization of the receptor.



Normal PI3K/Akt/mTOR signalling: Receptor activation

Step 3.

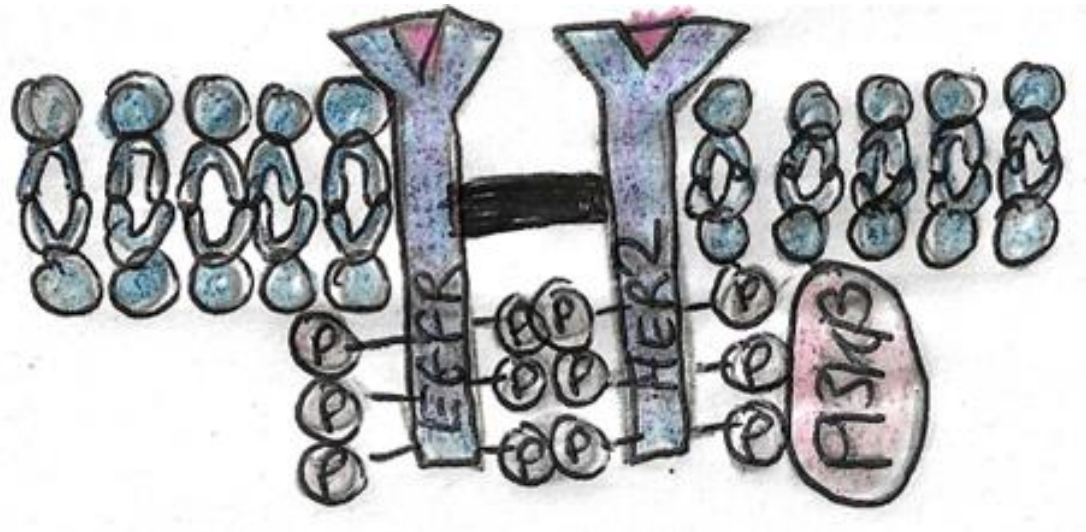
The **regulatory p85 subunit of PI3K binds to the receptor.**



Normal PI3K/Akt/mTOR signalling: Receptor activation

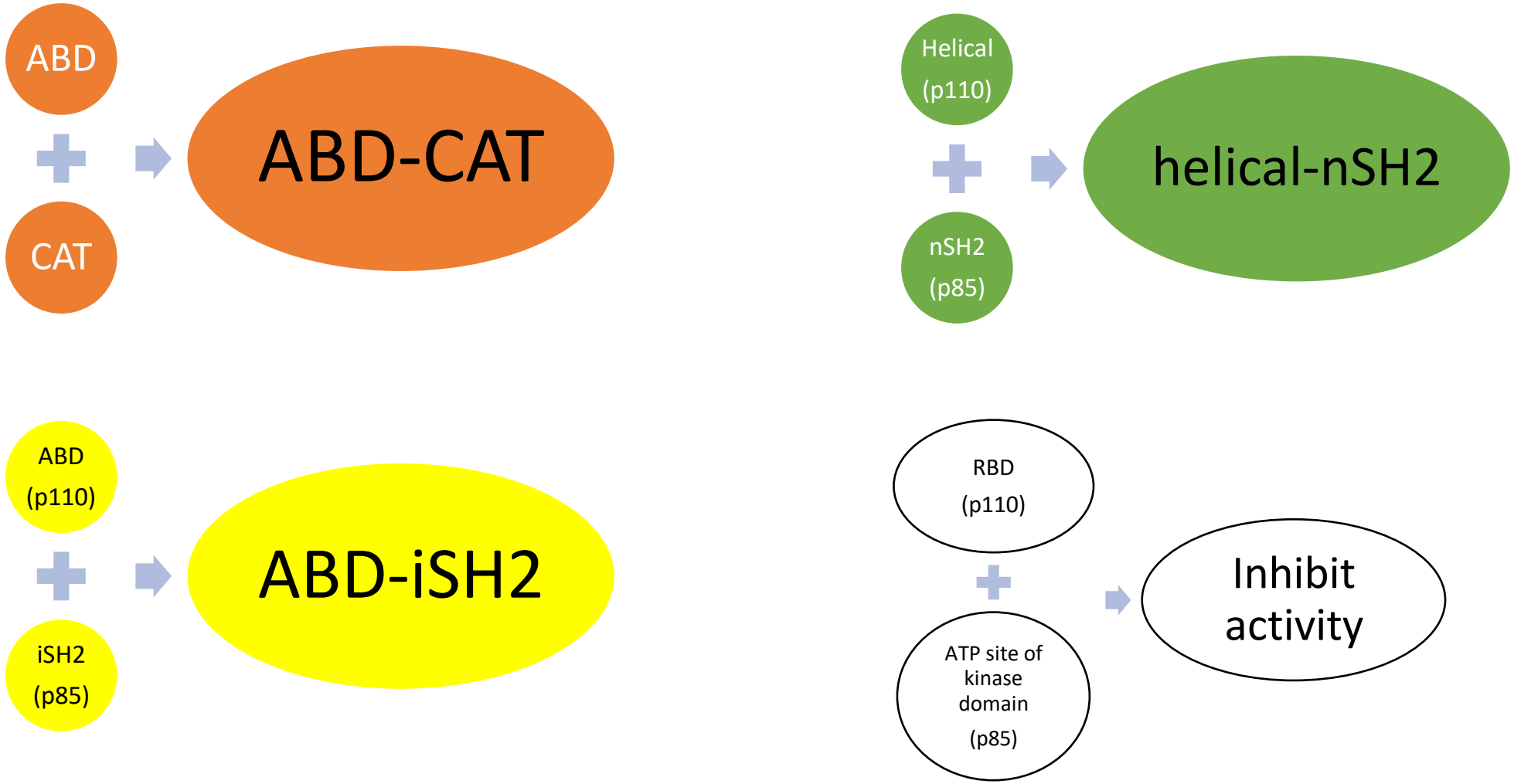
Step 4.

Phosphorylation of PI3 takes place.



Under the basal state:

Interactions between 4 domains of p110 and p85 takes place



Normal PI3K/Akt/mTOR signalling pathway:
Signal Transduction

Normal PI3K/Akt/mTOR signalling: Signal transduction

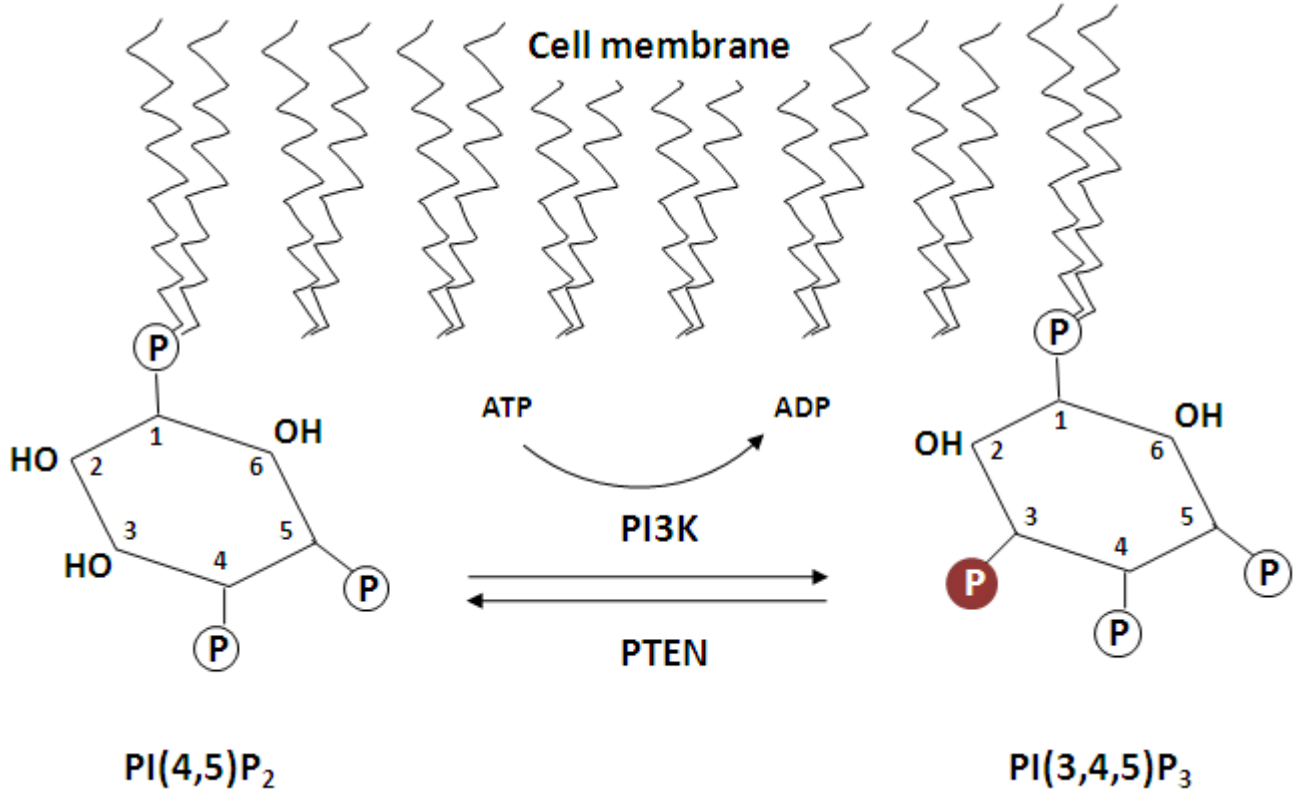
Step 5.

p110 subunit of catalytic domain of Phosphorylated PI3K

Class I produces **the second messenger Phosphatidylinositol (3,4,5)-trisphosphate (**PIP_3**)** otherwise known as **PtdIns(3,4,5)P3.**

PI3K phosphorylates the 3-OH group of the **membrane lipid phosphatidylinositol-4,5-bisphosphate (PIP_2)** to **generate phosphatidylinositol-3,4,5-triphosphate (PIP_3) .**

PI3K also indirectly stimulates the production of PIP_2.

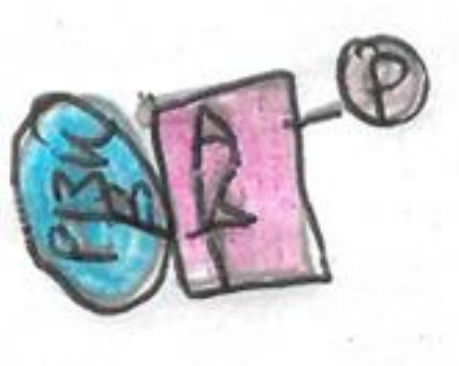


(Gribben and Joel 2013)

Normal PI3K/Akt/mTOR signalling: Signal Transduction

Step 6.

The **serine/threonine kinase AKT is translocated to the plasma membrane.**



Normal PI3K/Akt/mTOR signalling: Signal Transduction

Step 7

AKT is phosphorylated by **two enzymes**

to initiate activity:

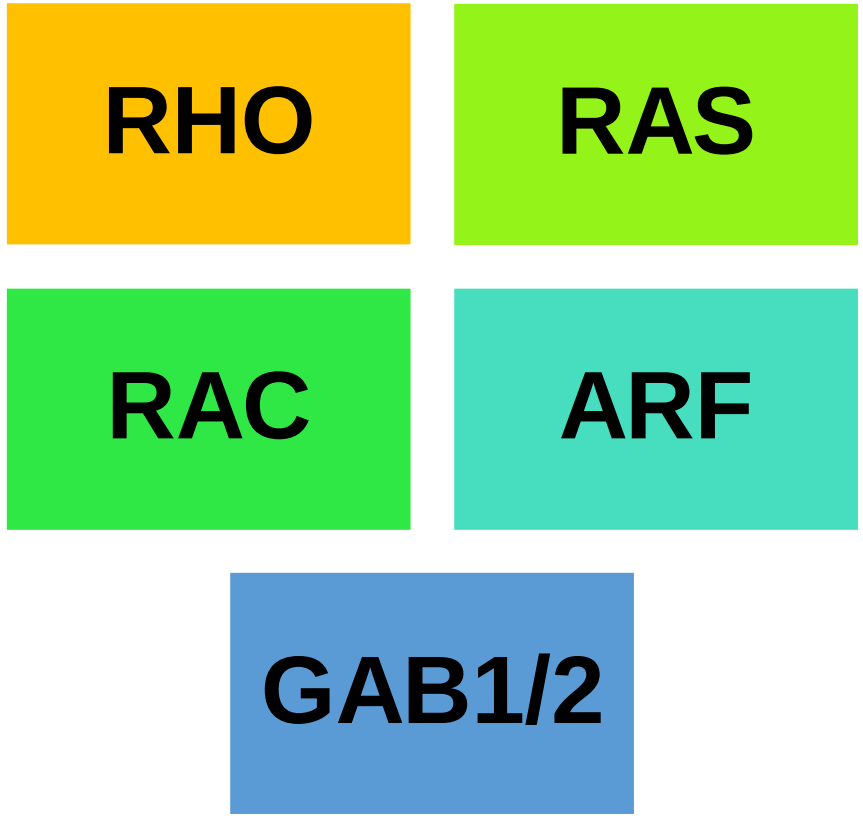
PDK1 **at Threonine 308 position on the kinase domain.**

Active PDK1 is autophosphorylated at S241 position.

mTORC2 at Serine 473 position in the tail domain

Other PI3K targets

All effector proteins have PH domains.



Negative regulation of AKT

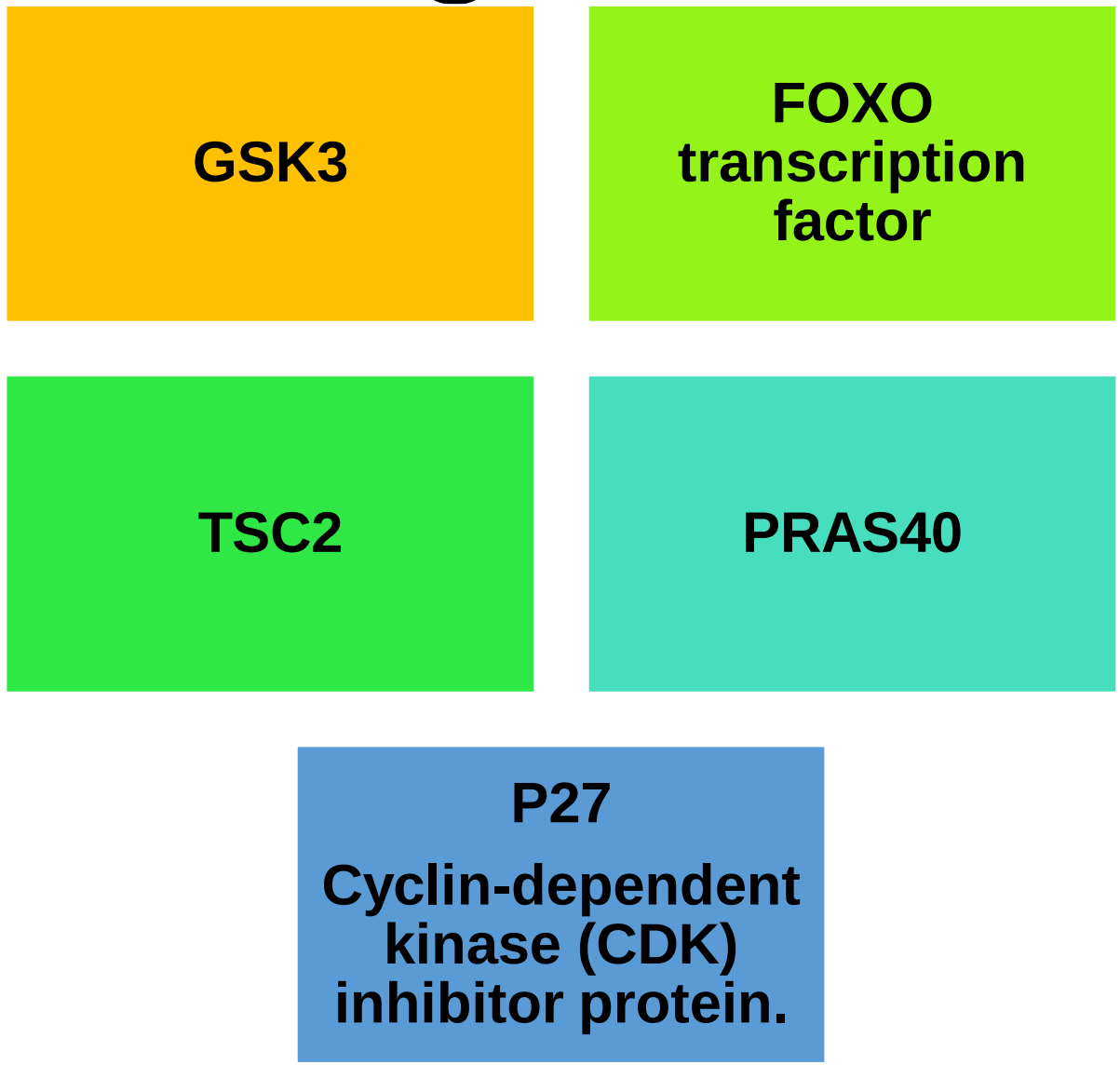
Phosphatase and tensin homolog(PTEN)

- **It converts PIP_3 to PIP_2.**
- **This prevents the translocation of AKT to the cell membrane.**

PH domain leucine-rich repeat protein phosphatase (PHLPP)

- **PP2A dephosphorylates AKT at positions S473 and T308.**

Downstream targets of AKT



Downstream targets of AKT

TSC2

The phosphorylation of TSC2 prevents TS1/TS2 complex.

The GTPase, Rheb binds to GTP.

This activates mTORC1 at position Serine 2448.

mTOR inhibits the protein 4E-BP.

4E-BP normally inhibits translation.

Its inhibition promotes the translation of Cyclin D1 that help with G1 phase with cdk4/6 activity.

CDK4/6 can also phosphorylate retinoblastoma (RB) protein which releases E2F transcription factor.

E2F is involved in the transcription of cyclin E that help with G1/S phase with cdk2.

Downstream targets of AKT

PRAS40

Step 1	Step 2	Step 3
PRAS40 negatively regulates mTORC1	AKT phosphorylates the inhibition of PRAS40	This is facilitated by Rheb protein

Downstream targets of AKT

GSK-3β

It is an enzyme that negatively regulates CYCLIN D1.

It degrades CYCLIN D1.

Downstream targets of AKT

FOXO

- **It is a transcription factor that negatively regulates CYCLIN D1.**
- **FOXO can repress CYCLIN D1 gene transcription.**
- **FOXO3 can increase apoptosis by stimulate expression of pro-apoptotic genes of Bcl-2 family.**
- **FOXO3 can increase expression of death receptors e.g. FAS ligand and tumour necrosis factor-related apoptosis-inducing ligand(TRAIL)**

Downstream targets of AKT

p27Kip1

A **CDK inhibitor protein that prevents CYCLIN D-CDK4/6 activity.**

C-myc

ERK

MAPK

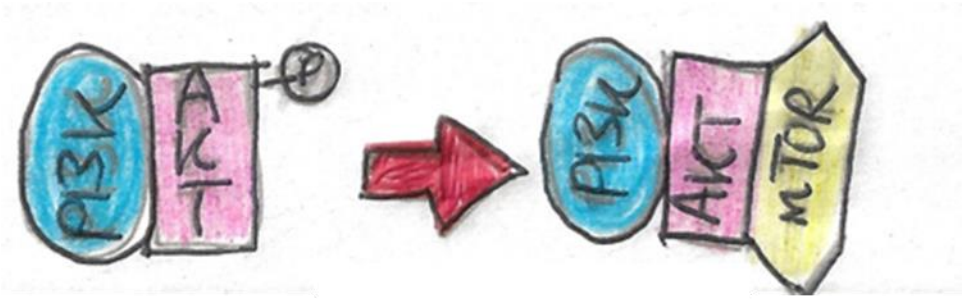
It can also **be phosphorylated by:**

Other cdk inhibitors are: p21CIP1/WAF1

Normal PI3K/Akt/mTOR signalling: Signal Transduction

Step 8.

mTORC1 signalling cascade is **activated** by **phosphorylated AKT.**



Targets of mTORC1

There is an **interaction between Raptor of mTORC1** and a **TOR signalling (TOS) motif** found in **S6K and 4EBP.**

The TOS motif: a **five amino acid segment found** in:

- In the ***N* terminus of S6K1 (Phe-Asp-Ile-Asp-Leu).**
- In the ***C* terminus of 4E-BP1 (Phe-Glu-Met-Asp-Ile)**

Targets of mTORC1

S6K1

- It is phosphorylated at position Thr389 by mTORC1.
- Phosphorylated S6K1 phosphorylates S6 (40S ribosomal protein S6).
- This increases translation of mRNAS for target proteins with regulatory elements in the 5′-untranslated terminal regions (5′-UTR) in target genes: ribosomal, growth factors and protein hormones. E.g. c-myc, ornithine decarboxylase and cyclin D1
- Besides mTORC1, S6K1 can be phosphorylated by PDK1 and MAPK.

4EBP1

- mTORC1 negatively regulates translation.
- This is achieved by deactivating eIF4E (eukaryotic translation initiation factor 4E).
- eIF4E dissociates from 4EBP1.
- Unphosphorylated 4EBP1 binds to eIF4E to prevent translation.

p70S6K1

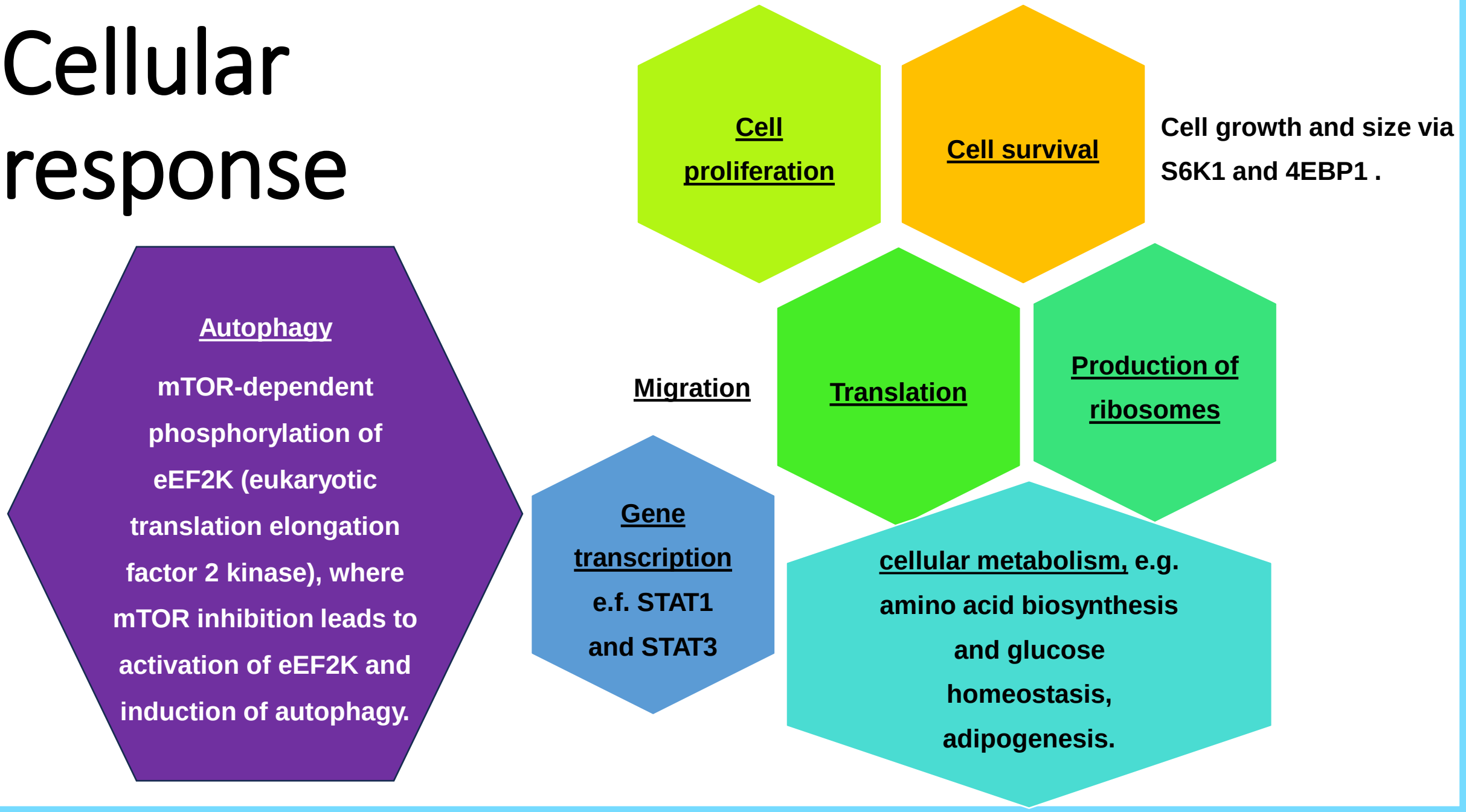
- Mtorc1 phosphorylates the serine/threonine kinase p70S6K1.

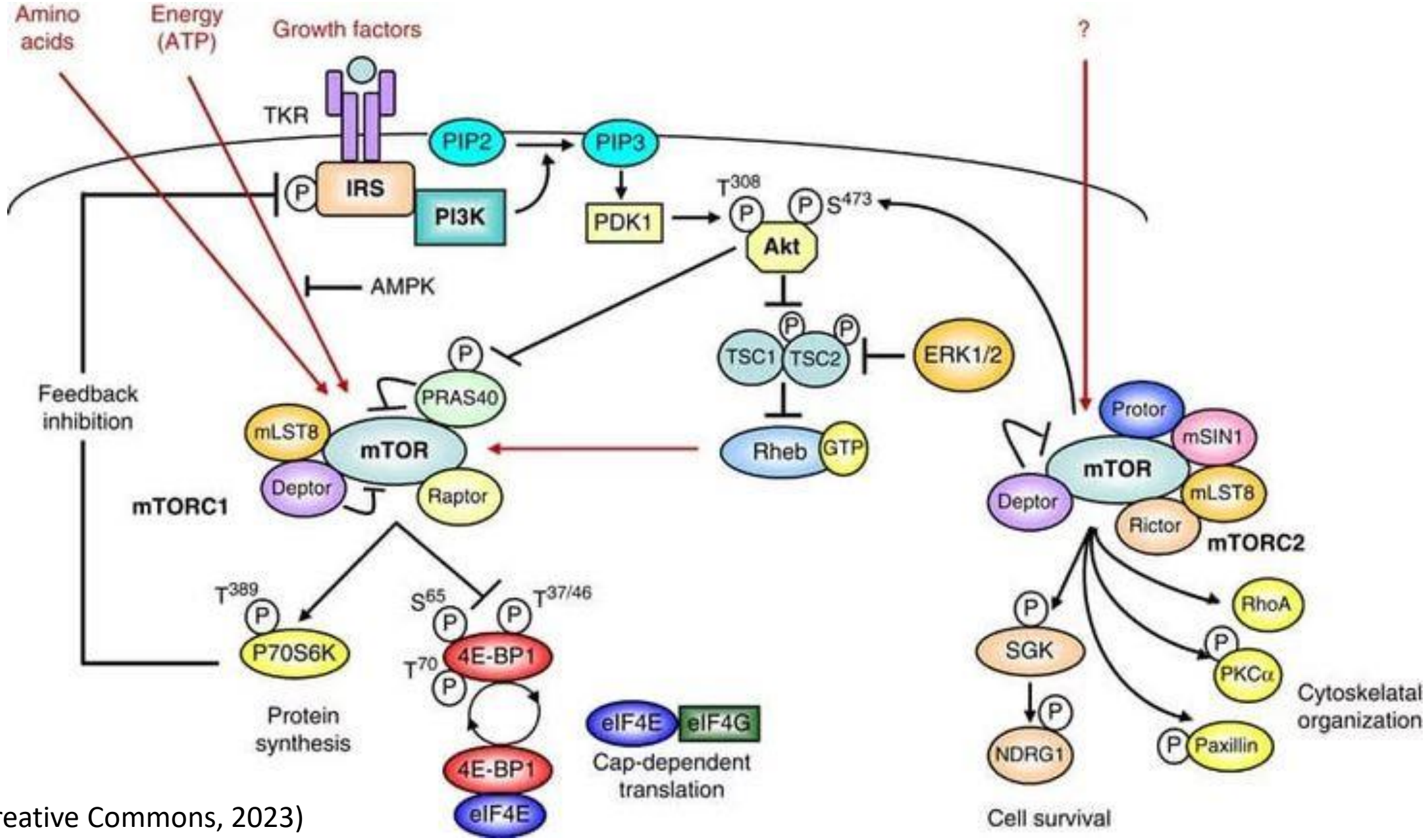
Targets of mTORC1

- **STAT1**
- **STAT3 (signal transducer and activator of transcription)**
- **Activate the nuclear receptor PPARγ.**

Normal PI3K/Akt/mTOR signalling pathway:
Cellular response

Cellular response





(Creative Commons, 2023)

The link between EGFR and PI3K

The link between EGFR and PI3K

Direct binding of PI3K with ERBB3 and ERBB4 via p85 SH2 domain of PI3K.

Indirect binding of PI3K with ERBB1 and ERRB2 via the adaptor protein GAB1. The GAB1 proline-rich domain binds with the GRB2 SH3 domain.

GAB1 is phosphorylated at Y446, Y472, and Y589 sites where p85 subunit of PI3K binds.

RAS can bind to PI3K by PI3K p110 subunit.

CBL can bind to the p85 of PI3K. This helps facilitate PI3K to the EGFR.

Dysregulated PI3K-Akt-mTOR pathway

Causes of dysregulation

The missense mutations in the PH domain of AKT1, E17 mutation increases the link of AKT and PIP3

Loss of the tumour suppress PTEN

Missense mutations e.g. deletions and overexpression of EGFR in various cancers e.g. HER-2 (human epidermal growth factor receptor 2) and IGFR (insulin-like growth factor receptor),

Overactivation of receptor tyrosine kinase

Inhibitors of AKT or mTOR increases expression and activity of growth factor receptors. This increases PI3K activity and RAS signalling

Amplification (20-fold) of AKT1

E542K and E545 mutations in the p110 subunit of PI3K increases activity

AKT and cancer.

This correlates with advanced stage of the disease and/or poor prognosis.

AKT1 mutations	• High levels found in bladder, ovarian, gastric and prostate cancer. 80% high grade carcinoma.
AKT2 mutations	• 30-40% in undifferentiated prostate, ovarian and breast cancer.
AKT3 mutations	• High levels found in Oestrogen receptor negative breast cancer and androgen- insensitive prostate cancer

Phosphorylated AKT and the hallmarks of cancer

Proliferation

Invasion

Metastasis

Angiogenesis

Evading apoptosis

Reprogramming of metabolism

AKT and evading apoptosis

Method 1

- **AKT phosphorylates FOXO to decrease expression of apoptotic genes.**

  Overexpression of AKT inhibits FOXO3 expression.

Method 2

- **AKT phosphorylate BAD ((Bcl-2-associated□agonist□of □cell□death) at position Serine 136 or 112.**

  The permeability of mitochondria is modified o prevent cytochrome-c release from mitochondria which prevents apoptosis

AKT and evading apoptosis

Method 3

To prevent caspase activity, AKT phosphorylates XIAP at position Serine 87.

AKT and invasion and metastasis

MMPs

- Matrix metalloproteinases (MMPs) are regulated by AKT.
- They are proteolytic enzymes that degrade extracellular matrix during invasion

4EBP1

- Translation of transcription factor proteins: Snail, Slug and Twist.This upregulates epithelial-mesenchyma transition (EMT)

p70S6K

- It promotes expression of MMP9 that mediate proteolytic activity in ovarian cancer.
- AKT expression knockdown affects mTOR. This downregulates mRNA of MMP2 and MMP9.

AKT and angiogenesis

Vascular Endothelial Growth Factor (VEGF)

- It activates Flk1/VEGFR2-PI3K-AKT pathway which increases angiogenesis and tumour survival

AKT and reprogramming of metabolism

Glucose metabolism

- AKT upregulates glucose transporters to increase glucose uptake.
- There are uptake of lipids, glutamine and nucleotides to facilitated proliferation of tumour cells.

mTOR and cancer

Inhibitors of mTOR

- **Increases expression and activity of growth factor receptors.**
- **This increases PI3K activity and RAS signalling.**
- **mTORC1 is sensitive to rapamycin. This activates S6K1 and 4EBP1 which facilitate translation of proteins.**
- **mTORC2 is resistant to rapamycin. This stimulates PKC-alpha and AKT which regulates actin cytoskeleton.**

Effector proteins of mTOR.

- **Overexpression of eIF4E, S6K1 and 4EBP1 causes cellular transformation.**

PI3K and cancer

P110-alpha catalytic subunit

- **The most mutated oncogene in cancers e.g. gastric, endometrial, ovarian, brain and blood cancers where it facilitates tumour progression, angiogenesis and metastasis.**

PIK3R1 or PIK3R2 regulatory subunit genes

- **Mutations increases PI3K activity.**

PTEN and cancer

PTEN (phosphatase and tensin homolog) is a tumour suppressor where its mutation and downregulation is found in prostate cancer, melanoma and non-small cell lung cancers.

By the end of this lecture, you should understand

- **Following activation of EGFR or TKR, PI3K is activated.**
- **PI3K consists of two subunits: p110-alpha catalytic subunit and p85 regulatory subunit.**
- **p110 subunit produces the second messenger Phosphatidylinositol (3,4,5)-trisphosphate (PIP_3).**
- **AKT is a serine-threonine kinase that is activated by PDK1 and mTORC2 effector protein.**
- **mTORC1 signalling cascade is activated by phosphorylated AKT.**
- **RAS can bind to PI3K by PI3K p110 subunit.**
- **Inhibitors of AKT or mTOR increases expression and activity of growth factor receptors. This increases PI3K activity and RAS signalling. This correlates with advanced stage of the disease and/or poor prognosis.**
- **Matrix metalloproteinases (MMPs) proteolytic enzymes are regulated by AKT.**

  AKT expression knockdown affects mTOR. This downregulates mRNA of MMP2 and MMP9.

  This effects invasion and metastasis

Reference list for further reading

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SEASON 2

Understanding Cancer

Lecture 9

Types of signalling pathway: normal and dysregulated PLC-γ1-PKC

DR HAFSA WASEELA ABBAS

www.hafsaabbas.com