HN

SEASON 2

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Understanding Cancer

Lecture 6

Types of signalling pathway: normal and dysregulated GPCR

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RECAP:

What you hopefully should understand so far from Lecture 5

- **The first messenger in the cell-signalling pathway is the ligand. The secondary messenger helps transduce the signal to elicit a response.**
- **Calcium ion channels are found in the mitochondria, endoplasmic reticulum and plasma membrane. It is regulated to maintain its low concentration in cells. It binds specifically to the calcium-binding protein Calmodulin.**
- **cAMP plays a key role in signal transduction pathway. It is activated by adenyl cyclase where it then binds to protein kinase A to activate more proteins in the signal cascade. cAMP is deactivated by phosphodiesterase.**
- **Diacylglerol (DAG) and Inositol triphosphate (IP_3) are secondary messengers that are involved in the phosphorylation of downstream targets and stimulate other secondary messengers e.g. calcium ions respectively.**
- **Transcription factors regulate the expression of genes which affects cellular response.**

What will we learn today?

- ***The structure of the G-protein coupled receptor (GPCR)***
- ***The subtypes of GPCR***
- ***Normal GPCR signalling pathway: Receptor activation***
- ***Normal GPCR signalling pathway: Signal transduction***
- ***Normal GPCR signalling pathway: Cellular response***
- ***Turning off GPCR signalling pathway***
- ***Causes of dysregulated GPCR signalling pathway***
- ***Examples of cancers caused by dysregulated GPCR signalling pathway***

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!

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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 the G-protein coupled receptor (GPCR)

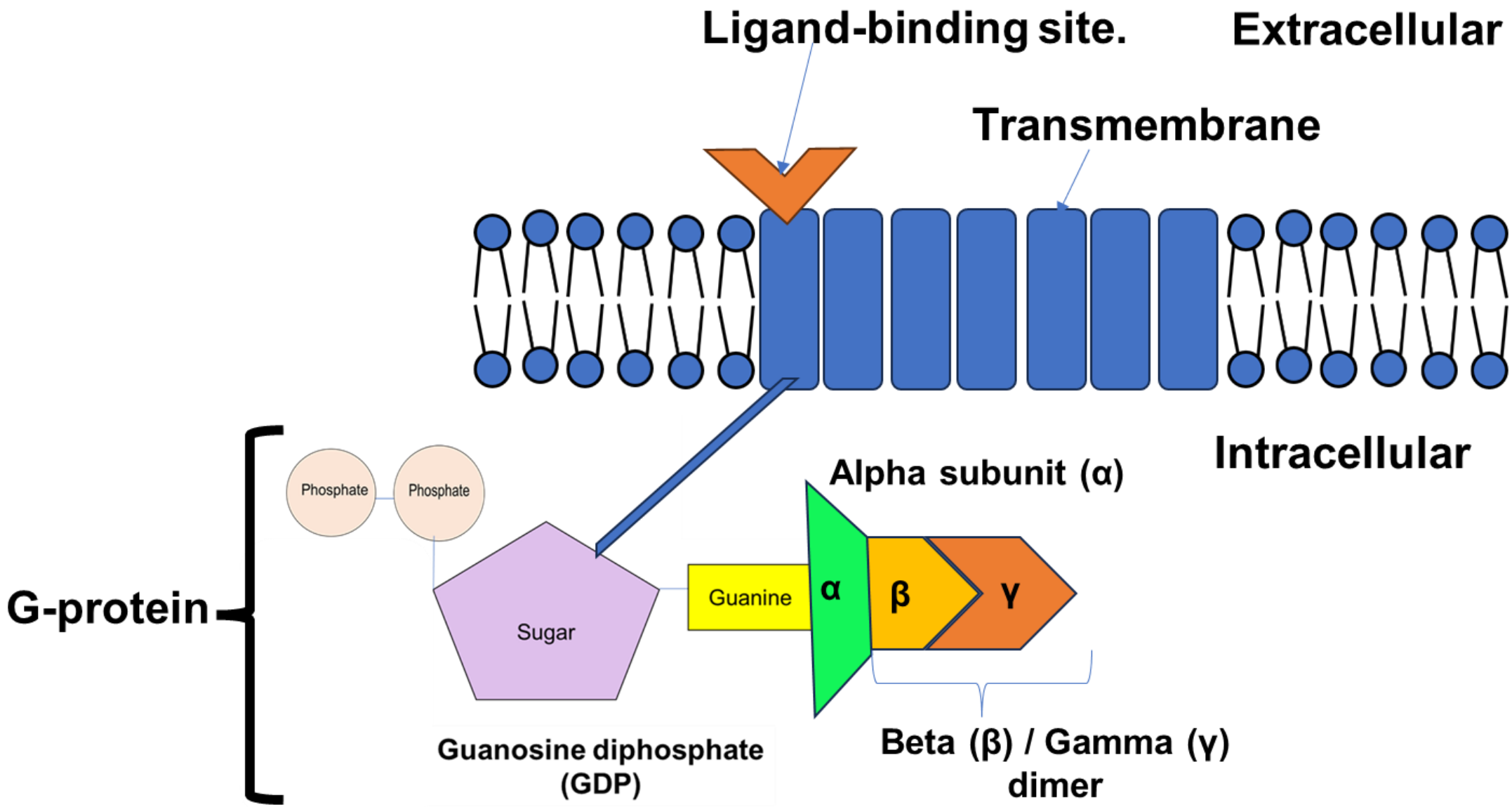
The structure of the G-protein coupled receptor (GPCR)

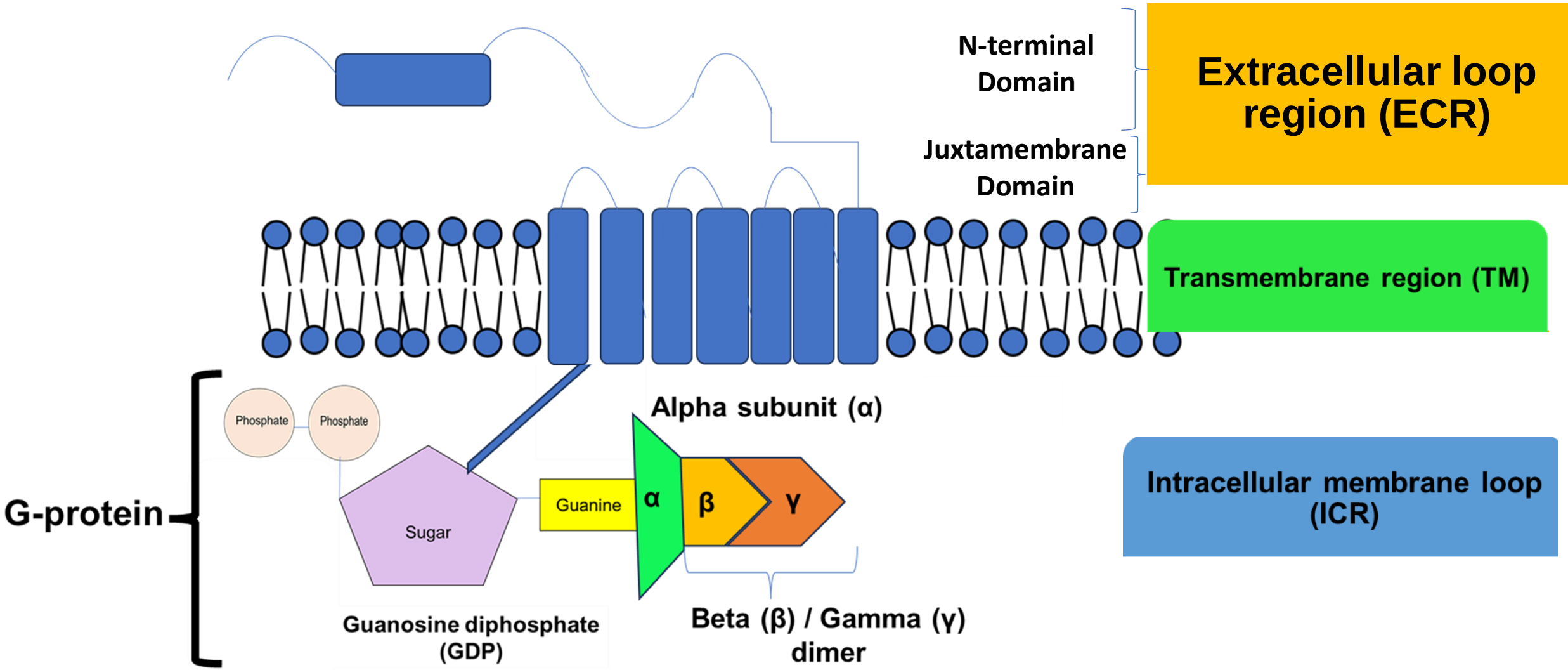
GPCRs are **helical transmembrane receptor proteins** found on the **cell surface.**

GPCR genes account for **5% of the human genome.**

The **cell surface receptor** is divided into three regions:

Extracellular loop region (ECR)	**This is where binding to specific ligand occurs**
Transmembrane region (TM)	**There are seven transmembrane proteins in the cell surface receptor.** **The shape of these proteins is helical and play an important role in how the intracellular and extracellular environments communicate. The conformational changes occurs here**
Intracellular membrane loop (ICR)	**It is where the signal transduction pathway occurs by interacting with intracellular proteins called G proteins.**


Ligand-binding site.
Extracellular
Transmembrane
Intracellular
Alpha subunit (α)
G-protein
Phosphate
Phosphate
Sugar
Guanine
α
β
γ
Guanosine diphosphate (GDP)
Beta (β) / Gamma (γ) dimer


N-terminal Domain
Juxtamembrane Domain
Extracellular loop region (ECR)
Transmembrane region (TM)
Intracellular membrane loop (ICR)
Alpha subunit (α)
G-protein
Phosphate
Phosphate
Sugar
Guanine
α
β
γ
Guanosine diphosphate (GDP)
Beta (β) / Gamma (γ) dimer

The subtypes of GPCR

The subtypes of GPCR

Most GPCRs contain **seven helices** and **three intracellular loops.**

Some members of the **rhodopsin family** may have **eight helices and four intracellular loops.**

Glutamate

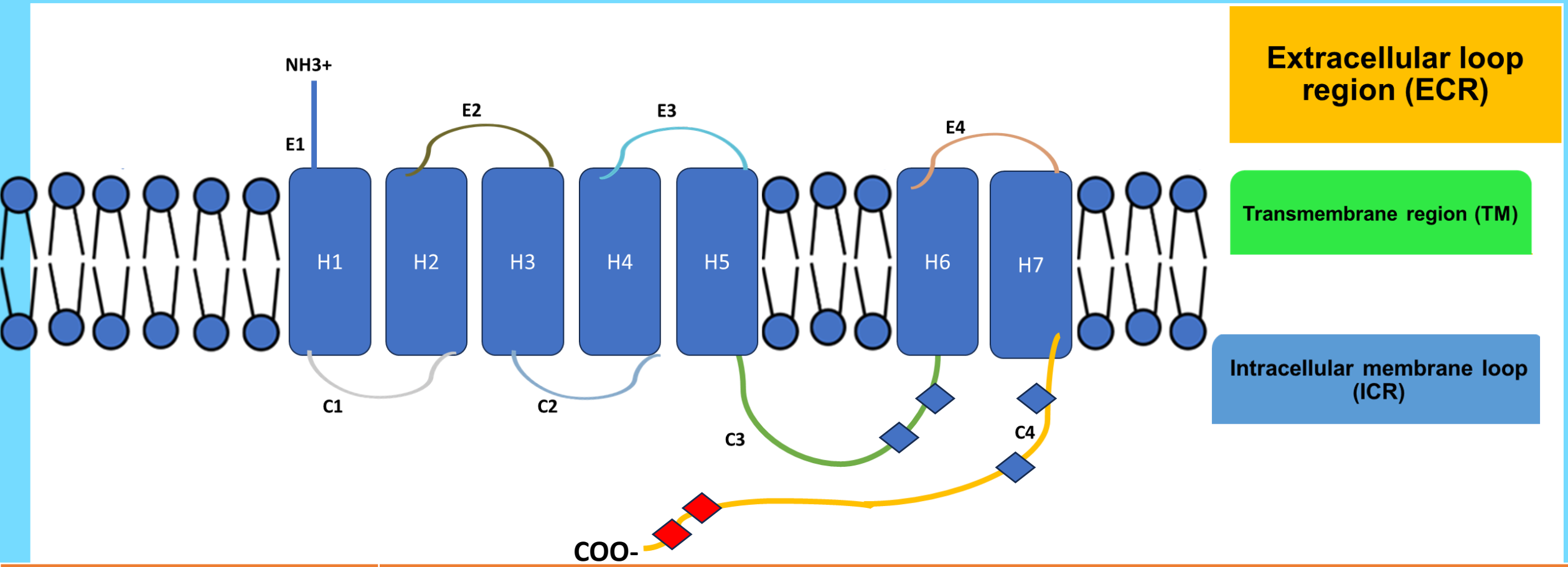
Adhesion

Secretin

Rhodopsin

Frizzled/taste2 .

Protease-activated receptors (PARs)



Name of loop segment	Role
C3	❑ Interacts with G-proteins ❑ Protein kinase A phosphorylation sites
C4	❑ G-protein coupled receptor kinase (GRK) phosphorylation sites. ❑ Protein kinase A phosphorylation sites ❑ Interacts with G-proteins
E4	❑ Messenger binding site.

Normal GPCR signalling pathway: Receptor activation

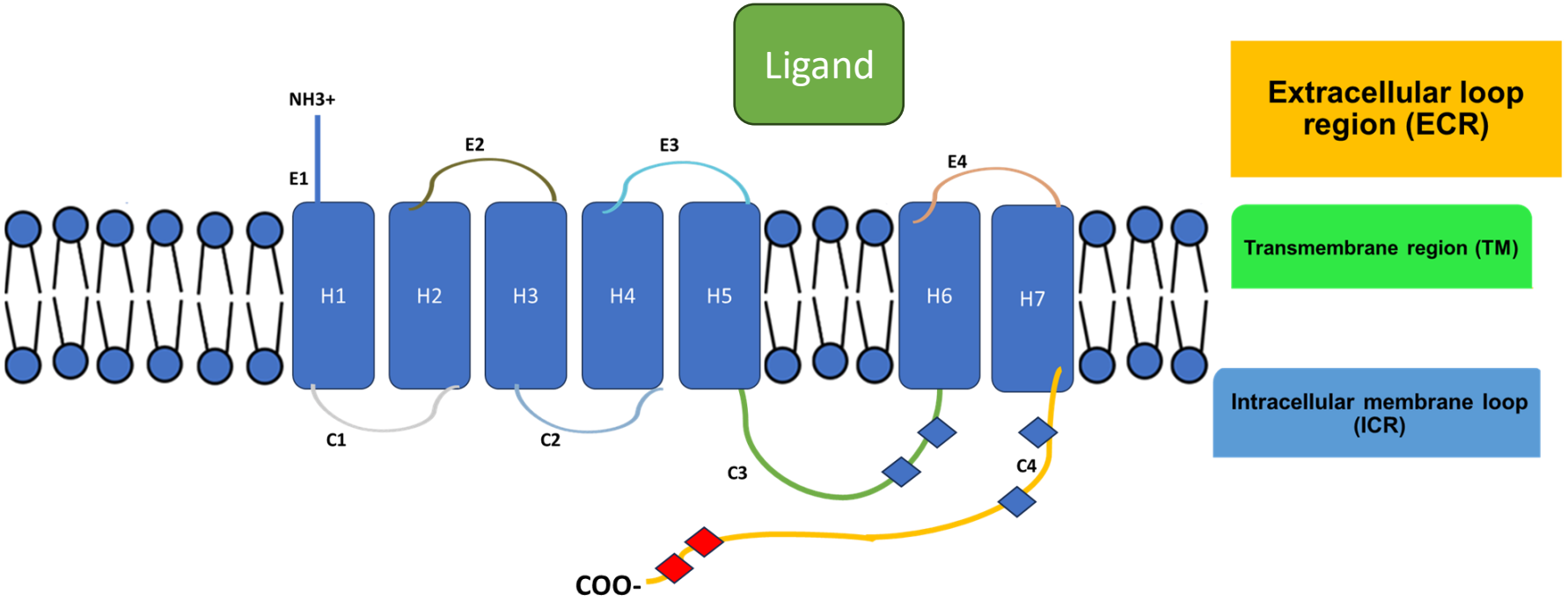
Normal GPCR signalling pathway: Receptor activation

1.The ligand binds to GPCR and this binding causes a conformational change.

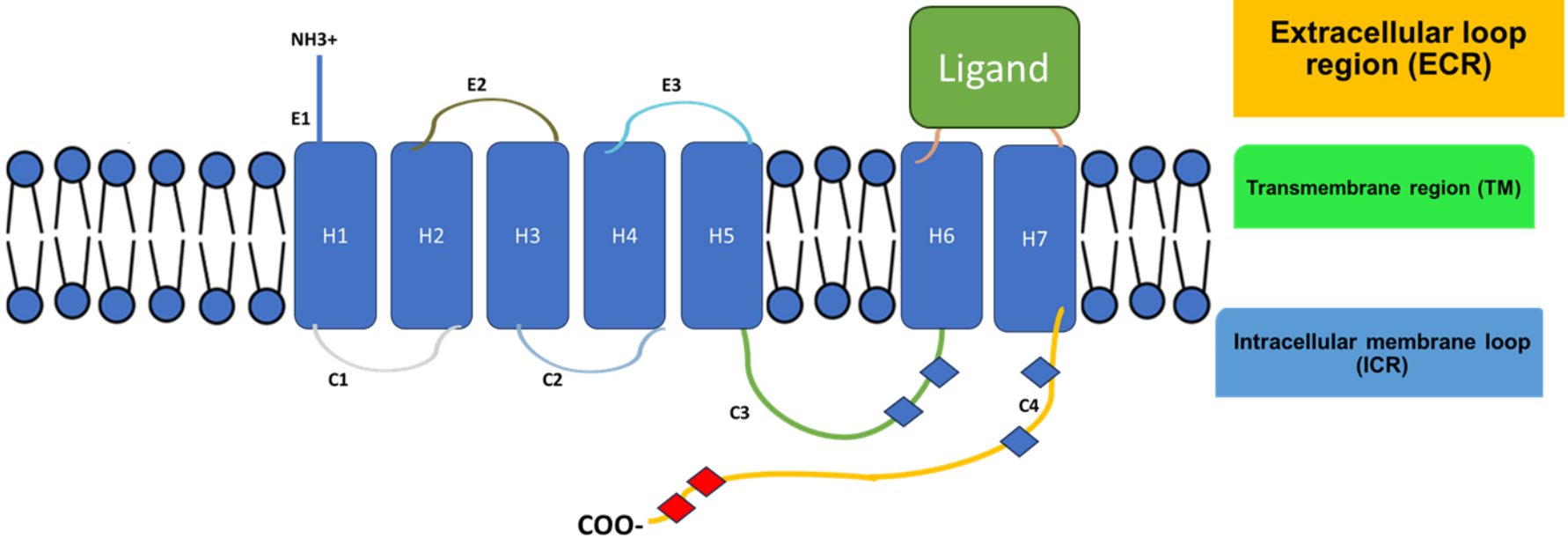
Common ligands are: amino acids, hormones, neurotransmitters, chemokines, proteins and small ions.

2. This leads to interaction with intracellular proteins called G proteins.

Inactive receptor

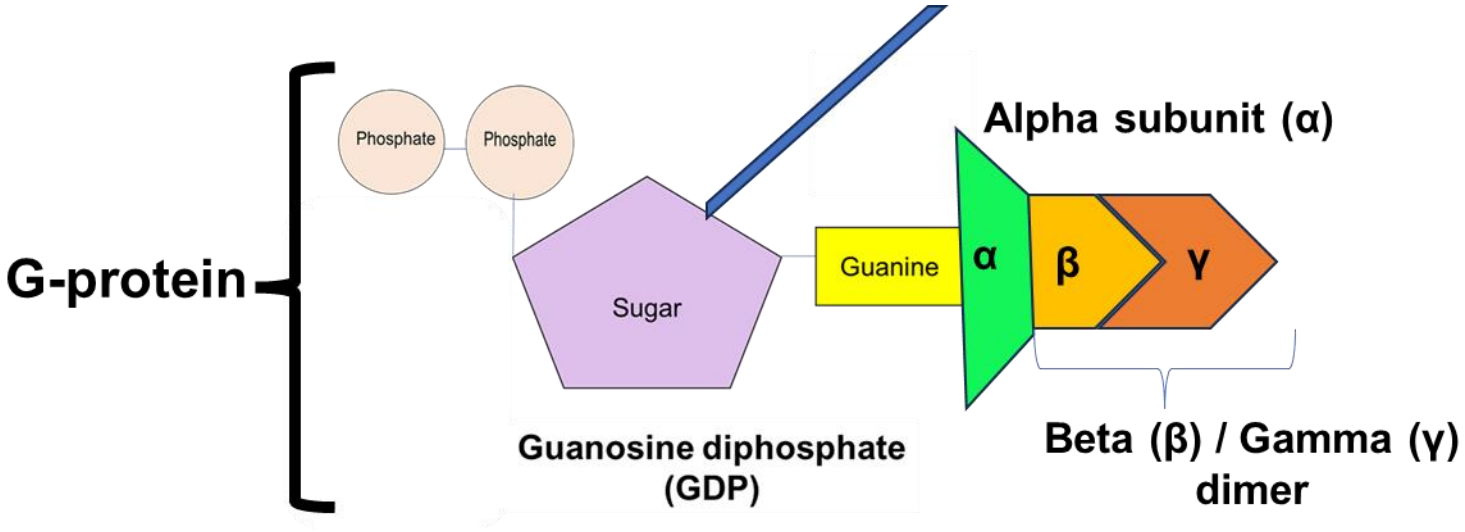


Active receptor



The structure of G-proteins

The G proteins consist of **three subunits (Gα, Gβ and Gγ) and is known as a heterotrimer.**

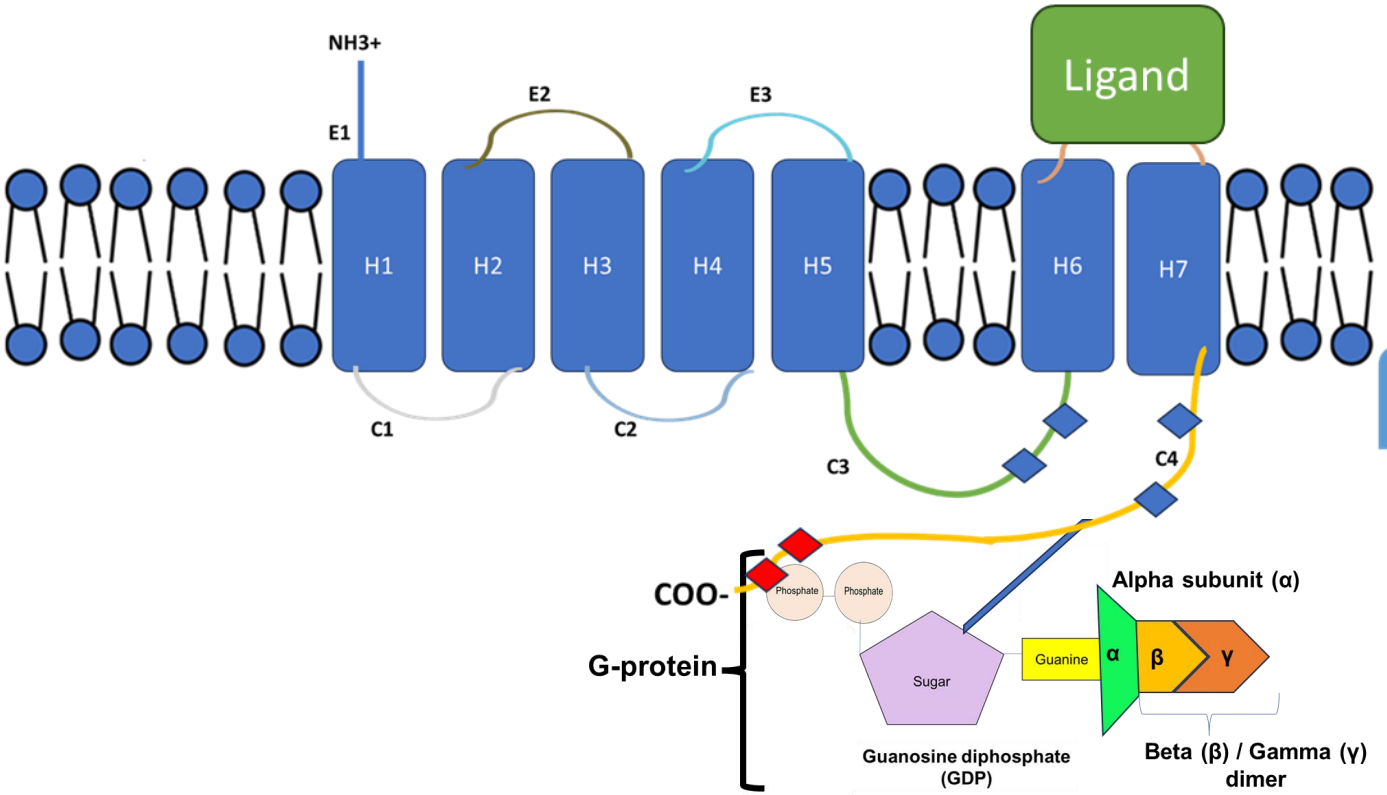


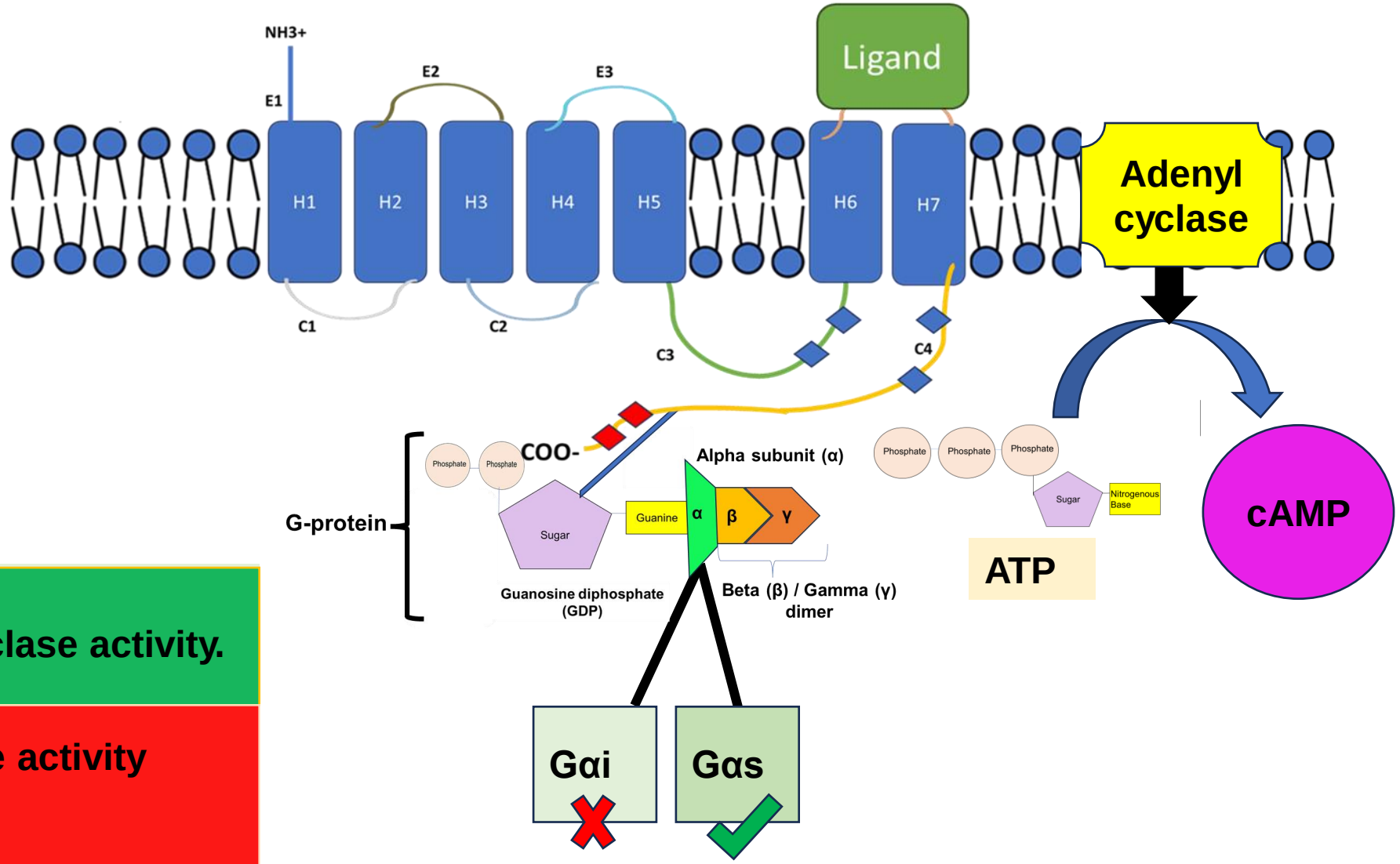
The structure of G-proteins

G proteins are classified according to their **α subunit; Gαi , Gαs, Gα12/13, and Gαq**.

Gαi and Gαs

- They **regulate adenylyl cyclase activity.**



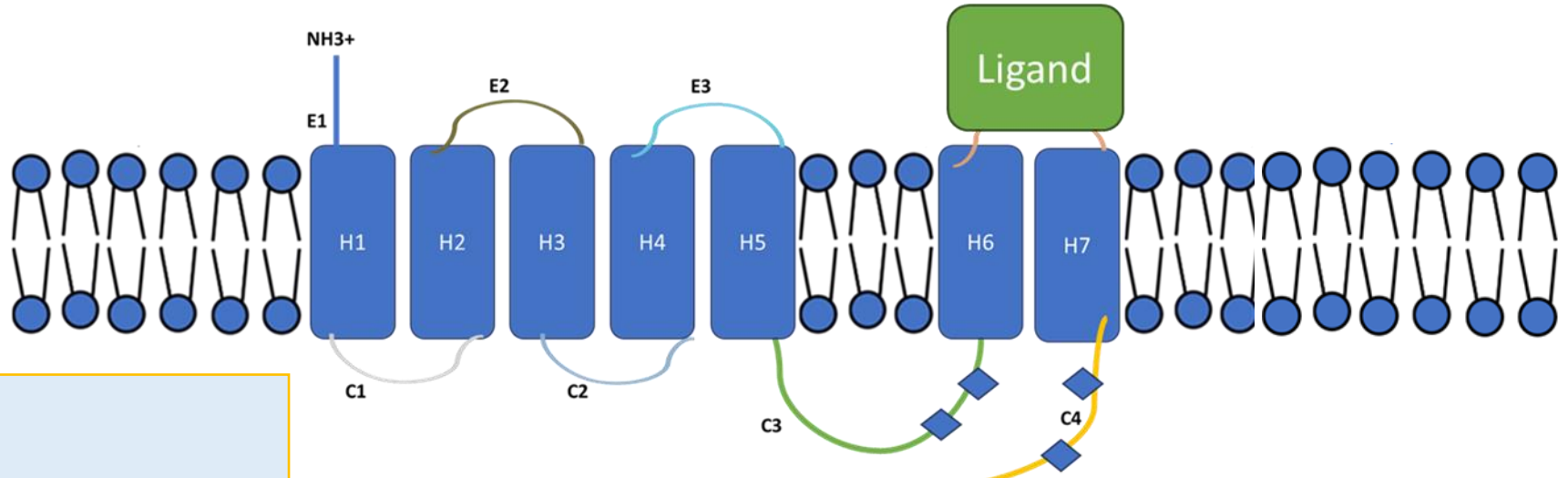


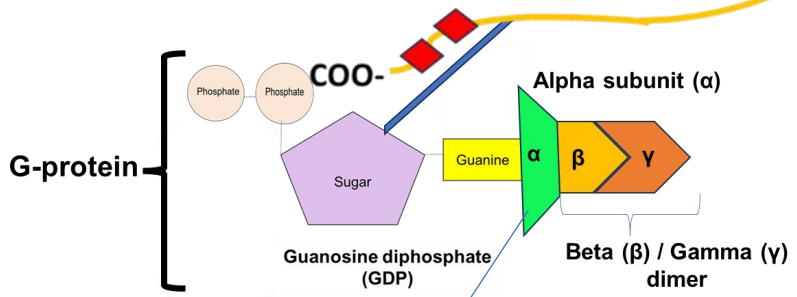
Gαs activates adenyl cyclase activity.

- **Gαi halts adenyl cyclase activity**

Gα12/13

- They can activate small GTPase families.
- Ras homolog family member A (RhoA), is a small GTPase protein that regulates cell division via Guanine nucleotide exchange factors (GEF) proteins that activate GTPases.
- This is achieved by releasing guanosine diphosphate (GDP) to bind guanosine triphosphate (GTP)



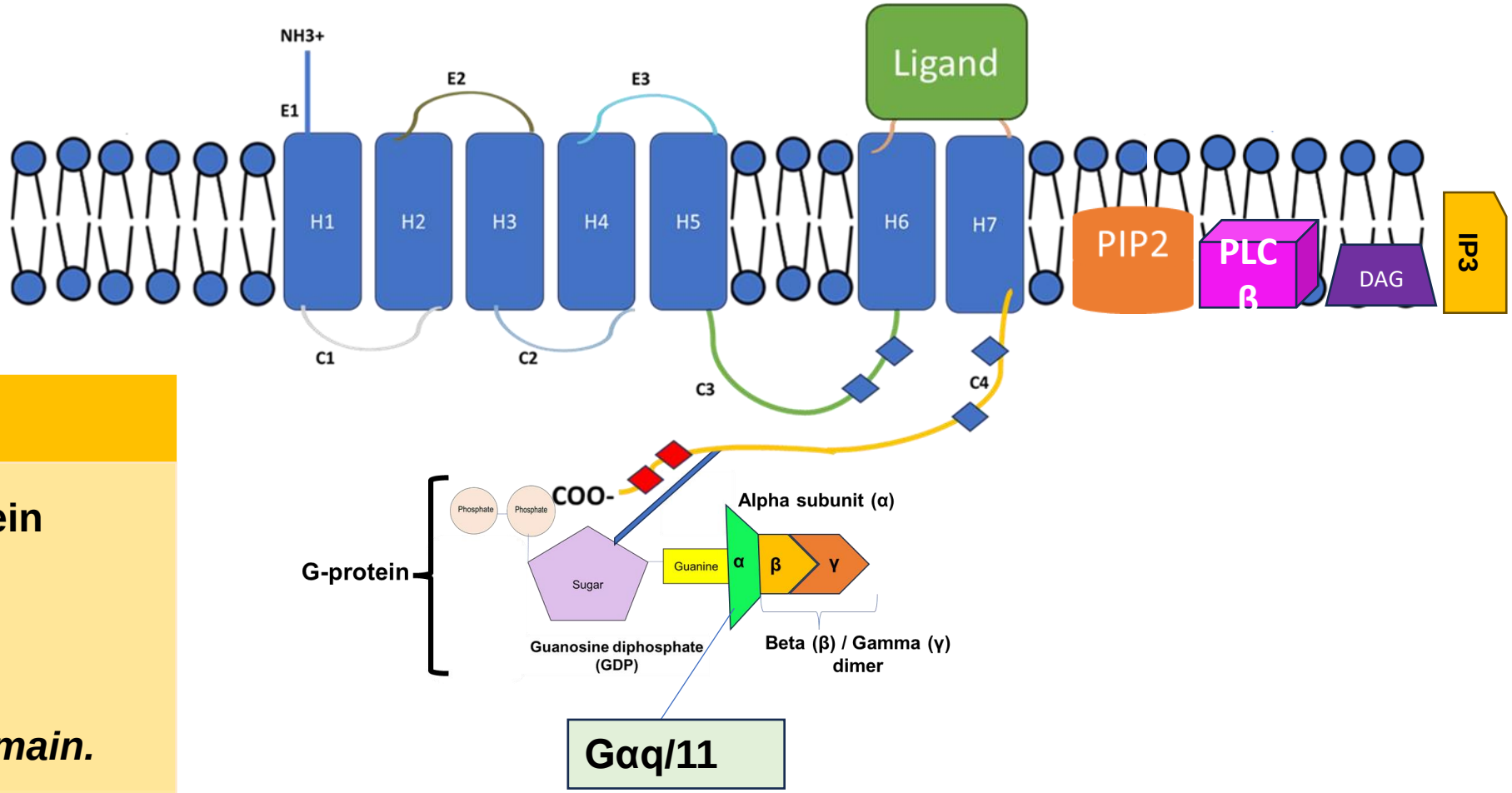


Gα12/13

Guanine nucleotide exchange factor (GEF)

Ras homolog family member A (RhoA)

ROCK



Gαq/11

- **359 amino acid protein**
- It has **two domains:**

1) *Helical domain*

2) *GTPase binding domain.*

Phosphatidylinositol (PI) phospholipid is phosphorylated by kinase enzymes to form PI-phosphate (PIP) and PI-bisphosphate (PIP_2).

The Gαq/11 activates the enzyme phospholipase c (PLC)who then cleaves PIP_2.

PLC cleaves PIP_2 to form two second messengers: Diacylglerol (DAG) and Inositol triphosphate (IP_3)

FUNCTION

GTPase binding domain

The exchange of bound GDP for guanosine triphosphate (GTP).

It has three switch regions that are flexible loops that change conformation when bound with GTP.

It also binds the Gβγ subunits and GPCR.

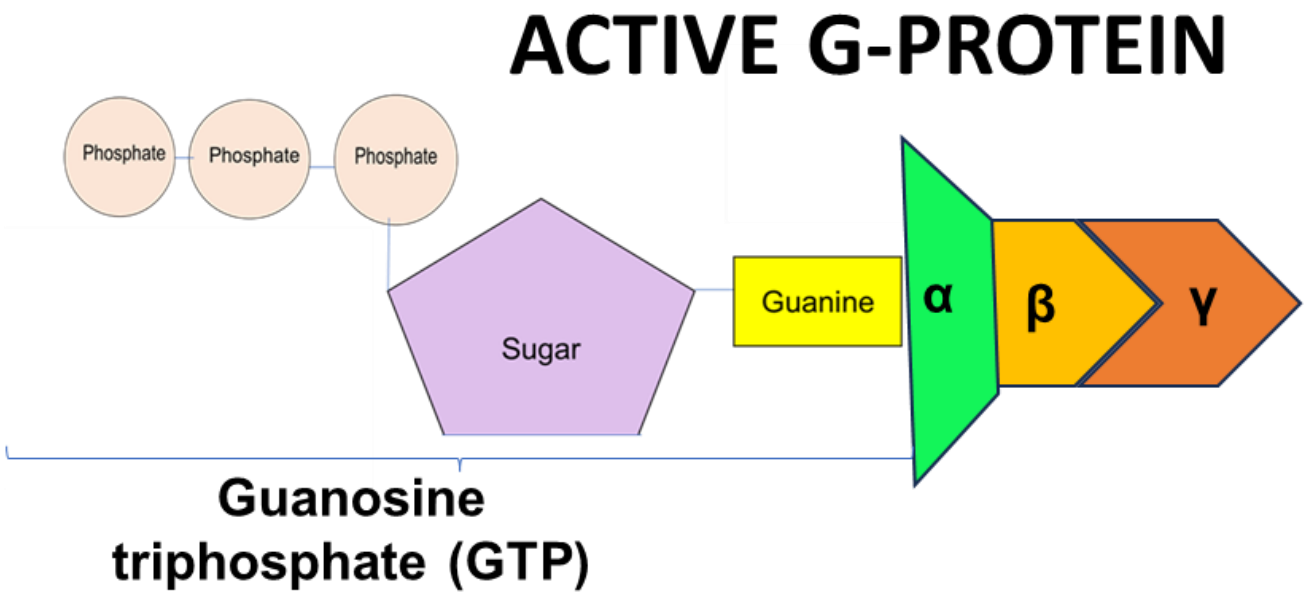
Helical domain

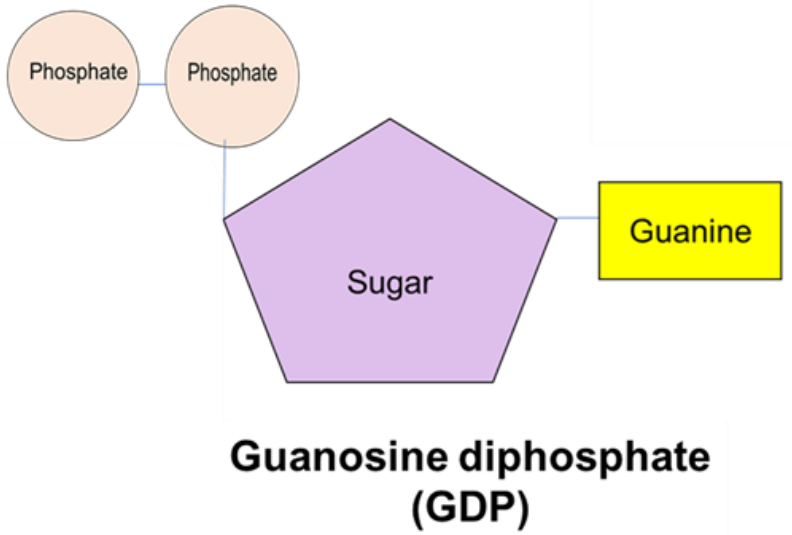
Six alpha helices that has nucleotides in the protein core.

Normal GPCR signalling pathway: Receptor activation

3. The activated receptor activates G protein and exchanges for guanosine-5'-diphosphate (GDP) for guanosine-5'-triphosphate (GTP).

4. Levels of the ligand decreases.





Active state

GTPase activity promotes **the exchange of bound GDP for guanosine triphosphate (GTP).**

Inactive state

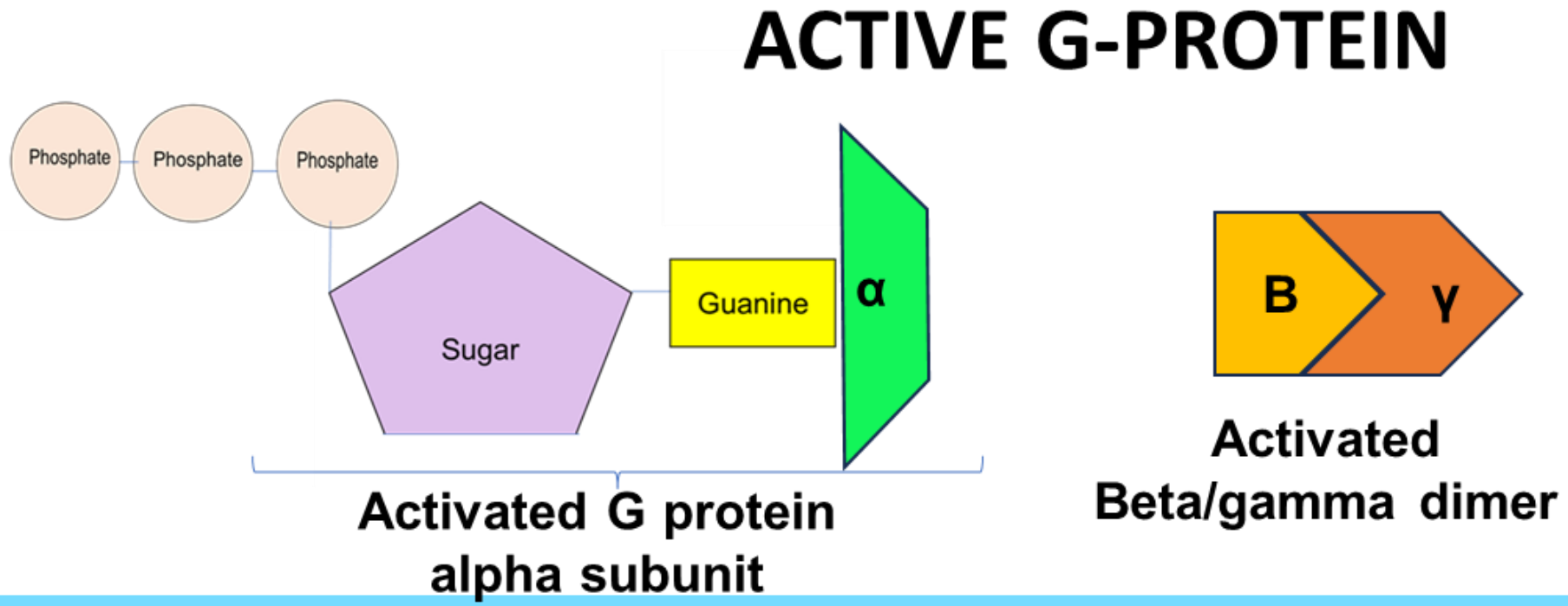
The α subunit bound to guanosine diphosphate (GDP).

Normal GPCR signalling pathway: Signal transduction

Normal GPCR signalling pathway: Signal transduction

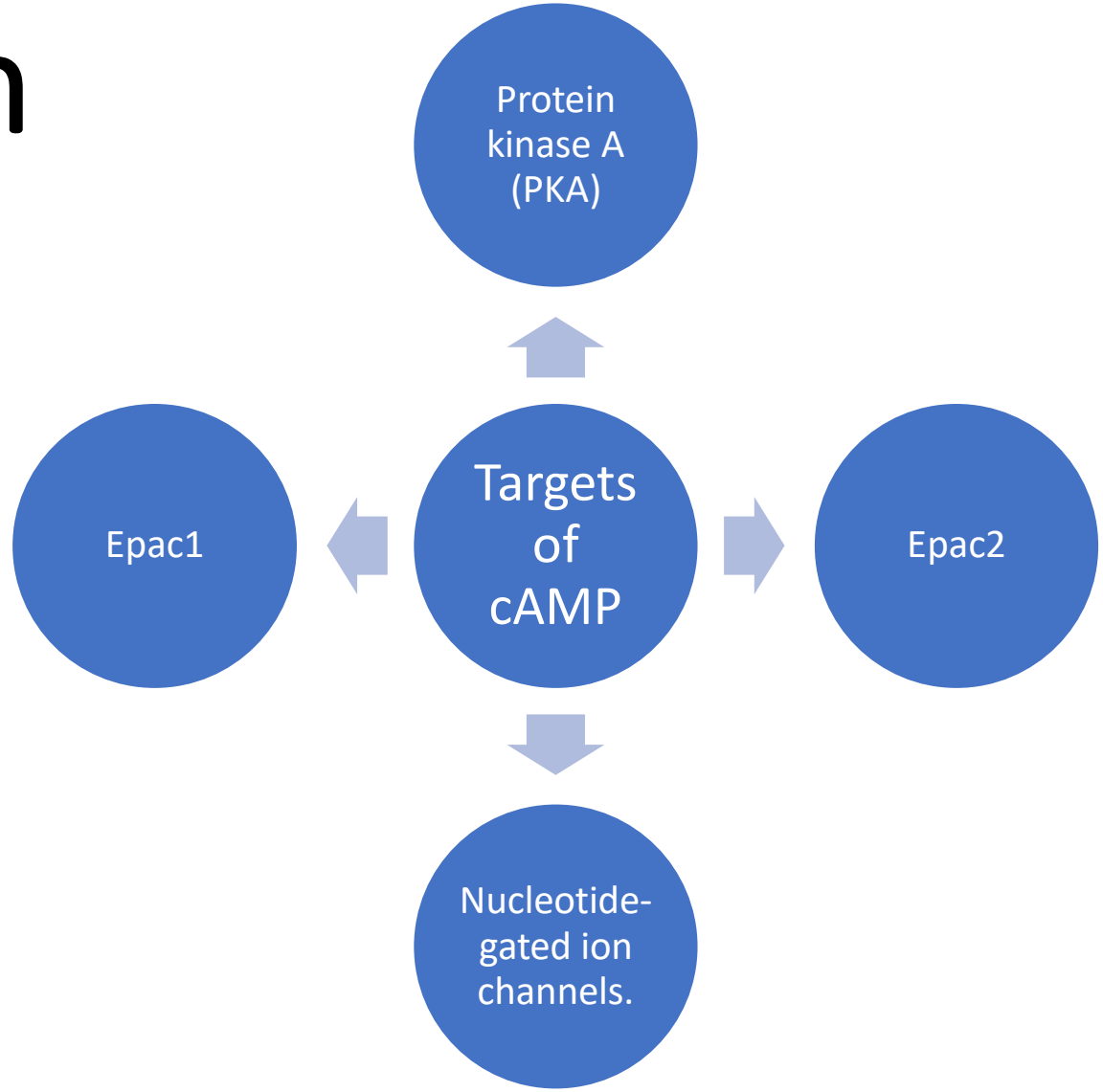
5. Alpha subunit of the G protein binds to the enzyme **adenyl cyclase on the plasma membrane**.

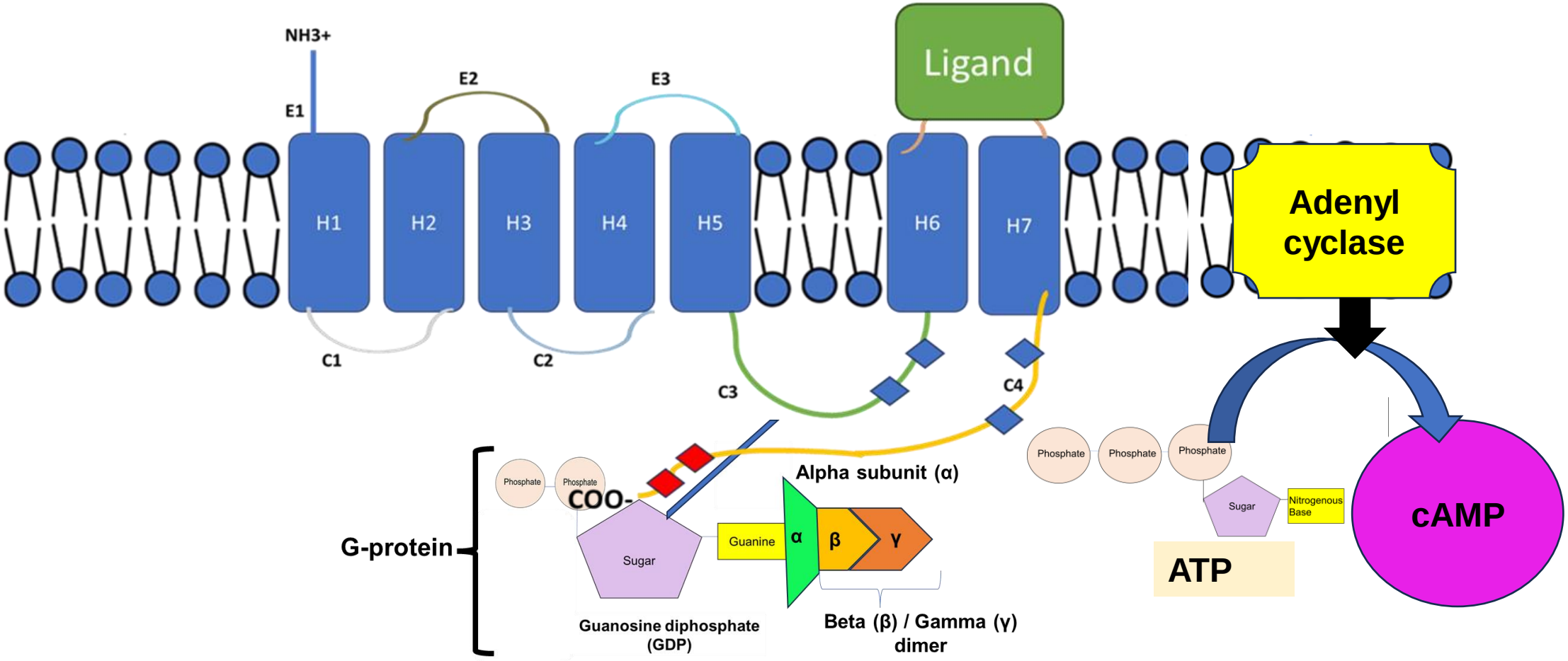
6. The α subunit and βγ complex then dissociate from one another



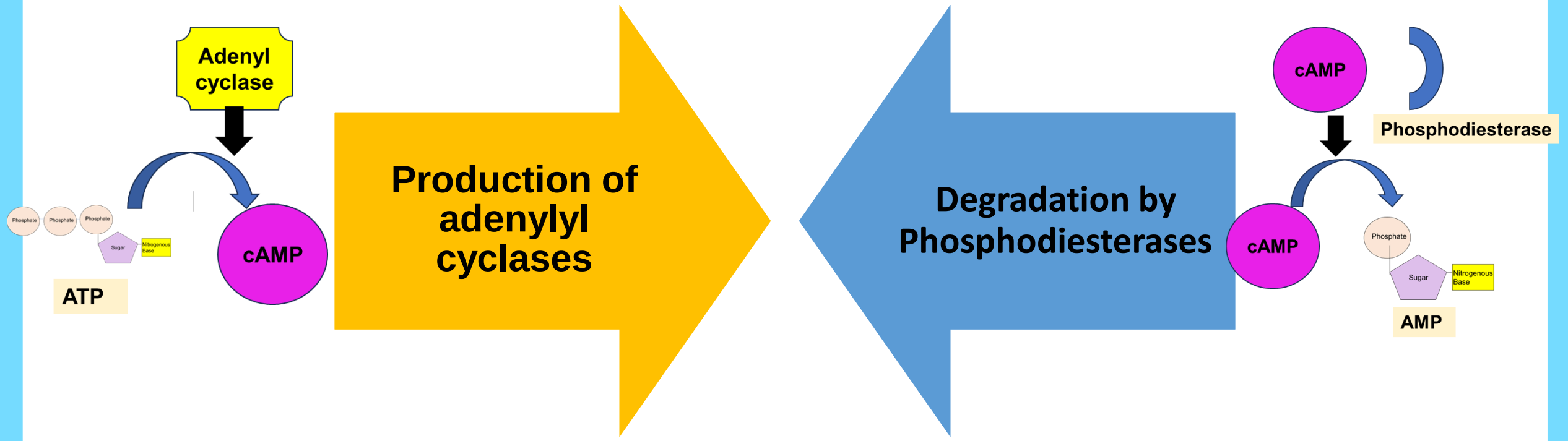
Normal GPCR signalling pathway: Signal transduction

7. The activation of adenyl cyclase stimulates the production of the intracellular second messenger cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP).




NH3+
E1
E2
E3
Ligand
H1
H2
H3
H4
H5
H6
H7
Adenyl cyclase
C1
C2
C3
C4
Phosphate
Phosphate
COO-
Alpha subunit (α)
G-protein
Sugar
Guanine
α
β
γ
Guanosine diphosphate (GDP)
Beta (β) / Gamma (γ) dimer
Phosphate
Phosphate
Phosphate
Sugar
Nitrogenous Base
ATP
cAMP

The concentration of intracellular cAMP depends on the relative balance between adenylyl cyclases and phosphodiesterases (PDE).



22 PDEs have been identified.

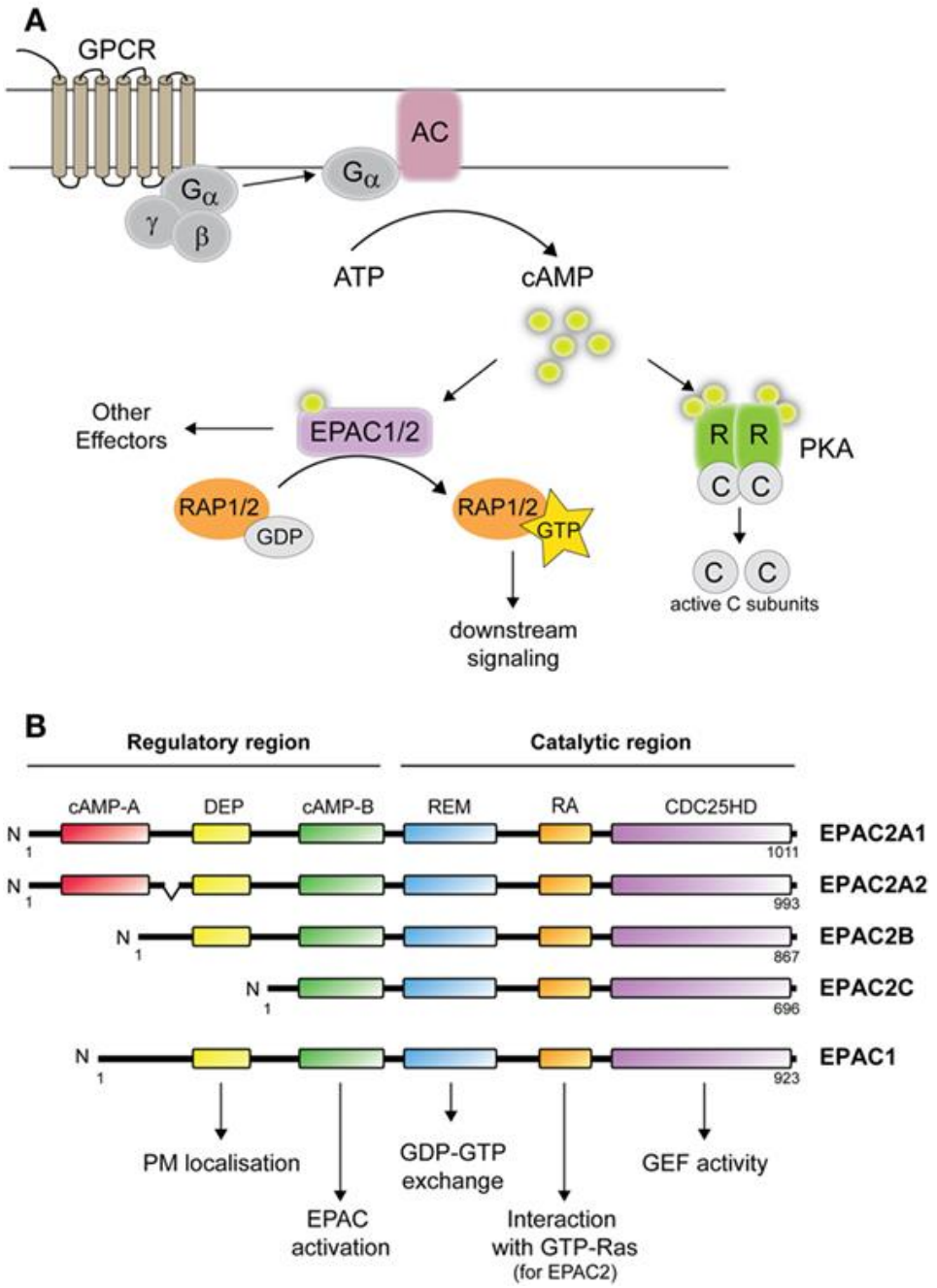
Types of cAMP targets: Epac

It is a **guanosine exchange factor (GEF).**

The structure of **Epac** has a **cAMP binding domain.**

This causes a **conformational changes of the protein**.

This exposes the **active site in the catalytic domain**.



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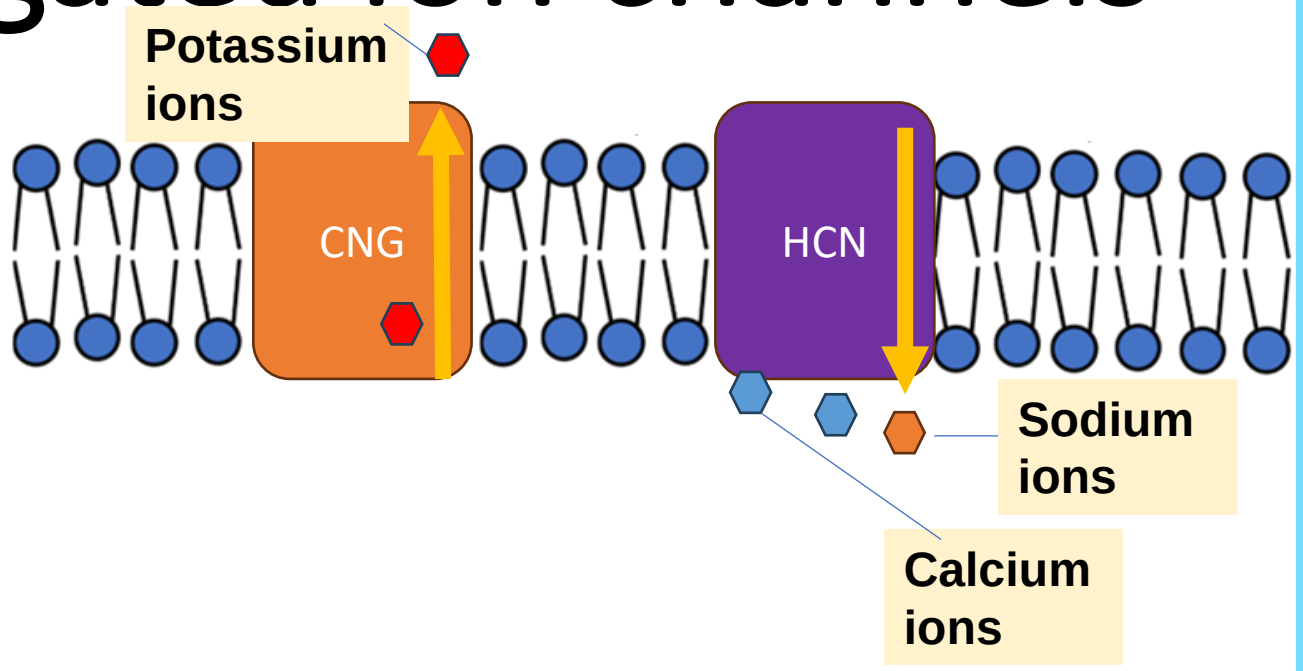
Types of cAMP targets: cyclic nucleotide-gated ion channels

They **cation channels that can conduct calcium, sodium and potassium ions** and **change the cell membrane potential.**

Cyclic nucleotide-gated (CNG) channels.

Hyperpolarization-activated cyclic nucleotide-modulated (HCN) channels.



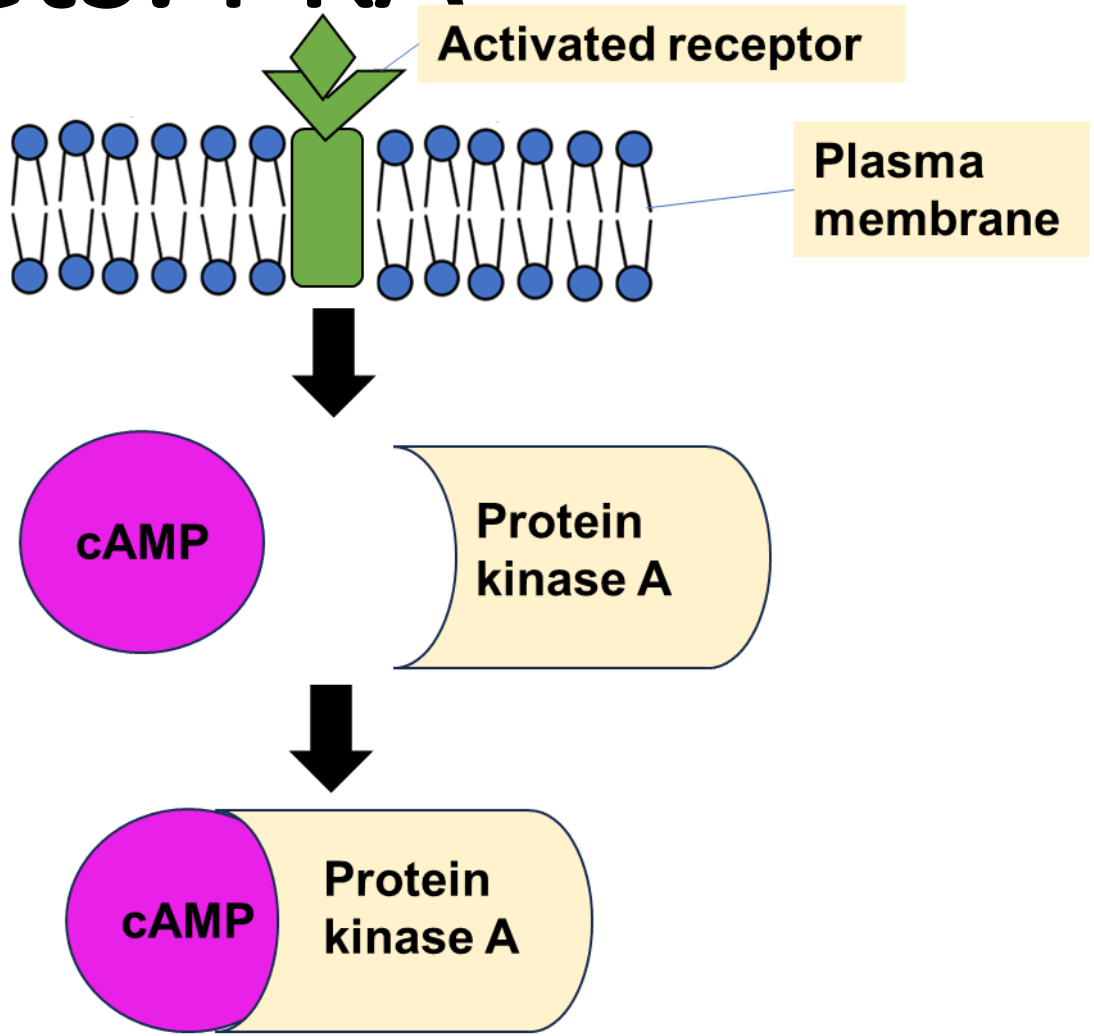
PKA

Types of cAMP targets: PKA

It is a **tetramer enzyme and can be classifled into:**

A) **PKA type I (RIα2C2, RIβ2C2) - cytoplasm**

B) **PKA type II (RIIα2C2, RIIβ2C2) - subcellular structures and compartments**



cAMP binds to the enzyme cAMP-dependent kinase (A-kinase)

Types of cAMP targets: PKA

PKA is made of **four subunits:**

- **Two catalytic subunits**
- **Two regulatory subunits.**

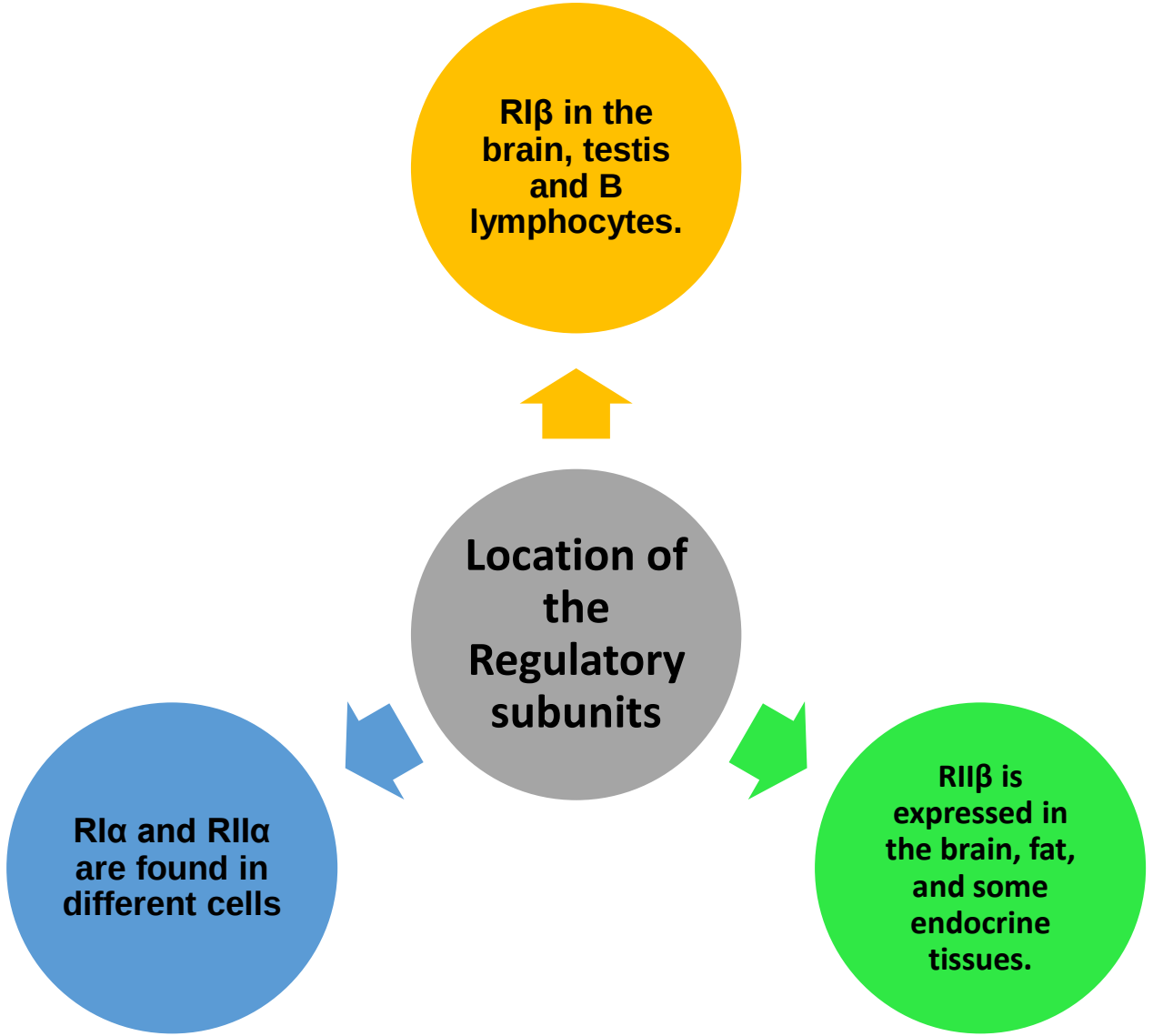
In mammals:

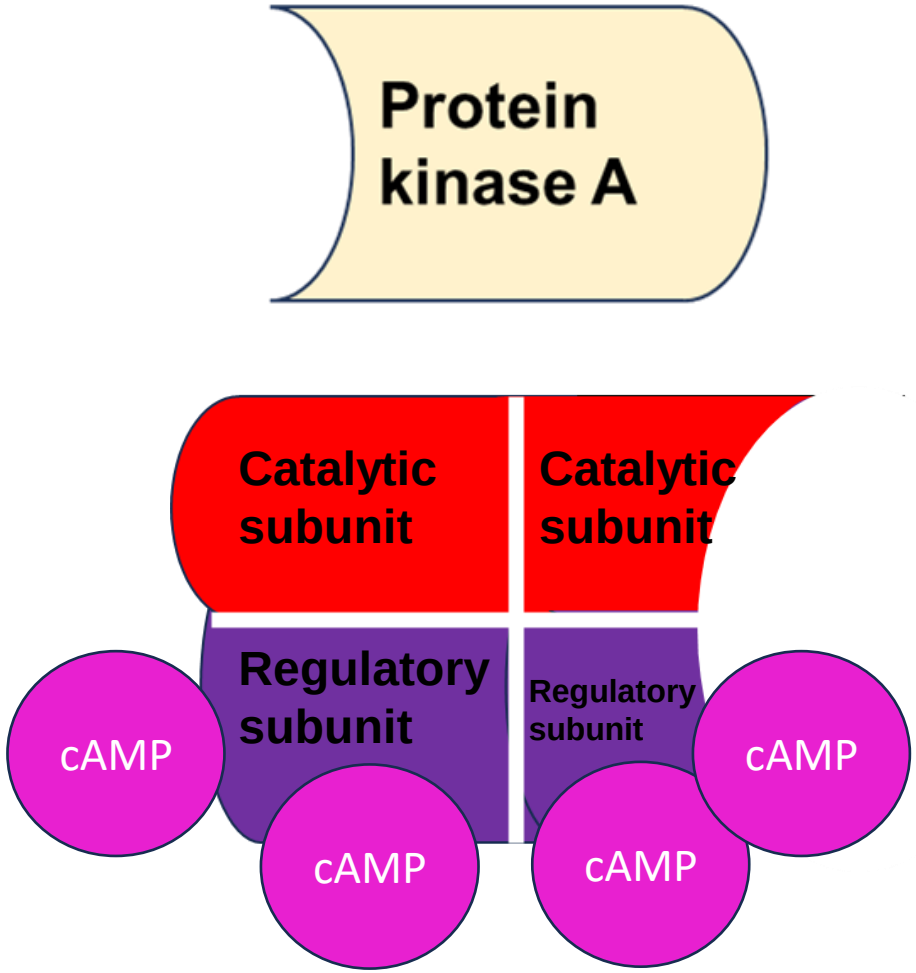
There are four types of regulatory subunits:

RIα, RIβ, RIIα and RIIβ.

There are three types of catalytic subunits:

Cα, Cβ and Cγ.




Protein kinase A
Catalytic subunit
Catalytic subunit
Regulatory subunit
Regulatory subunit
cAMP
cAMP
cAMP
cAMP

Types of cAMP targets: PKA

Catalytic subunit

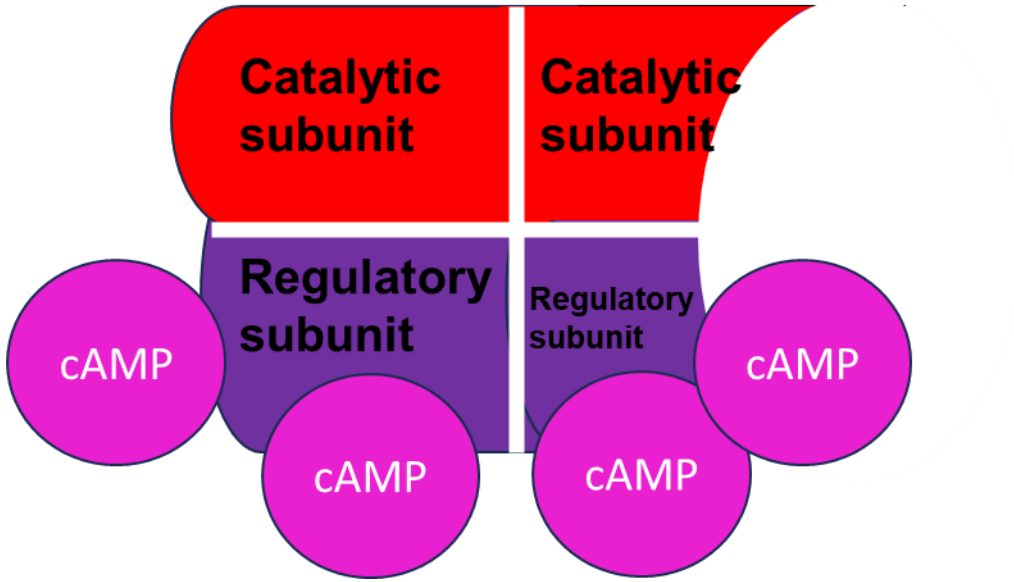
- **They phosphorylate specific cellular proteins.**

Regulatory subunits

- **They are bound to each other and initiate catalytic subunits.**

Normal GPCR signalling pathway: Signal transduction

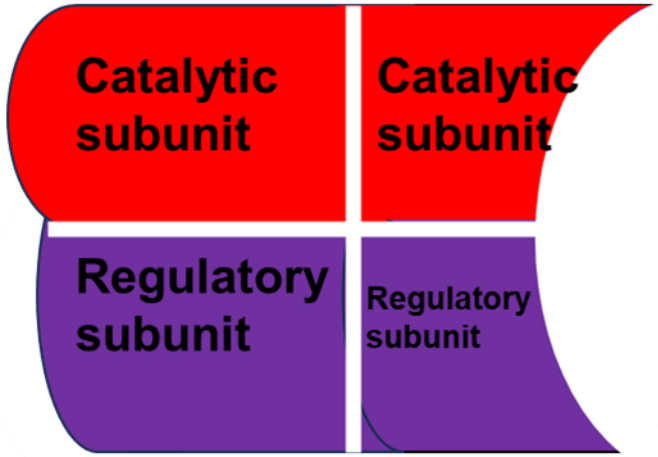
8. The regulatory subunits are bound to each other and initiate catalytic subunits.



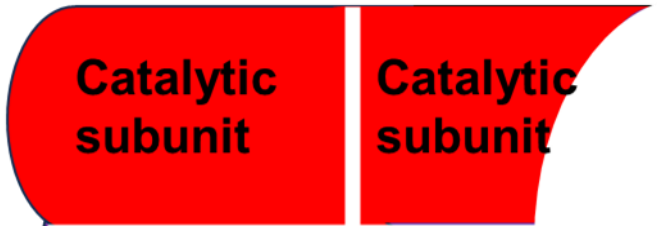
Normal GPCR signalling pathway: Signal transduction

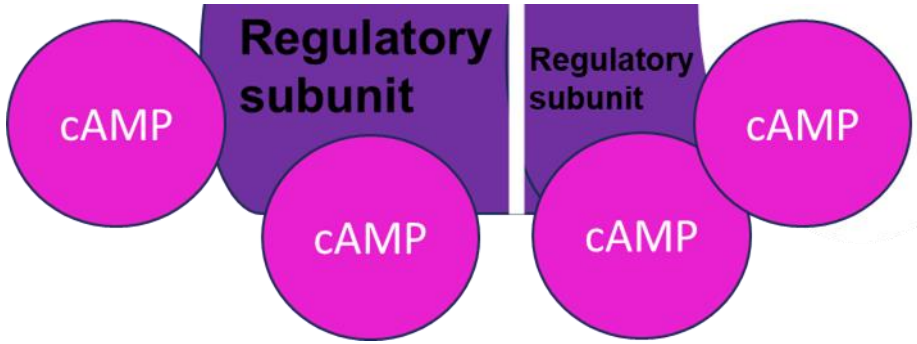
9. cAMP binds to the regulatory subunits of PKA.

This activates both catalytic subunits of PKA by separating the regulatory and catalytic subunits.



Inactive PKA

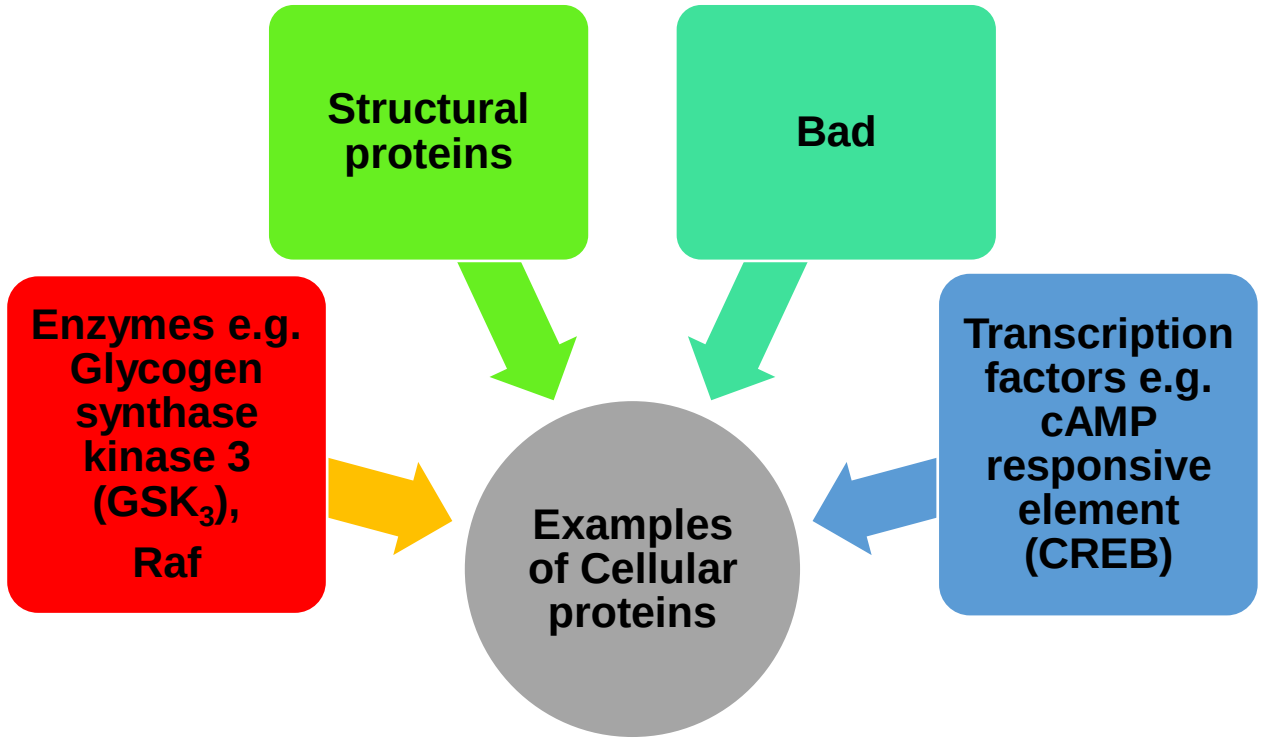




Active PKA

Normal GPCR signalling pathway: Signal transduction

10. The activated catalytic subunits of PKA phosphorylate specific cellular proteins in the serine and threonine residues.



Did you know?

Recent study 1

PKA is an actomyosin contractility-regulated effector involved in cell migration.

Recent study 2

PKA phosphorylates CDC42 interacting protein 4 (CIP4).

It facilitates membrane deformation and actin polymerization.

It promotes cancer cell invasion and metastasis.

Recent study 3

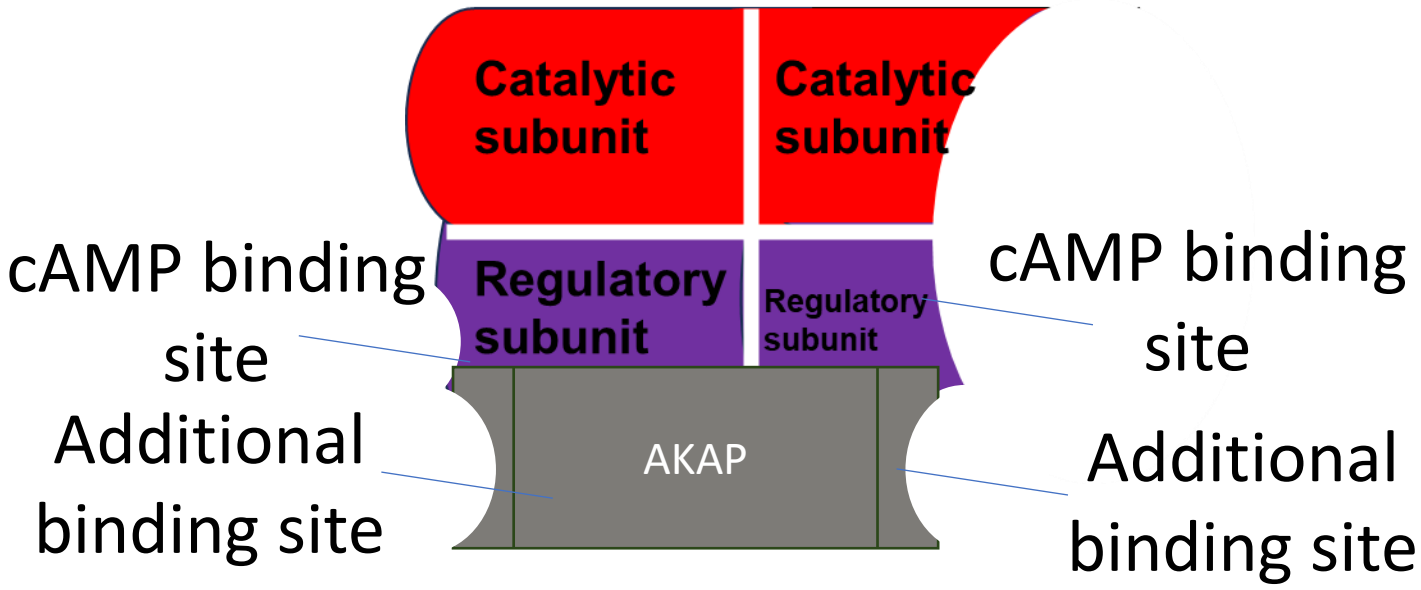
Activated PKA can inhibit adenylyl cyclase (AC5 and AC6) and activate phosphodiesterase (PDE3 and PDE4).

This lowers the levels of cAMP.

Did you know?

PKA anchored proteins (AKAPs)

It can bind to cytoskeleton proteins or organelles and to PKA regulatory subunits.



Examples of PKA targets: CREB

It is a member of **basic leucine zipper (bZIP) superfamily transcription factors:**

- ❑ cAMP response element-binding protein (CREB) – many tissues.
- ❑ cAMP responsive element regulatory protein (CREM) – many tissues.
- ❑ Transcriptional activator 1 (ATF1) - neuroendocrine

They can form **homodimers or heterodimers**.

They all have a **KID (kinase inducible domain)** is a 60-amino acid fragment located in the **central region and contains the PKA phosphorylation site (RRPSY).**

This is for cyclins, apoptotic proteins, growth factors, enzymes and transcription factors.

Examples of PKA targets: CREB

Structure of CREB

- **kinase inducible domain (KID)**
- **Two glutamate domains (Q1 and Q2)**
- **A basic leucine zipper domain (bZIP)**

CREB pathway

CREB/ATF1 can be phosphorylated by multiple kinases including Akt, RSK, MSK, PKA, CAMKII and CAMKIV.

Phosphorylation of CREB Ser133 residue and ATF1 Ser63 residue takes place.

Activated ATF1 and CREB can form homodimer or heterodimer and bind to the cAMP response element (CRE) in the promoter region of target genes.

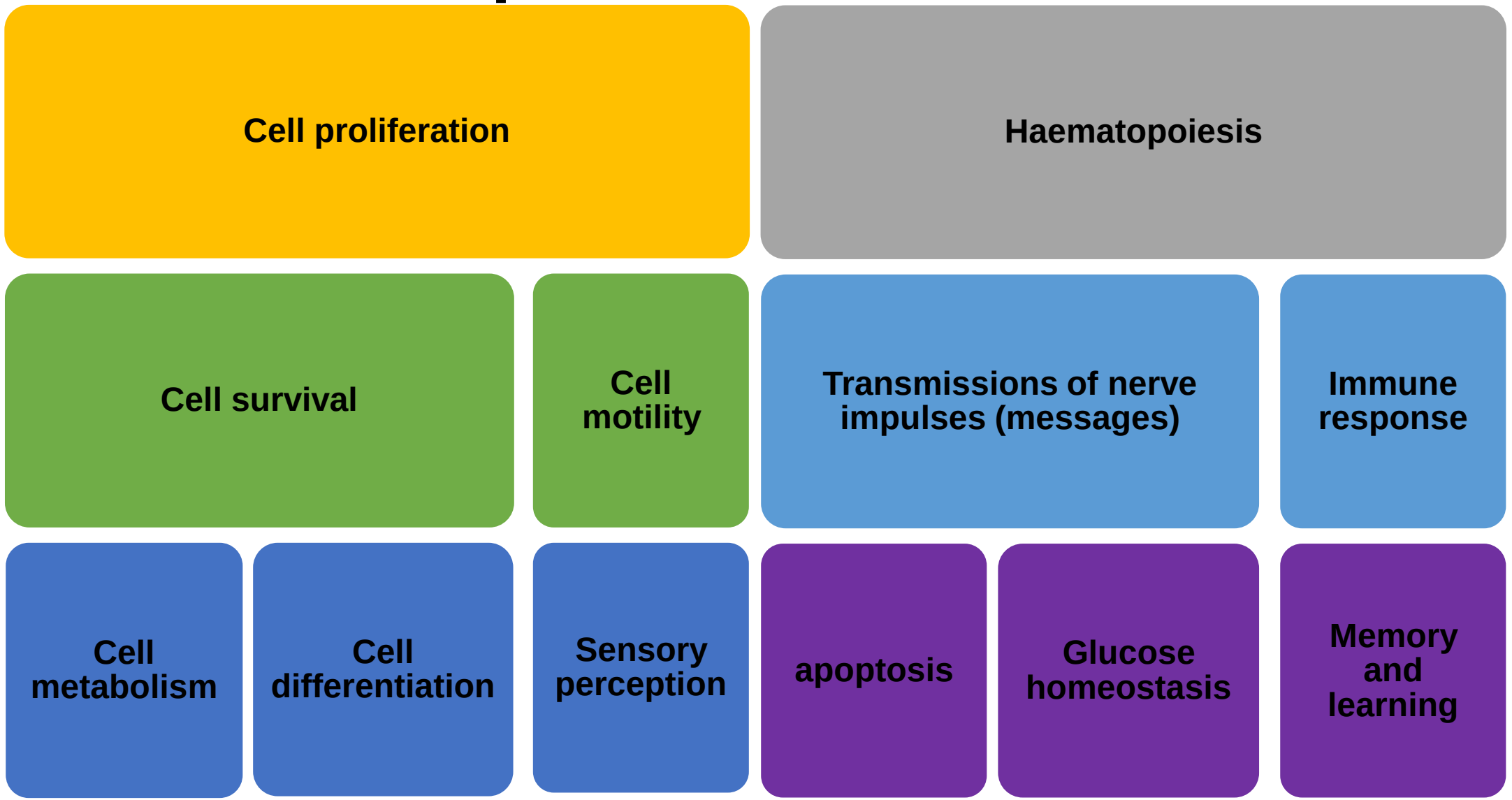
Regulate transcription of target genes to initiate cellular response e.g. oncogenes c-Jun and cyclin D1.

G-protein independent pathway

Bicarbonate (HCO_3^-) and calcium ions (Ca^{2+}) induce **cAMP synthesis** by **activating the soluble adenylyl cyclase (sAC) without G-proteins.**

Cellular response

Cellular response



Turning off GPCR signalling pathway

Turning off GPCR signalling pathway

11. The ligand dissociates from receptor which inactivates GPCR.

12. The ligand degrades.

13. The alpha subunit of the intracellular G-protein hydrolyses GTP to GDP+P.

Turning off GPCR signalling pathway

14. The alpha subunit and beta/gamma dimer reassociate to an inactive G protein.

15. The levels of cAMP decrease because the enzyme called phosphodiesterase converts cAMP to AMP.

16. The low levels of cAMP cause the regulatory subunits of PKA to release cAMP.

Turning off GPCR signalling pathway

16. The regulatory and catalytic subunits of PKA reassociate and is stimulated by protein phosphatases. This prevents the actions of PKA.

GPCR signaling pathway is involved in cancer growth and development and partakes in a number of hallmarks of cancer:

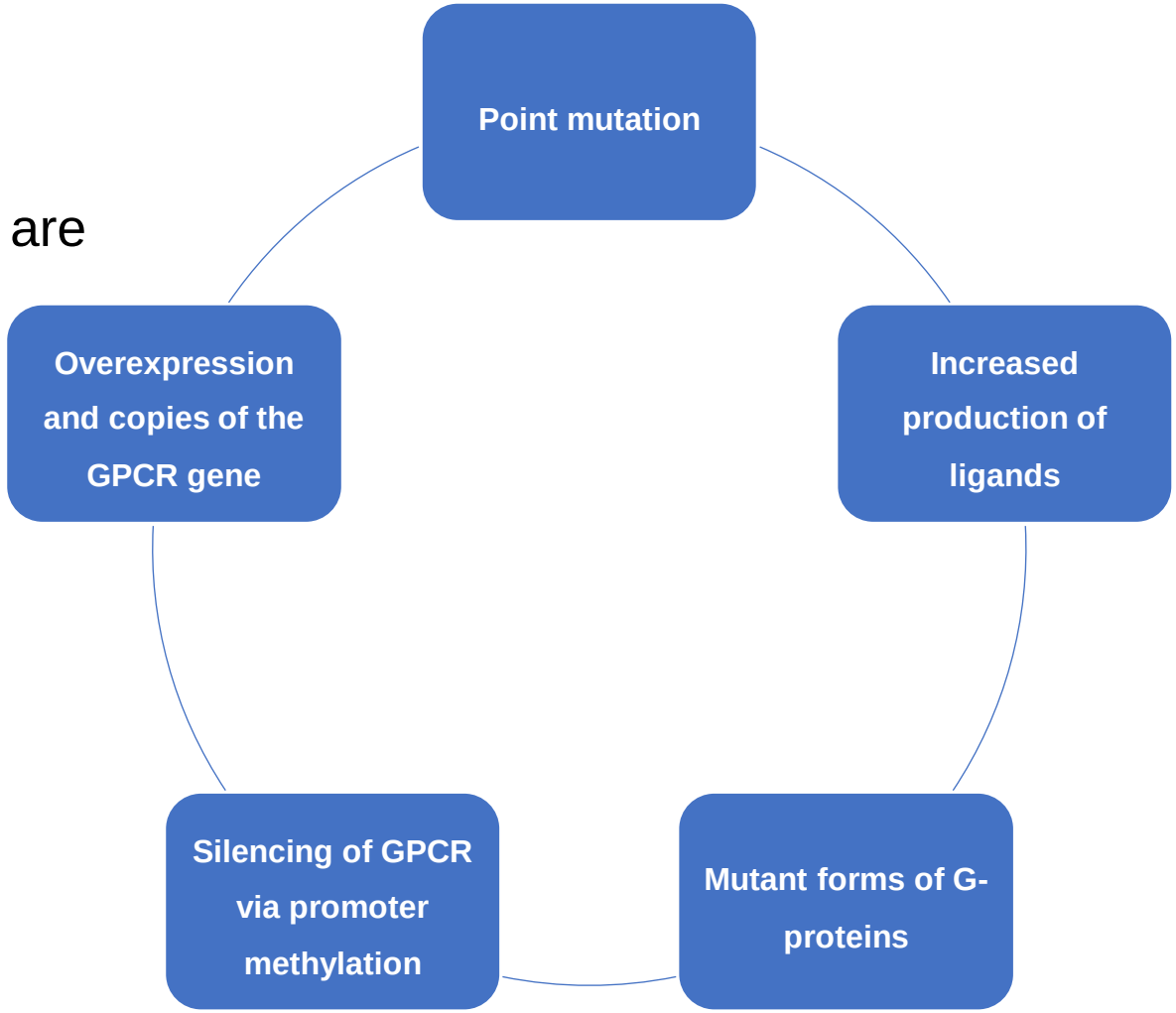
- ❑ **Unregulated growth**
- ❑ **Invasion**
- ❑ **Metastasis**
- ❑ **Evading apoptosis**
- ❑ **Evading immune response**
- ❑ **Angiogenesis.**

Causes of dysregulated GPCR signalling pathway

Causes of dysregulated GPCR signalling pathway

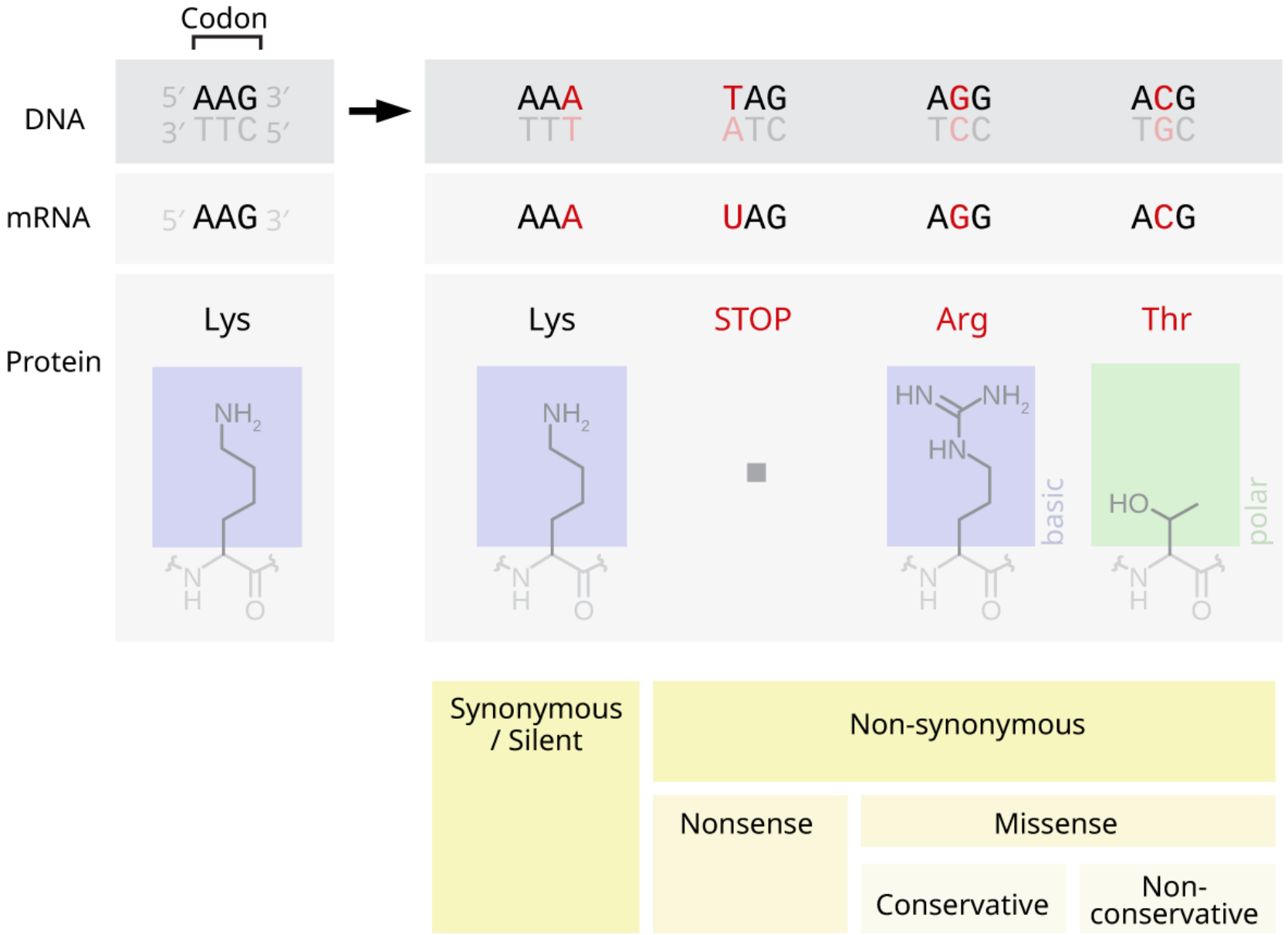
Dysregulated GPCR signalling pathway are involved in:

- ❑ Cardiovascular disease
- ❑ Cancer
- ❑ Asthma.



What is a point mutation?

SILENT MUTATION	***MISSENSE***	***NONSENSE***	***SPLICE-SITE***
It **changes DNA sequence but has no effect on the amino acid and protein.**	The **DNA sequence has been changed** because there was a substitution. This causes a different **amino acid to be made.** This affects **the shape and function of the protein.**	**A change the codon (substitution of base pair**) from an amino acid to create a **stop codon.** This **causes a short protein to form** that are either non-function or **functional but is affected.**	It affects: the **exons (coding regions) and introns (non-coding regions) where some introns are added** and **some exons are removed.** It **prevents splicing and form a different protein**



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Causes of dysregulated GPCR signalling pathway

Activation of alpha subunit of G proteins via these molecules:

- ❑ **Chemokines e.g. Interleukin 8 (IL8)**
- ❑ **Neuropeptides e.g., prostaglandin E2**
- ❑ **Lipids e.g., lysophosphatidic acid (LPA)**

This leads to activation of targets to increase:

Migration

Proliferation

Survival of tumour cells by increasing nutrient supply via angiogenesis.

Regulating the degradation of the extracellular matrix.

A number of biomarkers can be established to diagnose cancer early and develop cancer preventative treatments.

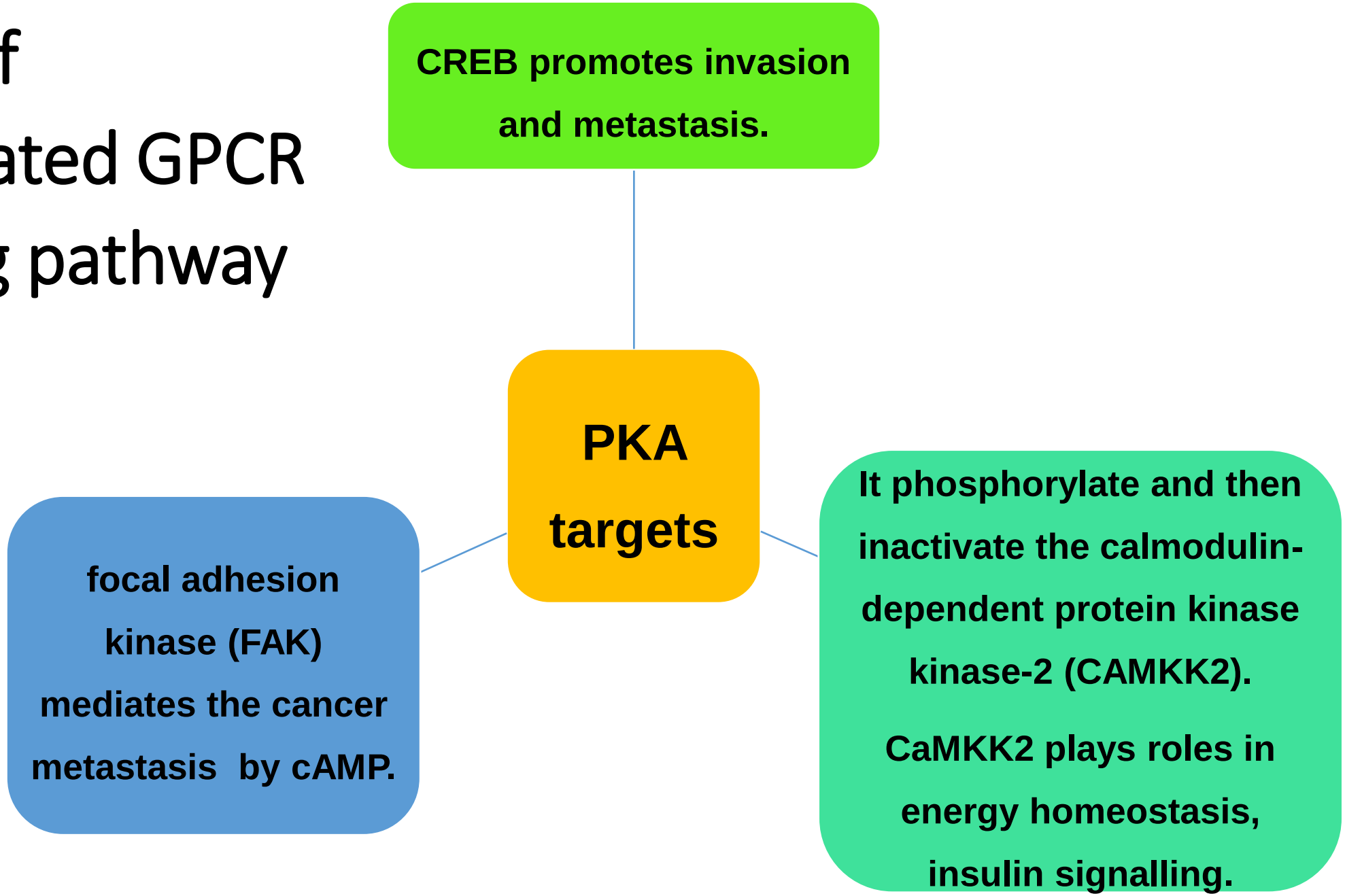
cAMP–PKA signaling

TUMOUR-SUPPRESSIVE

TUMOUR-PROMOTING

It depends the tumor types and case.

Causes of dysregulated GPCR signalling pathway

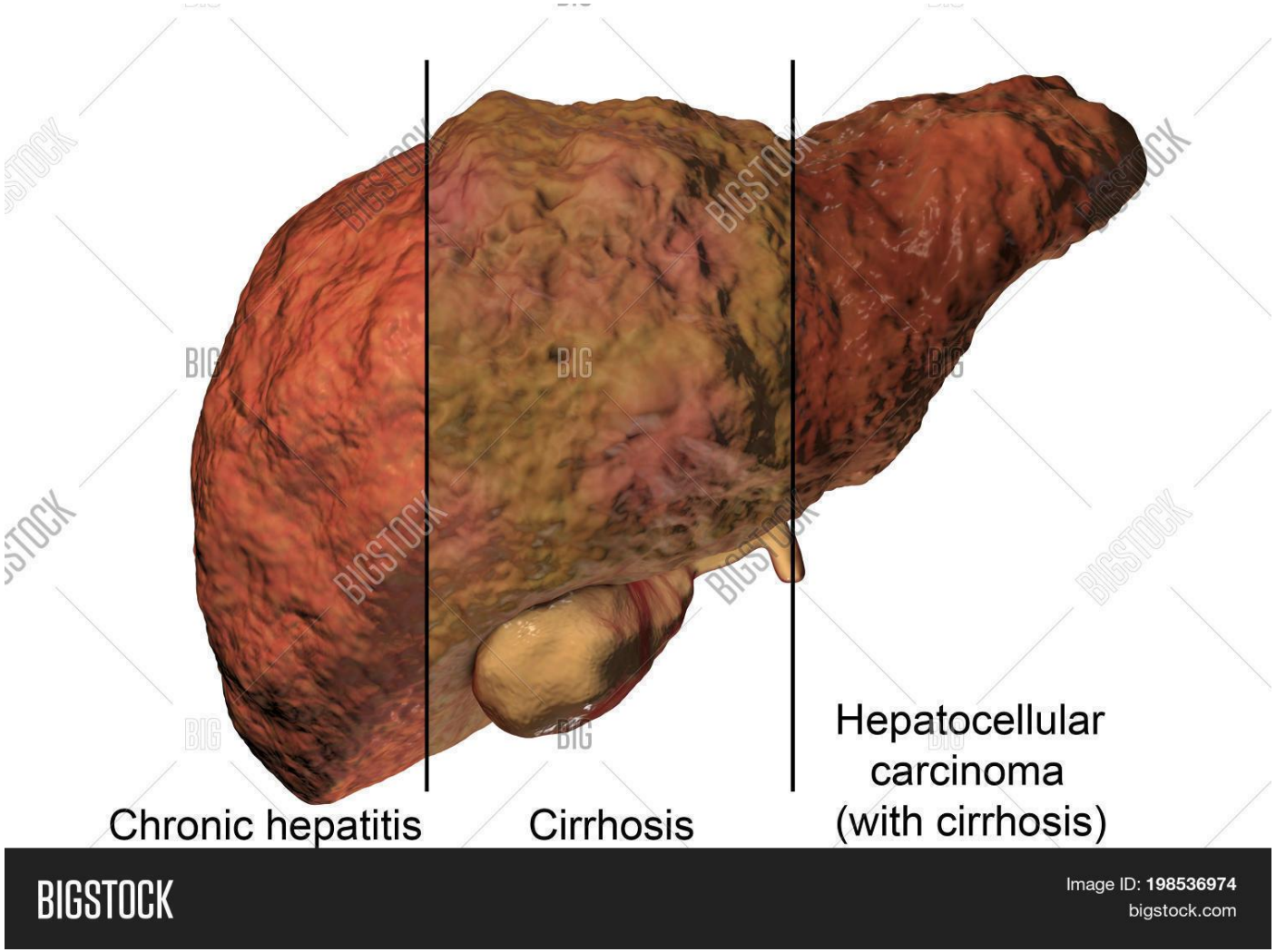


Examples of cancers caused by dysregulated GPCR signalling pathway

Examples of cancers caused by dysregulated GPCR signalling pathway

Endocrine	Thyroid (anaplastic)	Ovary	Gastrointestinal
Prostate	Bladder	glioblastoma (GBM)	atypical fibroxanthoma (AFX)
Colorectal	chronic lymphoblastic leukaemia (CLL)	pleomorphic dermal sarcoma (PDS)	Hepatocellular carcinoma (HCC)

Hepatocellular Carcinoma (HCC)



Hepatocellular Carcinoma (HCC)

Inhibition of CAMKK2 protects against HCC induced by a high-fat diet.

Fibrolamellar hepatocellular carcinoma (FL-HCC) is a primary liver cancer that occurs mainly in children and young adults.

80%-100% FL-HCC patients have DNAJB1–PRKACA gene fusion. This results in:

A) Deleting a 400 kb gene fragment on chromosome 19

B) The production of a chimeric protein that retains PKA kinase activity.

Hepatitis B virus (HBV) infection increases risk of HCC.

HBV X protein can promote liver carcinogenesis through CREB-miR-3188 and ZHX2-Notch signaling pathways. This increases cancer cell growth and invasion.

Brain cancer

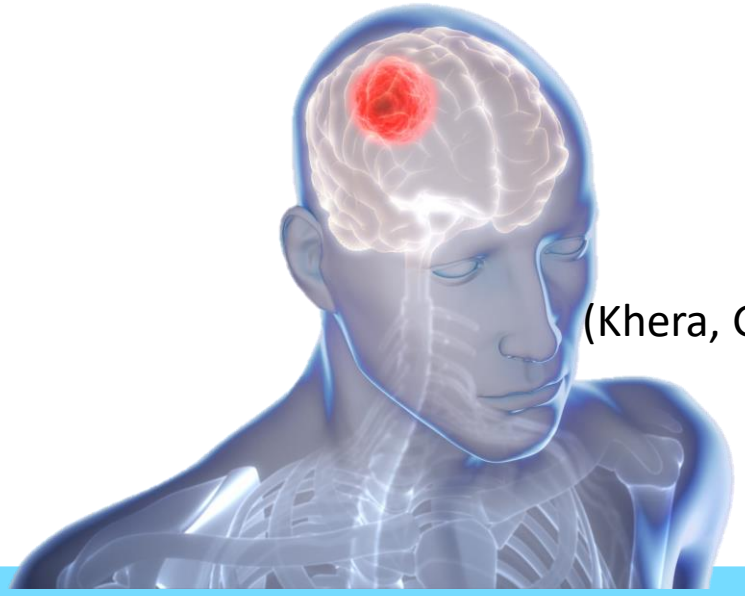
Glioblastoma

Activation of PKA:

Increases cAMP levels.

Upregulates the expression of p21 and p27.

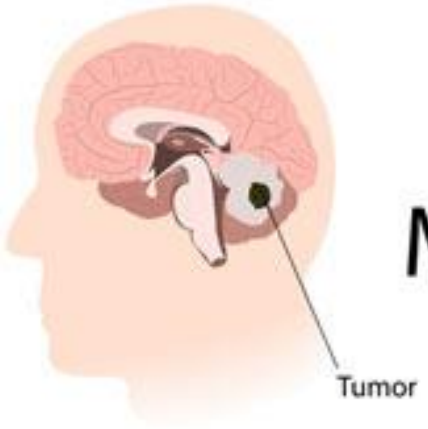
This increases proliferation, differentiation, and apoptosis.



(Khera, G., 2017)

Medulloblastoma

Pituitary adenylyl cyclase inhibits proliferation via the PKA-Gli1 pathway.



Medulloblastoma

(Netmeds.com, 2021)

Lung cancer

Non-small cell lung cancer (NSCLC)

Increased CREB expression and phosphorylation in tumour tissues.

This lowers patient survival.

cAMP can lower apoptosis.

Small cell lung cancer (SCLC)

Increased CREB expression induces

proliferation.

cAMP–PKA–CREB pathway could regulate the hypoxia response in lung cancer cells.

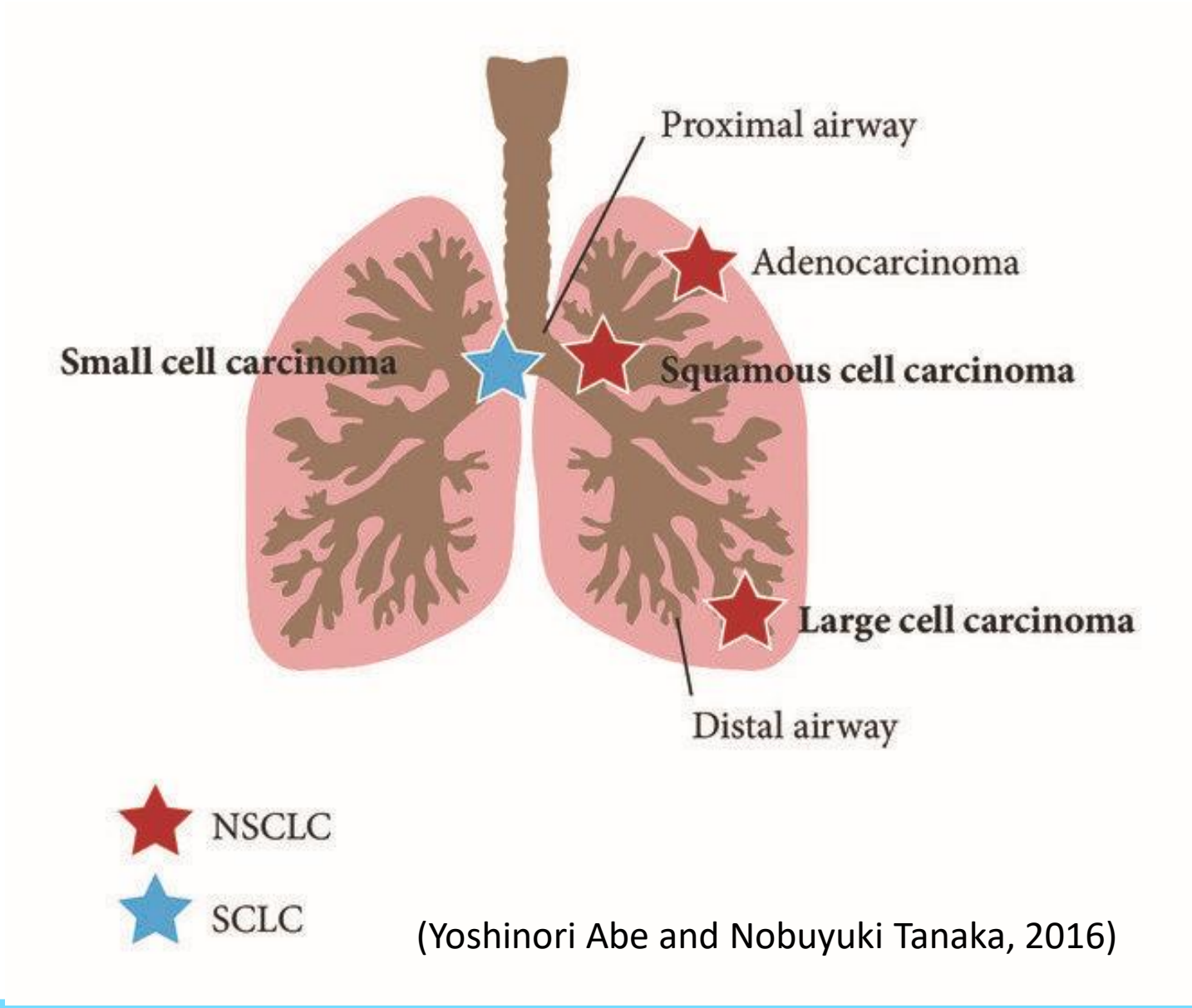
PKA increases cell migration and invasion.

PKA induces Protein phosphatase 2 (PP2A)

phosphorylation and AP1.

This increases apoptosis.

Lung cancer



(Yoshinori Abe and Nobuyuki Tanaka, 2016)

Prostate cancer

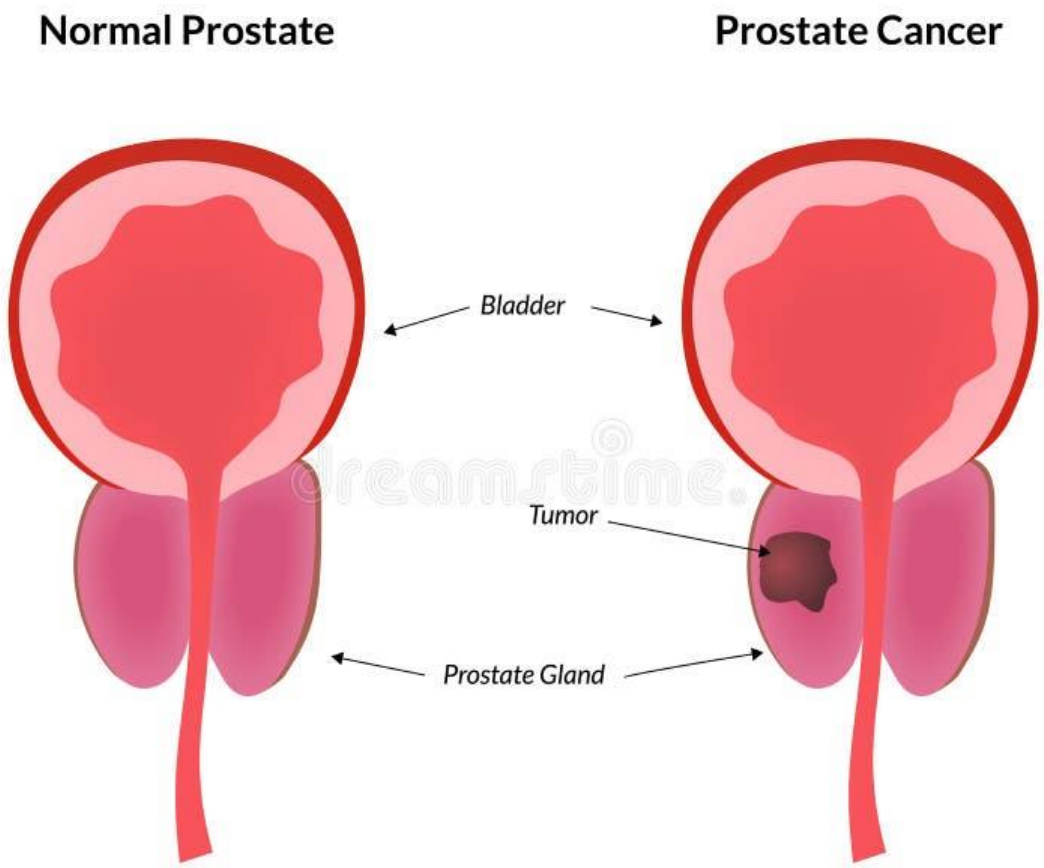
Inhibition of CAMKK2 protects against prostate cancer.

Progression of prostate cancer through PKA kinase

PKA subunit can be a **biomarker to predict the response of to radiotherapy and chemotherapy**.

PKA RIα overexpression is associated with **poor efficacy of radiotherapy and metastasis.**

Testosterone stimulates GPR56 directly and **activates the cAMP/PKA pathway.** This induces **Androgen receptor (AR) signalling** required for **prostate carcinogenesis.**

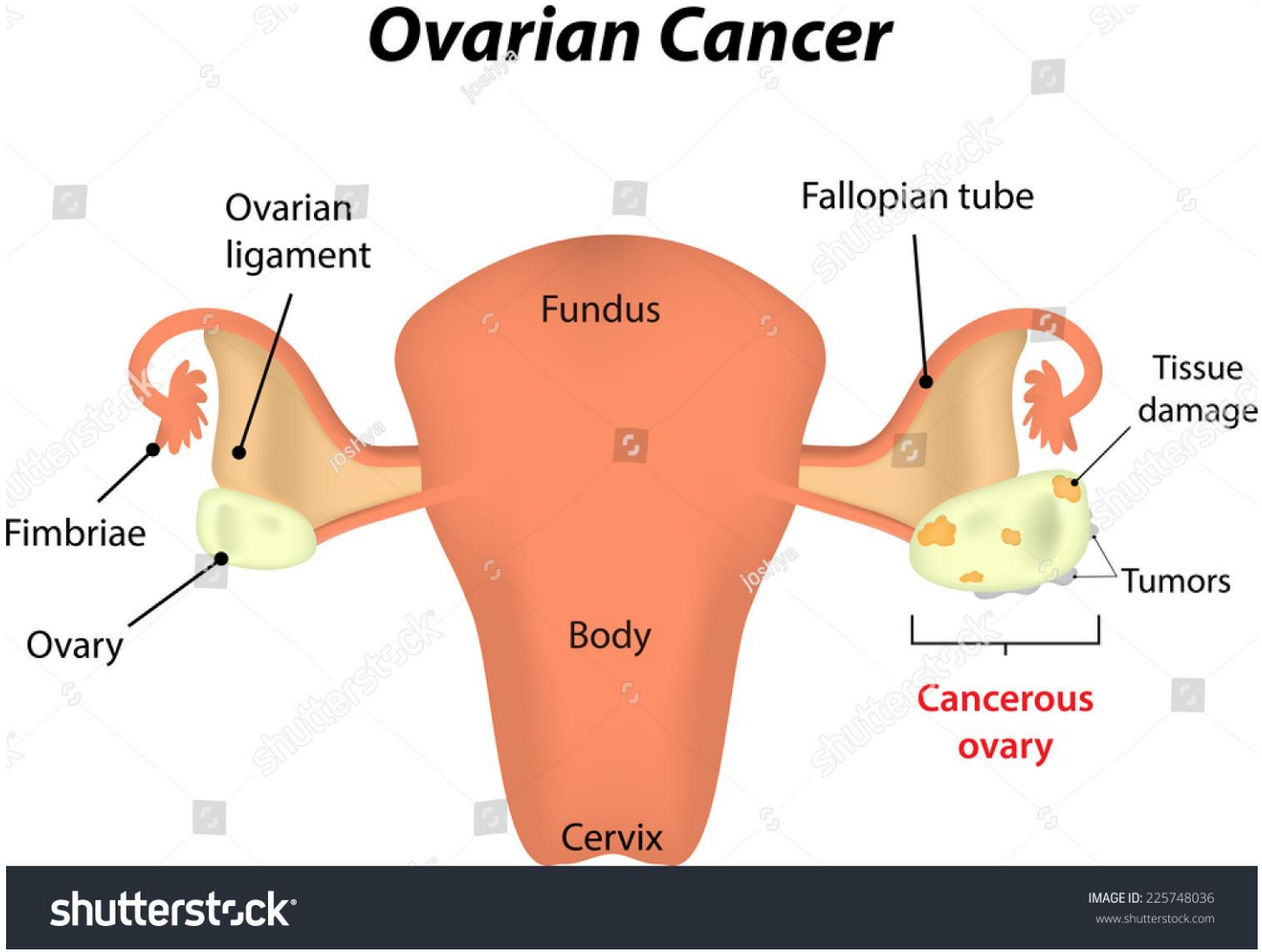


Ovarian cancer

PKA RIα is highly expressed in epithelial ovarian cancer

It promotes invasion and metastasis by phosphorylating claudin-3 protein which lowers the intensity of tight junctions and degrades the extracellular matrix.

Low CREB expression decreases proliferation but has no effect on apoptosis.

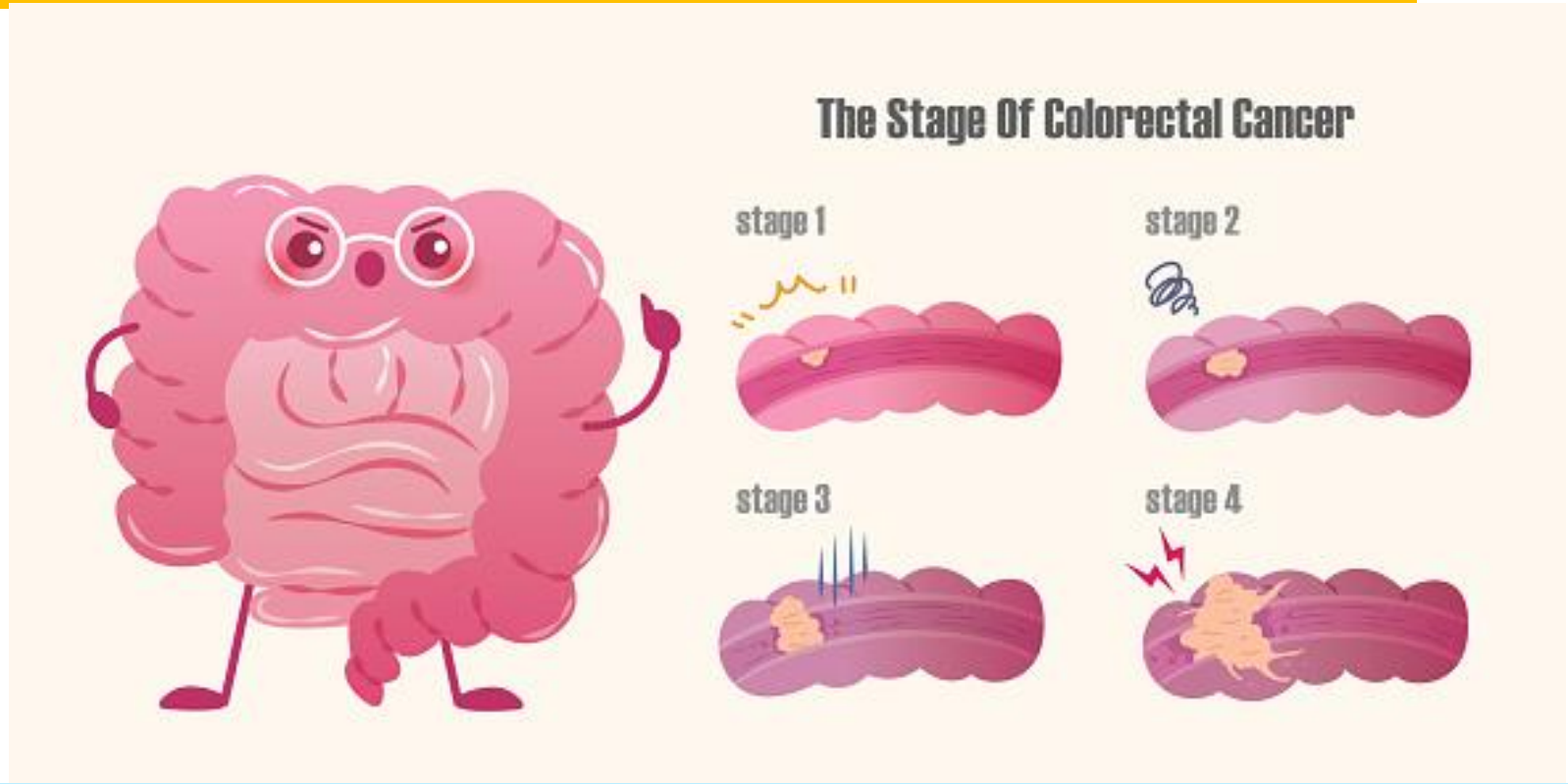


Colorectal cancer

PKA RIα and AKAP10 increased tumour progression and metastasis lowering survival.

Type-I insulin-like growth factor receptor (IGF-IR) signaling stimulates the phosphorylation of ezrin protein.

This leads to cAMP-PKA signalling and increase tumour survival.



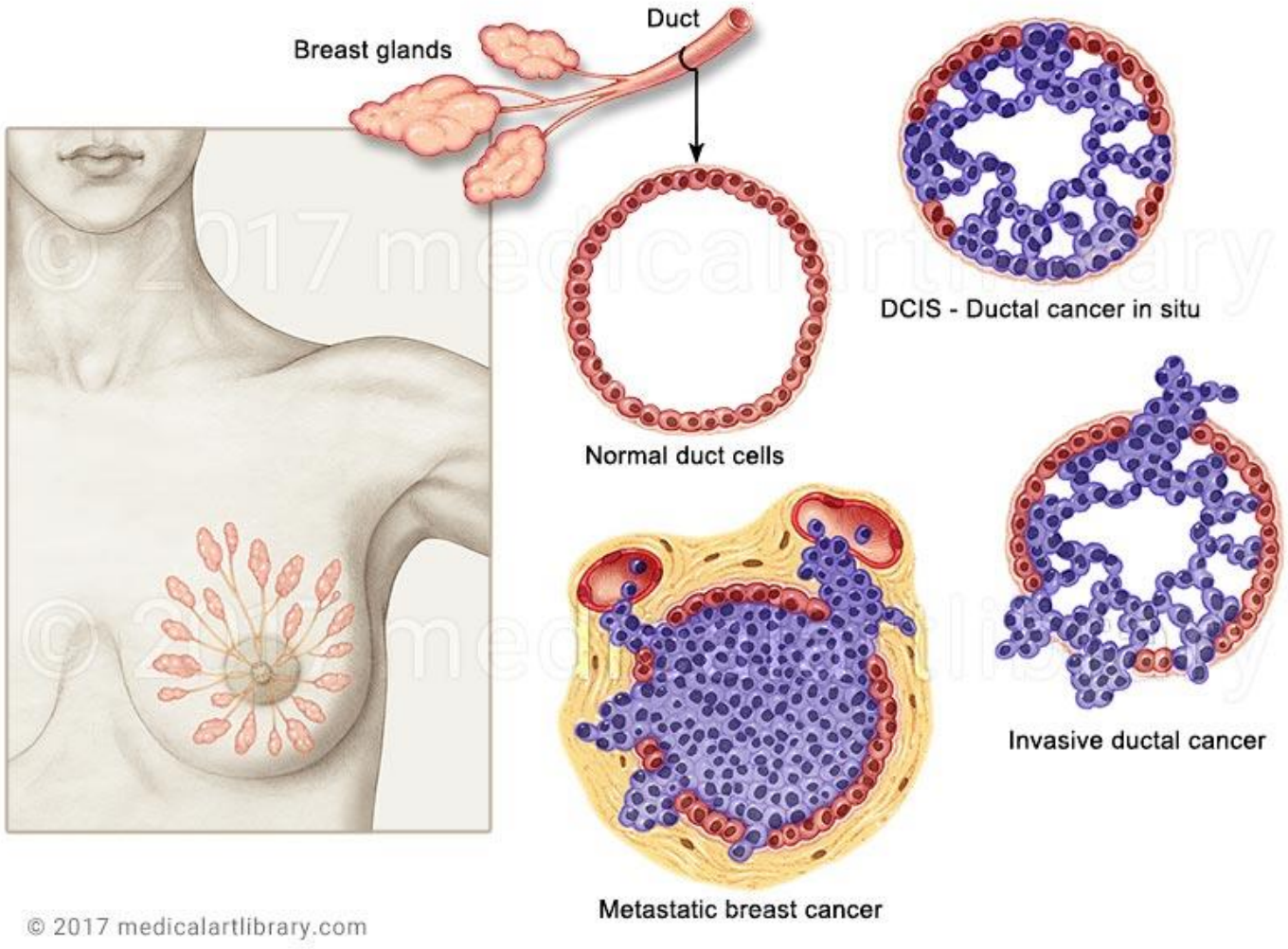
Breast cancer

PKA increases the growth and metastasis of triple negative breast cancer cells through GSK3-βcatenin pathway.

PKA induces chemotherapy resistance e.g. trastuzumab resistance in Her-2 positive breast cancer.

PKA RI subunit increases proliferation in normal cells and breast cancer metastasis

G-protein coupled estrogen receptor increases aerobic glycolysis through cAMP–PKA–CREB pathway.



Blood cancers

Leukaemia

Overexpression of CREB is found in the bone marrow of most leukemia cell lines

<u>B cell chronic lymphocytic leukemia (CLL)</u>

PDE4 inhibitors induces apoptosis by increasing cAMP levels and blocking Toll-like receptor (TLR) signalling.

(TLRs) have a major role in innate immune responses.

Chemokines CXCR4 and CXCL12 released from the microenvironment can bind to Gαi-conjugated GPCRs on CLL cells. This lowers cAMP synthesis and increasing tumour survival.

WHAT IS LEUKEMIA?

A cancer found in the blood and bone marrow, caused by too many white blood cells in the body. The white blood cells don't let the body fight disease and prevent the body from making red blood cells and platelets.

Normal White Blood Cell Count

Abnormal White Blood Cell Count

4 TYPES OF LEUKEMIA

Acute Lymphoblastic Leukemia

- Found in lymphoid cells
- Grows quickly
- Common in children
- 6,000 cases a year

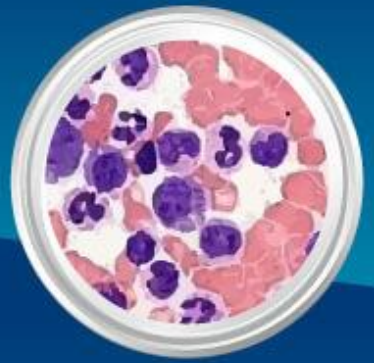
Acute Myelogenous Leukemia

- Found in myeloid cells
- Grows quickly
- Common in adults and children
- 18,000 cases a year

Chronic Lymphoblastic Leukemia

- Found in lymphoid cells
- Grows slowly
- Common in adults 55+
- 15,000 cases a year

Chronic Myelogenous Leukemia



- Found in myeloid cells
- Grows slowly
- Common in adults
- 6,000 cases a year

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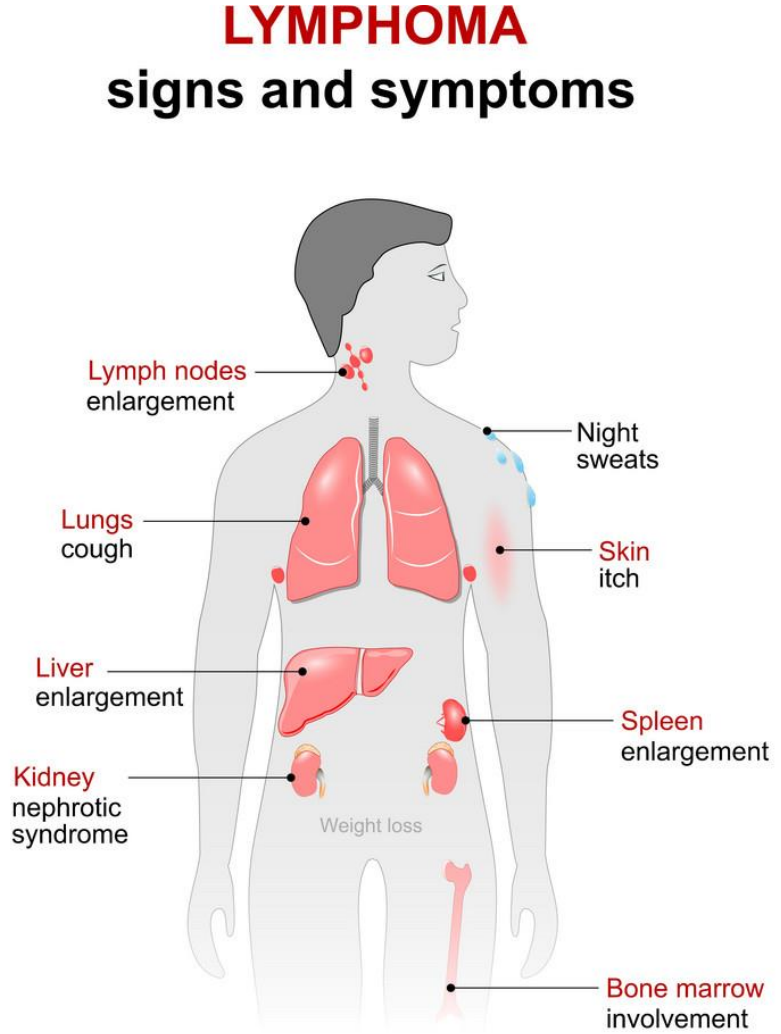
Blood cancers

Lymphoma

cAMP–PKA increases expression of Bax and lowers expression of anti-apoptotic proteins Bcl-2 and survivin. This increases the rate of apoptosis.



By the end of this lecture, you should understand

- GPCRs are **helical transmembrane receptor proteins** found on the **cell surface. It has three domains made of loops: Extracellular, Transmembrane and Intracellular**
- **The activated receptor activates G protein and exchanges for guanosine-5’-diphosphate (GDP) for guanosine-5’-triphosphate (GTP).**
- G proteins are classified according to their **α subunit; Gαi, Gαs, Gα12/13, and Gαq.**
- **Adenyl cyclase stimulates the production of the intracellular second messenger cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP).**
- **cAMP stimulates the protein kinase A made of two catalytic subunits and two regulatory subunits. cAMP binds to the regulatory subunits of PKA.**
- **cAMP response element-binding protein (CREB) is a transcription factor and one of PKA targets that regulate transcription of target genes to initiate cellular response..**
- **Dysregulated GPCR signalling is caused by point mutations. cAMP- PKA-CREB signalling has tumour suppressive and tumour promoting roles. Increase in PKA and cAMP levels increases proliferation, differentiation, cell migration and invasion and apoptosis.**

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SEASON 2

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Understanding Cancer

Lecture 7

Types of signalling pathway: normal and dysregulated EGFR

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