HN

SEASON 2

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Understanding Cancer

Lecture 7

Types of signalling pathway: normal and dysregulated EGFR

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RECAP:

What you hopefully should understand so far from Lecture 6

- 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.**

What will we learn today?

- ***What is Epidermal growth factor receptor (EGFR)?***
- ***The structure of the Epidermal growth factor receptor (EGFR)***
- ***Normal EGFR signalling pathway: Receptor activation***
- ***Normal EGFR signalling pathway: Signal transduction***
- ***Normal EGFR signalling pathway: Cellular response***
- ***Turning off EGFR signalling pathway***
- ***The link between GPCR and EGFR signalling pathways***
- ***Causes of dysregulated EGFR 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!

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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.

What is the Epidermal growth factor receptor (EGFR)?

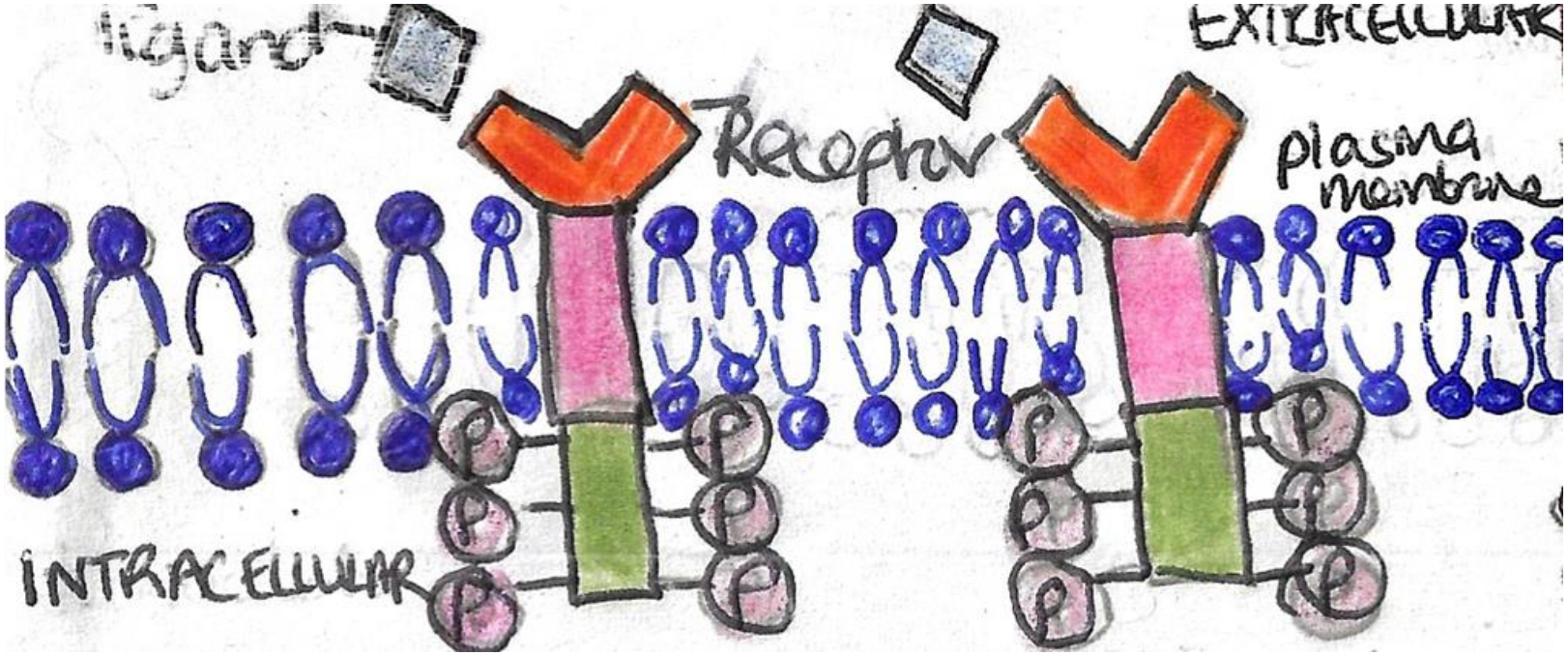
What is the Epidermal growth factor receptor (EGFR)?

The EGFR is an **1,186 amino acid transmembrane glycoprotein.**

In normal cells, the EGFR expression is between 40,000–100,000 receptors per cell.

It is a member of the **receptor tyrosine kinases (TK)** family that have **four subtypes:**

ErbB1/EGFR/ HER1 (humans)	**ErbB2/HER2/ Neu**	**ErbB3/HER3**	**ErbB4/HER4**


ligand
Receptor
plasma membrane
INTRACELLULAR

The structure of the Epidermal growth factor receptor (EGFR)

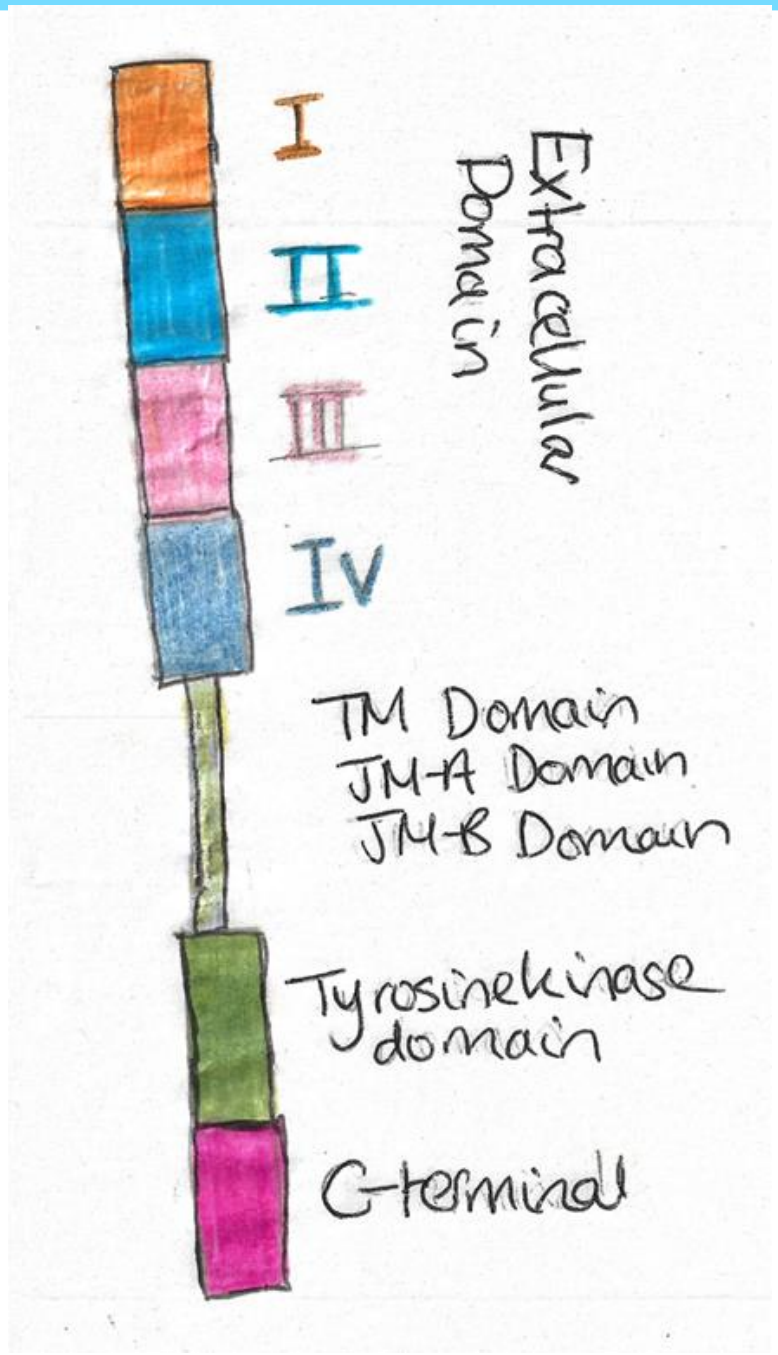
The structure of the Epidermal growth factor receptor (EGFR)

The EGFR has a **molecular weight** between **170 to 185 kDa** and has **three domains:**

Extracellular domain

Transmembrane domain

Intracellular domain


I
II
III
IV
Extracellular Domain
TM Domain
JM-A Domain
JM-B Domain
Tyrosinekinase domain
C-terminal

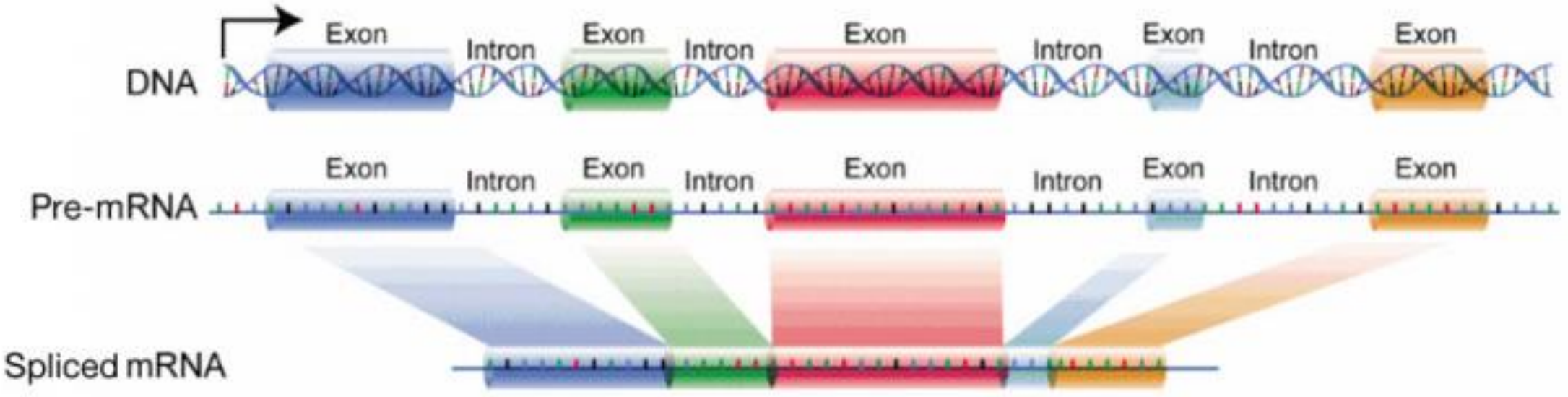
The structure of the Epidermal growth factor receptor (EGFR)

Extracellular domain

- It is a **N-terminal ligand binding domain**.
- It is a **conserved region with lots of cysteine residues.**
- It contains **621 amino acids (exons 18-28)**
- It has a **dimerization arm.**
- It divided into **four domains.**

Extracellular domain

Domain	Description	Function
I	It contains leucine-rich fragments. 1–133 amino acids (exons 1–4).	It binds to the ligand.
II	It contains the dimerization arm. It has cysteine-rich regions. 134–312 amino acids (exons 5–7).	It interacts with another dimerization arm of another receptor to form a homodimer. This helps maintain EGFR signalling. Hetero-dimers with the similar domain in the TK family. It does not make contact with the ligand.
III	It contains leucine-rich fragments. 313–445 amino acids (exons 8–12)	It binds to the ligand.
IV	It has cysteine-rich regions. 446–621 amino acids (exons 13–16).	It can form disulfide bonds to domain II, and links to the Transmembrane domain. It does not make contact with the ligand.



(Source: Creative Commons, 2023)

Coding regions: exons

Non-coding regions: introns

The structure of the Epidermal growth factor receptor (EGFR)

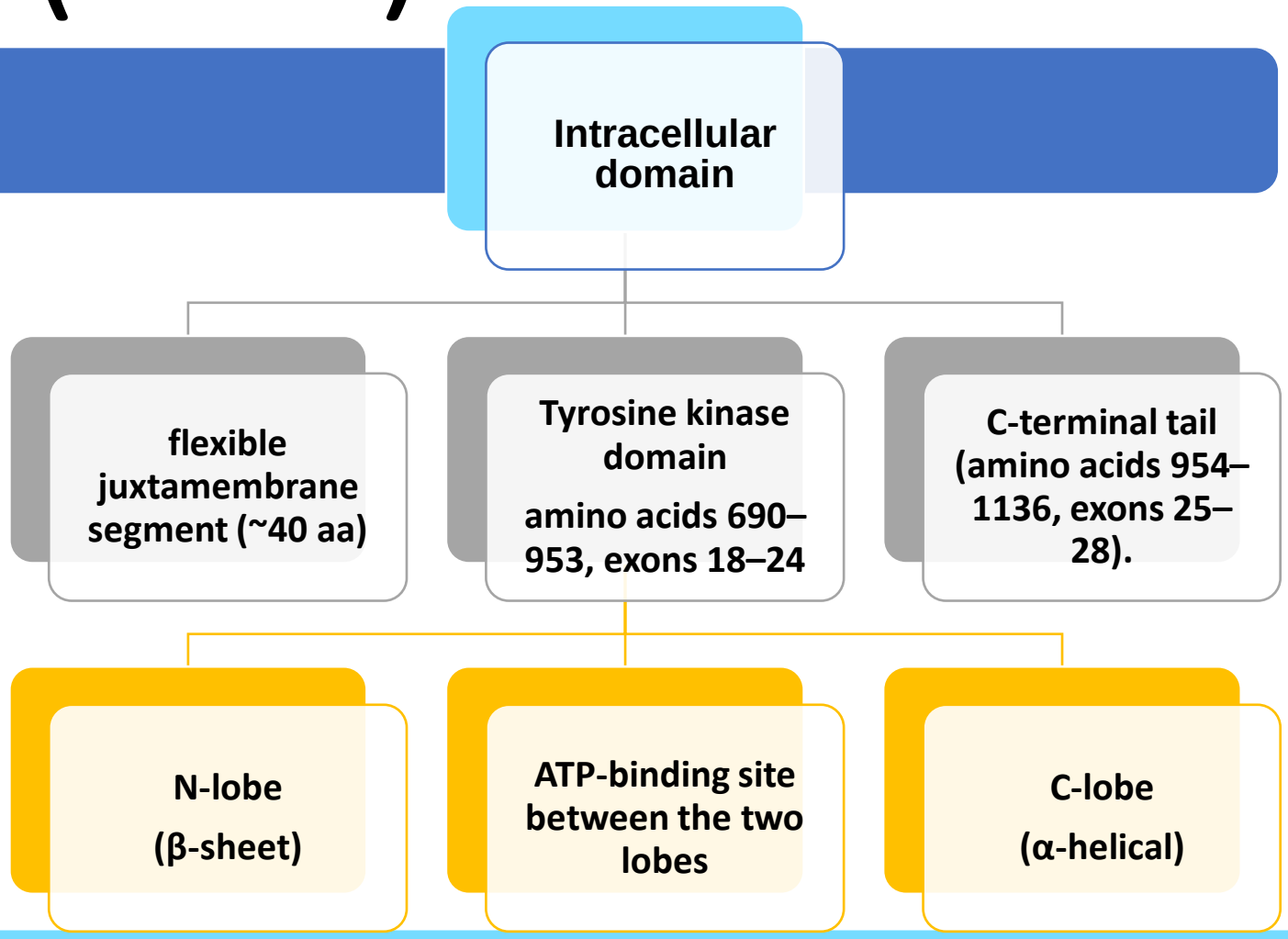
Transmembrane domain

- A **hydrophobic transmembrane domain**.
- It has **23 amino acids (exon 17).**
- It firmly **attaches the receptor to the membrane**.
- It is involved in the **dimerization** process.

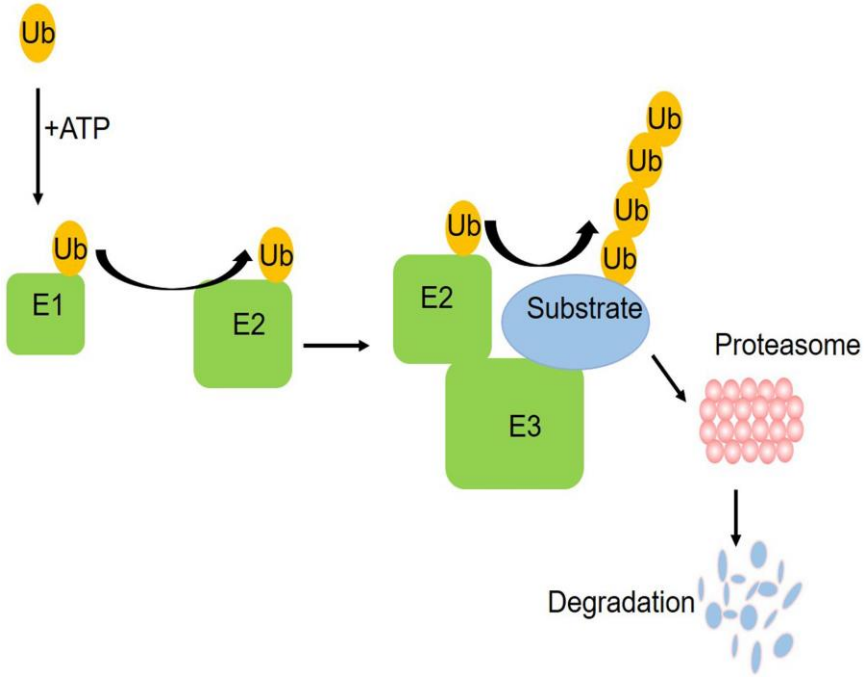
The structure of the Epidermal growth factor receptor (EGFR)

Intracellular domain

- It is a **cytoplasmic C-terminal tyrosine kinase domain**.
- It contains **542 amino acids.**
- It has a few **phosphorylation sites**.
- It has **lots of tyrosine residues** involved in **phosphorylation.**
- It has **lots of lysine residues** involved in **ubiquitination.**



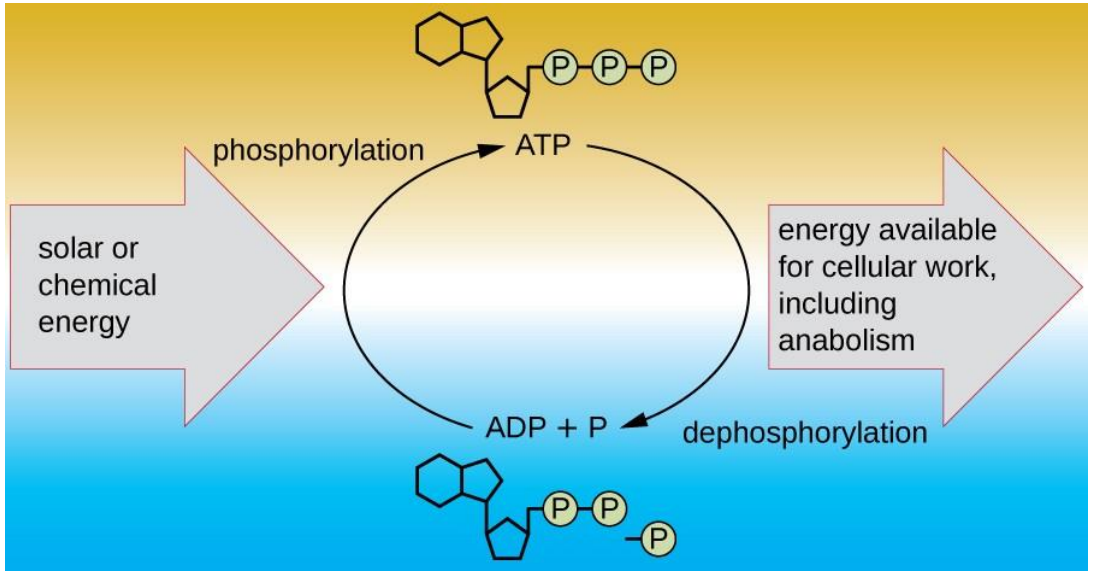
Ubiquitination



(Source: Creative Commons, 2023)

Ubiquitin is a small protein that directs proteins to the proteosome where proteins are degraded.

Phosphorylation



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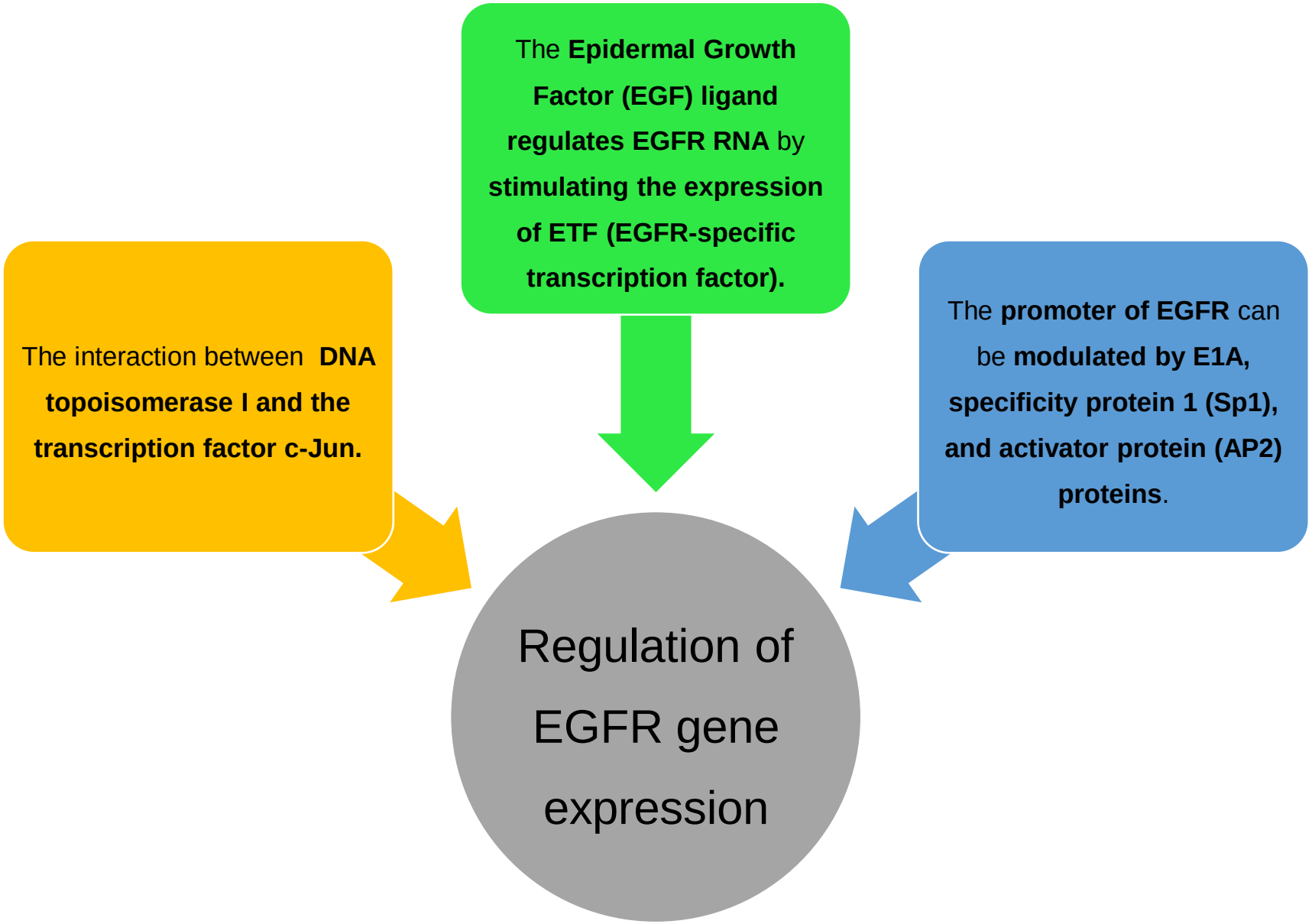
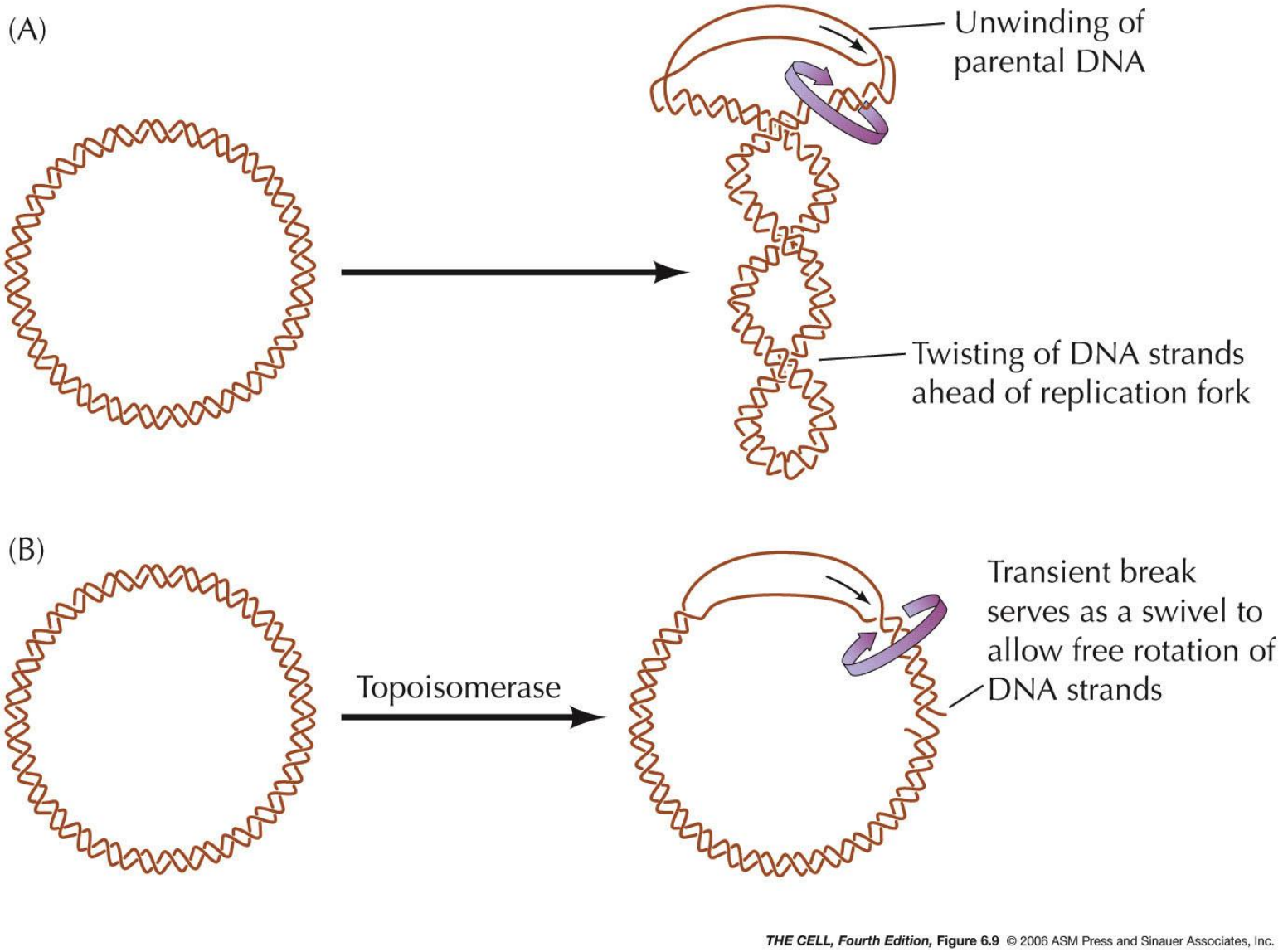
The addition of the phosphate group.


The **Epidermal Growth Factor (EGF) ligand regulates EGFR RNA** by **stimulating the expression of ETF (EGFR-specific transcription factor).**
The interaction between **DNA topoisomerase I and the transcription factor c-Jun.**
The **promoter of EGFR** can be **modulated by E1A, specificity protein 1 (Sp1), and activator protein (AP2) proteins**.
Regulation of EGFR gene expression

Name of protein	Abbreviation	Description
E1A		They stimulate gene transcription of adenovirus. The G0-arrested cells enter the S-phase where DNA synthesis take place.
Specificity protein 1	Sp1	A transcription factor involved in the transcription of genes that contain lots of cysteine-guanine binding sites in their promoter region. The following cellular activity: proliferation, differentiation, apoptosis and tumour formation.
Activating Protein 2	AP-2	A transcription factor that regulates gene expression during early development.
c-Jun		A transcription factor that binds with another transcription factor to produce the AP-1 (activator protein 1) complex. This binds to the cyclin D1 promoter region that plays a critical in G1 phase of the cell cycle.
Topoisomerase 1	TOP1	A type of enzyme that makes single-stranded breaks in DNA to relieve the stress of DNA supercoiling caused by unwinding of DNA during replication and the initiation step in transcription. Negative supercoiling facilitate the DNA separation of strands whilst positive supercoilings inhibit DNA strands separation. Topoisomerase II (TOP2) produces double-strand breaks in DNA.



THE CELL, Fourth Edition, **Figure 6.9**

(Johnson, D. 2017)

Normal EGFR signalling pathway: Receptor activation

Normal EGFR signalling pathway: Receptor activation

The Ligand

- The **Epidermal Growth Factor (EGF)** is a **protein that contains 53 amino acids**.
- The EGF is predominantly found in the **heart, gut (intestines), brain, teeth, reproductive tracts and eyes.**
- It shares **35-40% homology with another ligand called transforming growth factor (TGF-α)** composed of **50 amino acids.**

Normal EGFR signalling pathway: Receptor activation

Step 1	• **The binding of the ligand to the receptor.**
Step 2	• **Dimerization of the receptor.**
Step 3	• **Receptor transautophosphorylation of C-terminal domain**

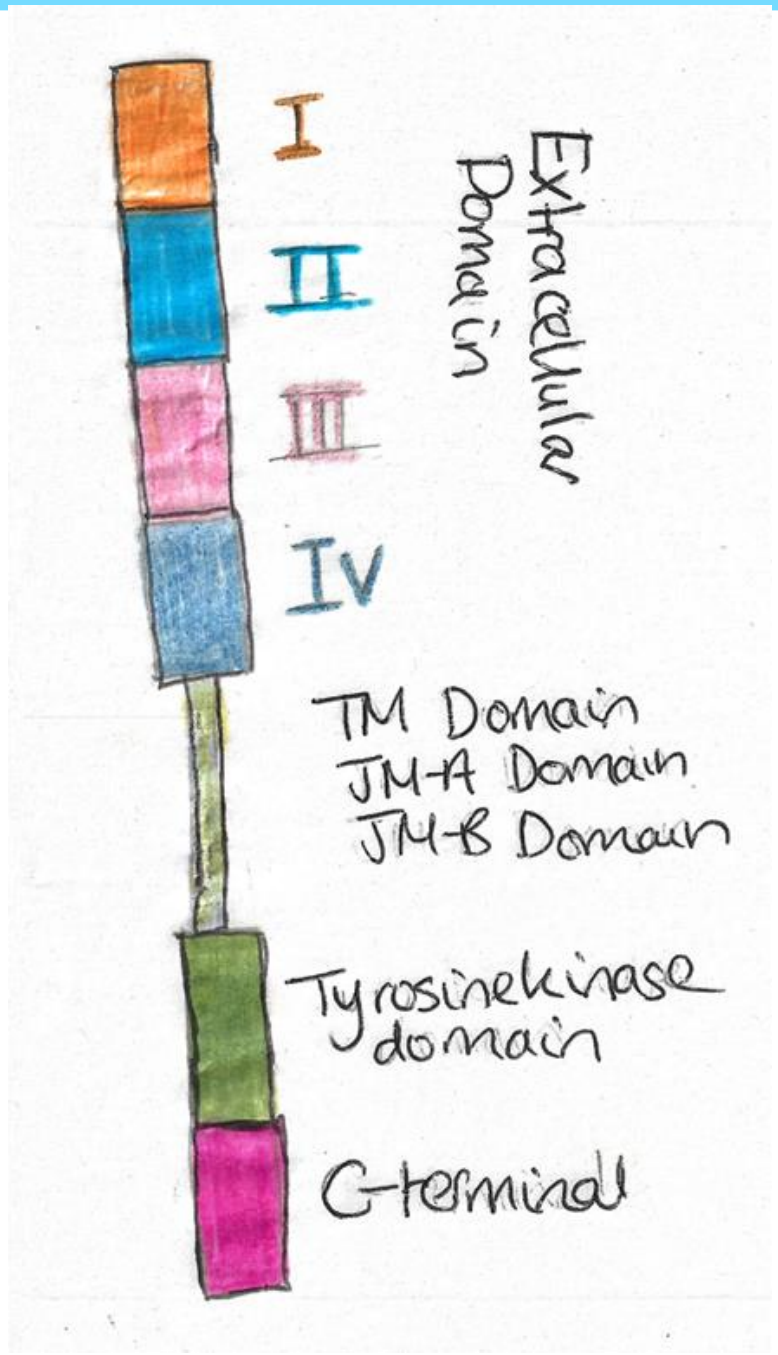
Normal EGFR signalling pathway: Receptor activation

Step 1

The binding of the ligand to the EGFR receptor.

The **extracellular domain (II and IV)** are **pushed away** to **facilitate the domains I and III to present their position and interact with the ligand.**

Each ligand specifically binds to a particular receptor


I
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Extracellular Domain
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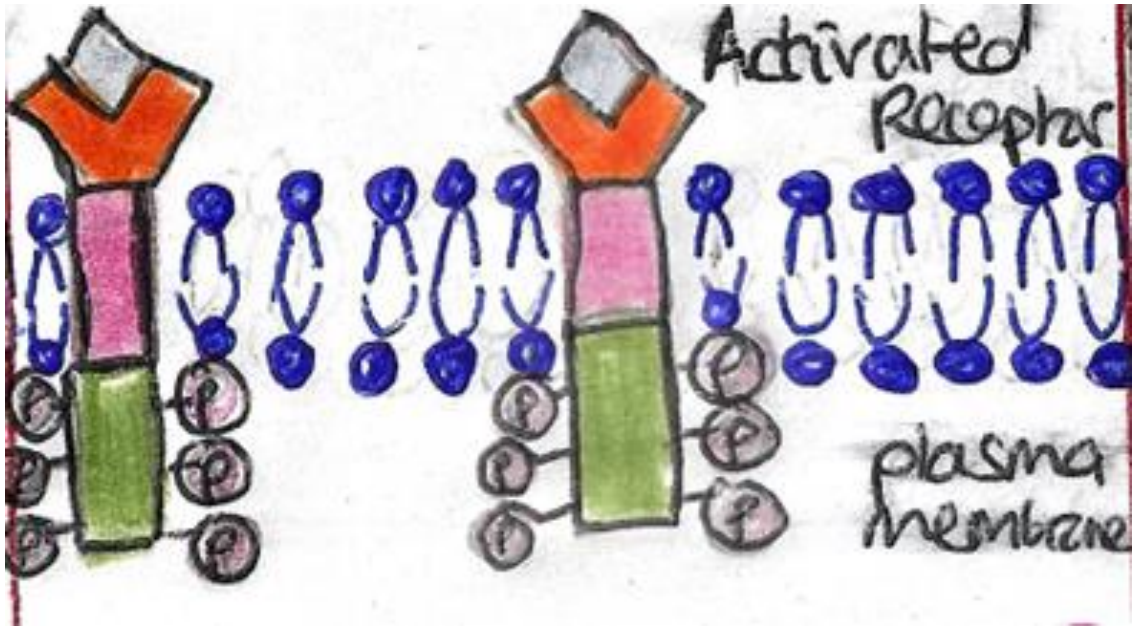
Normal EGFR signalling pathway: Receptor activation



Name of receptor	Ligand	Function of ligand
ErbB1/EGFR/HER1	EGF	Growth factor involved in proliferation and differentiation of EGF present in the heart, gut (intestines), brain, teeth, reproductive tracts and eyes.
	Heparin Binding EGF (HB-EGF)	Tissue repair and regeneration. It is widely expressed in organs e.g. liver, heart and bladder. Cellular proliferation, migration, adhesion, and differentiation.
	Amphi-regulin (AREG)	A membrane-anchored precursor protein that can engage in juxtacrine signaling (contact-dependent signalling) on cells close in contact. Cellular proliferation, motility and survival. The development and maturation of mammary glands, bone tissue and oocytes.
	Epigen (EPG)	Still unknown but studies suggest it plays a role in the epidermis (skin), the mammary gland and the sebaceous gland.
	Beta Cellulin (BTC)	Growth factor produced in the pancreas and small intestine. It enhances cell division via mitosis in the epithelial cells in the retina of the eye and smooth muscle cells in the vessels.
	Epiregulin (EPR).	A new member of EGF that helps tissue repair and would healing in the oral cavity. It increases in the epithelial tissues and malignancies such as colorectal, lung, and bladder carcinoma
	Transforming Growth Factor-α (Tgf-α)	Cell migration, tissue repair, homeostasis, growth, and differentiation. It is found in epithelial tissues: gut (intestines), liver, kidney, breasts, skeletal muscle, skin, reproductive organs.

Name of receptor	Ligand	Function of ligand
ErbB2/HER2/Neu	It cannot bind to any ligands. It is involved in receptor dimerization.	
ErbB3/HER3	Neuregulins (NRG-1 to 6)	Development and function of other organs e.g. nerves, breast and heart. (NRG4) - a brown fat-enriched hormone that modulates energy, glucose and fat metabolism.
	Herregulin-1(HRG-1) and (HRG-2)	A growth factor involved in cell proliferation, differentiation, invasion and survival of normal and malignant tissues.
ErbB4/HER4	neuregulins (NRG-1 to 6) BTC, HB-EGF, EPR	

Normal EGFR signalling pathway: Receptor activation

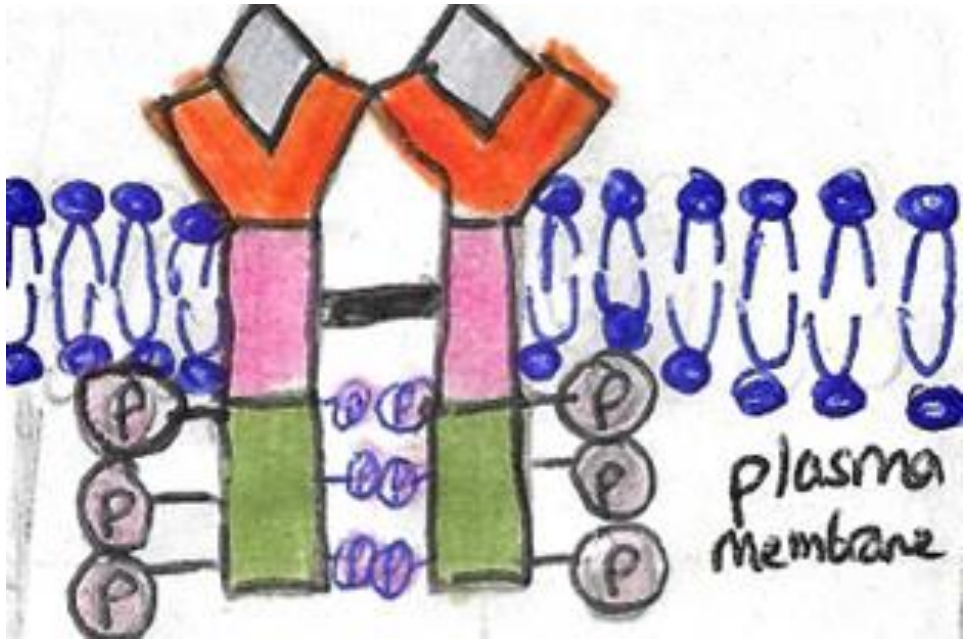
Step 2

Dimerization of the receptor.

The **dimerization arm in the extracellular domain II** interacts with another **dimerization arm of another to form a homodimer.**

Heterodimerisation between family members e.g.

- ❑ **EGF can induce heterodimerization of EGFR with HER2, HER3 or HER4.**
- ❑ **NRG4 stimulates heterodimerization of HER4 with HER1, HER2 and HER3**.


P
P
P
P
P
P
P
plasma
membrane

Normal EGFR signalling pathway: Receptor activation

Step 3

Receptor transautophosphorylation of C-terminal domain

The **cytoplasmic domain of the intracellular region of one EGFR (N-lobe)** contains **tyrosine residues** which **phosphorylates the cytoplasmic domain of the intracellular region of the other EGFR (C-lobe).**

This is known as ***Transautophosphorylation.***

Normal EGFR signalling pathway: Signal transduction

Normal EGFR signalling pathway: Signal transduction

phosphatidylinositol-3 kinase PI3K/Akt/mTOR

JAK-STAT

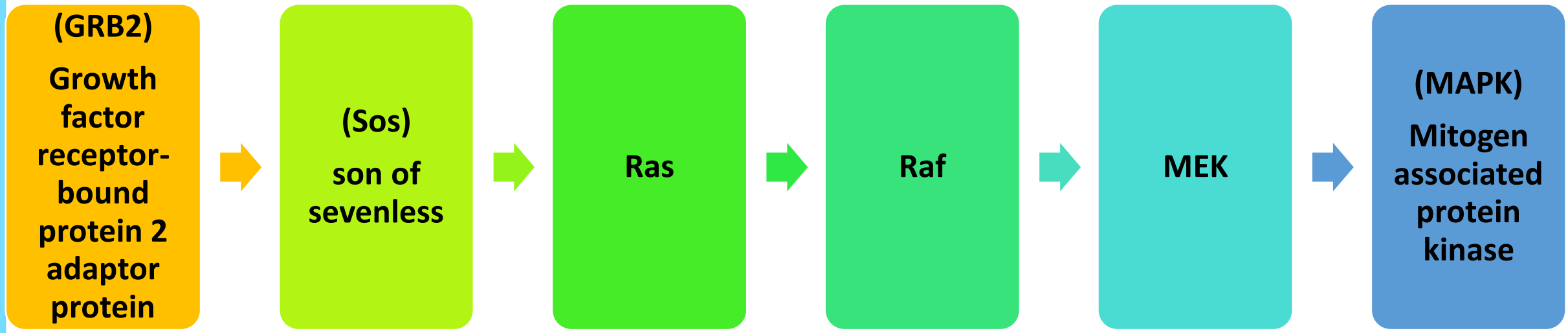
Ras/Raf/ MAPK/ERK

PLC-γ phospholipase C gamma protein-PKC

FOCUS

Ras/Raf/ MAPK/ERK

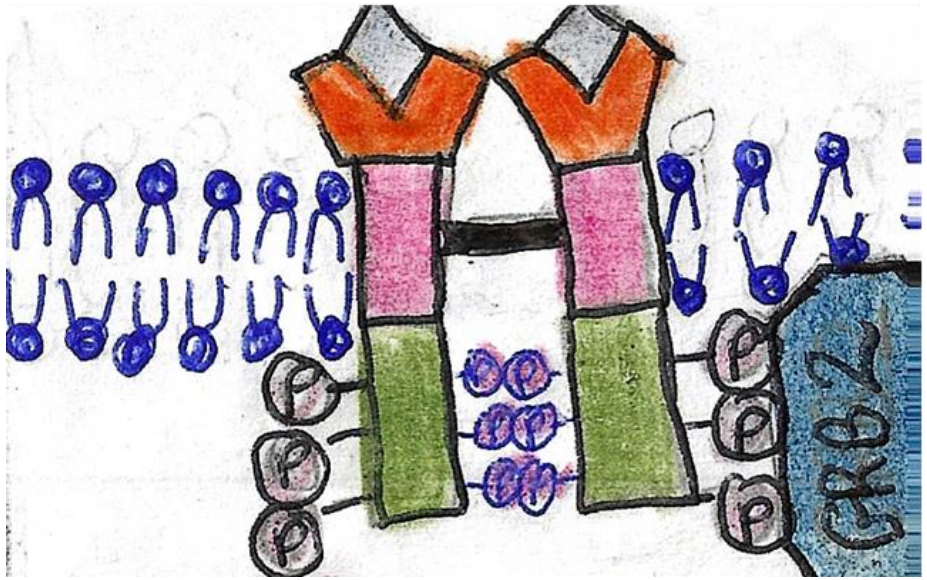
Recruitment of 6 effector proteins



Normal EGFR signalling pathway: Signal transduction

Step 4

The GRB2 adaptor protein binds to the **phosphorylation sites** on the **cytoplasmic domain of EGFR** via the **GRB2 SH2 (Src homology 2) domain.**

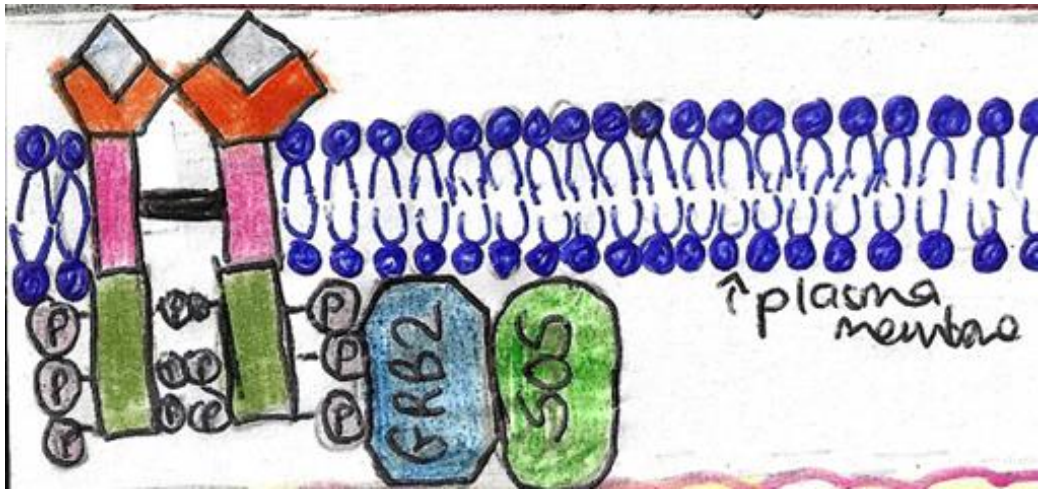


Normal EGFR signalling pathway: Signal transduction

Step 5

The PH (pleckstrin homology) domains of the **guanine nucleotide exchange factor (GEF)** called **son of sevenless (**Sos) **interacts with GRB.**

Sos is recruited to the plasma membrane (PM).



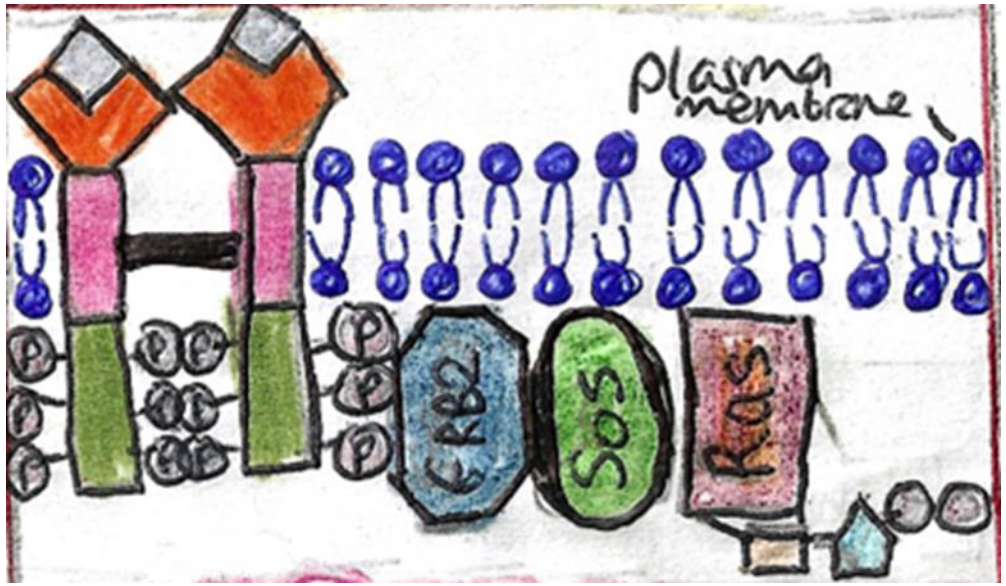
Normal EGFR signalling pathway: Signal transduction

Step 6

The Sos binds to a small guanosine triphosphatase (GTPase) enzyme called **Ras.**

RAS, including H-RAS, K-RAS, and N-RAS are oncogenes.

Ras is bound to **GDP (guanosine diphosphate).**



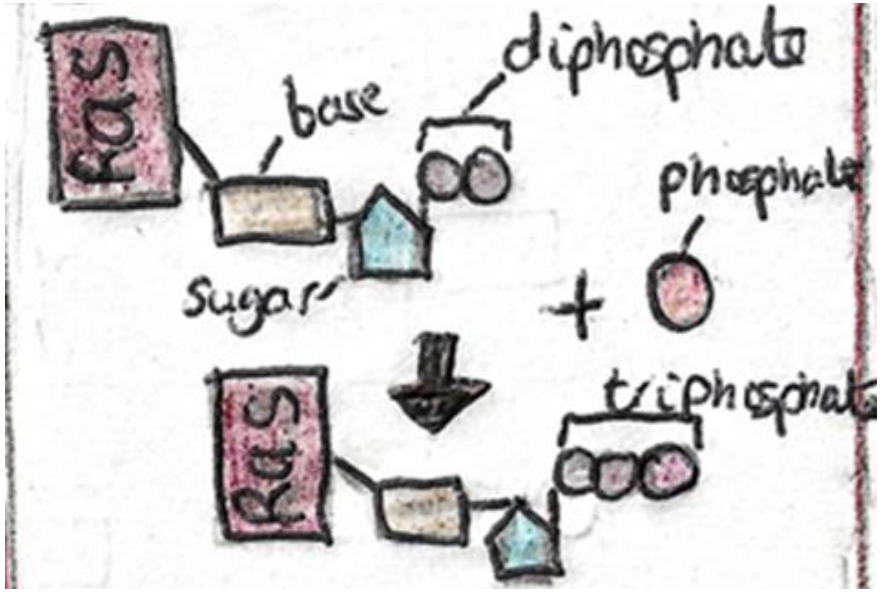
Normal EGFR signalling pathway: Signal transduction

Step 7

Sos catalyzes the conversion of GDP to GTP of RAS.

This causes a **conformational change in RAS**.

This turns on the **RAS activity.**



Normal EGFR signalling pathway: Signal transduction

Step 8

The GRB2 adaptor protein via its SH3 domain recruits the **proline-rich domains of Sos** to **initiate ERK MAPK protein kinase cascade.**

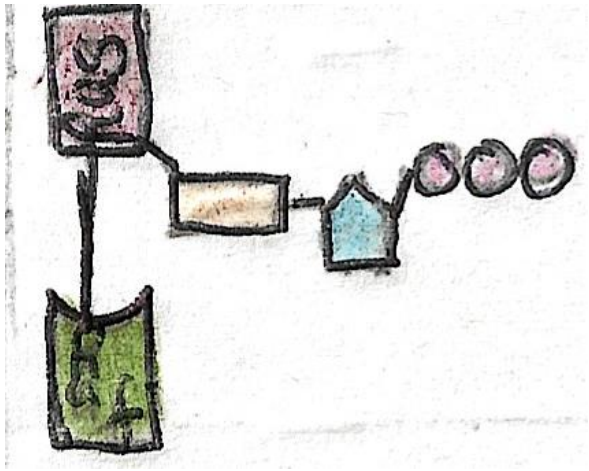
Normal EGFR signalling pathway: Signal transduction

Step 9

RAS activates the downstream effector RAF-1.

RAF-1 also known as **c-RAF is a serine-threonine protein kinase** and has **two domains:**

- ❑ **N-terminus regulatory domain**
- ❑ **C-terminus kinase domain**



Normal EGFR signalling pathway: Signal transduction

How is this achieved?

- **The RAF-binding domain (RBD) region of RAS translocates RAF-1 to the plasma membrane.**
- **The cysteine-rich domain (CRD) of RAS has 139-184 amino acids and activates of RAF-1.**
- **Phosphorylation of Serine 338 and Tyrosine 341 residues of Raf-1.**

This is 20 amino acids upstream of the ATP-binding domain in the regulatory region.

- **The phosphorylation of Serine 259 and Serine 621 of Raf-1 is inhibitory and is catalysed by AKT.**

Did you know?

Serine 338 in RAF1 maybe phosphorylated by the p21-activated kinase (PAK) family.

PAK1 phosphorylates RAF-1 in a growth factor-independent manner.

PAK3 phosphorylates small GTP-binding proteins CDC42 and RAC found in the plasma membrane.

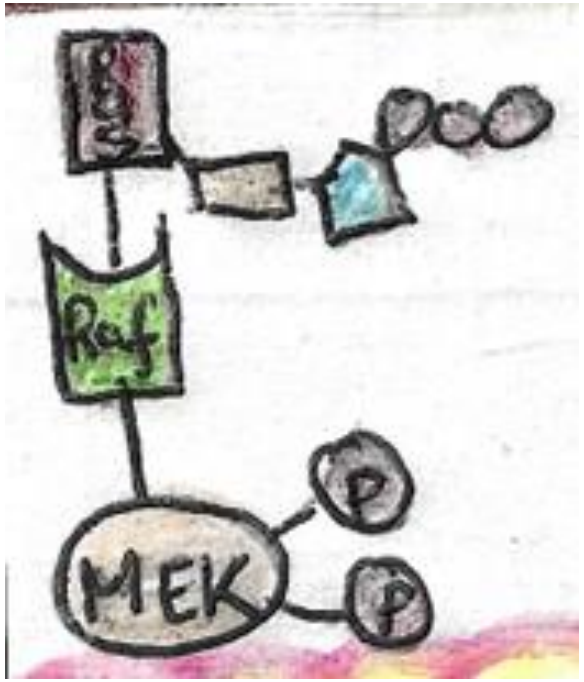
Normal EGFR signalling pathway: Signal transduction

Step 10

RAF-1 binds with **mitogen-activated protein kinase kinase-MAPKK (MEK) via Serine 338 and Tyrosine 341 sites on RAF-1.**

RAF-1 directly phosphorylates MEK at positions Serine residues 217 and 221.

MEK is a **rare tyrosine and threonine/serine dual-specificity kinases.**



Normal EGFR signalling pathway: Signal transduction

Step 11

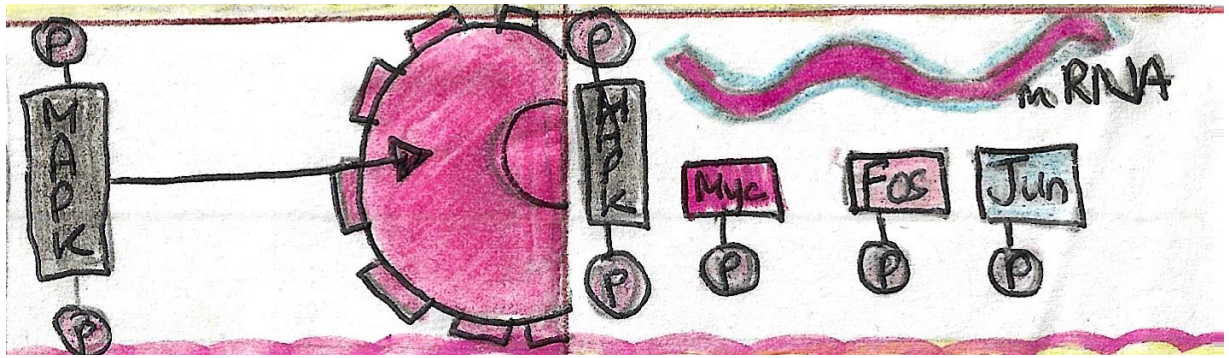
Activated MEK1/2 phosphorylates the Thr-Glu-Tyr motif in the activation loop of the ERK1/2 serine/threonine kinases.

Normal EGFR signalling pathway: Cellular response

Normal EGFR signalling pathway: Cellular response

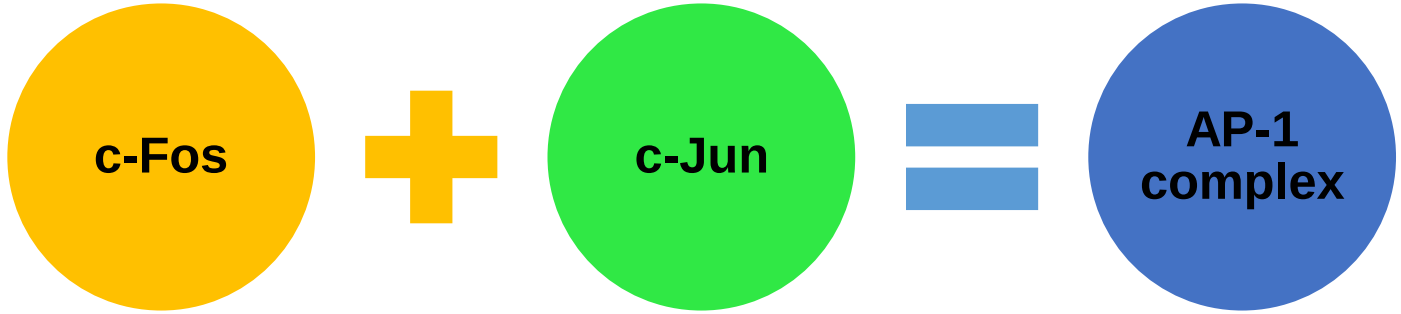
Step 12.

ERK1/2 serine/threonine kinases phosphorylates MAPK (mitogen-associated protein kinase) and is **translocated to the nucleus** where it **phosphorylates the transcription factors: c-myc, Jun and c-Fos.**

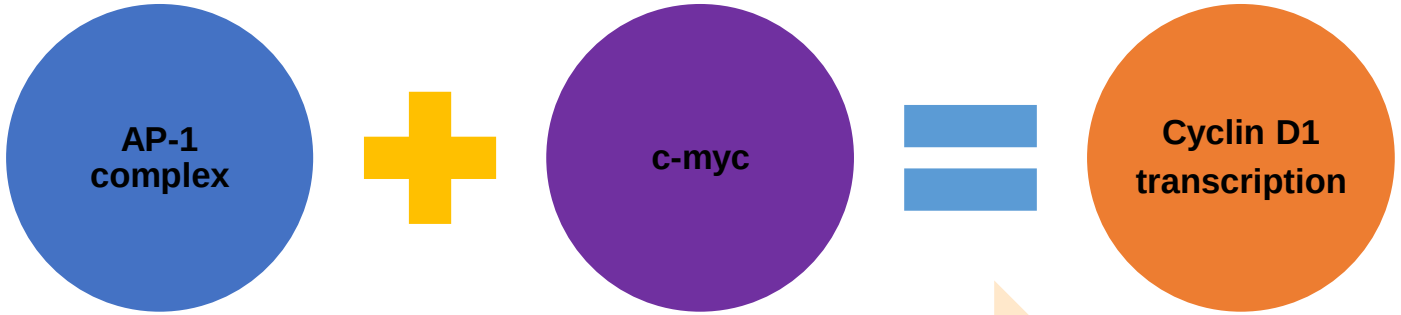


Production of the protein dimers from the Jun and Fos families (Jun, Jun B, Jun D, Fos, Fos B, FRA1, and FRA 2)

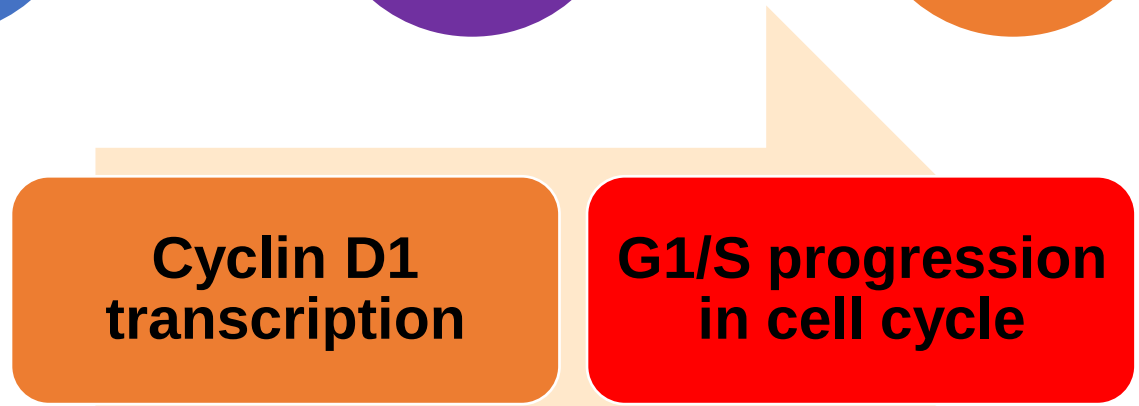
1. Production of the protein dimer.



2. Transcription of target genes



3. Cellular response



Normal EGFR signalling pathway: Cellular response

Cell migration	**Cell adhesion**	**Cell proliferation**	**Cell survival**
Angiogenesis	**Production of ribosomes**	**Translation of proteins**	**Cell division**

Normal EGFR signalling pathway: Cellular response

Step 13.

MAPK phosphorylates other targets.

❑ ***E-26 Transformation Specific (ETS) family of proteins.***

- **Tumour growth and progression in colorectal cancer.**
- **Regulates the normal cell cycle in the G1/S transition but the process is unclear.**

❑ ***Ephrin receptor EphA2***

- **Angiogenesis, growth of endothelial cells, cell survival and migration.**

❑ ***Anti-apoptotic genes***

Step 14.

ERK1/2 serine/threonine kinases has other targets it phosphorylates.

p90 ribosomal S6 kinase 1 (RSK1)

- It is phosphorylated at T573 located in the C-terminal kinase domain.
- RSK translocates to the nucleus to activate immediate early genes (IEG).
- Examples of IEGs are the transcription factors: c-FOS and SRF.
- c-FOS is phosphorylated at S374 by ERK1/2 and at S362 by RSK.
- Phosphorylation of S221, S363, and S380 positions is vital for RSK1 activity.

ternary complex factor (TCF)

- ERK translocates to the nucleus and activate TCF.
- This induces c-Fos and c-myc transcription factors.

ETS Like-1 protein (ELK)

- ERK translocates to the nucleus and activate ELK-1 at Serine residues:S383, S389 and S422 at the C-terminal transactivation domain.
- C-Fos and c-Jun make the AP-1 complex.

Apoptotic proteins

- ERK phosphorylates proapoptotic protein BIM.
- This causes ubiquitination and proteasome degradation.
- This negatively regulates apoptosis.

Did you know that the activated EGFR can translocate into the nucleus?

Did you know that the activated EGFR can translocate into the nucleus?

The activated EGFR receptor can bind to transcription factors E2F1 and STAT3 via importins.

This can upregulate Cyclin D-1.

Turning off EGFR signalling pathway

Turning off EGFR signalling pathway

SRC phosphorylates Y32 on RAS. This stops the binding of RAS to RAF-1.

GTPase catalyses GTP to GDP to turn off Ras.

This is accelerated by GTPase activating proteins (GAPs), such as NF1 (Neurofibromin 1).

The extracellular domain, II and IV stop domain I and III from the interaction with the ligand.

The EGF-EGFR complex enters pits called clathrin coated pits from the plasma membrane.

CCPs released into structures called endosomes via vesicles.

EGFR interacts with the clathrin-binding protein called AP-2 in the endosomes.

The EGFR can be degraded by lysosomes in the vesicles.

The EGFR can also be recycled back to the cell surface.

The AP-2 can also dissociated from the receptor-ligand complex and recycle back to the cell surface.

The link between GPCR and EGFR

The link between GPCR and EGFR

Protein Kinase A (PKA)

PKA phosphorylate Rap-1 protein which is part of Ras family. Rap-1 phosphorylates B-Raf-MEKs/ERK signalling pathway.

Epac

It is one of the targets of cAMP and it is a guanosine exchange factor (GEF).

It stimulates Rap1 and Rap2 to release GDP and bind GTP.

Protein Kinase C (PKC)

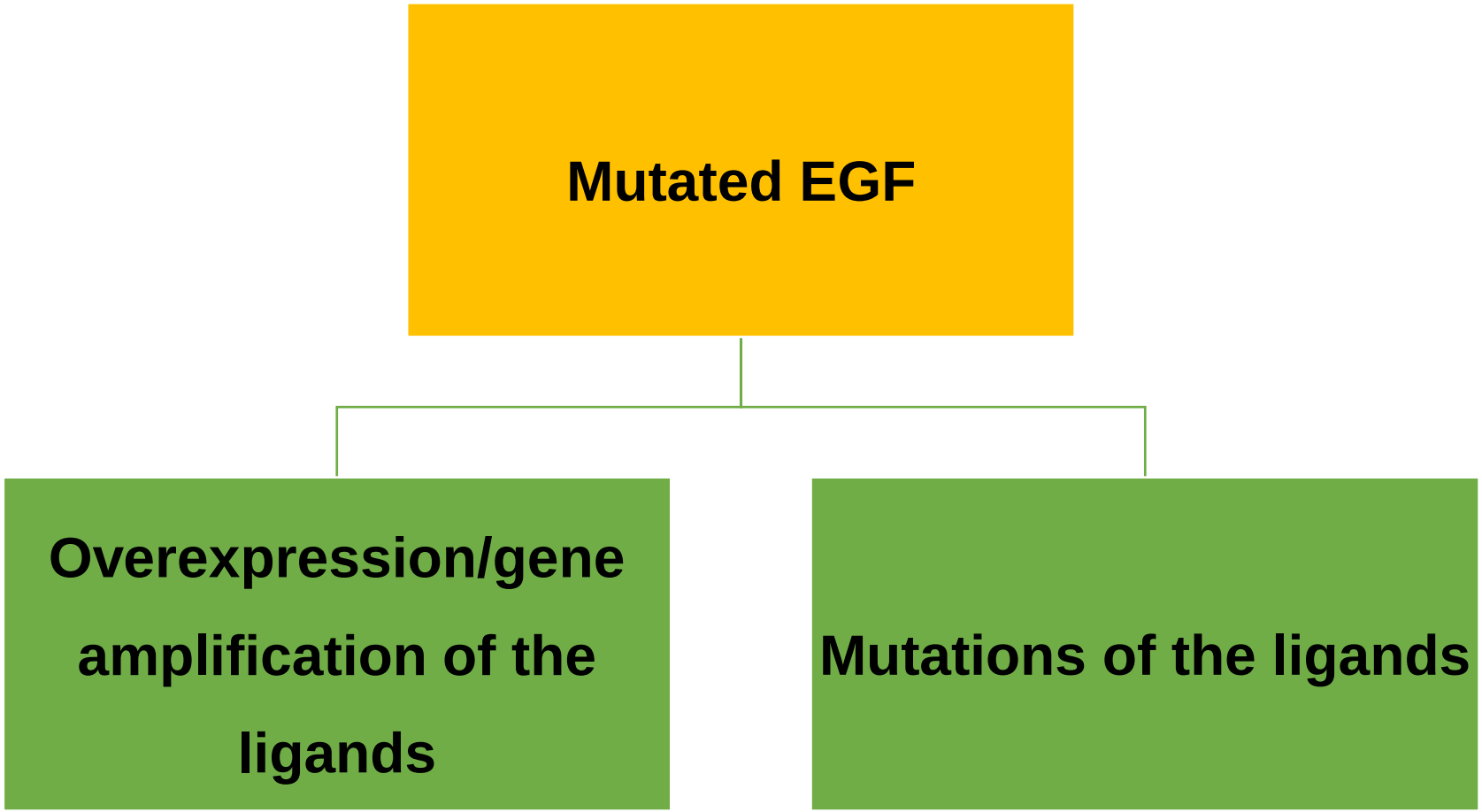
The activated EGFR and HER2 heterodimer by the EGF ligand stimulates PKC.

CREB

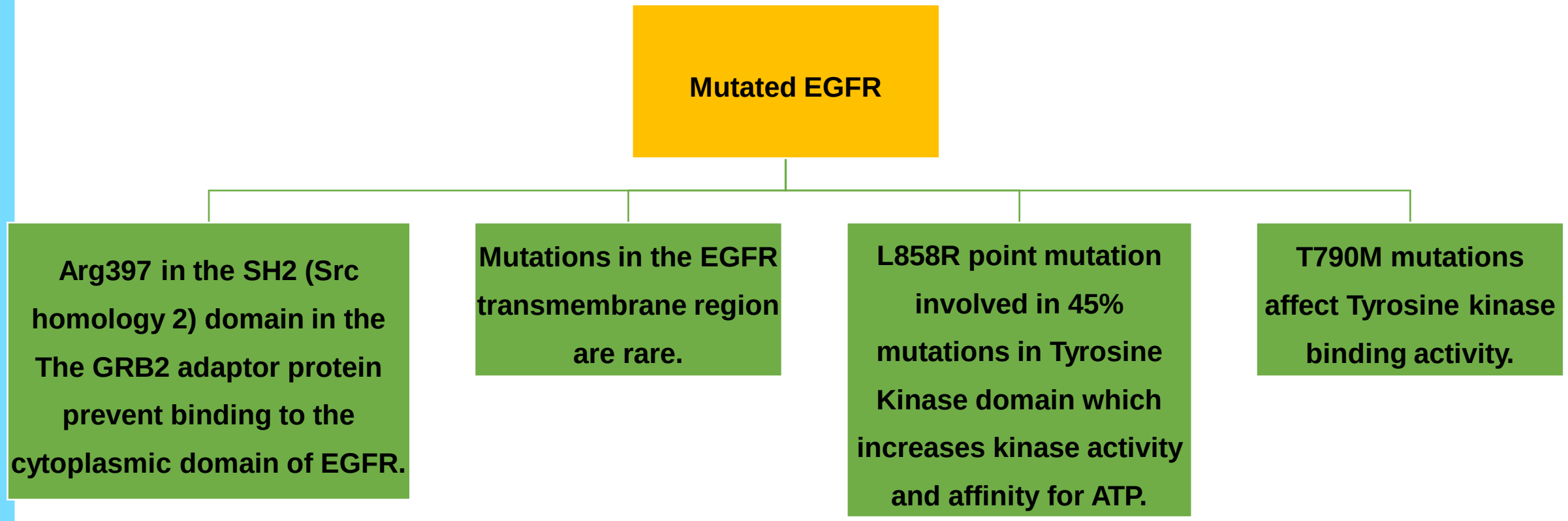
AP-1 complex made of Jun and Fos can bind to the cAMP response element (CRE) in the promoter region of their target genes.

Causes of dysregulated EGFR signalling pathway

Mutated EGF


Mutated EGF
Overexpression/gene amplification of the ligands
Mutations of the ligands

Mutated EGFR



Therapies target:

- ❑ ***Tyrosine kinase domain*: To inhibit phosphorylation and stimulate apoptosis**

e.g. small molecule inhibitors compete for ATP positions

- ❑ ***Extracellular domain* e.g. monoclonal antibodies to activate apoptosis**

Mutated RAS protein

Mutated RAS protein

30% of all human tumours carry *RAS* genes.

Ras is an oncogene that keeps cells dividing through hyperactivity.

A mutation in the amino acid sequence causes the production of the abnormal Ras protein and dysfunction which leads to:

Increased GTP because Ras decreases GTPase activity and increase the rate of exchange.

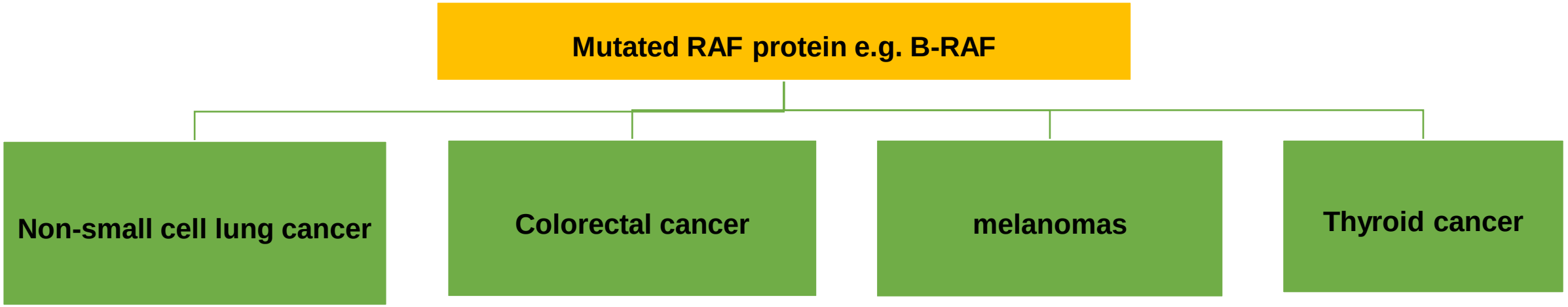
Dysregulation of the cell cycle and uncontrolled replication.

90% of prostate cancer patients have a mutation in KRAS in codon 12 (KRASG12D).

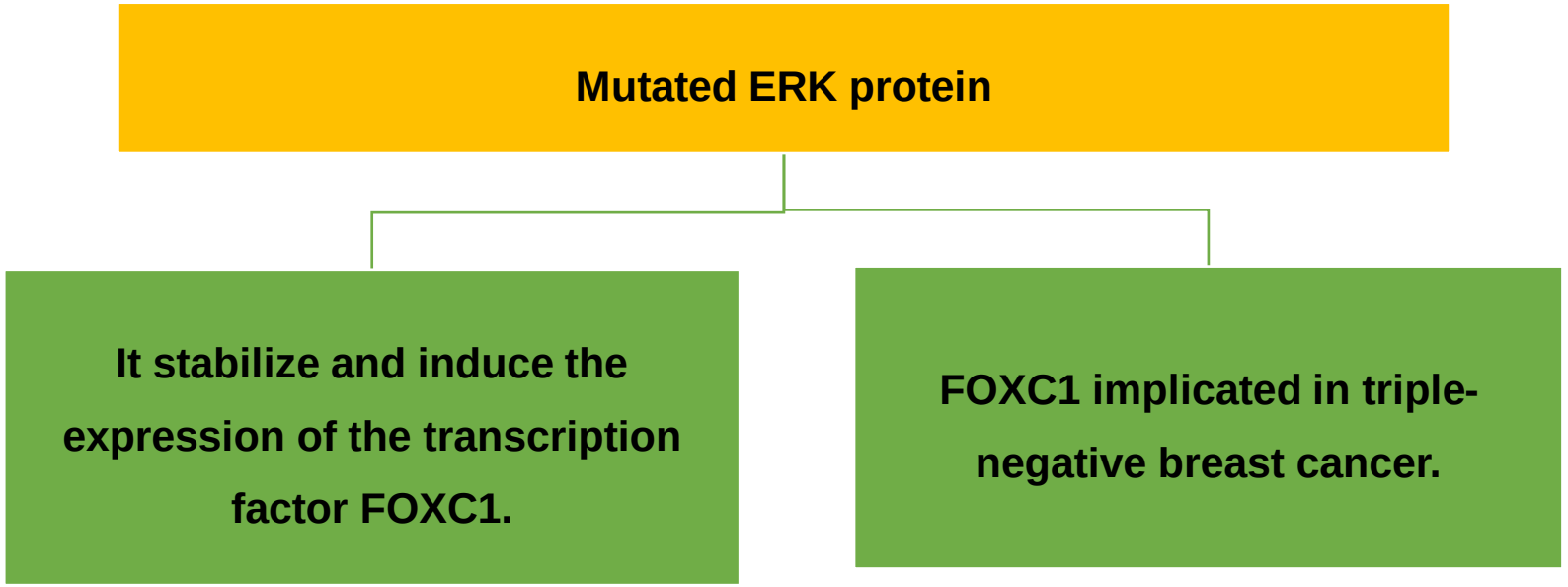
high rate of N-RAS mutations in melanomas

high rate of H-RAS mutations in salivary gland tumours

Mutated RAF protein



Mutated ERK protein



Mutated MAPK protein

Mutated MAPK protein

Missense mutation in a base is found in melanoma and thyroid cancer.

There is a substitution of valine for glutamic acid at codon 600 (V600E).

This leads to hyperactivity and carcinogenesis

This facilitates cell cycle progression, protein synthesis, invasion, apoptosis, angiogenesis, differentiation, motility, and chemotherapy resistance in many cancers.

By the end of this lecture, you should understand

- **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

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SEASON 2

Understanding Cancer

Lecture 8

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

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