SEASON 2

Understanding Cancer

Lecture 10

Types of signalling pathway: Transforming growth factor β (TGF-β)

DR HAFSA WASEELA ABBAS

www.hafsaabbas.com

RECAP:

What you hopefully should understand so far from Lecture 9

- Phospholipase C-gamma (PLC-γ) is an adaptor protein that binds to the activated EGFR-EGF receptor complex.
- PLC-γ hydrolyses phosphatidylinositol-4, 5-bisphosphate (PI(4,5)P2) (PIP_2) phospholipid in the membrane to produce the two second messengers: Diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3).
- Diacylglycerol (DAG) stays in the plasma membrane, binds and activates protein kinase C (PKC).
- IP_3 diffuses into the cytoplasm and binds to IP_3-receptors calcium channels in the endoplasmic reticulum membrane. The binding causes the calcium channels to open and release calcium ions into the cytoplasm.
- PKC phosphorylates its target cellular proteins: cell growth, differentiation and apoptosis.
- Mutation in PLC causes various hallmarks of cancer: angiogenesis, evade apoptosis, migration, invasion and metastasis.

What will we learn today?

- ***The structure of Transforming growth factor β (TGF-β)***
- ***What are SMADs?***
- ***SMAD-dependent pathway: Receptor activation***
- ***SMAD-dependent pathway: Signal transduction***
- ***SMAD-dependent pathway: Cellular response***
- ***SMAD-independent pathway***
- ***The role of Rho GTPases***
- ***Crosstalk with other pathways: GPCR***
- ***Causes of dysregulated pathways and examples of 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.**

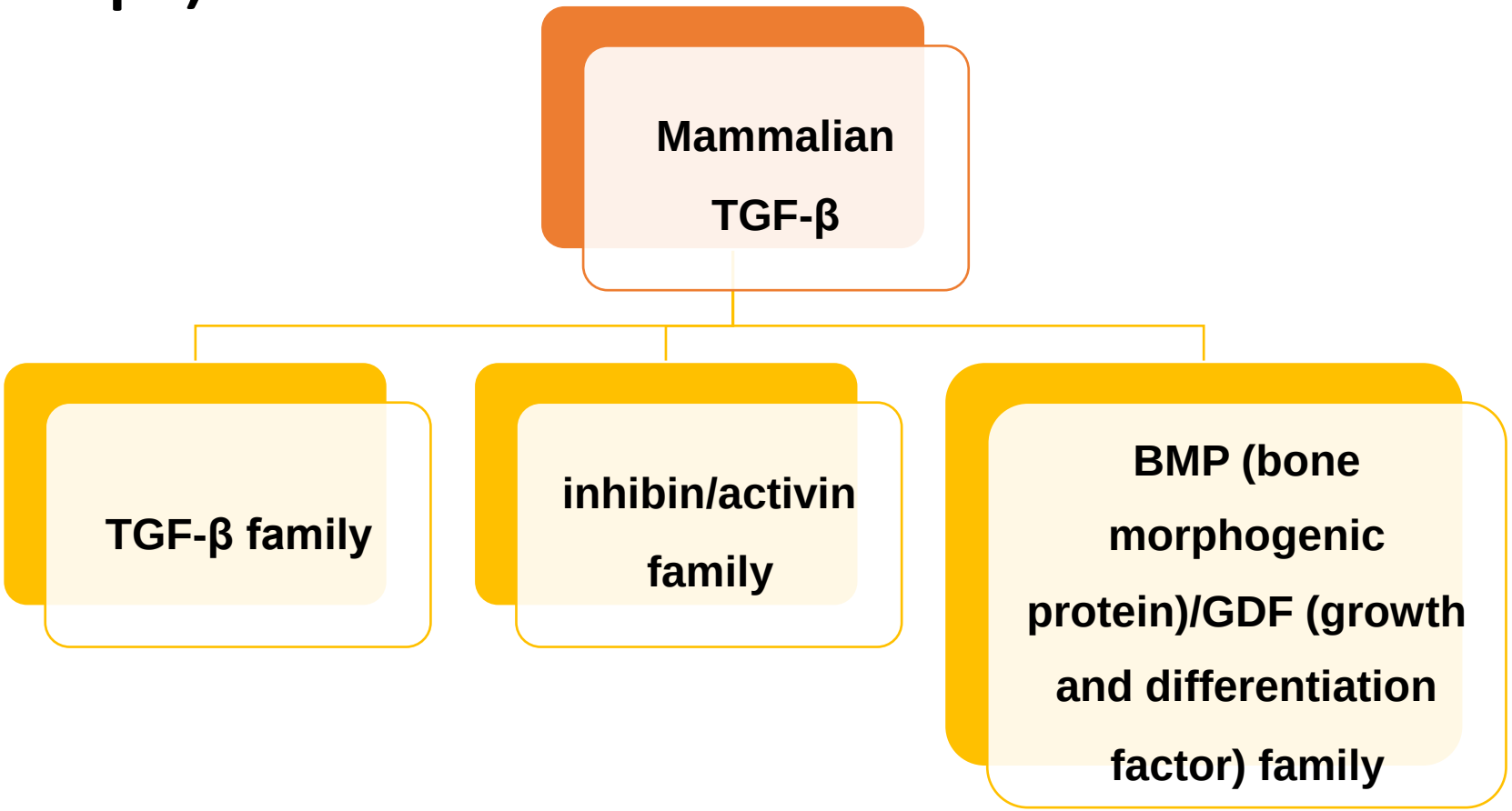
Acknowledgements: Special thanks to my parents, family, friends and colleagues for their support and the respected teachers and health professions who taught me and installed the passion of cancer/oncology.

The structure of Transforming growth factor β (TGF-β)

The structure of Transforming growth factor β (TGF-β)

TGF-β is a **pro-inflammatory cytokine protein** member of the **cell growth factor superfamily.**

There are three main groups.



(Aashaq *et al.* 2021; Marikawa *et al.* 2016; Yang *et al.* 2021)

The structure of Transforming growth factor β (TGF-β)

There are **five isoforms of TGF-β in vertebrates.**

Three are found in **mammals: TGF-β1, -β2, and -β3**.

They **share 60–80% homology.**

They **activate the same cell surface receptors.**

Isoform	Location	Role
TGF-β1	**Cartilage, bone and skin**	**Growth, differentiation**
TGF-β2	**Neurons, glial cells**	**proliferation**
TGF-β3	**Palate, Lungs**	**epithelial-mesenchymal interactions**

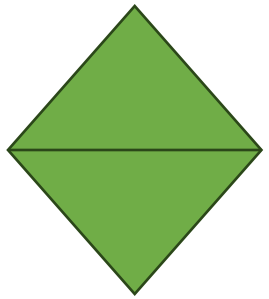
(Pervan, 2017)

The structure of Transforming growth factor β (TGF-β)

TGF-β is a **25 kDa disulfide-linked dimeric protein.**

Each isoform contains:

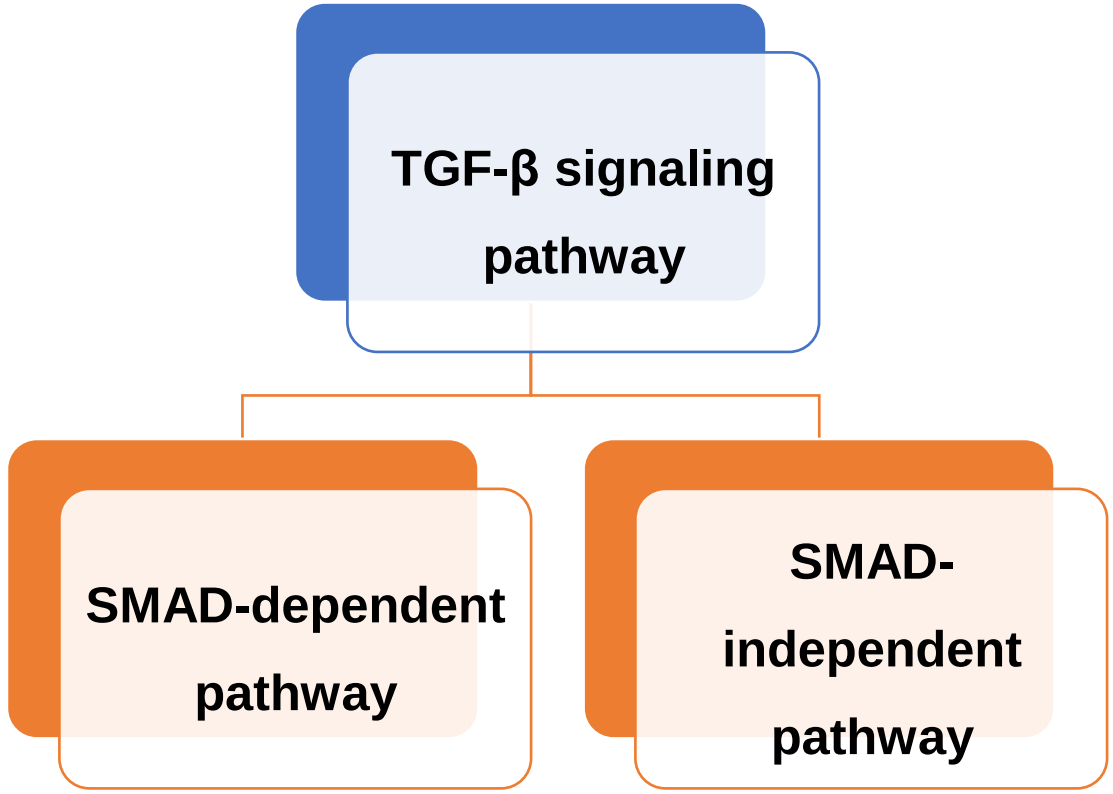
- **Nine conserved cysteine residues.**
- **Disulfide bonds to bind two TGF-β proteins as a dimer.**



(Hinck *et al.*, 2016)

The structure of Transforming growth factor β (TGF-β)

TGF-β **interact with proteins called SMADs** and therefore pathways are divided into:



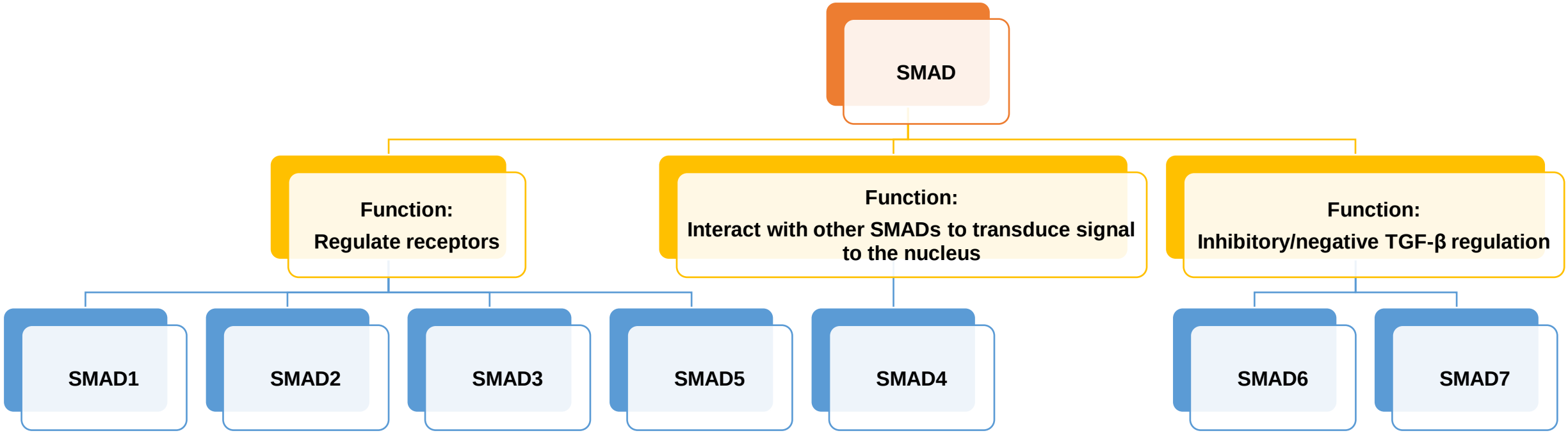
(Aashaq *et al.* 2021; Yang *et al.* 2021)

What are SMADs?

What are SMADs?

They are **proteins that transduce the signals for the receptors of TGF-β superfamily.**

This helps facilitate the **regulation of cellular growth and differentiation.**



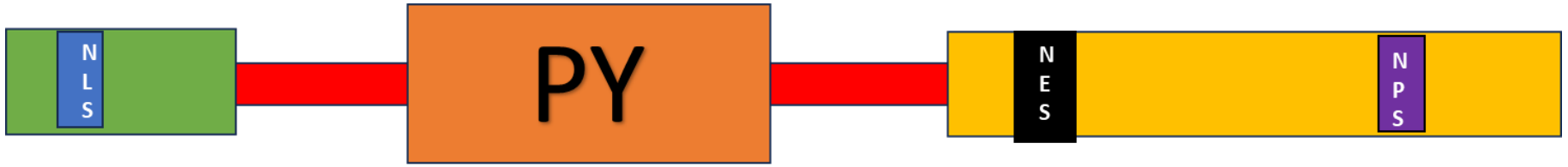
(Balogh *et al.* 2012; Hata and Chen, 2016)

The structure of SMADs

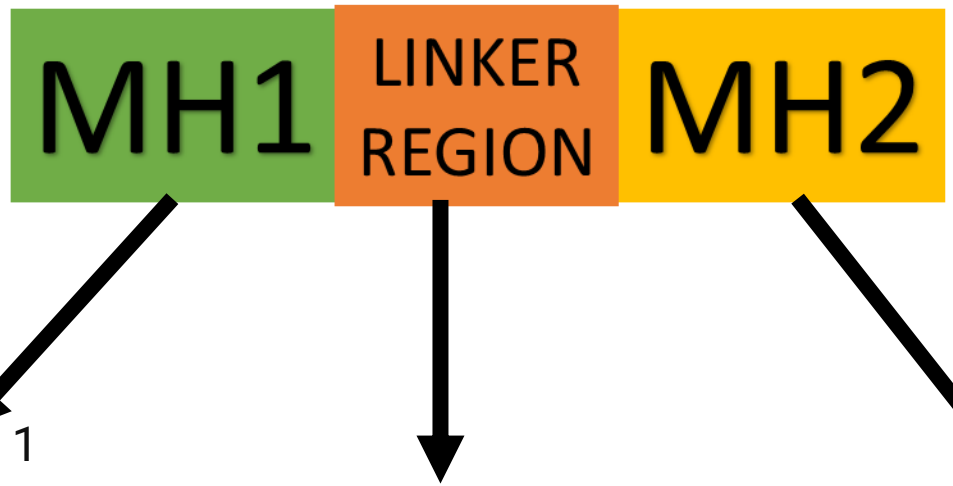
Regulatory e.g. Smad3

Co-Smad e.g. Smad4

Inhibitory Smad e.g. Smad7



The structure of SMADs



Mad homology 1

DNA-binding site
Except for SMAD2.

It induces interactions with transcription factors to stabilize the Smad complex

It is where phosphorylation takes place.

Mad homology 2

It binds to various proteins that are not associated by the sequence motif

The SMAD-dependent pathway: Receptor activation

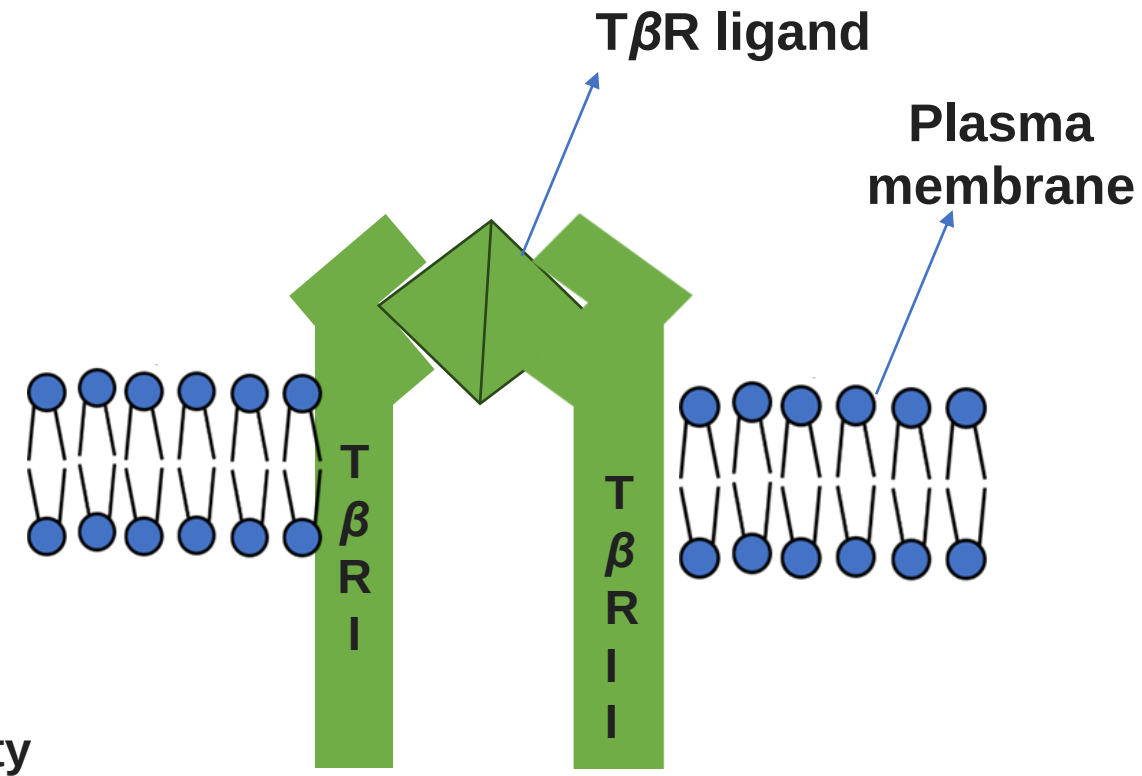
The SMAD-dependent pathway: Receptor activation

Step 1

The two transmembrane Serine/Threonine kinase receptors in the **cell membrane bind together.**

- ❑ **TGF-*β* receptor I (T*β*R I)**
- ❑ **TGF-*β* receptor II (T*β*R II)**

This activates the **C-terminal kinase domain and activity of T*β*R I**



How?

The SMAD-dependent pathway: Receptor activation

Step 2

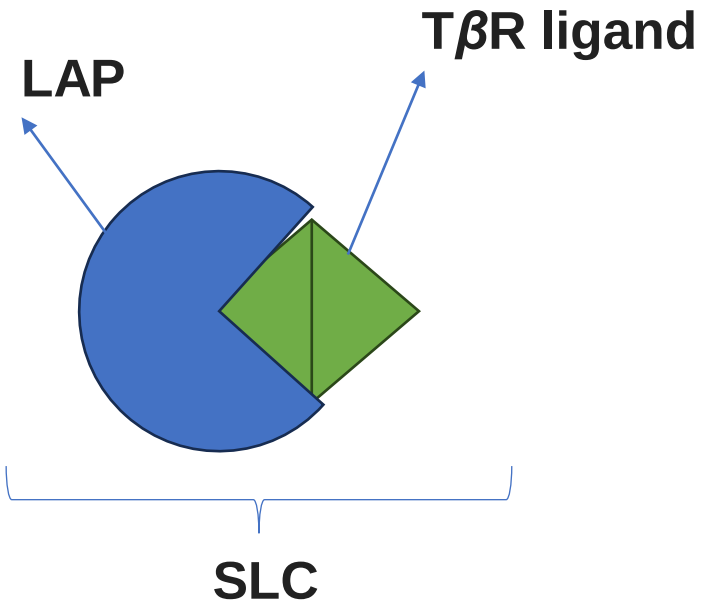
The binding of the ligand to the receptor.

Most TGF-*β* ligands are latent.

They cannot bind to its receptor directly.

It **binds to the C-terminal prodomain latency-related peptide (LAP)** to form **a small latency complex (SLC).**

(Yang *et al.* 2021)



The SMAD-dependent pathway: Receptor activation

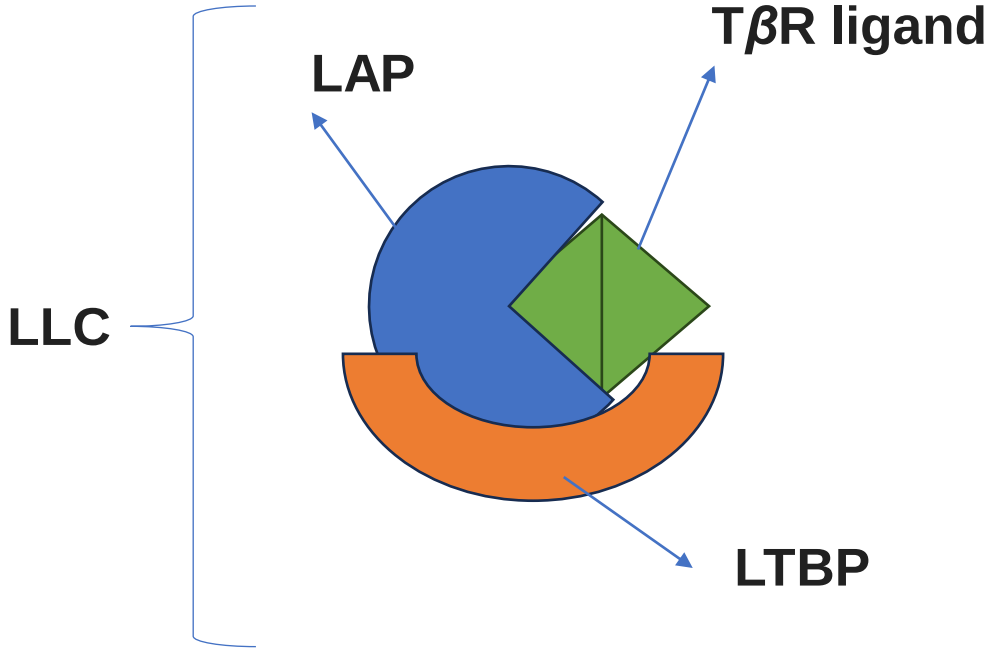
Step 3

The SLC becomes larger and binds with the TGF-*β* binding protein 1 (LTBP1).

This forms the **large latent complex (LLC).**

This allows **TGF-β to connect to the extracellular matrix.**

(Yang *et al.* 2021)

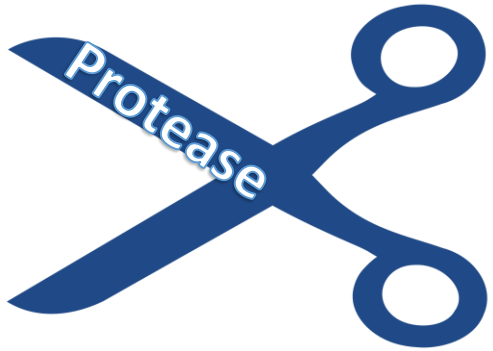


The SMAD-dependent pathway: Receptor activation

Step 4

LLC interacts with proteases to activate TGF-β

(Yang *et al.* 2021)



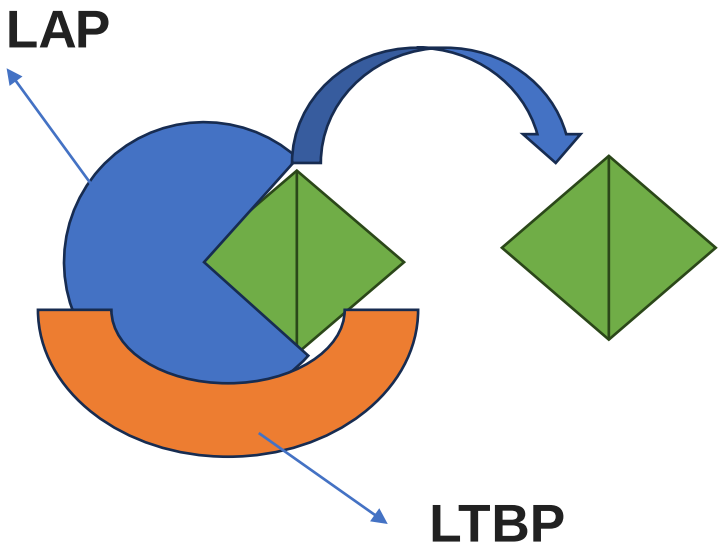
The SMAD-dependent pathway: Receptor activation

Step 5

The TGF-β ligand must be released from the LLC to make TGF-β ligand active.

To bind to receptor by either stimulating on LAP or LTBP.

(Yang *et al.* 2021)

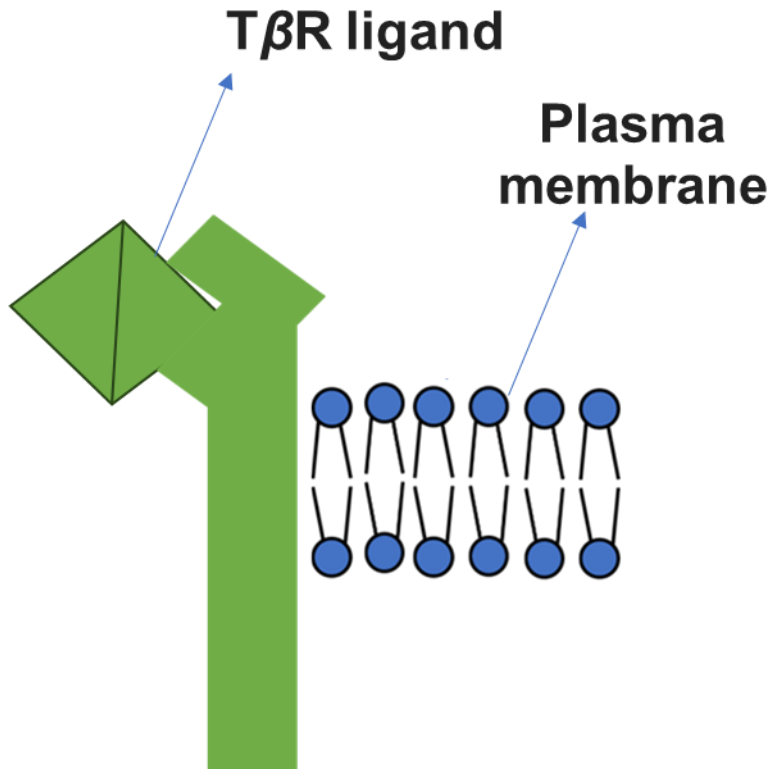


The SMAD-dependent pathway: Receptor activation

Step 6

The TGF-β ligand binds to the transforming growth factor-β receptor-2 (TβRII).

This is facilitated by **β-glycan/transforming growth factor-β receptor-3 (TβRIII)**



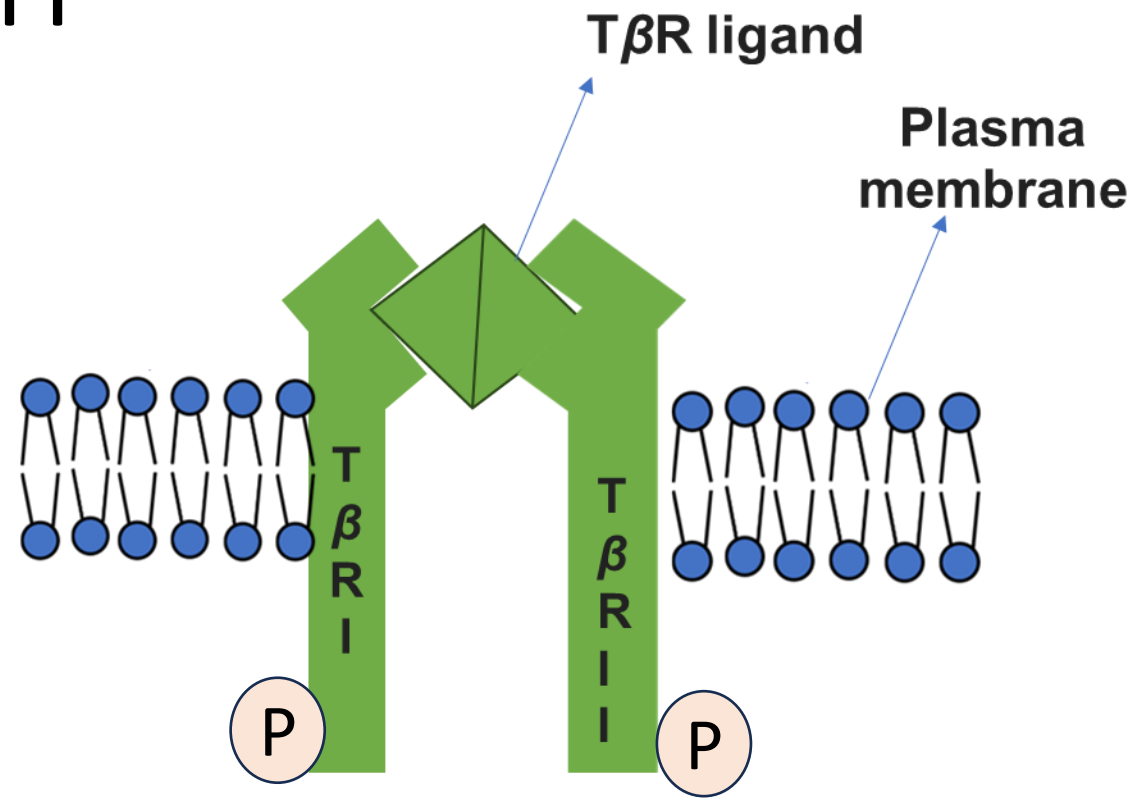
(Lopez-Casillas *et al.* 1993; Sankar *et al.* 1995)

The SMAD-dependent pathway: Receptor activation

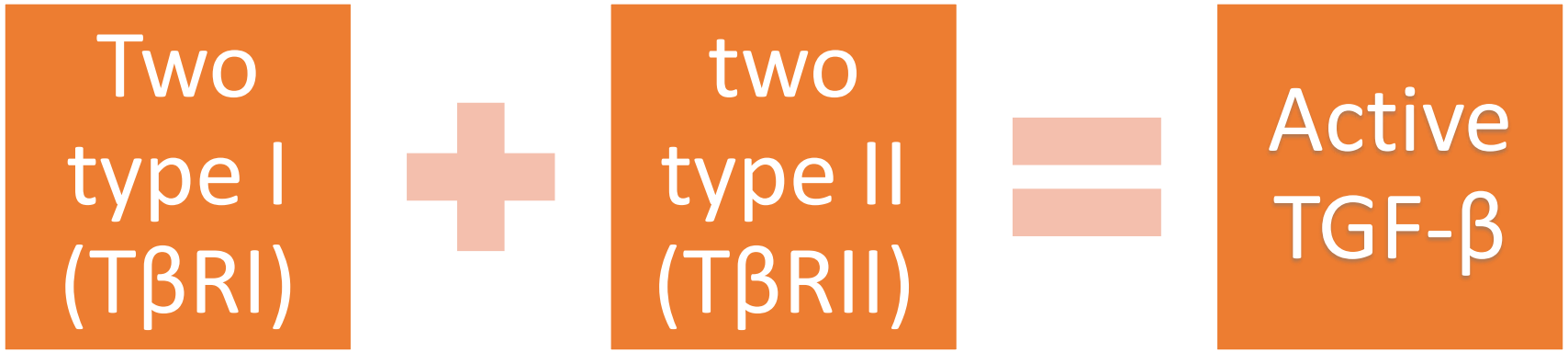
Step 7

The serine/threonine kinase activity takes place in the cytoplasmic domain.

The TGF-β receptor-1/ALK-5 (TβR1) is recruited to the TGF-β/TβRII complex.



(Haque and Morris, 2017)



(Liu and Chen, 2022)

The SMAD-dependent pathway: Receptor activation

CONFORMATIONAL CHANGE IN THE LATENT COMPLEX.

- **Proteases e.g. Metalloproteinases, serine,**
- **Neuraminidase expressed on the surface of viruses.**
- **Bone morphogenetic protein 1- (BMP1-) like protease directly cleaves LTBP1 in the LLC.**
- **Thrombospondin 1 (TSP1) and members of the *αv* integrin family (including *αvβ1*, *αvβ3*, *αvβ5*, and *αvβ6*) act on LAP to release TGF-*β*.**

ENVIRONMENTAL STRESS

- **Heat shock, reactive oxygen species, pH and ionizing radiation.**

The SMAD-dependent pathway: Receptor activation

Emilin1

- **A glycoprotein rich with cysteine residues expressed in the vascular tree.**
- **It prevents the binding of** TGF-*β* ligand with its receptor.

Cripto

- **A developmental cancer protein that prevent the ligand to its receptor.**

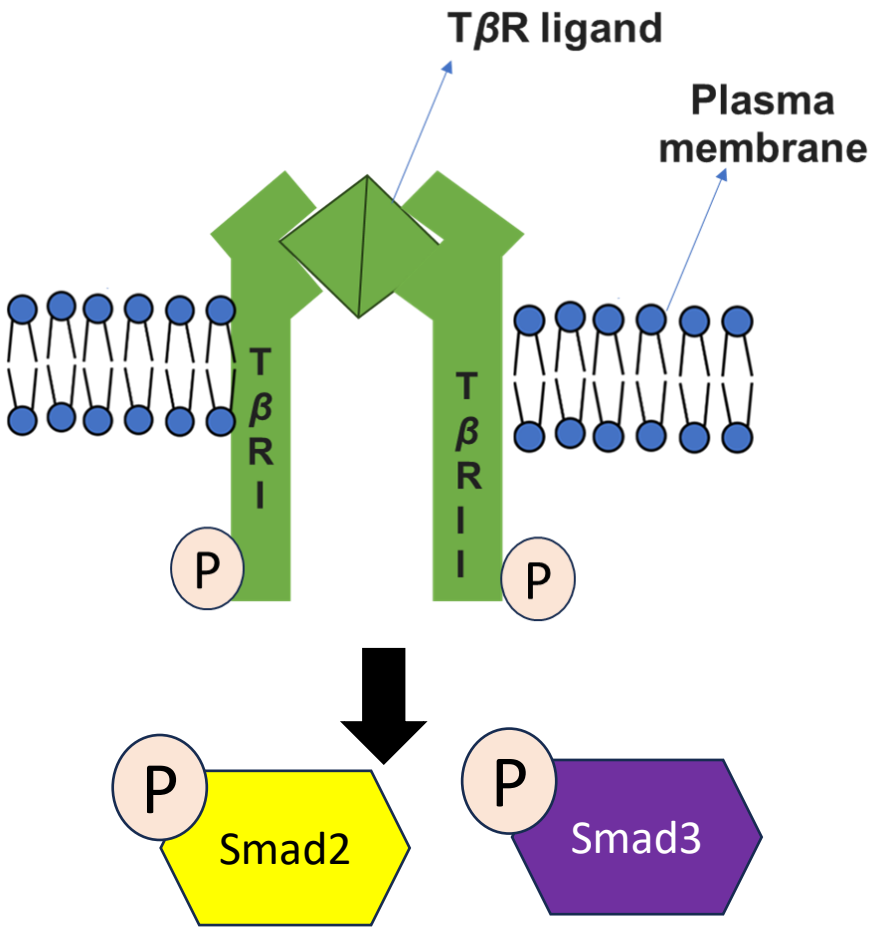
(Yang *et al.* 2021)

The SMAD-dependent pathway: Signal transduction

The SMAD-dependent pathway: Signal transduction

<u>Step 8</u>

The **activated TβR I receptor phosphorylates the SMAD proteins**: **SMAD2 and SMAD3** at **two serine residues in the SSXS motif.**



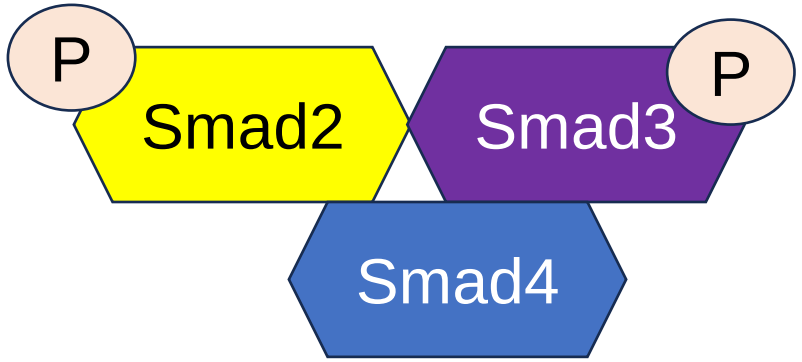
(Liu and Chen, 2022; Yang *et al.* 2021)

The SMAD-dependent pathway: Signal transduction

Step 9

The **phosphorylated SMAD2 and SMAD3 proteins** bind to the **chaperone protein** SMAD4 to form a **heteromeric complex**.

It dissociates from **the TβRI kinase domain.**

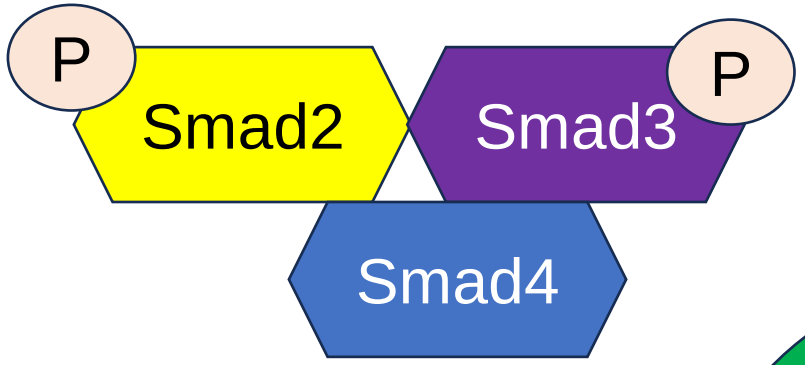


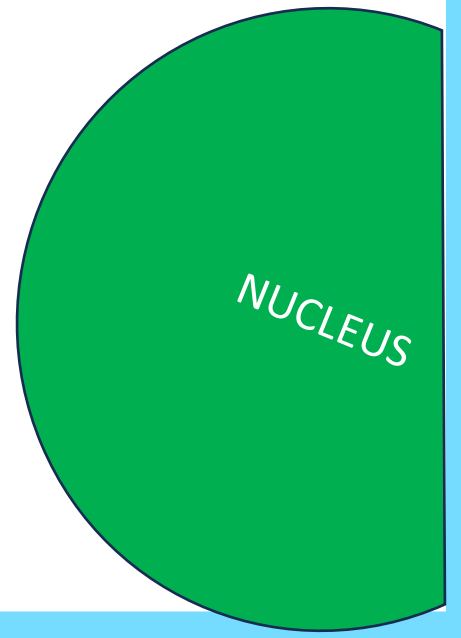
(Savage *et al.* 1996)

The SMAD-dependent pathway: Signal transduction

<u>Step 10</u>

Collectively, **the SMAD complex** are **transported to the nucleus** and **binds to DNA via their MH1 domains** and **to regulate the transcription of target genes.**





(Dou *et al.* 2000)

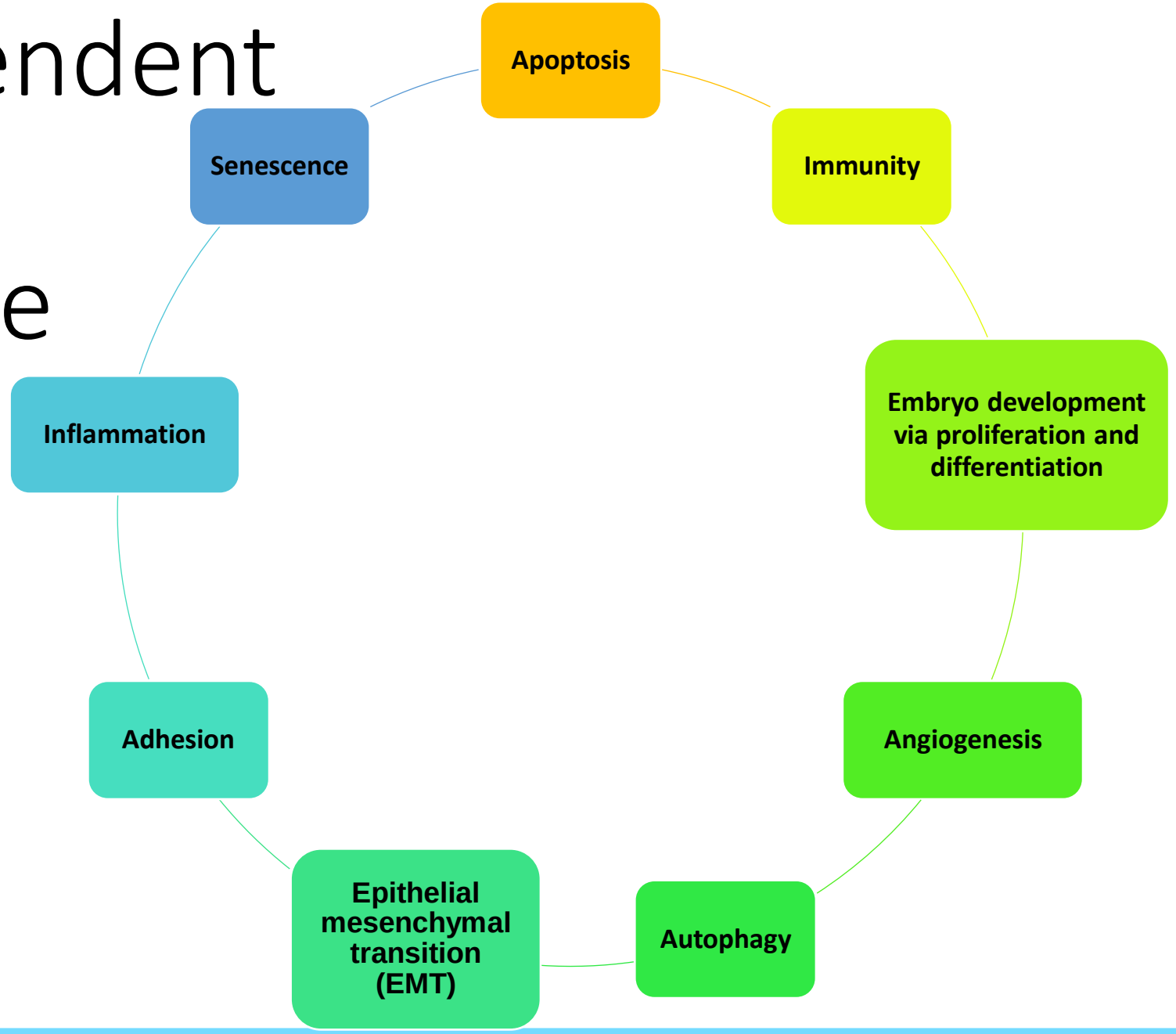
The SMAD-dependent pathway: Cellular response

The SMAD-dependent pathway: Cellular response

Death-related protein kinases (DAPK) stimulate **release of cytochrome C** and link SMADs with **intrinsic apoptotic pathway**.

TGF-*β* induced **early gene 1(TIEG1) stimulates oxidative stress via reactive oxygen species (ROS).**

(Zhao *et al.* 2020)



Apoptosis

TGF-β inhibit the expression of antiapoptotic genes

- **BCL-X**
- **BCL-2**
- **KIF5**
- **X-linked inhibitor of apoptosis (XLAP)**

TGF-β inhibit the expression of pro-apoptotic genes

- **Caspase 8**
- **Caspase 3**
- **Bcl-2-interacting killer (BIK)**

TGF-β associates with the Death domain-associated protein (DAXX) to induce apoptosis.

- **DAXX facilitates TGF-β to mediate apoptosis via The phosphatidylinositol 3-kinase (PI3K)/Akt signalling pathway and c-Jun N-terminal kinase (JNK) pathway.**

(Haque and Morris, 2017)

Epithelial mesenchymal transition (EMT)

- **The development of the embryo.**
- **Tissue repair.**
- **Wound healing**
- **Fibrosis**

Regulation of gene transcription:

E-cadherin, N-cadherin, vimentin and Snail

Cell-adhesion molecules (CAMs)

It creates **cell-to-cell junction.**

e.g. **Cadherin** is a dimer of identical subunits.

The **extracellular domain of one cadherin dimer binds to another cadherin** in another cell **to promote cell adhesion.**

Vimentin

An **intermediate filament** expressed in **normal mesenchymal cells** to **resist environmental stress and maintain integrity of cells.**

Snail

It **negatively regulates cell adhesion by downregulating E-cadherin** and **upregulate vimentin to increase cell migration and invasion.**

(Santelli and Li, 2011; Bhowmick *et al.*, 2001; Haque and Morris, 2017; Neal *et al.* 2011)

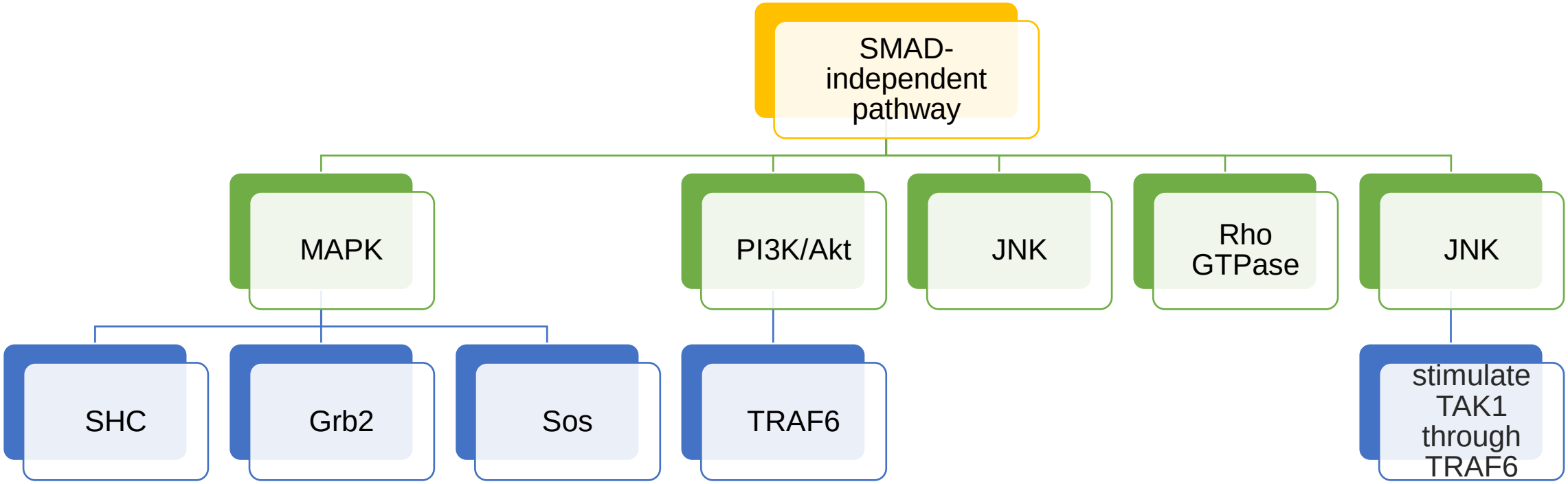
Metabolism

Glucose levels helps to:

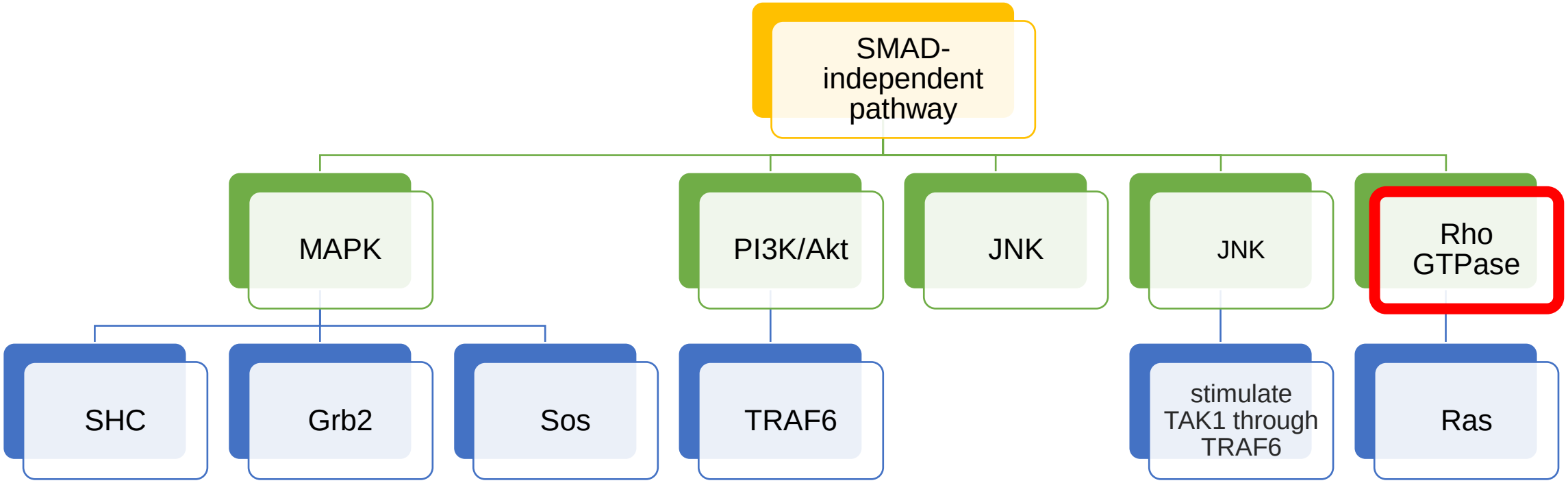
- ❑ Increase **TGF-β ligand production.**
- ❑ Increase **TβRI and TβRII in the cell membranes**.
- ❑ Increase **latent-TGF-β activation** by **matrix metalloproteinases.**

(Wu and Derynck, 2009).

The SMAD-independent pathway



(Bakin *et al.* 2002)



FOCUS

(Bakin *et al.* 2002)

What are Rho GTPases?

- ❑ A family of small GTPases.
- ❑ Key examples: RhoA, Rac1 and Cdc42
- ❑ They associate with GTP and hydrolyse it to GDP.
- ❑ They regulate actin for:
  - Cell migration and invasion.
  - Metastasis
  - Cell survival

(Guan *et al.* 2000)

Crosstalk with other pathways: GPCR

Crosstalk with other pathways: GPCR

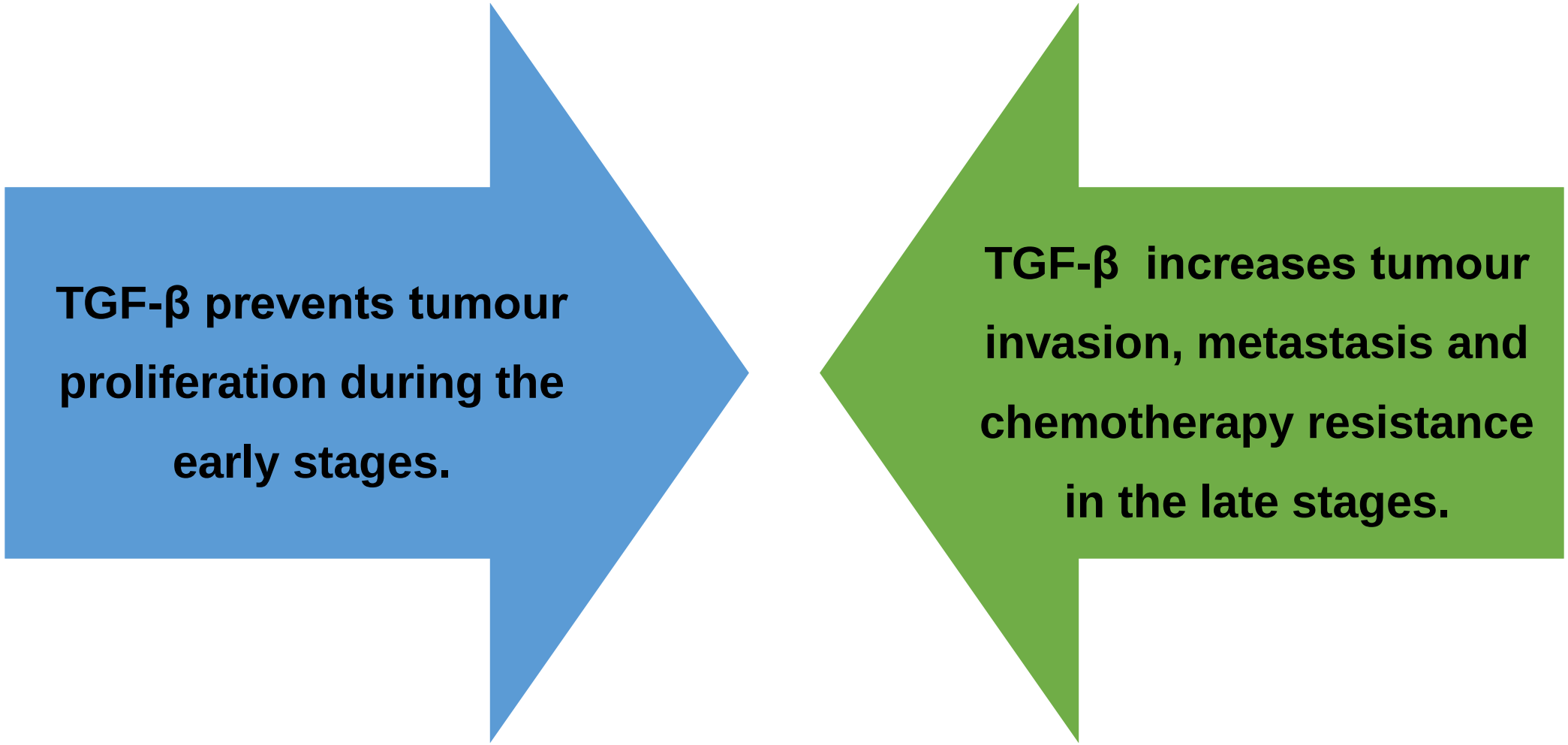
GPCR ligand involved in Rho pathway	Function
Thrombin	An **enzyme that hydrolyses the soluble fibrinogen** to the **fibrin protein involved in coagulation.**
lysophosphatidic acid	A **phospholipid** that can act as an **extracellular signal transmitter** and **intracellular second messenger.**
sphingosine-1-phosphate (S1P)	It is associated to **extracellular chaperone proteins.** It **binds to G protein-coupled S1P receptors (S1PRs)** to **regulate embryogenesis, homeostasis, immune cell, and organ function after birth.**
thromboxane A2	**Lipid released from platelets, macrophages, neutrophils and endothelial cells.** It **stimulates the activation of platelets and undergo aggregation**. **Vasoconstriction** during **tissue injury and inflammation.**

Crosstalk with other pathways: GPCR

G protein G-alpha 12/13	G protein alpha q/13
• They **activate RhoA via Rho guanine nucleotide exchange factors (Rho GEF).** • This facilitates **downstream signalling i.e Rho kinase (ROCK).**	• They **activate RhoA by releasing calcium ions.** • This **facilitates down-stream signalling via protein kinases**

Causes of dysregulated pathways and examples of cancer.

TGF-β ligand and cancer



TGF-*β* promotes angiogenesis

It promotes growth factors that facilitates angiogenesis, form capillaries, increase nutrients and oxygen in endothelial cells to promote cancer progression:

vascular endothelial growth factor (VEGF

connective tissue growth factor (CTGF)

TGF-*β*/SMAD4 promote growth of new blood vessels that upregulate miR-29a.

This crosstalks with PI3K/Akt pathway

TGF-β receptors increases the expression of matrix metalloproteinases MMP9 and promote the new blood vessels through one of its type I receptors, ALK5.

TGF-β promotes angiogenesis

Liver cancer	**Prostate cancer**	**Kidney cancer**	**non-small-cell lung cancer**	**Breast cancer**

TGF-*β* promotes apoptosis

Increase the expression of the death-related protein kinase DAPK in liver cancers.

Produces reactive oxygen species and regulate BCL-2 modifying factor (BMF) and BCL-2 interacting mediator (BIM) in liver cancers.

It activates BIM and caspase 9 to mediate apoptosis in gastric cancers.

Inhibits the expression of major gastrointestinal spectrum regulator, Krüppel-like Factor 5 (KLF5).

This promotes apoptosis in pancreatic cancers

(David *et al*. 2016; Yang *et al*. 2021)

SMAD-independent pathways and cancer

- **Rho GTPases increase invasion, metastasis and survival of tumour cells** in **the connective tissue of the organ called the stroma.**
- **MAPK pathway via Ras and B-Raf mutations** can **promote metastasis.**
- **Jun N-terminal kinase and p38-mediated pathways lowers the malignant potential.**

(Dhillon *et al*., 2007; Li *et al.,* 2014; Svensmark *et al*., 2019)

TGF-*β* promotes reprogramming of metabolism

- **Tumour cells require an energy source in order to grow.**
- **The Warburg effect is the process where glucose is broken down in the presence of oxygen (aerobic glycolysis).**
- **Overexpression of TβRI facilitates tumour growth**.
- **Overexpression of Smad2/3** requires **protein kinase C ε** for **phosphorylation and binding to genes involved in glycolysis.**
- **Phosphofructokinase 2 (PFK2) expression** is stimulated by **TGF-β required for invasion and is overexpressed in glioblastoma, pancreatic cancer and colon cancer cells.**

(Xu *et al*., 2018; Hanahan, D., and Weinberg, R. A.,2011; Guido *et al.* 2012).

TGF-*β* promotes invasion and metastasis

- ❑ **Decreased expression of E-cadherin.**
- ❑ **Increased expression of matrix-metalloproteinases, vimentin, fibronectin and N-cadherin**

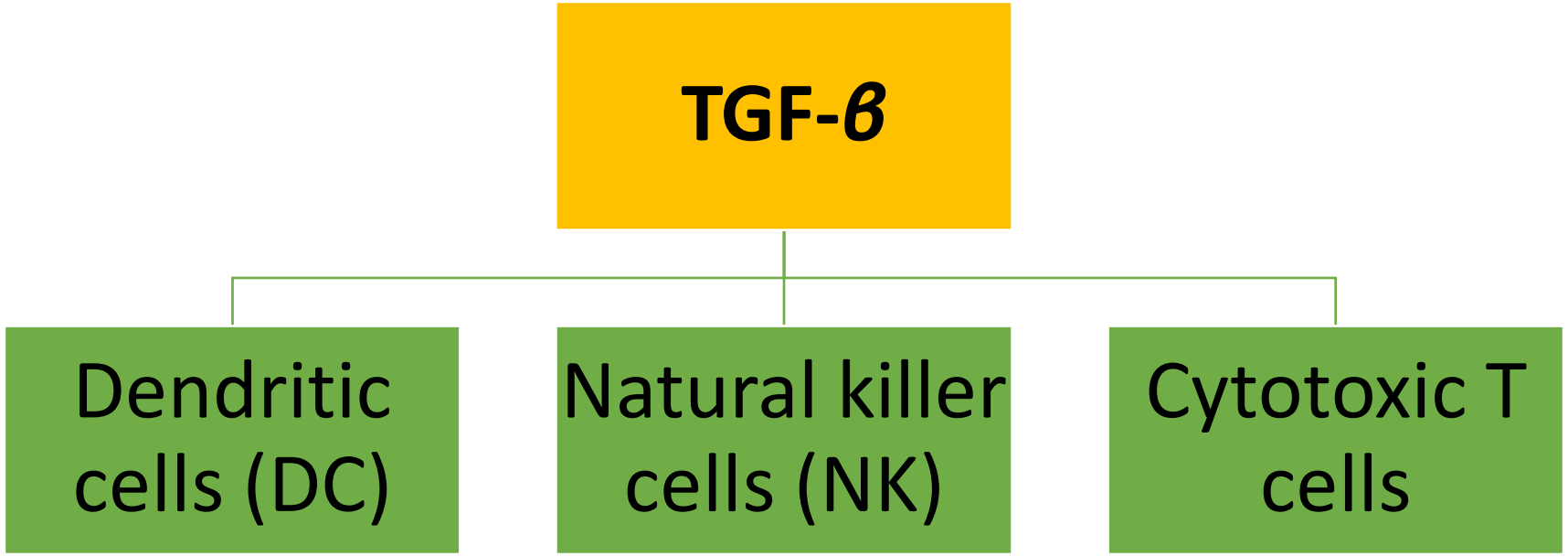
This lowers cell adhesion.

Change in cell shape.

Increase cell migration and cancer progression

(Loh *et al.* 2019).

TGF-*β* promotes inflammation



TGF-*β* promotes inflammation

Cytotoxic T cells

- TGF-*β inhibits* cytotoxic CD8+ T cells via SMADS
- Normal function: Produces cytokines e.g. interferon gamma (IFN-γ) and Fas ligand to induce apoptosis.

TGF-*β* promotes inflammation

Dendritic cells (DC)

- TGF-*β* inhibits DC via SMADS
- Normal function: They are antigen-presenting cells to induce T cell response.
- Overexpression of Id1 (differentiation inhibitor of TGF-*β)* which downregulates the differentiation of DC cells and suppresses the immune system.

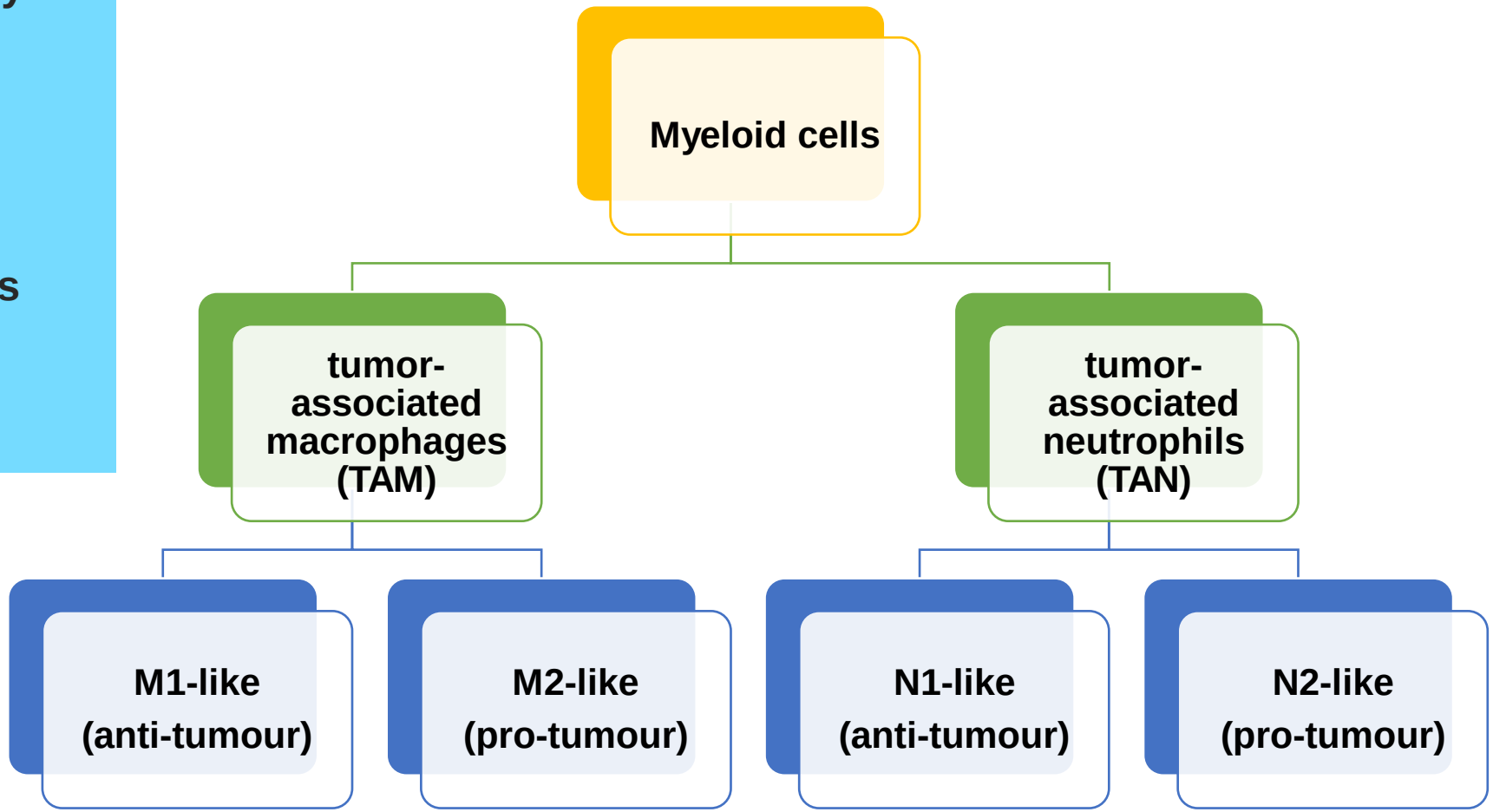
TGF-β promotes inflammation

Natural killer cells (NK)

- TGF-β inhibits production of Interleukin-15 and receptor natural killer group 2, member D (NKG2D).
- This prevents activation of NK cells.
- Examples of cancers: glioma

TGF-β promotes inflammation

TAMs are predominantly found in the tumour microenvironment.
It facilitates tumour progression, metastasis and chemotherapy resistance.




TAM derived from monocytes
TAM recruited to tumour microenvironment
Activation of M1 or M2 response

M1 and cancer

Stimulation

- Interferon-gamma (IFN-γ)
- TGFα
- GM-CSF granulocyte-macrophage colony-stimulating factor

Expression of surface proteins

- CD68 increases invasion and metastasis in breast cancer.
- CD80 tumour growth
- CD86 tumour growth
- intracellular protein suppressor cytokine signaling 3 (SOCS3)

Secretion

- IL-1β
- IL-6
- IL-12
- IL-23
- C-X-C motif chemokine (CXCL) 9
- CXCL10

(Wu *et al*. 2020)

M2 and cancer

Stimulation

- **Interleukin-10**
- **TGFβ**

Expression of surface proteins

- **CD163 migration and tumour cells penetrate the blood and lymphatic vessels.**
- **CD204 increases proliferation, migration and invasion.**
- **CD206 increases expression of metalloproteinases 2, 9 and 10 i.e ovarian cancer.**

Secretion

- **IL-10**
- **TNF tumor necrosis factor α**
- **CCL17**
- **CCL18**
- **CCL22**
- **CCL24**

(Wu *et al*. 2020)

N2 and cancer

TGF-*β* *stimulates neutrophils to develop into N2*

It is not cytotoxic to the tumour.

Stimulates antitumor cytokines

Cytotoxic T cells decreases

Immunosuppression

(Wu *et al*. 2020)

By the end of this lecture, you should understand

- **TGF-β is a pro-inflammatory cytokine that interacts with proteins called SMADs.**
- **SMAD proteins are divided into: regulatory, co-mediators and inhibitory proteins.**
- **TGF-β binds to the C-terminal prodomain latency-related peptide (LAP)** to form **a small latency complex (SLC). It then binds with the TGF-*β* binding protein 1 (LTBP1)** to the **large latent complex (LLC).**
- **The TGF-β ligand must be released from the LLC to make TGF-β ligand active and stimulate SMAD downstream signalling pathway.**
- **TGF-β can promote or inhibit tumour growth.**

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SEASON 2

Understanding Cancer

Lecture 11

Types of signalling pathway: normal and dysregulated BCR-ABL

DR HAFSA WASEELA ABBAS

www.hafsaabbas.com