SEASON 2

Understanding Cancer

Lecture 16

Types of signalling pathway: HER2

DR HAFSA WASEELA ABBAS

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RECAP:

What you hopefully should understand so far from Lecture 16

Principles of NF-κB signalling

- ❑ NF-κB proteins: five members of NF-κB family: p65 (RelA), RelB, c-Rel, p50/105 (NF-κB1) and p50/105 (NF-κB2). They all share Rel homology domain responsible for DNA binding and multidimerization.
  - C-terminal transcriptional activation domain (TADs) are present in RelA, p65 and RelB. They are not present in p50/100 or p52/105.
- ❑ IκB proteins
- ❑ IKK complex.

RECAP:

What you hopefully should understand so far from Lecture 16

Canonical pathway

- ❑ This pathway is induced by TLRs, TNFRs, and IL-1R is bound to their specific ligand.
- ❑ This leads to phosphorylation and degradation of inhibitory protein IκB.
- ❑ NF-κB is released from the IκB-containing complex, then translocating into nucleus.

Non-Canonical pathway

- ❑ This pathway is dependent on the activation of NF-κB2 (p100)/ RelB complex by BAFFR, CD40, and RANK.
- ❑ It induces phosphorylation of NIK, which phosphorylates IKKα.
- ❑ The p52-RelB heterodimer is activated and translocate to the nucleus for transcription

What will we learn today?

- ***The structure of HER2***
- ***Other members of the HER family***
- ***Receptor activation***
- ***Signal Transduction***
- ***Cellular Response***
- ***Dysregulated HER2 pathway: Causes of HER2 Overexpression***
- ***Dysregulated HER2 pathway: Examples of cancers***
- ***Dysregulated HER2 pathway: Rare forms of cancer***
- ***Dysregulated HER2 pathway: Effect 1 of HER2 Overexpression***
- ***Dysregulated HER2 pathway: Effect 2 of HER2 Overexpression***
- ***Dysregulated HER2 pathway: Effect 3 of HER2 Overexpression***

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 HER2

The structure of HER2

In Lecture 7, we discussed **the structure of the human epidermal growth factor receptor (EGFR) signalling pathway in normal and cancer cells.**

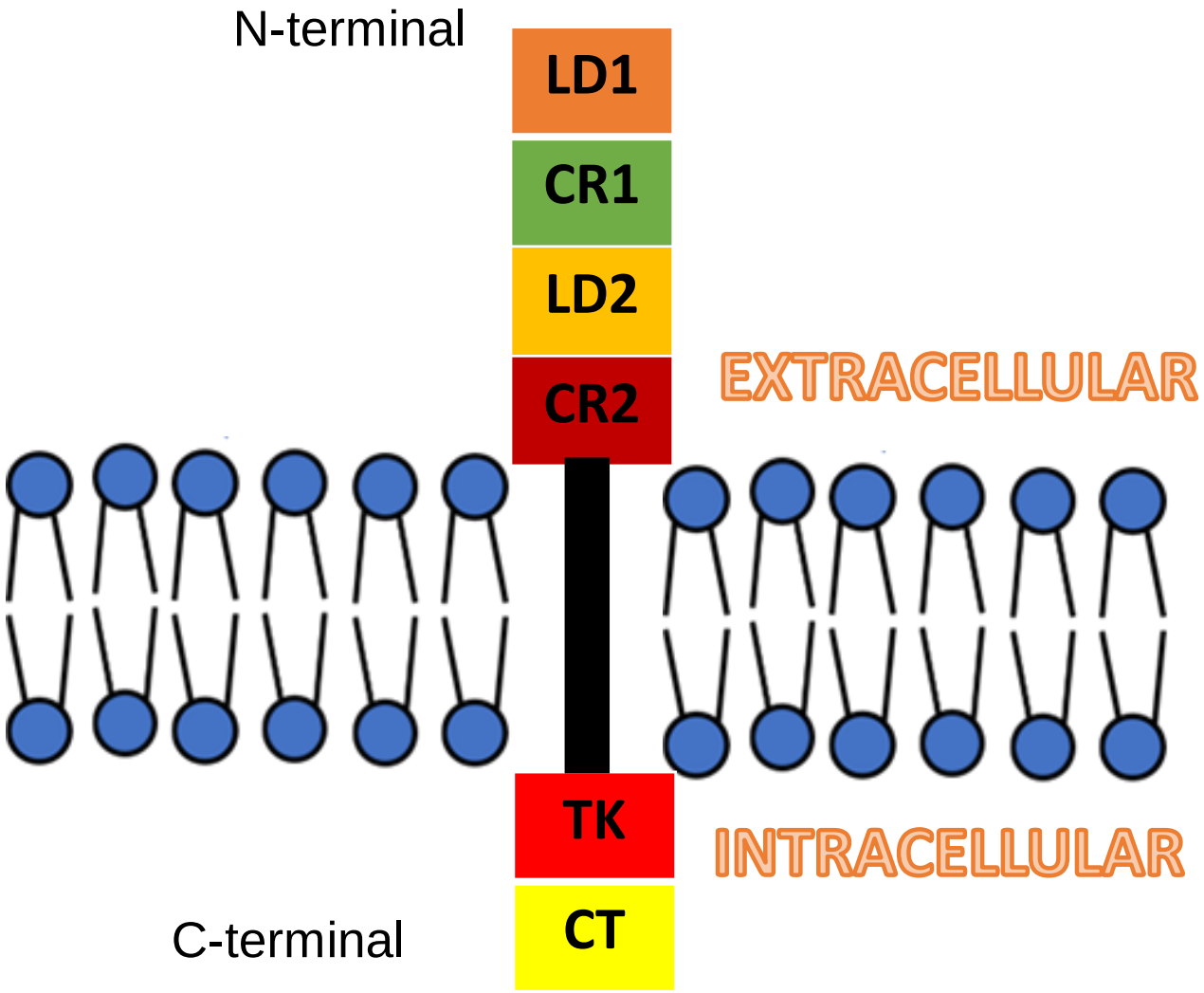
HER2 is a member of the human EGFR family.

It is also known as ERB2B, CD340 or Neu.

RECAP on EGFR structure:

- ***A type of enzyme***: tyrosine kinase
- ***A type of receptor***: type 1 transmembrane growth factor receptors.
- ***They have three domains***: extracellular ligand binding domain, a transmembrane domain, and an intracellular tyrosine kinase domain.

(Zhang *et al*. 2020; Genentech, 2023; de Lartigue, 2011)



Ligand binding regions (LD)

Cysteine-rich regions (CR)

Transmembrane domain (TM)

Tyrosine kinase domain (TK)

Carboxy terminal tail (CT).

Other members of the HER family

Other members of the HER family

- **EGFR (HER1, erbB1)**
- **HER2 (erbB2, HER2/neu)**
- **HER3 (erbB3)**
- **HER4 (erbB4)**

HER2 has the strongest catalytic kinase activity and signalling from all HER family.

(Mouasser, 2007; Tzahar *et al*. 1996; Graus-Porta *et al*. 1997; Genentech, 2023; de Lartigue, 2011; Zhang *et al*. 2020)

Receptor activation

Receptor activation

(Mouasser, 2007; Genentech, 2023; de Lartigue, 2011)

- In contrast to other proteins that bind to one or more ligands specifically.
- HER2 does not have any known ligands.
- There are two mechanisms:

Homodimerization

- **Two HER2 receptors join together to be activated.**

HOMO = SAME

- **This occurs on tyrosine amino acid residues on their intracellular domains.**
- **This also occurs if it is overexpressed on the cell surface.**

Heterodimerisation

- **A HER2 protein associates with other HER proteins.**

HETERO = DIFFERENT

Receptor form	Type of dimer	Ligand it associates with
HER2-HER3	heterodimer	• Epiregulin (EPR) • Neuregulin (NRG1-alpha) • Neuregulin (NRG2-beta)
HER2-HER4	heterodimer	• EGF • TGF-alpha • Heparin binding epidermal growth factor • EPR • Betacellulin BTC • NRG2-alpha • NRG3

(de Lartigue, 2011)

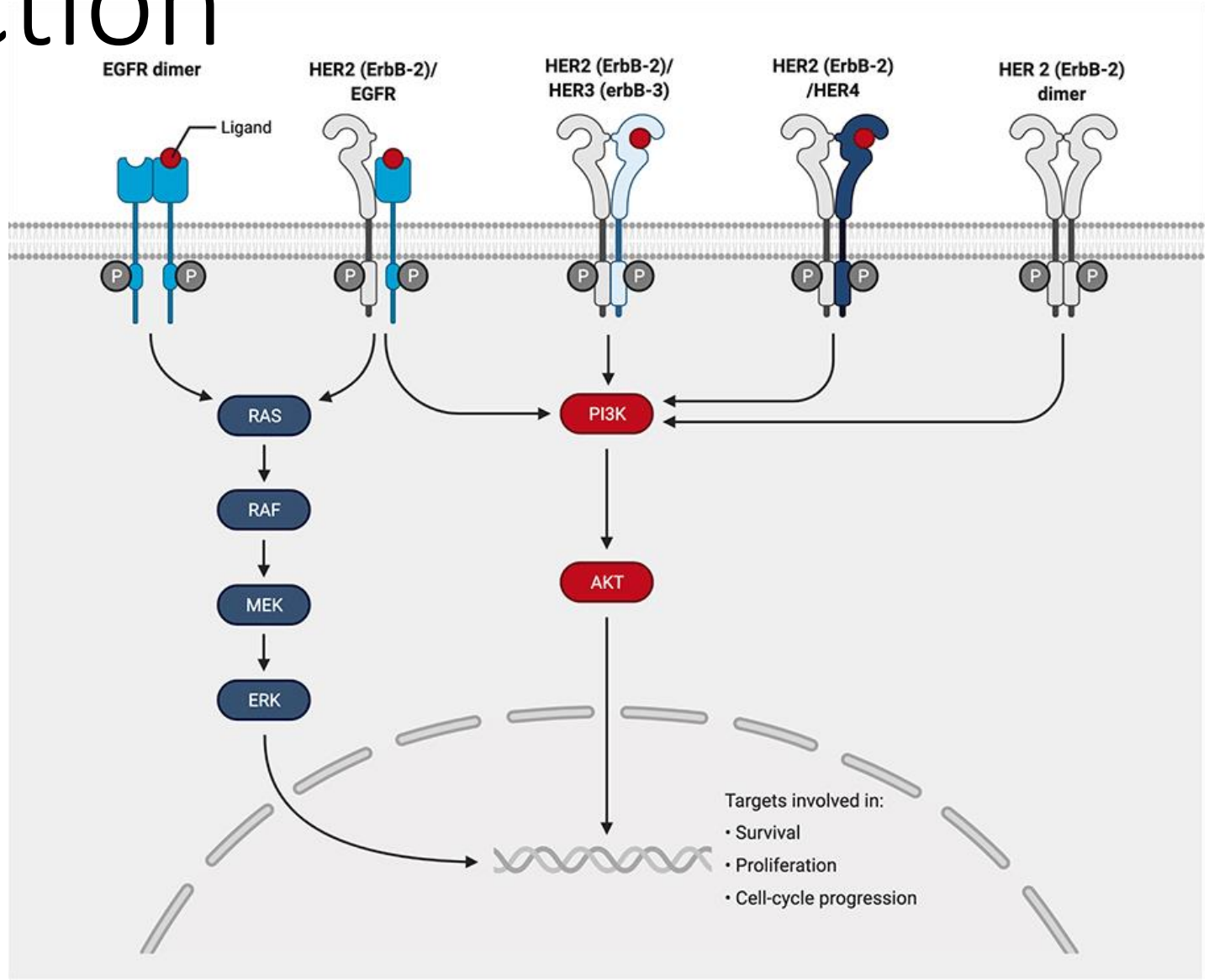
Signal Transduction

Signal Transduction

The activated HER2 receptors after dimerization can lead to autophosphorylation of the tyrosine residues.

This leads to binding with intracellular signalling molecules to initiate to three signalling pathways:

- **Phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway.**
- **Ras/MEK/MAPK**
- **STAT kinase**



(Genentech, 2023; de Lartigue, 2011; Rockland Immunochemicals, 2023)

Signal Transduction

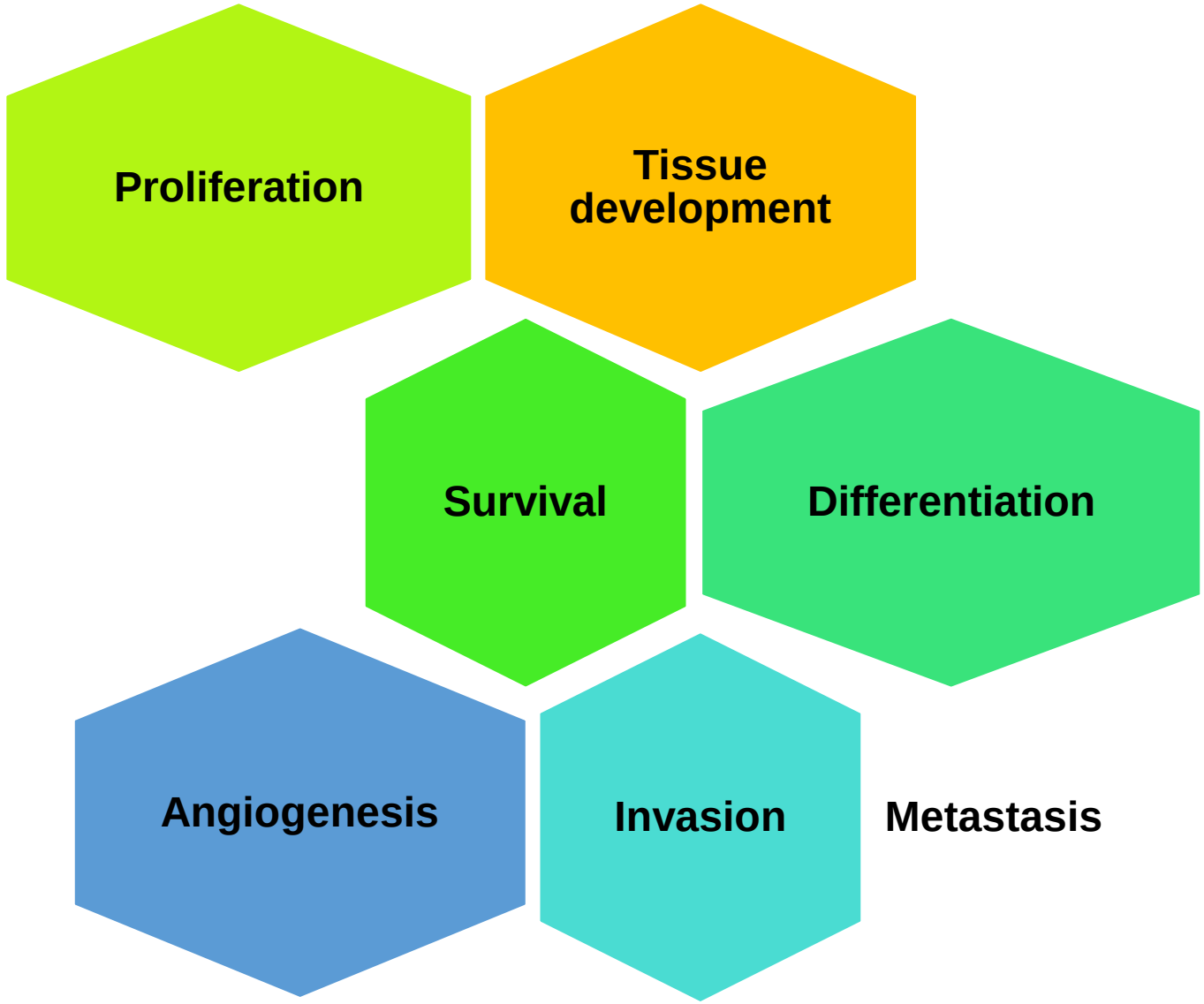
HER2 interacts with importin 2 and is internalized into the nucleus where it induces the transcription of the following genes:

- ❑ **Cyclo-oxygenase 2 (COX-2) induces production of prostaglandins, inflammation, invasion and angiogenesis**
- ❑ **p53-related protein kinase (PRPK): metastasis**
- ❑ **MMP-16: metastasis, survival**
- ❑ **CXCR4 chemokine receptor: metastasis**
- ❑ **E26 transformation specific (ETS) transcription factors: tumorigenesis**

(Mouasser, 2007)

Cellular response

Cellular response



(de Lartigue, 2011)

Dysregulated pathway

Causes of HER2 overexpression

Gene amplification

- 25-50 copies of HER2 gene in breast cancer
- 40-100 increase in protein expression in breast cancer

Deregulation of transcription of *HER2* gene

25-30% of breast and ovarian cancers has these forms.

(Shin, 2021; Moasser, 2007; Slamon *et al.* 1989)

Causes of HER2 overexpression

Mutations in kinase domain

This has been commonly found in lung cancer.

Rare forms were found in gastric, breast and colon cancers.

(Mouasser, 2007)

Causes of HER2 overexpression

Polymorphism

This has been commonly found in transmembrane domain. I665V variant of HER2 increased dimerization and signaling

(Fleishman *et al*. 2002; Mouasser, 2007)

Examples of cancers

Gastric

Thyroid

Head And Neck

Endometrial

Breast

(Mouasser, 2007; Shin 2021)

Rare forms of cancer

Lung

Oropharynx

Bladder

(Mouasser, 2007)

Effect 1 of Overexpression of HER2

Disruption of cell adhesion and cell polarity in epithelial cancers.

Normal role

HER2 interacts with ERBIN (ErbB2 interacting protein) and crosstalks with stromal cells that secrete ligands.

This occurs at the basolateral surface of epithelial cells.

Activation of HER2 via homodimerization causes loss of cell polarity, disrupt tight junctions, affect acinar cell structures in breasts.

How?

Interaction with PAR6 (partition protein 6) and aPKC (atypical protein kinase C)

(Mouasser, 2007)

Effect 1 of Overexpression of HER2

Disruption of cell adhesion and cell polarity in epithelial cancers.

- HER2 interacts with transmembrane protein Muc4 via the EGF-like domain in ASPG-1 present in Muc4.
- This regulates polarity of HER2.
- Muc4 can promote HER2 tumourigenesis even if there is no HER2 overexpression

(Mouasser, 2007)

Effect 2 of Overexpression of HER2

Promoting invasion

Activation of HER2 heterodimerisation with EGFR causes invasion via the following:

- PI3K
- PLCγ (phospholipase Cγ)
- PKC-α
- SRC
- Focal adhesion kinase (**FAK**)

(Mouasser, 2007)

Effect 3 of Overexpression of HER2

Cell cycle control deregulation

HER2 overexpression targets:

- Cyclin D1 and p27 which affects G1/S checkpoint control leading to uncontrolled proliferation.
- It degrades p27 through the MAPK signalling pathway.
- It activates Akt which then phosphorylates p27 preventing p27 from performing its cell cycle function.
- It maintains cancer stem cells that unlimits itself with self-renewal, differentiation and contributes to aggressive, metastasis and resistance to chemotherapy.
- Notch and Wingless/ β-catenin pathways.

Pupa et al.2021

By the end of this lecture, you should understand

- **HER2 is a member of the human EGFR family and has the strongest catalytic kinase activity and signalling.**
- **It has no known ligands and it activates via homodimerization and heterodimerization.**
- **The activated HER2 receptors after dimerization can lead to autophosphorylation of the tyrosine residues.**
- **Signal transduction can occur via three signalling pathways:Phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt), Ras/MEK/MAPK and STAT kinase pathway.**
- **A number of causes for HER2 overexpression: mutations in kinase domain, gene amplification, polymorphism and deregulation of HER2 genes.**

Reference list for further reading

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SEASON 2

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Lecture 17

Types of signalling pathway: NRF2

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