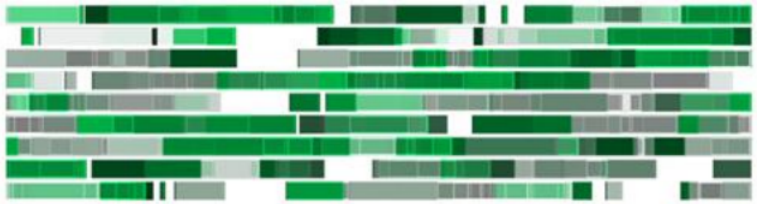
III JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:
A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN



Mecanismos biológicos de resistencia a tratamiento endocrino en CMRH+

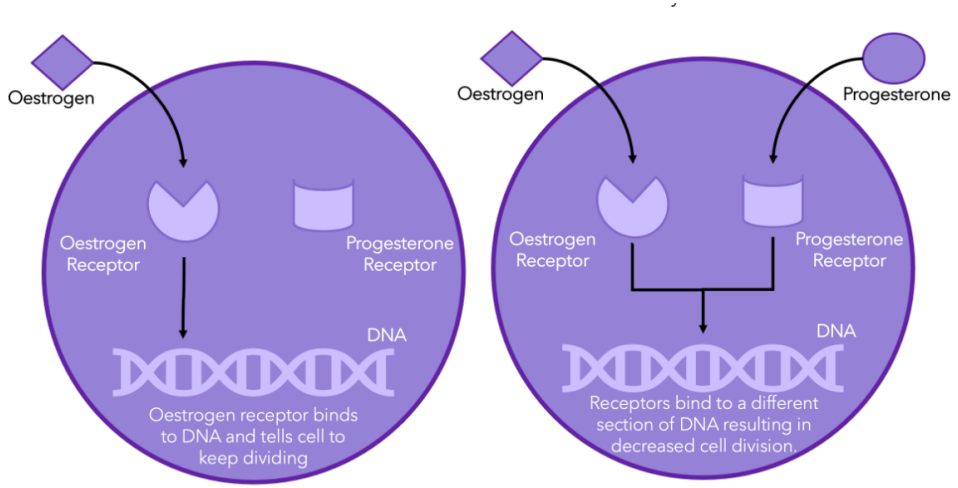
Dra. Begoña Vieites,

Hospital Universitario Virgen del Rocío, Sevilla

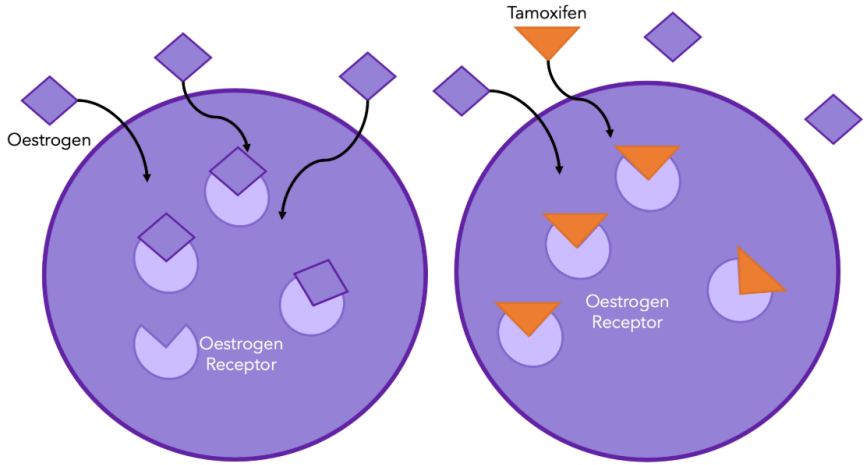
Sevilla, 12 02 2026

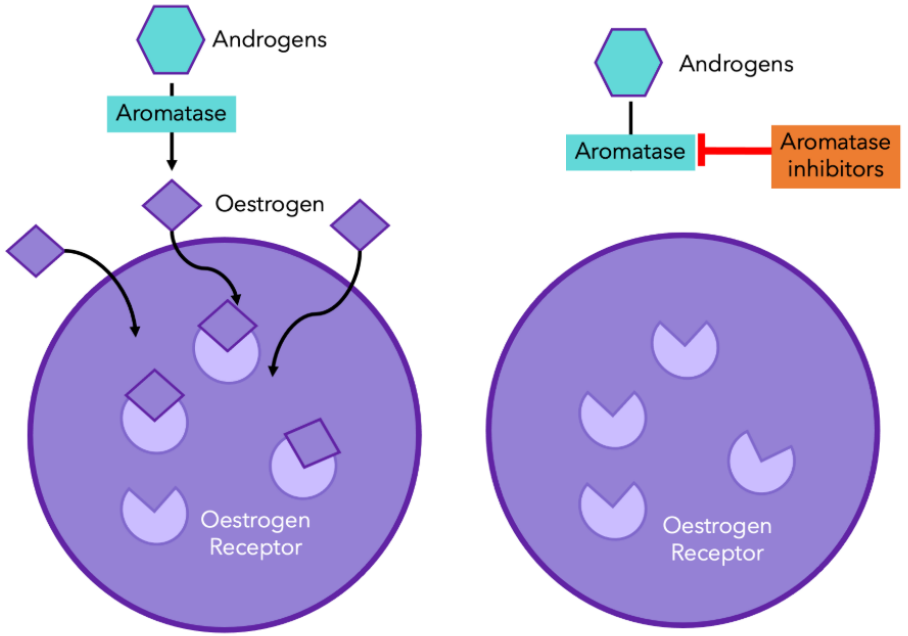
How do oestrogen and progesterone cause cancer growth?

Digital platfform
for cancer patients

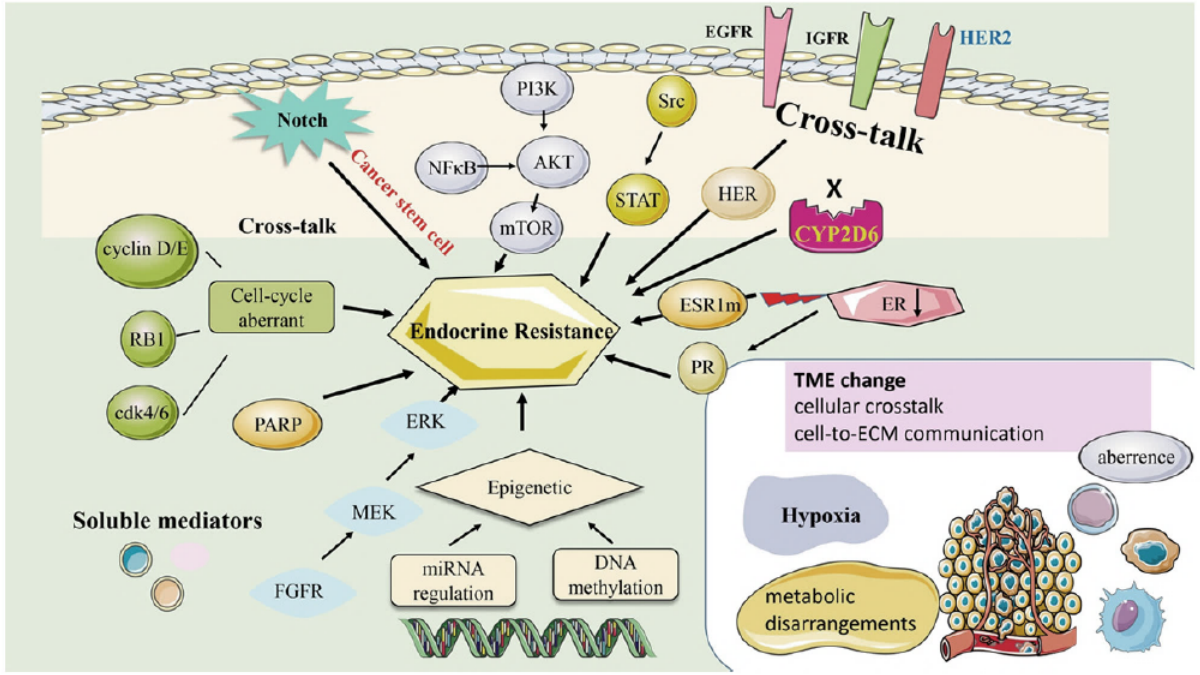


Hormone therapy and basic endocrine therapy





Modified from: https://owise.uk/hormone-receptor-hr/



Chien TJ. Am J Cancer Res 2021

❖ Estrogen receptor / ESR1

❖ **Cell cycle pathway**: CDK4/6

❖ **Cell signaling pathways**:
- ❖ PI3K-AKT-mTOR
- ❖ Notch
- ❖ NF-κβ
- ❖ FGFR
- ❖ IRE1-XBP1

❖ Tumor microenvironment

❖ Epigenetic changes

❖ Cross-talk

❖ Estrogen receptor / ESR1

Estrogens: main signal for tumor cells growth and progression in hormone-dependent BC.

ERα activation: regulates cell growth, proliferation, cell migration and other biological functions.

ERα activation: regulates de expression of different genes within nuclear genoma or by interaction with other transcriptional factors.

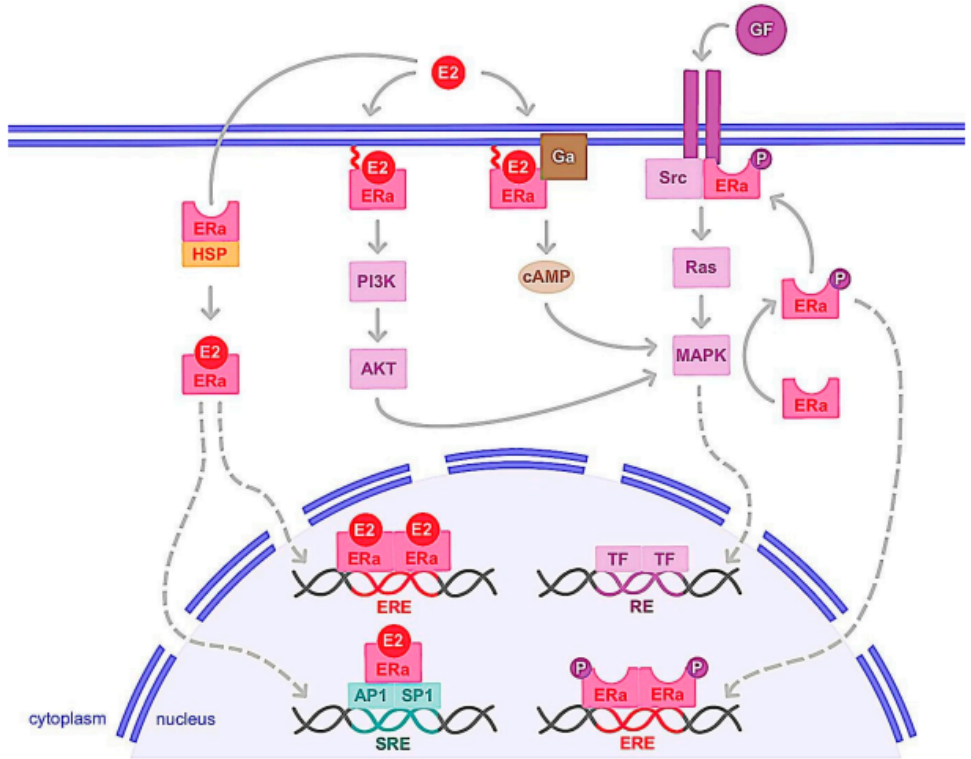
ERβ: protective factor, inhibits cell proliferation, antitumoral role.

Functional interaction between **ER and PR** in BC
(80% of ER+ BC are PR+)

Review

A Basic Review on Estrogen Receptor Signaling Pathways in Breast Cancer

Léa Clusan, François Ferrière, Gilles Flouriot and Farzad Pakdel *



Clusan L. Int. J. Mol. Sci. 2023
Wei S. Pathol Res Pract. 2023

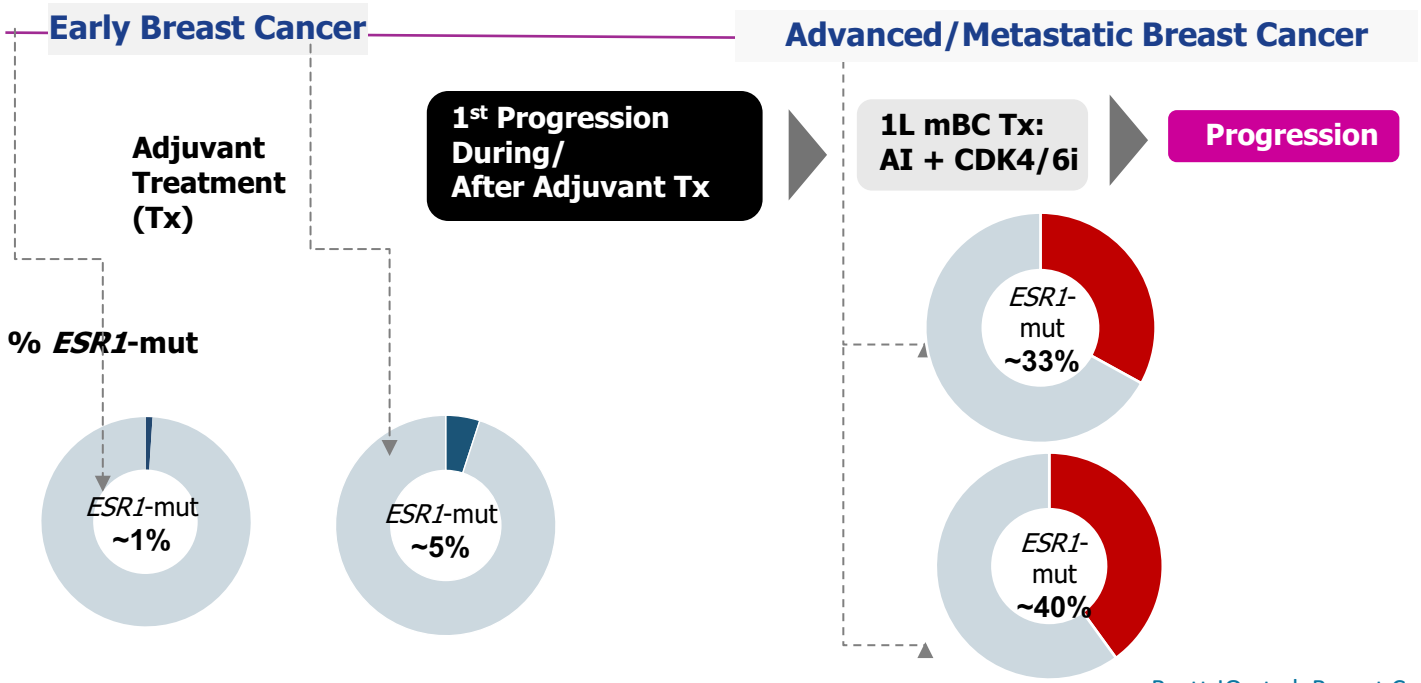
ESR1 mutations in BC

REVIEW Open Access

ESR1 mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer

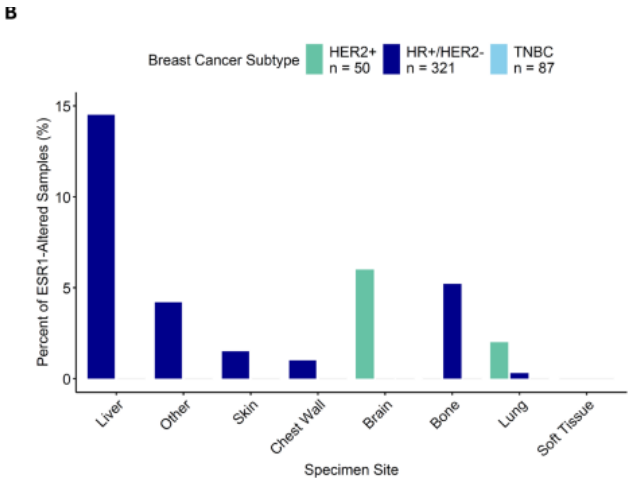
Jamie O. Brett[1,2], Laura M. Spring[2,3], Aditya Bardia[2,3] and Seth A. Wander[2,3*]

- **Mutations in ESR1 Ligand-domain**: most frequent cause of ET resistance in BC.
- **Prevalence** based on **type and duration of ET**
- *ESR1* mutations occur almost **exclusively after ET in the mBC setting**



Characterization of *ESR1* alterations in patients with breast and gynecologic cancers

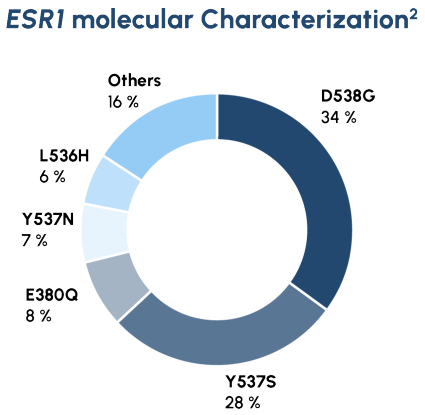
Gargi D. Basu[1], Paige E. Innis[1], Angela K. Deem[1], Arthur Starodynov[1], Sameer S. Udhane[1], Szabolcs Szelinger[1], Min Wang[1], Janine R. LoBello[1], Frederick L. Baehner[1], Jean-Paul De La O[1] and Joyce O'Shaughnessy[2*]



- Different distribution of ESR1alt across metastatic sites.
- Most prevalent in liver and bone.

Brett JO et al. Breast Cancer Res. 2021 / Arao Y et al. Essays Biochem. 2021 / Basu GD et al. Breast Cancer res 2026

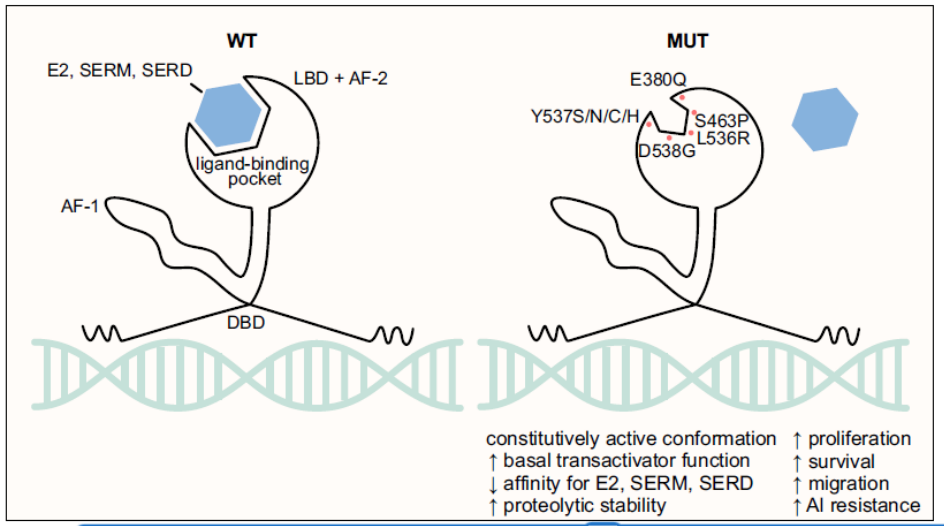
ESR1 mutations in ER+ tumors: **mechanism of action**



- **> 50 point mutations** in *ESR1* have been detected in clinical samples of BC, most are found in **codons 536–538** of the **ligand binding domain** (LBD).
- **Y537S** and **D538G** account for > 60 % of the *ESR1* mutations found in resistant cases.
- Prognostic and predictive influence: less sensitive to the ER antagonists (SERMs and SERDs).

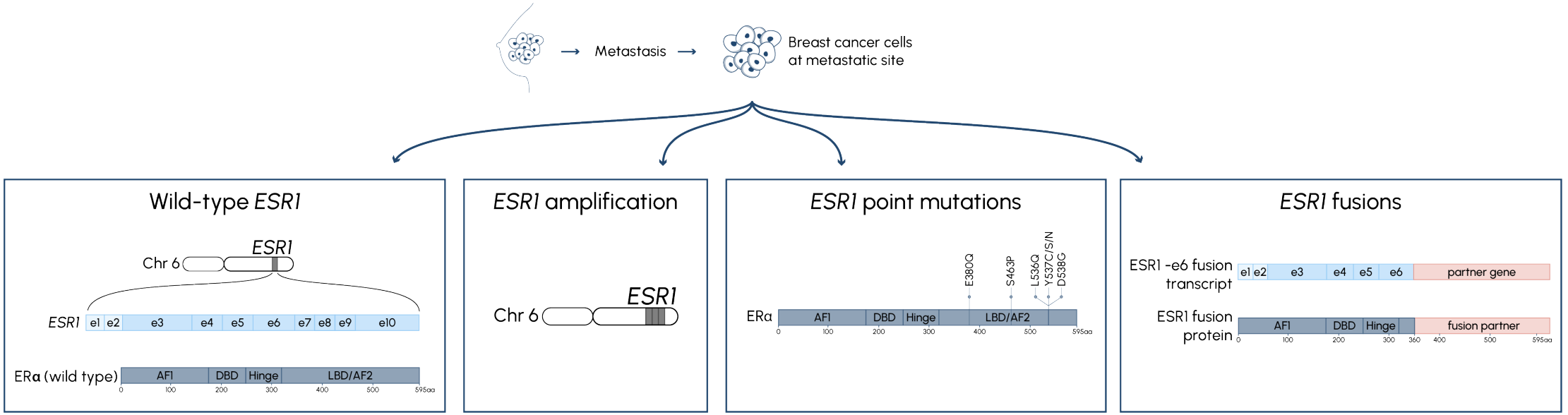
LBD-mut ESR1 is:

- **constitutively active**
- higher stable conformation
- it gains other activities: transactivation of targeted genes or higher affinity for other transcriptor factors (FOXA1, GEB1, ...)



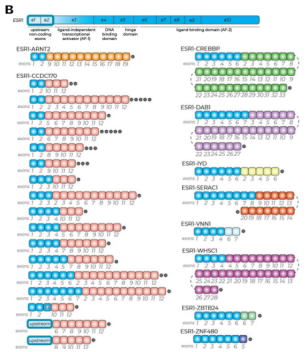
Reinert T, et al. Front. Oncol. 2017; 7:26 / Dustin D et al. Cancer 2019; 125: 3714.

Types of ESR1 genomic alterations in ER+ tumors



- Most are **point mutations** clustered within the ligand-binding domain (LBD) of ESR1

- **ESR1 fusion genes** encoding functional ESR1 fusion proteins are uncommon, but may be detected in mBC ER+. Ex: *ESR1-YAP1, ESR1-PCDH11X, ESR1-DAB2, ESR1-GYF1, ESR1-SOX9*



Basu GD et al. Breast Cancer res 2026

Lei JT et al. Breast 2019 / Grinshpun et al. Biochim Biophys Acta Rev Cancer 2023 / Nagy Z, Jeselsohn. Front Oncol. 2023 / Hartmaier RJ et al. Ann Oncol 2018.

❖ **Cell cycle pathway**: CDK4/6

Dysregulation of the cell cycle:a **hallmark** of cancer.

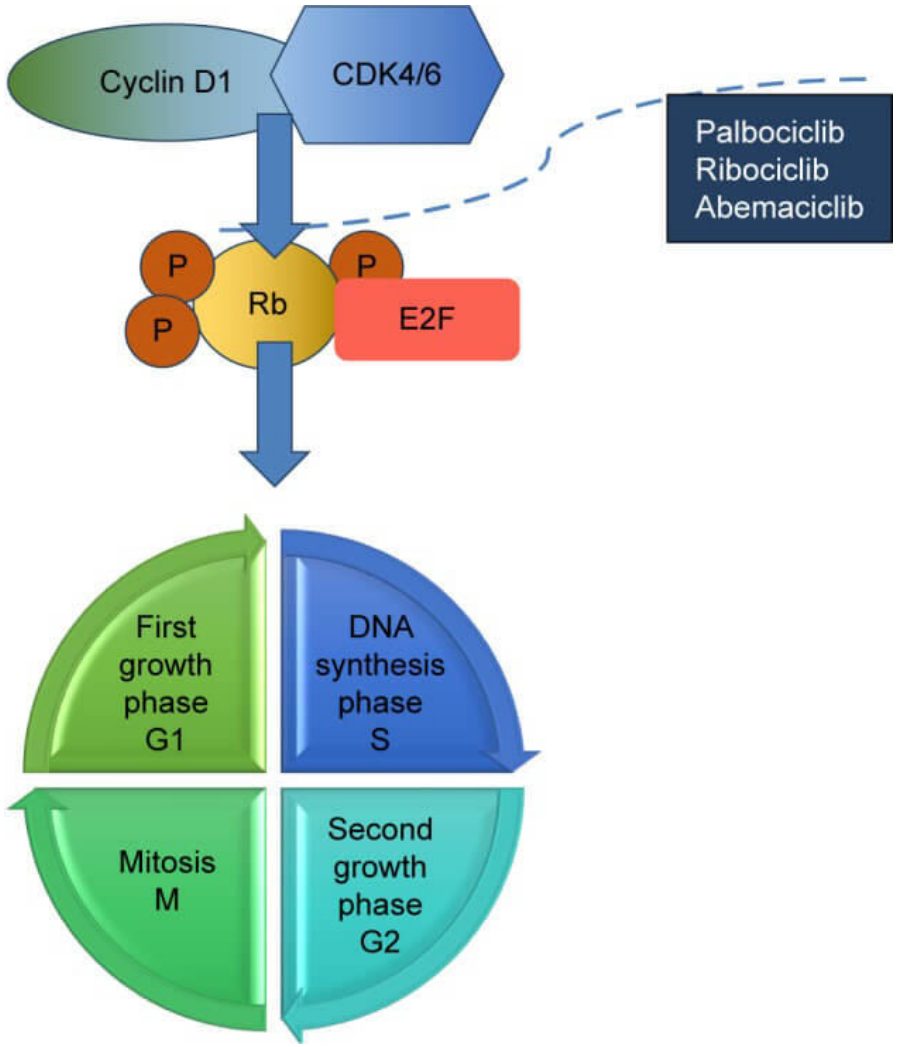
Amplification or overexpression of Cyclin-D1:

- 29% Luminal A
- 58% Luminal B

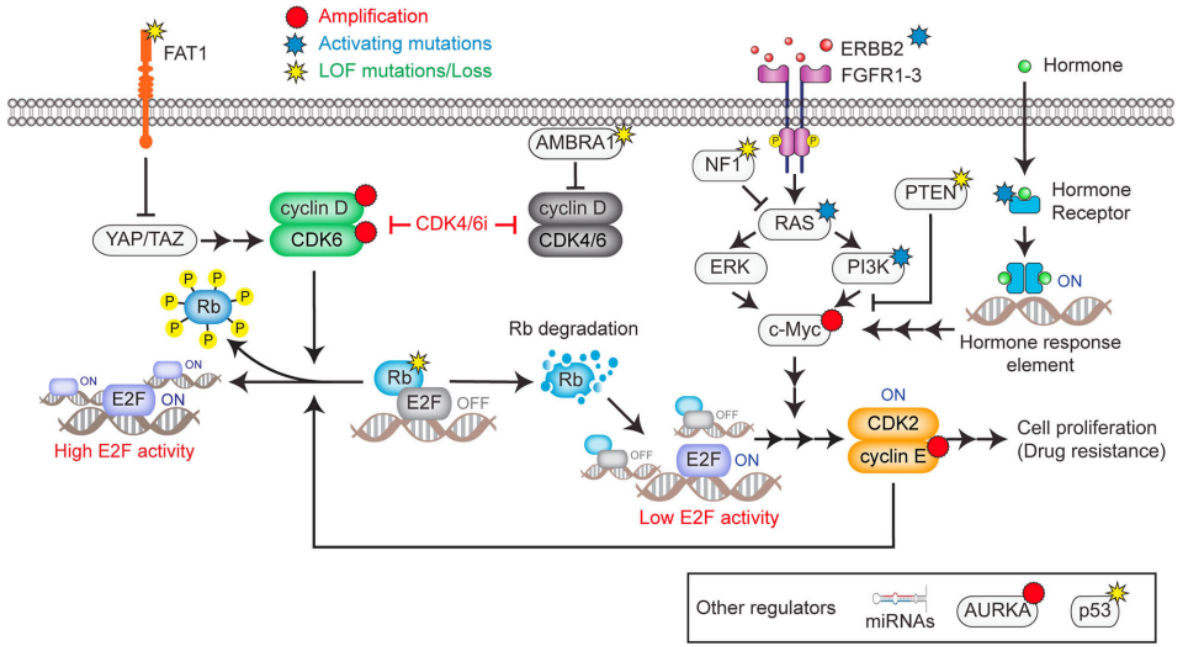
Amplification of CDK4:

- 14% Luminal A
- 58% Luminal B

CDK4/6 inhibitors effectivity is based on targeting abnormal cell cycle progression



Shanabag A, et al. Exp Mol Med. 2025.



≈30% HR+BC developing **resistance** to CDK4/6 inhibitors acquire **new genetic mutations**.

- **LOF mutations in *RB1***
- LOF mutations in *FAT1*

⟷

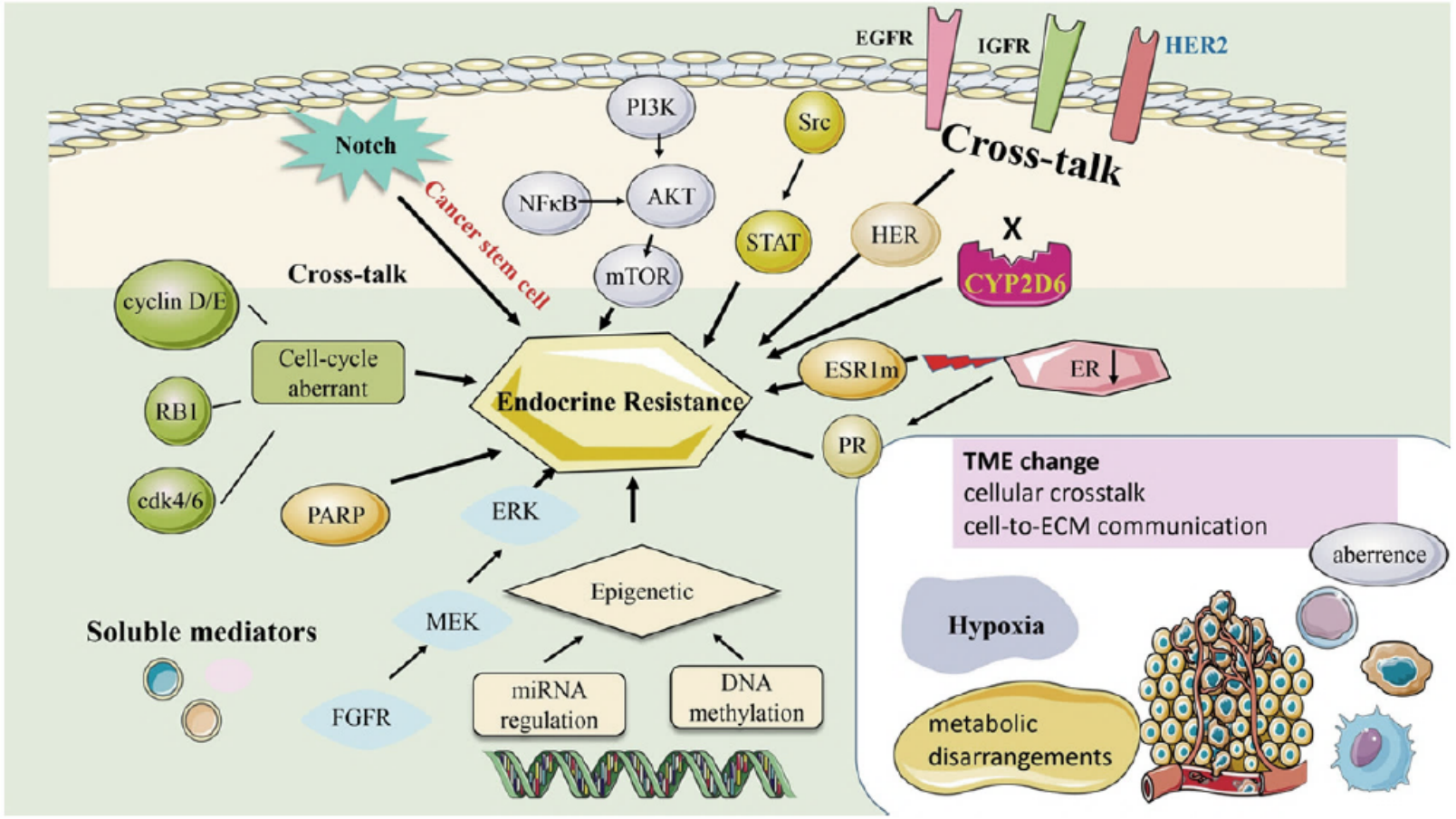
- **Amplifications of *CDK6***
- **Overexpression of Cyclin D/ amplifications of *CCNE1*** and *CCNE2*

70%: other genetic or epigenetic alterations:

- C-Myc amplification and NF1mutation (---→RAS activation-→MPAK/PI3K act)
- MAPK and *Hormone-signalling pathway* alterations--- regulate Cyclin D levels--→ CDK4/6 inh resistance
- Epigenetic changes: microRNA mediation: miRNA-432-5p, miRNA-29b-3p, miRNA223

Shanabag A, et al. Exp Mol Med. 2025. / Goel S et al. Nat Rev Cancer 2022 / Wander S et al. Cancer Discov 2020/ Miranda F. Mol Biol Rep. 2022.

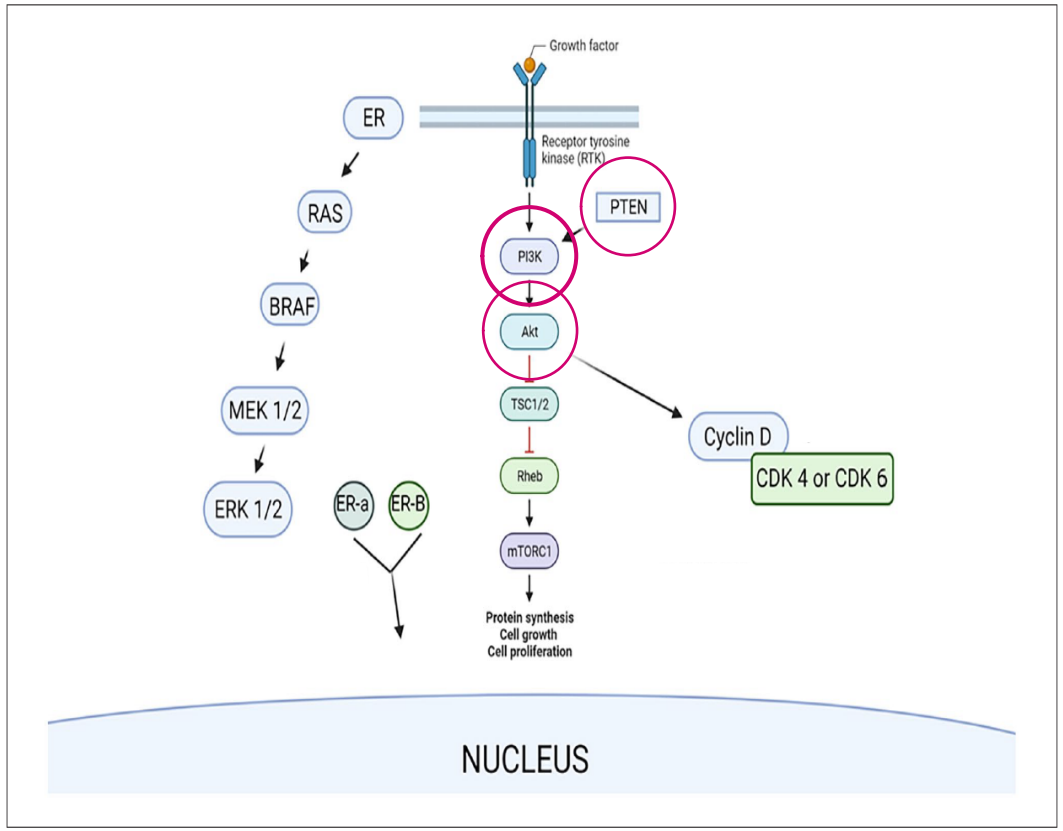
❖ Cell signaling pathways



- ❖ PI3K-AKT-mTOR
- ❖ Notch
- ❖ NF-κβ
- ❖ FGFR
- ❖ IRE1-XBP1

The main mechanism of ET resistance induction: estrogen-independent ER activation
Bidirectional cross-talk between ER and growth factor signaling

PI3K/AKT/mTOR pathway



- PI3K/AKT1/PTEN pathway is the most commonly deregulated signalling pathway and has been **associated with endocrine therapy (ET) resistance.**

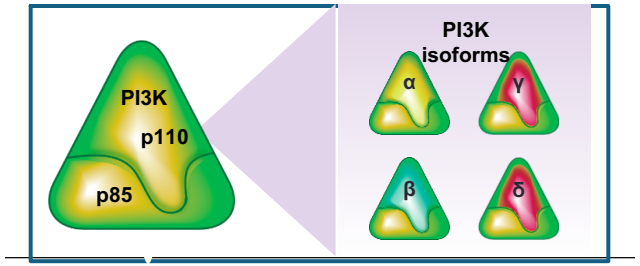
- Abnormal activation of the PI3K/AKT/mTOR pathway drives excessive cell proliferation and resistance to apoptosis and contributes to the initiation and progression of tumors

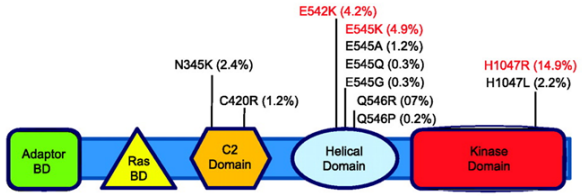
***PIK3CA* is the second most frequently mutated oncogene[1]**

- **Pan-cancer: >10%[1]**
- **HR+, HER2– BC: ~35–40%[6–8]**
- **HER2+ BC: ~23–31%[6–8]**
- **TNBC: <16%[6–8]**

1. Kandoth C, et al. Nature 2013; 2. Hutchinson KE, et al. Genome Medicine 2023;3. Van der Ploeg, et al. Gynecologic Oncology 2021; . LoRusso PM, et al. J Clin Oncol 2016; 6. Anderson EJ, et al. Int J Breast Cancer 2020; 7. Miller TW, et al. J Clin Oncol 2011; 8. Martínez-Sáez O, et al. Breast Cancer Res 2020.

PIK3CA mut: inductor of ET resistance and therapeutic target





- Somatic mutations at helical and kinase domain in PIK3CA gene
- More usual mut: ex 4, 9,20: **H107R, E545K, E542K**, N345 y H1047L
- Different types of PIK3CA mut are present in different subtypes of BC
- Possibility of **double mutations**

Breast Cancer Research and Treatment (2023) 201:161–169
https://doi.org/10.1007/s10549-023-07010-1

REVIEW

Discordance of PIK3CA mutational status between primary and metastatic breast cancer: a systematic review and meta-analysis

Justus Rosin[1] · Ella Svegrup[1] · Antonios Valachis[2] · Ioannis Zerdes[3,4]

Parameters	N studies (*n* pairs)	Pooled discordance, %	95% Confidence Interval, %	Statistical heterogeneity (I^2)	p-value for comparison
Direction of change					0.003
Mut to wild-type	24 (453)	14.9	11.8–18.2	35.3	
Wild type to mut	24 (943)	8.9	6.1–12.1	56.4	
Breast cancer subtype					0.577
HR+/HER2-negative	13 (583)	10.2	6.4–14.8	56.6	
HER2-positive	10 (149)	8.7	4.8–13.7	0.0	
TNBC	11 (151)	8.8	4.9–13.7	0.0	
Site of recurrence					0.839
Locoregional	8 (306)	9.6	6.6–13.1	29.0	
Distant (any)	11 (301)	9.9	6.8–13.5	49.4	
Metastatic site					0.330
Brain	5 (106)	9.6	1.1–24.9	77.2	
Liver	3 (59)	6.4	1.7–13.9	0.0	
Other	5 (67)	11.2	4.9–19.6	7.2	

- PIK3CA mutational status may change along metastatic BC progression.
- Need of obtaining **metastatic biopsies** for PIK3CA-mutation analysis and the possibility of testing of the primary tumor, in case a re-biopsy deemed non-feasible

Clin Cancer Res 2009;15(16) August 15, 2009 / Martínez-Sáez O, et al. Breast Cancer Res 2020

Rosi et- al; Breast Cancer Res and Treat 2023

AKT/PTEN and ET resistance

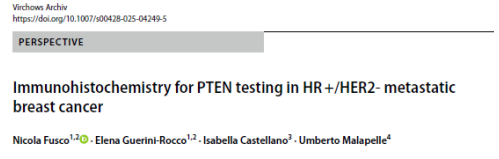
- **PTEN mutations/losses** in luminal A (13%) and B (24%) BC.
- PTEN loss could be more common due to epigenetic modifications (IHC).

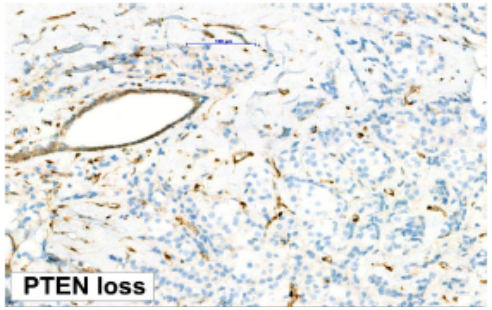
- **AKT1-activating mutations** are less frequent, up to **7.4%** across all BCs studied.

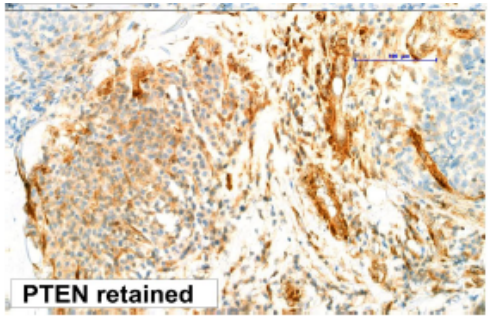
- **Loss of PTEN strongly activates AKT** through activation of p110β, leading to resistance to drugs that target p110α

- Loss of the PTEN gene is associated with **poor prognosis** in HR+ HER2- BC and represents a highly aggressive, treatment-refractory group of diseases.

- AKT1, PIK3CA and PTEN mutations are **mutually exclusive** in BC.







Modified froma Fusco N et al. Virchows Archiv 2025

Liu L et al. Cancers 2024 / Fusco N et al 2025. / Juric D et al. Nature 2015 / Smith LM et al. Breast Cancer 2021 / Miranda F. Mol Biol Rep. 2022

Other Cell signaling pathways

❖ FGFR

- FGFR signaling : ↑↑ 40% metastatatic ER+BC with endocrine resistance.
- Gene alterations: FGFR1, FGFR2 and FGFR3 amplifications or FGFR 2 mutations.
- Mechanism of ET resistance: **stimulation of MAPK and AKT** signaling pathways.

❖ Notch:

- Activated when ER expression is downregulated or ER pathway is inhibited
- Notch 1/3: **promotes ERα expression** or expression of ERα target genes.
- Role in **cancer stem cells** proliferation and in tumor **epitelial-mesenchimal transition** (EMT)

❖ NF-κβ

- NF-κβ expression in BC-HR recurrences and endocrine resistances.
- Influence the sensitivity of BC cells to ET by **regulating ERα expression** and its transcriptional activity throught different pathways (PI3K pathway).

❖ IRE1-XBP1 (stress sensor molecules / unfolded protein response-UPR-signaling pathway)

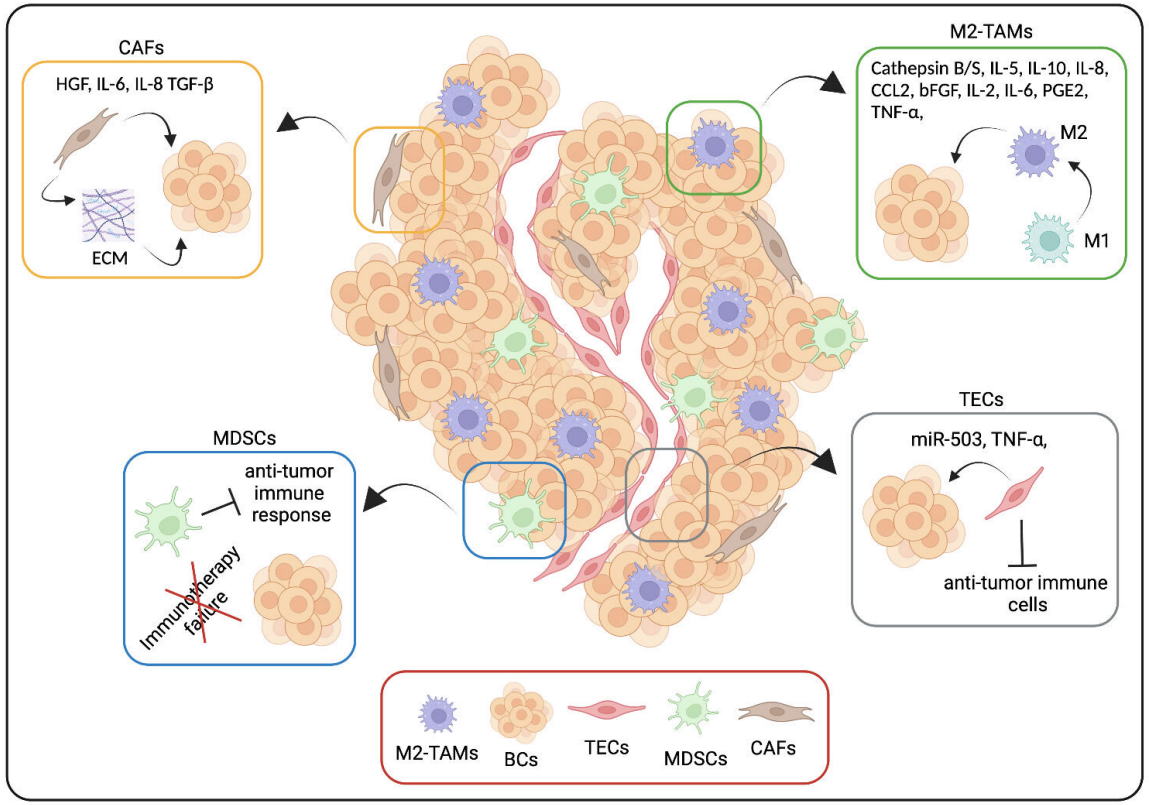
- Pivotal role in maintaining the functionality of ER.
- Crosstalk among different signaling pathways (↑ NF-κβ, ↓p53 degradation , ↑BCL2…)

Miranda F et al. Mol Biol Rep. 2022 / Gao Y. et al. Front Oncol 2024 / saatci O et al. J Molec Med 2021

❖ Tumor microenvironment

Secretion of soluble factors, that protect cancer cells from drug attacks

- Tumor-associated **macrophages** (TAMs)
- **TNF-α**
- Extracellular matrix , **cancer-associated fibroblasts** (CAFs), **tumor endotelial cells** (TECs) and **cancer-associated adipocytes** and other TME cells.
- PD-1 and T-cell Lymphocytes



Mechanisms of drug resistance:

- ❑ Activation of different signaling pathways (PI3K/AKT, MAPK, EGFR)
- ❑ Paracrine induction
- ❑ Modulation of ERα expression

Salemme V et al. Front Oncol 2023 / Hanker AB et al. Cancer Cell 2020

Biological mechanisms in ET resistance: Take-home messages

- High variability in genes alterations and many cross-talk among molecular pathways are responsable of ET resistance in ER+BC.

- **ESR1 mutations** is the more frequent cause of ET resistance.
  - Adquired mutations.
  - Prevalence dependieng on type an duration of ET.

- **Cell-cycle pathways:**
  - Acquired new mutations or los of function in RB1 or FAT1
  - Amplification /overexpression of CDK4/6 or Cyclin D, E---- MAPK and Hormone-signalling pathway

- **PI3K/AKT/PTEN**
  - PIK3CA mutation may be acquired with disease progression
  - PTEN loss of function (→ AKT1 activation)
  - AKT1 activation

- **Other signalling pathways:** *Notch* (tumor stem cells, EMT), *FGFR* (+MAPKas, AKT1)

- ***Tumor Microenvironment:*** secretion of soluble factors activating signalling pathways