Fulvestrant/Tamoxifen-induced resistant MCF-7 model

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OncoWuXi Newsletter

Outline

- **Background**
  - Classification of breast cancer and endocrine therapy
  - Mechanism of drug in the treatment of ER positive breast cancer
  - Mechanism of drug resistance in endocrine therapy
  - Strategies to overcome drug resistance
- **Fulvestrant/Tamoxifen-induced resistant MCF-7 model**

Classification of breast cancer and endocrine therapy

- **Breast cancer is a complex, heterogeneous disease classified into**
  - **based on histological features** ⇨
    - ✓ Hormone-receptor-positive (ER+/PR+)
    - ✓ Human epidermal growth factor receptor-2 overexpressing (HER2+)
    - ✓ Triple-negative breast cancer (TNBC)

- Fulvestrant monotherapy is recommended as the first-line endocrine treatment in advanced breast cancer (ABC) or postmenopausal women with hormone receptor-positive metastatic breast cancer (MBC).

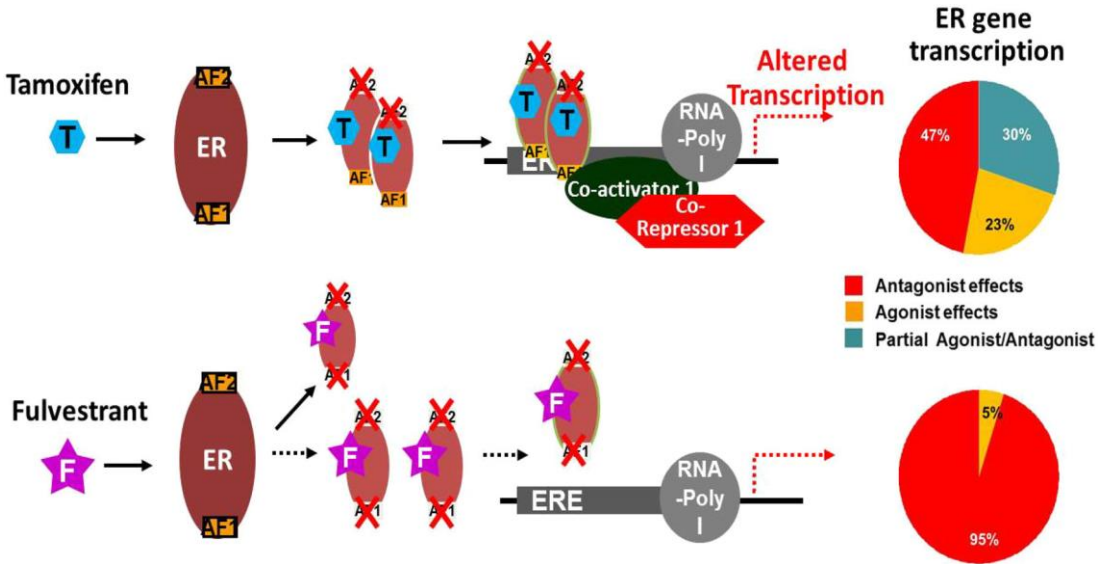
- However, Endocrine therapy could induce drug resistance long used. Crosstalk between ER and other signalling networks as well as epigenetic mechanisms have been verified to contribute to endocrine therapy resistance.

Mechanism of drug in the treatment of ER positive breast cancer

- Tamoxifen forms stable complexes with estrogen receptors and is transported into the nucleus to prevent chromosomal genes from opening up, thereby inhibiting the growth and development of cancer cells.

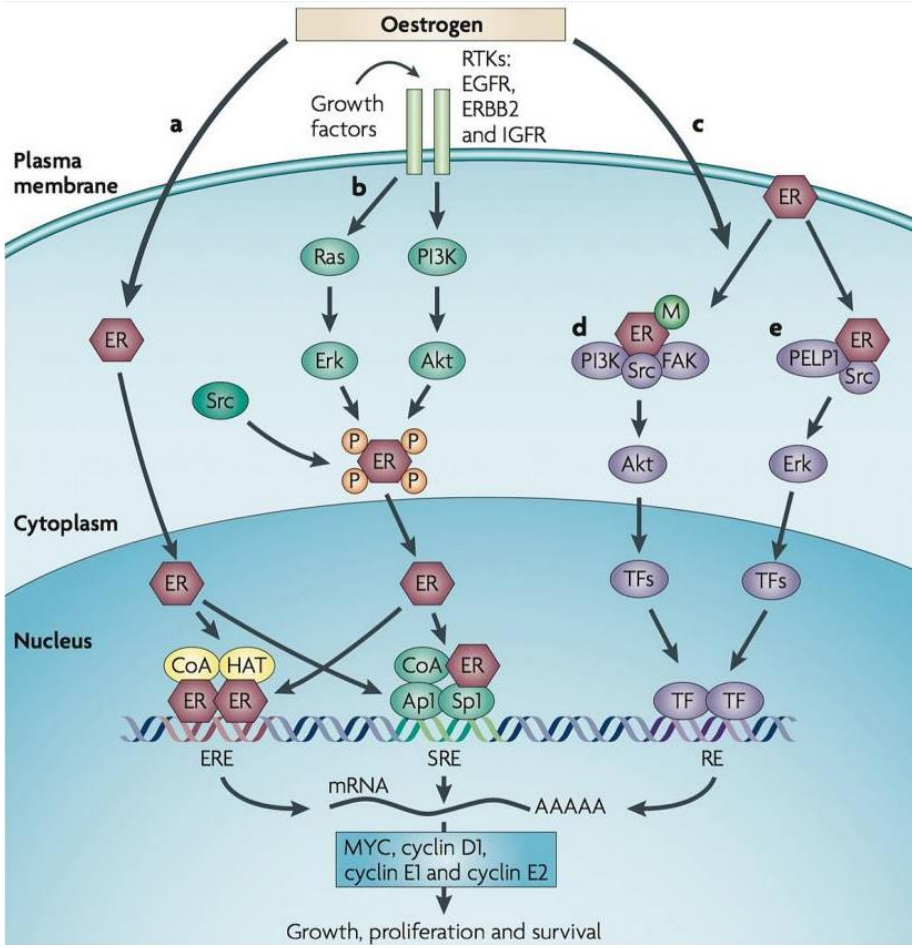
- Fulvestrant is a reversible antagonist of estrogen receptors, but also is a selective estrogen receptor down-regulators (SERDs).

Binding with estrogen receptor (ER+)



Cancer

Complexity of ER Signalling Pathways



Nathan MR, et al. Oncol Ther. 2017;5(1):17-29

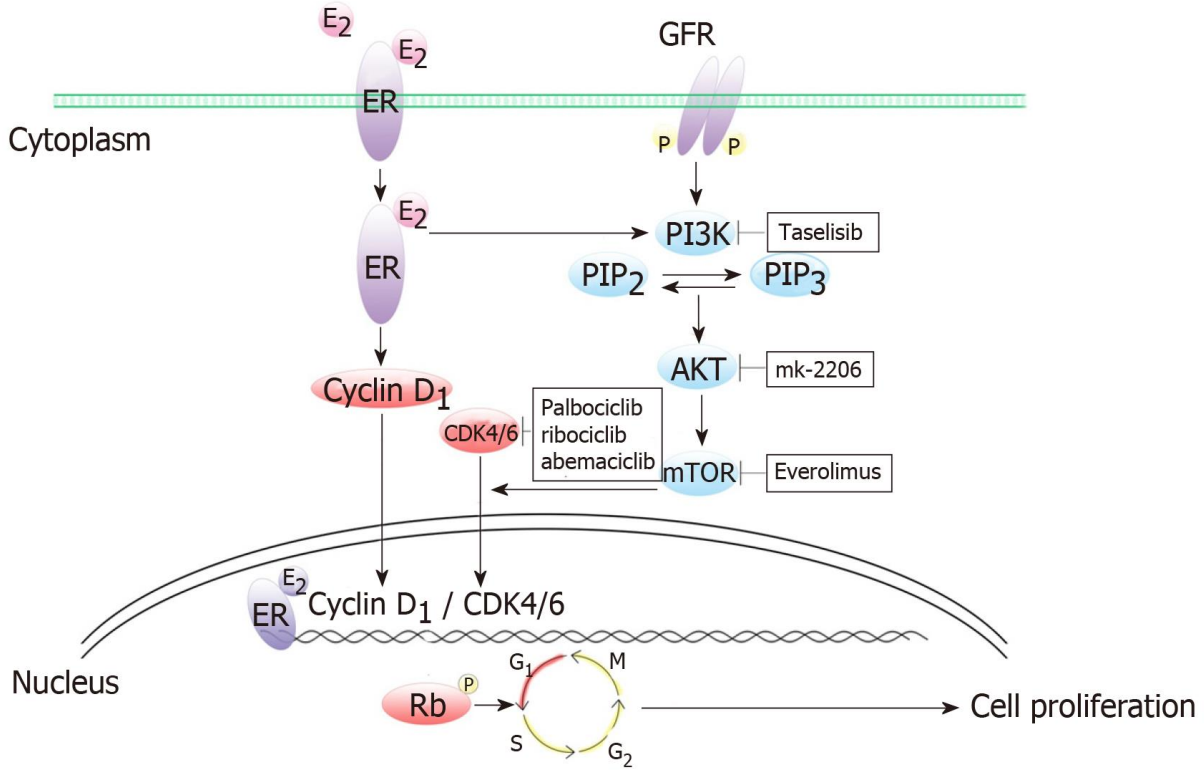
Mechanism of drug resistance in endocrine therapy

➢ Mechanism of resistance

- Growth factor receptors (GFRs) activate the downstream PI3K/AKT/mTOR signaling pathway and the Cyclin D1/CDK4/6 complex, while the ER-E2 complex has the same effect.
- The Cyclin D1/CDK4/6 complex drives cell proliferation by inducing Rb phosphorylation and promotes cell cycle from G1 phase to S phase in the nucleus.
- However, PIK3CA mutation induces PI3K pathway activation which lead to resistance to endocrine therapy (fulvestrant).

➢ Other mutation or alteration

- ✓ Overexpression or amplification of CDK6 and CCNE1
- ✓ FGFR2 alterations may lead to intrinsic resistance
- ✓ HER2 mutation leads to acquired resistance
- ✓ ESR1 mutation reduces sensitivity to Fulvestrant
- ✓ unidentified……



Yao LT, et al. World J Clin Cases. 2019;7(15):1937-1953.

Strategies to overcome drug resistance

➢ Clinical combinational therapies

- Novel targeted treatments, in combination with endocrine therapy, can improve outcomes in advanced breast cancer and inhibit the activity of key pathways in cell growth, proliferation, and metastasis.

✓ CDK4/6 inhibitor (Palbociclib, Ribociclib, Abemaciclib)

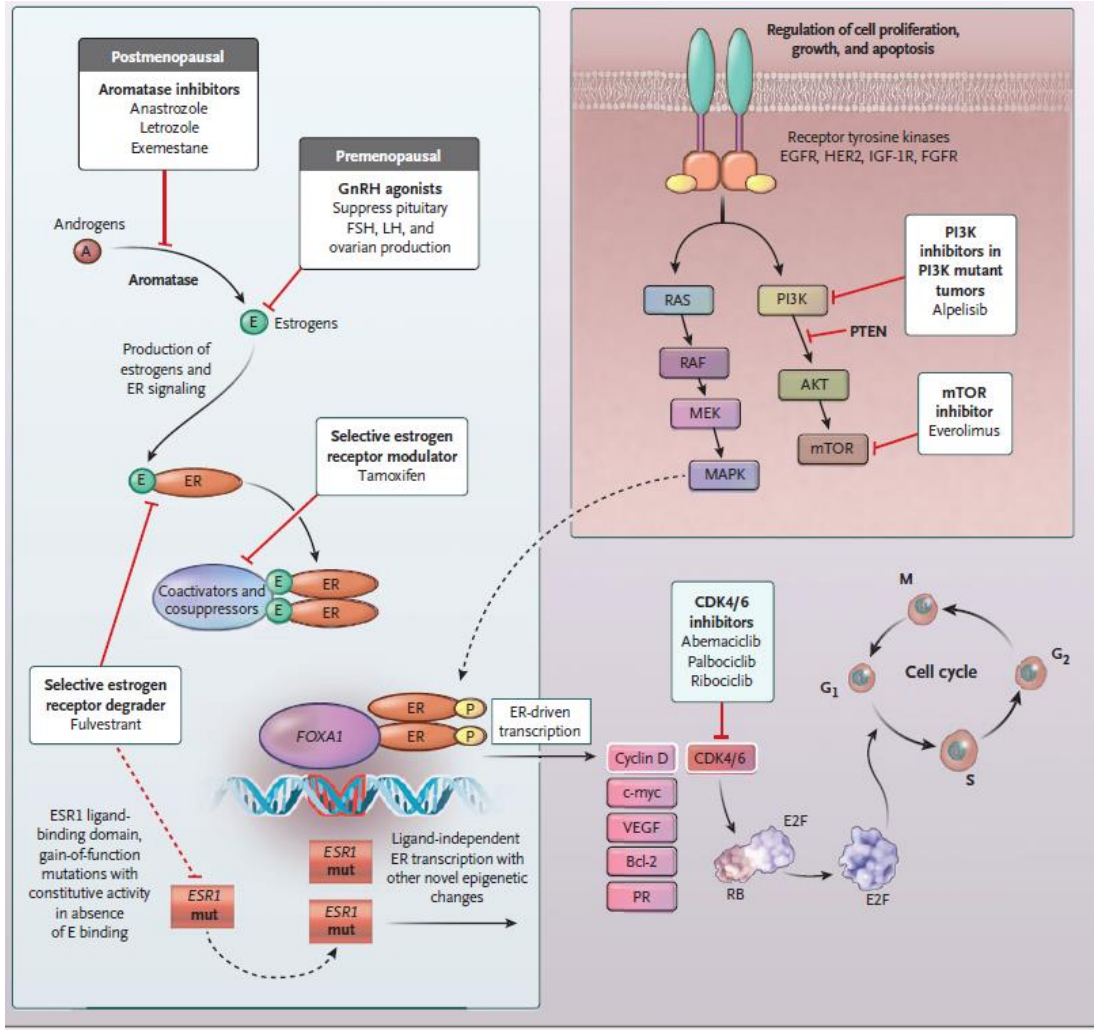
✓ PI3K inhibitor (Alpelisib, Taselisib)

✓ AKT inhibitor (MK-2206, Afuresertib, Uprosertib, Capivasertib)

✓ mTOR inhibitor (PKI597, INK128, GDC0980)

✓ FGFR2 inhibitor (FIIN-2, FIIN-3)

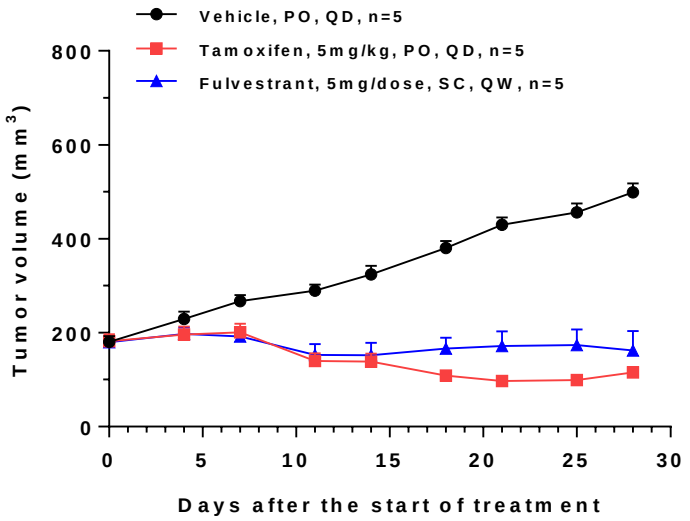
✓ HER2 inhibitor (Neratinib, Tucatinib, Trastuzumab)



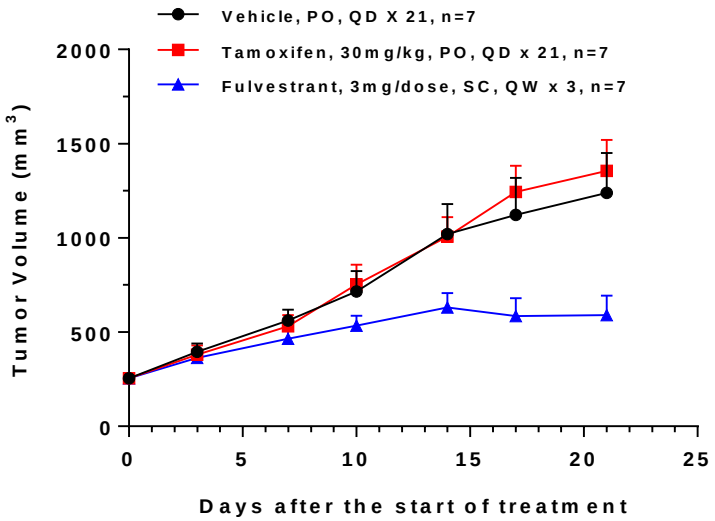
Burstein HJ. N Engl J Med. 2020;383(26):2557-2570.

Fulvestrant/Tamoxifen induced resistant MCF-7 model

Parental MCF-7 model

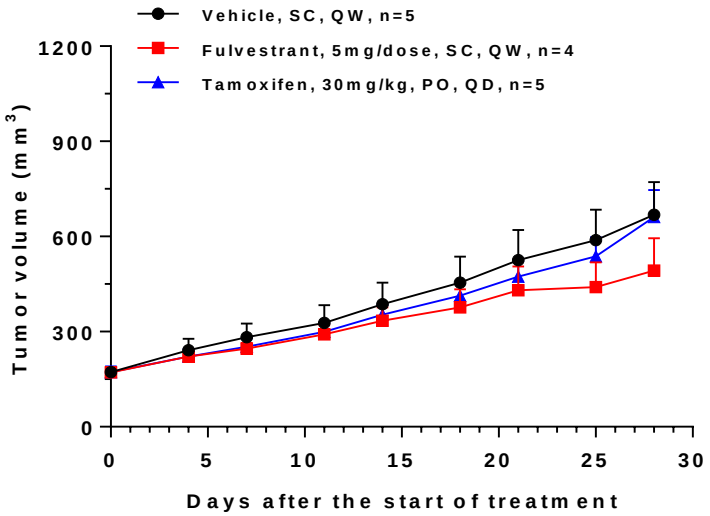


Tam-R-MCF-7 model

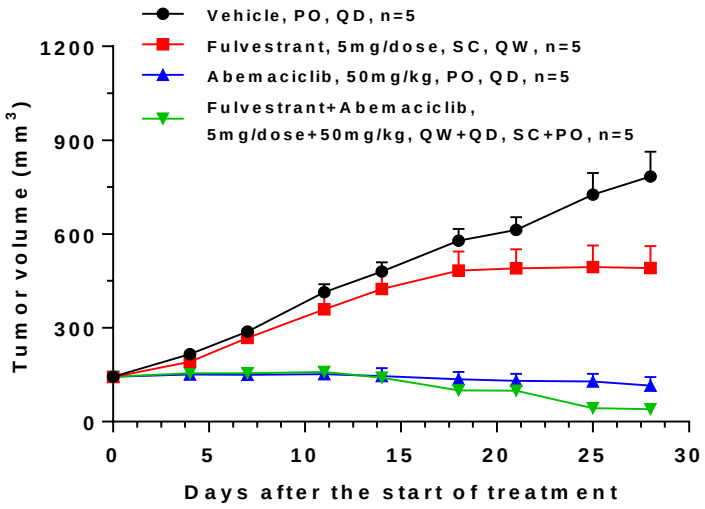


- Tam-R-MCF-7 model was established by long-term treatment *in vivo*, Tamoxifen treated tumors were passaged and dosed until a stable resistance phenotype occurred.
- Next, the Tam-R-MCF-7 model was further treated with Fulvestrant to establish Fulv/Tam-R-MCF-7 model.

Fulv/Tam-R-MCF-7



Fulv/Tam-R-MCF-7



- Fulv/Tam-R-MCF-7 model is resistant to both Tamoxifen and Fulvestrant.
- Genomics validation (RNAseq, WES) is in plan.

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