The answer is clear: The estrogen receptor is present and, when left exposed, may be activated and can drive tumor cell growth.²⁻⁵

Current dialogue focuses on the cell cycle’s role in cancer progression and its regulation by cyclin D1 and CDK4/6, which is highly dependent on estrogen receptor expression. However, it’s important to take the first step of recognizing the full influence of the estrogen receptor—and the multitude of ways it can drive disease.²⁻⁵

Examine the estrogen receptor’s role in mBC through multiple pathways of proliferation.⁴⁻⁶

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CDK4/6 = cyclin-dependent kinase 4/6
EGFR = epidermal growth factor receptor
ER = estrogen receptor
ER+ = estrogen receptor-positive
ERE = estrogen-response element
IGF1R = insulin-like growth factor 1 receptor
mBC = metastatic breast cancer
PI3K = phosphatidylinositol 3-kinase
Data suggest the effects of cyclin D1 and CDK4/6 in driving tumor progression are highly dependent on the estrogen receptor, causing it to impact cell division through the cell cycle.\(^5,7-9\)

- The estrogen receptor enhances expression of cyclin D1, which activates CDK4/6 to drive progression through the G1 phase of the cell cycle\(^7\).
- Cyclin D1 also activates estrogen receptor-mediated transcription, creating a positive feedback loop\(^8\).
- Data suggest that the estrogen receptor and CDK4/6 act together to upregulate E2F transcription by inhibiting the checkpoint regulator protein Rb, which correlates with an increase in Ki67\(^9\).

**Summary Analysis:**

Many mechanisms downstream of the estrogen receptor promote cell cycle activity, thereby encouraging cell division. Cyclin D1, an important cell cycle activator and a direct transcriptional target of the estrogen receptor, is required for estrogen-induced cell proliferation. Cyclin D1 activates cyclin-dependent kinases, such as CDK4/6, which allows progression through the G1 phase of the cell cycle via phosphorylation of the checkpoint regulator protein Rb. Cyclin D1 also activates the estrogen receptor without the aid of CDK4/6.\(^7,8\)

**Abbreviations:**

- E2F = transcription factors
- G0/1/2 = growth 0/1/2 phase
- Ki67 = proliferation marker
- M = mitosis phase
- P = phosphorylation
- Rb = retinoblastoma gene protein
- S = synthesis phase
A familiar means of estrogen receptor activation is via estrogen, through the genomic pathway\(^2-4,10-12\):

- Occurs when estrogen stimulates the estrogen receptor’s ligand-binding domain\(^3\)

- Activation of the estrogen receptor via this pathway causes it to participate in gene transcription in the nucleus, leading to increased cell survival and proliferation\(^3\)
  
  > In the absence of estrogen, the ESR1 estrogen receptor gene may acquire mutations\(^10\)
  > ESR1 mutations occur in an estimated 22% of advanced breast cancer, resulting in highly active receptors in the ligand-binding domain\(^11\)
  > ESR1 mutations lead to transcription and proliferation via expression of constitutively activated estrogen receptor\(^11\)

The typical strategy of blocking estrogen production causes tumors to respond either by becoming hypersensitive to estrogen or by activating the estrogen receptor pathway via other means. And, when activated, the estrogen receptor drives transcription through interaction with nuclear ERE with or without estrogen.\(^2,13\)
The estrogen receptor causes nongenomic signaling through activation of multiple growth factor pathway elements to promote cell survival and proliferation:

- A small pool of estrogen receptors is bound to the cellular membrane.
- When activated, these estrogen receptors interact with membrane receptors such as EGFR and downstream kinases such as PI3K.

Summary Analysis:
Membrane-bound estrogen receptors are activated rapidly by estrogen and interact directly with and/or activate IGF1R, EGFR, HER2, PI3K, and Src. In breast cancer cells with low levels of EGFR or HER2, the membrane functions of the estrogen receptor may be modest, but in cells with abundant EGFR or HER2, they may contribute substantially to tumor growth and resistance to endocrine therapy by altering the expression of genes normally regulated by growth factors.

**Akt** = protein kinase B  
**HER2** = human epidermal growth factor receptor 2  
**mTOR** = mammalian target of rapamycin  
**Src** = steroid receptor coactivator
In the absence of estrogen, growth factors activate pathways that cause nongenomic activation of the estrogen receptor:\(^2\):

- Growth factor pathways, activated by extracellular ligands or alterations in pathway activity, in turn activate the estrogen receptor:\(^2\)

- This crosstalk between the estrogen receptor and outside growth factor pathways contributes further to tumor cell survival and proliferation:\(^3\)

**Summary Analysis:**

The AF1 domain of the estrogen receptor is a convergence point of multiple signaling pathways. In the absence of estrogen, membrane receptors such as EGFR, IGF1R, and HER2 activate pathways that lead to estrogen-independent phosphorylation of the estrogen receptor and its coactivators, influencing their specific functions. Kinases within these pathways, including MAPK and Akt, phosphorylate the estrogen receptor at multiple serine residues within its AF1 domain. The stress kinase pathway also activates the estrogen receptor and its coactivators through the proteins p38 and c-Jun N-terminal kinase.\(^2,4,13\)

**MAPK** = mitogen-activated protein kinase

**S6K1** = ribosomal protein S6 kinase beta-1
Estrogen receptor activation can occur through positive feedback loops at both signaling and epigenetic levels:

- Estrogen receptors located at the cell membrane activate kinases that cause estrogen receptor phosphorylation in the cytoplasm.
- Activation of the estrogen receptor through its own activities leads to increased gene transcription.

Summary Analysis:
Growth factor receptors and membrane-bound estrogen receptors activate downstream kinases that phosphorylate cytoplasmic estrogen receptors. Enhancement of estrogen receptor transcription and phosphorylation by EGFR ligands leads to increased expression of EGFR ligands TGF-α and amphiregulin, which generates a self-propagating autocrine growth regulatory loop in some breast cancer cells that leads to increased estrogen receptor phosphorylation.

IGF1R may contribute to this loop by activating EGFR, furthering the impact on estrogen receptor signaling. The loop may be dominant under conditions in which growth factor receptors are elevated either de novo or during estrogen deprivation. HER2 overexpression may augment the loop, increasing activation of MAPK and estrogen receptor coactivators to enhance estrogen receptor activity in the nucleus.

**TGF-α** = transforming growth factor alpha

Questions?
For more information about the role of the estrogen receptor in ER+ mBC, please contact your AstraZeneca representative, who can put you in touch with the answers you need.