Acta Scientific CANCER BIOLOGY (ISSN: 2582-4473)

Volume 8 Issue 11 November 2024

Review Article

Physiology, Development, and Hormonal Evolution of Mammary Tissue: A Focus on Progesterone, Estrogen, Epidermal Growth Factor and Their Implication in Breast Cancer

Omayma Abidi[1,2]*, Ilhem Bettaieb-Dridi[3] and Oouajdi Souilem[2,4]

[1]*Faculty of Sciences of Tunis, University Tunis El Manar, Tunisia*

[2]*Laboratory of Physiology and Pharmacology, National School of Veterinary Medicine, University of Manouba, Sidi Thabet 2020 Ariana, Tunisia*

[3]*Immune-Histopathology Service, Salah Azaiz Institut, Tunis, Tunisia*

[4]*BiotechPole, Sidi Thabet 2020 Ariana, Tunisia*

***Corresponding Author:** Omayma Abidi, Faculty of Sciences of Tunis, University Tunis El Manar, Tunisia.

Received: October 17, 2024

Published: November 09, 2024

Abstract

The breasts are known as mammary glands that play important roles in the female reproductive system and beyond. One of its primary anatomic and physiologic functions is to produce milk to nourish infants. The breast undergoes several phases of development from sexual differentiation during fetal life to birth, puberty, pregnancy, and up to menopause. Some underlying mechanisms are primarily related and dependent on hormones, especially progesterone, estrogen, and the epidermal growth factor (EGF). All of these factors and others can influence breast development and may even be involved in some pathology such as breast cancer disease, which is the most common female cancer worldwide and the leading cause of female cancer-related deaths. Given the important role to the physiology of the mammary tissue we address here the development of the breast. A deeper insight into the mechanisms underlying hormone involvement in this process and determining their role in breast cancer. This knowledge is particularly crucial for comprehending breast cancer pathology and devising integrated oncology therapies.

Keywords: Breast Development; Hormone; Progesterone Receptor; Estrogen Receptor; Epidermal Growth Factor Receptor; Breast Cancer

Abbreviations

AKT: Protein Kinase B; BC: Breast Cancer; HER1: Human Epidermal Growth Factor Receptor 1; HER2: Human Epidermal Growth Factor Receptor 2; HER3: Human Epidermal Growth Factor Receptor 3; HER4: Human Epidermal Growth Factor Receptor 4; EGF: Epidermal Growth Factor; ERK: Extracellular Signal-Regulated Kinase; ER: Estrogen Receptors; ERα: Estrogen Receptor Alpha; ERβ ; Estrogen Receptor Beta; ErbB1: Human Epidermal Growth Factor Receptor 1; ErbB2: Human Epidermal Growth Factor Receptor 2; ErbB3: Human Epidermal Growth Factor Receptor 3; ErbB4: Human Epidermal Growth Factor Receptor 4; EREs: Estrogen Response Elements; FSH: Follicle-stimulating Hormone; NRG-1: Neuregulin-1; NRG-2: Neuregulin-2; MAPK: Mitogen-Activated Protein Kinase; mTOR: Mammalian Target of Rapamycin; PCOS: Polycystic Ovary Syndrome; PR-A: Progesterone Receptor A; PR-B: Progesterone Receptor B; PREs: Progesterone Response Elements; PI3K: Phosphoinositide 3 Kinase; STAT: Signal Transducers and Activators of Transcription; WHO: World Health Organization

Introduction

Breasts are organs located on the chest of women and men (less developed than in women) [1]. This organ is composed of different parts to ensure its functions of milk production, storage, and secretion [2]. Breast functions are carried out in part by the lobules, which are small gland-like structures located within the mammary tissue. One of its primary functions is to produce milk to nourish

infants (the breastfeeding period) [1,3]. After childbirth, the mammary glands are activated to produce and release milk in a process called lactation. The milk provides essential nutrients and immune factors for the baby's growth and development [1,3,4]. The breasts are responsive to hormonal changes, particularly estrogen and progesterone. These hormones influence the development and changes in breast tissue, especially during puberty, the menstrual cycle, pregnancy, and menopause [2,5]. It is a prominent secondary sexual characteristic in females. The size and shape of the breasts can change during puberty under the influence of hormones, contributing to the overall physical appearance associated with femininity [2]. The breasts are composed of glandular tissue, connective tissue, and fat. The connective tissue provides structural support, and the fat contributes to the breast's shape and size. While cooper's ligaments help maintain the breast's structural integrity [6,7].

At times, abnormal cell growth in the breast can lead to the formation of a malignant tumor [5]. Breast cancer is one of the most serious breast pathologies and may require treatments such as surgery, chemotherapy, and radiotherapy. According to the World Health Organization (WHO) data, breast cancer (BC) ranks first among frequently diagnosed cancers in women, both in developed and developing countries. Each year, approximately 2.3 million cases of BC are reported worldwide, accounting for 24.2% of new cases annually [8]. Furthermore, it represents the leading cause of cancer-related deaths in women. An estimated 685,000 women die each year due to BC [8]. In Canada, 78 Canadian women are diagnosed with positive cases of BC [9]. In Africa, Polynesia has the highest mortality rate, with 85,800 women dying from it in 2020 [8]. In Tunisia, it is the leading cause of cancer-related deaths in women (33%), with approximately 2500 new cases annually [10].

Given the key of understanding the basic anatomy-physiology of the breast itself and the mechanisms influencing normal mammary development is essential for deducing the pathophysiology of breast cancer and determining the importance of hormones in breast development and breast cancer disease.

Physiology and function of the breast

The milk produced in the lobules is transported to the nipple through tiny ducts called lactiferous ducts. These ducts are lined by a continuous layer of luminal cells, forming a single-layered epithelium around the lumen of the ducts [1]. This layer is surrounded by basal cells, including progenitor cells and myoepithelial cells. Thus, the lactiferous ducts cluster into larger structures to form lactiferous ducts. The lobules are surrounded by adipose (fatty) and connective tissue (stroma), which also make up a significant part of the breast [6]. They provide structural support to the glandular tissue of the breast and nourish the epithelial cells. The skin of the breast is attached to the chest wall through suspensory ligaments, also known as Cooper's ligaments, which maintain the shape and position of the breast [7]. The lymphatic tissue (composed of lymphatic vessels) plays a crucial role in draining fluids and waste from the breast, as well as transporting immune cells [1,6]. The anatomy of breast tissue can vary from person to person, particularly depending on age, menstrual cycle, and other hormonal factors [2,5,6]. It is important to study the physiology, development, and evolution of the breast in gaining a comprehensive understanding of the underlying mechanisms and processes. It is essential for unraveling the complexities of breast cancer, from its initiation to progression, and for developing effective and personalized therapies.

Breast development

Breast development is influenced by genetic, nutritional, and hormonal factors, especially estrogen, which plays a key role in the growth and maturation of the breasts.

In girls, puberty is the time when the body undergoes significant changes to prepare for reproduction. Breast development is one of the most visible signs of puberty in girls [3]. It is a complex process influenced by hormones [11]. At the onset of puberty, the ovaries begin to produce estrogen and progesterone, which trigger the budding of proliferative cells to form terminal buds at the ends of the lactiferous ducts [3]. These buds branch out and traverse the connective tissue, causing swelling and sensitivity in the chest region [1]. Once the mammary gland has reached full maturity, its state is influenced by hormonal fluctuations throughout the menstrual cycle, leading to the formation of tertiary branches, which regress in the absence of pregnancy [11].

Breast development during pregnancy and post-pregnancy involution are two processes regulated by hormonal changes (prolactin, corticoids, growth factors, especially estrogen and progesterone), which vary depending on the developmental phase [3,4]. During the first three months of pregnancy, the epithelium of the mammary gland begins to undergo a second phase of intense proliferation. Alveoli within the lobules develop, fill the interlobular space, and differentiate to produce milk (under the control of the prolactin receptor) [1,3,4].

Lactiferous ducts branch out further to facilitate milk transport. As pregnancy progresses, the breasts increase in size. During

the last trimester, the lactation hormone (prolactin) increases to stimulate milk production [12]. After childbirth, oxytocin causes an increase in pressure in the acini surrounded by muscle, which contracts, leading to the release of breast milk into the lactiferous ducts, then towards the nipple to feed the baby [3]. The involution phase of the breasts occurs when breastfeeding ends. The lactation hormone (prolactin) gradually decreases, the alveoli begin to regress, and the volume of produced milk decreases as a result. This phase is accomplished through remodeling of the ducts and lobules under the action of proteases and apoptosis phenomenon [3].

Breast development based on endocrine status

The development of the breasts is closely regulated by hormones, especially estrogen, progesterone, and prolactin. These hormones play a key role at different stages of a woman's life, notably during puberty [11], pregnancy, and breastfeeding [13].

During puberty, breast development begins under the primary influence of estrogen [11]. Estrogens are female sex hormones, produced in significant quantities during puberty. Estrogens stimulate the growth of glandular tissues and lactiferous ducts in the breasts, leading to an increase in breast size and volume. They also promote the development of mammary lobules, which are structures responsible for milk production [14].

During pregnancy, estrogen and progesterone levels increase significantly due to their production by the placenta to support fetal growth and development. These two hormones prepare the mammary gland for lactation by stimulating the proliferation of alveoli in the mammary lobules [3]. Prolactin is a hormone responsible for lactogenesis, which also increases during pregnancy. However, it is inhibited during pregnancy by high levels of estrogen and progesterone to prevent milk production before childbirth [3].

After that, when the placenta is expelled, estrogen and progesterone levels rapidly decrease, while prolactin is no longer inhibited, triggering the production of breast milk. When the baby suckles, nipple stimulation releases oxytocin, a hormone that causes contractions in the alveoli to release breast milk into the lactiferous ducts and eject it through the nipple to feed the baby. Prolactin maintains continuous milk production as long as the baby suckles regularly, making lactation an active and dynamic process [14].

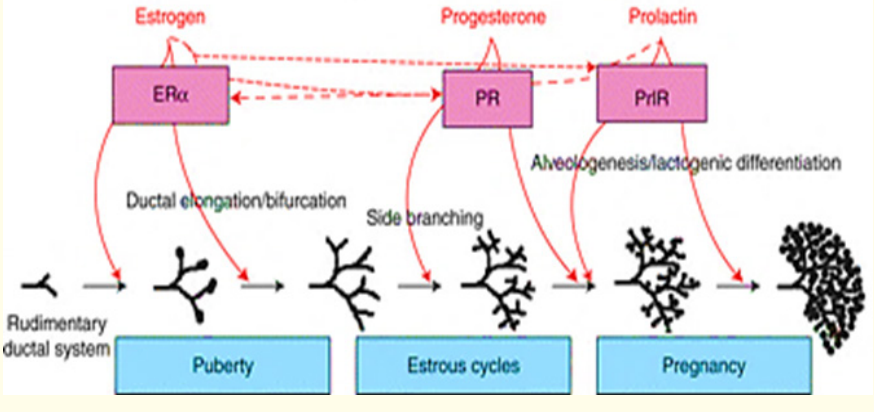

Figure 1: Hormones effects on breast development in variant stage of woman's life.

After the breastfeeding period, when the baby no longer needs to suckle, prolactin gradually decreases, leading to the involution of the mammary gland, where alveoli regress, and the volume of produced milk gradually decreases. Estrogens stimulate breast development during puberty, while estrogens, progesterone, and prolactin prepare the mammary gland for lactation during pregnancy and breastfeeding. Prolactin is particularly important for maintaining the production of breast milk during the breastfeeding period [3].

It is observed that estrogens and progesterone are two main hormones influencing the development of breast tissues. There

some others hormones can be implicated and can affect directly breast development like Inhibin B (hormone produced by the ovaries) that regulates the secretion of follicle-stimulating hormone (FSH) and plays a role in ovarian function (regulatory role in the menstrual cycle) [15] or indirectly such as cortisol (a stress hormone) and insulin (glucose metabolism) by affecting hormonal balance. Insulin resistance, often associated with conditions like polycystic ovary syndrome (PCOS), may impact hormonal regulation [16].

Estrogen receptors ER

Estrogen receptors (ER) are proteins that play a key role in cellular response to estrogen hormones, particularly estradiol. There are two main isoforms of estrogen receptors, namely Estrogen Receptor Alpha (ERα), primarily expressed in reproductive tissues such as the uterus, breast, and ovaries. It plays a significant role in regulating breast growth, differentiation, and uterine function [17]. Additionally, we mention Estrogen Receptor Beta (ERβ), which is more widely distributed in various tissues of the body, including the brain, liver, heart, bones, and prostate. They are involved in the regulation of growth, cell differentiation, and tissue metabolism. ERβ is sometimes considered a negative modulator of ERα signaling [18,19]. Estrogen receptors ERα and ERβ exist in monomeric form in the cytoplasm before binding to estrogen. Upon estrogen binding, the receptors form homo-dimers (two identical receptors) or hetero-dimers (ERα with ERβ) [17].

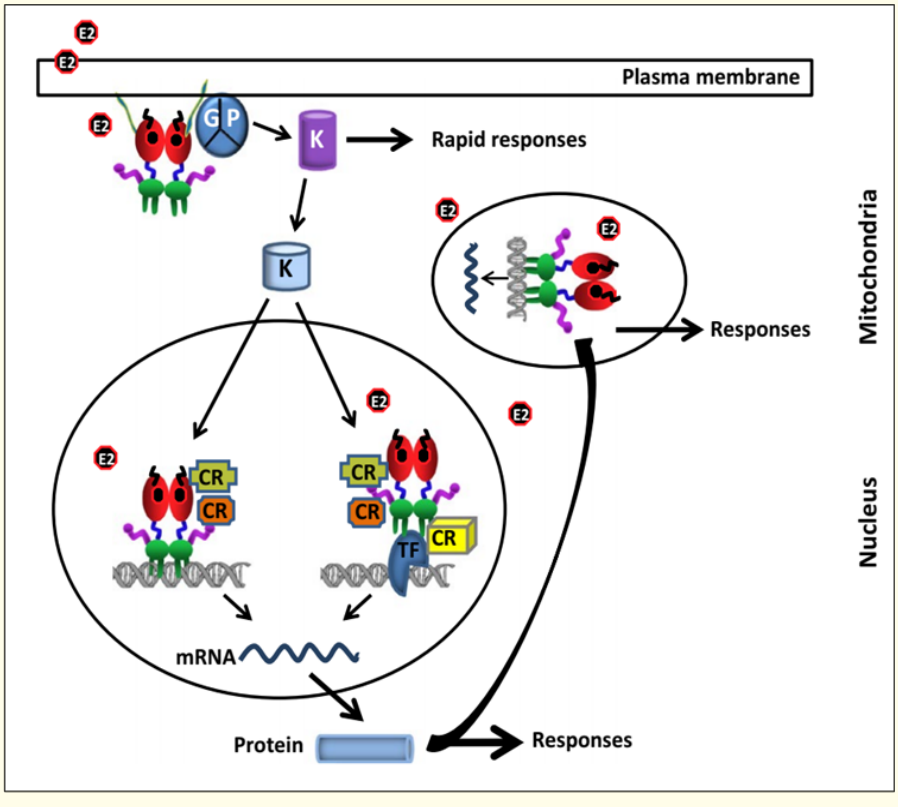

Figure 2: Estrogen receptor model with its down streaming signaling pathway [17].

Activated ER dimers migrate to the cell nucleus. This translocation is essential, as activated ERs act by stimulating transcription within the nucleus. They specifically bind to DNA sequences called estrogen response elements (EREs) at the promoter region of target genes. This binding activates or represses the expression of target genes by recruiting transcription cofactors. The regulation of gene expression by ERs has diverse cellular effects, including the promotion of growth, cell differentiation, and regulation of metabolism [18,19].

Progesteron receptors PR

PRs are proteins that play a crucial role in regulating various biological processes, including reproduction, pregnancy, the onset of secondary sexual characteristics, and metabolism [20].

There are two main isoforms of PR [21] including progesterone receptor A (PR-A), which is a truncated form of PR. It consists of fewer amino acids than progesterone receptor B (PR-B) and lacks a long N-terminal region. It is known as a PR receptor. It can modulate PR-B signaling and repress the expression of progesterone target genes. It is known as a PR receptor. It can modulate PR-B signaling and repress the expression of progesterone target genes [20].

Additionally, there is progesterone receptor B (PR-B), which is the full form of PR. It contains a long N-terminal region with important phosphorylation sites for receptor activity regulation. It is generally considered an active PR responsible for gene transcription activation in response to progesterone [20]. The regulation of the expression of PR-A and PR-B isoforms can vary depending on tissue and hormonal context. The balance between these isoforms can influence cellular response [22].

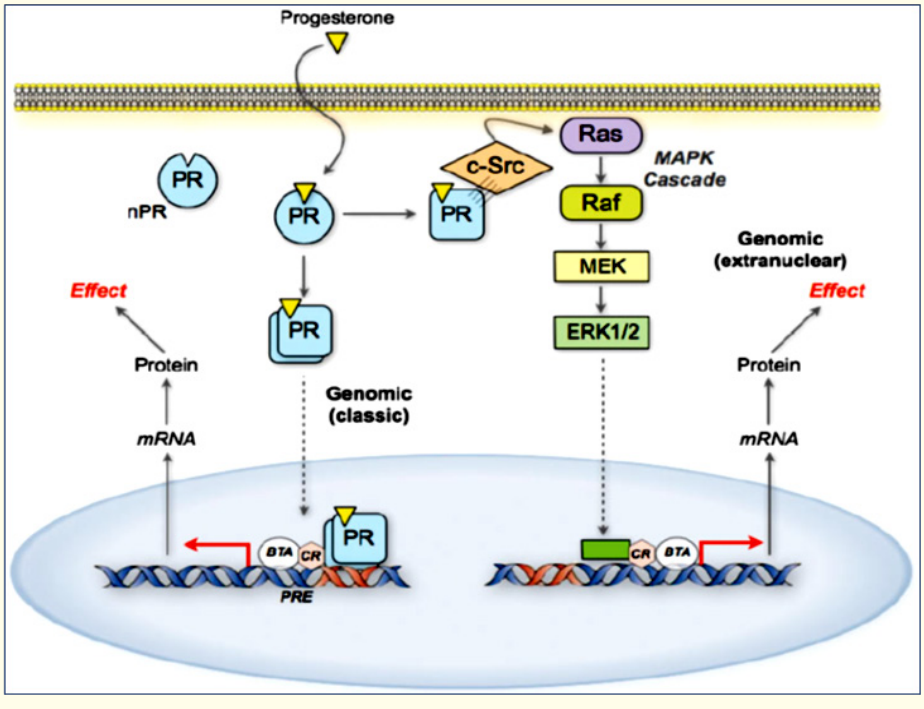

Figure 3: Progesteron Receptor genomic signaling pathway [5].

When progesterone binds to PRs, the structure of PRs changes. Located at the plasma membrane, this complex then moves to the nucleus, acting as a transcription factor.

This complex specifically binds to DNA sequences called progesterone response elements (PREs) present in the promoter regions of target genes, to stimulate or repress the expression of target genes by recruiting transcription cofactors [22]. The regulation of gene expression by PRs has diverse cellular effects, including the modulation of cell growth, regulation of cell differentiation, and preparation of the uterus for pregnancy and potential embryonic implantation [20]. PRs play a crucial role in regulating gene expression and modifying cellular functions.

Epidermal growth factor receptor (EGFR)

The HER1 (Human Epidermal Growth Factor Receptor 1) or ErbB1, is a trans-membrane protein located on the cell surface, is also known as Epidermal Growth Factor Receptor (EGFR). It belongs to the family of tyrosine kinase receptors and plays a key role in the regulation of survival, growth, differentiation, and division.

Activation of EGFR is triggered by its binding to specific ligands [23,24]. Members of EGFR and their ligands include the EGFR receptor (ErbB1 or HER1) is activated by various ligands, including EGF (Epidermal Growth Factor) and TGF-α (Transforming Growth Factor-alpha). It is involved in the regulation of cell growth, survival, and differentiation. The ErbB2 receptor (HER2) is included and does not have a specific soluble ligand and does not directly bind to EGFR ligands. However, it forms heterodimers with other ErbB receptors. Also, the ErbB3 receptor (HER3) is activated by ligands such as NRG-1 (Neuregulin-1) and NRG-2. It can form heterodimers with EGFR, ErbB2, and ErbB4. Finally, the ErbB4 receptor (HER4) is activated by ligands such as NRG-1 and NRG-2. It can form heterodimers with EGFR, ErbB2, and ErbB3.

EGFR activation begins when specific ligands bind to the extracellular domain of the receptor. This induces a structural change in EGFR, promoting the formation of dimers either as homo-dimers (EGFR-EGFR) or as hetero-dimers combined with another member of the ErbB receptor family, allowing the kinase domains of EGFR to mutually self-phosphorylate on specific tyrosine residues [25]. This phosphorylation activates the intracellular kinase, which in turn phosphorylates other intracellular signaling proteins. The phosphorylated tyrosine residues of EGFR serve as anchoring sites for intracellular signaling proteins that recruit other signaling proteins. The EGFR receptor also activates the PI3K/AKT/mTOR pathway (Phosphoinositide 3 kinase/Protein Kinase B/mammalian Target of Rapamycin), where the activation of PI3K leads to the phosphorylation of AKT (protein kinase B) [24,26]. AKT then activates mTOR (protein regulating cell growth and survival). Activation of this pathway promotes cell survival [25]. The EGFR receptor can also stimulate the JAK/STAT pathway (Janus Kinase/Signal Transducers and Activators of Transcription), where activation of Janus kinases (JAK) leads to the phosphorylation of STAT transcription factors that then move into the nucleus and regulate the expression of genes involved in growth and survival. These signaling pathways activated by the EGFR receptor can interact with other signaling pathways, creating a complex network of cellular regulation [15,17]. It is evident that understanding the basic anatomy of the breast itself and the mechanisms influencing normal mammary development is essential for deducing the pathophysiology of breast cancer and determining the stage of the disease, cancer type, subtypes, and molecular mechanisms involved. The EGFR receptor can also stimulate the JAK/STAT pathway, where activation of JAK leads to the phosphorylation of STAT transcription factors that then move into the nucleus and regulate the expression of genes involved in growth and survival. These signaling pathways activated by the EGFR receptor can interact with other signaling pathways, creating a complex network of cellular regulation [24,26].

Other factors

Other factors can also play various roles at different stages of a woman's life like the signaling protein (Stat5) involved in the response to certain hormones, including prolactin. It plays a particularly crucial role in lactation in response to prolactin, as well as in mammary gland development [27]. We found the Insulin-like Growth Factor (IGF) is involved in cell growth, development and works in conjunction with growth hormone to stimulate growth and development of the breast and all the body during childhood. It may also play a role in breast development [28]. Specially, the transcription factors A-myb and C/EBP that play a role in cell cycle regulation and are involved in the proliferation as well as differentiation of mammary epithelial cells and function of mammary epithelial cells [29].

These factors interact with each other and are part of complex regulatory networks that influence various physiological processes. The specific roles and interactions of these factors in different stages of a woman's life, including puberty, pregnancy, lactation, and postmenopausal stages, contribute to the overall development and function of the mammary gland. Disruptions or imbalances in these systems can contribute to various health conditions, including breast-related issues [13].

Implication of ER, PR, and EGFR in breast cancer

Involvement of ER and PR in breast cancer

Estrogen and progesterone are hormones that play crucial roles in the development and maintenance of the female reproductive system. However, their influence is not limited to reproductive functions; they also have significant implications in the development and progression of breast cancer. 60% of breast cancers are characterized by the presence of hormone receptors and are often classified into molecular subtypes and luminal subtypes (A and B). Luminal A tumors (40%) are often less aggressive than Luminal B tumors (20%) but are still influenced by estrogen and progesterone. Tumors that express estrogen receptors (ER+) and progesterone receptors (PR+) are influenced both hormones that promotes the growth of ER+ and PR+ breast cancer cells [30]. Hormone receptor status is often considered along with Human Epidermal Growth Factor Receptor 2 status (HER2) [31].

Involvement of EGFR in breast cancer

The expression of the EGFR receptor, known as HER2, is more frequently associated with certain subtypes of breast cancer, no-

tably triple-negative breast cancer characterized by the absence of expression of hormonal receptors (ER and PR) as well as amplification of the HER2 receptor [31,33,34]. EGFR can be overexpressed and play a role in the regulation of tumor growth. Activation of signaling pathways through EGFR receptor activation by ligands such as EGF can trigger intracellular signaling pathways, including the MAPK/ERK and PI3K/AKT/mTOR pathways, promoting cell survival, proliferation, and migration [26,40]. Due to its potential involvement in certain breast cancers, clinical trials have been conducted to evaluate the effectiveness of therapies targeting EGFR [33,36]. Drugs such as EGFR tyrosine kinase inhibitors (gefitinib and erlotinib) have been developed to block aberrant EGFR signaling in cancer treatment [24,35].

PR+ and ER+ breast cancer is influenced by hormone and endocrine therapy that interfere with the effects of this hormone are used in the treatment of hormone receptor-positive breast cancers such as tamoxifen (blocks estrogen receptors) and aromatase inhibitors (reduce estrogen production). While HER2-positive breast cancers may also be influenced by hormonal factors, and targeted therapies like trastuzumab used in combination with hormone therapy. For triple negative breast cancer, research is ongoing to develop therapies targeting specific AhR inhibitors.

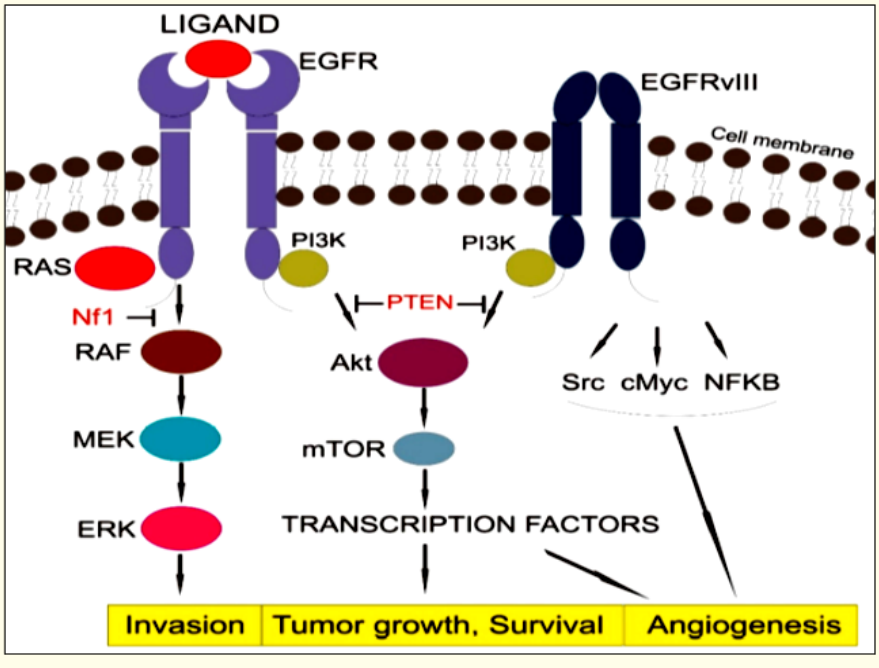

Figure 4: Epidermal growth factor receptor signaling pathway MAPK/ERK and PI3K/AKT/mTOR in breast cancer disease [23].

Conclusion

The importance of studying the physiology, development, and evolution of the breast lies in gaining a comprehensive understanding of the underlying mechanisms and processes from its initiation to progression, for developing effective and personalized oncology therapies. By exploring the intricate details of breast physiology and development, researchers and healthcare professionals can identify the molecular and cellular factors involved in normal breast function and how deviations from this normalcy contribute to diseases, such as breast cancer. Understanding the role of estrogen and progesterone in breast cancer is crucial for developing effective treatment strategies and identifying individuals at higher risk. Hormone receptor status is a key factor in determining the appropriate therapeutic approach for breast cancer patients. This knowledge forms a foundation for recognizing aberrations in these processes that may lead to the initiation and progression of breast cancer. Studying the physiological context also helps in identifying potential therapeutic targets for interventions and therapies.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Bibliography

1. Jesinger R A. "Breast anatomy for the interventionalist". *Techniques in Vascular and Interventional Radiology* 17 (2014): 3-9.
2. Boswell E N and Dizon D S. "Breast cancer and sexual function". *Translational Andrology and Urology* 4 (2015): 160.
3. Pandya S and Moore RG. "Breast development and anatomy". *Clinical Obstetrics and Gynecology* 54 (2011): 91-95.
4. Paine I S and Lewis M T. "The terminal end bud: the little engine that could". *Journal of Mammary Gland Biology and Neoplasia* 22 (2017): 93-108.
5. Patel H., *et al*. "Effects of hormones and hormone therapy on breast tissue in transgender patients: a concise review". *Endocrine* 68 (2020): 6-15.
6. Mcguire K P. "Breast anatomy and physiology". *Breast Disease: Diagnosis and Pathology*. 20161-14.
7. Darlington A J. "Anatomy of the breast, in Digital mammography: a holistic approach". Springer (2015): 3-10.
8. Oms Breast Cancer., Date.
9. Canadian.Cancer.Society Breast cancer statistics. (2023).
10. Mighri N., *et al*. "Association between epidemiological and clinico-pathological features of breast cancer with prognosis, family history, Ki-67 proliferation index and survival in Tunisian breast cancer patients". *PLoS One* 17 (2022): e0269732.
11. Howard BA and Gusterson B A. "Human breast development". *Journal of Mammary Gland Biology and neoplasia* 5 (2000): 119-137.
12. Laud K. «Contrôle hormonal et rôle des interactions tissulaires dans le développement de la glande mammaire normale et le cancer du sein: implication de la prolactine et de la leptine» 6 (2000).
13. Hamy-Petit, A. S. (2019).
14. Porter JC. "Hormonal regulation of breast development and activity". *Journal of Investigative Dermatology* 63 (1974): 85-92.
15. Seachrist D D and Keri RA. "The activin social network: activin, inhibin, and follistatin in breast development and cancer". *Endocrinology* 160 (2019): 1097-1110.
16. Kleinberg D L., *et al*. "Growth hormone and insulin-like growth factor-I in the transition from normal mammary development to preneoplastic mammary lesions". *Endocrine Reviews* 30 (2009): 51-74.
17. Rusidzé M., *et al*. "Estrogen receptor-α signaling in post-natal mammary development and breast cancers". *Cellular and Molecular Life Sciences* 78 (2021): 5681-5705.
18. Adlanmerini M., *et al*. "Effets membranaires du récepteur alpha des œstrogènes-Une question de spécificité tissulaire». *médecine/sciences* 31 (2015): 1083-1091.
19. Yaşar P., *et al*. "Molecular mechanism of estrogen–estrogen receptor signaling". *Reproductive Medicine and Biology* 16 (2017): 4-20.
20. Patel B., *et al*. "Role of nuclear progesterone receptor isoforms in uterine pathophysiology". *Human Reproduction Update* 21 (20145): 155-173.
21. Taraborrelli S. "Physiology, production and action of progesterone". *Acta obstetricia et gynecologica Scandinavica* 94 (2015): 8-16.
22. Tamega A d A., *et al*. "Gene and protein expression of oestrogen-β and progesterone receptors in facial melasma and adjacent healthy skin in women". *International Journal of Cosmetic Science* 37 (2015): 222-228.
23. Sabbah D A., *et al*. "Review on epidermal growth factor receptor (EGFR) structure, signaling pathways, interactions, and recent updates of EGFR inhibitors". *Current Topics in Medicinal Chemistry* (2020).

24. Ono M and Kuwano M. "Molecular mechanisms of epidermal growth factor receptor (EGFR) activation and response to gefitinib and other EGFR-targeting drugs". *Clinical Cancer Research* 12 (2006): 7242-7251.

25. Mitsudomi T and Yatabe Y. "Epidermal growth factor receptor in relation to tumor development: EGFR gene and cancer". *The FEBS journal* 277 (2010): 301-308.

26. Oprita A., *et al*. "Updated insights on EGFR signaling pathways in glioma". *International Journal of Molecular Sciences* 22 (2010): 587.

27. Johnson K J., *et al*. "PTP1B suppresses prolactin activation of Stat5 in breast cancer cells". *The American Journal of Pathology* 177 (2010): 2971-2983.

28. Ha W T., *et al*. "Effects of the insulin-like growth factor pathway on the regulation of mammary gland development". *Development and Reproduction* 20 (2016): 179.

29. Flanagan K C., *et al*. "c-Myb and C/EBPβ regulate OPN and other senescence-associated secretory phenotype factors". *Oncotarget* 9 (2018): 21.

30. Hortobagyi GN., *et al*. "New and important changes in the TNM staging system for breast cancer". *American Society of Clinical Oncology Educational Book* 38 (2018): 457-467.

31. Weigelt B., *et al*. "Histological types of breast cancer: how special are they?" *Molecular oncology* 4 (2010): 192-208.

32. Dong W., *et al*. "Dampness-heat accelerates DMBA-induced mammary tumors in rats". *Chinese Journal of Integrative Medicine* 24 (2018): 758-762.

33. Uribe M L., *et al*. "EGFR in cancer: Signaling mechanisms, drugs, and acquired resistance". *Cancers* 13 (2021): 2748.

34. Dowsett M. "Overexpression of HER-2 as a resistance mechanism to hormonal therapy for breast cancer". *Endocrine-related Cancer* 8 (2001): 191-195.

35. Caffa I., *et al*. "Fasting-mimicking diet and hormone therapy induce breast cancer regression". *Nature* 583 (2020): 620-624.

36. Gasmi-Boubaker A., *et al*. "In vitro gas production and its relationship to in situ disappearance and chemical composition of some Mediterranean browse species". (2005): 123-124, 303-311.