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Recent Improvements in Therapeutic Treatments of Breast Cancer

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Abstract

Breast cancer develops when cells in the breast tissue begin to grow in an uncontrolled manner. These cells usually form a tumor that can often be seen in an x-ray or felt as a lump. The tumor is malignant if the cells invade the surrounding tissues or metastasize to distant organs of the body. In the last ten years, various new drugs have been introduced in the international markets to treat breast cancer. These drugs are administered either orally or via an injection. In this review, an insight is provided into the different signal transduction pathways that are being targeted for the purpose of adjuvant breast cancer treatment by the use of hormone-blocking agents, chemotherapy and monoclonal antibodies.

Keywords: Breast cancer

Introduction

Breast cancer is a serious health problem among women [1]. It has a major impact on the quality of life and causes an economic burden in the form of reduced productivity and premature death. The average survival rate for breast cancer in the developed countries is 73% and in developing countries is 57% [2]. The development of breast cancer tumor consists of three stages: initiation, promotion, and progression (Figure 1). The developed breast cancer tumor comprises two parts [2]: (i) tumor parenchyma, and (ii) the stroma. The stroma contains the blood vessels and other supporting cells. As the tumor grows, the pre-existing blood vessels experience limited blood flow [3]. Around 5% of cases of breast cancers can be explained by the patient possessing mutations in *BRCA1* and *BRCA2* genes [4]. Cancer cells typically exhibit the alterations listed in Figure 2. These alterations are caused by mutations that affect growth factor receptors, signal transduction genes, cell cycle regulatory genes, DNA repair genes, or genes controlling apoptosis [5].

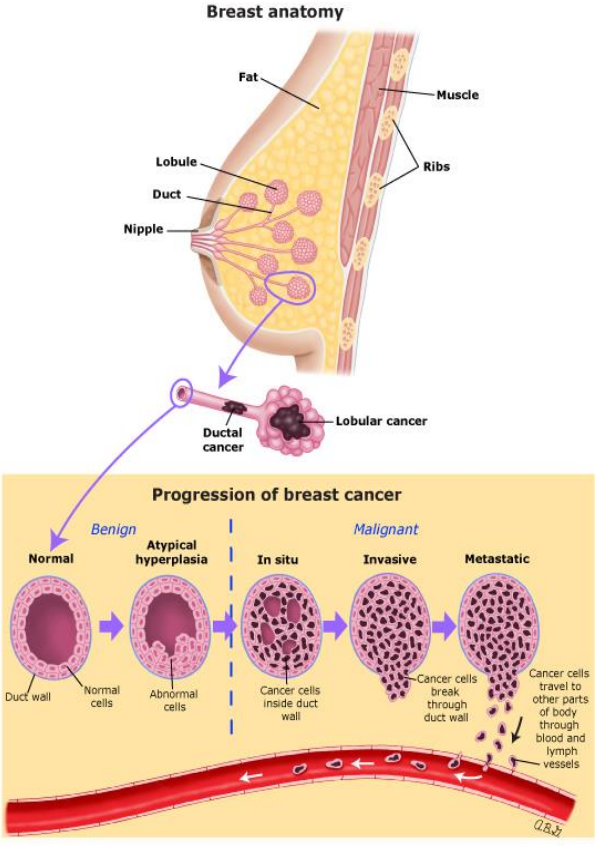

Figure 1*: The different stages of tumor development.*

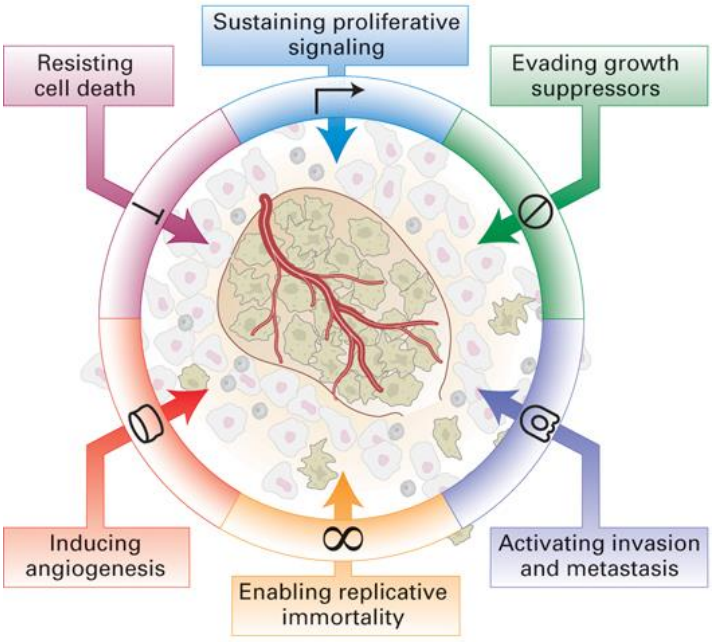

***Figure 2**: Different alterations in function exhibited by cancer cells.*

Literature Survey

The etiological factors and pathogenesis of breast cancer are very complex. At present, three different signal transduction pathways arebeing targeted for therapeutic reasons by various drugs that are available in the market:

EGFR (HER2)/neu signaling Pathway: The human epidermal growth factor receptor (EGFR or HER2) is a tyrosine kinase receptor (Figure 3) that serves as a cell surface receptor in healthy cells [6]. Various kinase inhibitors such as Trastuzumab [7], Pertuzumab and Lapatinib [8,9]. Have been introduced commercially.

Estrogen Receptor (ER) Signaling Pathway: The estrogen receptor (ER) α regulates transcription and causes proliferation of ER+ tumor cells (Figure 4) [10]. A study has shown that normal ER signaling is lost and tumor-specific ER signaling is gained during breast tumorigenesis [11]. Abnormal estrogen receptor (ER) signaling drives the majority of breast cancers and is targeted by endocrine therapies. Aromatase Inhibitors, Tamoxifen, and Fulvestrant can be used to treat ER+ breast cancers, especially in post-menopausal women [12].

Vascular Endothelial Growth Factor Receptor-2 (VEGFR2) Signaling Pathway: Vascular endothelial growth factors (VEGF) and their receptors are involved in lymphangiogenesis, vascular permeability, and hematopoiesis [13]. (Figure 5). VEGF is released by tumor cells and induces tumor neovascularization [14]. Absence of VEGF ligands or receptors in mice results in defects in formation and maturation of the vascular system [15].

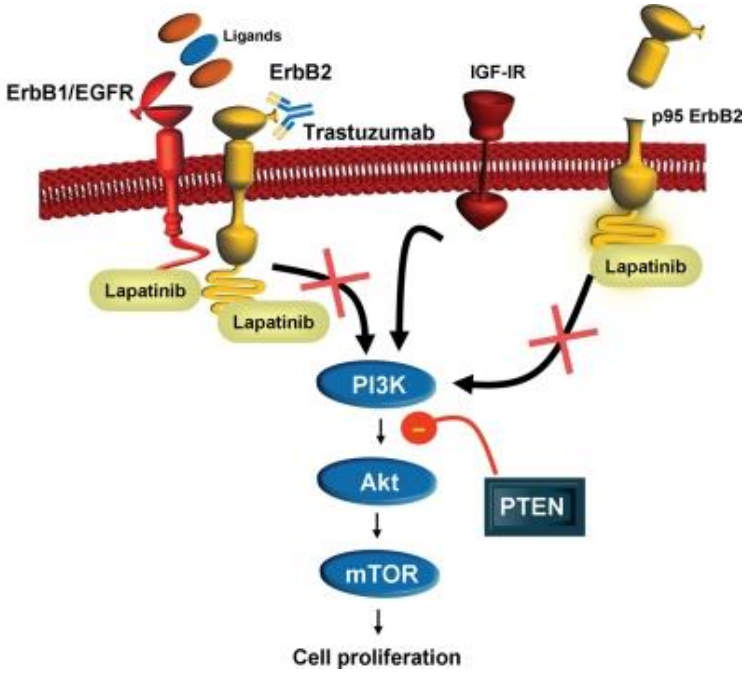

***Figure 3**: Various therapeutic strategies employed to block HER2/neu (EGFR) signaling pathway.*

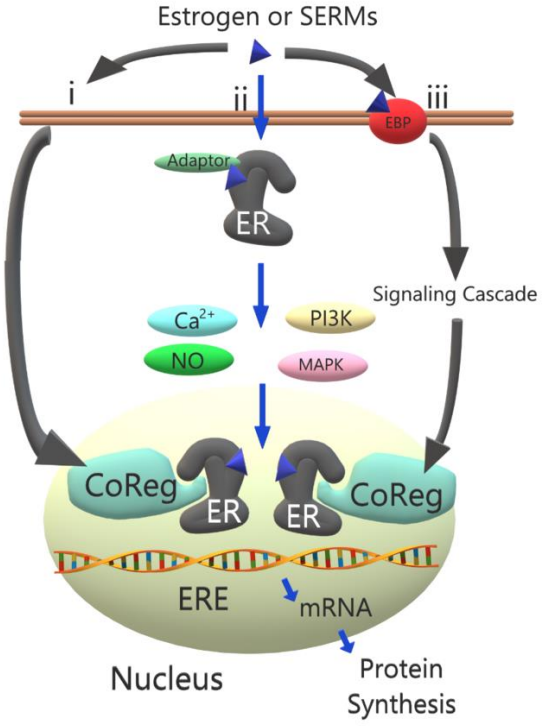

***Figure 4:** Overview of the action of the Estrogen receptor (ER).*

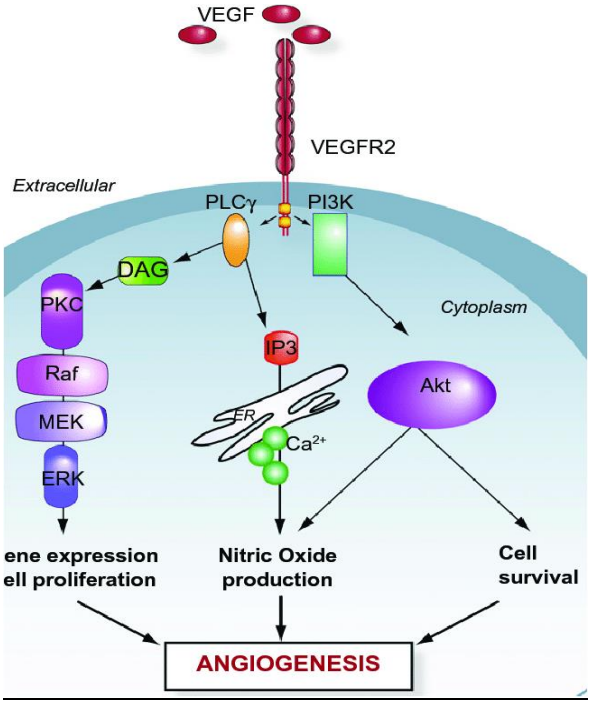

***Figure 5**: Overview of the Vascular Endothelial Growth Factor Receptor-2 signaling pathway.*

Discussion

ER and HER2 signaling pathways are the key therapeutic targets in the treatment of breast cancer. The drugs that target these receptor proteins are used for treating neoadjuvant, adjuvant and advanced forms of breast cancers.Hormone treatment strategies that include selective ER modulators (such as Tamoxifen, Raloxifene), Estrogen deprivation using Aromatase Inhibitors (such as Exemestane, Letrozole) and selective ER down-regulators (such as Fulvestrant) [16-20], are also being used. At present, new ERα antagonists (such as SERCAs) are also being developed [21]. Monoclonal antibodies such as Trastuzumab and Pertuzumab can be used to treat both early-stage and advanced breast cancer. This drug is often given alongsidechemotherapy, but it might also be used alone. When administered before (neoadjuvant) or after (adjuvant) surgery to treat early breast cancer, these drugs are usually given for 6 months to a year [22]. The drugs targeting HER2 pathway can sometimes cause heart damage during or after treatment. This can lead to congestive heart failure [5]. Lapatinib, Neratinib, Tucatinib, and the combination of Pertuzumab with Trastuzumab can cause severe diarrhea [12]. Lapatinib and Tucatinib can also cause hand-to-foot syndrome, in which the hands and feet become sore and red, and may blister and peel. Lapatinib, Neratinib, and Tucatinib can cause liver problems [23].

Conclusion

Estrogen receptor and HER2 signaling pathways have emerged as the most important targets for newly designed drugs. Anti-HER2 targeted therapies have improved survival rates by 15%-23% in patients suffering from HER2 over-expressing breast cancers.

References

1. Jemal A, Center MM, DeSantis C, Ward EM. Global Patterns of Cancer Incidence and Mortality Rates and Trends. Global Patterns of Cancer. 2010; 19: 1893-907.
2. Buchner A, Merrell PW, Carpenter WMJ. Relative frequency of central odontogenic tumors: a study of 1,088 cases from Northern California and comparison to studies from other parts of the world. 2006; 64: 1343-1352.
3. Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. 2000; 407: 249-257.
4. Mehrgou A, Akouchekian M. The importance of BRCA1 and BRCA2 genes mutations in breast cancer development. 2016; 30: 369.
5. Devereux T, Risinger J, Barrett JJISP. Mutations and altered expression of the human cancer genes: what they tell us about causes. 1999; 146: 19-42.
6. Yarden Y. The EGFR family and its ligands in human cancer: signalling mechanisms and therapeutic opportunities. 2001; 37: 3-8.
7. Vogel CL, Cobleigh MA, Tripathy D, Gutheil JC, Harris LN, Fehrenbacher L, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. 2002; 20: 719-726.
8. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. 2006; 355: 2733-2743.
9. Nahta R, Yu D, Hung M-C, Hortobagyi GN, Esteva FJ. Mechanisms of disease: understanding resistance to HER2-targeted therapy in human breast cancer. 2006; 3: 269-280.
10. Osborne CK, Yochmowitz MG, Knight III WA, McGuire WLJC. The value of estrogen and progesterone receptors in the treatment of breast cancer. 1980; 46: 2884-2888.
11. Chi D, Singhal H, Li L, Xiao T, Liu W, Pun M, et al. Estrogen receptor signaling is reprogrammed during breast tumorigenesis. 2019; 116: 11437-11443.
12. Kunte S, Abraham J, Montero AJ. Novel HER2-targeted therapies for HER2-positive metastatic breast cancer. 2020; 126: 4278-88.
13. Shibuya MJBR. Differential roles of vascular endothelial growth factor receptor-1 and receptor-2 in angiogenesis. 2006; 39: 469-478.
14. Ferrara N, Gerber H-P, LeCouter J. The biology of VEGF and its receptors. 2003; 9: 669-676.
15. Dumont DJ, Jussila L, Taipale J, Lymboussaki A, Mustonen T, Pajusola K, et al. Cardiovascular failure in mouse embryos deficient in VEGF receptor-3. 1998; 282: 946-949.
16. Burstein HJ, Griggs JJ, Prestrud AA, Temin SJJoop. American society of clinical oncology clinical practice guideline update on adjuvant endocrine therapy for women with hormone receptor–positive breast cancer. 2010; 6: 243-246.
17. Howell A, Robertson JF, Quaresma Albano J, Aschermannova A, Mauriac L, Kleeberg UR, et al. Fulvestrant, formerly ICI 182,780, is as effective as

anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. 2002; 20: 3396-3403.

18. Mouridsen H. Letrozole in advanced breast cancer: the PO25 trial. 2007; 105: 19-29.
19. Nabholtz J, Buzdar A, Pollak M, Harwin W, Burton G, Mangalik A, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. 2000; 18: 3758-3767.
20. Paridaens RJ, Dirix LY, Beex LV, Nooij M, Cameron DA, Cufer T, et al. Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. 2008; 26: 4883.
21. Puyang X, Furman C, Zheng GZ, Wu ZJ, Banka D, Aithal K, et al. Discovery of Selective Estrogen Receptor Covalent Antagonists for the Treatment of ERαWT and ERαMUT Breast CancerSERCA H3B-5942 for Treatment of ERαWT and ERαMUT Breast Cancer. 2018; 8: 1176-1193.
22. Bernard-Marty C, Lebrun F, Awada A, Piccart MJ. Monoclonal Antibody-Based Targeted Therapy in Breast Cancer. Drugs. 2006; 66: 1577-1591.
23. Fanny LD, Veronique D, Curigliano G. The Role of Tyrosine Kinase Inhibitors in the Treatment of HER2+ Metastatic Breast Cancer. European Journal of Cancer. 2021; 154: 175-189.