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CURRENT STATE OF TECHNOLOGY FOR THERAPEUTIC TREATMENT OF BREAST CANCER

Chemistry

Naila Mahmood School of Life & Environmental Sciences, Faculty of Science, The University of Sydney, NSW 2006, Australia.

Marjan Assefi Joint School of Nanoscience & Nanoengineering, University of North Carolina at Greensboro, Greensboro, NC 27403, USA.

Nadeem Kizilbash Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, Northern Border University, Arar-91431, Saudi Arabia.

Abdul Hai Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, Northern Border University, Arar-91431, Saudi Arabia.

Syeda Huma H. Zaidi Department of Chemistry, Faculty of Science, Northern Border University, Arar-91431, Saudi Arabia.

Jaweria Ambreen Colloid & Surface Chemistry Laboratory, Department of Chemistry, The Chinese University of Hong Kong, Hong Kong, China.

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. Tumors are often unresponsive to normal physiological stimuli. At the center of a tumor are typically dead or dying cells that produce biomarkers that can be analyzed for the presence of the tumor. In the last ten years, various new drugs have been introduced in the international markets to treat breast cancer tumors. 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 for adjuvant breast cancer treatment by the use of hormone-blocking agents, chemotherapy and monoclonal antibodies.

KEYWORDS

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)

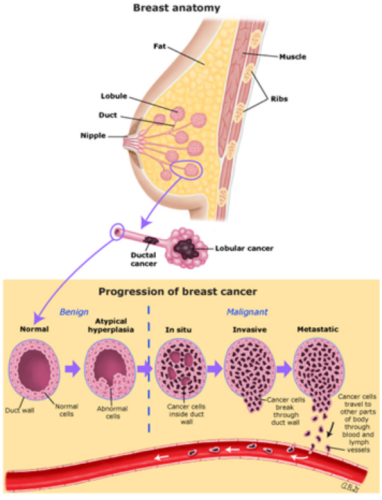

Figure 1: The Different Stages Of Tumor Development.

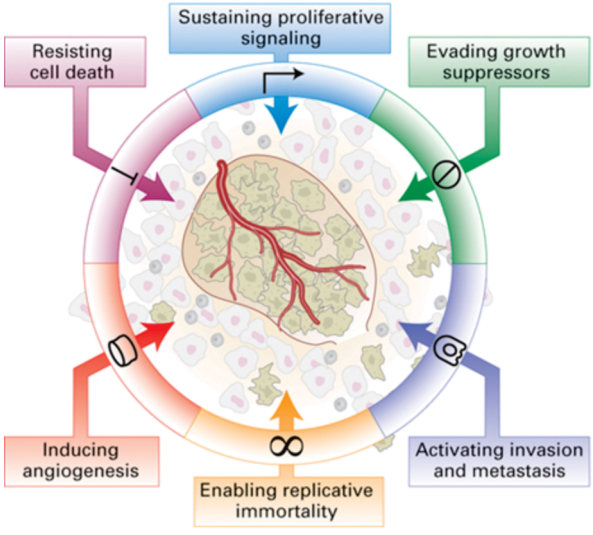

Figure 2: Different Alterations In Function Exhibited By Cancer Cells.

Literature Survey:

At present, three different signal transduction pathways are being targeted for therapeutic reasons by various drugs that are available in the market:

EGFR (HER2)/neuSignaling 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 causes tumor neovascularization (14). The absence of VEGF ligands or receptors in mice results in defects in the formation and maturation of the vascular system (15).

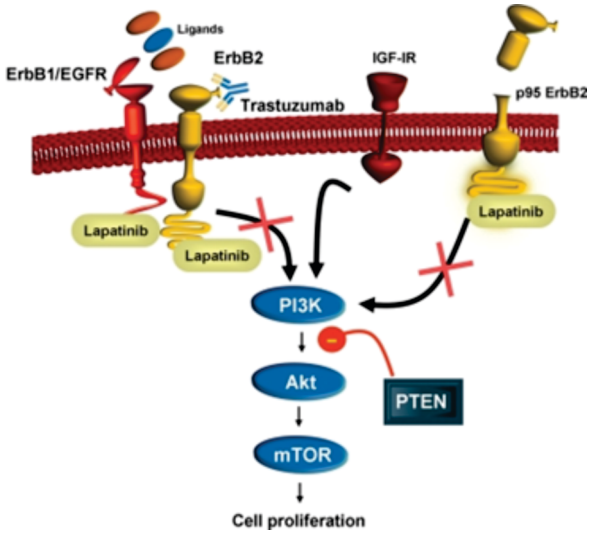

Figure 3: Various therapeutic strategies employed to block HER2/neu (EGFR) signaling pathway.

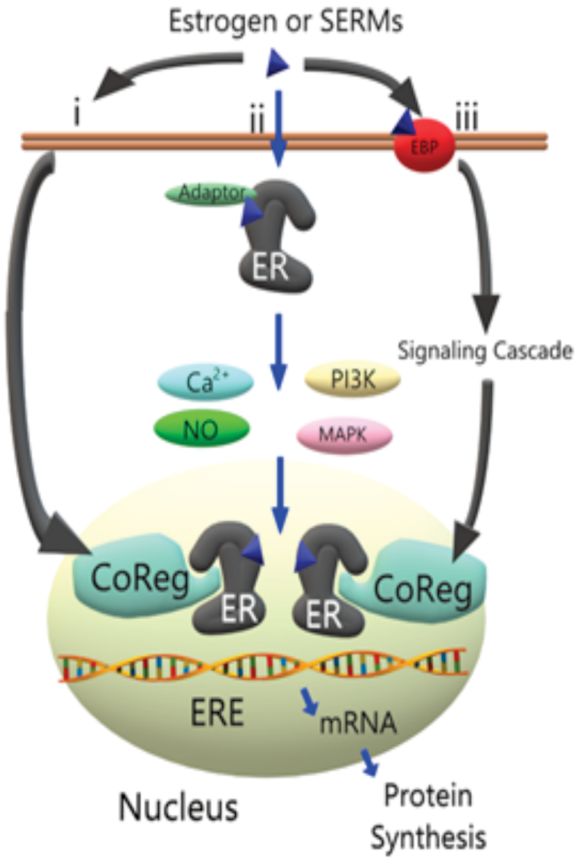

Figure 4: Overview Of The Action Of The Estrogen Receptor (ER).

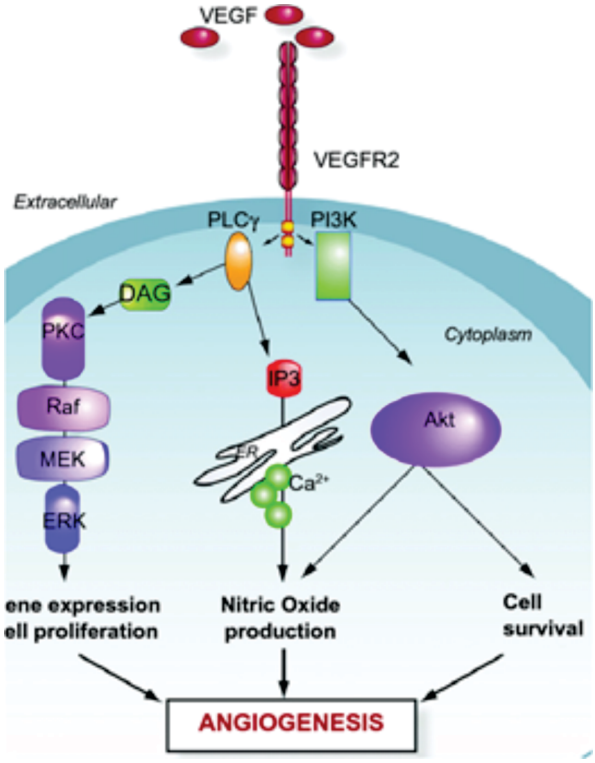

Figure 5: Overview Of The Vascular Endothelial Growth Factor Receptor-2 Signaling Pathway.

DISCUSSION

ER and HER2 signaling pathways are 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 under development (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 alongside chemotherapy, 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). The use of 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 inflamed and may blister and peel. In addition, Lapatinib, Neratinib, and Tucatinib have been reported to 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.

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