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Analysis of *her2* Genes in Breast Cancer

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Abstract—*Breast cancer is the cancer in the breast. Genetic proteins may affect how breast cancer behaves and the treatment response. HER2 is one such gene that can play a role in this cancer. HER2(Human epidermal growth factor receptor 2) gene , a proto-oncogenic receptor tyrosine kinase of the EGFR family present on chromosome 17q12 is the gene which dramatically increases the rate at which a tumour grows as very high levels of it are present in breast cancer cells. Patients with HER2 positive breast cancers show better survival and outcome rates since the development of drug trastuzumab which blocks the HER2 positive cells from replicating. Researchers are now looking at how this can be applied to a wider range of cancers and improve the survival and therapy side effect rates in cancers.*

1. INTRODUCTION

Cancer is the malignant growth or tumour because of uncontrolled division of cells. Cancer can be grouped into types depending on stages which can be assigned a number from I to IV to a cancer, with I being an isolated cancer and IV being a cancer which has spread to the limit of what the assessment measures. The stage generally takes into account the size of a tumour. Breast cancer is a cancer that develops from breast tissue. Breast cancer is now the most common cancer in most cities(Mumbai, Delhi, Bengaluru, Bhopal, Kolkata, Chennai, Ahmedabad etc.) in India, and 2nd most common in the rural areas.

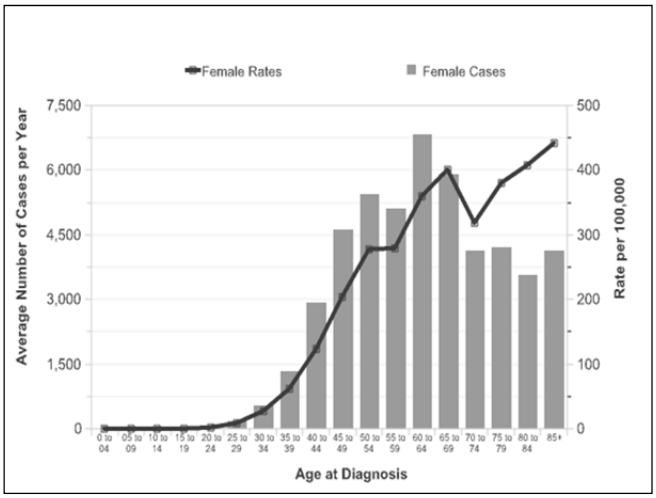

Fig. 1: Graph showing age at diagnosis of women for breast cancer versus average number of cases reported per year

According to Fig. 1; average number of cases of breast cancer is rising with the age of diagnosis; the maximum being 450 cases at the rate per 100,000 between 60 to 64 years of age.

2. GENES INVOLVED IN BREAST CANCER

Breast cancers that cluster in families are associated with inherited mutations in particular genes, such as *BRCA1* or *BRCA2*. These genes are described as "high penetrance" because they are associated with a high risk of developing breast cancer. Then there is the *HER2* gene. Scientists and researchers in mid 1980s found that HER2 was present at very high levels in about 25 to 30 percent of breast cancer cells dramatically increasing the rate at which a tumour grew. Building on HER2 as an initial suspect, they also found that high levels of HER2 were linked to a greater likelihood of metastasis and relapse and an overall decrease in patient survival.

3. STRUCTURE OF HER2

HER2 a proto-oncogenic receptor tyrosine kinase of the EGFR family. Essential component of a neuregulin-receptor complex, although neuregulins do not interact with it alone. Not activated by EGF, TGF- alpha and amphiregulin. Amplified in breast cancer. The antibody Herceptin is approved for treatment of metastatic breast cancer with HER2 amplification/overexpression. According to Fig. 2, Receptor tyrosin-kinases (RTKs) are cell surface allosteric enzymes consisting of: an extracellular ligand-binding domain (light grey); a single transmembrane (TM) domain has an extensive homology to the epidermal grow factor receptor (brown with 653 labelling); a cytoplasmic domain with catalityc activity (dark brown).

Protein type: Oncoprotein; Kinase, protein; Protein kinase, TK; Protein kinase, tyrosine (receptor); Membrane protein, integral; TK group; EGFR family

Chromosomal Location of Human Ortholog: 17q12

Molecular Function: ATP binding; ErbB-3 class receptor binding; growth factor binding; identical protein binding; protein binding; protein C-terminus binding; protein dimerization activity; protein heterodimerization activity; protein phosphatase binding; protein-tyrosine kinase activity;

receptor signaling protein tyrosine kinase activity; transmembrane receptor activity; transmembrane receptor protein tyrosine kinase activity.

Gene Symbols: ERBB2
Molecular weight: 137,910 Da
Basal Isoelectric point: 5. 58

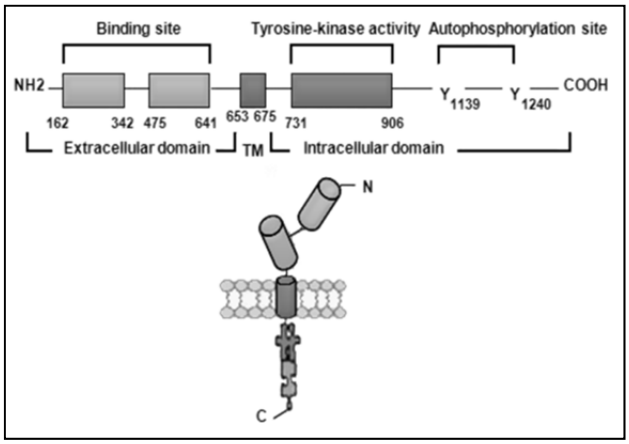

Fig. 2: Schematic representation of HER2 protein

4. MECHANISM OF HER SIGNALLING PATHWAY IN CANCER:

HER pathways play a critical role in cancer**.** Dysregulation of HER-mediated signalling pathways results in the growth and spread of cancer cells. The HER family which consists of 4 structurally related receptors:

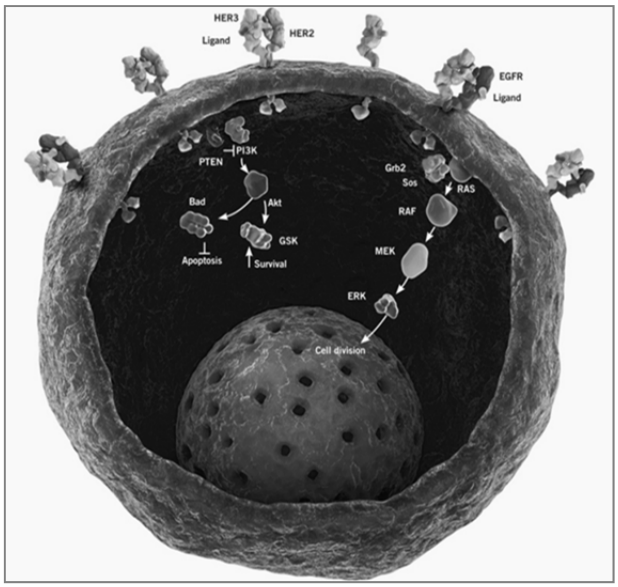

Fig. 3: HER signaling pathway

HER1 (EGFR), HER2, HER3, and HER4. HER family receptors are activated by ligand-induced dimerization, or receptor pairing. Dimerization is a critical step in HER family-mediated signalling, and HER receptors are able to homodimerize or heterodimerize with other HER family members, allowing for multiple receptor combinations. The formation of dimers leads to activation of the intrinsic tyrosine kinase domain and subsequent phosphorylation on specific tyrosine residues, which serve as docking sites for a variety of molecules. Recruitment of these molecules leads to the activation of different downstream signalling cascades, including the MAPK proliferation pathway and/or the PI3K/Akt prosurvival pathway. Inappropriate signalling may occur as a result of receptor overexpression or dysregulation of receptor activation, which may lead to increased/uncontrolled cell proliferation, decreased apoptosis (programmed cell death; enhanced cancer cell motility or angiogenesis.

5. HER2 TESTING ACCURACY :

Inaccurate HER2 test results may cause women diagnosed with breast cancer to not get the best care possible. If all or part of a breast cancer is HER2-positive but test results classify it as HER2-negative, doctors aren't likely to recommend Herceptin or Tykerb treatment — even though the woman could potentially benefit from those medicines. If a breast cancer is HER2-negative but test results classify it as HER2-positive, doctors may recommend Herceptin or Tykerb treatment — even though the woman is unlikely to get any benefits and is exposed to the medicines' risk.

6. TREATMENTS OF *HER2* POSITIVE BREAST CANCER

Some breast cancer cells make (overexpress) too many copies of a particular gene known as HER2. The HER2 gene makes a protein known as a HER2 receptor. HER2 receptors are like ears, or antennae, on the surface of all cells. These HER2 receptors receive signals that stimulate the cell to grow and multiply. But breast cancer cells with too many HER2 receptors can pick up too many growth signals and so start growing and multiplying too much and too fast. Breast cancer cells that overexpress the HER2 gene are said to be HER2-positive. Herceptin works by attaching itself to the HER2 receptors on the surface of breast cancer cells and blocking them from receiving growth signals. By blocking the signals, Herceptin can slow or stop the growth of the breast cancer. Herceptin is an example of an immune targeted therapy. In addition to blocking HER2 receptors, Herceptin can also help fight breast cancer by alerting the immune system to destroy cancer cells onto which it is attached. The most commonly used medication is Herceptin (chemical name: trastuzumab), which works by attaching itself to the HER2 receptors on breast cancer cells and blocking them from receiving growth signals. By blocking these signals, Herceptin may help to slow or even stop the growth of the breast cancer. In addition to blocking HER2 receptors, Herceptin can also help fight breast

cancer by alerting the immune system to destroy cancer cells onto which it is attached.

7. DISCUSSION ON PRESENT RESEARCH GOING ON HER2 GENES:

New treatments have come to light now. Because many breast cancer patients do not always benefit from current HER2-targeted treatments or they become resistant after initiating treatment, researchers are continuing to test new or modified drug combinations to improve survival. One antibody being tested is pertuzumab, which blocks HER2 from sending signals to other HER-family proteins that instruct them to grow and replicate. In June 2012, the FDA approved pertuzumab (Perjeta®) as a new treatment for HER2-positive breast cancers. Results are also seen in gastric cancer treatment. Findings of a major clinical trial showed that trastuzumab, when used in combination with chemotherapy drugs, resulted in longer survival (13. 1 months) for advanced HER2-positive gastric and gastroesophageal junctioncancers when compared with treatment using chemotherapy drugs alone (11. 7 months). *NCI's(National cancer Institute) discovery of linking HER2 to aggressive breast cancer continues to be a core building block of today's cancer research community*. In 2013, the FDA approved another drug combination that holds promise for patients who become resistant to trastuzumab treatment using ado-trastuzumab emtansine (Kadcyla®), also known as T-DM1. Studies show the potential of T-DM1 as an effective initial treatment with fewer side effects compared with *trastuzumab* alone for patients with metastatic breast cancer.

8. FUTURE PROSPECTIVE :

Understanding the role of HER2 in promoting cancer cell growth is a strong foundation for more effective breast and gastric cancer treatment in the future. A number of clinical trials are trying to determine if using trastuzumab is an effective treatment for breast cancer tumors not classified as being HER2-positive. Serendipitously, researchers discovered that HER2 also works in some HER2 negative tumors. In 2014, animal studies showed that the drug combination of trastuzumab and T-DM1 reduced or got rid of HER2-positive ovarian cancer tumors in mice. This holds promise for future studies in humans and continues to build on the early NCI-supported initial discovery. Researchers are continually seeking treatments, including combination treatments that can effectively destroy cancer cells without causing severe side effects. One potential treatment uses an antibody that recognizes both the HER2 protein on a cancer cell's surface and a protein on the immune system's T cells, which fight infection. This allows the patient's own immune system to attack the cancer by bringing the T cells directly to the cancer cell.

9. CONCLUSION

Patients with HER2 positive breast cancers show better survival and outcome rates since the development of drug trastuzumab which blocks the HER2 positive cells from replicating. Researchers are now looking at how this can be appied to a wider range of cancers and improve the survival and therapy side effect rates in cancers.

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