Advances in diagnosis and treatment of breast cancer recurrence.

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Abstract

Breast cancer is one of the leading causes of cancer-related deaths in women across the world which is mainly due to its ability to metastasize and pose a high risk of recurrence after treatment. In this review, some of the key factors that lead to breast cancer have been summarized and a more in-depth analysis of the factors involved in its recurrence has been explored. The different metabolic pathways and the role of genetic and epigenetic mechanisms that account for such aberrant processes have also been discussed. New therapies and drugs that have shown good efficacy against recurrent breast disease have been highlighted and an insight into new treatment modalities currently available has been provided. Also, new therapeutic approaches to treat recurrence in breast disease have also been explored.

Keywords: Breast cancer, Recurrence, Management of recurrence, Advances in treatment, Molecular mechanisms, Epigenetics of breast cancer.

Introduction

According to the GLOBACON 2020, breast cancer has now surpassed lung cancer worldwide as the most diagnosed cancer in women with 2.3 million cases (11.7%) followed by lung at 11.4%. Breast cancer mortality rates are steadily decreasing in developed countries owing to better treatment facilities. However, the incidence rates of cancers have steadily risen in these countries [1]. This is largely due to frequent testing and screening of programs but also to some extent, the prevention systems currently being implemented to treat this malignancy are not effective enough [2]. It is assumed that by 2024 breast cancer will be the most common cancer among women with 19.7 million cases in the next decade worldwide and 10.6 million cases alone in less developed countries [3]. It has been observed that in India, one woman dies for every two women, newly diagnosed with breast cancer. Like all other cancers, breast cancer also has a genetic origin and shows a mutation in key genes categorized into 3 groups; proto-oncogenes, tumor suppressor genes, and DNA repair genes. About 5% to 10% of women diagnosed with breast cancer may have germline mutations of genes BRCA1 and BRCA2 which are genes and proteins contributing towards the development of breast cancer or failing to prevent it to a larger extent. Gene BRCA1 at chromosome 17 is involved in promoting cell death along with other genes involved in the repair of DNA [4]. Any mutation in this gene results in the incorrect repair of DNA damage which further increases the risk of mutations that may lead to cancer [5]. Along with BRCA1, BRCA2 present on chromosome 13 is a DNA repair and a tumor suppressor gene [6]. Its function is quite like that of BRCA1 and any mutation in these genes will result in the damaged DNA not being repaired correctly, which will eventually lead to Breast cancer [7]. The estimated lifetime risk of developing breast cancer for women with BRCA1 and BRCA2 mutations is 40% to 85% re-spectively and carriers with a history of breast cancer have an increased risk as high as 5% per year of contralateral disease that is either a metastatic lesion or the second primary cancer [8]. Toll-like receptors (TLRs) play an important role in tumor progression as they activate the production of several bio factors, induce Type1 interferons and cytokines, which in turn lead to an inflammatory response and activate the adaptive immune system. Tumors show high expression of TLR levels by cancer cells specially TLR4 and TLR9. The expression level of TLR3, 4, 9 also acts as indicators of tumor aggressiveness in breast cancer [9]. The PTEN gene, a regulator of the phosphatidylinositol-3-kinase (PI3K)/Akt oncogenic pathway, is mutated in various cancers and its expression is associated with tumor progression and gene expression profile in breast cancer [10].

Sometimes after treatment, the residual tumor cells are still detected in most patients. These tumours remain dormant for years before resuming their growth. This results in tumor recurrence with time. Some of the factors resulting in abnormalities associated with cell growth posinga risk of breast cancer and its recurrence are socioeconomic status, heredity, early menopause, late menarche, obesity, age, environmental toxins, high-fat diet, exogenous estrogens, oral contraceptives, alcohol, or cigarettes. It is believed that the overall risk

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of breast cancer is higher in old age due to the exposure to carcinogens over a longer period and the decreasing power of the immune system with age [11]. Although there have been numerous advancements for the management of breast cancer and its recurrence for increasing the patient's survival rate, yet there are there is a long way ahead to develop effective methods to eliminate breast cancer completely. Further knowledge in this regard would provide deeper insight and a broader perspective so more effective steps could be taken for prevention, early diagnosis, and treatment of this patients.4

Classification

Breast cancer can be classified based on histopathological and molecular characteristics. Based on histopathological characteristics, there are two types, non-invasive and invasive carcinoma. In non-Invasive breast cancer such as Ductal Carcinoma *in Situ* (DCIS), the cells are confined to the ducts and do not invade surrounding fatty and connective tissues of the breast. Lobular Carcinoma *in Situ* (LCIS) is a type of invasive breast cancer where the cells break through the duct and lobular wall and invade the surrounding fatty and connective tissues of the breast. These cells can be invasive but not metastatic (spreading) to the lymph nodes or other organs. The molecular classification is based on protein expression patterns that involve several markers such as Estrogen Receptor (ER), Progesterone Receptor (PR), Human Epidermal Growth Factor Receptor 2 (HER2), Human Epidermal Growth Factor 1 (HER1), and basal cytokeratin. The differential protein expression gives rise to the molecular classification of breast cancer into different subtypes including luminal A & B, HER2-enriched, basal-like, claudin-low, and normal breast-like [12].

The most frequently occurring types of breast cancer are LCIS where there is an increase in number of cells within the lobules of the breast and DCIS which is confined to the ducts of the breast [13]. Less common types of breast cancer are medullary carcinoma (a type of invasive breast cancer that forms a distinct boundary between tumor tissue and normal tissue) [14] . Mucinous carcinoma (a rare type of breast cancer that is formed by the mucus-producing cancer cells) [15]. Tubular carcinoma (well-differentiated invasive carcinoma with regular cells arranged in well-defined tubules surrounded by an abundant fibrohyaline stroma), [16] inflammatory breast cancer (this blocks lymph vessels or channels in the skin over the breast)[17], Paget's disease (disorder of the nipple-areola complex), and phyllodes tumor which can either be benign or malignant can develop in the connective tissues of the breast and may be cured by surgical removal [18,19].

Recurrence

Despite tumor regression in response to neoadjuvant chemotherapy, residual tumor cells are still detected in most patients after treatment. These residual tumors are then seen to remain dormant for years even before resuming their growth which results in tumor recurrence with time [20].The cells which play an important role in the formation, growth, and recurrence of tumors, particularly following therapeutic intervention are the cancer stem cells. Recently, therapeutic drugs like Salinomycin have received a lot of attention for their ability to target these breast cancer stem cells, [21] yet the proper mechanism of action involved is not fully understood. Hence, it is impera-tive to understand and investigate these mechanisms to design strategies to prevent the recur-rence of breast cancer. Apart from cancer stem cells, there are tumor-initiating cells which are seen to be responsible for tumor initiation, maintenance, and recurrence. In breast cancer, these cells are identified as CD44(+)/CD24(-) [22]. In these cells certain genes called the Notch target genes are aberrantly expressed [23]. These genes are under the control of Notch signaling pathway, a highly conserved cell signaling pathway found in most animals. This signaling pathway plays a crucial role in cell-to-cell communications, cell proliferation, angiogenesis, apoptosis, hypoxia, and metastasis [24]. With respect to breast cancer, aberrant expression of notch receptors has been seen on epithelial metaplastic lesions and neoplastic lesions inferring that they might play the role of a proto-oncogene. In a study done in mouse it was concluded that since Notch1 and Notch4 homologs are essential for the normal development of mammary glands, any mutation in them results in the development of mammary tumors [25]. Based on the crucial role of notch signaling in tumor-initiating cells, a study hypothesized that notch might be a key signaling pathway targeted by BXL0124 (a Gemini Vitamin D analogue belonging to the family of Vitamin D derivatives capable of treating cancer) to suppress the CD44+/CD24−/low subpopulation in breast cancer. The potent inhibitor of notch signaling to target tumor-initiating cells in basal-like breast cancer is BXL0124. This compound represses the expression of a tumor-initiating cell marker CD44 and reduces the CD44+/CD24−/low subpopulation in MCF10DCIS cells, a basal-like human breast cancer cell line derived from the MCF10A cell line with the ability to form ductal carcinoma *in situ* (DCIS)-like lesions in animals. It has been shown that 10-15% of all breast cancers account for triple-negative type breast cancer (TNBC) that do not express the genes for ER, PR, and HER2/neu. Morbidity and mortality rates are disproportionate due to its aggressive characteristics and lack of targeted therapies [26]. TNBC has a high recurrence rate during the first three years and falls rapidly after five years. It is for this reason; the five-year survival rate for TNBC patients tends to be lower (77%) than other breast cancer types (93%). Treatments such as chemotherapy, surgery, and poly (ADP-ribose) polymerase (PARP) enzyme inhibitors are promising for this type of cancer [27]

The recent genomic studies have shown that gene expression profiles are similar in in-situ and invasive type breast cancer therefore, suggesting that several bio-functional modifications of the transformation process occur before or during the development of *in situ* lesion. Three new bio markers which are used for the prediction of *in situ* breast cancer evolution are TG2 (transglu-taminase), HJURP (Holliday Junction Recognition Protein), and HIF-1a (Hypoxia-InducibleFactor-1 *alpha*) [28]. Despite advancements in breast cancer treatment, there is still a significant propor-tion of patients who continue to experience recurrence even after adjuvant chemotherapy treat-ment and the survival of stage

IV solid tumors still remains low. This is largely due to acquired resistance of cancer stem cells to chemotherapeutic and biological agents used in treatment with a high risk of metastasis to distant organs and lymph nodes [29]. Up to 30% of patients with early breast cancer still experience distant disease relapse [30]. While relatively low values for sensitivity (71%) and specificity (56%) have been found for Axillary Lymph Node (ALN) involvement as an indicator of risk and pattern of distant relapse, the nodal status remains the most powerful predictor of metastases [31]. HER2-positive subtypes show a stronger association with systemic spread than other subgroups. Tumors with HER2 overexpression show a significantly high risk for distant relapse compared with HER2-negative tumors and shows higher central nervous system and lung metastatic potential and low risk of bone disease progression.

Multivariate analysis shows that the HER-2 status of breast cancer is an independent factor of Ipsilateral Breast Tumor Recurrence (IBTR). Patients with the ER-positive/HER2-negative subtype of IBTR had a significantly better second IBTR-free survival rate than those with other subtypes of IBTR (88% vs. 75%, respectively). The high-risk factors of recurrence after Breast-Conserving Therapy (BCT) are ER/ PR, HER-2, age, lymph node involvement, tumor diameter, neoadjuvant chemotherapy, and pathological status. The lymph node status, HER-2 status, and age are signif-icant risk factors for ipsilateral breast tumor recurrence on univariate analysis [32]. In Korea, when the comparison of clinical characteristics of patients with Invasive Lobular Carcinoma (ILC) and Invasive Ductal Carcinoma (IDC) was done, it was observed that ILC showed a larger tumor size, was more ER and PR positive and HER2 negative and more likely to be of the luminal a sub-type. Patients with both ILC and IDC experienced disease recurrence with a median follow up of 56.4 months [33]. The IBTR peak showed a delay for ERP tumors as compared to the corresponding recurrence timing peaks for ERN tumors and the mortality dynamics for both ERP and ERN tumors is different with more deaths in ERN patients [34].

Upon studying HER protein expression in TNBC patients via Time Resolved-Forster Resonance Energy Transfer (TR-FRET) it was seen that HER1 levels ranged 4000-2 million receptors per cell, HER2 levels ranged from 1000- 60,000 receptors per cell, whereas HER3 expression was exceptionally low with less than 5500 receptors per cell. From this observation, it was concluded that HER2 expression is linked with recurrence and consequently its expression can be used as a prognostic biomarker in patients with TNBC [35]. Thymidine kinase 1 (TK1), an enzyme responsible for DNA synthesis and a proliferation marker was explored for Recurrence-Free Survival (RFS) in breast cancer patients. The activity of TK1 was measured in serum of healthy and breast cancer patients and elevated TK1 activity was associated with advanced T stage, higher grade, presence of tumor necrosis, vascular invasion, and lack of ER and PR expression. In multivariate cox analysis, it was found that TK1 activity is an independent prognostic factor for RFS and an important predictor for the recurrence of the disease [36]. The Matrix Metallo Proteinases (MMPs) are secreted as inactive precursors, activated by cleavage of an N-terminal pro-peptide. The mechanisms of action of these proteinases include cancer cell growth, differentiation, apoptosis, migration and invasion, and the regulation of tumor angiogenesis, and immune surveillance. The expression of MMP2 and MMP9 is associated with high metastasis potential in breast cancer. Strong expression of MMP9 was observed in recurring tumors [37].

Recent studies have indicated the occurrence of some non-related diseases to breast cancer recur-rence. Bell's palsy is a neurological condition that result in the paralysis of facial muscles results mainly from viral infection. Some patients, who were affected with this condition during their treatment, were subsequently diagnosed to have a recurrence in their cancer [38].

Epigenetic and heritable changes in gene expression have played a role in the pathogenesis of various diseases. An epigenetic modification involves methyl transferase nuclear receptor SET domain containing 2 (NSD2) that can modify the histone code by transferring methyl groups to a lysine residue in histone [39]. NSD2 overexpression has been seen in multiple types of aggressive solid tumors including breast cancer and can be used as a valuable biomarker to check for recur-rence and prognosis of a tumor [40]. Along with DNA methylation, aberrant expression of histone modification and non-coding RNA play a pivotal role in the pathogenesis of cancer and can be used as markers for the diagnosis and treatment of breast cancer [41].

Management of recurrence

Tumor recurrence is largely responsible for an increased rate of mortality. Therefore, there is an urgent need to study the signaling pathways involved in tumor recurrence which can aid in iden-tifying novel therapeutic targets for the prevention of tumor recurrence. The use of biomarkers has improved breast cancer diagnosis, prognosis, prediction of therapeutic response, and follow up of disease during and after treatment [42]. However, it is important to identify the early-stage biomarkers which can help in the prevention of the recurrence even before it occurs [43]. For example, Cyclin E, a protein expressed in the late phase of the cell cycle can be considered as an acceptable biomarker as its overexpression has been seen to correlate with an increased risk in breast cancer recurrence [44]. Cathepsin D, a lysosomal aspartyl endopeptidase is also an effective biomarker as its overexpression is often related to an increased risk of recurrence and death [45]. When patients with early-stage breast cancer were treated with endocrine therapy, they had about 90% 5-year disease-free surviva [46]. On performing LASSO Cox regression analysis on breast cancer patients with high sensitivity and specificity, it was found that novel miRNA-based Overall Survival (OS) and Recurrence-Free Survival (RFS) signatures are independent prognostic indicators for BC patients [47]. CD133 (cluster of differentiation) and ALDH1 (aldehyde dehydrogenase 1) were associated with the size of tumor, cancer stage, ER negativity, and recurrence. CD133 alone or along with ALDH1 was more involved in presenting the biomarkers of breast cancer as

compared to ALDH1 alone therefore, playing a predictive role in the management of invasive breast cancer in patients [48]. Other indicators like aromatase inhibitors, a class of drugs used in the treatment of breast cancer in postmenopausal women and gynecomastia in men have played a central role in endocrine therapy for the treatment of ER-positive breast cancer. Patients showcasing advanced disease exhibit an increased circulating miR-30b-5p expression as compared to patients with localized BrC suggesting that miR-30b-p can be utilized to identify patients with a higher risk of disease progression and therefore can be used as a clinical tool to monitor a patient and suggest earlier and better treatment [49]. Bone-morphogenetic protein-4 (BMP4) has been shown to block metastasis in animal models of breast cancer by sensitizing cancer cells to anoikis via canonical BMP-SMAD signaling. Elevated BMP4 and SMAD7 levels can also be utilized as a good diagnostic marker for improved recurrence-free survival in breast cancer patients [50]. Endocrine-related Progesterone Receptor (PgR) status combined with Body Mass Index (BMI) may serve as a tool in the management of ER+ and HER2- breast cancer in patients treated with adjuvant aromatase inhibitors [51]. Biomarkers can also be used to study the effectiveness of an ongoing treatment such as rising levels of indicators like Carcino Embryonic Antigen (CEA) in BRC patients that can signal a recurrence in cancer after treatment or may indicate the ongoing treatment as ineffective [52]. Common techniques like radiotherapy play a major role in detecting breast cancer and if used effectively can be used to study the likelihood of recurrence in patients. One study set forth to distinguish between different clinical targets that can lead to recurrence. The study concluded that for patients having undergone a mastectomy, there is a higher risk of recurrence in the skin, subcutaneous tissues, pectoralis, and area around the incision and should be paid more attention in chest wall radiotherapy [53].

Different combination of the surgeries and therapies has helped to eliminate the problems associ-ated with management of breast cancer recurrence. Combined Sentinel Lymph Node Biopsy (SLNB) and Axillary Node Sampling (ANS) were studied in Clinically Node-Negative Breast Cancer patients.54 ANS is done to check the status, staging and local control of breast cancer management. The axillae of node-negative patients were staged using patent blue dye/ SLNB/ ANS technique. In the study conducted on 230 clinically node-negative patients undergoing breast-conserving surgery 1.5% showed positive axillary lymph nodes, 15% showed SLN metas-tases, 87.5% had single node involvement, 27 complete axillary clearances and the rest were treated with radiotherapy. There was no axillary recurrence at a 5 year follow up [54]. In Occult Breast Carcinoma (OBC) patients, the disease-free survival and overall survival rate of patients treated with a mastectomy had improved significantly when compared to those treated with quadrantectomy. Patients treated with radiotherapy had higher local recurrence and overall survival rates compared to patients treated with no radiotherapy [55]. The therapeutic efficacy of certain drugs like Eribulin (a chemotherapeutic drug used to treat metastatic breast cancer) and Trastuzumab (a monoclonal antibody used to treat HER2 positive breast cancer, sold in the name of *'herceptin'*) was checked and the results indicated that the clinical benefit rate was 80%, therefore indicating that the drugs have good potential to treat recurrent breast cancer [56]. Although Trastuzumab is a standard drug for treating HER 2+ breast cancer, there has been an increasing number of cases that are showing resistance to Trastuzumab treatment. Combined with different chemotherapies Trastuzumab treatment can work quite effectively but in resistive patients, the effect generally lasts for 5-9 months. Some new drugs like Lapatinib and Pertuzumab have been introduced in the market to treat the patients showing resistance to Trastuzumab but they are not as effective as its predecessor which is still the best drug for HER2+ BC patients [57]. Statins, or 3-hydroxy-3-methylglutaryl-coenzyme reductase inhibitors, are medications that have been used for decades to lower cholesterol and to treat cardiovascular diseases and now have been used in the management of breast cancer. Statins in breast cancer cell lines, increase apoptosis and radio-sensitivity, inhibit proliferation and invasion, and decrease the metastatic dissemination of tumors [58]. A study done on postmenopausal Chinese women suffering from advanced or recurrent breast cancer showed that Fluvestrant treatment has good efficacy in women having hormone-sensitive advanced breast carcinoma. Progression-free survival time is also increased with first-line Fulvestrant therapy especially in patients without prior adjuvant treatment . To check the disease progression of TNBC patients biomarkers such as stomal tumor-infiltrating lymphocytes has been taken into consideration as TILs has been seen to be a vital factor to ensure a better distance-recurrence free survival, disease-free and overall survival in early stage TNBC patients undergoing standard/neoadjuvant chemotherapy.

With the advent of technological advancement in the field of biology, certain bioinformatic stud-ies can also be used to identify potential genes and their interaction to get a better statistical analysis which can help in the diagnosis and treatment of a patient. A study was carried out to recognize Differentially Expressed Genes (DEG) for HER-2 positive breast cancer patients using Kaplan-Meier plotter survival analysis. The study reported that RAC1 and RRM2 overexpression leads to an undesirable prognosis in HER-2 positive breast cancer patients.

prospects in epigenetics

Inrecent years, alteration in theepigenome of a cell hasprovided valuable for understanding cancer through DNA methylation, post-translation modification like Histone modification and non-coding RNA. These provide valuable targets for drug delivery as the epigenome changes quite frequently in a person mainly triggered by diet and environmental changes and act as valuable prognostic markers for diagnosis and treatment of cancer. Here we propose some of the epigenetic mechanisms that can be studied for a better diagnosis of breast cancer and its recur-rence along with some pathways that can be exploited in the future for its treatment.

Hypermethylation of promoter genes results in gene silencing and is a hallmark of carcinogenesis. Therefore,

it is no secret that many tumor suppressor genes have been found hypermethylated in human cancer cells and primary tumors. RASFF1A, a tumor suppressor gene is found to be hypermethylated at its promoter site in Triple Negative Breast Cancer (TNBC), and is seen as an early event in DCIS and LCIS. RASFF1A hypermethylation can act as a biomarker for diagnosis as it is found in nearly 60-70% of the cells in a breast cancer tumor and its hypermethylation is rarely observed in normal tissues.67 RASFF1A can also be utilized as a biomarker in post-surgery patients on adjuvant tamoxifen treatment. Methylation post-surgery indicates re-sistance to tamoxifen and loss of methylation indicates the effectiveness of the treatment.

The epigenetic process is quite a complex process. To establish DNA methylation, polycomb proteins need to be associated with DNMTs by recruiting them to the promoter region of the si-lenced gene. A study was conducted to demonstrate that dysregulation of normal signaling in cancer cells can result in silencing downstream targets maintained by epigenetic machinery which utilized RNAi to disable ERα in breast cancer. The study reported that polycomb repressor and histone deacetylase assemble in the promoter region of an ERα target gene. DNA methylation accumulated in these silenced targets could be passed down through cell progeny. Down-regulation of pro-apoptotic protein Par-4 also promoted tumor recurrence in mouse models. It was observed that the down regulation is initiated by epigenetic silencing of this protein via epithelial-to-mesenchymal transition. The study concluded that this process could be resolved by reversing the epigenetic silencing of Par-4 thereby making recurrent tumor cells more sensitive to chemotherapy.

In the aforementioned overview, the importance of epigenetic markers and the epigenetic mechanisms for cancer detection and therapies have been explored. The genome wide sequencing techniques are becoming more affordable which can facilitate bisulfite sequencing on patient samples to study the epigenetic patterns in tumors. This can further aid in designing personalized medicines that are patient-specific and more effective in treating the disease. Drugs that incorpo-rate RNAi can also be used to impede different signaling pathways essential for epigenetic ma-chinery for aberrant expression. Although some DNMT and HDAC inhibitor type drugs are available in the market, their dosage, schedule, and duration of therapy needs to be recognized as epigenetic changes can be reversed with time and lead to prolonged drug treatments that can be fatal patient and reduce the quality of life. Drugs that target the epigenetic pathway can also be used in combination with traditional therapies allowing for better treatment approaches for improved survival and low recurrence rate. In conclusion, the role of epigenetic machinery in tumor progression cannot be ignored and could be considered as potential drug targets and biomarkers for the management of breast cancer and its recurrence in patients.

Conclusion

Breast cancer is one of the most common cancers affecting a significant number of women worldwide. Although there are effective treatment modalities and therapies available, complications such as recurrence often led to metastatic breast cancer leading topoor prognosis andmortality. It is exceedingly difficult to anticipate and identify in time for effective therapy to improve the quality of life and reduce mortality. With rapid progress and technological advancement in healthcare, better therapeutic approaches have been developed for breast cancer and its recurrence. These advancements aim not just to correct the aberrations at the genetic level but consider exploiting different pathways and molecular mechanisms in the body to manage breast cancer recurrence.

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