Risk Factors in Breast Cancer Progression and Current Advances in Therapeutic Approaches to Knockdown Breast Cancer

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Abstract

The complicated coding of tumorous cells requires emerging molecular biology tools for early diagnosis and for the better understandings of cancer progression. In spite of the advancement in diagnostic and therapeutic approaches to hit breast cancer, it is still a second major cause of cancerous deaths among women globally. In therapeutic vibes, deregulation in the expression of genes such as BRCA1, BRCA2, PIK3, RB, MDM2, TPK53 and HER2 involved in breast cancer prevalence. Furthermore, microRNAs such as miR-200, miR-27a, miR-182 and let-7 have been demonstrated that hold some potential hope to extricate from the complexity of cancerous cells. This review elaborates the different risk factors that lead to breast cancer progression and the current therapeutic approaches ongoing to tackle the tangled cellular behavior of cancerous cell. Moreover, for the better understandings of various signaling cascades involved in breast cancer development and to design effective therapies, researchers further needed to take interest in upcoming approaches including biophysics and nanotechnology based gene therapy and drug delivery.

Keywords: MicroRNAs; BRCA; Nanotechnology; Gene therapy; Molecular biology

Introduction

Breast cancer is the second major leading cause of cancerous deaths among women worldwide with poor prognosis and tangled cellular coding that requires in-depth understandings of signaling cascades involved in cell proliferation and cancer progression. Broadly breast cancer has 3 major types invasive, non-invasive and other include paget's disease of nipple that accounts 1-4% of breast cancer [1]. The most common symptoms associated with the onset of breast cancer are; appearance of lumps, redness, soreness, and compactness of dimple. The environmental factors have been reported as the major cause of the breast cancer after the genetic mutations. Most epidemiology researches have made the association between fat present in diet and breast cancer risks [2].

Breast cancer is the second major leading cause of death among women; more than one million cases of breast cancer have been documented globally. In the recent research on breast cancer prevalence, 90,000 cases of breast cancer have been registered in Pakistan but due to the lack of suitable markers these cases are unable to diagnose. In Pakistan breast cancer accounts for 38.5% of other types of cancer in the country. Among Pakistani females the ratio of developing breast cancer is increasing at an alarming rate. About 10% of the breast cancer cases are diagnosed and treated while 75% patients do not get any treatment and after diagnosis die within five years. It is observed that early detection of breast cancer also increases the chances of survival up to 90% [3].

Different types of breast cancer caused by different types of mutations in genes mainly BRCA1, BRCA2, PIK3, RB, MDM2, TPK53 and HER2 that affects the body differently. Deregulation of expression of some genes like TPK53, MDM2 and RB play role in therapeutic vibes of breast cancer, research classified that 90% of breast cancer cause by genetic mutation in any of the two genes namely BRCA1 and BRCA2 [4]. To untangle the complexity of signaling cascades of cancerous cells, there is a need of complete molecular understandings of epigenetics and genetics events including the tumor suppressor and oncogenic miRNAs associated with the cancer development. miRNA plays important role in cellular homeostasis by regulating the apoptosis, cell differentiation and proliferation by number of events including gene silencing, translational inhibition and deregulation of targeted mRNA. miRNAs act as both tumor suppressor and oncogenic, the up-regulation of the oncogenic miRNAs such as miR-21, miR-27a and miR-182 down regulates the tumor suppressor miRNAs that leads to modulate the downstream signaling pathways and thus induce cancer. Nanotechnology based miRNA replacement therapies has a potential hope to treat breast cancer [5].

Emerging hybrid technologies and therapeutic approaches against breast cancer is the requirement of the time to support the traditional therapies such as immunotherapy, chemotherapy and radiotherapy. This review highlights the current effective therapeutic approaches including nanotechnology based drug delivery with controlled drug release at the site of disease and the use of natural drugs with their anti-cancerous and anti-oxidant properties [6].

Breast Cancer Awareness

Mostly countries in world are facing resources containment that confines accommodation to improve early diagnosis, detection and treatment of breast cancer. BHGI (breast cancer global initiative) combat to establish evidence-based, culturally appropriate and economically feasible guidelines that can also use in nations along confined health care supplies to promote breast cancer outcomes. In
Types of Breast Cancer

Different types of breast cancer have now been reported caused by different types of mutations in genes that affect the body differently in Figure 1. In invasive breast cancer, the affected cells of breast break out the duct and lobular walls and access to the fatty and connective tissues surrounding the duct in breast. It has been reported that in invasive breast cancer BRCA1 gene activity particularly decreased [13]. In noninvasive breast cancer, affected cells remain bounded with the duct of breast. It has been demonstrated recently that 90% of the noninvasive breast cancer is due to ductal carcinoma in situ that considered very common type of it. Lobular carcinoma considered as a marker for increase in breast cancer possibilities. In the case of lobular carcinoma in situ rapid increase of the number of cancerous cells occurs and it accounts 10-15% of the breast cancer [14].

Another type of breast cancer is Paget's disease of nipple starts from the milk duct and metastatic to the skin of breast nipple and areola and accounts 1-4% of breast cancer. Mostly shave biopsy, surface biopsy, punch biopsy and wedge biopsy used for it diagnosis. Women with the Paget's disease of the nipple have poor characterizes of cancer. There is an association present between underlying invasive carcinoma and Paget's disease of the nipple [15]. Males also have chances of breast cancer since the underestimation of disease but also with impingement on intimate relationships to husbands, extended and immediate family, is not unanticipated that there is also a scarcity of concentrated research of breast cancer in the Pakistan [10].

Molecular Aspects of Breast Cancer

In family linkage or due to the mutation in the genes, breast cancer is highly identified in BRCA1, BRCA2, PTEN and TP53, also there are some other genes that have been reported recently that are involved in DNA repairing like RAD59C, PALBL, ATM, CHEK2, ATM, BRTP1 also affiliated with modest breast cancer [4]. It has now been clear that signaling pathway of phosphatidylinositol-3-kinase (PI3K) denaturalize different cancer types. PIK3CA gene mutation in breast cancer consider for approximately 20%. PIK3CA gene mutation is 20% to 25% approximately has been reported for HER2 positive breast cancer, which is depending upon PI3K pathway [17]. HER2 is an epidermal growth factor constituent that receptor family has an activity of tyrosin kinase, resulting in the auto-phosphorylation of receptor in cytoplasmic domain that starts different pathways of signaling that leads to proliferation of cell and tumor-genesis. HER2 overexpression occurs 15-30% approximately in breast cancer and act as a predictive and prognostic biomarker for breast cancer [18].

IGF family biological activates not only the development of normal organism but also have implicated in tumorigenesis. This signaling family IGF consists of IGF ligands (IGF1 and 2), also have cell receptors (IR, IGF-1R and IGF-2R) and a binding protein group (IGFBPs). High levels of IGF-1 indicated as a constituent risk factor in development of breast cancer. Overexpression and activation of IGF-1R have been suspected in different cellular processes containing cell migration, attenuation and proliferation of cell survival. Transduction routes for IGF signaling are PI-3K and MAPK pathways, which act as a key moderator of cell propagation. Recently, it has been reported that MAPK4/42(ERK) act as an important constituent in resistance of MCF-7 apoptosis from cell to cell, which demonstrated the significance of ERK signaling in the prolonged endurance for breast cancer cells. Additionally, there is substantiation that JNK (c-Jun N-terminal kinase) signaling regulates IGF-1 negatively to cell proliferation in breast cancer [19].

BRCA1 and BRCA2 genes mutations have been demonstrated that elevates the risks of ovarian, breast and contralateral breast cancer. Approximate range for BRCA1 and BRCA2 mutation for the breast cancer is 40% to 87% and 18% to 88% have been reported [20]. Comparatively 30% of breast cancer is caused by tumor protein p53 (TP53) mutation but this constancy alternates extensively between
 subclasses. Epigenetic and genetic changes have been determined in p53 activity regulators [21].

S-phase kinase protein-2 (Skp-2) role in breast cancer development

It has been reported recently that in breast cancer pathogenesis, F-box protein skp2 (S-phase kinase protein-2) plays important role. Skp2 related to system of ubiquitin-proteasome that plays important role in different biological processes by regulating the appropriate turn-over of proteins [22]. S-phase kinase associated protein-2 is a particular determinant of SCFskp2 E3 ligase that involved in progression of cell cycle by deregulating its target. p27 is a substrate for skp2, its lower level caused by Skp2 overexpression which shows expression of cancer in humans. Skp2 act as a prognostic marker in breast cancer. Apparently, evidences have also show that skp2 act as an important factor in cell growth, invasion, apoptosis and metastasis in breast cancer [23].

Different signaling pathways, for instance ERK (extracellular signal-regulated kinase) PI3K/Akt (phosphatidylinositol-3 kinase), PPAR-γ (peroxisome proliferator-activated receptor-γ), mTOR and insulin growth factor-1 (IGF-1) signaling pathways have been originated for cross-talk to Skp2, which indicated that this cross-talk present between these signaling pathways and Skp2 plays substantial role in breast cancer occurrence [23]. Skp2 protein and mRNA protein both play exhilarated level in cell lines of breast cancer and also in primary breast tumor. Skp2 overexpression promotes growth of cancerous cells of breast. In recent studies it has been inaugurated that Skp2B interact to REA and then high level of Skp2B leads to low level of REA and indicates Skp2 overexpression enriched for breast cancer by modulating ER activity. Skp2 overexpression was encountered more commonly in tumor metastatic in axillary lymph nodes in case of breast cancer demonstrated that Skp2 stimulates breast tumor metastasis shown in Figure 2 [24].

MicroRNAs for Breast Cancer

Small single stranded functional RNAs having range between 19-25 nucleotides commonly known as microRNAs have been demonstrated as a biological active RNA subtype involved in various biological functions to regulate the cellular homeostasis by regulating cell differentiation, apoptosis and proliferation by the degradation of functionally active mRNAs. The biogenesis of microRNAs must be tightly regulated for the proper functioning of cell. It has been reported that any kind of de-regulation in the biogenesis of miRNAs effect the expression of several miRNAs associated with the particular miRNA and thus it leads to induce cancer [25]. Numbers of enzymes are involved in the synthesis of miRNA such as RNA Pol II forms the pri-miRNA and then the premature miRNA processed by number of enzymes to form mature miRNA shown in Figure 3. Reduced expression of any of these enzymes involved in the maturation of miRNAs leads to induce cancer [26].

The miRNAs can act as both tumor suppressor miRNAs and oncogenic miRNAs. In breast cancer, the oncogenic miRNAs are up-regulated while the expression of tumor suppressor miRNAs is down regulated [27]. Numbers of events have been reported that leads to the aberrant function of miRNAs such as epigenetic factors, SNPs and defect in the maturation of mature miRNA pathway. Increased and decreased level of miRNAs can now be easily detected by the use of emerging molecular biology and sequencing techniques [28]. Expression of tumor suppressor miRNAs inhibit by the up regulated oncogenic miRNAs and thus the lower expression of tumor suppressor miRNAs leads to the augmentation of signal pathways involved in the progression of cancer (Table 1) [29].
miRNA-200 ZEB1, ZEB2, HER3 Involved in tumor growth and cell differentiation Decreased
miRNA-145 ER-α, N-Ras, RTKN, OCT4, MUC1 Initiate tumor growth, angiogenesis, metastasis, cell differentiation and metastasis Decreased
miRNA-126 PITPN1, MERTK, Involved in metastatic angiogenesis Decreased
miRNA-21 TPM1, PTEN, TIMP3, PDCD4 Involved in cancer metastasis Increased
miRNA-182 RECK, FOXO1, MIM Involved in cancer invasion Increased
miRNA-27a ZBTB10, HOXO1 Involved in angiogenesis and cell viability and increased
miRNA-155 SOCS1, FOXO3a Involved in cell apoptosis and proliferation Increased

Table 1: Tumor suppressor and oncogenic miRNAs linked with breast cancer are listed.

miRNAs as therapeutic tool for breast cancer

Three layered polyplex (microRNA) used as a targeted delivery system for breast cancer gene therapy. Gene therapy is use as a drug to treat diseases i.e., therapeutic delivery of nucleic acid into patient's cell. MicroRNA is small in size and has low molecular weight due to this property it has now became the promising therapeutic drugs in cancer treatment. Major challenge of miRNA is to attain specificity, affectivity and safe delivery to the cancerous cells. Therefore, use of three-layered polyplex with folic acid as a target to deliver miR-210 into breast cancer cells and thus it is useful to inhibit the breast cancer progression by this method [30].

Immunotherapy

Breast cancer has been considered as an immunologically silent, but now it is clear that the immune system has role in this disease [31]. Moreover, at the earliest stages of the disease, immunity to breast cancer begins in some patients prior to detection. Immune cells also emerged as a promising target against breast cancer as both the innate and adaptive immune system is necessary for the design and development of immunotherapies in breast cancer. The role of immunotherapies against cancerous cells refers as active and passive treatments shown in Figure 4 [32].

![Immunotherapy](image)

Figure 4: Immunotherapy and its role in breast cancer.

Immunotherapy encircles both vaccines and checkpoint blocking antibodies and both of these approaches are being examined as a future for the treatment of breast cancer. Vaccine therapy may be ideal to damage ductal carcinoma in situ (DCIS) by the activation of type I T-cells against DCIS antigens and thus inhibit its reoccurrence [33]. Some of the vaccines against breast cancer have been reported that use new approaches for its delivery such as liposome formulation and nanoparticles that further enhance the efficacy of vaccines (Table 2).

| Vaccines                        | Immune Response                                                                 | References |
|---------------------------------|---------------------------------------------------------------------------------|------------|
| Dendritic cell based vaccines   | Have known specificity for tumor associated-antigen and also generate its own immune response | [34]       |
| Peptide based vaccines          | These help to generate immune responses (including antibodies, helper T-cells and cytotoxic T lymphocytes CTLs) using antigenic epitopes | [35]       |
| DNA based vaccines              | It stimulates a 'physiological' immune response against antigens.               | [36]       |
| Whole-cell-based vaccines       | These may deliver by new technology like nanotechnology and liposome.          | [37]       |
| CDB+Tcell vaccines              | These target immunosuppressive pathways allowing for greater anti-tumor response | [38]       |

Table 2: Some of the vaccines are listed.

Natural Cure for Treatment of Breast Cancer

For many centuries, plants and herbs have been used for medicinal purposes as they possess therapeutic properties to treat number of diseases including cancer. The main goal of these natural drugs is to retain the immune stimulating and anti-tumor properties by different
types of plants. The emerging research in the development of medicines has now more concern towards the use of herbal medicines because of the lower proportion of toxicity cause by these natural drugs. In different types of herbs, vast variety of active phytochemicals has been reported such as flavonoids, terpenoids, sulfides, ligands, lignans, polyphenolics, plant sterols and carotenoids possessing anti-oxidant properties. These phytochemicals either stimulate the protective enzyme (glutathione transferase) or it may prevent the cell growth. It it has been demonstrated that the extracts and juices of Amoora rohituka, Withania somnifera, Vaccinium macrocarpon and Dysoxylum bicarboxyferum have anti-tumor properties and is useful for the treatment of breast cancer [39].

Common herbs for the treatment of breast cancer

Great progress has now been made in medicinal fields to fight against the life-threatening disease. Wide variety of natural herbs having anti-tumor properties have been identified that cause low toxicity (Table 3).

| Natural drugs | Anti-cancer properties of natural drugs | References |
|---------------|---------------------------------------|------------|
| Carotenoids   | Carotenoids substances have vigorous antioxidants that exhibit different therapeutic activities, such as protecting against oxidative damage to cells, searching of free radicals, modulation of immune system and enzyme’s activity regulation involved in cancer production and also simulates the activity of immune system. | [40] |
| Turmeric (Curcuma longa) | Curcumin (active ingredient of turmeric) has role in anticancerous activity due to its phenolic substances. Curcumin has inhibitory action in all phases like initiation, promotion and propagation of tumor. | [8] |
| Garlic (Allium sativum) | Garlic has Anti-cancer activity due to presence of polysulfide’s and organic sulfides. Mechanism of anti-tumor activity stimulates the lymphocytes and macrophages. They also interfere with cancerous cells metabolism and kill the cancerous cells. | [41] |
| Black Cohosh (Cimicifuga recemosa) | Black cohosh has synergistic effects for patients of breast cancer when use in combination with chemotherapeutic agents. | [42] |
| Green Tea (Camellia sinensis) | Polyphenolic compounds show anti-tumor activity. Green tea also stimulates the necrosis and apoptosis of tumor cells and possess anti mutagenic activity. All these properties are due to the anti-oxidant activity of phenolic compounds present in green tea. | [43] |
| Burdock (Arctium lappa) | It may contain active ingredients that alter the oncogenes. Burdock seeds also contain Arctigenin that has an ability to inhibit tumor cells. Most important active ingredient is Tannin which is a phenolic compound and regulates the macrophages action and reduces the cancer propagation. | [44] |

Table 3: Some of the effective natural herbs use for the treatment of breast cancer is listed.

Emerging Therapeutic Approaches to Hit Breast Cancer (Nano Based Drug Delivery)

Today breast cancer is arguably the most common cancer faced by females and world widely it is the second major cause of death in women. Certainly, this disease has gathered much attention in the field of pharmacology research. Modern chemotherapeutic treatments also use for the breast cancer treatment, but it has a limiting use because of number of limitations. Nanotechnology as compared to chemotherapy is a highly focused approach that may provide very effective and less toxic treatment. For the treatment of metastatic breast cancer, emerging nanotechnologies also guaranteed new approaches that require delivery of nanomaterials and thus it controls the release of a particular drug to the site of action [45]. An important step in identifying novel targets in breast cancer is provided by ability to profile molecular pathways in drug responsive and drug resistant tumors [46]. However, applications of diagnostic and therapeutic interventions require treatment related cognitive state, also determine the subgroup of breast cancer patients is still a challenge [47].

It has been reported that method of drug delivery system by the use of magnetic polyurethane is biocompatible and has lower toxicity; these magnetic polymers can be used as an external magnet to direct chemotherapeutic drugs to cancerous cells in body. For the successful treatment of cancer, nanotechnology-based combination drug delivery system also summarized facing challenges and perspectives i.e., in this approach enhanced cytotoxicity is mainly due to reduction of multidrug resistance and synergistic effects as a result it may reduce toxicity towards normal cells [48].

Conclusion

Breast cancer is a second major cause of cancerous death among females globally, deregulation of genes such as BRCA1, BRCA2, PIK3, RB, MDM2, TPK53 and HER2 are involved in breast cancer prevalence. Different oncogenic miRNAs also have been reported that leads to breast cancer progression. Different therapeutic approaches against breast cancer such as immunotherapies and the use of natural drugs are currently available. Inspite of all currently available treatments, there exist some limitations and side effects on healthy cells, while the nanotechnology based drug delivery and miRNA therapy have potential of targeted and controlled drug release to execute tumorous cells, for further advancement Biological scientists further needed to take interest in upcoming nanotechnology based approaches to untangle the complexity of cancerous cells.

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