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Review Article

A Review Article on Emerging Role of Hybrid Molecules in Treatment of Breast Cancer

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Abstract

Breast cancer is the most common cancer in women; however, many of them relapse following primary treatment. The pattern of treating breast cancer has been changed over last decades. Dendritic Cell/tumour hybrid, hydroxyphenyl-tyrosinamide-chlorambucil, SNIPER, hybrid radiopharmaceutical and photoactive hybrid nanoparticles should be regarded as potential molecular targets for novel anti-cancer therapies. DC-based vaccines have emerged as a promising tool in cancer immunotherapy because of their low toxicity. Nanotechnology-based differential combination therapy and the hybrid radiopharmaceutical could be potentially useful as a therapeutic agent for the treatment of breast cancers. The protein knockdown system with SNIPERs would expand a possibility to develop a variety of novel molecular target drugs. The meta-hydroxyphenyl-tyrosinamide-chlorambucil derivatives have shown high anticancer efficacy in hormone dependent and hormone-independent breast cancer cell lines compared to ortho- and para- analogs. Thus, the hybrid molecules are effective in controlling breast tumors, however; long-term confirmation is required. This article reviews the emerging role of hybrid molecules in the breast cancer treatment.

Keywords: Breast cancer; Hybrid molecules; Dendritic Cell/tumor hybrid; Hydroxyphenyl-tyrosinamide-chlorambucil; Hybrid radiopharmaceutical; Photoactive Hybrid Nanoparticles

Abbreviations

HR: Hormone receptor; HER-2/neu: Human Epidermal Growth Factor Receptor 2; NBC: Triple Negative Breast Cancer; DC: Dendritic Cell; PEG: Polyethylene Glycol; HNPs: Hybrid Nanoparticles; CRC: Capture & Recovery Chip; PDT: Photodynamic Therapy; PS: Photosensitizer; ROS: Reactive Oxygen Species: NPs: Nanoparticles; Tc-BN: Technetium 99m-Bombesin; SNIPER: Specific and Non-genetic IAP-dependent Protein Eraser; ERα: Estrogen receptor alpha

Introduction

Breast cancer, most common cancer in women both in the developed and developing countries has profound social and economic impact [1]. Worldwide over 508,000 women died in 2011 due to breast cancer (Global Health Estimates, WHO 2013) [2-4]. In 2011, approximately 230,000 women were diagnosed with breast cancer in the U.S. alone. Hence it is the second most common cause of cancer related death in women [5]. According to the World Cancer Report 2000, the incidence of cancer at any localization would increase by 50 % by the year 2020 [1].

The biological basis of breast cancer and the major pathways involved in the tumor progression and metastases are still not fully understood. Based on the presence and absence of three receptors found on cancer cells, the breast cancer has been classified into three different subtypes [6]:

1) Hormone receptor (HR) positive breast cancers express estrogen and/or progesterone receptors (ER/PR),

2) Breast cancer that expresses oncogene human epidermal growth factor receptor 2 (HER-2/neu) and

3) Triple negative breast cancer (TNBC) that is negative for the expression of ER,PR, and HER-2/neu [7-9].

The advance understanding of tumor biology is helping individual patients' treatment selection and guide in steering the direction of new drug development. Today's technologies that are integrated with high-throughput can relatively quickly render comprehensive molecular portraits of tumors. Through the analysis of these data, new tumor subtypes, therapy response markers, and potential new drug targets can be identified. The pattern of treating breast cancer has been changed over last decades. In this article, we will review the recent hybrids molecules like dendritic cell (DC)/tumor hybrid hybrid nanoparticles, hybrid radiopharmaceutical, SNIPER (specific and non-genetic IAP-dependent protein eraser), hydroxyphenyl-tyrosinamide-chlorambucil and their role in the treatment of breast cancer.

Dendritic Cell (DC)/tumor hybrid

The use immune therapy by directing immune response toward tumor antigens is one of the strategies to control cancer. This can be achieved by loading the DC (antigen presenting cells) with tumor antigens. Tumor antigens initiate a multifactorial immune response directed against tumor antigens after being processed and presented to naïve T lymphocytes in MCH I and II [10].

Today the DC/tumor cell fusion model is widely used to load the whole tumor cell in the DC. DC provide the hybrid with an

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immunogenic presentation of known and unknown tumor antigens in both MHC I and II context as well as with co-stimulatory molecules which are necessary for efficient lymphocyte activation [11].

The hybrid DC/tumor cells have been obtained using various methods including Polyethylene Glycol (PEG) [12-14], electro-fusion [15,16] and viral fusogenic membrane glycoproteins [17,18]. Hybrid cells have proved their in vitro and in vivo efficiency [19,20] and proven to be safe in phases I and II clinical trials, with no toxic side effects or autoimmune reaction [21,22].

Serhal et al [11] fused human monocyte-derived DC with T-47D cells which overexpress Her2/neu, one of the most common tumor-associated antigens in breast cancer. The fusion process aims at charging the DC with unknown but potentially immunogenic tumor antigens as well as identified tumor-associated antigens. This model have the advantage as it allows easy identification of fused cells based on the expression of Her2/neu and DC markers using flow cytometry and confocal microscopy [11].

In the optimized conditions for DC/T-47D fusion, hybrid cells express membranous presentation and co-stimulatory molecules as well as membranous and cytoplasmic tumor antigens. These cells secrete cytokines and perforin. The hybrid cells appeared to be good candidates for anti-tumor therapies.

DC-based vaccines have emerged as a promising tool in cancer immunotherapy because of their low toxicity. Conservation of Her2/neu validates the use of fused cells as a breast tumor vaccine and supports the new vaccine approaches based on DC. Only fused cells are functional and appear to be good candidates for vaccination protocols however. The number of fused cells produced was always a limiting factor, hence efforts must be made to improve production and standardizing procedures in view of clinical trials [5].

Hybrid nanoparticles

Lee et al used Hybrid Nanoparticles (HNPs) to demonstrate simultaneous capture, analysis of in situ protein expression and identification of cellular phenotype of Circulating Tumor Cells (CTCs). Each HNP consists of three parts: (1) antibodies binding specifically to a known biomarker for CTCs, (2) a quantum dot emitting fluorescence signals, and (3) biotinylated DNA that will allow to capture and release CTC-HNP complex to an in-house developed Capture & Recovery Chip (CRC) [23].

The cells representative of different breast cancer subtypes like MCF-7: luminal; SK-BR-3: HER2; and MDA-MB-231: basal-like were captured onto CRC and concurrently the expressions of EpCAM, HER2, and EGFR were detected. The average capture efficiency of CTCs and identification accuracy were 87.5% and 92.4% respectively. The in situ expression can be counted and analyzed using HNPs, and also culture same set of CTCs that enables a wide range of molecular and cellular based studies using CTCs [23].

The cancer treatment by chemotherapy, surgery, and radiation therapy usually suppresses the immune system. Chemotherapy and radiation therapy delivered at doses that are sufficient to destroy tumors, may be toxic to the bone marrow. Bone marrow is the source of all immune system cells, and neutropaenia and other forms of myelosuppression are often the dose-limiting toxicity of these therapies. The ideal cancer therapy destroys the primary tumor, but also triggers the immune system will recognize, track down and ultimately destroy any remaining tumor cells [24]. Photodynamic therapy (PDT) is the only cancer treatment that stimulates anti-tumor immunity [24,25]. PDT involves administration of a photosensitizer (PS) followed by illumination of the tumor with a long 600-800 nm wavelength light producing Reactive Oxygen Species (ROS) resulting in vascular shutdown, cancer cell apoptosis, and induction of a host immune response [26].

Though the exact mechanism involved in the PDT-mediated induction of anti-tumor immunity is not yet understood, but possible mechanisms may include alterations in the tumor microenvironment by stimulating pro-inflammatory cytokines and direct effects of PDT on the tumor that increases immunogenicity [24]. PDT leads to generation of tumor specific cytotoxic CD8 T cells by increasing Dendritic Cells (DC) maturation and differentiation that in turn can destroy distant deposits of untreated tumor [24,27-29]. PDT can be combined with DC activating agent and can be used in metastatic tumor treatment [24,30].

One of the promising therapies for the treatment of breast cancer is nanotechnology-based differential combination therapy. Thus, by combining controlled release Nanoparticles (NPs), PDT, and immune activation, PS can be delivered with synergistic immunoadjuvants in a temporally regulated manner that will results in a safer and more effective management of the deadly form of metastatic breast cancer.

Marchea et al. [31] synthesized a hybrid NP system that can be loaded with a photosensitizer and an immunoadjuvant for combination therapy. Metastatic mouse breast carcinoma cells 4T1 cells were used as a model and was demonstrated that the phototoxicity of this hybrid NP containing CpG-ODN and the photosensitizer, ZnPc, is significantly higher than the free PS, PS alone in a NP, or a combination of the PS and the immunoadjuvant in their free forms. Several cytokines were involved in the PDT-induced immune response after treatment with CpG-ODN-Au-ZnPc-poly-NPs. These results indicate that the PDT-induced antitumor immune response and its further enhancement using synergistic immunoadjuvant in a suitably designed NP construct might play an important role in successful control of malignant diseases. These results support that a rational choice of an immunostimulant can be an ideal addition to PDT regimen if both the photosensitizer and the immunoadjuvant can be delivered using a single delivery vehicle. These results showed that by combining PDT with a synergistic immunostimulant in a single NP system, a significant immune response is generated, which can be used for the treatment of metastatic cancer [31].

From a PEG linking chain of various length and a 2-(2'-aminoethyl) pyridine ligand, a series of 17 beta-estradiol-platinum (II) hybrid molecules were made. The best activity against breast cancer cell lines MCF-7 and MDA-MB-231 was shown by the derivative with the longest PEG chain [32].

The hybrid nanostructure is recognized as promising candidates for biomedical applications and forms a firm foundation for further study and improvement. It was observed that the molecular self-assemblies quickly transfer through the cell membrane, releases the drug into the intracellular environment slowly and degrade back into

individual molecules that can be further broken down by the cell metabolically. Hence, these can be used as new drug-delivery systems for future cancer therapy that will show high treatment efficacy with minimum side effects [33].

The Functionalized-Quantum-Dot-Liposome (f-QD-L) incorporates both drug molecules and QD within the different compartments of a single vesicle. It offers many opportunities for the combinatory therapeutic development as well as imaging modalities. Poly (ethylene glycol)-coated QD was encapsulated in the aqueous phase (internal part) of different lipid bilayer vesicles to engineer the f-QD-L hybrid nanoparticles. Cationic f-QD-L hybrids lead to dramatic improvements in cellular binding and internalization in tumor-cell monolayer cultures [34].

Hybrid radiopharmaceutical

Over expression of the Gastrin-Releasing Peptide Receptor (GRP-r) is seen in breast cancers. Technetium-99m-bombesin (Tc-BN) is a radiopharmaceutical with specific cell GRP-r binding. A radiopharmaceutical of type Tc-N2S2-Tat-Lys-BN (Tc-Tat-BN) is a new hybrid was internalized in cancer cell nuclei that could act as an effective system of targeted radiotherapy. Cuevas et al in their study showed that 61.2% (MCF7) and 41.5% (MDA-MB231) of total disintegration per unit of Tc-Tat- BN activity binds to the cell occurred in the breast carcinoma cell lines nucleus. A significant decrease in MCF7 (45.71%) and MDA-MB231 (35.80%) cellular proliferation was produced by Tc-Tat-BN with respect to untreated cells. Hence, it was reported that the hybrid radiopharmaceutical may be considered as a potential useful therapeutic agent for breast cancers [35].

SNIPER (Specific and Non-genetic IAP-dependent Protein ERaser)

Estrogen receptor a (ERa), a member of the nuclear receptor family is expressed in 75% of breast cancer [36]. When estrogen binds to Era, its conformation changes with dimerization of the receptor facilitating the binding of the receptor complex with co-regulators to the promoter of target genes in order to activate transcription [37]. This process will results in cancer cell's proliferation and growth [38].

Tamoxifen is a selective ER modulator. It is the most widely used anti-cancer drug primary breast cancers for hormonal treatment. It causes cell cycle arrest and inhibits cell growth by competitively inhibiting the binding of estrogen to Era. The conformational change of ERa induced by tamoxifen favors the recruitment of co-repressors that inhibit transcriptional activity [39]. Tamoxifen have some detrimental effect as it increases incidence of the endometrial cancer [40] and up to 40% of early-stage breast cancer patients who receive tamoxifen eventually develop resistance and relapse with a more aggressive cancer [41].

Down-regulation of ERa protein is an alternative strategy to kill the estrogen signaling. Hence, a protein knockdown system was developed that induces degradation of target proteins via the Ubiquitin-Proteasome System (UPS) in cells [42-46]. The molecule for protein knockdown was named SNIPER. It composed of two distinct molecules: N-((2S, 3R)-3-amino-2-hydroxy-4-phenyl-butyryl)-L-leucine (bestatin, BS) and a ligand for a target protein, chemically linked as a single molecule. SNIPERs consisting of MeBS, a ligand for cIAP1 and another ligand for a target protein were developed to crosslink cIAP1 and the target protein in the cells.

The novel SNIPERs targeting ER (SNIPER(ER) was synthesized by using 4-hydroxy tamoxifen (4-OHT) as an ERa ligand that degrades the ERa protein by inducing ROS production and necrotic cell death in the ERa-expressing breast cancer cells. The cIAP1 involvement in the SNIPER(ER)-induced ERa degradation strongly suggested that the degradation depends on the cIAP1-mediated ubiquitylation of ERa. SNIPER has a dual activity on ERa depending on its concentration; at lower concentration it inhibits ERa as an antagonist like 4-OHT, while at a higher concentration it induces ERa degradation as a SNIPER. Thus, a possibility to develop a variety of novel molecular target drug through the protein knockdown system is expected [38].

Hydroxyphenyl-tyrosinamide-chlorambucil

It was observed that during the treatment of the breast cancer, the new compounds were up to 4.2 times more active on the cancer cells than chlorambucil itself. Hence, three distinct tyrosinamide molecules was constructed by linking L-para-Tyrosine lto ortho, meta and para-hydroxyaniline.

The tyrosinamides were then linked to chlorambucil in order to obtain a more specific chemotherapeutic agent target cancerous cells that express estrogen receptor alpha (ERα).

The anticancer efficacy of the tyrosinamide-chlorambucil molecules were evaluated in hormone dependent and hormone-independent (ER+; MCF-7 and ER-; MDA-MB-231) breast cancer cell lines. It was reported that the meta-hydroxyphenyl-tyrosinamide-chlorambucil derivatives were more active as compared to the ortho- and para- analogs [47].

Isothiocyanate-progesterone conjugates

New hybrid molecules of isothiocyanate and progesterone and their metal complexes show promising anti-proliferative and pro-apoptotic activity against breast. The metal complex compounds used an existing cellular transport pathway for the delivery of cytotoxic isothiocyanate moiety across cell membrane that resulted in cell viability inhibition and induced apoptosis. The copper complex had shown the highest apoptotic action similar to isothiocyanate compounds, which was mediated through the inhibition of Akt signaling. Hence with appropriate isothiocyanate pharmacophores, novel active compounds could be synthesized [48].

Discussion

Breast cancer is the most common cancer in women worldwide, however, many of them relapse following primary treatment Comprehensive cancer control involves prevention, early detection, diagnosis and treatment, rehabilitation and palliative care Raising the general awareness among people on the problem of breast cancer and the mechanisms to control and to advocate appropriate policies and programmes are the key strategies of population-based breast cancer control [1,2].

So far the only breast cancer screening method that has proved to be effective is mammography. The rapid development of molecular technologies has contributed in the area of breast cancer significantly.

An insight into the molecular complexity of the disease has been provided with a realization that the biological heterogeneity may have implications and opportunities for new forms of treatment [49].

DC/tumor hybrid, hydroxyphenyl- tyrosinamide- chlorambucil, SNIPER, hybrid radiopharmaceutical, photoactive Hybrid Nanoparticles should be regarded as potential molecular targets for novel anti-cancer therapies.

The upcoming new treatments, hybrid molecules being one of them, are improving the ways in which breast cancer is controlled. It is believed that we can make more informed decisions on which combinations shall be brought forward into the clinic if a thorough preclinical testing is done. The next decade will hopefully bring new treatment paradigms that will continue to build on progress made over preceding two decades, and further improve clinical outcomes and survival rates for patients with breast cancer.

Conclusion

In conclusion the hybrid molecules like DC/tumor hybrid hybrid nanoparticles, hybrid radiopharmaceutical, SNIPER, hydroxyphenyl-tyrosinamide-chlorambucil is effective in controlling breast tumors, however long-term confirmation is required.

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