Chapter

Targeted Breast Cancer Treatment Using New Photochemotherapeutic Compounds

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Abstract

The deregulation of cell growth in milk-producing glands, milk-carrying tubes, or connective tissues is known as breast cancer. It originates from genetic mutations and has the ability to metastasize. Primary tumor cells repetitively divide and lead to inappropriate mechanisms, tumorigenesis, and carcinogenesis, characterized by improper cell type, function, lifetime, and self-destruction. The tumor-specific activation is considered to be an effective strategy for selective cancer destruction, which remains an issue with conventional therapeutic approaches. The tumor microenvironment can be regulated and adapted through an interaction between pH, proteins, and other factors. Principally, human breast cancer genes, BRCA1 and BRCA2, produce tumor suppressors that prevent changes in genetic materials, as well as ensure their stability. Photodynamic therapy is a targeted cancer modality that depends on the photochemotherapeutic agent and light characteristics used to activate the compound. The possibility of eradicating breast cancer depends on continuous development of therapeutic approaches using third-generation photochemotherapeutic compounds to improve targeting this cancer and its stem cells.

Keywords: breast cancer, cell cycle regulation, genetic mutation, tumor microenvironment, cancer therapies, new photosensitizers

1. Introduction

Both males and females have breasts, which are composed of adipose (fat) tissues, supplied by nerves, blood vessels, lymph nodes and vessels, connective tissues, and ligaments. The breasts superimpose the pectoral muscles and are predominantly pronounced in females after puberty. Breasts consist of mammary glands that contain at least a dozen of lobes, further subdivided into lobules, and stimulated lobules are able to initiate and produce milk. The lobules are specially structured and connected to a system of ductal channels to deliver milk to the nipple. The glandular and ductal structures are surrounded by dense fat and connective tissues, which determine the size of a breast (**Figure 1**) [1, 2]. This anatomy is completed by a network of connective tissues, ligaments, nerves, and both lymph and blood vessels for proper structural and functional processing [3].

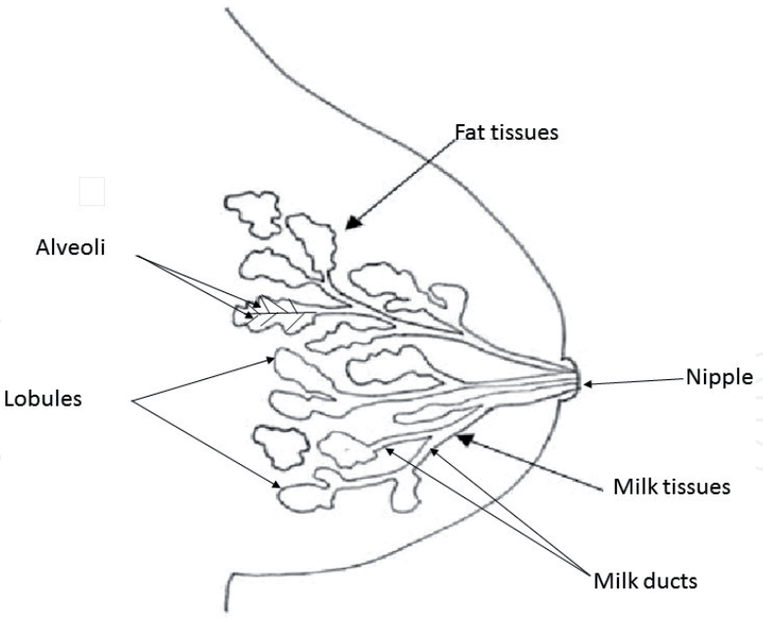

Figure 1.
Schematic representation of the breast. Milk passages from the alveoli through the milk ducts to the nipple during breast feeding.

Like any other cell cycle, the breast cell cycle endures proper cell proliferation and functioning by duplicating cell genetic materials and giving off two daughter cells during each cycle. It consists of four distinctive phases and in the first or quiescence phase (G0), the cell remains in a resting state, where cell division is stationary. The second is known as the intermitotic phase and is further subdivided into a gap 1 phase (a prior-DNA synthesis stage) in which cell size increase and control mechanisms ensure readiness for DNA replication (genetic synthesis) and post-DNA synthesis (gap 2) to ensure readiness for actual cell division. The mitotic phase or sequential cell division consists of prophase, metaphase, anaphase, and telophase. The fourth and final is the cytokinesis phase in which the cytoplasm of eukaryotic cells is divided into two identical cells [4, 5]. To guarantee the integrity of this outcome, a special group of cyclin-dependent kinases (CDKs) play crucial roles in regulating cell cycle progression and are also involved in other processes including regulation of transcription, mRNA processing, and differentiation [6, 7]. When combined with cyclins in dividing cells, stimulated CDKs regulate the sequential events of cell cycle and ensure proper cell division [6]. Cyclins belong to a family of proteins without catalytic ability, expressed at specific subcellular locations, but are able to bind to CDKs and activate the regulatory and catalytic activities [8]. The regulation of downstream proteins and specific cell cycle checkpoints at different phases of cell cycle is dictated by the cyclin-CDK interactions and combinations of those. For instance, during the G1 phase, the combination of cyclin D-CDK4 and cyclin E-CDK2 induces phosphorylation of Rb protein, subsequent activation of E2F proteins, and further expression of E2F reactive genes. These genes encode for cell cycle regulators responsible for G1/S transition. Similarly, during G2 phase, the combination of cyclin A-CDK2 and cyclin B-CDK1 prompts phosphorylation and activation of FoxM1 and recruitment of a histone deacetylase p300/Creb-binding protein that further leads to the expression of FoxM1 target genes. These genes encode for cell cycle regulators that are essential for the mitosis and effectors of the chromosomal segregation (**Figure 2**) [9].

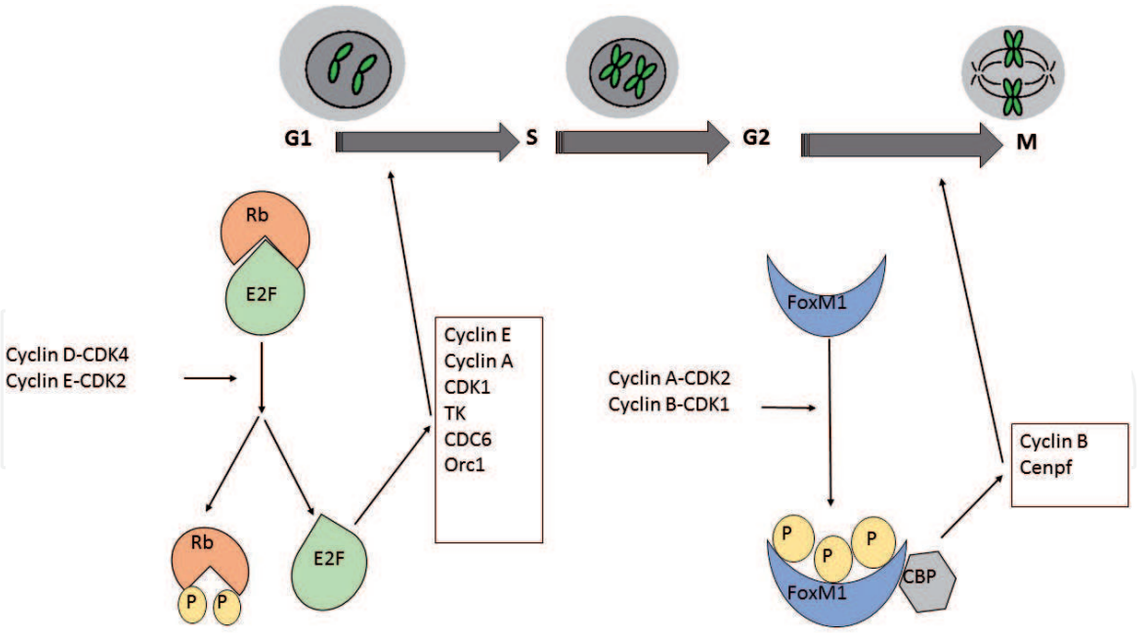

Figure 2.
Cyclin-dependent kinase (CDK) combinations control Rb/E2F- and FoxM1-induced transcription. During the G1 phase, cyclin D-CDK4 and cyclin E-CDK2 combinations disassemble Rb-E2F dimer and phosphorylate Rb, causing the activation of E2F proteins and the expression of E2F-responsive genes. The genes encode for cell cycle regulators required for G1/S transition (cyclin E, cyclin A, CDK1, TK, CDC6, and Orc1). During the G2 phase, cyclin A-CDK2 and cyclin B-CDK1 combinations phosphorylate and activate FoxM1, causing the recruitment of a histone deacetylase p300/CBP that further activates the expression of FoxM1 target genes. These genes encode for mitotic regulators (cyclin B) and chromosomal segregation effectors (Cenpf). Rb = retinoblastoma protein CDK = cyclin-dependent kinase, TK = thymidine kinase, CDC6 = components of the DNA replication machinery, Orc1 = origin recognition complex subunit 1, CBP = CREB binding protein, Cenpf = centromere protein factor.

2. Genetic mutation and types of breast cancer

Abnormal expression or change occurring in the activity of cyclin-CDK combinations leads to the loss of cell cycle control, where cells no longer follow the distinctive progression and go into a malignant formation [6]. Breast cancer is a heterogeneous disease characterized by change in morphology, invasive behavior, metastatic ability, and hormone receptor expression, leading to malignant cells multiplication in breasts with ability to spread to other parts of the body, if the condition is not treated [10, 11]. Breast cancer is the most commonly diagnosed invasive cancer in women, and second main reason of cancer-related death, after lung cancer. Common symptoms include and are not limited to thickness of breast tissues, lumps in the armpits, persistent pain through monthly cycle, pigmentation change or peeling or scaling of the skin of the breast, altered breast size and shape, inverted nipples and rash around the nipple area with a likely discharge [11]. Mutations in some genes controlling checkpoints like the cell cycle inhibitors, Rb and p53 may induce dysregulated cell cycle and so encourage tumor formation [12]. These strategic checkpoints prevent cell cycle progression till the verification of essential phase processes and nuclear repair have been completed. Other genes like BRCA, which is an abbreviation for breast cancer gene, have been found influencing the development of breast cancer. In fact, there are two types of BRCA genes, BRCA 1 and BRCA 2, and they do not cause but prevent breast cancer by repairing DNA breaks, which could encourage uncontrolled growth of tumors and cancer. Thus, BRCA genes are tumor suppressor genes. However, in some people (around 1 in 400), these tumor suppressor genes do not function properly, leading to gene

mutation. When mutated, BRCA genes can no longer carry out their function of repairing broken DNA and preventing breast cancer. Due to this genetic malfunction, mutated BRCA gene carriers are more prone to develop breast cancer even at a younger age and can equally pass this mutation down to offspring. This seems to be rare with less than 10% of diagnosed women having BRCA mutation. Individuals with the BRCA1 mutation have 55–65% chance of developing cancer before age 70, compared to a lesser portion, 45%, for individuals with the BRCA2 mutation. The BRCA1 mutation is the worse of the two and BRCA1 mutated individuals are more likely to develop a triple negative breast cancer, a hormone dependent form, more aggressive and lesser curable, with higher risk of developing second cancer after successful treatment, known as breast cancer recurrence. However, the majority of breast cancer cases can be successfully cured when detected early, even those with a BRCA1 or BRCA2 mutation [13].

There are several types of breast cancers, and ductal carcinoma in situ (DCIS) is a non-metastatic and non-invasive type that occurs in the ductal cells and this type might be highly curable. Lobular carcinoma (LCIS) is another in situ non-metastatic and non-invasive type, which occurs in cells of the milk-manufacturing lobules, but has the potential to evolve into an invasive type of breast cancer. The most common type is certainly the invasive ductal carcinoma that occurs in the ductal cells and then invades other breast areas with metastatic abilities. Similarly, the invasive lobular carcinoma starts in the lobules and has metastatic abilities; however, it is a very uncommon type of breast cancer. The breast cyst is a noncancerous (benign) type with fluid-filled sac that may be drained. This type is usually diagnosed in females who are in their 30s or 40s. Another early and noncancerous solid type is breast fibroadenoma, commonly affecting vicenarian and tricenarian women in their 20s and 30s and is characterized by the presence of a pain-free and mobile lump in the breast. Fibrocystic breast is a common noncancerous condition with a breast lump that may be altered throughout the menstrual cycle. The breast hyperplasia is characterized by the abnormal proliferation of noncancerous cells in ductal areas and may increase the risk of developing breast cancer. An atypical breast hyperplasia may develop either in ductal or lobular areas and might significantly increase the rsik of breast cancer by four to five times when compared to a healthy woman. The intraductal papilloma is a noncancerous wart-like growth within the ducts that may cause bloody fluid leakage from the nipple. Another noncancerous condition is breast adenosis that is caused by lobular expansion and has to be diligently diagnosed, as it may resemble breast cancer in some occurrences. Another difficult to diagnose type of breast cancer (as it might bear a resemblance to fibroadenoma) is phyllodes tumor, a rare and immense breast tumor that may be benign or malignant and develop around age 40. Fat necrosis may seem like breast cancer but is a lump scar tissue as a result of repairs occurring in the fat tissues of the breast. Commonly occurring in nursing mothers, mastitis is an inflammation of the breast as a result of infection accompanied by redness, pain, warmth, and swelling. Breast calcification refers to the calcium deposits in the breast and has to be diagnosed accordingly, as it may suggest something else. More and more seen is the overdevelopment of male breasts, known as gynecomastia, and it may affect men of all ages [14, 15].

3. Chemistry, pathophysiology, and staging of breast cancer

The characteristics of the environments where breast cancer develops are similar to those of any other cancer. In order to survive, cancer cells must maintain a suitable acid-base balance. As a result of extensive carbon dioxide and lactic acid production, cancer cells are constantly experiencing acid–base fluxes, which severely

affect the pH, especially intracellular pH. To maintain a suitable intracellular pH level, specialized pH-dependent transporters regulate the exchange of H^+ or HCO_3^- ions [16]. These specialized proteins are able to induce pH changes by facilitating new interactions or eliminating others [17]. Cancer cells need substantial input of energy for their ever-increasing metabolic demand. Human tumors tend to grow around blood vessels, causing extracellular acidity in tumors and outermost cells to become necrotic. The low microenvironmental oxygen tension and pH are the hallmarks of cancer [18–20]. Swiftly, tumors become poorly perfused and require extra diffusion mechanisms, and carbonic anhydrase plays essential functions in controlling extracellular pH and giving cancer cells alternatives to adjust to microenvironmental acidity and drive disease progression [16].

Although individuals with family history of breast and ovarian cancers have higher risk, both myoepithelial and epithelial cells found in the stratified epithelium of breast are understood to be able to initiate breast carcinogenesis or stem cells that give rise to them [21, 22]. Immune mechanisms aim to identify and destroy cancer cells and DNA-damaged cells. Moreover, RAS/MEK/ERK and PI3K/AKT pathways control the mechanisms of cell suicidal events. Breast cancer commonly arises due to genetic mutations and environmental factors that alter these mechanisms. Exposure of epithelial and/or stromal cells to a certain level of estrogen or adipose-derived hormones or signaling factors can promote cell proliferation and carcinogenesis in breast [23, 24]. Telomerases cease to perform chromosomal shortening roles, extensive cell replication occurs, cancer cells continue to proliferate beyond boundaries through blood and lymph systems, and form secondary tumors [25, 26].

The deepness, size, and type determine the stage of breast cancer from non-invasive to metastatic tumor [27]. Starting in confined localization, tumor initiates without evidence in neighboring cells and a well-known instance of stage 0 breast cancer is DCIS [28]. The next is the invasive stage and is characterized by two categories: stage 1A is a tumor with a diameter lesser than 2 cm and absent in lymph nodes, while stage 1B describes a tumor greater than 2 cm in diameter and present in lymph nodes [29]. Then, there are two other sub-categories where 2A designates tumor localization in axillary lymph nodes with a diameter lesser than 5 cm and 2B tumor has a diameter greater than 5 centimeters and is not in axillary lymph nodes [30]. The third stage is characterized by three sub-categories: 3A describes tumor in 4–9 axillary lymph nodes, while 3B tumor can be inflammatory or not with up to 9 axillary lymph nodal sites and is able to cause ulcer and various skin alterations including red, warm, and swollen breast skin. Stage 3C describes a tumor affecting at least 10 axillary lymph nodal sites and area below the clavicle [31]. The final and advanced stage 4 defines a metastatic tumor that has spread to other organs like lungs, bones, liver, brain, and others [32].

4. Some of the current breast cancer therapies and limitations

Breast feeding women have a lesser risk of developing breast cancer and the defensive mechanisms have not yet been identified [33]. Breast cancer treatments differ and depend on the stage, mass, site, metastatic ability or not of the condition, and the health status of the patient. Currently, the main forms of treatment for breast cancer employ surgery, radiation therapy, hormone therapy, and chemotherapeutic agents [15]. Surgery is the foremost utilized strategy for non-metastasized breast cancer and varies according to the affected tissues [34]. Lumpectomy is known as a breast-conserving surgery, where a partial mastectomy procedure is performed at initial stages of the condition and aims to save the major part of the breast by removing the affected breast part, together with limited healthy tissues

and surrounding lymph nodes. It is often complemented with other forms of treatment in order to prevent mastectomies [35]. However, some of the adverse effects are removal of healthy tissues along with the cancer, soreness, short-term inflammation, altered breast appearance, and sclerosis [36]. When not the first choice, mastectomy is often recommended whenever the disease persist after lumpectomy was not sufficient. Nevertheless, the loss of breast is usually accompanied with a profound sense of loss of a woman's self-esteem and further depression in most women [37]. Radiation therapy utilizes high-energy rays to eradicate cancer cells and highly proliferating cells, like those in nails, skin hairs, and others as well. Brachytherapy is a faster partial breast irradiation that directs radiation mostly to and around the affected cancer area, which is better than to irradiate the entire breast [38].

Estrogen and progesterone receptors play important roles in the management of breast cancer as they are used to enhance the selectivity of the treatment. Hormone-dependent treatments using estrogen receptors yield better responses than those with progesterone [39]. The anti-estrogen drugs are commonly used for breast cancer treatments. Tamoxifen had been one of the foremost of these drugs and highly recommended for women with positive estrogen receptor breast carcinoma. Tamoxifen prevents estrogen from entering into breast cancer cells and further development of the condition [40]. Although its therapeutic efficacy for breast cancer has relatively low adverse effects when compared to other anti-estrogen counterparts, this anti-estrogen drug tends to compete with estrogen for binding to estrogen receptors in breast and other organs including uterus, liver, and bones [41]. Both raloxifene and tamoxifen are recognized as selective estrogen receptor regulators and able to prevent or stimulate estrogen-like activity in different tissues by disturbing the estrogen receptors [42]. Additionally, various side effects are associated with the use of anti-estrogen agents, and tamoxifen affects venous thrombosis, cataract, endometrial cancer, menstrual disorders, and hot flushes, while raloxifen brought about lesser damages in some cases and minor danger of cataract and thromboembolism than tamoxifen [43, 44]. Chemotherapy can be used prior to surgery or postsurgery depending on the condition of the patient; it refers to the usage of medicines to eradicate rapidly proliferating and metastatic cancer cells or to minimize their development [45]. The most commonly used chemotherapeutic medicines are Docetaxel, Paclitaxel, Cisplatin, Carboplatin, Vinorelbine, Capecitabine, Liposomal doxorubicin, Cyclophosphamide, and Carboplatin, and they are associated with numerous side effects [46, 47].

5. Targeted breast cancer therapy

Sometimes, the success of treatment is hindered by drug resistance, which has emerged as a main concern for the fight against cancer. Targeted therapy uses drugs to target specific genes or proteins to manage some types of breast cancer from developing and spreading. The human epidermal growth factor receptor 2 (HER2) is a gene involved in the development of breast cancer and Herceptin is a commonly used drug to target HER2-positive breast cancer [48]. Gene therapy utilizes virus to deliver and replicate new genes into patients' cells to replace damaged genes. This approach is a very selective targeted approach for precise molecular abnormalities associated with development of breast cancer, like mutated BRCA1 and p53 genes [49, 50].

Cancer stem cells (CSCs) are potential effectors of self-renewal, proliferation, and differentiation and play crucial roles in cancer survival and recurrence [51]. The necessity for cancer stem-cell therapy for breast cancer is justified by the recognition of stem cells in normal as well as in malignant tissues of the breast. CSCs

have been identified as the source of molecular complexity of breast carcinoma in human. Thus, anti-CSC therapeutic approach would assist with prevention and management of various forms of cancer cells, including therapeutically resistant breast cancer cells by efficient targeting of breast CSC surface markers such as ESAþ, CD44þ, CD24−/low, Lineage- and ALDH1high [52, 53]. Owing to unpredictable physico-chemical properties of certain therapeutic agents in physiological environments, the exploitation of such targeted approaches, like the anti-CSC therapy, rests on the usage of suitable delivery systems. Nanomedicine offers the option of using specially designed drug-nanocarriers to integrally deliver therapeutic agents into cancer sites and CSCs niches [52]. Additionally, this option offers additional advantages including the designing of therapeutic systems directed towards pump-mediated drug resistant (ATP-driven) while having limited side effects on healthy cells and normal stem cells [52].

6. Photodynamic therapy for breast cancer

Photodynamic therapy (PDT) is a minimally invasive and clinically approved procedure for eradicating designated malignant cells with precise light activation of a non-toxic photochemotherapeutic agent, known as photosensitizer (PS). PDT is a

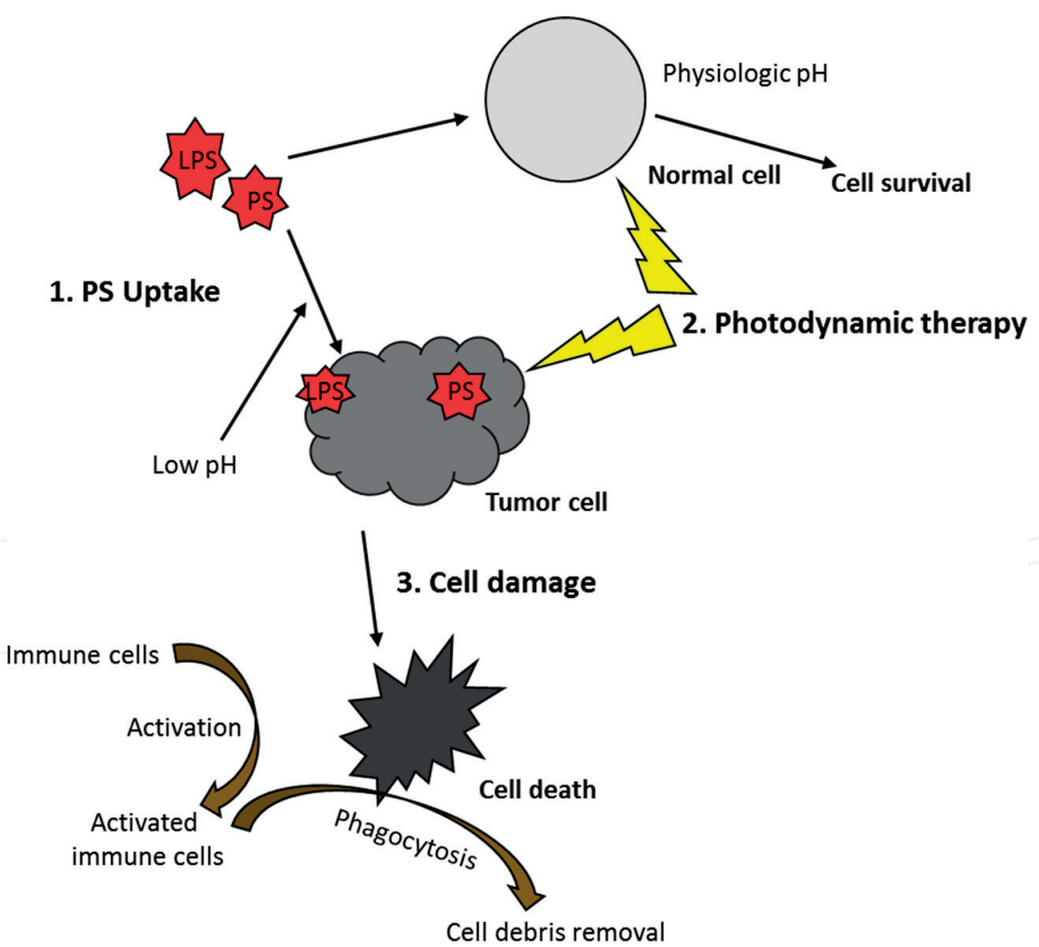

Figure 3.
Photodynamic cancer therapy actions: (1) administration and uptake of a photosensitizer (PS) and ligand-conjugated PS (LPS), which accumulate into either tumor cells/surrounding. The lower extracellular pH improves PS uptake by tumor cells. Conjugation of PS with specific ligands helps to target the vasculature surrounding breast tumor cells. (2) light irradiation at a wavelength matching the absorption properties of PS and (3) light activation of PS/LPS and induction of cell death. Immuno-activation stimulates phagocytosis of PDT-damaged tumor cells and cell removal. PDT may mediate an immune response causing tumor cell death at distant sites.

sequential procedure involving three main steps: (1) administration of a PS, which is internalized into either tumor cells or immediate vasculature; (2) local irradiation at a wavelength matching the absorbance peak of the PS; and (3) light activation of the PS, which mediates energy transfer cascades, generation of cytotoxic reactive oxygen species, and subsequent cell death [54, 55]. PDT is a selective approach and capable of using the specific traits of the tumor microenvironment of breast cancer. The low pH in tumor microenvironment enhances PS uptake into cells and this uptake can be further improved by conjugating PS to endothelial cell (EC)-specific ligands and target vasculature surrounding tumor (**Figure 3**). The effect of PDT is derived from three mechanisms: direct cytotoxic effects on tumor cells, indirect damage to tumor vasculature, and induction of immune responses [56]. Both parenchymal (tumor) and stromal (non-tumor) populations coexist in the tumor microenvironment, making it different from those of normal cells. There is a strong interrelation between these two populations within the tumor microenvironment as the ECs (which are stromal) are essential in providing the required hormones, oxygen, and other essential nutrients to both populations, while tumor cells develop and maintain the endothelial angiogenesis [57, 58]. PDT dosimetry depends on the complexity of the parenchymal cells and should take into consideration the stromal cells, so as to only attain complete tumor eradication [57]. Hence, the effective use of ligands for targeted PDT for breast cancer by conjugating factor VII (fVII) (ligand) with verteporfin or chlorin e6 (PSs) to exclusively prompt cell death mechanisms in the breast cancer cell population [59, 60]. Such approaches were efficient to target neovasculature and drug-resistant breast tumors, but paved the way for the improvement of future targeted PDT complexes [59–61]. The high recurrence and poor prognosis of breast cancer are directly related to the overexpression of certain receptors in breast cancer cells, such as estradiol receptors, the human epidermal growth factor receptor 2, gonadotropin-releasing hormone receptors, and tisular factor VII receptors [62]. They are appropriate sites for receptor-targeting approaches and beneficial for development of better PDT agents.

7. New photosensitizer-mediated PDT for breast cancer

The uptake and retention of PS by neoplastic cells is a decisive event in the progression and success of PDT. In its ground state, the singlet PS possesses two electrons with opposed spins. When irradiated at appropriate quantum energy (wavelength), the PS absorbs a photon and one of its electrons is excited into a higher energy level, which lasts for a few nanoseconds. The excited and unstable PS may lose the excess energy by fluorescing (light emission), internal conversion (heat emission), or undergoing intersystem crossing to reach a stable and excited triplet state with parallel spins and longer lifespan (microseconds). Due to the quantum selection rules, the triplet excited PS can interact and transfer its energy to molecular oxygen to form singlet oxygen (type II reaction, more common) or undergo electron transfer reactions to form reactive oxygen species (type I reaction) before returning to its ground state. The most common PSs are porphyrins, chlorins, bacteriochlorins, and phthalocyanines, they all possess tetrapyrrolic structures and many are clinically used. Phenothiazine, squaraine, and boron-dipyrromethene are major synthetic dyes, while hypericin, riboflavin, and curcumin are natural PSs. More and more PSs are being conjugated to antibodies, peptides, proteins, and other ligands for targeted PDT. Nanoparticles are multifunctional materials with various medical applications and they are mostly used in PDT to deliver PSs to the tumor-targeted sites, and recently to increase light penetration into tissue [63]. The increased use of nanoparticles as drug carriers significantly reduces the risk

of non-specific accumulation and adverse effects in normal cells, while increases neoplastic targeting and therapeutic efficiency. Micelles, dendrimers, liposomes, and nanotubes are among the commonly used carrier systems in PDT. They do so by utilizing the enhanced permeability and retention effect and the acidic conditions created around the tumor microenvironment due to the high metabolic activities, developing porous endothelial junction and neovascularization [64, 65].

For the last two decades, extensive effort has been directed to the development of new PSs from first to third, and from simple to more complex PS entities for enhancing PDT outcomes in neoplastic-bearing animals and patients. Currently, third-generation PSs are under development in order to improve the PDT outcomes with two main research focuses, namely gene engineering-induced PDT and nanomedicine in PDT [66]. These PSs are synthesized based on specific cancerous characteristics like the Warburg effects, a recognized phenomenon arising due to the fact that cancer cells consume higher levels of glucose than normal cells. So, sugar-conjugated chlorin (glucose-chlorin) PSs which were synthesized showed improved cancer cell selective accumulation, induced immunogenic cell damage, and stronger antitumor effects than second-generation PSs. Such sugar-conjugated PSs induce very robust antitumor effects by targeting sugar receptors on the surface of cancer cells and tumor-associated macrophages in stromal cancer cells [67]. Other third-generation nanomaterial-mediated PSs like Chlorin E6 have shown strong ROS generation through formation of ion complexes. They are able to be encapsulated in gold nanoparticles as vesicles to achieve better penetration and are used for both diagnosis and treatment of cancer due to their strong absorption properties in the near-infrared range of 650–800 nm [68]. The cancer cell specificity and selectivity of PDT were inadequate with first- and second-generation PSs. With the development of third-generation PSs, PDT has become significantly beneficial for enhancing tumor targeting, tissue penetration depth, and therapeutic efficacy.

8. Conclusions

Breasts are well-developed organs in females for the production of milk during lactation. A special group of CDKs are required for proper breast cell cycle and functioning at all times. When the cell cycle is no longer under control, breast cancer begins to develop and is characterized by several breast morphological alternations, as well as chemical and pathophysiological changes. Various means of breast treatments are available and the targeted options seem to provide better therapeutic value than conventional therapies. PDT has emerged as an effective and potent breast cancer treatment; however, it is highly dependent on the development of more effective PSs. Thus, the development of new PSs is encouraged and PS complexes containing nanoparticles are one of the most recent developments to enhance delivery into tumor sites and treatment efficiency and decrease the adverse effects, which characterize the nontargeted therapies.

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Conflict of interest

The authors report no conflict of interest in this work.

Future directives

In relation to PDT being utilized as an alternative treatment therapy for breast cancer, further research is required for the development of targeted third-generation PSs as drug carriers in order to enhance the effectiveness of this treatment, as well as for investigating the upregulation of BRCA1 and BRCA2 breast cancer tumor suppressor genes in order to prevent changes in genetic materials and so their eradication.

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