

Review Article

Targeted Photodynamic Therapy: A Novel Approach to Abolition of Human Cancer Stem Cells

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Cancer is a global burden that has prompted extensive research into prevention and treatment, over many decades. Scientific studies have shown that subset of cells within a tumour, known as cancer stem cells (CSCs), are responsible for tumourigenesis, metastasis, drug resistance, and recurrences. CSCs have characteristic features of enhanced self-renewal, proliferation, and limited but multidirectional differentiation capacity. The discovery of CSCs has initiated extensive research into novel cancer treatment regimes. Evidence indicates that CSCs are resistant to conventional chemo- and radiation therapy leading to treatment failures, cancer metastasis, secondary cancer formation, and relapse. Because of the observed phenomena in the course of cancer prognosis, a need for treatment modalities targeting CSCs is important. Photodynamic therapy (PDT) is a clinically approved, minimally invasive, therapeutic procedure that can exert a selective cytotoxic activity toward cancerous cells while reducing toxicity to normal cells. It uses a photosensitizer (PS) that becomes excited when subjected to light at a specific wavelength, and the PS forms reactive oxygen species (ROS) killing malignant cells. Currently, PDT is being investigated as a target specific treatment for CSCs by the addition of carrier molecules and antibody conjugates bound to the PS. Targeted PDT (TPDT) may be able to not only eradicate the tumour mass but kill CSCs as well.

1. Introduction

Cancer is a global burden, affecting people from all socioeconomic backgrounds, in all geographic regions of the world. This disease is responsible for 1 in 7 deaths worldwide and is predicted to affect 21.6 million people and 13 million deaths by the year 2030 [1]. To effectively combat cancer in modern medicine, much attention is being directed toward cancer prevention and treatment, while concurrently investigating causes of cancer and cancer dynamics [2]. Cancer is caused by a genetic mutation, on a cellular level, where errors in DNA instructions lead to cells evading normal cell cycle functions specifically cell cycle arrest [3]. Along with cancer cells evading cell cycle arrest cancer can have the ability to metastasize and recur even after conventional therapy. Recent evidence has shown that a subset of cells called cancer stem cells (CSCs) can initiate tumour formation [4]. This small subpopulation of cells resides within the tissue mass and has characteristics that include self-renewal, differentiation, and

tumourigenicity when transplanted into an animal host. A number of cell surface markers such as CD44, CD24, and CD133 are often used to identify and enrich CSCs. The clinical relevance of CSCs has been strengthened by emerging evidence demonstrating that CSCs are resistant to conventional chemotherapy and radiation treatment and that CSCs are very likely to be the origin of cancer metastasis. CSCs are believed to be an important target for novel anticancer drug discovery [5].

Photodynamic therapy (PDT) is a well-documented therapy that has emerged as an effective treatment modality of cancer [6]. It involves the use of a nontoxic dye, or photosensitizer (PS), which is effectively activated by light at a specific wavelength [7]. This then generates singlet oxygen, or other reactive oxygen species (ROS), causing degradation of cellular components by damaging different biomolecules including proteins, DNA, and lipids leading to cancer cell destruction and death [8, 9]. According to Abrahamse et al. (2016) optimum standards of a good PS include being a single

pure compound, having a strong absorption peak in the red to near infrared spectral region (between 650 and 800 nm), possessing a substantial triplet quantum yield, and having no dark toxicity and a relatively rapid clearance rate from normal tissues [6]. Along with a PS having optimum standards, what distinguishes PDT from conventional therapies such as chemotherapy is its affinity for malignant cells that results in selective cytotoxic effects, killing cancer cells with minimal effects on normal cells, unlike chemotherapy and genotoxic drugs that destroy the cancer cells and its surrounding normal tissue [10].

PDT can further be enhanced by making it target definitive. This can be done with the addition of nanoparticles and monoclonal antibodies to enhance tumour selectivity, PS absorption, and cell specificity. Nanoparticles (NPs) are currently being used for tumour imaging *in vivo*, profiling of cancer biomarkers, and targeted drug delivery [11]. They have also been used to increase solubility and improve the transcytosis of PSs through membranes and endothelial barriers. The combined use of NPs and monoclonal antibodies concurrently has potential for a very high therapeutic efficacy. This review will focus on the aspect of the stem cell theory, CSCs, and the potential role of targeted PDT using nanoparticles and monoclonal antibodies.

2. Cancer

The National Cancer Institute defines cancer as a collection of diseases in which cells of the body begin to grow uncontrollably and spread to other tissues. Although there are different theories of how cancer develops and many derangements involved, they are all attributed to DNA damage that alters the normal cellular growth pathways. Mutations in genes that control normal cellular functions result in a dysregulated growth of cells, followed by uncontrolled replication of cells that finally outgrow normal cells to form a tumour mass [12]. Biologically, cancer is a genetic disease but not, with a few exceptions, inheritable. Only a few cases where mutations are inherited as a single gene disorder can cause cancer.

2.1. Molecular Biology of Cancer. Since the beginning of the era of oncology, a multitude of research has been done to understand the molecular mechanisms of cancer. Hippocrates was among the first scientists to describe the different forms of tumours and called them “cancer” that described the crablike shape of the tumour invading normal tissue. Research is still ongoing in hopes to elucidate on cancer biology at the molecular level and new discoveries are documented on regularly [13].

A deep understanding of the molecular mechanisms of cancer is, however, essential for the development of novel therapeutic modalities. As described previously, cancer is a result of dysregulated cell growth. In a normal cell, all cellular processes from cell birth, growth, proliferation, division, and death respond to stimulatory or inhibitory signals transmitted from regulatory genes and signalling molecules, both intracellularly and extracellularly [13, 14]. Thus, the cell cycle is an extensively regulated process. In addition to the key proteins in cell cycle regulation, Cyclins, and Cyclin

TABLE 1: Characteristics of cancer cells.

Impairment of cell cycle control
Replicative senescence
Accumulated mutations
Dedifferentiation
Lack of Contact inhibition
Formation of blood vessel network
Invasiveness
Metastasis

Dependent Kinases, there are genes that normally stimulate cell growth called proto-oncogenes which when mutated become dominant-acting stimulatory genes that cause cancer. These cancer causing genes are, therefore, termed oncogenes. A cell also has inhibitory genes that suppress cell growth, called tumour-suppressor genes, which code for regulatory proteins, the most common of which are p53 and the Retinoblastoma [14]. When a cell suffers a dysfunction of these proteins, unregulated growth issues occur. Mutations in regulatory genes may result in the activation of oncogenes and downregulation of genes that suppress tumour formation; this alongside other mutations inactivating genes responsible for maintaining genomic integrity initiates cancer [15].

2.2. Characteristics of Cancer Cells. Biologically, cells in the same tumour differ in virtually all phenotypic features. Cancer cells, at different levels of development arising from the same clone of cells, have variations in morphology, gene expression, metabolism, motility, proliferative, immunogenic, and metastatic potential. Cancer begins at a cellular level in a multistep process involving the activation of cells that produce cancer cells commonly referred to as Cancer Stem Cells (CSCs) [16, 17]. These cells lose their cellular features of terminal differentiation (dedifferentiation) and increase in fraction of tissue outgrowing normal cells alongside faulty tissue repair. Finally, for a cancer cell to proliferate it overrides the process of replicative senescence to become immortal and obtains a supply of nutrients and oxygen that maintains the high rate of proliferation. This phenomenon is achieved by the cells ability to secrete a protein, called vascular endothelial growth factor in response to hypoxia. A cancer cell also secretes its own hormones and signal transduction molecules [14]. The molecules that are not expressed in normal cells are a characteristic feature that makes it possible to target cancer cells for drug delivery. These and other characteristics of cancer cells are summarised in Table 1.

3. Cancer Stem Cells

3.1. The CSC Hypothesis. The cancer stem cell hypothesis is grounded by the following conditions: a tumour is defined, on a cellular level, by uncontrolled proliferation caused by the addition of random mutations in critical genes that control cell growth. Although gene mutations cause cancer, it has been reported that malignancy can be caused by a

TABLE 2: Specific CSC markers and function [adapted from [25]].

CSC	Marker	Function
Glioma	CD 49f	Cell adhesion
Ovary	CD 117	SC-factor receptor
Liver	CD 13	Kidney disease marker
Lung	CD 56	Cell adhesion
Renal	CD105	Co-receptor TGF- β
Neuroblastoma	CD 114	Colony stimulating factor 3 receptor
Gastric	CD 54	Cell adhesion
Leukaemia	TIM-3	Immune checkpoint receptor
	CD 96	T-cell specific receptor
	CD 9	Cell adhesion
Breast	CD 55	Complement inhibitor
Melanoma	CD 20	B-cell lineage
	ABCB 5	ABC transporter

subpopulation (SP) of cells found within the tumour, called CSCs, thought to be responsible for tumorigenesis, tumour maintenance, tumour spread, and tumour relapse [18]. Adult stem cells (ASCs) are responsible for tissue renewal and repair. Stem cell characteristics include their ability for self-renewal without loss of proliferation capacity; they are per-durable and drug resistant and capable of differentiating into any type of adult cell in the body due to the influence of micro environmental and some other factors. Asymmetric division allows for stem cell (SC) survival giving one daughter cell the ability for self-renewal and the other differentiation and proliferation capacity. Cancer stem cells share characteristics similar to normal SCs and express SC representing markers [19]. These CSCs make up as few as 1% of the cells in a tumour, making them difficult to detect and study. Like normal SCs, CSCs have a number of properties permitting them to survive traditional cancer chemotherapy and radiation therapy. These cells express high levels of ATP-binding cassette drug transporters, providing for a level of resistance, are relatively quiescent, and have higher levels of DNA repair and a lowered ability to enter apoptosis [20]. The mechanism by which CSCs originate is (either) by normal SCs that underwent genetic and epigenetic changes and (or) by dedifferentiation from somatic tumour cells [19].

3.2. CSC Identification and Enrichment. The first evidence of CSCs was seen in a study conducted on acute myeloid leukaemia in 1994. This SP of cells was transplanted into immunocompromised mice. The cells were enriched using surface markers (CD34+/CD38-) and were identified as tumour initiating [21]. Cancer stem cells have been identified in solid tumours, including breast, brain, colon, pancreas, lung, prostate, melanoma, and glioblastoma, all capable of inducing malignancy in nonobese diabetic/severe combined immune deficient (NOD/SCID) mice [22, 23]. A variety of cell surface markers have been used to isolate and enrich CSCs. The expressions of CSC surface markers are tissue type and tumour type-specific. Enhanced identification and targeting of CSCs involve the use of multiple and a combination of surface markers [24]. Kim et al. (2017) conducted a study

where 40 CSC surface markers were classified into 3 different categories, depending on their expression on human embryonic SCs, ASCs, and normal tissue cells. More than 80% of the markers were shown not to be expressed on normal tissue cells, making the CSC surface markers useful therapeutic targets against CSCs due to their low cross-reactivity to normal tissue cells [25]. The similarity between normal SC and CSC surface markers suggests that CSCs predominantly originate from normal SCs via the accumulation of epigenetic and genetic alterations [26]. Table 2 highlights some of the CSC markers, and the markers are specific to the type of CSC, as well as their function.

3.3. CSCs and Conventional Cancer Therapy. The role CSCs play in cancer relapse and metastasis is seen in their ability to be chemo- and/or radiation-therapy resistant (Figure 1). This has been proven by different researchers, whereby the proportion of cell SPs was examined before and after chemotherapy. The SP consisting of CSCs had a significant increase in their mean value after treatment [5]. However, controversial results have also been reported, where two patients being treated for CSC therapy resistance were assessed. The radiation resistance of breast CSCs was tested using early passage, patient-derived xenografts from two separate patients. The CD44+CD24-/low Lineage- and ALDH+ breast CSCs from one patient showed depletion of the SP of cells after radiation therapy as well as decreased tumour sphere frequency and tumorigenic capacity. In contrast, CSCs from the other patient displayed enrichment after irradiation and resistance to therapy [27].

4. Photodynamic Therapy

Photodynamic therapy is a well-studied therapy for cancer. It uses PSs (nontoxic dyes) that are activated by absorption of visible light to initially form the excited singlet state, followed by transition to the long-lived excited triplet state. This triplet state can undergo photochemical reactions, in the presence of oxygen, to form ROS (including singlet oxygen) that can destroy cancer cells [6]. The therapeutic effect of PSs lies in

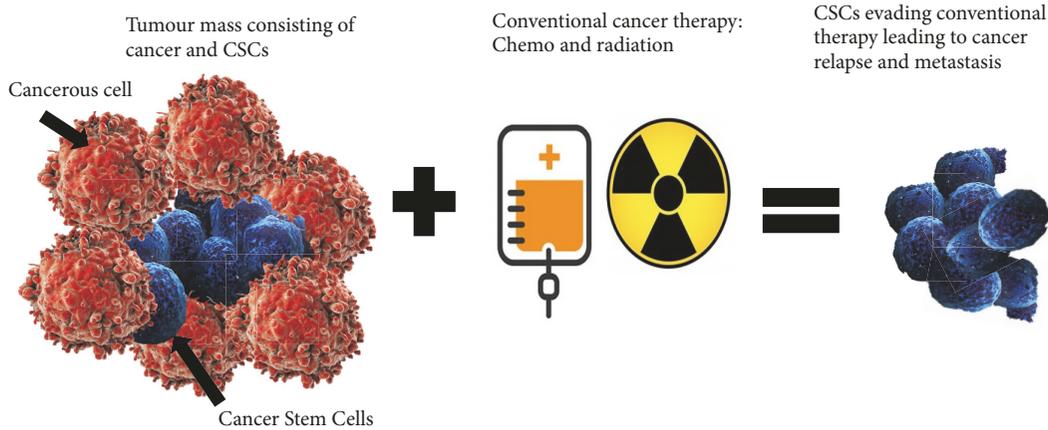


FIGURE 1: CSCs and conventional cancer therapy. Chemo- and radiation therapy fail to eradicate CSCs, which can lead to cancer relapse and metastasis.

their binding capacity, as they preferentially bind to intracellular organelles causing photo-oxidative damage to proteins and lipids that reside within a few nanometres of the PS binding sites [28]. Selective cell destruction of PDT is achieved through its enhanced permeability retention (EPR), seen in malignant cells, minimizing destruction of noncancerous tissue [29]. Other theories document localization to increased expression of certain receptors on tumour cells, decreased intratumoural pH, or tumour-associated macrophages that phagocytise PS molecules [30]. Depending on the structural characteristics of the PS it will be localized in different organelles. It has been shown that overall charge, charge distribution, lipophilicity, and overall structure predominantly determine cellular uptake and subcellular localization of a PS and ultimately determine its therapeutic effect [31].

4.1. PDT and Cancer. Photodynamic therapy proves to be operative as an anticancer treatment as well as improving patient survival. Efficacy is seen when PDT is part of a multimodal approach and is used as the first-line treatment for premalignant or early disease and as stand-alone palliative treatment. Even though PDT shows great potential, there are still some limitations that prevent a firm position for PDT in the standard care regimen of cancer [21]. A drawback commonly seen is decreased efficacy of PDT for larger lesions, due to inadequate tissue penetration of light or PS [32]. Besides larger lesions, PDT is also not indicated for metastasizing tumours. Metastasis remains one of the largest challenges in cancer therapy and PDT is no exception. Tumour recurrence is often reported where inadequate tumour eradication is noted. This is said to be due to insufficient penetration, but also the presence of PDT resistant tumour tissues [33]. The limitations of PDT mentioned above can be ascribed to CSCs having characteristics significant to PDT evasion, such as metastasis and drug evasion through their multidrug efflux pumps. This has been proven in a study conducted by Morgan et al. (2010), where a SP of cells containing the ATP-dependent transporter ABCG2 gene, a multidrug resistant pump, was responsible for initiating tumour regrowth after PDT treatment. The ABCG2 may lower intracellular levels of

substrate PS below the threshold for cell death in tumours treated by PDT, leaving resistant cells to repopulate the tumour [34]. Hence the need to revolutionise PDT by making it more target specific.

4.2. Targeted Photodynamic Therapy Using Immunoconjugates and Carrier Molecules. In cell biology, the nucleus is shown to be the most hypersensitive intracellular organelle and hence therapies targeting the nucleus tend to be more effective than those that are limited to the cytoplasm [35]. To achieve a targeted drug delivery system, suitably engineered biomolecules have been the field of focus for oncology researchers. A cell targeting biomolecule can be synthesized by combining two or more particles each having specific functions to target biological components of living systems, including antigens and molecules inside, or on the surface of cells.

Studies have been focused on developing antibody-directed phototherapy (ADP), where antibody conjugation is used to deliver PSs to the tumour via tumour-associated surface markers. Targeting improves both specificity and efficiency and overcomes some of the current limitations of nontargeted PDT. The PS, when passing into the tumour microenvironment, can diffuse into cells or reside in the extracellular/cell surface environment depending on their physical properties. This in turn may also depend on the antibody. Photosensitizers that are hydrophobic in nature may be able to cross cellular membranes directly along their concentration gradient, and PS-drugs that have associated with lipid binding proteins such as low-density lipoprotein or human serum albumin can get taken up, specifically via cell surface receptors. Antibody-directed phototherapy refines this receptor delivery by using antibodies (Abs) to deliver PS-drugs to cell surface markers overexpressed on tumour cells; these can then specifically induce ADP-drug internalisation [36]. This theory was proven by Vrouenraets et al., where the PS aluminium (III) phthalocyanine tetrasulfonate [AlPc(SO₃H)₄] a hydrophilic compound was used. This PS in its free form does not reach the critical intracellular target, making it ineffective. A monoclonal antibody was conjugated to the PS and had shown preservation of integrity

and immunoreactivity and full stability [37]. Internalisation of this ADP-drug showed increased cytotoxicity and selective tumour targeting making it an ideal approach to enhance PDT. Another form of ADP is Near Infrared-Photoimmunotherapy (NIR-PIT), which is cancer therapy utilizing an antibody-photoabsorber conjugate (APC) and specifically near infrared light (NIR-light) to activate the PS. The significance of using a PS that is activated by NIR is the properties of the light being harmless to surrounding normal tissue and its penetration depth of 1-2 cm, making it specifically useful on surface tumours [38]. This treatment also exploits the overexpression of specific antigens on a variety of cancer cells, such as mesothelin. The Ab directed against mesothelin (hYP218) shows a high binding affinity between the Ab and antigen pair, supporting highly selective cell killing when applied as an ADP. A study that demonstrated the use of NIR-PIT was conducted by Nagaya et al. (2016), where they used a PS (IR700) conjugated to hYP218 on an epidermoid carcinoma cell line. The results showed high tumour accumulation and a high tumour-background ratio as well as a significant decrease in cancer cell survival when compared to their controls [39]. Another study that evaluated the use of NIR-PIT *in vivo* was conducted by Mitsunaga et al. (2011), where they conjugated IR700 to epidermal growth factor (EGF) receptors. This form of molecular-targeted cancer therapy showed tumour shrinkage, where cells expressing the EGF showed membrane damage leading to tumour cell death [40]. The results obtained from the studies indicate that ADP whether it be internal or external targeting using an Ab directed at specific antigens expressed by cancer cells can successfully be implemented as a method for advancing PDT.

Along with ADP, the anticancer response of a PS can further be enhanced using a carrier molecule. Carrier molecules in the form of nanoparticles (NPs) can accumulate in a tumour because of the well-known enhanced permeability retention (EPR) effect. These molecules can be adapted specifically to their application by changing its composition that will enable receptor targeting through overexpression of surface markers on the malignant cells, and they can enhance photon absorption and improve singlet oxygen by the surface plasmon resonance effect specifically gold nanoparticles [41], which can lead to increased ROS and cancer cell destruction. Biodegradable and nonbiodegradable NPs can be used in this application. Biodegradable NPs degrade in their biological environment through a hydrolytic process, releasing the PS.

Using a NP that is internalised by the cell has an advantage over external NPs loaded with PSs. It can be said that the photoactivity of a PS loaded NP depends on its photochemical and cell penetrating properties; furthermore the NP activity *in vivo* is governed by pharmacokinetics and tissue distribution. Extravasation of the NP is dependent on its size, also affecting photodynamic activity. A smaller NP has greater photodynamic effect and clears out faster from the bloodstream. Nonbiodegradable NPs have the advantage of actively delivering singlet oxygen. This can be achieved externally through membrane contact, as well as internalisation through its cell penetrating properties giving photosensitivity to the targeted tumour tissue. They have

enhanced particle residence time allowing for the photo action to be monitored over time. Nonbiodegradable NPs also have the following advantages over biodegradable NPs: they are stable in fluctuating pH and temperature and they are easily manipulated to specificities during development, evading bacterial contamination and they allow for PS retention and singlet oxygen diffusion due to its pore size [41].

Figure 2 graphically represents the advantages of using multicomponent photosensitizing molecules and their different roles in TPDT.

In a study by Stuchinskaya et al., a 4-component photosensitizing compound composed of phthalocyanine PS, an antibody (anti-HER2 monoclonal Ab), polyethylene glycol and an Au-NP, was used as a potential drug for targeted photodynamic cancer therapy. This multicomponent drug proved to be more stable toward aggregation and efficiently produced cytotoxic singlet oxygen under irradiation with visible red light. This study showed that the coupling of PSs, NPs, and antibodies in one biomolecule selectively targeted breast cancer cells that showed overexpression of HER2 EGF cell surface receptor [42].

A study conducted on mice for central- and peripheral-type early-stage lung cancer using tissue factor to improve the selectivity and effectiveness of nontargeted PDT (ntPDT) showed that factor VII-targeted PDT (fVII-TPDT) using fVII-Sn(IV) chlorin e6 Dihydroxide Trisodium Salt significantly enhanced (up to 25-fold) the *in vitro* effect, destroying A549 and H460 lung cancer cells via the rapid induction of apoptosis and necrosis. *In vivo* administration of fVII-TPDT significantly inhibited or eliminated subcutaneous A549 and H460 tumour xenografts in an athymic nude mouse model without any obvious side effects [43].

Work conducted by Yu et al. [44] using an effective PS, methylene blue (MB), combined with Au-NPs, was prepared using an intermolecular interaction between a polystyrene-alt-maleic acid layer on the Au-NPs and MB. The Au@polymer/MB NPs produced a high quantum yield of singlet oxygen molecules, 50% more than that of free MB, and they were then excited by laser with a wavelength of 660 nm, having little to no dark toxicity. Furthermore, transferrin was conjugated on the Au@polymer/MB NPs via an EDC/NHS reaction to enhance the selectivity to HeLa cells compared to 3T3 fibroblasts. With a hand-held single laser treatment (32 mW/cm²) for 4 min, the new Au@polymer/MB-Tf NPs showed a 2-fold enhancement of PDT efficiency toward HeLa cells over the use of free MB at 4 times dosage. Biological experiments showed that the HeLa cells reacted well with Au@polymer/MB-Tf NPs and PDT was achieved leading to apoptosis.

One of the first nanoplateforms to be applied in drug delivery systems are liposomes. Their ability lies within their containment of hydrophilic drugs in their aqueous core and hydrophobic agents within their lipid bilayers, making them efficient delivery vehicles. 5-Aminolevulinic acid (ALA) prodrugs for PDT were encapsulated in dipalmitoyl-phosphatidyl choline-based liposomes. *In vitro* experiments demonstrated an increased uptake of the conjugated molecule into human cholangiocarcinoma HuCC-T1 cells

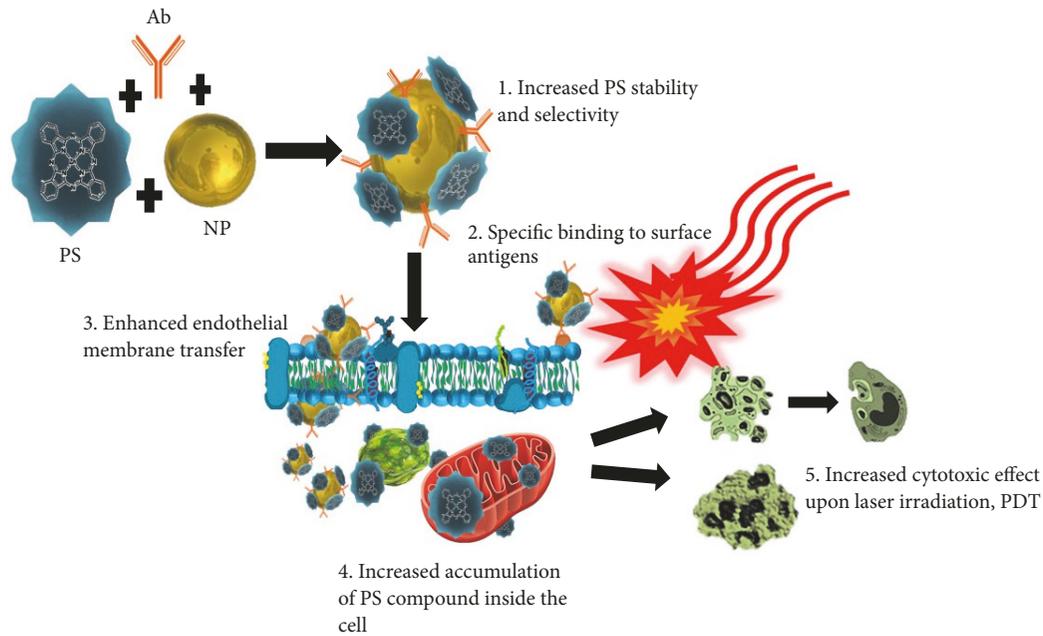


FIGURE 2: Advantages of using multicomponent photosensitizing molecules and their different roles in TPDT: (1) Conjugating a PS to NPs and antibodies increases its stability in the circulation and tumour selectivity. (2) Antibodies recognise specific antigens on the surface of cells enabling specific binding. (3) Nanoparticles enhance endothelial membrane by increasing solubility. (4) Because of increased solubility, there is maximum absorption resulting in efficient accumulation of photosensitizer inside the cancer cell. (5) Ultimately, there is increased cytotoxic effect in PDT.

compared to ALA alone having an increased photocytotoxic effect [45]. Magnetoliposomes (MLs) loaded with zinc phthalocyanine (ZnPc)/cucurbituril (CB) complexes (CB:ZnPc-MLs) were synthesized for TPDT and magnetohyperthermia in malignant melanoma cells. Significant reduction in cell viability was observed with melanoma cells treated with CB: ZnPc-MLs after application of both 670 nm light and AC magnetic field. The combined PDT and magnetohyperthermia by CB:ZnPcMLs were much more effective than each therapy alone [46].

In a study conducted by Governatore et al., they explored the use of ADP constructed from mAbs targeted against colorectal cancer antigens, to increase the selectivity of the PS for tumour over normal tissue. The PS chlorin e6 (ce6) was conjugated to anticolon cancer monoclonal antibody 17.1A. Polylysine linkers bearing several ce6 molecules were covalently attached in a site-specific manner to partially reduced IgG molecules, which allowed photoimmunoconjugates to bear either cationic or anionic charges. The conjugates retained immunoreactivity. The cationic photoimmunoconjugate delivered 4 times more ce6 to the cells than the anionic photoimmunoconjugate, and both 17.1A conjugates showed, in comparison to nonspecific rabbit IgG conjugates, selectivity for antigen positive target cells. Illumination with only 3 J cm^{-2} of 666 nm light reduced the cell viability over 90% for the cationic 17.1A conjugate and by 73% for the anionic 17.1A conjugate after incubation with $1 \mu\text{M}$ ce6 equivalent of the respective conjugates. By contrast, $1 \mu\text{M}$ free ce6 gave only a 35% reduction in viability [47].

The results of this study strongly suggest the significance of using NPs and antibodies in TPDT.

Table 3 is a representation of where targeted therapy through conjugation of NPs or antibodies has advanced conventional cancer therapies.

This technology can be applied to CSCs as well, allowing for not only the cytotoxicity of the tumour but the SP of cells (CSCs) residing within it, sparing side effects in surrounding normal tissues. A representation of the above mentioned therapy is illustrated in Figure 3.

5. Conclusion

Conclusive evidence indicates that CSCs play the major roles in therapeutic resistance due to their significant characteristics of self-renewal, drug resistance, differentiation, and metastasis. Other studies also suggest that the proportion of CSCs within a tumour may correlate with the severity of the cancer. Because CSCs are able to evade the effects of conventional therapies there is, therefore, a need for targeted therapies with the purpose of enhancing patient survival by minimizing cancer recurrence, side effects, and metastasis. Scientific evidence suggests that improved cancer treatment and targeted therapies are expected to yield the highest cure rates. However, current methods are limited by their low sensitivity to early disease and a lack of specificity for targeted cell killing, as well as therapy resistance due to CSCs. PDT using targeted drug delivery systems comprised of PSs coupled to nanoparticles and monoclonal antibodies has potential to successfully treat cancer. Antibodies can assist in the accurate detection of tumour cells and provide increased PS accumulation in CSCs, along with nanoparticles that can increase EPR and cellular uptake, making TPDT

TABLE 3: Cancer and TPDT.

Cancer	TPDT	Reference
Breast Cancer	Phthalocyanine conjugated to anti-HER2 monoclonal Ab, polyethylene glycol and Au-NP	[42]
Lung Cancer	Sn(IV) Chlorin e6 Dihydroxide Trisodium Salt conjugated to factor VII	[43]
Cervical Cancer	Methylene Blue conjugated to Au-NPs and Transferrin	[44]
Cholangiocarcinoma (Bile Duct Cancer)	5-Aminolevulinic acid conjugated to dipalmitoyl-phosphatidyl choline-based liposomes	[45]
Melanoma	zinc phthalocyanine (ZnPc)/cucurbituril (CB) conjugated to Magnetoliposomes	[46]
Colon Cancer	chlorine6 (ce6) conjugated to anti-colon cancer monoclonal antibody 17.1A	[47]

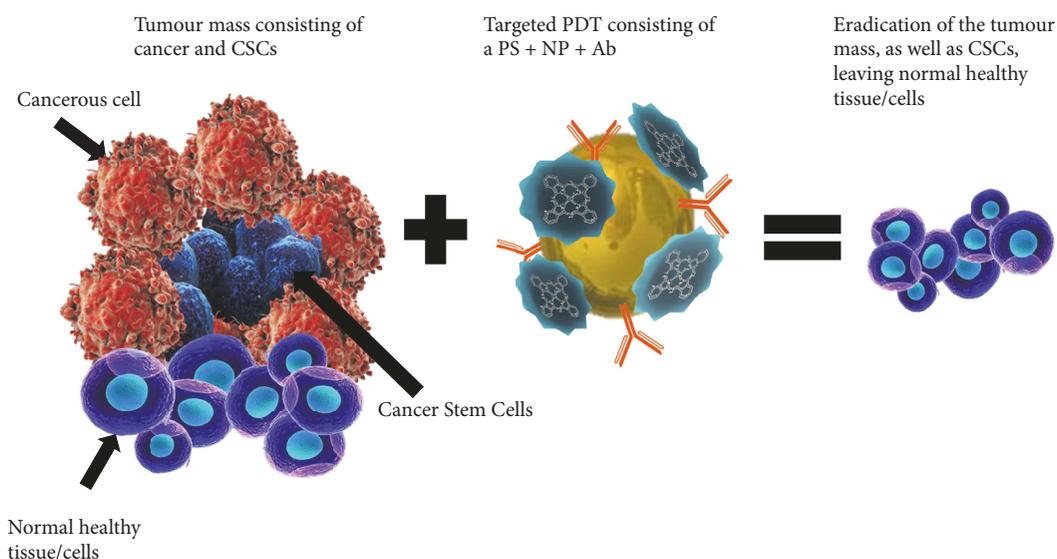


FIGURE 3: CSCs and targeted PDT using antibodies and nanoparticles. TPDT targeting cancer as well as CSCs, eradicating the entire tumour that advocates for normal healthy tissue growth.

a study of interest due to its therapeutic enhancements including efficacy, specificity, marginal toxicity to normal cells, biocompatibility, and minimal side effects.

Conflicts of Interest

The authors indicate no potential conflicts of interest.

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