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The role of quantum dots in enhancing the therapeutic targeting of cancer stem cells

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In recent years, cancer stem cells have emerged as an interesting field in oncology due to their metastatic and resistance potential to chemotherapy and radiation therapy, thus resulting in the resurfacing of cancer even after multiple treatment attempts. The interest in these cells aims to address the key challenges associated with cancer treatments and to offer insights that may aid in better understanding the biology of cancer, with the possibility of introducing advanced or novel treatment methods. Conventional treatments often fail to eradicate the cancer stem cells, which then results in the resurfacing of this gruesome disease called cancer. An advanced therapeutic treatment using quantum dots has emerged as a potential treatment for cancer cells and their resistant cancer stem cells. Quantum dots are semiconducting light particles used in research areas such as photodynamic therapy for the treatment of various diseases, including cancer. These particles are only a few nanometres in size, can be tuned to a specific wavelength, have excellent optical properties, and can generate reactive oxygen species upon their exposure to light, thus making them attractive therapeutic targets for anticancer treatment. In this review, we focus on providing a comprehensive overview of cancer stem cells and introducing the role of quantum dots in addressing key limitations associated with conventional treatment modalities aimed at eradicating cancer.

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1. Introduction to cancer stem cells

1.1 History

Cancer stem cell (CSC) research dates back to the late 19th and early 20th centuries, with a long and interesting history. At the time, it began with a hypothesis that certain stem or embryonic cells might keep their tendencies for infinite growth and become cancerous. However, these claims were merely hypotheses without experimental proof.[1] In 1838, Müller described tumor cells as a result of the abnormal continuation of embryonic cell development. Another postulation was later made in the late 1870s by Cohnheim, who suggested that tumors were a result of dormant embryonic cells.[1] During the 20th century, research emphasized that cancer arises from genetic mutations, but most body cells, with limited lifespans, lack the opportunity to accumulate enough mutations to become cancerous. Instead, cells capable of continuous proliferation, such as stem cells, were believed to be the origin of tumors.[2] Key milestones included Furth and Kahn's 1937 mouse leukemia model,[3] Till and McCulloch's 1961 discovery of self-renewing stem cells,[4] and Dick and Bonnet's 1997 identification of leukemia stem cells with a $CD34^{+}CD38^{-}$ marker in acute myeloid leukemia.[2,5] This discovery suggested that the rare, self-renewing cells within tumors drive cancer progression.[2] Although the CSC theory gained broad acceptance, experimental results revealed inconsistencies. Only a small percentage of transplanted CSCs successfully formed tumors in mice.[3] Moreover, research began to show that CSCs are diverse, varying in origin, genetic makeup, and function. This complexity was seen in both leukemia and solid tumors, with different markers being identified across cancers. For example, CD133 has been used as one of the prominent markers to identify CSCs in various tumors. In some cases, $CD133^{+}$ cells did not reproduce tumor structures, while $CD133^{-}$ cells could still initiate tumors.[2] The proportion of CSCs within tumors also varied widely, from less than 1% in some cases to over 80% in others, although the latter is rare.[6,7] There is, therefore, a growing interest in the study of CSCs, which has continued to increase over the years.

1.2 The Biology of CSCs

In oncology, CSCs have emerged as an interesting topic due to their resistance potential, thus resulting in the resurfacing of cancer even after multiple treatment attempts. The interest in these cells aims to address the key challenges associated with cancer treatments and to offer insights that may aid in better

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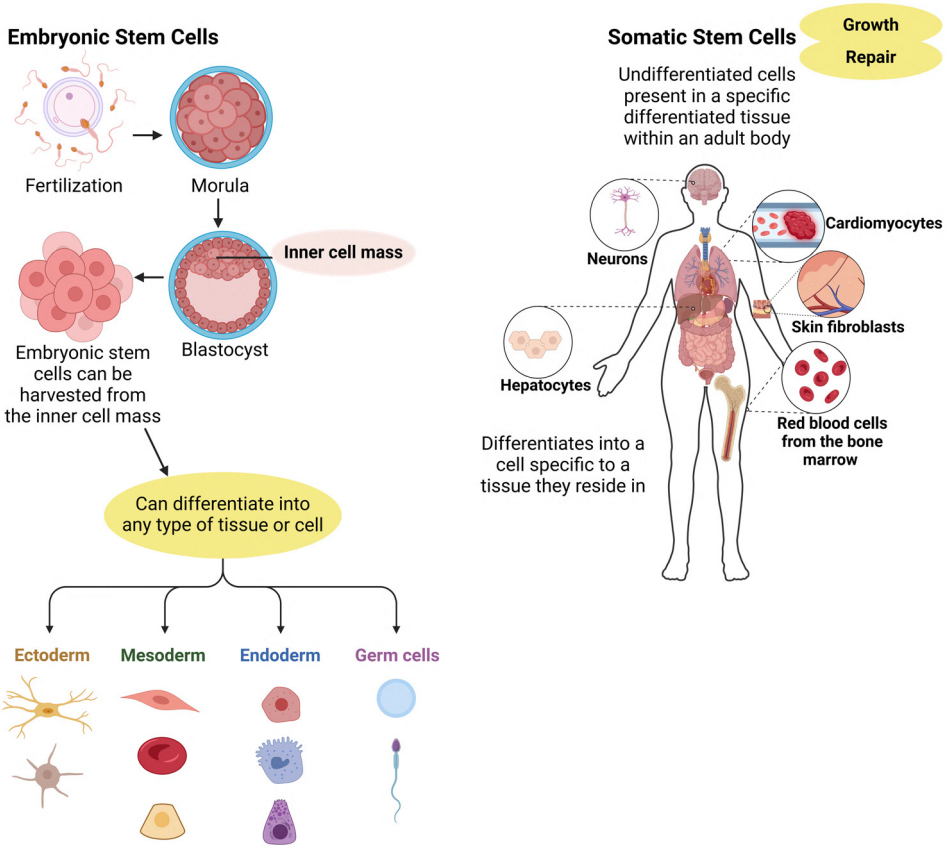

Fig. 1 Embryonic *versus* somatic stem cells comparison. Embryonic stem cells are derived from the inner cell mass, and they can potentially differentiate into any cell or tissue type in the body, such as the ectoderm, mesoderm, endoderm, and germ cells. While somatic cells, involved in growth and repair mechanisms, are undifferentiated cells found in a differentiated tissue within an adult body, and can only differentiate into a cell specific to the tissue they were found in.

understanding the biology of cancer, with the possibility of introducing advanced or novel treatment methods. To better understand the role of CSCs in cancer, it is crucial to understand the basic biology of normal stem cells and how this concept applies to cancer.

Normal stem cells can be attributed to functioning like a blank software program, waiting for instructions in the form of a specific code to perform a particular task or function. Depending on the instruction (or a "code" received from the body), the software can be programmed to perform any function. Similarly, stem cells can be "programmed" by biological signals and pathways (depending on the needs of the host) to become different types of cells. These cells are versatile and wait for a specific code that determines what they will become. In basic biological terms, stem cells are progenitor cells that can differentiate into any cell in the body (Fig. 1).

Divided into two categories, namely the embryonic and non-embryonic, these cells can self-renew and divide during the early life stages of a living organism.[8] Embryonic, also known as pluripotent stem cells, are early-stage embryo-derived cells that can differentiate into any adult body cell.[8] These cells are found in the inner part of the blastocyst, also known as the inner cell mass (Fig. 1), and they can differentiate into any cell, organ, or tissue of the host.[1] In a lab setting, researchers can harvest embryonic stem cells from this inner cell mass, and they can be cultured to remain undifferentiated or be developed into specific cell types.[1] However, this type of research is still under development due to ethical considerations and the question of whether the success of *in vitro* studies will be applicable to animal models. The second stem cell type is non-embryonic, somatic "adult" stem cells. These cells are naturally present in the host cell and are responsible for promoting growth and repairing damaged cells and tissues. When compared to embryonic stem cells, adult stem cells are not pluripotent, and depending on their location, they differentiate into only a specific type of cell in the body.[1]

This then leads to a more complex field of stem cells in the context of cancer, which are termed CSCs. The origin of CSCs is complex and multifactorial, involving various mechanisms. CSCs are a specific subset of cells with tumorigenic, metastatic, and self-differentiation capabilities essential for cancer cells' survival (Fig. 2). Regarding their origin, it is still a common debate among researchers whether cancer is a result of mutated normal stem cells or if it is attributed to cancer cells that possess stem-cell-like properties.[9] In addition to this, other theories suggested that CSCs may have been a result of adult

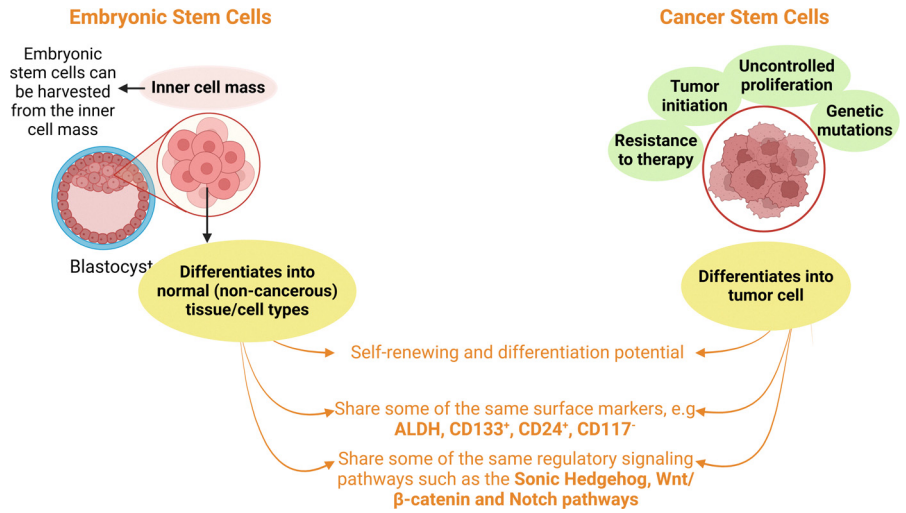

Fig. 2 Key features between embryonic and cancer stem cells. Embryonic stem cells support the healthy, normal development of normal cells and tissues. Cancer stem cells support the development of cancerous cells, promoting tumor initiation, tumor progression, uncontrolled cell proliferation, and driving cancer resistance to therapy.

differentiated cells after a process of reversed differentiation, known as dedifferentiation.[10] Others have also suggested that CSCs are a result of oncogenic mutations accumulating in normal cells.[11] Also, normal stem cells and CSCs have similarities (Fig. 2). Like normal stem cells, CSCs possess self-renewal and differentiation capabilities, as well as share similar regulatory signaling pathways and surface markers.[12] However, in contrast to normal stem cells, CSCs have tumorigenic capabilities and are often resistant to conventional cancer treatments, which may lead to cancer recurrence. Moreover, CSCs drive tumor initiation and metastasis.[2] Interestingly, some CSCs can arise from progenitor cells that are undergoing changes due to mutations or external stressors, resulting in tumor formation. For example, in prostate cancer, researchers have noted that CSCs can resemble normal prostate stem cells, hinting that tumors may develop from these already stem-like cells when they encounter the right set of circumstances that turn them into cancer.[13] In a study by Barker and his colleagues, it was discovered that CSCs can originate from normal stem cells through mutations in genes such as adenomatous polyposis coli (APC).[14] Using a tamoxifen-inducible Cre recombinase in a mouse model with Lgr5-marked intestinal stem cells, they demonstrated that deletion of APC in these long-lived stem cells rapidly transforms them into cancerous cells. This transformation leads to the formation of microadenomas, which exhibit unimpeded growth and develop into macroscopic adenomas within 3–5 weeks. The study also revealed that a hierarchical structure of stem and progenitor cells is maintained within early neoplastic lesions, indicating an integral function that stem cells play in tumorigenesis. In contrast, when APC was deleted in short-lived transit-amplifying cells using a different model, the resulting microadenomas showed stalled growth, and large tumors were rarely observed even after 30 weeks. This suggests that normal stem cells, rather than transient cells, may be essential for sustaining tumor growth. Barker's findings emphasize that mutations in stem cells are critical for the progressive development of cancer, supporting the idea that normal stem cells could give rise to CSCs, which drive tumor initiation and long-term tumor progression.[14]

1.3 Isolation techniques of CSCs

To better understand the mechanisms and biology of CSCs for potential treatment purposes linked to tumorigenesis, metastasis, and resistance effects of cancer to current treatment regimes, it is a requirement that they are first isolated from different tissues. Isolation of CSCs from the total tumor mass is challenging yet attainable. The proportion of CSCs derived from the tumor mass is generally very low, thus accounting for less than 2% of the total tumor cells' population.[9] Moreover, CSCs can be isolated by identifying specific signaling pathways involved in their regulation, transcription factors, and/or cell surface biomarkers.

1.3.1 FACS and MACS. Isolating CSCs by identifying specific cell surface markers includes various separation techniques with specific antibodies that can recognize surface markers expressed on the CSCs. Fluorescence-activated cell sorting (FACS) and magnetic-activated cell sorting (MACS) are commonly utilized methods. Both are advantageous for multicell processing and can achieve isolation with high purity. However, FACS faces constraints with its time-consuming process compared to MACS, which is less time-consuming and generally not as expensive.[15]

1.3.2 Side population. Within tumors, side population (SP) cells are a minute percentage of cancer cells with properties of stem-like cells. The SP assay is based on the differential ability of CSCs to efflux the Hoechst dye at a faster rate *via* the ATP-binding cassette (ABC) transporter that can be detected within the membrane of the cell.[16] The application of the SP assay was discovered in 1996 using mouse bone marrow hematopoietic stem cells.[17] These hematopoietic stem cell SPs in the bone

marrow can potentially restore all adult hematopoietic lineages throughout the animal's lifetime and are also known to overlap phenotypically with $CD117^{+}Sca\text{-}1^{+}Lin^{-}Thy1^{lo}$ cells that form part of the hematopoietic stem cell-containing population.[18,19] Many SP cells can also be found in several tumor tissues displaying characteristics of multipotency, self-renewing capabilities, and tumorigenicity following their transplantation into immunocompromised mice.[20,21] In addition, SP cells from breast and lung tissues have a high expression of genes related to stem cells, thus making them a potential representation of one of the putative CSC populations.[22] However, it should be noted that not all CSCs have this SP property in their composition. Therefore, the use of the SP method is limited. In addition, the isolation of CSCs is not achieved at the highest purity, and other limitations, such as low specificity and dye toxicity, can render the technique not always ideal for application.[23]

1.3.3 Aldefluor assay. This assay uses a non-immunological fluorescent reagent that identifies CSCs based on their ability to exhibit aldehyde dehydrogenase (ALDH) activity. Many normal and CSCs, including mammary, hematopoietic, and neural cell lineages, have shown a high expression of ALDH.[24] According to research, a high expression of ALDH in cancer is usually associated with the survival mechanisms of CSCs aimed at combating chemotherapy and driving resistance.[24] Only cells with an intact cell membrane can exhibit high ALDH levels, which can be identified using the Aldefluor assay and analyzed using a flow cytometer.[25]

2. Cell surface biomarkers and molecular pathways of CSCs

2.1 Cell surface biomarkers

Cell surface biomarkers are used to distinguish CSCs from other cell populations. The markers are protein molecules found on the surface or membrane of all cells and act as receptors that can recognize and bind to other cells to elicit a cellular response.[26] It is also known that most of the CSC surface markers known today were first derived from known adult or embryonic stem cell surface markers.[2] These include SSEA-1, CD133 (Prominin-1), CD47, CD44, CD90, CD19, $ALDH1^{+}$, CXCR4, CD24, CD34, CD38, CD13, just to name a few. SSEA-1, also known as CD15, is a key marker that is usually expressed in malignant thyroid follicular epithelial CSCs and is responsible for tumor initiation and progression.[27] CD133 is one of the most prominent CSC markers with multipotent properties, such as anti-apoptosis, playing a key role in tumorigenesis and resistance to therapy. It is commonly used to identify CSCs in many solid tumor types, including tumors located in the ovaries, prostate, lungs, brain, and colon.[28] CD47 is expressed in many ovarian and breast tumor tissues and plays a key role in evading the host immune response through a phagocytosis process.[29] CD44 is another CSC marker expressed in breast, glioblastoma, lung, and ovarian cancers, and it is involved in tumor initiation and invasion. It also has metastatic potential.[30] Most of these CSCs are associated with breast cancer and can aid in the isolation of breast tumors using complementary antibodies. Depending on the surface marker that is specific to a tumor type, its CSCs can be successfully isolated. Additionally, more than one surface marker can be used to isolate a certain subtype of CSCs, thus potentially resulting in greater isolation efficiency, purity, specificity, and percentage yield.

2.2 Molecular pathways

Many CSCs are regulated by several molecular signaling pathways such as Wnt/β-catenin, Notch, Hedgehog, transforming growth factor-β (TGF-β), Hippo, JAK/STAT3, NF-κB, and PI3K/Akt/mTOR pathways. These molecular pathways regulate the function and characteristics of CSCs. Dysregulation in these molecular pathways promotes abnormal proliferation, tumor dissemination, treatment failure, differentiation, and self-renewal capacity of several cancer types. Also, these pathways work simultaneously to sustain and maintain the activity and function of CSCs.[31–34] Thus, this section will elucidate the role of these pathways in fostering the stemness attribute of CSCs.

2.2.1 Wnt/β-catenin signaling/cascade. The Wnt/β-catenin pathway coordinates several cell-signaling networks. It performs an integral function in many physiological and pathological activities, ranging from cell growth, differentiation, cell death, cell migration/invasion, and tissue regulation.[35–38] The Wnt/β-catenin signaling controls early cell development, stem cell sustenance, and self-regeneration. Aberration of the Wnt/β-catenin often facilitates the development of many severe diseases, including cancer and non-cancer-causing sicknesses. The Wnt/β-catenin cascade plays a vital role in maintaining and sustaining the stemness properties of CSCs *via* several mechanisms, thereby fostering carcinogenesis. Aberration of the Wnt/β-catenin signaling pathway has been observed in different cancers, including oesophageal, pancreatic, gastric, cervical, lung, liver, thyroid, and brain cancers.[32,35,38]

The association of Wnt signaling in carcinogenesis mainly arises from its potential to foster the growth of CSCs, facilitating cancer treatment failure and resistance. Furthermore, the Wnt signaling also promotes the invasion and spread of CSCs into adjacent organs.[35–38] Therefore, blocking the Wnt signaling provides an efficient strategy to eliminate CSCs.

2.2.2 Notch signaling. The Notch signaling cascade controls several physiological activities such as embryogenesis, differentiation, cellular development, and homeostasis. This signaling pathway comprises two pathways: the canonical and non-canonical, consisting of three key components: the Notch receptors, ligands, and effectors of Notch signaling.

Supporting evidence suggests that the Notch signaling cascade drives oncogenesis and promotes tumor suppression in many cancers.[39,40] Aberration in this signaling cascade facilitates angiogenesis and epithelial–mesenchymal transition (EMT) in cancer, which is associated with excessive cell growth, invasion, and tumor progression/metastasis. The Notch signaling pathway is also known to maintain CSC self-renewal, differentiation, carcinogenesis, and drive chemoresistance.[41,42] Abnormal regulation of the Notch signaling cascade has been

implicated in several cancer types.[43,44] Several reports have demonstrated that Notch-1 facilitates CSC-like features in colorectal cancer,[45] glioma,[46] and hepatocellular carcinoma.[47] Furthermore, studies have shown that the Notch signaling coordinates the activity of gastric stem cells and antral stem cells, thereby promoting gastric tumorigenesis.[48,49] Targeting the Notch signaling pathway may offer promising measures to eradicate CSCs.

2.2.3 Hedgehog pathway. The Hedgehog pathway is a critical pathway involved in several cellular processes during embryogenesis. It also plays vital roles in cell growth/survival, invasion, and self-regulation of several cellular pathways.[50,51] Dysregulation of the Hedgehog pathway has been shown to drive the sustenance of CSCs and cancer progression in several cancers through the regulation of CSCs' self-regeneration, proliferation, and cellular homeostasis in cancer, such as breast cancer, myeloid leukaemia, melanoma, and pancreatic cancer.[52–56]

A study in multiple myeloma CSCs showed that hedgehog stimulation is associated with the upregulation of the SMO gene and high Gli1 transcriptional factor, and the blockage of this pathway decreases the growth and stemness of multiple myeloma CSCs.[57] A study by Ko and colleagues demonstrated that targeting the Hedgehog signaling pathway and yes-associated protein 1 (YAP1) decreases the stemness of breast cancer cells.[58] The Hedgehog signaling pathway also promotes cancer treatment failure/resistance through the functional activity of CSC-associated Hedgehog HH signaling.[59]

2.2.4 PI3K/Akt/mTOR pathway. The PI3K/Akt/mTOR signaling cascade plays a vital function in cellular systems such as cytoskeletal structure, cell growth, proliferation, migration, invasion, and cell survival.[60,61] The PI3K/Akt/mTOR signaling is essential for tumor cell proliferation and treatment evasion. Reports have shown that the PI3K/AKT pathway is implicated in transforming normal stem cells into CSCs. Also, this pathway regulates and maintains the stemness phenotypes in many cancer types.[62–65]

A study by Madsen *et al.* (2021) observed a positive relationship between breast cancer stemness score and upregulation of PI3K/AKT/mTOR signaling pathway.[62] Hakeem and colleagues demonstrated that piperine potentiates doxorubicin response in triple-negative breast cancer *via* the PI3K/Akt/mTOR pathway and CSCs targeting.[66] Cancer suppressor Connexin 32 (Cx32) modulates the PI3K/AKT signaling effect, consequently inhibiting the stemness and tumor-initiating potential of liver CSCs.[67] In a recent study, the attenuation of the PI3K-Akt-mTOR pathway suppresses the stemness phenotypes of chemoresistant lung cancer cells[68] and liver CSCs.[69]

2.2.5 TGF β/SMAD signaling. Transforming growth factor β (TGF-β) performs vital functions in embryonic development and adult tissue maintenance by coordinating cellular growth, differentiation, cell death/survival, and cell migration and invasion.[70] TGF-β performs a dual function in cancer that involves a differentiation signal that prevents cancer development at the initial stage and activates EMT that drives cancer stemness features.[71,72] The TGF-β signaling pathway plays a crucial role in maintaining CSCs, facilitating self-regeneration and differentiation. Abnormal regulation of the TGF-β pathway in CSCs is often linked with cancer relapse and progression.[73]

TGF-β triggered the activation of EMT-related genes such as Snail and Twist in CSCs[74] and can potentially induce a stemness phenotype in non-CSCs in colorectal cancer.[72] Inhibiting the TGF-β/Smad pathway has been demonstrated to sensitize CSCs to treatment. While TGF-β interacts with Hedgehog signaling, it drives chemoresistance.[75,76] The role of the TGF-β pathway in cancer metastasis has been reported. Zhang and Xu showed that pancreatic cancer cells acquire stemness through the TGF-β/Smad pathway *via* the activation of the Frizzled receptor 7 (FZD7), and the upregulation of this interaction facilitated EMT in pancreatic cancer liver metastasis.[77]

2.2.6 JAK/STAT signaling. The Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway is a key network node in cell function. The JAK/STAT signaling pathway involves several biological processes and diseases such as cellular growth, differentiation, and immune response, inflammation, and cancer.[78–80] The JAK/STAT signaling is made up of the tyrosine kinase-associated receptors, JAK (a tyrosine kinase), STAT (transcription factors) and several ligands such as interleukins, hormones, and interferons.[79] The modulation of the JAK/STAT signaling is also associated with the maintenance of CSCs.

The activation of the STAT signaling is shown to promote stemness phenotypes in liposarcoma, stenosarcoma, and thyroid cancer.[81–83] A study showed that selectively blocking STAT3 decreases stemness-associated gene expression in breast CSCs.[84] Upregulation of interleukin (IL)-6 mediated by the inhibition of androgen receptor (AR) activates the STAT3 pathway, resulting in prostate CSCs expansion.[85] In liver cancer, non-CSCs sustain CSCs *via* interleukin-17E by activating the JAK/STAT3 signaling.[86]

2.2.7 NF-κB pathway. The nuclear factor-κB (NF-κB) pathway is essential in several cellular processes, including cell proliferation, differentiation, survival, cell death, inflammation, innate and adaptive immune responses.[87,88] Dysregulation of the NF-κB pathway facilitates the development and progression of different cancers and the regulation of CSCs.[89] The involvement of the NF-κB signaling pathway in maintaining CSCs was initially established in acute myelogenous leukaemia, where the primitive acute myelogenous leukaemia cells abnormally expressing NF-κB were identified as potential leukemic stem cells.[90] NF-κB signaling is implicated in the proliferation and self-renewal of acute myeloid leukaemia stem cells.[91] Other cancer types have also demonstrated the aberrant regulation of the NF-κB signaling pathway in driving the stemness phenotypes of CSCS. For example, the activation of the NF-κB signaling plays a vital role in maintaining glioblastoma CSCs.[92] The attenuation of the NF-κB signaling suppressed the stemness traits of breast CSCs[93] and reduced the CD133+/CD44 + CSC stemness in triple-negative breast cancer.[94] In addition, the NF-κB pathway-associated proteins are overexpressed in ovarian CSCs, and attenuating this pathway inhibits the CSCs.[95]

2.2.8 Hippo signaling pathway. The Hippo pathway performs vital functions in biological processes and pathological states, including organogenesis, cell growth, tissue regeneration, and carcinogenesis. The Hippo signaling also plays essential roles in CSC biology, such as self-regeneration, treatment resistance, EMT, invasion, and metastasis.[96–98] Studies have shown that the Hippo signaling pathway maintains CSCs and facilitates cancer development and progression.[96,99] Aberration of the Hippo pathway promotes the stemness traits and metastatic potential of breast CSCs.[100,101] The Hippo pathway also promotes the stemness properties, drug resistance, and metastasis in oesophageal cancer.[31] Furthermore, inhibition of the Hippo signaling pathway prevents EMT and suppresses the stemness in ovarian cancer cells.[102]

2.3 Molecular crosstalk between CSC signaling pathways

The development and regulation of CSCs involve the interactions of several signaling transduction networks.[103] NF-κB and Wnt/β-catenin pathways interact to facilitate the cell growth and proliferation of CSCs. β-catenin modulates TNFRSF19 (a TNF receptor superfamily member) while its receptor molecules stimulate the NF-κB signaling to initiate the formation of colorectal cancer.[104] Inhibiting SCD1 (a lipid desaturation enzyme) preferentially eradicates colon CSC by attenuating the Wnt and NOTCH signaling pathway.[105] In leiomyosarcoma, NK6 Homeobox 1 (NKX6-1) facilitates stemness features *via* hedgehog and Notch signaling activation.[106] Cancer with upregulated Notch/hedgehog signaling pathways potentiates stemness traits by hypoxia and immune evasion.[107] Similarly, Liu *et al.* demonstrated the crosstalk between Wnt/β-catenin and Hippo signaling pathways in colorectal cancer.[108] In acute myeloid leukaemia, protein kinase CK2 activates multiple signaling cascades (such as AKT, NF-κB, and STAT3) to regulate the CSC phenotypes.[109] A study also demonstrated that the Hedgehog signaling pathway is a positive modulator of Wnt signaling, essential for regulating colon CSC.[110]

The interplay between signaling networks enhances tumor tumorigenicity, differentiation, and metastasis by regulating the CSCs.[2] A study by Liu and coworkers showed that JAK/STAT3 is essential for TGF-β/Smad mediated EMT in lung cancer, which enhanced the proliferative and metastatic potentials of lung CSCs.[111] Attenuation of Notch1 and IKKα activates NF-kB pathways, potentiating the CD133+ expressing melanoma CSCs.[112] Wu and colleagues demonstrated that the suppression of prostate CSCs by baicalin reduced the stemness properties by inhibiting Notch1/NF-κB signaling cascade.[113] Supporting findings above show that the molecular signaling and their interaction promote and regulate the stemness features of CSCs in many cancer types, thereby rendering them promising targets for the design of new cancer therapeutics.

3. Cancer stem cells in cancer therapy resistance

Recently, several therapeutic measures have been employed in treating and eliminating cancer. These measures include surgery, chemotherapy, radiotherapy, immunotherapy, and molecular targeted therapy.[2,114] Many of these treatments can be used alone or in combination and have proven effective in many cases.[115] However, tumor recurrence and resistance pose significant challenges in cancer treatments, primarily due to the presence of CSCs. CSCs are often resistant to conventional cancer treatments, which may lead to cancer recurrence. Moreover, CSCs possess a tumorigenic potential and can drive tumor initiation and metastasis.[2] Additionally, some CSCs can arise from progenitor cells that are undergoing changes due to mutations or external stressors, resulting in tumor formation. CSCs also constantly drive a phenotypic change between stem and non-stem cells to escape therapeutic pressure.[116] They achieve this by employing multiple intrinsic and extrinsic mechanisms to promote therapy resistance in many cancer types, such as metabolic reprogramming, dormancy, overexpression of drug transporters, enhanced DNA repair, reactive oxygen species (ROS) scavenging system, upregulation of anti-apoptosis, tumor microenvironment, hypoxia, and immune evasion.[2,117,118] CSCs utilise metabolic reprogramming to exert therapy resistance, which relies on the presence of oxygen, facilitating the change between glycolysis and oxidative phosphorylation, regulated by signalling interactions such as Wnt/b-catenin and Notch pathways.[119,120]

CSCs display a continuous state of tumour growth and dormancy. They decrease their metabolic function during dormancy, promoting sustained survival in a quiescent state. Following an extracellular trigger, CSCs revert into the cell cycle, restoring proliferative ability. This bifunctionality presents a significant limitation for anti-cancer therapy, as dormant CSCs develop resistance with more aggressive resistant phenotypes.[121–123]

CSCs are endowed with high expression of drug transporters such as ABC transporters, multidrug resistance protein 1 (MDR1), and P-glycoprotein, which serve a crucial function in the efflux of anticancer agents.[117,118] A recent study noted the ability of graphene quantum dots to self-insert into DNA major groove sites, enhancing interfacial inhibition and downregulating key CSC genes such as ALDH1, Notch1, and Bmi1. Additionally, at non-toxic concentrations, graphene quantum dots have been demonstrated to reverse multidrug resistance by inhibiting MDR1 expression and thereby, sensitizing CSCs to standard cytotoxic agents.[124]

Increased DNA repair mechanisms have been demonstrated as an effective mechanism employed by CSCs to confer therapy resistance. This is achieved through the activation of the DNA damage checkpoints, which promote the cellular repair mechanism to facilitate cell survival.[125] Cancer stem cells can induce anticancer resistance by inhibiting DNA-mediated damage and apoptosis *via* efficient ROS reduction through the increased expression of ROS scavengers. Reactive oxygen species scavengers such as superoxide dismutase, glutathione peroxidase, *N*-acetylcysteine (NAC), and catalase are highly expressed in CSCs, and they play vital roles in restoring and maintaining the stemness features of CSCs.[126,127]

Evasion of apoptosis is another mechanism employed by CSCs to drive resistance to therapy. CSCs possess high

expression of antiapoptotic proteins (B-cell lymphoma 2, B-cell lymphoma-extra-large, and the myeloid cell leukemia 1), upregulation of antioxidant pathways, and expression of inhibitors of apoptosis proteins.[123]

Therefore, it is crucial to not only understand the tumor biology underlying CSCs but also to explore additional therapeutic options that effectively target both cancer and its resistant CSCs, as a way of ultimately combating issues associated with resistance, recurrence, and relapse of cancer. Among emerging approaches, photodynamic therapy (PDT) has gained attention as a minimally invasive tool aimed at destroying cancer cells while causing minimal damage to normal cells within the host cell.[128]

4. Photodynamic therapy

The act of tumor killing depends on the action of the photosensitizers to produce ROS upon light exposure. It is not the PS itself that interacts with biomolecules, however, when administered intravenously or topically, the light exposure through the form of a laser as the sole source of light excites the PS at a specific wavelength thereby leading to the transfer of light energy to molecular oxygen for the production of ROS such as superoxide and hydroxyl radicals, and hydrogen peroxide.[129–133] Through this action, PDT can destroy cancer cells, and it has already shown success in the killing of various cancers, including those of the oesophagus, breast, lung, cervix, and skin.[129,134] Despite its potential as a more advanced and effective treatment method compared to conventional treatments such as surgery, radiation, and chemotherapy, PDT also faces challenges such as limited light penetration to deeply located tumors, non-specific accumulation of PS in normal tissues, and difficulty in effectively targeting CSCs due to their resistant nature to treatment. Due to their ability to maintain a dormant or slow-dividing state for preserving their stemness, CSCs express low levels of ROS by upregulating enzymes such as glutathione peroxidase and thioredoxin,[135,136] which provides them with an antioxidant advantage and can reduce the amount of ROS generated during PDT. In addition, CSCs also express high levels of ABC transporters, including ABCG2, which is known to provide an efflux advantage by promoting drug efflux.[137] In the case of PS absorption, this results in poor drug absorption and, consequently, reduced PDT efficacy. To address these challenges, the application of quantum dots in PDT is a promising approach.

5. Quantum dots

With only a few nanometers in size, typically around 1–10 nm, quantum dots are fluorescent semiconductor nanostructures with size-unique optical properties and an intrinsic band gap that allows for the excitation and bridging of electrons.[132,138] When light is absorbed by these nanostructures, electrons in the valence band (lower electronic energy level) are elevated to the conduction band (higher electronic energy level), generating an electron–hole (e–h) pair. When this e–h pair recombines, a photon is emitted (radiative recombination).[138] In the bulk crystal lattice, the e–h pair may extend over the delocalized lattice. But if the particle size is smaller than the Bohr radius, the e–h pair will be formed at a higher energy. This is due to the effect of ''quantum confinement,'' which is usually found in ultrasmall-sized, crystalline semiconductor materials.[138] For smaller quantum dots, they tend to have a larger band gap energy and would essentially emit higher-energy photons (blue shift). Conversely, larger quantum dots would possess a smaller band gap energy and emit photons of lower energy (red-shifted).[138] This size-dependent emission property enables the precise tuning of the optical characteristics of quantum dots by simply altering their dimensions during synthesis, thus making them highly valuable for their application in PDT. In addition to tunable optical properties, quantum dots are also valued for their multifunctionality to act as target agents when conjugated to photosensitizers and also as energy donors in Förster Resonance Energy Transfer (FRET), providing a dual functionality for use in PDT to destroy cancer cells.[133,139] Despite the excellent properties that quantum dots possess, there is limited research surrounding their PDT application specifically for the eradication of CSCs. Some of the recent studies include improving the drug localization mechanism of Doxorubicin, a chemotherapeutic drug. The researchers loaded Doxorubicin onto the surface of red-emitting carbon quantum dots.[140] This improved the internalization of the drug into the nuclei of cervical CSCs. Compared to unconjugated Doxorubicin, the conjugated counterpart was more effective as an anticancer drug carrier, thus exhibiting enhanced tumor killing effects and enhancing the therapeutic efficacy, while minimizing possibilities of tumor recurrence, a major challenge with most treatment modalities. Although this study was focused on chemotherapy, this mechanism can also work well for photosensitizers in PDT, whereby improving drug internalization using quantum dots could improve the amount of photosensitizer that enters the cells, leading to a better delivery strategy that would ultimately improve PDT.

5.1 Mechanism of intracellular uptake of quantum dots

As the promising application of Quantum dots in the biomedical field evolves, it is imperative to understand the interaction of quantum dots in mammalian tissues. Effective cellular internalization is critical for quantum dots to exert their biological actions. In recent times, investigations have proposed that interaction between various cells in the body and quantum dots leads to different entry routes and intracellular delivery of quantum dots.[141–143] Effective cellular uptake relies on the quantum dot's physicochemical characteristics, such as surface modification, shape, size, stability in polar solvents, and the ability to withstand precipitation and degradation in the cells until arrival at the target cells. Capping quantum dots with polymers can enhance their biocompatibility/stability and limit agglomeration/precipitation/degradation.[142,143] Nevertheless, polymer-capped quantum dots are prone to an increase in size, limiting their cellular uptake/internalization. Hence, their biological role and intracellular

delivery approach depend on the balance between quantum dot size and stability.[141,143–145]

The cellular internalization of quantum dots is suggested to occur through passive, facilitated, and active delivery mechanisms based on their physicochemical features. Passive delivery mechanism employs the innate characteristics of quantum dots material, like surface charge and coating, to drive internalization mainly by endocytosis.[143,145] Facilitated quantum dots delivery is reliant on the link or functionalization of the quantum dots' surface with biomolecules (such as peptides, proteins, antibodies) to promote the first cellular communication of the quantum dots *via* the specific receptor on the plasma membrane, and finally their intracellular internalization by receptor-driven endocytosis. Active delivery mechanism requires a direct mechanical delivery of the quantum dots into the cell through electroporation and microinjection.[141,143–145]

For quantum dots internalization through receptor-driven endocytosis, there are three classic pathways/mechanisms by which cells interact with ligand-functionalised quantum dots: Clathrin-driven endocytosis, caveolae-driven endocytosis, and micropinocytosis mechanisms. The receptor-driven endocytosis depends on the type of ligand employed, the desired specific receptor, and the chemical nature of the quantum dots.[144,146]

5.1.1 Clathrin-driven endocytosis. In this pathway, the quantum dots accumulate at the specific receptor site. They are internalized by Clathrin-enveloped vesicles, which are formed by the engulfment of the quantum dots by the Clathrin-enveloped vesicles through Clathrin-driven Endocytosis. The quantum dots are then delivered into the cytosol and are ready to release their content. If they erupt from the endosome, they will be degraded *via* lysosomal degradation.[141,143,145]

5.1.2 Caveolae-driven endocytosis. This mechanism links the functionalised quantum dots to their specific receptor *via* caveolae. Caveolae are a membrane invagination containing cholesterol that breaks out from the cell membrane, forming caveosomes. The caveosomes facilitate the intracellular uptake of the functionalized quantum dots into the desired cells.[141,143]

5.1.3 Micropinocytosis. Quantum dots internalization *via* the micropinocytosis pathway is achieved by macropinosomes, which engulf the quantum dots/nanoparticles and facilitate their release into the cytosol. This pathway is mediated by specific ligands that trigger cell membrane fold formation.[143,145,147]

6. Quantum dot for active targeting of cancer and CSCs

Quantum dots have several promising applications for cancer therapy. Their distinct physicochemical features play a vital role in the functioning of treatment strategy *via* uncommon techniques that have the potential to circumvent treatment resistance and increase therapeutic efficiency.[148] Quantum dots are endowed with great photothermal conversion capacities, which means they can unleash cancer cell antigens upon laser irradiation, enhancing the cancer cell immune niche. Furthermore, some quantum dots can be designed to function as a drug delivery cargo, facilitating anti-cancer effects *via* different mechanisms. The near-infrared luminescence optical attributes of quantum dots can aid in directing targeted treatments, evaluating the immune state of the patient, and measuring treatment responsiveness.[149] Studies have reported that quantum dots conjugated with cancer drugs enhance drug delivery and efficiency of cancer treatment by overcoming the setback of drug carriers for conventional therapy.[148–151] Quantum dots allow surface functionalization with various functional ligands, molecules, proteins, such as peptides and/or antibodies, to increase the attraction toward tumor cells. The targeting ligands preferentially regulate the interaction between the quantum dot and specific biomolecules overexpressed on the surface of tumor cells and CSCs, preserving normal cells and enhancing cellular uptake. Quantum dots can be functionalized with different biomolecules and/or ligands that bind to cancer cells and CSCs' surface and intracellular receptors. This targeted strategy not only reduces systemic adverse effects but also enhances the targeted delivery of anti-cancer agents and, as a result, improves the treatment efficiency better than single cancer drugs.[148–151] Therefore, quantum dots are required for actively targeting various components such as biomarkers, signaling pathways, and tumor microenvironment (TME) implicated in cancer and CSCs.

6.1 Quantum dot for targeting biomarkers of cancer and CSCs for diagnosis and treatment

Cancer biomarkers are biological molecules such as proteins, ligands, peptides, antibodies, or genes that exist on the surface and within a tumor tissue and can provide information pertaining to the characteristics, prognosis, and stage of cancer.[152] Quantum dots can be conjugated with tumor-targeting molecules that can identify and bind to the surface receptors of a tumor or a CSC (Fig. 3), thereby enforcing specific or targeted therapy. By directly targeting the population of CSCs, issues associated with cancer resistance and relapse can be overcome. Additionally, the careful detection of CSCs may aid in diagnosis, drug delivery, and improving overall therapeutic outcomes.

6.1.1 Interleukin-13 receptor alpha 2 (IL13Rα2). This is a cell surface receptor that is overexpressed in glioblastoma and many tumor types and is a marker of tumor progression, invasion, and metastasis.[153] In an investigation aimed at improving the detection of glioma stem cells and tumor-associated exosomes secreted by tumor cells in cerebrospinal fluid in the early stages of brain cancer, the interleukin 13 (IL13) protein was successfully conjugated to Cadmium selenide (CdSe) based quantum dots.[154] The IL-13 protein exhibits a specific binding affinity for IL-13Rα2, a receptor that is overexpressed in cancer cells and CSCs of glioblastoma, as opposed to its normal physiological receptor, IL-13Rα1. Moreover, unlike other known markers, such as CD44, which are overexpressed in both normal and tumor tissues, IL13Rα2 is explicitly overexpressed in tumor tissues only. Thus, its expression is rarely observed in normal brain tissues, making it a specific marker for glioblastoma detection. Therefore, for this study, CdSe-based quantum dots were employed for the

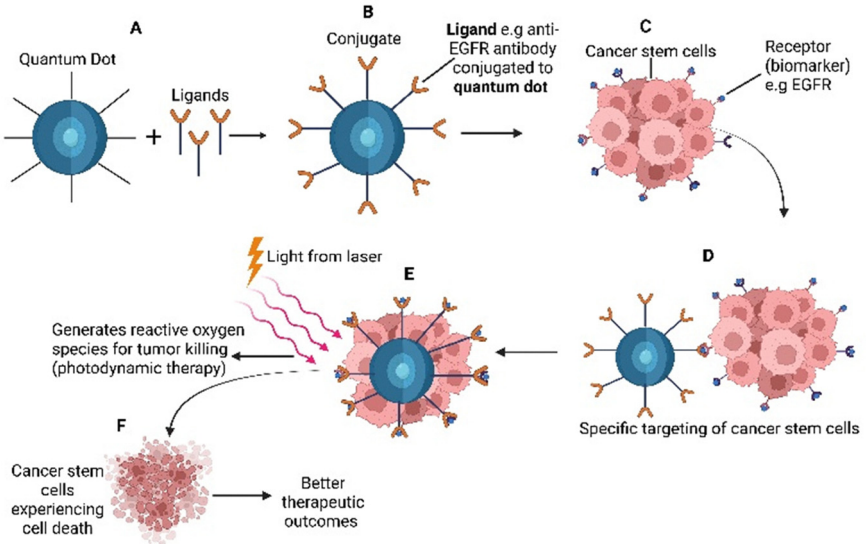

Fig. 3 Targeted photodynamic therapy using quantum dots conjugated to ligands for receptor recognition on cancer stem cells. Quantum dot and ligand (A) form a conjugate (B). The complex is used to target specific surface receptors/biomarkers on CSCs (C). The quantum dot then binds to the receptors on the CSC (D). Upon receiving light from a laser (photodynamic therapy) through photochemical pathways, the quantum dot generates reactive oxygen species (E), which are cytotoxic to CSCs (F), thus improving overall therapeutic outcomes (G).

detection of IL13Rα2, due to their optimal size distribution that ranges between 1–25 nm and excellent fluorescent properties. These two properties were beneficial in allowing the researchers to monitor quantum dots' dynamics in membrane and solution form. They then investigated the interaction of IL13QD with glioma stem cells and exosomes to test its potential as a detection tool for early-stage glioblastoma. It was revealed that IL13Rα2 is indeed expressed on exosomes of glioblastoma multiforme stem cells (including glioma stem cells) and can be detected in cerebrospinal fluid by using IL13 conjugated to quantum dots. Additionally, atomic force microscopy results confirmed a strong binding interaction between IL13-quantum dots conjugate and the surface of the exosomes, supporting their high affinity for IL13Rα2 receptors. The conjugate also showed significantly greater binding forces, which were over four times higher with U251 glioma cells and glioma stem cell-derived exosomes compared to non-conjugated quantum dots ($P < 0.0001$). This discovery could aid in differentiating and identifying exosomes by how strongly they interact or bind, which might lead to better ways to diagnose patients in the future. Flow cytometry results further confirmed this. When IL13 was conjugated to quantum dots, the side scatter signals decreased, suggesting that the complexes formed were more uniform and specifically bound to the receptor. This pattern was observed in both glioma stem cell exosomes and patient cerebrospinal fluid, and was validated using fluorescently labelled exosomes, where the binding of the conjugate onto the exosomes led to decreased green fluorescence, likely due to quenching caused by receptor interaction. These findings suggest that the conjugate not only binds specifically to tumor-derived exosomes *via* IL13Rα2 but may also aid in distinguishing malignant exosomes based on the binding strength, which would indirectly be linked to the expression level of IL13Rα2 on the exosomes, thus correlating with disease pathology and scatter patterns.[154] Although not covered in this study, CdSe-based quantum dots can also generate reactive oxygen species, which is beneficial for tumor killing.[155] This could enable the possibility of developing IL13-quantum dots constructs not only as diagnostic agents but also as theranostic agents, simultaneously.[154]

6.1.2 Nanog. Gene expression is a regulated process controlled by transcription factors, *i.e.*, proteins that bind to specific sequences of DNA and can either upregulate or repress transcription.[131,156] Research has shown that the abnormal expression of certain transcription factors within the transcriptome of a specific host organism has been linked to the development and spread of cancer.[12] Nanog is a transcription factor that is upregulated and overexpressed in CSCs to drive metastasis.[157] However, accurately detecting the Nanog antigen remains a major hurdle due to its low concentration in biofluids. A recent study demonstrated a novel fluorescence-based method using green carbon dots to achieve a precise and selective detection of Nanog in CSCs.[158] To do so, fluoroimmunosensors incorporating magnetic nanoparticles were conjugated with anti-Nanog antibodies. Antibodies such as anti-Nanog have a high binding affinity and specificity for CSC markers like Nanog, which is overexpressed in CSCs and plays a key role in maintaining their stemness. In this case, the choice of an antibody over other ligands, including aptamers or peptides, was key in promoting a stronger binding interaction. Anti-Nanog was covalently linked to green carbon dots using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC)/*N*-hydroxysuccinimide (NHS) chemistry, which allowed for a stable, high-density antibody loading. This strong interaction could enhance the complex's resistance to degradation and maintain its biofunctionality. Upon the binding of green carbon dots and magnetic

nanoparticles conjugated with the target Nanog antigen, the complex was magnetically separated, resulting in a fluorescence signal that increased proportionally with Nanog antigen concentration. The method exhibited a linear detection range from 0.05 ng L^{-1} to 1.0 ng L^{-1}, with a detection limit as low as 0.01 ng L^{-1}, indicating its high detection sensitivity.[158] Moreover, this antibody-carbon dots system maintained its functionality, specificity, and long-term stability when tested in urine samples from the hospital to detect Nanog. Unlike peptides or aptamers, which are often degraded in biological environments or bind with lower affinity, this complex did not lose its biofunctionality or affinity when tested on clinical samples. While smaller ligands may be beneficial in lower immunogenicity or simpler synthesis, their lower structural stability and susceptibility to enzymatic degradation could limit their performance in tumor-like environments. This study made it clear that the success of CSC targeting depends not only on the presence of any ligand, but on how well its biochemical properties match the required needs of a particular study. This was the first application of high quantum efficiency green-emitting carbon dots in such a fluoro-immunosensor that provided a highly sensitive and rapid tool for Nanog detection in both cancer research and clinical diagnostics.[158]

6.1.3 CD44. As previously mentioned, CD44 is another CSC marker and glycoprotein expressed in breast, glioblastoma, lung, and ovarian cancers. It is also involved in tumor initiation and invasion and has metastatic features.[159] For example, breast cancer cells expressing the $CD44^{+}/CD24^{low}$ phenotype have been identified to possess CSC features, which can be attributed to their increased tumorigenicity and self-renewal potential in immunodeficient mice.[160]

It has also been reported that breast cancer cells expressing this phenotype are involved in chemoresistance, as their percentage in treated cells was higher than in the same cells before chemotherapy.[161]

Another study found that coupling anti-CD44v6 and CD24 antibodies with quantum dots did not alter their ability for antigen recognition, but instead, it retained this recognition ability in formalin-fixed, paraffin-embedded tissue sections. The application of both antibodies allowed the researchers to visualize all possible cell populations defined by these two surface antigens. The study then assessed the proliferation of each sub-population of breast carcinoma cells after performing triple staining using CD44v6, Ki67, and CD24 cell proliferation markers. From their results, differences between $CD44v6^{+}$ and $CD44v6^{-}$ breast carcinoma cells were identified *in vivo*, thereby concluding that antibodies coupled with quantum dots can be utilised to study specific sub-populations of cancer cells stained using multiple markers in a single tissue section.[162] The application of quantum dots in this study was important as traditional immunohistochemistry only shows a couple of markers at the same time on one breast cancer tissue sample. However, to understand CSCs better in this case, several markers would need to be visualised all at once. Quantum dots and spectral unmixing were used to increase the number of antigens that could be identified in a single tissue section. Each type of quantum dot emitted a different color without overlapping, allowing many of them to be used together to label different markers in the same tissue slice. A special software called spectral unmixing was applied to separate the colors and to generate a composite image of each signal. In summary, their results suggested that $CD44v6^{+}$ cells have distinct properties in human breast cancer cells, but only in specific subtypes. They further suggest future work with mouse models or other cell lines.[162]

In another study, a quantum dot-mediated drug delivery system targeting CD44 receptor, a CSC biomarker in melanoma, was fabricated using lanthanum-doped zinc oxide (La–ZnO) quantum dots integrated with hyaluronic acid (CD44 ligand) and Adriamycin (anti-cancer drug). The study showed enhanced anti-cancer activity of the quantum dot-based drug delivery and improved bioimaging.[163] Furthermore, Cai and coworkers conjugated ZnO quantum dots with hyaluronic acid and doxorubicin targeting CD44 expressed in lung cancer cells. The study showed improved cellular drug uptake and significantly enhanced anti-cancer effects.[164]

6.1.4 Epidermal growth factor receptor (EGFR). This is a transmembrane receptor that binds to specific ligands, including epidermal growth factor (EGF).[165] Upon dimerization, it undergoes phosphorylation and activates intracellular signaling pathways involved in differentiation, adhesion, and cell growth and survival.[166] In cancer, the mutated or overexpressed form of this receptor promotes tumor development, metastasis, and progression.[165]

Another application of quantum dots has been discovered in medical imaging to study certain inter- and intracellular biomedical processes. However, their application tends to be limited by size when conjugated. A surface-coated quantum dot is often bulky and consists of amphiphilic molecules that contribute to an increase in the nanoparticle's hydrodynamic diameter.[167] This increase in size is a limitation, especially in the application of quantum dots to study the intracellular molecular mechanisms. More importantly, when the surface-coated quantum dots are large, they can be taken up by the cell as nonfunctional aggregates in the cytoplasm[168] and interfere with the normal signaling inside the cell, leading to false-positive results in experiments. Therefore, using quantum dots to label and identify the dynamic intracellular protein populations and multiple markers, respectively, has become a key area of interest in the rapid characterization of glioblastoma.[169]

Protocols aimed at the rapid identification of specific markers during the early stage of diagnosis may aid in improving the lifespan of affected patients. In a study, quantum dots were used to label and detect the EGF receptor in live cells acquired from glioma and medulloblastoma.[170] This key receptor, chosen for its high expression in brain tumors, was labeled with functionalized quantum dots extracellularly for the intracellular labeling of activated EGF receptor populations. The study established a clear correlation, demonstrating that intracellular quantum dot detection is EGF-dosage dependent and corresponds with the PI3 kinase pathway activity.[170] Therefore, their method allowed for the rapid, specific identification of tumor markers and supports nanoparticle-based studies on the EGF

receptor's role in supporting tumor growth and invasiveness. This research addressed a gap in cancer research by focusing on the covalent binding of quantum dots directly to activated receptors, rather than to ligands, in order to track the dynamic intracellular receptor populations in real-time, thereby providing key information for grading brain tumors and guiding treatment options for patients. Moreover, this type of approach could overcome issues associated with tumor heterogeneity by profiling the entire tumor site, instead of one region.

6.1.5 Human epidermal growth factor receptor 2 (HER2). Human epidermal growth factor receptor 2 (HER2) is a member of the EGFR family that plays an integral function in cell growth, sustenance, and differentiation. Dysregulation of the HER2 pathway is amplified in several cancer types. Upregulation of the HER2 gene is found to drive tumor aggressiveness and poor prognosis, especially in breast and gastric cancers.[171] In 2013, Zheng and colleagues designed a graphene quantum dots-based targeted therapy against breast cancer consisting of graphene quantum dots conjugated with titanate nanoflowers (TN), anti-HER-2 antibodies, and doxorubicin (DOX). The study showed that the nanoconjugate increased the targeted delivery of the anti-cancer drug to HER2-expressing breast cancer cells, enhanced cellular internalization, and remarkably promoted cytotoxicity.[172] Ghomi and colleagues developed a fluorescent carbon quantum dot nanogel directed towards breast cancer expressing HER2 receptors to improve the target delivery of Herceptin and bioimaging. This was achieved by coupling creatinine-modified carbon quantum dots and Herceptin into a nanogel (consisting of lecithin-inulin). The study demonstrated that the quantum dot nanogel was rapidly taken up by the HER2-positive breast cancer cells, and remarkable ROS production was observed. Also, the quantum dot nanogel enhanced the delivery of Herceptin towards the HER-2 expressing cells compared to non-HER-2 expressing cells.[173]

6.1.6 Other cancer stem cells/cancer biomarkers. Recently, a study by Aziz *et al.* observed that a carbon-mediated quantum dot conjugated with a PLD1 antibody remarkably promotes cytotoxicity, inhibits cell viability, and suppresses the proliferation of breast cancer cells than the antibody alone, making it an excellent drug delivery system.[174] In another research, graphene quantum dots integrated with ZIF-8 (zeolitic imidazolate framework-8), coated with PEG (polyethylene glycol) and EpCAM (epithelial cell adhesion molecule) peptide, were designed to target colorectal cancer expressing EpCAM receptors. The quantum dot-based system enhanced the release of the anti-cancer drug and remarkably reduced the tumor.[175]

6.1.7 Multiple biomarker system to overcome tumor heterogeneity. Tumor heterogeneity is a phenomenon in which diverse therapeutic and clinical presentations of cancers vary between tumors at different sites within a single cancer patient.[176] The challenge with this is that it can negatively affect diagnosis and treatment, due to possible sampling biases during biopsies, where only one region of the tumor is assessed, potentially missing aggressive subtypes.[176] A recent study notes the challenges associated with the alpha-fetoprotein (AFP) biomarker-based early diagnosis of liver cancer due to its limited diagnostic specificity. The researchers developed a multiplexed biomarker detection system to aid in early diagnosis. To do this, they labelled three biomarkers, glypican-3 (GPC3), dickkopf-1 (DKK1), and AFP, with fluorescent quantum dot nanoprobes (emission wavelengths at 565 nm, 605 nm, and 655 nm). Simultaneous fluorescence detection of the biomarker system was demonstrated using mixed reference samples containing human recombinant GPC3, DKK1, and AFP antigens, which were successfully detected within a linear range of 0.625–2.5 ng mL^{-1}, which is sensitive, quantifiable, and practical for real sample detection.[177] By enabling multiplexed quantification in a single assay with high accuracy, their strategy could potentially also address issues with tumor heterogeneity, where variable expression of individual markers across different tumor regions or cell populations can cause false negatives. Their approach could potentially increase detection reliability and support further clinical validation for accurate serum biomarker quantification.

6.2 Quantum dots actively targeting cancer and CSCs signaling pathways

Cancer and CSCs signaling pathways are essential mechanisms that play vital roles in cancer development, cancer relapse, tumor cell resistance to treatment, cancer proliferation, metastasis, and maintaining the stemness features of cancer.[116,178,179] Therefore, targeting cancer and CSCs signaling systems through a nanomedicine-based approach has the potential to enhance treatment efficiency,[180,181] especially with quantum dots.[182] In a study by Jung *et al.* (2010), a siRNA-based quantum dots fabricated with Tat, RGD peptides, and EGFRvIII (epidermal growth factor receptor variant III) targeting siRNA was constructed to evaluate the efficiency of siRNA-based quantum dots in knocking down EGFRvIII expressed in glioblastoma cells. The functionalized siRNA-quantum dots substantially decreased cell proliferation and inhibited the PI3K/AKT signaling pathway *via* attenuating the EGFRvIII gene.[183] In another study, different antibodies (PTEN, PDK1, and AKT) were conjugated to a semiconductor quantum dot to assess the protein expression levels implicated in the PI3K/AKT/PTEN pathway in colorectal cancer. The findings showed that tumor tissues with reduced or total loss of PTEN promote the upregulation of the PI3K/AKT/PTEN pathway *via* the activation of phosphorylated PDK1 and AKT.[184] In addition, a study conducted by Fakhroueian and coworkers (2022) developed a ZnO quantum dot against breast CSCs. The results showed that ZnO quantum dots significantly reduced the stemness genes, inhibited cell growth/viability, induced apoptosis *via* the extrinsic signaling pathways, and attenuated the JAK/STAT signaling pathways.[182]

Moreover, in one study, a quantum dot-based drug nanocarrier consisting of anti-CD22-coupled with cadmium–tellurium quantum dots (CdTe QDs) and doxorubicin (DOX) and gambogic acid (GA) (DOX/GA-CdTe-CD22) was designed to target CD22-positive lymphoma. The study demonstrated that the quantum-based nanocarrier preferentially increases drug accumulation in the tumor cells, enhancing the drug's anti-cancer effects with limited side effects on non-cancer cells. The study also showed increased apoptotic cell death by activating

the BAX/caspase-3/PARP signaling cascade.[185] In a recent study, Gong *et al.* (2025) fabricated a nano-drug delivery system made of silver (Ag), indium (In), and sulfur (S), $AgInS_2$ quantum dot (AIS QDs) coupled with celastrol (AIS QD@Cel) to assess its effect on cell death and signaling pathways in hepatocellular cancer.[186] The AIS QD@Cel enhances the cellular uptake of celastrol and facilitates more than ten-fold inhibition of hepatocellular cancer compared to the free celastrol. Also, the AIS QD@Cel induced apoptosis and autophagy cell death signaling. Furthermore, the study also reported modulation of key vital regulatory genes implicated in cancer and CSC signaling, such as WNT7B and NOTCH3, implicated in the Wnt/β-catenin and Notch signaling pathway, respectively.[186]

6.3 Quantum dots actively targeting cancer and CSCs tumor microenvironments

The TME (tumor microenvironment) is a critical obstacle that limits the efficiency of current conventional cancer and CSC treatment measures. The TME comprises several cellular and non-cellular components that work together to create an immunosuppressive tumor niche that facilitates carcinogenesis, treatment failure, and cancer relapse. The TME remarkably influences the efficiency of cancer therapeutics by creating physiological hindrances like reduced blood circulation (vascularisation), decreased oxygen (hypoxia), and immunosuppressive cells, which reduce drug transport and drive tumorigenesis, drug resistance, and circumvent immune response.[187–189] Targeting the cellular and non-cellular components of the TME (such as tumor cells, the extracellular matrix (ECM), immune and stromal cells, mesenchymal cell, exosomes, hypoxia, low pH, matrix metalloproteases (MMP)) using quantum dot mediated strategies offers a promising strategy to improve target delivery of cancer drugs and cancer/CSC treatment efficiency.

6.3.1 Actively targeting tumor-associated macrophages. Tumor-associated macrophages (TAMs) are key tumor-resident immune cells that play a vital role in cancer progression, angiogenesis, immune modulation, tumor invasion/migration, and drug resistance. The TME can reprogram TAMs into subpopulations of M1 and M2 subtypes. The M1 subtype TAMs promote anti-cancer activity. Meanwhile, M2 subtype TAMs can exert cancer development, angiogenesis, and tumor proliferation and attenuate T cell-triggered anti-cancer immunity. Hence, targeting TAM, especially the M2 subtypes, offers a promising cancer treatment modality to reprogram the immunosuppressive TME, eradicate remnant cancer cells, and circumvent cancer recurrence.[190–192] A study by Yuana and coworkers developed a carbon quantum dots integrated with TAM repolarisation promoter, TMP195 (CQDs@TMP195), to reprogramme the M2 TAM subtype to M1 TAM subtype. The study showed increased anti-cancer activity/immune responses.[193] Yao and colleagues (2025) designed a quantum dot-nanoplatform targeting the macrophage in the TME to enhance targeted drug delivery and anti-cancer effects in osteosarcoma. The nanoplatform consisting of folic acid (FA), macrophage membrane functionalized with a carbon quantum dot (CQD), Zoledronic acid (ZOL), and small interference inhibin subunit beta A (siINHBA), referred to as ZOL-siINHBA@CQD@RM-FA. The study demonstrated that the quantum dots-mediated nano system facilitated increased drug internalization, inhibited cancer cell growth, and invasion *in vitro*. Also, an *in vivo* study showed reduced tumor volume and attenuated the spread of the tumor cells to the lung with no systemic toxicity.[194]

6.3.2 Quantum dots targeting hypoxia. Hypoxia is a common attribute of the TME that arises from the continuous tumor proliferation rate that exceeds the oxygen present, consequently leading to inadequate vascularisation and the formation of poor tumor blood vessels. Hypoxia has a significant influence on the biological activity and neoplastic features of tumor cells, alters the therapeutic efficacy of cancer therapy, and drives tumor growth, tumor invasion, angiogenesis, and poor prognosis.[195,196] Studies have shown that nanoparticle carriers can efficiently improve the oxygen levels in the TME, increase drug target delivery, and enhance anti-cancer activity.[181,197] Hence, conjugated nanocarriers targeting vital genes implicated in hypoxia and a nanoplatform that enhances the oxygen levels in the TME are critical. In a recent study, Cui *et al.* (2024) designed a quantum dot-based system that has the potential to identify and treat hypoxic tumor cells using 4-(2-aminoethyl) benzenesulfonamide (ABS), an inhibitor of carbonic anhydrase IX (CA IX) commonly expressed in hypoxic tumor cells. The ABS was coupled into Ag_2S quantum dots *via* pegylation to form Ag_2S@PEG-ABS, which preferentially targets hypoxic colon cancer. The study effectively detected and eliminated hypoxic tumor cells.[198] Moreover, Pt-loaded and polyethene glycol (PEG)-functionalized graphene quantum dots were designed as a drug nano-cargo system to circumvent the hypoxia-driven treatment resistance in oral cancer. The system increases drug retention in hypoxic and normoxic conditions and reduces cancer proliferation.[199] In another study, pH-dependent composite quantum dots effectively deliver a siRNA in hypoxia-associated cancer cells. The study demonstrated enhanced anti-cancer effects and reduced toxicity.[200]

6.3.3 Quantum dots targeting the acidic tumor microenvironment. In physiological states, extracellular tissues and fluid pH are often regulated at about 7.4. While in pathological states like cancer, the pH is about 5.0–6.8 due to increased and continuous tumor embolism. A general characteristic of TME is an acidic environment (a low pH) strongly associated with cancer immune evasion, tumor development, and treatment resistance. The low pH arises from the acidic substances generated by the excessive tumor glycolysis.[201,202] Given that the TME is characterized by low pH, a quantum dot pH-responsive drug transport platform can potentially target acidic TME. For example, by harnessing the acidic tumor environment, a carvacrol-zinc oxide-based quantum dots (CVC-ZnO QDs) was fabricated as a pH-responsive drug nanocarrier for targeted treatment against breast cancer. The CVC-ZnO QDs specifically release the drug in the acidic TMC, with limited toxicity on normal cells. The CVC-ZnO QDs increase anti-cancer efficacy, trigger cytotoxic cell death, lipid peroxidation, and promote apoptosis in breast cancer cells.[203] In 2025, a study conducted by Su and coworkers developed a pH-responsive drug delivery system based on boric acid-mediated quantum

dots (BA-QDs) for bioimaging and hepatocellular cancer treatment. The BA-QDs were loaded with baicalein, hesperetin, and quercetin. The results demonstrated a pH-responsive drug discharge, enhanced bioimaging features, and a remarkable inhibitory effect on the cancer cells.[204]

6.4 Quantum dots for synergistic combinational cancer/cancer stem cell therapies

Combination therapy is a strategy that combines two or more cancer treatment strategies to enhance treatment outcome and overcome limitations associated with monotherapy. Combination therapy is the key principle of cancer therapy.[205] This approach targets vital mechanisms in a significantly synergistic and additive way. This strategy overcomes drug resistance and at the same time enhances the anti-cancer effects, such as inhibiting cancer growth, metastasis, suppressing mitotically active cells, eliminate CSCs, promote cell death and reduce the relapse of cancer cell.[205]

Quantum dot offers great potential for combination therapy for photodynamic and photothermal cancer therapies. Their distinct physiochemical features, such as photoluminescence, photothermal conversion potentials, and surface modification abilities make them excellent modalities for targeted cancer therapy.[206,207] By incorporating a quantum dot-based combination treatment strategy, scientists aim to attain improved treatment efficiency through synergistic actions.[208] A study by Yang and colleagues developed graphene quantum dots to enhance PDT and photothermal therapy (PTT) as a multifunctional nanosystem. The nanosystem has enhanced magnetic resonance imaging and fluorescence that responds to tumour cells, enabling simultaneous imaging and tumour treatment. Hence, this nanocomposite provided a novel multifunctional method for cancer diagnostics and treatment.[209]

In a similar way, Wo *et al.* designed a multimodal system consisting of magnetic nanospheres-based graphene quantum dots with silica shells. The multimodal system, together with four various treatments such as PDT, PTT, chemotherapy, and mechanical agitation were integrated to eliminate cancer cells.[210] In another study, quantum dots were utilized as PDT and sonodynamic therapy (SDT). Nene *et al.* created a nanocomposite using a cationic thiazole phthalocyanine-based graphene quantum dots against breast and cervical cancer cells.[211] Their findings showed PDT and SDT effects on both cell models, while the graphene quantum dots stimulate ROS production and induced cell death. Furthermore, Habiba and coworkers developed a quantum dots-based nanoconjugates in conjunction with PDT and chemotherapy to treat HeLa and DU145 cells. The results demonstrated that the nanoconjugates synergistically enhanced the anticancer effects.[212]

Integrating quantum dots with different cancer treatments improves the therapeutic efficiency and reduces treatment failure/drug resistance.[213] Nevertheless, quantum dots multimodal systems specifically targeting CSCs are limited. Hence, further investigations are required to develop a quantum dot multimodal approach to effectively target CSCs. In addition, critical evaluation is required to maximize dosing, limit adverse effects, and understand the mode of action between quantum dots and other treatments for enhanced and efficient therapeutic effects.

7. Limitations of quantum dots for clinical applications

Indeed, the application of quantum dots in cancer diagnosis and treatment has shown outstanding features in cancer research. Their physicochemical and optical features and quantum effects present distinct benefits compared to conventional fluorescent markers, rendering them ideal for several cancer detection and treatment applications. Challenges concerning safety still pose a serious threat.[146,214] Though quantum dots present several benefits in many applications, it is crucial to recognize their setbacks. Different setbacks, such as cytotoxicity, stability/pharmacokinetics, and non-specific binding must be tackled to maximise the application of quantum dots for cancer therapeutics.[151,214]

7.1 Cytotoxicity

Among the main limitations in leveraging quantum dots for cancer therapeutics is the potential toxic effects. Quantum dots, especially those formulated with heavy metal elements, like cadmium (Cd), lead (Pb), have been recorded to display cytotoxicity. The release of this heavy metal at the cellular level can cause cell damage and stimulate inflammatory reactions.[146,215] Moreover, different surface ligands and coating agents can impact their biological compatibility and possible cytotoxic effects. Hence, thorough safety evaluations and compliance with regulatory standards are required for safe biological and clinical application of quantum dots. To overcome the cytotoxicity of quantum dots, investigations using biocompatible quantum material using silicon, biomolecules, and carbon, are currently ongoing.[216] And safety evaluation of these biocompatible quantum materials and their long-lasting actions in the body are needed to limit any side effects.[216]

7.2 Quantum dots stability and pharmacokinetics

Another important hurdle to address with quantum dots is their stability and pharmacokinetics in the biological system. Quantum dots can encounter degradation, impacting their function as drug-delivery carriers.[151] Several approaches, like surface functionalization, coating, and encapsulation methods, are currently utilized to improve the stability and pharmacokinetics of quantum dots. The goal of these approaches is to shield the quantum dots from degradation/disintegration by cellular components, thereby prolonging their biodistribution time and boosting their internalization within the cells/tissue.[217,218]

In addition, the long-lasting effects, tissue distribution, and elimination mechanism of quantum dots in the body system are not clearly stated and need further investigation. Safeguarding the use of quantum dots requires not just tackling their toxic impact but also taking account of their long-lasting impacts, possible tissue accumulation, and environmental consequences. Understanding the aftermath biodistribution

and elimination processes of quantum dots is very important in safeguarding their application in clinical settings, and this will require extensive *in vivo* and translational studies.[219]

7.3 Quantum dots non-specificity binding

Usually, quantum dots have reactive surfaces that can result in non-targeted binding of molecules, thereby limiting the amount of drug delivered to the target cells/tissues. Hence, effective coupling/conjugation of quantum dots with ligands is vital for successful drug delivery to the targeted cancer cells/CSCs. Another impact of the conjugation process is the risk of reducing the optical attributes of quantum dots. The standard conjugation methods may interfere with the optical features of the quantum dots, impacting their efficiency in theranostic applications. Therefore, maximizing the quantum dots' optical characteristics and simultaneously allowing for targeted ligand binding are required to address this limitation.[220–222] Moreso, further investigations should be centred on the design of targeted biomolecule-based quantum dots that display strong affinity for CSCs and cancer cells by exploring unique targeting ligands besides conventional antibodies, to enhance specificity and internalization.

7.4 Clinical translation and regulatory perspective of quantum dots.

The quantum dots should be extensively examined for their safety, effectiveness, and quality before their applications in clinical settings. Regulatory authorities require detailed data on quantum dots in biological systems as it relates to their pharmacokinetics, biodistribution, toxicity, and long-term effects in the body. The primary regulatory focus is to establish a comprehensive nature of toxicity.[223,224] Meanwhile, studies have demonstrated that biomolecule-based quantum dots display less toxicity in preclinical settings with no remarkable adverse reactions.[225] Though the use of biomolecule-based quantum dots resonates with regulatory guidelines for sustainability and enhanced biocompatibility, there are still limitations. These limitations include the possibility for toxicity as a result of membrane alteration, oxidative imbalance, biological carriers, as well as issues with inadequate solubility, degradation, and immunogenicity.[226] Regardless of the remarkable preclinical findings, the scarcity of clinical trials and non-standardized treatment strategies hinders the translation of quantum dots for clinical cancer applications. Overcoming these limitations will involve long-term period toxicity examinations, authentic preclinical models, scalable production systems, and the establishment of regulatory standards that uphold safe, efficient, and cost-effective translational/clinical applications.[223,224,226,227]

8. Conclusion and future perspectives

Although our insight and knowledge of CSCs/cancer and its biological activities have increased, CSCs remain challenging to eradicate, particularly as a result of the limitations of current cancer diagnostic and therapeutic methods. As a result of tumor heterogeneity, treatment resistance, and the complicated interaction between CSCs and cancer cells, CSCs have become a major barrier to effectively eliminating cancer cells. Because of the complex biological structures and cellular processes of CSCs, it is crucial to examine their cell biology and mechanisms to identify biomarkers, signaling pathways, and components of the TME for selective targeting and eradication of CSCs. Cancer therapeutic approaches targeting CSCs may offer a promising breakthrough in abolishing tumor cells. The development of quantum dot-based strategies provides several opportunities for targeted diagnosis and treatment of CSCs. Their properties can be optimized through quantum dot functionalization to develop a multifunctional and smart nanosystem for targeting CSCs, providing excellent benefits and great research prospects. This review highlights the advancement of quantum-dot-based techniques targeting CSC and examines potential future research paths.

Quantum dots have ushered in a new paradigm in detecting and treating cancer and CSCs. This transformative technique unveils different quantum dot-based fabrications that have remarkably influenced cancer management. The prospect of cancer and CSCs diagnoses and therapies stands to leverage quantum dots that seamlessly incorporate molecular targeting, anti-cancer agents, and bioimaging potentials. Indeed, the application of quantum dots in cancer diagnosis and treatment has shown outstanding features in cancer research. Their physicochemical and optical features and quantum effects present distinct benefits compared to conventional fluorescent markers, rendering them ideal for several cancer detection and treatment applications. Nevertheless, challenges concerning safety still pose a serious threat. Though quantum dots present several benefits in many applications, it is crucial to recognize their setbacks. Possible cytotoxicity is a significant setback associated with quantum dots, affecting their safe use for clinical applications. Quantum dots, especially those formulated with heavy metal elements, such as cadmium, have been recorded to display cytotoxicity. Moreover, different surface ligands and coating agents can impact their biological compatibility and possible cytotoxic effects. Hence, thorough safety evaluations and compliance with regulatory standards are required for safe biological and clinical application of quantum dots. Furthermore, the long-lasting effects, tissue distribution, and elimination mechanism of quantum dots in the body system are not clearly stated and need further investigation. Safeguarding the use of quantum dots requires not just tackling their toxic impact but also considering their long-lasting impacts, possible tissue accumulation, and environmental consequences. Looking forward, some critical areas need additional research: (a) toxicity and biological safety. Further investigation is required to elucidate and address quantum dots' toxicity impacts, particularly those with heavy metal ions. Surface functionalization and heavy-metal-free integration present possible strategies to address toxicity and biological safety concerns. (b) Distribution and elimination. Understanding the aftermath biodistribution and elimination processes of quantum dots is

very important in safeguarding their application in clinical settings, and this will require extensive *in vivo* and translational studies.

CSC research aims to identify efficient targeting markers, drug delivery approaches, and anti-cancer drugs that can abolish CSCs in different cancers. Effective elimination of CSC could be accomplished by integrating advancements in CSC biology and quantum dot nanotechnologies. In conclusion, quantum dots provide great potential for CSCs and cancer diagnosis and treatment through targeted biomarker detections and target drug delivery to the tumor cells. Notwithstanding, their medical application requires a collective effort on biological safety, compatibility, and translational studies. With continuing advancement, quantum dots are positioned to contribute significantly to furthering CSCs and cancer research. In the coming years, quantum dot multifunctional nanoplatform will be a solution for the timely diagnosis and treatment of CSCs and cancer.

Author contributions

Conceptualization, M. T. M., O. C. D.; funding acquisition, H. A.; project administration, M. T. M., O. C. D., and H. A.; resources, H. A.; supervision, O. C. D. and H. A.; writing – original draft, M. T. M., O. C. D., and H. A.; writing – review and editing, M. T. M., O. C. D., and H. A. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software, or code have been included, and no new data were generated or analysed as part of this review.

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