MoS₂-based nanocomposites for cancer diagnosis and therapy

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ABSTRACT

Molybdenum is a trace dietary element necessary for the survival of humans. Some molybdenum-bearing enzymes are involved in key metabolic activities in the human body (such as xanthine oxidase, aldehyde oxidase and sulfite oxidase). Many molybdenum-based compounds have been widely used in biomedical research. Especially, MoS₂-nanomaterials have attracted more attention in cancer diagnosis and treatment recently because of their unique physical and chemical properties. MoS₂ can adsorb various biomolecules and drug molecules via covalent or non-covalent interactions because it is easy to modify and possess a high specific surface area, improving its tumor targeting and colloidal stability, as well as accuracy and sensitivity for detecting specific biomarkers. At the same time, in the near-infrared (NIR) window, MoS₂ has excellent optical absorption and prominent photothermal conversion efficiency, which can achieve NIR-based photothermal therapy. The modified MoS₂-nanocomposite can specifically respond to the tumor microenvironment, leading to drug accumulation in the tumor site increased, reducing its side effects on non-cancerous tissues, and improved therapeutic effect. In this review, we introduced the latest developments of MoS₂-nanocomposites in cancer diagnosis and therapy, mainly focusing on biosensors, bioimaging, chemotherapy, phototherapy, microwave hyperthermia, and combination therapy. Furthermore, we also discuss the current challenges and prospects of MoS₂-nanocomposites in cancer treatment.

1. Introduction

Cancer is one of the main causes of human death. The global cancer statistics released by the World Health Organization show that there were 18.1 million new cancer cases and 9.7 million deaths from cancer in 2018 [1]. The current main methods of cancer treatment are surgery, chemotherapy, and radiotherapy [2]. These therapies can only show limited efficacy [3]. The size of nanomaterials is between the size of biomolecules and cells. In theory, carefully designed nanomaterials can realize the regulation of cell state and function like organelles and exosomes. Nanomaterials for cancer treatment have been intensively studied in the past two decades. The latest advances in nanotechnology have made it possible to engineer complex nanostructures with unique physical properties and surface chemistry. Currently, nanomedicines for cancer have shown great potential compared to traditional therapeutic agents. Nanomaterials such as MoS₂, gold nanoparticles, MnO₂, iron oxide, carbon nanotubes and others have been widely developed for detection of cancer markers, imaging diagnosis, and treatment of cancer. Gold nanomaterials have a unique SPR effect and high X-ray attenuation coefficient, and can be used as efficient photothermal reagents and CT contrast agents for cancer. MnO₂ nanoparticles can catalyze H₂O₂ to generate oxygen (O₂), relieving tumor hypoxia and inhibiting cancer cell
proliferation and migration. Carbon nanotubes can be used as a good carrier of anti-cancer drug. Iron oxide nanoparticles (IONPs) that are one of the most promising magnetic resonance imaging (MRI) contrast agent precursors, which can be used for cancer diagnosis [4]. At the same time, IONPs can convert the magnetic energy of an alternating magnetic field into heat energy, effectively ablating cancer cells at high temperatures [5].

Among many nanomaterials, MoS\(_2\) nanomaterials are extremely attractive in cancer diagnosis and treatment [6–9]. First, MoS\(_2\) is a two-dimensional (2D) semiconductor nanomaterial, so it has the unique characteristics of 2D materials and the properties of semiconductors. These characteristics make it have great application prospects in cancer marker detection, cancer imaging, and treatment. Second, MoS\(_2\) is easy to achieve controllable preparation. Many 2D nanomaterials such as graphene, Ti\(_3\)C\(_2\)Tx MXene, black phosphorus and others are generally prepared in a top-down manner. It is difficult to control the size, morphology and surface properties of 2D nanomaterials. MoS\(_2\) nanomaterials can be synthesized in two ways, top-down and bottom-up. As a result, the controllable and precise synthesis of MoS\(_2\) nanomaterials can be achieved according to the needs of cancer diagnosis and treatment. Third, MoS\(_2\) nanomaterials is easy to functionalized with biomolecules and combined with other nanomaterials. Mo is a transition metal element with multiple valence states (from +1 to +6). MoS\(_2\) nanomaterials is extremely flexible and easy to achieve surface modification and doping of other elements. Therefore, MoS\(_2\) nanomaterials can also be used as a platform material to integrate other nanomaterials to form a multifunctional nanomedicine according to the require of cancer diagnosis and treatment. Finally, unlike many inorganic nanomaterials, such as gold nanomaterials, up-conversion nanomaterials, MoS\(_2\) (sulfur and molybdenum) are composed of elements that exist in the human body. Mo is a trace element necessary for human survival [10]. Molybdenum-bearing enzymes play a key role in human metabolism, such as xanthine oxidase, aldehyde oxidase and sulfite oxidase. Insufficient intake of molybdenum in humans can lead to esophageal cancer [11]. Many studies have shown that MoS\(_2\) nanomaterials has very good biocompatibility. In general, these advantages make MoS\(_2\) nanomaterials very promising in cancer treatment and diagnosis.

MoS\(_2\), as a diamagnetic compound with the property of semiconductor, exhibits excellent chemical and thermal stability. As shown in Fig. 1a, MoS\(_2\) has a typical two-dimensional layered structure, which belongs to the hexagonal crystal system. Each layer consists of two sulfur (S) atoms and a molybdenum (Mo) atom, forming an S–Mo–S sandwich plate with a spacing of 0.315 nm. Meanwhile, each Mo atom and six S atom coordinating ligand to form a triangular prism or octahedral structure [12,13]. The layers with the spacing of 0.349 nm connected through the weak van der Waals force, as well as the stacking order of different S–Mo–S layers for the C axis constitute various MoS\(_2\) crystal structures (Fig. 1b) [14].

As shown in Fig. 1c, 1T-MoS\(_2\), 2H-MoS\(_2\), and 3R–MoS\(_2\) are three different crystal structures of MoS\(_2\). The 1T-MoS\(_2\) has a metastable phase structure that Mo atoms adopt octahedral coordination, while each S–Mo–S unit constitutes a crystal cell, resulting in metallic or metallic properties of MoS\(_2\). The 2H–MoS\(_2\) structure is more stable that Mo atoms adopt trigonal prismatic coordination, in which two S–Mo–S units form a sandwich structure that Mo atoms adopt octahedral coordination, while each S–Mo–S unit constitutes a crystal cell, resulting in metallic or metallic properties of MoS\(_2\). The 2H–MoS\(_2\) structure is more stable that Mo atoms adopt trigonal prismatic coordination, in which two S–Mo–S units form...
a unit cell. The 3R–MoS₂ structure is also a metastable phase and Mo atoms adopt trigonal prismatic coordination, while every three S–Mo–S units form a crystal cell [15].

MoS₂-nanomaterials have been widely used in a lot of fields, on account of the unique physical and chemical properties, including electronic devices, a transistor, and a catalytic energy storage device [15–17]. In recent years, MoS₂-nanomaterials have attracted more attention in cancer diagnosis and treatment [7]. Firstly, MoS₂ has the large specific surface area and can effectively adsorb various molecules through covalent or non-covalent interactions, such as nucleic acids, proteins, drugs, fluorescent probes, and other molecules, forming MoS₂-nanocomposites with radioactivity, magnetism and imaging, also achieving excellent controlled release by specifically responding to the tumor microenvironment [18]. Secondly, the high absorption rate of MoS₂ in a wide wavelength range promotes its application in phototherapy, including the energy receptor of fluorescence resonance energy transfer, photodynamic therapy agent, and photothermal therapy agent. Meanwhile, a large number of negative charges are distributed on the surface of the MoS₂-nanocomposite, which enables them to be stably dispersed in the aqueous medium without obvious aggregation [19]. Finally, MoS₂ has the advantages of high electron mobility, tunable energy band, photoluminescence, good flexibility, and biocompatibility [14,20–24], which further promote its application in the biomedical field.

However, research MoS₂-nanocomposites in the biomedical field is still at an early stage, especially in terms of diagnosis and treatment of cancer [25]. In this review, we describe the latest developments of MoS₂-nanocomposites in cancer diagnosis and treatment systematically, mainly focusing on bioimaging, chemotherapy, phototherapy, and various combination therapy, with brief introduction of achievements in nanomaterials. In this review, we mainly focus on the detection sensitivity and accuracy [37]. MoS₂-based FET biosensors can better control static electricity and reduce low-frequency flicker noise due to interface traps and low surface roughness in its pristine surfaces.

MoS₂ is a biomarker for diagnosing prostate cancer, the second most common cancer among men worldwide [1]. The survival time of prostate cancer patients can be prolonged if it is detected early. Wang et al. [38] designed a label-free FET sensor based on MoS₂ to detect PSA detection, which was the first demonstration and application of the biological functionalization of MoS₂-nanosheet field-effect devices in the liquid phase. The specific binding of PSA with the antibody fixed to the mechanical exfoliated MoS₂ membrane caused a significant change of drain current. The method had high sensitivity, high specificity, and timeliness. However, the mechanical exfoliation method for obtaining single-layer or multi-layer MoS₂-nanomaterials has many limitations, such as long synthesis time, low yield, and batch-to-batch variations [39, 40]. Kukkar et al. [41] obtained few-layered MoS₂ nanosheets by electrolytic intercalation of sodium (Na⁺) ions into an original molybdenum sheet to produce Mo ions which could combine with S ions. During the process, the raw materials were easy to obtain, and the preparation of few-layered MoS₂ nanosheets was simple, without inorganic or organic byproducts. The MoS₂ nanosheets and anti-PSA antibodies were introduced into FET microdevices for constructing a particular PSA immunosensor that had a wider detection area (10⁻⁵ to 75 ng/mL). Although many studies have reported the sensitivity and specificity of FET sensors, the repeatability and accuracy have not been explored. Park et al. [42] prepared a MoS₂-based FET in which the 30–45 nm thick MoS₂ flakes had high field-effect mobility (μ = 30–50 cm²/V·s) on SiO₂/Si substrate, and Al₂O₃ could improve the electrical performance of the device and it was easy to be functionalized by 3-aminopropyltriethoxysilane (APTES) and glutaraldehyde (GA). The anti-PSA was fixed to the CHO end of GA via the reaction of lysine and aldehyde. Casein is used as a blocking agent to reduce non-specific molecular binding events in the immune response while uniformly chemisorbed anti-PSA on the surface of MoS₂, which could reliably and quantitatively detect PSA in a non-aqueous environment with excellent accuracy and repeatability (Fig. 2). Most traditional methods of diagnosing PSA are laboratory tests, which are inconvenient and expensive. In contrast, point-of-care (POC) testing has become a trend with the development of biosensors [43]. Yoo et al. [44] designed an epidermal skin-type POC device for real-time monitoring of PSA, which integrated the MoS₂ FET biosensor, readout circuit, along with the light-emitting diode (LED) that as an indicator into a system. PSA antibody could physically absorb on MoS₂ channel by van der Waals force without pre-surface chemical treatment. Meanwhile, the channel conductivity of the MoS₂ FET channel was affected when anti-PSA combined with PSA. Therefore, highly sensitive detection of PSA could be achieved through the current change of MoS₂ channel. The POC testing device had good electrical performance and mechanical durability under various mechanical stress conditions, and its detection limit (1 pg/mL) was much less than the clinical cut-off.

Recently, Yang et al. [45] prepared a FET sensor based on MoS₂ nanosheets to simultaneously detect the bladder cancer biomarkers (NMP22 and CK8) in patients’ urine. The recognition molecules of
NMP22 and CK8 were conjugated on different sensing channels of MoS\(_2\) nanosheets, and the channel current would change and achieve highly sensitive detection of NMP22 and CK8 when NMP22 and CK8 bound to their specific recognition molecules (the detection limits of NMP22 and CK8 as low as 0.027 aM and 0.019 aM, respectively).

2.2. Fluorescent biosensors

The traditional fluorescence methods easily are interfered with background fluorescence, leading to inaccurate detection results [46]. Fluorescence resonance energy transfer (FRET) requires the transfer of energy from donor to the recipient to sensitively detect biomolecules [47]. Fluorescence sensors based on nanomaterials can overcome the shortcomings of traditional fluorescence methods and selectively combine with target substances to ensure a high labeling success rate, obtain strong fluorescence detection signals, facilitate detection equipment to capture signals, and significantly improve detection sensitivity and reliability. MoS\(_2\) has been regarded as an effective energy receptor for quenching fluorescence, on account of its high surface area and particular optical characteristics [48]. Meanwhile, MoS\(_2\) is suitable for intracellular analysis due to its low cytotoxicity [49].

miRNAs play important roles in molecular pathways and are promising molecular biological markers to predict the early tumorigenesis or metastasis [50]. Currently, miRNAs are mainly detected by end-point technologies, including northern blotting, qualitative reverse transcription-polymerase chain reaction (qRT-PCR) [51], Northern blotting [52], and microarrays [53], which require a good deal of samples simultaneously take a long time. MoS\(_2\) nanomaterial-based fluorescent biosensors can overcome the above defects and improve detection sensitivity and specificity [54,55]. Xiao et al. [56] found that polycytosine (polyC) DNA could non-covalently functionalize MoS\(_2\) nanosheets to retain DNA activity and increase the recognition ability of probes. They synthesized diblock molecular beacons that possessed polyC tails attached to MoS\(_2\) nanosheets to detect miRNA. During co-incubation with layered MoS\(_2\), the van der Waals force make the polyC-MB adsorbed on MoS\(_2\) [57], and then the fluorescence of the dye is quenched by FRET [58]. DNA/RNA heteroduplex could be formed with the target miRNA because of the specific affinity between MB block and miRNA, while the duplex-specific nuclease (DSN) would cleave it, leading to fluorescence recovery. Furthermore, DSN could cause signal amplification by target recirculation. Considering that the extracellular detection of miRNA is complicated and time-consuming, Ouqeng et al. [59] prepared the folic acid (FA)-poly (ethyleneglycol)-modificatory MoS\(_2\) nanosheets and used fluorescent-labeled ssDNA probes to fix it (ssDNA-MoS\(_2\)-PEG-FA) for the first time, realizing one-step in-situ to detect endogenous miRNAs in the single cancer cell. After the cancer cells internalized the ssDNA-MoS\(_2\)-PEG-FA, the high binding force of miRNA-21 and ssDNA made the probe fall off from the MoS\(_2\) nanosheet, resulting in the rapid fluorescence recovery (Fig. 3 a, b). Nevertheless, there are many challenges in intracellular detection due to the high homology, small size and low abundance of miRNAs. For example, the signals read by a single step of in situ hybridization are relatively low and the sensitivity of miRNA detection is limited [59]. Besides, false-positive signals may be caused by the complex intracellular environment, nuclease degradation, or non-specific binding. A living cell detection strategy related to isothermal amplification and enzyme-catalyzed cycling reaction can increase the sensitivity of the intracellular analysis [50,61]. To this end, Zhu et al. [62] used the DNA
catalytic hairpin supported by MoS₂ as a signal amplifier to detect the low expression of miRNA-21 in living cells. Three kinds of DNA molecular beacons modified with Cy3 in the terminal consist of the three-branched catalyzed hairpin assembly (TB-CHA) probes that form “Y”-shaped three-branched duplex nanostructure when miRNA-21 is presented, releasing from the surface of the MoS₂ nanosheet. In the microenvironment of living cells, multi-site fluorescence modification and cyclic reaction enable TB-CHA probe to achieve significant fluorescence recovery.

Cancer cells secrete lactic acid to maintain their weakly acidic microenvironment (pH 6–7). Therefore, tumor sites can be confirmed by pH [64]. Detecting the regional pH of the tumor microenvironment via traditional ways (e.g., a pH meter or litmus test paper) is difficult because of its limited accessibility. pH-responsive polymers [65] with good biocompatibility can link the fluorescent molecules and optical quenchers to produce pH-dependent FRET compounds [66,67]. The MoS₂ nanosheets have a large specific area and abundant sulfur binding sites, thus the oligomeric or polymeric molecules can briefly functionalize them under mild conditions [68,69]. Park et al. [65] synthesized a FRET-based microsensor and encapsulated it in a microcapsule by attaching a pH-responsive polymer that contain a fluorescent terminal to the surface of a MoS₂ nanosheet (F–MoS₂ NSs). The pH-sensitive polymer could respond to subtle pH changes through conformational changes and converted it into FRET signals at a lower pH for detecting cancer cells. The microcapsules ensured that MoS₂ NSs did not leak while preventing the entry of adhesion proteins and lipids, avoiding the inactivation of encapsulated MoS₂ NSs, meanwhile realizing home position pH monitoring (Fig. 3 c-e).

EpCAM protein can be applied as a biomarker for cancer diagnosis, treatment, and prognosis because its overexpression was found in most cancer [70–72]. The majority of EpCAM-based diagnoses and treatments depend on anti-EpCAM antibodies, which cannot supply accurate clinical outcomes due to their instability and large-size under the physiological condition [73,74]. Aptamers, with small size and high specificity towards biomolecules, have been widely used in the sensor field [75]. On the other hand, Graphene quantum dots (GQDs) can serve as good FRET donors to detect specific biomarkers because of their high light stability [76]. Meanwhile, MoS₂ has a good light absorption capacity at a wide wavelength range and can be used as an efficient energy acceptor. For these reasons, Shi et al. [77] designed a novel GQD-PE-G-aptamer/MoS₂ “turn-on” fluorescent biosensors based FRET mechanism for the rapid and sensitive detection of EpCAM. Since EpCAM aptamer and the EpCAM protein have a stronger affinity, the separation between MoS₂ nanosheet and GQD-PEG-EpCAM aptamer could be promoted in the existence of EpCAM proteins, causing the restoration of fluorescence intensity. The biosensor could sensitively and selectively detect EpCAM in the detection range of 3 nM–54 nM, with a low detection limit (450 pM).

Recently, Xu et al. [78] synthesized silver nanocluster (AgNC) @ MoS₂ to detect ATP in Hela cells. ATP aptamer was as templates to prepare DNA-AgNCs, which was as a fluorescent label and an Ag element tag to quantitatively analyze ATP. In addition, DNA-AgNC was loaded on MoS₂ nanosheets by van der Waals forces, and its fluorescence was quenched by MoS₂ nanosheets. The interaction between DNA-AgNCs and MoS₂ nanosheets could be weakened when ATP specifically bound to its aptamer. As a result, DNA-AgNC was released from the surface of MoS₂ nanosheets, and its fluorescence was recovered. The detection limits of this nanoplatform as low as 0.18 nmol/L. Similarly, Zhao et al. [79] used fluorescein (FAM) labeled DNA to functionalize MoS₂ for detecting CA15-3. The fluorescence of FAM-DNA was quenched by MoS₂ via FRET and was restored when CA15-3 bound to FAM-DNA. The fluorescent biosensor not only had a low detection limit (0.0039 U/mL) but also displayed high sensitivity.

2.3. Electrochemical biosensors

The electrochemical biosensor converts the interaction of biomarkers and bioreceptors into electrical signals, which has many advantages such as simple preparation, low cost, simple operation, fast speed, good stability, strong specificity, high sensitivity. The introduction of nanomaterials in electrochemical biosensor systems can further enhance the detection signal, improve detection specificity and
accuracy, and has been widely used in the biomedical field. As a semiconductor that possesses an indirect energy band of 1.29 eV, MoS2 has good electrocatalytic activity due to the enhancement of planar electrical transmission performance [80]. Furthermore, MoS2 modified by monometallic, bimetallic or even trimetallic nanoparticles exhibits higher catalytic performance [81,82]. Currently, the MoS2-based electrochemical sensors have detected multiple tumor markers, such as H2O2, carcinoembryonic antigen (CEA), circulating tumor cells (CTCs) and miRNA.

MoS2-based nanocomposites can electrochemically catalyze the reduction of H2O2 to produce H2O and O2, detecting H2O2 via the current change induced by redox reaction [83]. In situ detecting H2O2 secreted by cells is extremely significant because the intracellular H2O2 concentration level is a key physiological parameter for early screening and diagnosis of primary cancer [84]. Electrochemical methods can be utilized for detecting H2O2 secreted from living cells because they can offer an interface to bridge cells and sensing electrodes [85]. However, electrochemical sensors currently used for in situ detecting H2O2 not only require complicated manufacturing processes but also are not feasible for cell adhesion and growth. Dou et al. [86] synthesized Au–Pd–Pt nanoflower-modified MoS2 nanosheet-based sensor through a wet chemical method to in-situ monitor the secretion of H2O2 that from living MCF-7 cancer cells, which enhanced the electrochemical catalytic activity through synergistic action of the MoS2 nanosheets and the highly dispersed tri-metal hybrid nanoflower, and improved the biocompatibility of cell adhesion and growth by immobilizing laminins on the surface of nanocomplexes. Although loading noble metals on MoS2 can improve detection sensitivity, it would decrease stability and increase costs. Interlayer expanded MoS2 (2H-MoS2) without noble metal nanoparticles can also provide high sensitivity, clarity, and resolution for H2O2 detection. Shu et al. [87] used excessive thiourea to synthesize IE-MoS2 with a wide interlayer spacing of 9.4 Å via the one-step hydrothermal reaction with good electrical conductivity and strong combining ability with ‘OH intermediates, realizing the rapid kinetics reduction of H2O2 (H2O2 + 2e− → 2OH−). The sensitivity of the first-rank IE-MoS2 is considerably high (1706.0 μA/(mM-cm2)), while the detection limit is very low (0.2 μM). Thanks to Mo2C advantages of high conductivity, Mo2C/MoS2 co-axial nanorods had a higher sensitivity of H2O2 (1080 μA/(mM-cm2)) and lower detection limit (0.2 μM) than IE-MoS2. At the same time, Mo2C@MoS2 had rich surface amino groups, and could be used to specifically detect MDA-MB-231 cells after functionalized folate ligand [88]. Besides, studies found that self-supporting nanorays with a three-dimensional (3D) structure could further enhance the sensitivity of H2O2 detection because they had more catalytic sites and larger contact areas than the two-dimensional electrode [89]. Du et al. [90] designed a MoS2 nanosheet array that distributed over the carbon cloth (MoS2/CC) for ultrasensitive detection of trace amounts of H2O2 secreted by living cells. MoS2/CC with low charge transfer resistance and abundant surface area as a good electron conductor facilitated the electron transfer from the MoS2/CC electrode to reduce H2O2, which led to significant current changes to sensitively detect the concentration of H2O2. As a result, MoS2/CC modified electrode had an outstanding sensitivity of 5300 μA/(mM-cm²). Recently, Yang et al. [91] prepared 3D MoS2/reduced graphene oxide composite (3D-MoS2/rGO) as a sensitive sensor of H2O2. Graphene could not only serve as the supporting structure for the growth of MoS2 but also increase the specific surface area of MoS2/rGO to promote reaction with H2O2. The 3D-MoS2/rGO composite had a good anti-interference ability, a lower detection limit (0.19 μM), and a wider linear range (2 μM–23.18 mM).

CEA (tumor-associated glycoprotein) is a crucial marker to detect multiple tumors but its concentration is ultralow in the early stages of cancer. Hence, in order to early diagnosis cancer, high sensitivity detection of CEA is very vital. MoS2 can easily modify with specific antibodies to prepare highly sensitive electrochemical sensors to detect tumor-specific antigens. Wang et al. [92] integrated MoS2–Au with strong catalytic activity and Ag nanoparticles (AgNPs) with good electricity into an electrochemical immunosensor for detecting CEA. MoS2–Au used as the solid support for CEA primary antibody (Ab1) and AgNPs were served as the supporter of glucose oxidase (GOx) and CEA secondary antibody (Ab2), which could combine with CEA respectively to form a sandwich-type immunosensor. The H2O2 was produced after glucose was added and MoS2–Au could catalyze reduction of H2O2 to cause the current to vary with the concentration of CEA. The biosensor had a range of linearity from 1 pg/mL to 50 ng/mL and a limit of detection of 0.27 pg/mL. Analogously, Ma et al. [93] also synthesized a sandwich-type electrochemical immunosensor with a broader detecting range (10 fg/mL to 100 ng/mL) and a lower limit of detection (3.09 fg/mL). The trimetallic yolk–shell Au@AgPt nanocubes (Au@AgPt YNCs) with good catalytic activity loaded on amino-modified MoS2 nanoflowers to form MoS2 NPs/Au@AgPt YNCs as the marker of Ab2, which could catalyze the reduction of H2O2 more effectively and thus amplify the current signal. At the same time, gold triangle nanoprism (Au TNPs) as substrate materials offered a steady environment for immunosensors. The reduction reaction of H2O2 was triggered to realize the detection of CEA concentration. When CEA was combined with Au TNPs and MoS2 NPs/Au@AgPt YNCs respectively, Jia et al. [94] used MoS2/CuS–Au as sensing platform and Au@Pd porous nanorods (Au@PdPd MP-Ab1) as signal amplifiers to fabricate sandwich-type biosensor for detecting CEA. MoS2/CuS–Au could increase the loading rate of Ab1 and the electron transport rate. Au@PdPd MP-Ab1 had excellent catalytic activity and could generate highly sensitive current signal, which could efficiently detect CEA in human serum samples. Despite tremendous progress of electrochemical immunosensors have been achieved, ultra-sensitive high-performance immunosensors with multiple amplified signals are still challenging [95]. In order to further improve their detection performance and amplify detection signal of CEA, the reducing substrate (o-phenylenediamine-o-PD), CuS@O, and Ferrocene(Fc) and enzyme amplifiers were introduced into the detection system of MoS2 and H2O2 [96–99]. Su et al. [100] used MoS2 nanocomposites (MoS2–AuNPs) decorated with gold nanoparticles to construct an enzyme-assisted signal amplification sensor for CEA analysis. MoS2–AuNPs could load anti-CEA (Ab1) after being modified onto the cleaned glassy carbon electrode (GCE) to form anti-CEA/MoS2–AuNPs/GCE. Meanwhile, HRP-anti-CEA (Ab2) was loaded on the surface of MoS2–AuNPs to produce HRP-anti-CEA/MoS2–AuNPs nanoprobe for blocking the nonspecific absorption. The effective amplification of the electrochemical signal is attributed to the following three strategies. Firstly, MoS2–AuNPs catalyze the reduction of H2O2 to produce ‘OH intermediates which could oxidize o-PD to form o-PDOx, amplifying the changes of current response signal. Second, the HRP-anti-CEA could also generate the above reaction to further amplify the current change. Third, the introduction of HRP could not only prevent non-specific adsorption but also catalyze the redox reaction of H2O2 and o-PD to enhance the electrochemical properties of the sensor. Such immunosensor has a lower limit of detection of 1.2 fg/mL. CTCs, the malignant cells found in biological fluids and indicate the invasion and metastasis of tumor, which ultimately lead to the death of the patient [101,102]. At present, multifarious methods have been used to capture and detect CTCs, such as immunomagnetic separation [103], microfluidic chip [104], as well as flow cytometry [105]. Nevertheless, majority of methods are complicated to operate or require expensive instruments [106–108]. Label-free detection of CTCs by electrochemical methods will greatly simplify analytical techniques and accelerate the capture of CTCs [109,110]. MoS2-based nanocomposites that possess good electrical conductivity and easily functionalized surface, and it is thus a very suitable candidate for electrodes. Chen et al. [111] constructed MoS2/FA-modified AuE (AuE/MoS2/FA) by using folic acid-modified two-dimensional MoS2 (MoS2/FA) as a signal indicator and assembling it on the surface of the gold electrode (AuE), which could detect CTCs by an alternating current (AC) impedimetric method. Since the conductivity of MoS2 (0.14 S/m) and cancer cells (0.13–0.23 S/m) is approximate, the sensitivity of the MoS2 electrochemical sensor
may be enhanced after adding cancer cells. This is because that an insignificant change in the conductivity caused by cancer cells causes a conspicuous change in the impedance of the semiconductor electrode. Meanwhile, MoS₂/FA with a high specific surface area might increase the contact sites between semiconductor and CTCs, further improving the sensitivity. Besides, the FA loaded on 2D MoS₂ could specifically recognize HeLa cells that is enrichment of folate receptor (FR), significantly increasing the impedance even in the presence of a few HeLa cells, because MoS₂ is loaded with a lot of FA. Therefore, the prepared electrochemical sensor could detect cancer cells in a linear range of 1 to 10⁵ cell/mL, and the limit of detection is 0.43 cell/mL (S/N = 3) (Fig. 4).

However, the captured CTCs were incapable of effectively releasing, greatly hindering the further proliferation and downstream biomedical applications of cells [112]. It is known that most of the current cell release strategies based on enzymes or other chemical methods would seriously damage cells, reduce cell viability and affect analysis results [106,107]. Light-induced cell release has highly precise controllability [108]. MoS₂ nanosheets (NFs) can be used as the NIR-regulated control element to effectively release CTCs. Wang et al. [113] designed a NIR optical switch biological platform to capture, detect, and release CTCs. Firstly, the surface of ITO was modified with PEG-MoS₂ NFs@ gelatin as the working electrode. The MUC1 aptamer is then fixed to its surface by amination between the aptamer and gelatin. Thus, it could specifically bind to the MUC1 protein overexpressed on the membrane of MCF-7. The rapid electron transfer between the nanoplatform and the redox probe could result in a significant change of impedance when cancer cells were added, which was attributed to the quite high conductivity of MoS₂ NFs. Meanwhile, MoS₂ with strong photothermal ability could make the NIR-light transform into heat that would melt the gelatin, releasing cancer cells. Notably, the nanoplatform had a remarkable release efficiency of 92.5% and the released cells remained in good cellular shape and proliferative ability.

In addition, electrochemical sensors based on MoS₂ can also sensitively detect miRNA, triiodothyronine, cytokeratin 19 fragment antigen 21-1, EpCAM, and α-methylacyl-CoA racemase [114–119]. These probes were prepared by functionally modifying specific ligands at the MoS₂-based nanocomposites. The current or impedance of the probes would change when the target substances and the ligands on the probe surface specifically interacted. In this way, highly sensitive detection of target substances could be achieved. For example, Su et al. [120] prepared highly sensitive miRNA-21 probe (MLNP) by functionally modifying specific DNA (specifically binds to miRNA-21) on MoS₂–AuNPs. In the presence of miRNA-21, MLNPs formed a typical “sandwich” structure to cause changes of impedance. The miRNA-21 detection limit of the probe was as low as 38 aM and the detection range was as wide as 10 aM - 1 μm.

2.4. Other biosensors

Surface-enhanced Raman scattering (SERS) overcomes the inherent limitations of traditional Raman spectroscopy and improves its sensitivity by SERS substrates [121]. SERS substrates are dependent on plasmonic effects in electromagnetic “hotspots” and highly concentrated charges originating from surface roughness [122]. SERS biosensors have obvious advantages, such as fingerprint recognition and single-molecule sensitivity. Recently, MoS₂ were prepare MoS₂/precious metal nanocomposites to fabricate highly sensitive SERS substrates [123]. For example, Liu et al. [123] designed Ti₃C₂ (MXene)/MoS₂@Au nanoparticles (AuNPs) (MMA) to detect miRNA-182. AuNPs not only were used to enhanced the signal of SERS, but also could graft the hairpin probe DNA labeled with Cyanine 5 (Cy5) via Au–S bonds. Cy5 were released from the MoS₂ nanocomposites when the probe DNA bound with miRNA-182, and then reduced the intensity of the SERS peak at 1362 cm⁻¹. In this way, miRNA-182 could be detected with high sensitivity and the detection limit of miRNA-182 was 6.61 aM.

MoS₂ nanomaterials usually have weak peroxidase activity. Recently, Sun et al. [124] found that the peroxidase activity of MoS₂ could be greatly increased by modifying MoS₂ with gold nanoparticles. On this basis, the MoS₂/Au could catalyze H₂O₂ to generate *OH with strong oxidizing properties that could oxidize 3,30,5,5-tetramethylbenzidine (TMB) to the colorimetric assay of H₂O₂. Electrochemiluminescence (ECL) has many advantages, such as low background, high sensitivity, simple operation, good controllability. Recently, MoS₂ nanocomposites also have been used in ECL biosensors.

Fig. 4. (a) The fabrication of AuE/SC/FA for CTC capture. (b) Schematic model of HeLa cell binding with FA and repelling NC on a negatively charged AuE/SC/FA electrode surface. (c) The corresponding impedance curves. SC: Semiconductor; AuE: gold electrode; BSA: albumin from bovine serum; CTC: circulating tumor cells; FA: folic acid; NC: normal cells with low folic receptor expression. (d) Relative impedance at 10 Hz with time for AuE/MoS₂/FA electrodes scanned while being immersed in HeLa cell with different concentrations in PBS. The grey solid lines indicate fittings using exponential association. (e) Calibration plots of relative impedance at 10 min for determining HeLa cells at AuE/MoS₂/FA electrodes while changing the concentration of HeLa cell in PBS. (f) Relative impedance at 10 min at AuE/MoS₂/FA electrodes for PBS, 10% FBS solution, MG3T3-E1 cell suspension, HeLa cell suspension and the mixture of all, indicating a good selectivity of AuE/MoS₂/FA electrodes. (g) Relative impedance at 10 min at AuE/MoS₂/FA electrodes for HeLa, MCF-7, MG-63 and SMMC-7721 cancer cell suspensions. Three replicates were performed. Reprinted with permission from Ref. [111]. Copyright 2019, Biosensors & Bioelectronics.
due to their strong fluorescence quenching ability and electrocatalytic performance [125,126]. For example, Delnia Bahari et al. [127] prepared MoS\textsubscript{2} based electrochemiluminescence sensor (GO-HBP-Ru-complex-NCND-anti-CA19-9 Ab\textsubscript{1}) to detect carbohydrate antigen 19-9 (CA19-9). In this sensor, amine-rich nitrogen-doped carbon nanodots (NCNDs) linked to Ru(bpy)\textsubscript{2}((phen-NH\textsubscript{2})\textsuperscript{2+}) was loaded on graphene oxide grafted hyperbranched aromatic polyamide (GO-HBP) to generate and amplify the ECL signal, and MoS\textsubscript{2} was used as a strong quencher. The sandwich complex of GO-HBP and MoS\textsubscript{2} would be formed and cause ECL signal quenching via FRET effects when CA19-9 antigen and MoS\textsubscript{2}-Ab\textsubscript{2} were added.

3. Bioimaging

Early biological behavior analysis and high-precision positioning of tumors improve the accuracy of tumor qualitative, tumor staging and curative effect analysis. Therefore, high-precision imagological examinations play an increasingly important role during the treatment process to achieve personalized medicine, optimize treatment effect, and monitor the treatment response [128-132]. The common tumor imaging method is fluorescence (FL) imaging which has good selectivity, fast response, high resolution that can observe subcellular structures and realize real-time imaging. For example, Zhang et al. [133] fabricated poly(N-isopropylacrylamide) (PNIPAM)-peptide-Au nanospheres with red fluorescence for observing its endocytosis pathway in HeLa cells. FL imaging usually obtained under ultraviolet rays or visible light irradiation, but hemoglobin and other biomolecules have strong absorption of visible light and ultraviolet rays, leading to a weaker penetration depth of FL imaging. Most tumors are located inside the body that requires imaging methods have longer penetration depth and high resolution, implying that common FL is not very suitable for deep tumor imaging.

Currently, there are many imaging methods used to overcome the above difficulties. These methods are mainly divided into three categories: The first category mainly uses near-infrared light as the excitation light source or detection signal, including near-infrared fluorescence imaging (NIRF), two-photon imaging (TPF), and photoacoustic imaging (PA); The second category is to use ultra-short wavelength, high-energy rays as the excitation light source or detection signal, including positron emission tomography (PET, γ-photons) and X-ray computed tomography (CT, X-ray); The third category is the use of ultra-long wavelength electromagnetic waves as the excitation light source (such as MRI). The penetration depth of these imaging is longer than common FL imaging (Table 1). MoS\textsubscript{2} has various physicochemical properties (such as strong near-infrared absorption and easy functional modification), which enables it to be combined with other materials to fabrication powerful imaging platforms. MoS\textsubscript{2} nanocomposites have aroused great concern from scientific researchers in recent years (Table 2). In this part, we will introduce the NIRF imaging, PA imaging, CT imaging, PET imaging and MRI based on MoS\textsubscript{2} nanomaterials according to the penetration depth from shallow to deep.

3.1. FL imaging

Near-infrared light can be divided into two areas: the first area (NIR-1, 650–900 nm) and the second part (NIR-2, 1000–1700 nm). NIR-1 and NIR-2 both have a longer penetration depth in the body than visible light because biological tissues have a low absorption for them [134-136], indicating that NIR-1 and NIR-2 are biological transparent windows. Meanwhile, the normal biological tissues hardly get damage and not emit light (without background fluorescence) when exposed to the NIR light. Once special nanomaterials absorb NIR light and then transform into required signal or energy at tumor site, good contrast imaging of tumor can be achieved by NIR light irradiation, as shown in Fig. 5. These advantages have made NIRF imaging widely used in cancer imaging in recent years.

NIRF imaging is a novel in vivo imaging method with low background signal, high resolution, and high stability. Zero-dimensional (0D) semiconductor nanocrystals, commonly called quantum dots (QDs), have a variety of special optical characters, including wide excitation and narrow emission spectra, strong fluorescence, and high photobleach resistance [137]. Therefore, QDs have become fluorescent labels for biomedical imaging [138]. Nevertheless, it is difficult to prepare multifunctional MoS\textsubscript{2} nanoplatform with excellent luminescence due to the strong quenching effect when QDs directly bind with MoS\textsubscript{2}. Zhang et al. [139] prepared RGD-QD-MoS\textsubscript{2} nanosheets (NSs) that could successfully be used for targeted fluorescence imaging under NIR (785 nm) laser. MoS\textsubscript{2} NSs adsorbed BSA (bovine serum albumin) on its surface by the van der Waals force, and BSA was conjugated QDs (CdSe/ZnS, 580 nm) by forming amide bonds. Subsequently, RGD (arginine-glycine-aspartic) with outstanding tumor-targeting capability combined with the carboxyl-activated QDs to obtain RGD-QD-MoS\textsubscript{2} NSs. BSA not only acted as an anchor to conjugate QDs but also decreased the fluorescence quenching of QDs by broadening the distance between QDs and MoS\textsubscript{2} NSs. Meanwhile, MoS\textsubscript{2} NSs with lots of defect sites could be efficiently modified with thiolated PEG to enhance their colloidal stability. Compared with QD-MoS\textsubscript{2} NSs (without RGD), RGD-QD-MoS\textsubscript{2} NSs could specifically combine with integrin αvβ3 that is highly expressed on HeLa cells membrane, which is beneficial to produce a stronger fluorescence signal on the HeLa cell membrane and in the tumor areas of HeLa tumor-bearing Balb/c nude mice when treated with RGD-QD-MoS\textsubscript{2} NSs (Fig. 6 a-d).

MoS\textsubscript{2} must be modified by NIR fluorescent substance to obtain the function of NIRF imaging because themselves cannot emit NIR light [142,143], which requires careful design and complex synthesis process. The TPF excitation is a kind of fluorescence process, in which simultaneously absorb two photons to excite the fluorophore. The excitation light source of TPF usually is near-infrared laser which can emit fluorimetry under the visible light region. Compared with traditional fluorescence (SFF) imaging technology, TPF imaging technology has deeper tissue penetration, lower tissue autofluorescence and less photobleaching [144,145]. Monolayer MoS\textsubscript{2} has great photoluminescence because of their indirect-direct band gap transition, but its applications in TPF imaging are rare due to its extremely low room-temperature TPF quantum yield (QY) (Φ ≈ 1%) [146-151]. Different from monolayer MoS\textsubscript{2}, MoS\textsubscript{2} quantum dots (QDs, their size are below 10 nm) have unique optical and electrical properties that attributed to the size and quantum confinement effect [152,153]. MoS\textsubscript{2} QDs have a higher two-photon absorption cross-section than organic dyes and common semiconductor QDs, representing it can be applied to TPF imaging [154]. Dai et al. [140] fabricated controllable-size MoS\textsubscript{2} QDs which had high TPF QY (Φ = 9.65%), long fluorescence lifetime (4.66 ns), and favourable fluorescent stability in the pH range of 4–10. The bright blue fluorescence could be observed in HeLa cell treated by MoS\textsubscript{2} QDs when irradiated by NIR-1 (700 nm) and the fluorescence brightness had not changed significantly after continuous excitation 30 min, indicating that

| Imaging modality | Incident light | Detection signal | Depth | Resolution |
|------------------|---------------|------------------|-------|------------|
| Common FL imaging | 350-650 nm | Vis | −1 mm | 0.2–0.4 μm |
| FL imaging | 650–900 nm | NIR | −6 mm | 0.35–0.5 μm |
| NIRF imaging | 1000–1700 nm | Vis-NIR | −7 mm | 0.3–1 μm |
| PA imaging | 650–950 nm | Ultrasonic | −50 | 20–300 mm |
| CT imaging | 0.01 nm–10 nm | X-rays | No limit | 50–500 μm |
| PET imaging | −0.002 mm (511 keV) | γ-photons | No limit | 2–7 mm |
| MR imaging | −7 m (42.6 MHz) | Radio wave | No limit | 25–100 μm |
## Table 2

MoS₂-based nanocomposites for cancer imaging and therapy.

| Materials                          | Physically trigger | Therapy                          | Imaging modes | In vivo models | Therapeutic effect                  | Refs |
|-----------------------------------|--------------------|----------------------------------|---------------|---------------|-------------------------------------|------|
| DOX-MoS₂/Pt                       |                    | drug delivery                     |               |               | /                                   | [378]|
| DOX-PSMS-PEG                      | NIR laser(808 nm)  | drug delivery                     |               |               | /                                   | [206]|
| DOX/DNA/MoS₂-NS                   | ATP                | drug delivery                     |               |               | /                                   | [379]|
| MoS₂/GO@DOX                       | GO-targeting       | drug delivery                     |               |               | Mice bearing B16 tumor              | [213]|
| DOX@MoS₂-PEI-HA                   | NIR laser(808 nm)/pH| drug delivery                     | PET          | Mice bearing MCF-7-| Completely eradicate | [181]|
| F-MoS₂ NSs.                       | NIR laser(808 nm)  | PTT                              |               |               | ADR tumor                           | [184]|
| MoS₂-CS-Cype                      | NIR laser(808 nm)  | PTT                              |               |               | /                                   | [280]|
| MoS₂-PEG nanoflakes               | NIR laser(808 nm)  | PTT                              |               |               | Mice bearing 4T1 tumor              | [244]|
| MoS₂-PFG                         | NIR laser(808 nm)  | PTT                              |               |               | Delay tumor growth                  | [240]|
| MoS₂-PPEG                         | NIR laser(808 nm)  | PTT                              |               |               | Mice bearing 4T1 tumor              | [254]|
| MoS₂-GSH nanodots                | NIR laser(808 nm)  | PTT                              |               |               | Completely eradicate                | [252]|
| RGD-QD-MoS₂ NSs                  | NIR laser(785 nm)  | PTT                              | NIF          | Mice bearing HeLa | Reduce tumor volume            | [110]|
| MoS₂@PZAC                        | NIR laser(808 nm)  | PTT                              | MRI          | Mice bearing 4T1 tumor              | [178]|
| MoS₂-Gd-BSA                      | NIR laser(808 nm)  | PTT                              | MR/PA        | Mice bearing 4T1 tumor              | [305]|
| Layered MoS₂ hollow spheres      | NIR laser(808 nm)  | PTT                              | CT/IR        | Rabbit bearing VX2 tumor            | [242]|
| HA-MoS₂                          | NIR laser(808 nm)  | PTT                              | FL/PA        | Mice bearing HCT116 tumor           | [293]|
| 64Cu-MoS₂-IO-(d)PEG              | NIR laser(808 nm)  | PTT                              | MRI/PAT/PET  | Mice bearing 4T1 tumor              | [177]|
| p-MoS₂/n-rGO-MnO₂-Pc              | NIR laser(980 nm)  | PDT                              |               |               | /                                   | [262]|
| MoS₂-PFGT/C66                    | NIR laser(808 nm)  | PTT/PDT                          |               |               | Mice bearing 4T1 tumor              | [269]|
| MoS₂-LA-K11(DMA)-TBO              | NIR laser(808 nm)/ | PTT/PDT                          |               | Mice bearing SCC-7 tumor            | [270]|
| MTR                               | 630 nm             |                                   |               |               | Delay tumor growth                  | [270]|
| MoS₂-UCNPs-FA/ZnPc               | NIR laser(808 nm)/ | PTT/PDT                          | NIF          | Mice bearing HCC38 tumor             | [289]|
| 980 nm                            |                     |                                   |               |               | Delay tumor growth                  | [289]|
| PEG-MoS₂-Au-C66                   | NIR laser(808 nm)/ | PTT/PDT                          | CT/NIF       | Mice bearing 4T1 tumor              | [381]|
| 660 nm                            | 660 nm             |                                   |               |               | Reduce tumor volume                 | [381]|
| Cy5.5-BSA-MoS₂                    | NIR laser(808 nm)  | PTT/PDT                          | FL/PAT       | Mice bearing HepG2 tumor             | [292]|
| MoS₂-UCNPs@C66@SiO₂               | NIR laser(808 nm)  | PTT/PDT                          | CT/MRI/UCL   | Mice bearing U14 tumor              | [382]|
| BSA-MoS₂                          | MW irradiation     | MW thermal therapy               |               | Mice bearing H22 tumor models       | [279]|
| MoS₂ encapsulated in nanocapsules | MW irradiation     | MW thermal therapy               | CT           | Rabbit bearing VX2 tumor            | [280]|
| sandwich-like MoS₂@MOS            | NIR laser(808 nm)  | PTT/drug delivery                 |               |               | /                                   | [334]|
| Fe₃O₄@MoS₂@En3D-DOX               | NIR laser(808 nm)  | PTT/drug delivery                 |               |               | /                                   | [334]|
| HMSNs/DX(1@MoS₂/Tf)              | NIR laser(808 nm)  | PTT/drug delivery                 |               |               | /                                   | [207]|
| Mn-doped Fe₃O₄@MoS₂               | NIR laser(808 nm)  | PTT/drug delivery                 | MRI          | Mice bearing MCF-7 tumor             | [307]|
| PMO-DOX@MoS₂-PFG                  | NIR laser(808 nm)  | PTT/drug delivery                 |               | Mice bearing 4T1 tumor              | [307]|
| MoS₂-HPG-DOX                     | NIR laser(808 nm)  | PTT/drug delivery                 |               | Mice bearing 4T1 tumor              | [307]|
| MoS₂-PFG-FA/DOX                   | NIR laser(808 nm)  | PTT/drug delivery                 |               | Mice bearing 4T1 tumor              | [307]|
| MoS₂/HSA-DOX                     | NIR laser(808 nm)  | PTT/drug delivery                 |               | Mice bearing 4T1 tumor              | [307]|
| HA-PEI-LA-MoS₂-PG@DOX/Mei          | NIR laser(808 nm)/ | PTT/drug delivery                 |               | Mice bearing MCF-7 tumor             | [314]|
| HA-PEI-LA-MoS₂-PG@DOX/Mei          | pH                  |                                   |               | Mice bearing SCC-7 tumor            | [314]|
| MoS₂-Lipid-DOX                   | NIR laser(808 nm)/pH| PTT/drug delivery                 |               | Mice bearing 4T1 tumor              | [314]|
| NIR-CD/DOX/MoS₂                   | NIR laser(808 nm)  | PTT/drug delivery                 | CT           | Mice bearing 4T1 tumor              | [314]|
| MoS₂-HA-DTPA-Gd/Gef               | NIR laser(808 nm)  | PTT/drug delivery                 | MRI          | Mice bearing A549 tumor             | [384]|
| Fe₃O₄@MoS₂-PFG(DOX)-2DG           | NIR laser(808 nm)  | PTT/drug delivery                 | MRI          | Mice bearing MDA-MB-23 tumor        | [303]|
| MoS₂-CS-DOX                      | NIR laser(808 nm)  | PTT/drug delivery                 | CT           | Mice bearing Panc-1 tumor           | [237]|
| PLGA/MoS₂-DOX (PMD)               | NIR laser(808 nm)  | PTT/drug delivery                 | PA           | Mice bearing 4T1 tumor              | [290]|
| MoS₂/Cu₃S₅-DOX                   | NIR laser(980 nm)  | PTT/drug delivery                 | PLL/PAT/PT   | Mice bearing A549 tumor             | [295]|
| MoS₂@Fe₃O₄-ICP/Pt(IV)            | NIR laser(808 nm)  | PTT/PDT/drug delivery            | MR/IR/PA     | Mice bearing H22 tumor              | [301]|
| MoS₂-PFG-PEI/siPLK1               |                    | gene delivery                     |               | Mice bearing 4T1 tumor              | [352]|
| G5-MoS₂-Bel-2 siRNA              | NIR laser(808 nm)  | PTT/gene delivery                 |               | Mice bearing 4T1 tumor              | [363]|
| FA-MoS₂/siRNA (HDAC1+KRAS)        | NIR laser(808 nm)  | PTT/gene delivery                 |               | Mice bearing Panc-1 tumor           | [361]|

(continues on next page)
Table 2 (continued)

| Materials                | Physically trigger | Therapy                  | Imaging modes | In vivo models                  | Therapeutic effect                  | Refs    |
|--------------------------|--------------------|--------------------------|---------------|---------------------------------|-------------------------------------|---------|
| MoS₂-AKT scaffolds       | NIR laser(808 nm)  | PTT/tissue regeneration  |               | Mice bearing Saos-2 tumor       | Reduce tumor volume                 | [346]   |
| AuNiBPs@MoS₂             | NIR laser(808 nm)  | PTT/CDT                  | TPF           | /                               | /                                   | [369]   |
| MoS₂@PANI                | NIR laser(808 nm)  | PTT/RT                   | CT/PA         | Mice bearing 4T1 tumor          | Delay tumor growth                  | [189]   |
| FePt/MoS₂-FA             | NIR laser(808 nm)  | PTT/immunotherapy        | /             | /                               | /                                   | [366]   |
| PC₁₀A/DOX/MoS₂           | NIR laser(808 nm)  | PTT/PDT/drug delivery/   | CT/MRI        | Mice bearing 4T1 tumor          | Completely eradicate tumor          | [374]   |
|                          |                    | immunotherapy            |               |                                 |                                     |         |

MoS₂ QDs was an outstanding multiphoton imaging probe (Fig. 6 e). NIR-2 has a longer penetration depth in the living body, lower phototoxicity and better image contrast than NIR-1 [155–160]. Sweet et al. [141] designed a water-soluble anti-PSMA antibody-conjugated MoS₂ QD-based TPF probe for targeted bioimaging of LnCaP prostate cancer cells. Firstly, they used LA-PEG to modify MoS₂ quantum dots (QDs) to improve the stability in physiological environment. LA can effectively form a covalent bond with Mo on the edge of molybdenum sulfide. Subsequently, anti-PSMA antibody conjugated with MoS₂ QDs via PEG to make the TPF probe has targeting ability for prostate cancer cells. The QY of MoS₂ QDs was as high as 54% and their two-photon brightness was detected to be $4.7 \times 10^3$ GM, which indicated that MoS₂ QDs were a good TPF imaging probe under the excitation of NIR-2 light (1064 nm). Furthermore, the TPL imaging data proved that anti-PSMA antibody-conjugated MoS₂ QDs could selectively target LnCaP prostate cancer cells and achieve effective TPL imaging in living cells (Fig. 6f and g).

3.2. PA imaging

The principle of PA imaging is that a NIR laser pulse is transmitted into biological tissue, and some of the laser energy is absorbed and transformed into heat, causing a transient thermoelastic expansion, resulting in broadband ultrasonic emission. The resulting ultrasonic waves are then examined by ultrasonic transducers, which are ultimately analyzed to produce an image. The penetration depth of PA imaging can reach ~50 mm thanks to strong penetration of ultrasonic waves. PA imaging technology combines advantages of optical imaging and ultrasound imaging to achieve the tissue image of high resolution and high contrast [161–165]. MoS₂ has outstanding photothermal conversion efficiency and excellent NIR absorption capacity, which can be used for high-quality PA imaging. Yu et al. [166] developed a MoS₂/Fe₃O₄ composite (MSIOs) for photoacoustic tomography (PAT) imaging. MSIOs were prepared by attaching Fe₃O₄ nanoparticles to the surface of the MoS₂ nanoflakes. It’s worth noting that MSIOs was a highly sensitive PAT imaging contrast agents and the PAT signals of MSIOs exhibited a concentration-dependent manner with a good linear relationship ($r^2 = 0.995$). The data in vivo showed that the PAT signals were remarkably increased with the prolonging of time after intravenously injecting MSIOs into PANCl-1 tumor bearing mice, confirming the gradual accumulation of MSIOs into tumor sites to generate strong PAT contrasts. Furthermore, the relatively long residence time (24 h) of MSIOs in tumors further improved their PAT imaging effect, realizing more effective cancer diagnosis.

In order to further enhance the effect of PA imaging and obtain more accurate information of cancer diagnosis, it is a very effective way to modify nanomaterials with specific targeting functional groups of cancers. Jiang et al. [167] developed transmembrane peptide LNP-modified porous MoS₂ nanoflowers (MNFPLP) as PA contrast agents that could actively target breast cancer. MNFPPL was spiny nanoparticle composed of three dimensional (3D)-stacked MoS₂ nanosheets with large surfaces and abundant pores and the 3D nanostructure could trap the near-infrared light through multiple reflection to strengthen the signal of PA imaging. MNFPPL and porous MoS₂ nanoflowers (MNF) had...
similar near-infrared absorption curves around 808 nm, manifesting that the modification of transmembrane peptide LNP did not change the NIR absorption of MNF. Meanwhile, MNFPPL was absorbed by tumor cells faster and more efficiently than MNF. This result could be attributed to the targeting effect of transmembrane peptide LNP. After intravenously injected MNFPPL or MNFP (MAL-PEG-PEI-MoS$_2$), the PA signals reached the maximum at 4 h in carcinoma tissues of 4T1 tumor-bearing mice but PA signal of MNFPPL more rapidly enhanced than MNFP, which implied that MNFPPL could target the tumor site (Fig. 7 a-c).

Highly sensitive PA signals of MoS$_2$ can also be obtained by reducing the number of its layers. The PA signal of MoS$_2$ will further increase along with the number of layers lessen because MoS$_2$ with less layers has a higher light absorbance. Currently, PA molecular imaging of deep cerebral tumors remains a challenge partly because the available PA molecular probe has insufficient sensitivity and limited selectivity [168,169]. Chen et al. [170] directly obtained single-layer (S-MoS$_2$), few-layer (F–MoS$_2$), and multi-layer (M – MoS$_2$) nanosheets through albumin-assisted exfoliation without further surface modification. The results showed that reducing the number of nanosheet layers from M–MoS$_2$ to S–MoS$_2$ could improve the elasticity of nanomaterials and enhance the absorption of near-infrared light, greatly increasing the PA effect. Meanwhile, S–MoS$_2$ could be effectively endocytosed by U87 glioma cells and generated a strong PA signal to detect brain tumor cells with high sensitivity. Tumor tissue with a size less than 1.5 mm of skull was still observed in vivo (Fig. 7 d-h).

### 3.3. CT/PET/MR imaging

NIF-based imaging technology usually can only detect tumors whose subcutaneous depth is less than 50 mm (Table 1). Ultra-short electromagnetic wave like X-rays, $\gamma$-photons and long-wavelength electromagnetic wave (42.6 MHz, its wavelength is 7 m) all have extremely longer tissue penetration depth that represents CT/MRI/PET imaging based on these rays can realize a better imaging effect in most tumors located inside the body, as shown in Table 1.

CT is a kind of medical imaging technology, it uses computer to handle multiple X-ray measurements taken from different angles combined to generate the tomographic image of human body.
with fast detection speed can provide tissue density distribution of a certain section and visualize deep cancer structures in the body [171, 172]. MoS\textsubscript{2} nanomaterials can be applied to contrast agents in CT imaging [68, 173, 174] because Mo atom with high absorption coefficient and atomic number has stronger X-ray attenuation than the components of the body. Liu et al. [175] synthesize antitumor nanocomposites (PEG-MoS\textsubscript{2}-Au-Ce6) through adsorbing chlorin e6 (Ce6) onto PEG-MoS\textsubscript{2} nanosheets decorated with gold nanoparticles (AuNPs). The Hounsfield unit (HU) value, represents CT contrast ability, was increased from 121.0 ± 20.1 (0 h) to 245.7 ± 18.6 (6 h) when intravenously injected PEG-MoS\textsubscript{2}-Au-Ce6 into 4T1 tumor bearing Balb/c nude mice, indicating excellent CT imaging effect (Fig. 8 a-c). Besides, Researchers found that MoS\textsubscript{2} nanocomposites had a stronger CT imaging ability in tumor-bearing mice than iohexol [171] or iopromide [176], both are common clinical X-ray contrast agents.

PET imaging has outstanding sensitivity, excellent temporal resolution and superb tissue penetration, which makes it receive much attention in cancer diagnosis, staging and treatment monitoring [179]. Isotope-labeled drugs (PET imaging agents) with positron emission can happen annihilation effects during the physiological metabolism after injecting them into body, producing two \(\gamma\)-photons with equal energy and opposite directions. Radioisotope \(^{64}\)Cu (the half-life of the positron emitter is 12.7 h) could successfully modify MoS\textsubscript{2} for PET imaging [180]. Liu et al. [177] straightforwardly efficiently labeled \(^{64}\)Cu onto double-PEGylated MoS\textsubscript{2}-iron oxide (MoS\textsubscript{2}-IO-(d)PEG) by mixing \(^{64}\)CuCl\textsubscript{2} with MoS\textsubscript{2}-IO-(d)PEG, which was attributed that the Cu\textsuperscript{2+} ions could anchor on the Mo defect sites of MoS\textsubscript{2} nanosheets. The serum stability test indicated that \(^{64}\)Cu-MoS\textsubscript{2}-IO-(d)PEG had a strong stability within 48 h and quantitative PET data, a percentage injected dose per gram of tissue (%ID/g), and confirmed that the enhancement of \(^{64}\)Cu signal was time-dependent. Therefore, \(^{64}\)Cu-MoS\textsubscript{2}-IO-(d)PEG could be applied to PET imaging contrast agent for real-time monitoring the body distribution of MoS\textsubscript{2}-IO-(d)PEG and therapeutic effect in 4T1 tumor-bearing mice (Fig. 8 d-f). Furthermore, HA could specifically bind to a CD44 receptor overexpressed in MCF-7-ADR cancer cells to improve the tumor-targeting of PET imaging contrast agent. Dong et al. [181] also synthesized \(^{64}\)Cu-NOTA labeled MoS\textsubscript{2}-PEI-HA for PET imaging of MCF-7-ADR tumor-bearing mice. PET imaging indicated that the signals at tumor site were remarkably stronger in the HA-targeted group than no targeting group when \(^{64}\)Cu-NOTA labeled MoS\textsubscript{2}-PEI-HA and MoS\textsubscript{2}-PEI were intravenously injected into MCF-7-ADR tumor-bearing mice for 4 h. Meanwhile, the quantitative results of biodistribution for the MoS\textsubscript{2}-PEI and MoS\textsubscript{2}-PEI-HA acquired by \(\gamma\)-counter indicated that the accumulation of \(^{64}\)Cu- MoS\textsubscript{2}-PEI-HA-NOTA was 10.486 ID/g in MCF-7-ADR tumor area at 4 h post-injection but \(^{64}\)Cu– MoS\textsubscript{2}-PEI-NOTA was only 5.015 ID/g, which proved that MoS\textsubscript{2}-PEI-HA has high targeting ability to achieve more accurate PET imaging.

MRI is a non-invasive bioimaging technology with a high spatial...
puter for obtaining the MRI image. Gadolinium (Gd) complexes are hydrogen nucleus in the body, making the hydrogen nucleus absorb (the frequency must match the magnetic field strength) to stimulate the diseased and the tissues normal tissues [183, 184]. Using Fig. 8.

J. Wang et al.

commonly clinical T1-weighted MRI contrast agents, but free Gd gathered by a receiver in vitro and treated through an electronic computer for obtaining the MRI image. Gadolinium (Gd) complexes are commonly clinical T1-weighted MRI contrast agents, but free Gd³⁺ has high biotoxicity. Zwitterions are expected to be a substitute to PEG because they have systemic circulating stability and can avoid nonspecific protein adsorption [185,186]. Also, the carboxybetaine monomers of zwitterion polyamides are rich in –COOH groups which can coordinate with MoS₂ to form a stable conjugated system [187]. Yu et al. [178] prepared paramagnetic zwitterionic copolymer (PZAC) by introducing the zwitterionic monomer carboxybetaine methacrylate (CBMA) into the amphiphilic copolymer backbone to lengthen systemic circulation, and the paramagnetic crosslinker was the Gd³⁺-monomer complex. Subsequently, PZAC interacted with ammonium tetrathiomolybdate (ATTM) to form MoS₂@PZAC under microwave irradiation. The synergistic effect of the combination between the edge Mo atoms in MoS₂ and the –COOH groups of the CBMA chain in PZAC and the non-covalent interactions between Mo and N on the CBMA promoted the hybridization of MoS₂ and PZAC. The result showed that MoS₂@PZAC had a higher relaxivity ($r_1 = 11.2$ mmol⁻¹ s⁻¹) than Magnevist ($r_1$ of approximately 4.4 mmol⁻¹ s⁻¹) due to two reasons. One was that the hydrophilic CBMA enhanced the rotational correlation time and water exchange rate based on Solomon-Bloembergen-Morgan (SBM) theory, and the other was that the multiple Gd³⁺ centres in the MoS₂@PZAC could also enhance the relaxivity. Meanwhile, the circulation time could be prolonged because MoS₂@PZAC had an appropriate and uniform size (28.5 ± 5.5 nm). Therefore, the PZAC in the spherical MoS₂ nanohybrid (MoS₂@PZAC) acted as a T₁-weighted MRI contrast agent to effectively guide MRI imaging in Balb/c mice bearing 4T1 tumors (Fig. 8 g). 3.4. Multi-mode imaging

Single-mode imaging usually has its inherent limitations, such as FL imaging has high resolution but limited penetration, while CT/PET/MRI has strong penetration but low resolution. Multi-mode imaging can overcome the deficiency of single-mode imaging, increasing the accuracy of a cancer diagnosis. In the field of multi-mode imaging, nanocomposites based on MoS₂ have attracted extensive attention because of their unique physicochemical property [188–190].

The most common is to combine the two imaging modes to achieve highly sensitive cancer diagnosis. For instance, Gao et al. [191] prepared rod-shaped heterogeneous Bi₂S₃–MoS₂ nanoparticles (BMNPs) served for CT/PA dual-mode imaging contrast agents. The slope of the HU value against the Bi concentration (8.84 HU L/mmol) was twice higher than commercial I (4.47 HU L/mmol) and BMNPs had a stronger CT imaging brightness. In the meantime, the CT value in 4T1 tumor-bearing mice increased from 37.43 HU to 160.66 HU after injection of BMNPs, manifesting BMNPs possessed excellent CT imaging ability. Moreover, PA signals could be generated by BMNPs even at low aqueous solution concentration (6.25 mM) based on Bi and the intensity of PA signal is positively correlated with concentration of BMNPs within the linear range of 3.125–25 mM. BMNPs with CT/PA imaging capability could improve the precision in cancer diagnosis. Tang et al. [192] also constructed a micrometer-sized materials (mPEG-PLGA@DMF) that integrated MoS₂ nanosheets and Fe₃O₄ nanoparticles into methoxy poly (ethylene glycol) poly(lactic-co-glycolic acid) (mPEG-PLGA) microparticles. T₂-weighted intensity of Fe₃O₄ nanoparticles became gradually stronger and CT signal intensity of MoS₂ nanosheets was progressively enhanced with the increase of mPEG-PLGA@DMF concentration in
vitro. Meanwhile, the tumor site was markedly darken that observed by MRI and the CT signal was increased from 45 HU to 356 HU after injecting mPEG-PLGA@DMF into VX-2 liver orthotopic transplantation tumor, which proved that microcapsules could be successfully applied to MR/CT dual-modal imaging.

Triple-modal or Multi-modal imaging has also been designed to further increase the accuracy of cancer diagnosis. Liu et al. [194] obtained a multifunctional nanocomposites based on an aluminum phthalocyanine chloride (AlPc) loaded MoS$_2$ nanodot core/SiO$_2$ shell, which coated by chitosan (CS) to form AlPc-MoS$_2$@SiO$_2$-CS. AlPc used as the NIRF imaging contrast agent and MoS$_2$ nanodot served as PA and CT imaging contrast agent, realizing NIRF/PA/CT imaging in the 4T1 tumor-bearing mice and the signals of the three types of imaging all increasing with the concentration of AlPc-MoS$_2$@SiO$_2$-CS increased. NIRF imaging in vivo displayed that AlPc-MoS$_2$@SiO$_2$-CS widely distributed all over the body at the early stages after injection and subsequently the NIRF signal at tumor sites gradually increased and reached peak value at 8 h after injection, which implying that the nanocomposites could circulate in the bloodstream and quickly targeted tumors to achieve high precision imaging. MoS$_2$ nanosheets also have the ability of multispectral optoacoustic tomography (MSOT) imaging due to their strong NIR light absorbance. Yang et al. [193] synthesized mesoporous silica nanoparticles (MSNRs)@MoS$_2$-HSA/Ce6 nanocomposites for FL/MSOT/CT triple-modal imaging in 4T1 tumor-bearing nude mice. Human serum albumin (HSA) which used as tumor-targeting agents to increase the accumulation of MSNR@MoS$_2$-HSA/Ce6 in tumor cells via albumin receptor (gp60) and albumin-binding protein SPARC. The FL and MSOT imaging signals showed that the accumulation of MSNR@MoS$_2$-HSA/Ce6 in the tumor site was gradually increased after 8 h and the peaked at 12 h. Meanwhile, CT signals were positively correlated with the concentration of MSNR@MoS$_2$-HSA/Ce6 (Fig. 9).

4. Chemotherapy

Compared with surgery and radiotherapy, chemotherapy is a means of systemic treatment. However, chemotherapy usually produces significant side effects due to its low solubility, poor stability, and easy absorption by non-cancer tissues. Hence, it ought to be design effective drug delivery systems (DDSs) to enhance the stability and load rate of drugs, and control the drug release in the tumor tissue, enhancing the therapeutic effect [195–197]. MoS$_2$-nanomaterials have many merits, including effective load rate, good stability, excellent biocompatibility, and are easy to be functionalized, which can be used as carriers to deliver drugs. Meanwhile, the nanostructure will be destroyed to achieve the release of drugs under the NIR irradiation because MoS$_2$ can effectively convert the absorbed NIR light into heat energy. Therefore, MoS$_2$-nanomaterials are promising candidates for drug delivery (Table 2).

Traditional DDSs can successfully deliver drugs to the treatment site, such as ethyl cellulose/chitosan/g-C$_3$N$_4$/MoS$_2$ core-shell nanofibers could co-deliver folic acid and doxorubicin into MCF-7 and HeLa cells [198]. The latest researches focus on how to control drug release to reduce side effects. Drugs can be released accurately and controllably by increasing the sensitivity of DDS to the applied stimuli [199,200]. The pH value of tumor microenvironment (TME) is about 6.5, which is lower than that of normal cells, so pH can act as an excellent internal stimulus to promote the effective release of drugs at cancer sites [201]. Among various stimuli, NIR light with low cytotoxicity can penetrate deep tissues that make it have prominent advantages [202,203]. Local heating

![Fig. 9.](image-url)
will destroy the stability of the endosomal membrane, promoting the escape of drugs and their carriers from the endosomal. The single-layered MoS$_2$ obtained by lithium intercalation is easily prepared into a dispersion in aqueous solution, which is appropriate for biomedical applications [19]. However, the newly synthesized single-layered MoS$_2$ has a strong aggregation in the aqueous solution, and thus further modification is needed to increase the stability of the dispersion [204,205]. Related studies showed that using polymer or silica to modify the MoS$_2$ surface can significantly improve drug loading and colloidal stability. Lee et al. [206] synthesized a photothermal controlled nanoplate to load anticancer drug DOX, which consisted of single-layered MoS$_2$ coated with porous silica and modified with polyethylene glycol (PEG). The modification of porous silica and PEG significantly enhanced the colloidal stability of the nanocomposite. Meanwhile, the escape of the carrier from the endosome and the release of DOX from nanoplateform were both achieved upon exposure to NIR light radiation. The corresponding half maximal inhibitory concentration ($IC_{50}$) values of the MoS$_2$-nanocarrier against HeLa, HepG2, and HCT-8 cell was 1.4-, 36-, and 12-fold that of free DOX respectively, suggesting that MoS$_2$-nanocarrier had a stronger anti-cancer effect (Fig. 10).

DDSs with a single stimulus-response can only release the drug under a specific stimulus. Therefore, DDSs sensitizing to double or multiple stimuli have attracted more concerns to further improve the therapeutic effect. Since GSH can reduce disulfide bonds (–S–S), it is possible to develop GSH-sensitive DDS by capping hollow mesoporous silica nanoparticles (HMSN) with disulfide cross-linkable polymers to achieve controlled release of drugs. Zhao et al. [207] prepared a dual-functional DDS (HMSN@MoS$_2$/Tf) that could effectively release DOX from HMSN when degraded by GSH and high temperature. Firstly, they used MoS$_2$ nanosheets to cap the pores of HMSN via disulfide linkage after encapsulating DOX into HMSN. Then transferrin (Tf) was covalently attached on the surface of HMSN@MoS$_2$ by forming –S–S to improve the tumor-targeting of HMSN@MoS$_2$/Tf. MoS$_2$, a NIR light response element, could not only prevent the pre-release of DOX but also realize controlled drug release by NIR and intracellular reducing agents such as GSH, realizing more accurate release of DOX.

To reduce the absorption of non-cancer tissues during drug delivery and decrease the side effects of chemotherapy, it is essential to explore DDSs with good biocompatibility that can target cancer tissues. Graphene oxide (GO) is capable of localizing in the lung through various pathways (e.g., intravenous (iv) injection) [208–211] and has a high water-solubility [212]. Liu et al. [213] synthesized a MoS$_2$/GO nanocomposite with high dispersion and excellent biocompatibility that could selectively target the lung. Results showed that the accumulation of MoS$_2$/GO in the lung is 9-fold greater than bulk MoS$_2$ and 50-fold greater than Lys-MoS$_2$, and FA-MoS$_2$. Meanwhile, compared with GO, the MoS$_2$/GO possessed better biocompatibility, such as lessened pro-inflammatory effects, improved lung fibrosis and compromised macrophagic activation, which attributed to the decreased reactivity of MoS$_2$ in the complexes. Furthermore, the drug loading and the killing effect for cancer cells were both increased, and metastatic tumor growth of B16 cells in the lung of mice was also dramatically repressed by MoS$_2$/GO nanocomplexes.

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**Fig. 10.** (a) Schematic illustration of single-layered MoS$_2$-based nanoplate as a NIR-responsive system. NIR-induced cytotoxicity of DOX-PSMS-PEG or PSMS-PEG against (b) HeLa and (c) HCT-8 cell line (**p < 0.01, ***p < 0.001). (d) Confocal microscopic images of DOX-PSMS-PEG treated HeLa cells which were further irradiated or not irradiated by 808 nm laser (5 W/cm$^2$). Nucleus was stained by DAPI (blue) and DOX was false-imaged as red (scale bar = 50 μm). (e) Photo-responsive drug release of DOX from DOX-PSMS-PEG in vitro. Reprinted with permission from Ref. [206]. Copyright 2016, Chemistry of Materials.
Multidrug resistance (MDR) will reduce the accumulation of drugs in the tumor tissue, reducing the therapeutic effect during cancer chemotherapy [214,215]. Overexpression of p-glycoprotein (P-gp) is the main reason for MDR [216], inhibiting its expression can therefore enhance the therapeutic effect. Hyaluronic acid (HA) with excellent biocompatibility can specifically bind to the CD44 receptors that are highly expressed in drug-resistant cancer cells [217], and be degraded by hyaluronidase (HAase) overexpressing in the tumor microenvironment [218]. Dong et al. [219] designed polyethyleneimine (PEI) and aluronidase (HAase) overexpressing in the tumor microenvironment expressed in drug-resistant cancer cells [217], and be degraded by hyaluronidase can specifically bind to the CD44 receptors that are highly expressed in drug-resistant cancer cells [217].

Importantly, the nanocarrier could significantly inhibit the expression of P-gp to improve sensitivity of chemotherapy, which attributed to the wide interlayer spacing could improve the accessibility of water, which conduced to increase the capacity of near-infrared light absorption and the ability of repeated light reflections. Furthermore, the heat storage and transport of E-MoS2 nanosheets could be improved by the large interlayer spacing.

Although MoS2 nanosheets with controllable size can increase the therapeutic effect of PTT, to how successfully construct tumor-targeted PPT agents is still a challenge. Studies have shown that adjusting the size of PTT agents to 50–300 nm can enhance their targeted delivery capabilities [243]. Feng et al. [244] synthesized a three-dimensional flower-shaped MoS2 nanoflake with an average size of 90 nm, which had good colloidal stability after modifying with lipopeptide-terminated polyethylene glycol (LA-PEG). Compared to single modification with thiol PEG, the LA-PEG modified with two S atoms has stronger binding force to MoS2. The nanocomplexes could destroy the lysosomal membrane and reduce the adhesion of tumor cells when radiated by NIR light at 808 nm, promoting cancer cell death.

Although changing the size of the PPT agent can heighten its tumor targeting, most of them would be cleared by the reticuloendothelial system (RES), so only less than 5% of them could reach the cancer tissue after intravenous injection [245,246]. Therefore, the PTT agents can arrive at tumor areas directly via transarterial administration (TA) [247]. Tan et al. [242] constructed layered MoS2 hollow spheres (LMHs), which had higher photothermal conversion efficiency (34.46%) than MoS2 nanosheets (24.37%). At the same time, intra-arterial (i.a.) injection in New Zealand white rabbits with hepatic metastasis of VX 2 carcinoma demonstrated significantly improved the tumor-targeting efficiency of LMHs. Studies showed that cancer cells could be ablated by single NIR light irradiation (Fig. 11c, d).

With the deepening of research, the biodegradability of PTT agents has attracted more attention because most inorganic nanomaterials cannot be degraded by the body, significantly hindering their clinical application [248,249]. Nanomaterials can be quickly excreted from the body via the renal-clearance pathway when the hydrodynamic diameter of nanoparticles is less than the glomerular filtration threshold (less than 10 nm) [250,251]. Liu et al. [252] synthesized ultra-small MoS2 nanodots by one-step solvothermal decomposition. The hydrodynamic diameter of the MoS2-GSH nanodots was less than 10 nm and without aggregation in physiological buffers when being modified with GSH. The MoS2-GSH nanodots could induce local high temperature to ablate tumor cells, and was almost completely cleared by the kidney within 7 days at the injected dose.

Although the retention time of ultra-small nanoparticles with a size smaller than the glomerular filtration threshold in normal organs is decreased [253,254], the accumulation concentration and retention time in tumor tissues will also be affected due to the relatively short cycle time and weakened enhanced permeability and retention (EPR) effect [255]. Therefore, biodegradable nanomaterials with large size can not only exert the advantage of inorganic nanoparticles but also avoid long-term biotoxicity [256,257]. Chen et al. [258] used polyacrylic acid (PAA) to synthesize biodegradable MoS2 nanosheets. Amino-terminated PEG could conjugate with active carboxyl groups in PAA of MoS2-PAA via amide interaction to form biocompatible nano-complexes (MoS2-PPEG). PAA not only promoted the modification of PEG, but also made MoS2 nanosheets degradable. Meanwhile, MoS2-PPEG had excellent stability and photothermal properties in various media. Importantly, the degradation rate of MoS2-PPEG was distinct under different pH conditions, probably because the concentration of hydroxide ions played an important role, and the primary MoIV in MoS2-PPEG was ultimately oxidized to MoV during the degradation process. MoS2-PPEG degraded rapidly in neutral pH solution but slowly in the acidic environment.
microenvironment, promoting its accumulation in tumor tissues and enhancing the anti-cancer effect.

5.2. Photodynamic therapy

PDT is mediated by photosensitizer (PS) [259]. Under light irradiation, PS transitions to the excited singlet state and subsequently returns to the ground state, and transfer the energy released from the process to oxygen molecules in the medium to generate ROS. ROS with high reactivity can oxidize biomolecules such as lipids, proteins, and DNA, leading to cell death [260,261]. PDT has the characteristics of minimally invasive. It can also eliminate small recessive cancer nests
and reduce the chance of tumor recurrence.

Local hypoxia of the tumor microenvironment can result in increased synthesis of lactic acid, promoting proliferation and migration of cancer cells. Photosensitive nanomaterials are capable of alleviating local hypoxia to improve the therapeutic effect of cancer. Kapri and Bhattacharyya [262] adopted the concept of p-n heterojunction to synthesize rGO-MoS2 nanosheets (MoS2/rGO-MoS2) as a PDT agent, which could obtain effective electron-hole separation to promote the generation of ROS in tumor tissues when irradiated by NIR (980 nm) light. Meanwhile, p-MoS2/rGO-MoS2 could alleviate the hypoxic microenvironment because MnO2 can reduce H2O2 to produce O2 via the Fenton reaction. Therefore, the cell mortality rate of p-MoS2/rGO-MoS2 was 3 times and more than 5 times that of MoS2/rGO-P EG or p-MoS2/rGO-P EG, respectively, at the same concentration (Fig. 12).

PTT and PDT have inherent limitations due to their distinct mechanisms. PTT usually requires high-power laser irradiation to generate sufficient heat [263]. Besides, the self-protective effect of cancer cells will cause a heat shock response, weakening the curative effect during PTT [264,265]. Meanwhile, the therapeutic effect of PDT will be suppressed by the hypoxic microenvironment, because of the strong dependence on the oxygen concentration [266,267]. Studies found that the photothermal effect may increase blood flow in the tumor area, subsequently increasing the tumor area’s oxygen supply and improving the efficiency of PDT [268]. Therefore, the combination of PTT and PDT will provide new strategies for cancer treatment.

For example, Liu et al. [269] utilized PEGylated MoS2 (MoS2-PEG) to physically adsorb the photodynamic agent chlorin e6 (C6e) for PDT treatment. Compared with free C6e, MoS2-PEG/C6e could enhance cell uptake and the curative effect of PDT via mild NIR light radiation, given the fact that moderate hyperthermia can increase cell membrane permeability. The synergistic effects of PDT and PTT could achieve more effective cancer cell killing when simultaneously irradiated at 808 nm and 660 nm. Peng et al. [270] designed a 2D MoS2-based pH-responsive nanosystem that firstly used pH-responsive charge-switchable peptide (lipic acid (LA)-K11 (DMA)) to modify MoS2, then loaded the toluidine blue O (TBO, photosensitizer) on MoS2 by physical adsorption. The negatively charged LA-K11 (DMA) peptides were turned into a positively charged peptide under acidic conditions, whose charge conversion reduced the binding force between positively charged TBO and MoS2, resulting in the release of TBO and realizing fluorescense imaging. Besides, the positively charged nanoplatforms were easily endocytosed by cancer cells. The pH-responsive MoS2 nanosystem combined PTT and PDT into a platform which possessed highly specific and effective anti-tumor effects. Multidrug resistance is one of the main obstacles to cancer treatment, and p-glycoprotein (P-gp) is the main protein to mediate multidrug resistance. Curcumin (Cur) can inhibit the effect of P-gp and reduce the efflux of nano-drugs by cancer cells. Li et al. [271] integrated indocyanine green (ICG), Cur and layered MoS2 hollow spheres (LMHSs) into one nanoplatform for PTT–PDT. LMHSs and ICG could trigger PTT and PDT respectively under 808 nm NIR radiation. Meanwhile, Cur repressed the activity of P-gp to increase the accumulation of ICG&Cur@MoS2. The LMHSs had a very good anti-cancer effect because it effectively overcame multi-drug resistance. In their experiment, ICG&Cur@MoS2 + NIRD group exhibited the strongest anti-cancer ability than ICG@MoS2 + NIRD group and MoS2 + NIRD group.

6. Microwave hyperthermia

The microwave beam can be focused with a suitable shape to concentrate the energy. This feature makes it suitable for local minimally invasive treatment of tumors. Compared with other hyperthermia methods, the main advantages of microwave hyperthermia are longer penetration depth, quicker heat generation, larger ablation area. However, due to the irregular tumor or the large tumor volume, there is the possibility of incomplete microwave ablation. These surviving tumor cells will become a hidden danger of tumor recurrence and metastasis. Researchers have shown that the space between MoS2 layers can retain molecules or ions [21,272,273]. Meanwhile, dipole polarization and ionic conduction are the two main causes of microwave hyperthermia [274]. The dipoles or ions would arrange in the oscillating electric field under MW irradiation, and generate heat through molecular friction and dielectric loss [275]. Besides, the sandwich structure of nanometer scale-spaces (NSSs) can markedly enhance the heating effect by changing the state of dipoles and ions [276–278], which promotes the application of MoS2 in microwave hyperthermia (Table 2).

Wang et al. [279] prepared layered MoS2 nanoflowers and used them as the MW sensitizer for MW hyperthermia for the first time. BSA-MoS2 nanoflowers had low systemic toxicity and outstanding microwave sensitivity. MoS2 nanoflowers were composed of many NSSs and the layered structure enhanced the microwave heating effect. There were two reasons that might result in enhancement of the MW heating effect of NSSs: (1) layered nanoflowers could efficiently recruit and enrich ions due to their large specific surface, enabling a high concentration of ions within BSA-MoS2, and (2) the frictional collision frequency of dipoles or ions marked increased because the small volume prolonged the contacting time by repressing the precursor diffusion. In vivo results showed that the tumor could be 100% eliminated after MW radiation at 1.8 W and 450 MHz.

However, microwave hyperthermia is still not feasible for treating large tumors due to insufficient heat accumulation around the whole tumor, owing to the heat-sink effect (HSE) [281–283]. Arterial embolism (TAE) and chemoembolization (TACE) are two common clinical treatments that can block tumor blood vessels to treat unresectable hepatocellular carcinoma (HCC). The means of combining TAE with a specific targeted embolization agent can be utilized for blocking the tumor blood vessels and alleviating the HSE [284,285]. Fu et al. [280] synthesized a microwave embolization agent (MSMC) by encapsulating MoS2 nanosheets in sodium alginate microparticles (MCs) for effectively treating large tumors. Compared with free ions participating in microwave hyperthermia, the microwave-heat conversion ability of ions confined in the MC is much higher due to the lamellar structures that could divide the microcapsule into smaller spaces, which would further raise the temperature surrounding solution. Besides, MSMC could be simultaneously used as an outstanding embolic and a microwave sensitizer for dual-enhanced microwave ablation therapy. MR imaging showed that the ablation area of MSMC was larger than that of the microwave treatment alone after injection of MSMC to the VX2 liver cancer tissue via hepatic artery. Meanwhile, persistent hyperthermia could nearly completely ablate the large tumor and prevent its recurrence (Fig. 13).

7. Multifunctional nanoplatforms for cancer therapy

Multifunctional nanoplatforms are mainly divided into two categories: cancer treatments combining different therapy methods and cancer theranostics. The combination of multiple treatment methods can improve the treatment effect, eliminate residual lesions, and prevent metastasis and recurrence for prolonged the survival time of patients. Cancer theranostics is a multifunctional nanoplatform that combines cancer imaging and treatment. The multifunctional nano-platforms can accurately and timely provide diagnostic information and pharmacokinetics to doctors, which not only make doctors to design personalized treatments according to the cancer patient’s condition, but also accurately obtain the information of the therapeutic effect for prognosis. Compared with traditional treatment methods, the main advantage of cancer theranostics is that it can distinguish cancer lesions from healthy tissues, which minimize systematic toxicity of cancer treats and improve curative effects. However, multifunctional nanoplatforms need a key flexible platform material that can combine many different functional components together. MoS2 nanomaterials is easy to functionalized with biomolecules and combined with other nanomaterials. Therefore, MoS2
nanomaterial can be used as a good platform material for building multifunctional nanoplatorms \([286–288]\) (Table 2).

### 7.1. Near-infrared/PA imaging-guided cancer therapy

Han et al. \([289]\) prepared a multifunctional nanocomplex \(\text{MoS}_2\)-UCNPs-FA/ZnPc by integrating PTT, PDT and up-conversion luminescence (UCL) imaging into one platform to strengthen the anti-cancer effect. First, chitosan-functionalized \(\text{MoS}_2\) (\(\text{MoS}_2\)-CS) with good biocompatibility was covalently grafted with hydrophilic \(-\text{COOH}\)-functionalized upconverted nanoparticles (UCNPs). Thereafter, \(\text{MoS}_2\)-UCNPs were conjugated with FA through a carbodiimide cross-linking reaction between the \(-\text{COOH}\) of \(\text{MoS}_2\)-UCNPs and the \(-\text{NH}_2\) of FA. Finally, phthalocyanine (ZnPc), was loaded on the surface of \(\text{MoS}_2\) to construct \(\text{MoS}_2\)-UCNPs-FA/ZnPc. Results showed that the nanoplateform could convert optical energy into heat by \(\text{MoS}_2\) and generate ROS by ZnPc under NIR light irradiation at 808 nm and 980 nm, respectively. Meanwhile, the unique UCL emission afforded a significant method for cell bioimaging, achieving a more effective therapeutic effect of tumors.

However, the sensitivity and spatial resolution of UCL imaging are relatively lower than those of PA imaging. PA imaging possesses stronger penetration, higher contrast, and more sensitive spatial resolution on account of combining the advantages of optical imaging and acoustic imaging. Wang et al. \([290]\) dissolved polyactic acid-glycolic acid copolymer (PLGA), \(\text{MoS}_2\) and DOX into N-methylpyrrolidone (NMP) for preparing PLGA/\(\text{MoS}_2\)/DOX (PM) oleosol with good injectability, which did not diffuse into the body fluid circulation and could be biodegraded in vivo. \(\text{MoS}_2\) nanosheets serve as high-performance contrast agents to monitor the position of solid PMD implants via PA imaging. Besides, \(\text{MoS}_2\) could also be used as PPT agent to control the release of DOX and generate heat, enhancing the anti-cancer effect in tumor-bearing nude mice. Compared with NIR-1, NIR-2 has a longer penetration depth and better image contrast. Zhou et al. \([291]\) developed 1T-\(\text{MoS}_2\) nanodots as effective nano-agents for PA imaging-guided PTT in the NIR-2 window. 1T-\(\text{MoS}_2\) nanodots gave an extinction coefficient of 25.6 L g\(^{-1}\) cm\(^{-1}\) and photothermal power conversion efficiency (PCE) of 43.3% under 1064 nm laser irradiation. The strong NIR-2 absorption of 1T-\(\text{MoS}_2\) could be attributed to the metallic properties. In an attempt to further enhance the sensitivity of imaging, Song et al. \([292]\) designed the “four-in-one” nanoplatorm consisting of fluorescent imaging, PA imaging, PTT, and PDT to achieve imaging-guided phototherapy. BSA-\(\text{MoS}_2\) could simultaneously generate local high temperatures, singlet oxygen, and PAT signals after 808 nm NIR laser excitation. Besides, the biodistribution of nanocomplex at the tumor site could be detected by fluorescence imaging when \(\text{MoS}_2\) conjugates with Cy5.5 fluorescent molecules, realizing multimode imaging-guided precision treatment.

Enhancing the tumor targeting of multifunctional nanomaterials can reduce the side effects on normal tissues. Shin et al. \([293]\) reported a multifunctional HA-\(\text{MoS}_2\) with the tumor-targeting capability as well as integrated fluorescence imaging, PAT, and PTT. Thiolated HA (HA-SH) was first prepared by chemically modification of hyaluronate (HA) with cystamine. The as prepared HA-SH was then conjugated with \(\text{MoS}_2\) via the disulfide bond formation. HA promoted the accumulation of
HA-MoS$_2$ at the tumor site through HA receptor-mediated endocytosis. Meanwhile, the disulfide bond of HA-MoS$_2$ could be reduced by GSH in the cytoplasm, releasing MoS$_2$ sheets to strengthen the optical signal and photothermal conversion efficiency, realizing effective tumor ablation effect in Balb/c nude mice inoculated with HCT116 (Fig. 14 a-f).

The synergistic effect between MoS$_2$ and other photothermal conversion agents can increase the photothermal conversion efficiency and the therapeutic effect of PTT, also enhancing the sensitivity of PA imaging. Copper sulfide (CuS) is an excellent photothermal conversion material because of its good thermostability, photostability and high photothermal conversion efficiency [294]. For this reason, Meng et al. [295] prepared a multifunctional nanoplatform (ATPMC) through

Fig. 14. In vivo fluorescence and PA imaging of HA-MoS$_2$ conjugates. (a) IVIS imaging of PBS and HA-MoS$_2$ conjugates after intradermal injection into the tumor (red circle) region. (b) Quantitative fluorescence analysis of PEG-MoS$_2$ and HA-MoS$_2$ conjugates in the organs for the assessment of tumor targeting affinity (**p < 0.01, PEG-MoS$_2$ vs HA-MoS$_2$ conjugates). (c) The PA amplitude enhancement of HA-MoS$_2$ conjugates compared to the control (PBS) image at both 680 and 850 nm wavelengths with the depth profile of the highest signals for 240 min. (d) A photo-image and PA MAP image of mouse in respect to depth (left) and amplitude (right) before injection of HA-MoS$_2$ conjugates. The PA signals at 30 and 240 min after intratumoral injection of HA-MoS$_2$ conjugates at (e) 680 and (f) 850 nm wavelengths in respect to depth (upper) and intensity (bottom). Reprinted with permission from Ref. [293]. Copyright 2019, Advanced Healthcare Materials. g) ATPMC-CD (ATPMC nanoplatform loaded with DOX) for multimodality bioimaging and NIR-laser irradiation-induced chemotherapy. Reprinted with permission from Ref. [295]. Copyright 2017, Advanced Functional Materials.
conjugating aptamer and PEG on the surface of MoS$_2$–Cu$_{1.8}$S, which not only served as photoluminescence/PA/photothermal imaging contrast agent but also used as carriers of DOX and miRNA-155 probe, realizing triple-modal bioimaging-guided diagnosis and synergistic therapy. The combined effect of MoS$_2$ and Cu$_{1.8}$S made ATPMC have stronger heat conversion ability (32.5%) than MoS$_2$ or Cu$_{1.8}$S alone, which indicated that ATPMC was a superb photothermal conversion agent. Meanwhile, ATPMC could selectively release DOX under NIR light radiation to kill lung cells (Fig. 14 g).

7.2. MRI-guided cancer therapy

Due to the different relaxation times of normal tissues and cancerous tissues, MRI can provide anatomical information. Conventional MRI cannot recognize the boundary and microstructure of tumor lesions due to its relatively low resolution [296]. Nanoparticle-based MRI contrast agents can provide high-quality and sensitive anatomical information [297,298]. For example, superparamagnetic Fe$_3$O$_4$ nanoparticles are commonly used as T2-weighted MRI contrast agents [299,300]. A novel multifunctional complex (Mo@Fe-I CG/Pt) was prepared by covalently grafting Fe$_3$O$_4$ nanoparticles (≈6 nm) on MoS$_2$ and then loading indocyanine green molecule (ICG, photosensitive agent) and platinum (IV) prodrug. The resulting multifunctional nanoparticles possessed remarkable bioimaging capacity of MRI ($r_2=71.8$ mM$^{-1}$ s$^{-1}$)/infrared thermal/PA and could trigger PTT, PDT, and chemotherapy under NIR light irradiation [301]. Notably, the T2-weighted contrast ability may be affected by the morphology and size of Fe$_3$O$_4$ nanoparticles [302]. Generally, the larger cubic iron oxide (IO) nanoparticles have lower $r_2$ value and higher imaging sensitivity. Xie et al. [303] combined MoS$_2$ (MS) film with IO nanocubes (≈100 nm) to form Fe$_3$O$_4$@MoS$_2$ nanocubes (IOMS NCs), which could easily load DOX for MRI-guided chemo-photothermal therapy. Compared with the nanomaterials containing small-size Fe$_3$O$_4$ nanoparticles ($r_2=71.8$ mM$^{-1}$ s$^{-1}$), the IOMS NCs containing large-size Fe$_3$O$_4$ nanoparticles displayed more sensitive MRI capabilities ($r_2=48.86/(mM\cdot s)$) (Fig. 15).

T1-weighted MRI contrast agents, as positive contrast agents, can enhance the signal in the affected area, thus making this area brighter than other areas. Nanoparticles containing Gd$^{3+}$ are commonly used as

![Fig. 15. (a) Schematic illustration of the fabrication process of IOMS-PEG(DOX)-2DG NCs for MRI-guided chemo-photothermal therapy of cancer. (b1) and (b2) SEM and TEM images of IO clusters. (c1) and (c2) SEM and TEM images of IOMS NCs. (d1) and (d2) SEM and TEM images of IOMS-PEG NCs. Reprinted with permission from Ref. [303]. Copyright 2018, Nano Research.](image-url)
T1-weighted MRI contrast agents [304]. Chen et al. [305] synthesized the multifunctional MoS$_2$-Gd-BSA through conjugation of BSA-gadolinium (Gd) complexes with MoS$_2$ nanosheets via an amide bond. BSA-Gd complexes served as MRI contrast agents, while MoS$_2$ nanosheets used for PTT agents and PA imaging contrast agents, realizing dual-mode MRI/PA imaging-guided PTT in tumor-bearing mice. Besides, Mn$^{2+}$ also serves as T1-weighted MRI contrast agents [306]. The generated T1/T2-weighted MRI contrast agents have demonstrated a higher sensitivity than single-mode contrast agents in cancer identification. Therefore, Mn-doped Fe$_3$O$_4$ nanoparticles can be utilized for T1/T2-weighted MRI bimodal probes. Jing et al. [307] synthesized multifunctional nanosystems by loading chitosan (CS) and metformin (MET) on Mn-doped Fe$_3$O$_4$@MoS$_2$ nanoflowers. The Mn-doped Fe$_3$O$_4$@MoS$_2$ nanoflowers were applied to the T1/T2-weighted MRI with high sensitivity ($t_2 = 18.46$ mM$^{-1}$ s$^{-1}$, $t_2 = 63.75$ mM$^{-1}$ s$^{-1}$) and had a quick magnetic response. Meanwhile, it could suppress and kill hepatoma cells when MET was released from the nanosystems under NIR irradiation or weakly acidic tumor microenvironment. Therefore, T1/T2 MRI-guided chemo-photothermal combined therapy was realized in vitro. Furthermore, Researchers discovered that incorporating MoS$_2$ nanosheets and Fe$_3$O$_4$ into microcapsules can be used in MRI/CT-guided microwave hyperthermia for HCC [192].

7.3. Combination of phototherapy with chemotherapy

Studies have shown that PTT-induced hyperthermia can interfere with DNA repair [308] and increase membrane permeability [309,310], promoting the entry of drugs into the tumor cells and improving the sensitivity of tumor cells to drugs. Meanwhile, PDT can enhance the penetration of tumor blood vessels and increase the intake of nanoparticles, improving the anti-tumor efficacy of nanodrugs [311,312]. Overall, the combination of phototherapy and chemotherapy can achieve a better therapeutic effect [313–324].

Liu et al. [68] first discovered that MoS$_2$ could be used as a novel 2D nanocarrier to deliver drugs and also used for PTT. The PEGylated MoS$_2$ nanosheets with the large specific area could efficiently deliver DOX via hydrophobic action and had strong NIR light absorption efficiency. Results displayed that about 95% of cancer cells died when they co-incubated with MoS$_2$-PEG-FA/DOX and radiated by the 808 nm laser at 1.07 W/cm$^2$ for 5 min, which was much higher than DOX or PPT treatment alone (Fig. 16 b-f). Furthermore, studies demonstrated that MoS$_2$ nanosheets modified by chitosan [237], hyperbranched polyglycidyl (HPG) [325] or egg yolk phospholipids [326] could also serve as platforms with good colloidal stability and biocompatibility to realize the synergistic treatment of chemotherapy and PTT. Time-staggered administration of erlotinib (Er) and DOX can enhance the anticancer effect, but its clinical application is limited due to different administration routes and formulation parameters. Recently, Liu et al. [327] designed a MoS$_2$-based nanoplatform to co-deliver Er and DOX. Under NIR irradiation, the MoS$_2$-based nanoplatform could simultaneously release Er and DOX, and greatly improve the anti-cancer effect by synergistic treatment of Er and DOX.

Because MoS$_2$ with a large specific surface area is easy to modify, many molecules can be combined with MoS$_2$ to construct various types of multifunctional nanoplatforms for combined phototherapy and chemotherapy. Many outstanding characters, such as organic-group-doped frameworks, high surface area, and excellent blood compatibility, making periodic mesoporous organosilicas (PMOs) become ideal platforms for drug delivery [329–331]. MoS$_2$ nanosheets might efficiently wrap the PMOs due to its excellent flexibility in chemical reactions [332–334]. To this end, Shao et al. [322] designed PMO-DOX@MoS$_2$-PEG that has high DOX loading efficiency (160 µg/mg in this experiment, KB cells were incubated with MoS$_2$-PEG-FA, free DOX, MoS$_2$-PEG/DOX and MoS$_2$-PEG-FA/DOX for 1 h, and then irradiated with the 808-nm laser at different power densities for 5 min or kept dark as controls. Afterwards cells were washed with PBS, placed into fresh cell medium, re-incubated for additional 24 h before the MTT assay. Error bars were based on four parallel samples. (c) Scheme of combination therapy based on intratumorally injected MoS$_2$-PEG/DOX. (d) IR thermal images of 4T1 tumor-bearing mice recorded by an IR camera. The doses of DOX and MoS$_2$-PEG were 5 mg/kg and 3.4 mg/kg, respectively, in this experiment. Laser irradiation was conducted by using 808-nm NIR laser at the power density of 0.56 W/cm$^2$ for 20 min on the tumors. (e) Temperature change of tumors monitored by the IR thermal camera in different groups during laser. (f) Tumor volume growth curves of different groups of mice after various treatments (5 mice for each group). Reprinted with permission from Ref. [68]. Copyright 2014, Advanced Materials.
PMO) and outstanding photothermal conversion capacity, which could successfully release DOX with the irradiation of NIR laser. The release of DOX in PMO-DOX@MoS$_2$-PEG could be controlled by NIR laser. Benefiting from these properties, a combination therapy of chemotherapy and PTT in multiple cancer cells was achieved.

Researchers have found that improving the tumor targeting and specific response-ability of multifunctional nanomaterials to the tumor microenvironment can further enhance the anticancer effect. Yang et al. [320] prepared a novel type of cage-like Fe$_2$O$_4$@MoS$_2$@ZnO nanocomposite with magnetism, extensive pore structure, large surface area, and high DOX loading capacity, which could effectively deliver drugs to tumor lesion areas under magnetic targeting. Meanwhile, the efficient PTT could be realized because MoS$_2$ has strong photothermal conversion ability, and the controlled release of DOX in slightly acidic environments (pH 6.5) could be achieved by using the pH-dependent ZnO as an encapsulating component to cover the mesopores. Xu et al. [328] synthesized MoS$_2$/HSA with strong photothermal conversion ability which constructed with MoS$_2$ hollow nanocapsules and human serum albumin (HSA) by a layer-by-layer coating method. The MoS$_2$/HSA were uniform in size (280 nm), large in the cavity, low in Young’s modulus (222 ± 20 MPa), and high in load rate of DOX (27 wt%). The uptake rate of MCF-7 cells was dramatically increased due to the targeting ability of HSA. Simultaneously, the longer mean retention time (170.9 h) of MoS$_2$/HSA made it has a higher tumor tissue accumulation (27%) than its solid counterpart, dramatically improving the treatment effect of breast cancer (Fig. 16 a). Melanin (Mel) is a biocompatible biopolymer that exists in human tissues and has the ability to absorb NIR light. Our groups developed dopamine-melanin colloidal nanospheres (Dpa-melanin CNSs) as efficient PTT agents for cancer therapy [335]. The combination of Mel and MoS$_2$ nanosheets would further strengthen the photothermal effect. Yang et al. [314] synthesized a multipurpose nanosystem based on MoS$_2$ and Mel nanocomposites (HPMP@DOX/-Mel) that could deliver DOX. They first prepared the multi-functional HA-PEI-LA-MoS$_2$-PEG (HPMP). HA could selectively bond with CD44 receptor which expresses highly in MCF-7 cells to enhance the targeting ability of HPMP, while PEI made HPMP to obtain the function of responding to pH. Subsequently, melanin and DOX were loaded into HPMP to prepare HPMP@DOX(Mel). The efficiency of HPMP@DOX(Mel) photothermal conversion could reach 55.3% due to the synergistic enhancement of Mel and MoS$_2$, which was higher than Mel and MoS$_2$. The DOX could be released from HPMP@DOX(Mel) with the dual stimuli of weakly acidic environment and NIR light irradiation at 808 nm. Besides, experiments in vivo demonstrated that chemo-photothermal therapy had a better treatment effect than single therapy. Recently, Zhang et al. [336] constructed urchin-like MoS$_2@$C with high photothermal conversion ability (40.8%) and high DOX loading rate (52.34%), which could effectively release DOX under the mediation of pH and temperature. The cumulative release rate of DOX was as high as 64.59% when irradiated by NIR, which was about twice as high as that without laser irradiation, and the survival rate of MCF-7 cells was only 25.8%.

7.4. Combination of phototherapy with other therapy

In addition to the synergistic effect of chemotherapy and phototherapy, PTT can also be combined with radiation therapy, tissue regeneration, gene therapy, immunotherapy, and catalytic therapy to overcome the inherent limitations of monotherapy for enhancing anti-cancer effects and prolonging the survival period of patients. Nevertheless, PTT alone hardly completely eliminates tumors due to its depth-dependent. Radiation therapy (RT) without depth restriction generally utilizes ionizing radiation to generate oxygen-centered radicals which can promote cancer cell death by causing the DNA damage [337,338]. But the hypoxic tumor microenvironment is the main barrier to RT. Moderate high temperature induced by PTT may increase the bloodstream within the tumor lesions and improve the tumor hypoxic microenvironment, making the cancer cells more sensitive to RT. MoS$_2$ with high Z value is expected to be a candidate of RT radiosensitizers [339]. Wang et al. [189] designed inorganic-organic nano-hybrid particles based on MoS$_2$ quantum dots@polyaniline (MoS$_2$@PANI), which not only enhanced PA/CT signals but also performed RT and PTT for cancer. Firstly, they dispersed MoS$_2$ QDs powder in the water when polyvinylpyrrolidone (PVP) existed and PVP served as a dispersing and stabilizing agent to control the size of MoS$_2$ QDs during the process. Subsequently, MoS$_2$ QDs could absorb aniline molecules onto its surface to form MoS$_2$@PANI-COOH via the electrostatic forces and then conjugated with PEG-NH$_2$ by forming the amide bond, constructing MoS$_2$@PANI nanohybrids. The MoS$_2$ QDs could be used as fluorescence probes and PANI could serve as a PTT agent due to its strong photothermal conversion efficiency capacity. Besides, MoS$_2$@PANI could also serve as CT imaging agents because the molybdenum has a high X-ray absorption coefficient. Results showed that oxygenation at the tumor site could be enhanced under moderate PTT. RT/PTT combination therapy guided by PA/CT images could nearly eliminate tumors in 4T1 tumor-bearing mice (Fig. 17 a, b). Besides, MoS$_2$ can also be combined with other nanoradiosensitive agents to form a PTT-RT combined treatment platform. Hafnium dioxide (HfO$_2$) nanoparticles have strong X-ray attenuation ability, and are regarded as potential radiosensitive agents. Recently, Fu et al. [340] integrated MoS$_2$, HfO$_2$ and dextrin into new nanoplatforms (M/H-D) for CT/PA imaging-guided PTT/RT. HfO$_2$ produced ROS to kill cancer cells under X-ray irradiation. Meanwhile, local high temperature caused by MoS$_2$ could relieve the hypoxia of tumor cells and improve the therapeutic effect of RT under NIR irradiation. In addition, MoS$_2$ could catalyze H$_2$O$_2$ to produce hydroxyl radicals to further damage cancer cells. M/H-D could eliminate tumors in MMC-7721-fluc tumor-bearing mice after X-ray and NIR irradiation. Malignant bone tumor is usually treated with a collaborative strategy of surgery, chemotherapy, and radiotherapy [233,341], but cannot thoroughly ablate cancer cells and lead to large bone defects which need bioactive graft materials to repair [342,343]. Fortunately, the osteogenesis and angiogenesis can be induced by three-dimensional (3D)-printed bioactive scaffolds with bioactive elements [344,345], while these scaffolds gradually degrade with the formation of new bone tissue. Wang et al. [346] prepared new dual-function scaffolds (MS-AKT scaffolds) via the technology that combines a 3D printing technique and a hydrothermal method. First, they immersed AKT bioceramic scaffolds in the nutrient solution including (NH$_4$)$_2$MoO$_4$, 4H$_2$O and H$_2$NCSNH$_2$. Next, H$_2$NCSNH$_2$ could be decomposed and attach on the surface of AKT scaffolds under hydrothermal conditions. Finally, AKT scaffolds were used as templates to promote the nucleation and growth of the sheet-like MoS$_2$ in situ, producing MS-AKT scaffolds. MoS$_2$ nanosheets with photothermal properties and bifunctional three-dimensional (3D) scaffolds with osteogenic potential could be used to induce PTT and repair bone defects caused by large tumors, respectively. PTT significantly increased the death rate of osteosarcoma cells and breast cancer cells, and the MS-AKT scaffold could support the attachment, proliferation, and osteogenic differentiation of bone mesenchymal stem cells, inducing tissue regeneration in vivo (Fig. 17 c-k).

Gene therapy (GT) induced by small interfering RNA (siRNA) promises to be an alternative means for traditional treatment. It can selectively kill cancer cells by silencing specific genes [347]. However, the naked siRNA with negative charges is easily degraded by nucleases and difficult to cross the negatively charged cell membranes, therefore, safe and effective carriers are highly needed [348]. MoS$_2$ can efficiently deliver genes to the target area for cancer therapy due to its flexible physicochemical properties. Polo-like kinase 1 (PLK1), a vital regulatory factor of cell cycle and overexpressed in various cancer. The proliferation of cancer cells will be inhibited by silencing PLK1 expression [349-351]. Kou et al. [352] developed a PLK1 siRNA nano-transport system based on MoS$_2$ (MoS$_2$-PEG-PEI nanosystem). In this nanosystem, PEG could prevent nonspecific binding of proteins and
nanomaterial to strengthen the stability of MoS\textsubscript{2} in serum and positive charge amino end of PEI could promote the combination of MoS\textsubscript{2}-PEG-PEI and siRNA due to the electrostatic interaction. The expression of PLK1 was significantly decreased and the flow cytometry analysis demonstrated that the number of apoptotic cells were increased markedly when HepG2 cells treated by MoS\textsubscript{2}-PEG-PEI/siPLK1. Pancreatic carcinoma usually has properties including a very poor prognosis and a high mortality rate. Therapeutic effects of pancreatic carcinoma are mainly suppressed by the high molecular heterogeneity and surrounding stromal and inflammatory components [353–356]. Yin et al. [361] designed a multi-gene delivery nanoplatform based on MoS\textsubscript{2}/LA/PEG/FA/PAH) for co-delivering HDAC1 and KRAS siRNAs into pancreatic tumor cells. FA-PEG polymers and polyallylamine hydrochloride (PAH) were used to functionalize the surface of MoS\textsubscript{2} nanosheets, which was conducive MoS\textsubscript{2}/LA/PEG/FA/PAH to bond with siRNA and internalize by Panc-1 cells. The growth rate of Panc-1 cells and tumor volume was decreased by 70% and 80% respectively thanks to the synergistic effect of GT and PTT. By targeting antiapoptotic B-cell lymphoma-2 (Bcl-2) that overexpresses on tumor cells [362], Kong et al. [363] synthesized dendrimer-modified MoS\textsubscript{2} nanosheets as carriers to condense Bcl-2 siRNA, realizing combination therapy of gene silencing and PTT. The results indicated that G5-MoS\textsubscript{2}/Bcl-2 siRNA polyplexes with the hydrodynamic size (300 nm) and positive surface potential could be used to deliver siRNA. Meanwhile, the inhibition rate of G5-MoS\textsubscript{2}/Bcl-2 siRNA polyplexes on the expression of Bcl-2 gene was 47.3%. Under 808 nm NIR laser radiation, the survival rate of cells treated with G5-MoS\textsubscript{2}/Bcl-2 siRNA complex was only 21.0%, which is much lower than PTT (45.8%) or GT (68.7%) alone (Fig. 17 l-n). In conclusion, MoS\textsubscript{2}-based nanocomposites could effectively load siRNAs of specific genes which overexpressed in a variety of cancer cells and successfully delivered them to tumor cells, inhibiting the proliferation and migration of cancer cells to delay cancer progression through synergistic effect of GT and PTT.

Tumor immunotherapy aims to activate the immune system of the body and kill tumor cells via the immune reaction, and is emerging as a promising anti-tumor strategy [364]. Cytosine-phosphate-guanine (CpG) can be absorbed by lysosomes, inducing the generation of innate immune responses characterized by Th1 cells and...
proinflammatory factors [365]. However, CpG is difficult to penetrate cell membranes and easily degraded by nucleases. Therefore, an ideal vector is needed to transport CpG to target cells and protect them from degradation. Han et al. [366] designed a uniform MoS\textsubscript{2}-PEG-CpG for photothermal enhanced immunotherapy. First, the few-layered MoS\textsubscript{2} nanosheets obtained from bulk MoS\textsubscript{2} via Li ion intercalation and ultrasonication. Then SH-PEG and CpG modified MoS\textsubscript{2} nanosheets through the Mo–S bond. Importantly, MoS\textsubscript{2}-PEG-CpG with uniform morphology had a mean diameter of 100 nm after probe sonication and modification, which more applicable to immune response. The enhanced immune response could be attributed to two aspects: (1) MoS\textsubscript{2}-mediated photothermal effect enhanced the permeability of the cell membrane, promoting the endocytosis of MoS\textsubscript{2}-PEG-CpG; (2) MoS\textsubscript{2}-PEG-CpG could protect CpG from degradation by nucleases. Therefore, the production of pro-inflammatory factors and Th1 cells could be induced by increasing the uptake of CpG under near-infrared irradiation, realizing a stronger anti-cancer effect.

Chemodynamic therapy (CDT) uses the weakly acidic microenvironment of the tumor as the reaction conditions, \( H_2O_2 \) as the reaction raw material, and nanomaterials with enzyme-like activity as the catalyst. Therefore, it can induce Fenton or Fenton-like reactions in tumor cells to reduce \( H_2O_2 \) to ROS with strong oxidizing property, promoting cancer cell apoptosis [367]. MoS\textsubscript{2} nanosheets have a peroxidase-like activity (POD) that can detect \( H_2O_2 \) and glucose in serum [368]. Maji et al. [369] designed hybrid gold nanobipyramid nanocomposites coated with MoS\textsubscript{2} (AuNBPs@MoS\textsubscript{2}) that possessed enzymes-like activity and could be used for anticancer treatment and TPF bioimaging. The AuNBPs@MoS\textsubscript{2} possessed significantly localized surface plasmon resonance (LSPR) performance under excitation ascribing to its anisotropic nature and the rich electron density in MoS\textsubscript{2}. Meanwhile, the peroxidase-like activity of AuNBPs@MoS\textsubscript{2} could further heighten in the presence of TMB and \( H_2O_2 \) that due to LSPR speciality, leading to in situ photogeneration of ROS. TPF imaging demonstrated that AuNBPs@MoS\textsubscript{2} was endocytosed into tumor cells, and synergistic treatment of CDT and PTT was achieved in the presence of \( H_2O_2 \) and NIR laser irradiation, which promoted cancer cells death. Similarly, Mei et al. [370] synthesized MoS\textsubscript{2}@CGTC NCR by co-loading tirapazamine (TPZ) and glucose oxidase (GOx) on the surface of MoS\textsubscript{2} for combination therapy of CDT and chemotherapy. First, GOx could catalyze glucose to generate \( H_2O_2 \) and gluconic acid, which could promote the reduction reaction between MoS\textsubscript{2} and \( H_2O_2 \) to produce a great deal of \(-OH\). MoS\textsubscript{2} also could react with GSH to decrease the consumption of \(-OH\). Second, TPZ could convert into toxic TPZ radical under hypoxia conditions to kill cancer cells. MoS\textsubscript{2}@CGTC NCR could effectively ablate A549 cells in vivo and in vitro. Recently, copper ions and iron ions have been incorporated into MoS\textsubscript{2} to enhance the CDT effect of MoS\textsubscript{2} [371,372]. For example, Jiang et al. [373] prepared MoS\textsubscript{2}-CuO heterostructures to promote the generation of \(-OH\) by inducing Fenton or Fenton-like reactions.

To further strengthen the anticancer effect, Zhang et al. [374] integrated immunotherapy, CDT, and PTT into a platform (FePt/MoS\textsubscript{2}-FA-CpG ODN), eliminating tumor and prevent tumor recurrence. The multipurpose FePt/MoS\textsubscript{2}-FA nanocomplexes were constructed by immobilizing FePt nanoparticles (PPFM NCs) and FA on MoS\textsubscript{2} nanosheets. FePt nanoparticles used as competent iron death agents to catalyze Fenton reaction for generating ROS, and MoS\textsubscript{2} nanosheets could ablate primary tumor cells by PTT. Furthermore, oligodeoxynucleotides containing cystosine-guanine (CpG ODNs) anchored on the surface or of MoS\textsubscript{2} nanosheets could strengthen the body’s immune reaction to antigens, which combined with systemic checkpoint blockade therapy using an anti-CTLA4 antibody could effectively eliminate the metastatic tumor. At the same time, the combination of CpG ODNs and Toll-like receptor-9 (TLR9) could up-regulate the expression of co-stimulatory factors, promote the secretion of inflammatory factors, and enhance the immune response of CD8\(^+\) T cells. Compared with FA receptor-negative L02 cells, FA receptor-positive 4T1 cells had a lower survival rate, indicating that FePt/MoS\textsubscript{2}-FA-CpG ODN had a strong targeting ability, which could effectively kill cancer cells and inhibit tumor growth. What’s more impressive was that this synergistic treatment had obtained a strong immune memory, thereby inhibiting cancer recurrence (Fig. 18). Phototherapy could trigger body’s immune response to improve the effectiveness of cancer therapies [259,375–377]. Cancer cells were destroyed by phototherapy and then released tumor associated antigens which can be captured by antigen presenting cells (particularly dendritic cells, DCs) and presented to T cells, subsequently inducing immune reactions to kills tumor cells. Jin et al. [377] synthesized an injectable PC\textsubscript{10}A/DOX/MoS\textsubscript{2} hydrogel that could be used for chemotherapy, phototherapy and immunotherapy of 4T1 tumor. MoS\textsubscript{2} nanosheet loaded with positively charged DOX and negatively charged PC\textsubscript{10}A to form hybrid PC\textsubscript{10}A/DOX/MoS\textsubscript{2} nanoparticles by electrostatic interaction and then dispersed them in PC\textsubscript{10}A hydrogel to prepare the multifunctional PC\textsubscript{10}A/DOX/MoS\textsubscript{2} hydrogel. MoS\textsubscript{2} nanosheets were used as efficient PTT agents and PDT agents to generate hyperthermia and ROS, respectively. Meanwhile, the secretion of immune-stimulatory cytokines would increase when PTT and PTT could promote the maturation of DCs, which was contributed to the activation of T cells. The result showed that the number of mDCs, CD4\(^+\) T cell, CD8\(^+\) T cell, and immune-stimulatory cytokines was significantly increased and the anti-cancer effect was remarkably enhanced due to the combination of chemotherapy, phototherapy and immunotherapy.

8. Conclusions and perspectives

Efficient and reliable cancer diagnosis and treatment methods can extend the survival period of patients and improve the quality of life [385]. Two-dimensional nanomaterials (MoS\textsubscript{2}, MoSe\textsubscript{2}, WS\textsubscript{2}, WSe\textsubscript{2}, and etc.) have attracted great interest in the biomedical field [8,18,386–397], especially MoS\textsubscript{2}-based nanocomposites due to their outstanding physio-chemical properties and good biocompatibility. MoS\textsubscript{2} with a large specific surface area can load various biomolecules, drugs, fluorescent molecules, and other nanomaterials to improve its colloidal stability and tumor targeting, increase its sensitivity and accuracy in detecting specific biomarkers, and enhance its specific response to the stimulation of tumor microenvironment, which reduces side effects during treatment. At the same time, the strong photothermal conversion capacity and near-infrared light absorption ability of MoS\textsubscript{2} have promoted its application in phototherapy, PA imaging. Moreover, MoS\textsubscript{2}–nanocomposites can be used for bioimaging, microwave hyperthermia, radiation therapy, immunotherapy, and combination therapy. However, most the research of MoS\textsubscript{2}–nanocomposites for cancer diagnosis and treatment are still at an early stage, and there are still many problems to be solved [16].

Firstly, the long-term safety of MoS\textsubscript{2}–nanocomposites in biomedical applications needs to be considered. Most experiments in vivo are limited to animal models, and only the short-term effects of these nanocomplexes on animal major organs, hematological indexes and blood biochemical indexes have been tested. Whether their long-term toxicity and efficacy in humans are consistent with the results of animal models has not been confirmed [398]. Quantum size effects and surface effects of MoS\textsubscript{2}–nanocomposites may cause toxicity or enhance toxicity in organisms. MoS\textsubscript{2}–nanocomposite may interact with channel proteins and various receptors on the surface of the cell membrane or inside the cell, resulting in conformational changes of proteins, changing of signal transduction pathways, and leading to dysfunction of the body. At present, there is no research to prove whether nanomaterials can interfere with the reproductive system and affect offspring [394]. In summary, the realization of clinical transformation of nanomaterials still faces great challenges, and more efforts are needed to fully demonstrate their long-term bio-safety.

Additionally, the bioavailability of MoS\textsubscript{2}–nanocomposites in human tumor sites should be considered. It is very important to design MoS\textsubscript{2}–nanomedicines that can specifically respond to the tumor.
microenvironment to enhance efficacy. For example, designing nano-
materials that can selectively bind to tumor cell-specific receptors to
increase their accumulation in tumor sites and reduce the uptake of non-
cancerous tissues. The rapidly established mouse orthotopic tumor
model has an obvious EPR effect. However, the cancer progression and
growth rate of many patients is much lower than that of mouse models,
resulting in the patients’ EPR effect is not obvious. Therefore, the uptake
of nanomaterials through the EPR effect may not be suitable for the
cancer patients. It is necessary to synthesize nanomaterials that can
enter human tumor sites through other effects for improving their
bioavailability in the human body.

Finally, synthesis of MoS₂-nanocomposites with stable performance
is another challenge. On the one hand, the size and thickness are the key
factors that affect the physicochemical property of MoS₂. Although there are existing methods to adjust the size and thickness of MoS₂, the cost is
expensive, the operation steps are cumbersome and the morphology of
MoS₂ will be affected. Therefore, exploring a simple and easy synthesis
method can not only reduce costs, but also better optimize the properties
of MoS₂ and improve its therapeutic effect. On the other hand, excellent
stability is a necessary condition for nanomedicines to achieve clinical
transformation. Therefore, it is urgent to optimize experimental
methods to improve the stability of nanomaterials, prolonging their
storage time and promoting clinical transformation.

Declaration of competing interest
The authors declare no conflict of interest, financial or otherwise.

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