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Multi-target tyrosine kinase inhibitor nanoparticle delivery systems for cancer therapy

Wenjing Xu [a,1], Chunping Ye [d,1], Xin Qing [a], Shengli Liu [e], Xinyi Lv [c], Wenjun Wang [b], Xiaochen Dong [c,f,**], Yewei Zhang [e,*]

[a] School of Medicine, Southeast University, Nanjing, 210009, China
[b] School of Physical Science and Information Technology, Liaocheng University, Liaocheng, 252059, China
[c] Key Laboratory of Flexible Electronics (KLOFE) and Institute of Advanced Materials (IAM), Nanjing Tech University (NanjingTech), Nanjing, 211816, China
[d] Department of Obstetrics and Gynecology, Nanjing Maternity and Child Health Care Hospital, Women's Hospital of Nanjing Medical University, Nanjing, China
[e] Hepatopancreatobiliary Center, The Second Affiliated Hospital of Nanjing Medical University, Nanjing, 210011, China
[f] School of Chemistry & Materials Science, Jiangsu Normal University, Xuzhou, 221116, China

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ABSTRACT

Multi-target Tyrosine Kinase Inhibitors (MTKIs) have drawn substantial attention in tumor therapy. MTKIs could inhibit tumor cell proliferation and induce apoptosis by blocking the activity of tyrosine kinase. However, the toxicity and drug resistance of MTKIs severely restrict their further clinical application. The nano pharmaceutical technology based on MTKIs has attracted ever-increasing attention in recent years. Researchers deliver MTKIs through various types of nanocarriers to overcome drug resistance and improve considerably therapeutic efficiency. This review intends to summarize comprehensive applications of MTKIs nanoparticles in malignant tumor treatment. Firstly, the mechanism and toxicity were introduced. Secondly, various nanocarriers for MTKIs delivery were outlined. Thirdly, the combination treatment schemes and drug resistance reversal strategies were emphasized to improve the outcomes of cancer therapy. Finally, conclusions and perspectives were summarized to guide future research.

1. Introduction

Cancer is a disease that seriously threatens human health worldwide, ranked as a leading cause of death [1]. A variety of strategies have been extensively explored to cure cancers, including surgery, radiotherapy, chemotherapy, biological therapy, etc. [2–4] However, these traditional therapies are unable to completely cure malignant tumors [5]. Therefore, it is vital to seek novel, high-efficiency and low-toxic cancer treatment means.

Since imatinib is approved by US Food and Drug Administration (FDA) in 2001, tyrosine kinase inhibitors (TKIs) have attracted considerable research interest of researchers owing to their superior therapeutic outcomes compared to conventional chemotherapeutic drugs [6]. This marks that oncotherapy has gradually entered the targeted therapeutic era. TKIs are capable of targeting tumor cells and vascular endothelial cell kinase receptors, blocking cell proliferation signal transduction pathway [7]. The main targets of TKIs include vascular endothelial growth factor receptors (VEGFR), epidermal growth factor receptor (EGFR), mitogen-activated protein kinase (MEK), colony-stimulating factor 1 receptor (CSF1R), anaplastic lymphoma kinase (ALK), FMS-related tyrosine kinase 3 (FLT3), platelet-derived growth factor receptor (PDGFR), etc. However, drug resistance is universally occurred in cancer therapy of the single target agents [8]. In 2005, sorafenib, the first multi-targeted TKIs (MTKIs), was approved by FDA for the treatment of advanced renal cell carcinoma. Two years later, sorafenib was used to treat hepatocellular carcinoma and has been listed as the first-line therapeutic scheme for advanced liver cancer. In recent decades, a variety of MTKIs have been developed continuously, making molecular targeted therapy a vital strategy of tumor therapy [9]. MTKIs can not only directly or indirectly inhibit tumor growth via promoting tumor cell apoptosis

* Corresponding author. Hepatopancreatobiliary Center, The Second Affiliated Hospital of Nanjing Medical University, Nanjing, 210011, China.
** Corresponding author. Key Laboratory of Flexible Electronics (KLOFE) and Institute of Advanced Materials (IAM), Nanjing Tech University (NanjingTech), Nanjing, 211816, China.
E-mail addresses: iamxcdong@njtech.edu.cn (X. Dong), zhangyewei@njmu.edu.cn (Y. Zhang).
[1] These authors contributed equally to this work.ik

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and activating antitumor immunity, but also hamper tumor angiogenesis (VEGFR-associated MTKIs) [11]. MTKIs can be used for many cancers, including metastatic renal cell carcinoma (mRCC), differentiated invasive thyroid carcinoma (DITC), non-small cell lung cancer (NSCLC), inoperable or distant metastatic hepatocellular carcinoma, and so forth [12]. Importantly, MTKIs are listed as the first-line treatment strategy for various malignant tumors according to international treatment guidelines [13]. In terms of clinical efficacy, MTKIs indeed improve the median survival time of tumor patients and have become an important pattern of oncotherapy in clinical trials and real-world studies. However, although MTKIs exhibit outstanding anticancer effectiveness, the occurrence of resistance and adverse effects seriously hinder their further application [14]. On the one hand, MTKIs display a low tumor response rate and only inhibit tumor growth which cannot eradicate tumor cells. The patients with effective responses gradually generated drug resistance after several months of treatment [15,16]. Drug resistance has gradually become the most critical issue for future MTKIs development. On the other hand, the severe dose-related systemic side effects of MTKIs are also the main hurdle in practical application [17]. Furthermore, most MTKIs are hydrophobic drugs and have low oral bioavailability, which impedes their absorption and transportation in vivo. Consequently, how to deal with these critical issues will be crucial for the study of MTKIs. As we all know, nanotechnology has gained widespread attention owing to its efficient, minimally invasive, and multifunctional properties, and it could fulfill higher specific drug delivery with minimum undesirable effects [3, 18–22]. It seems quite attractive to cope with these oncologic therapy problems of MTKIs through nanomedicine technology. The modified nanoscale therapeutic drugs not only increase the biocompatibility, realize the combination or synergistic therapy, but also possess attractive passive targeting ability (treatment of solid tumors) owing to the enhanced permeability and retention effect (EPR) of nanoparticles (typically 10–200 nm in size) [23]. It should be pointed out that various targeting groups (polypeptides, folic acid, antibodies, etc.) that bind specific receptors on the surface of tumor cell membranes can be modified to the surface of nano-delivery carriers, which enhances the active targeting capability [24–26]. For the past few years, the studies related to MTKIs nanoparticles for treating malignant tumors have increased observably [27,28]. Various kinds of nanodrug delivery platforms have been devised to ameliorate bioavailability, facilitate therapeutic efficiency, and conquer drug resistance [29]. For instance, the researchers prepared suitable size hydrophilic MTKIs nanoparticles to realize passive targeting and facilitate absorption efficiency in tumor tissues by the hydrophilic modification method. In addition, the co-delivery of numerous other antitumor drugs (such as photothermal reagents, photodynamic therapeutic drugs, chemotherapy drugs, etc.) and MTKIs achieved a combination or synergistic enhanced therapeutic effect, thus reducing the therapeutic dose of MTKIs drugs and overcoming MTKIs resistance [30,31].

In this review, the applications of MTKIs nanoparticle delivery systems for cancer therapy were summarized. Firstly, the anticancer mechanism and corresponding adverse effects of MTKIs were represented. What's more, the anticancer tactics of MTKIs nanoparticles were highlighted specially. Finally, the challenges and perspectives of MTKIs nanoparticles were discussed. The main content of this review was depicted in Fig. 1.

2. The introduction of tyrosine kinase and TKIs

Human genome data suggest more than 500 members of the protein kinase family. Among them, protein tyrosine kinases (an organic compound) are closely related to tumourigenesis and progression. Protein tyrosine kinases include receptor tyrosine kinases and non-receptor tyrosine kinases [32,33]. Both of them have been involved in many tumors, and receptor tyrosine kinases have become a preferred target in cancer therapy due to their high oncogenic potential. The activation of protein tyrosine kinases could promote cell proliferation and prevents

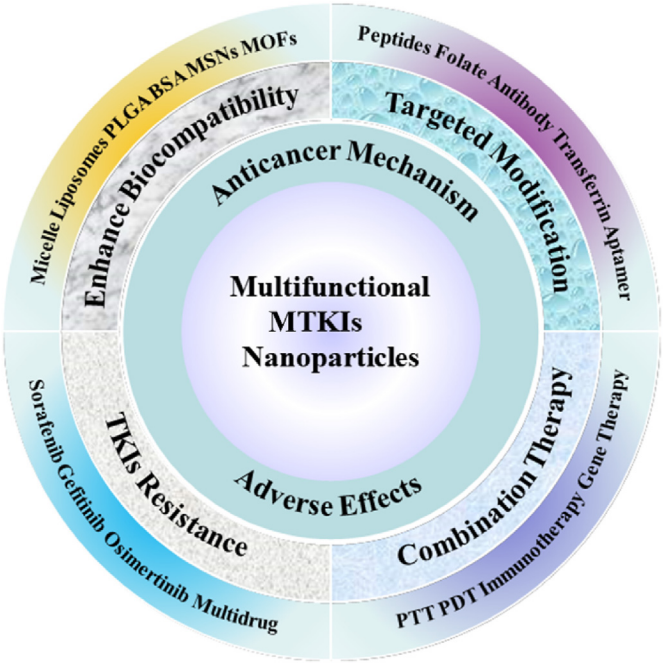

Fig. 1. The anti-cancer applications of MTKIs nanoparticles.

apoptosis by activating a cascade of downstream signaling pathways after binding to various tyrosine kinase receptors. In September 1998, the humanized monoclonal antibody Herceptin, produced by Gentech company, was approved by FDA for the therapy of metastatic breast cancer, which marked MTKIs officially entering the clinical practice [34]. Three years later, the first small molecule BCR-ABL tyrosine kinase inhibitor, imatinib (Gleevec), was approved as a therapeutic regimen for chronic myeloid leukemia, which indicated that oncotherapy entered the era of molecular targeted therapy. Over the following 20 years, all kinds of MTKIs have been incessantly emerging and wide-ranging applied in the preclinical and clinical treatment of various tumors (Fig. 2, Table 1). MTKIs have developed to the third generation, including first-generation drugs (erlotinib, lapatinib, etc.), second-generation drugs (canertinib, afatinib, brigatinib, etc.), and third-generation drugs (osimertinib, lorlatinib, almonertinib, etc.). Tumor heterogeneity is regarded as a dominant factor when considering selective MTKIs. These inhibit display variable tumoricidal effects on malignancies with different driver kinases [35]. MTKIs can also be classified into monoclonal antibody drugs and small molecule drugs. The monoclonal antibody drugs regulate cell proliferation, metastasis, and angiogenesis mainly via acting on extracellular matrix binding sites. While small molecule drugs regulate through intracellular phosphorylation, which maybe leads to more adverse effects [36]. Therefore, the side effects of MTKIs in clinical applications deserve a great deal of attention.

3. The adverse effects of MTKIs

While MTKIs inhibit tumor signaling pathways, they can also have a particular impact on normal cells, causing a range of adverse events, in particular for small-molecule targeted drugs. It is found that the incidence of adverse effects in blood, digestion, respiration, skin, and other systems is high, and may be complicated by multiple systems. However, the degree of adverse reactions mainly was graded 1–2 (Fig. 3, Table 1) [37]. We take one of the MTKIs, sunitinib, as an example to introduce the adverse effects of MTKIs. Pharmacokinetic studies showed that sunitinib was absorbed relatively slowly, roughly 8 h, and the half-life was up to 60 h. The inhibitory concentrations and steady-state of sunitinib are obtained with a 50-mg daily dosage for 14 days [38,39]. Accordingly, long-term drug accumulation will produce a series of undesirable side

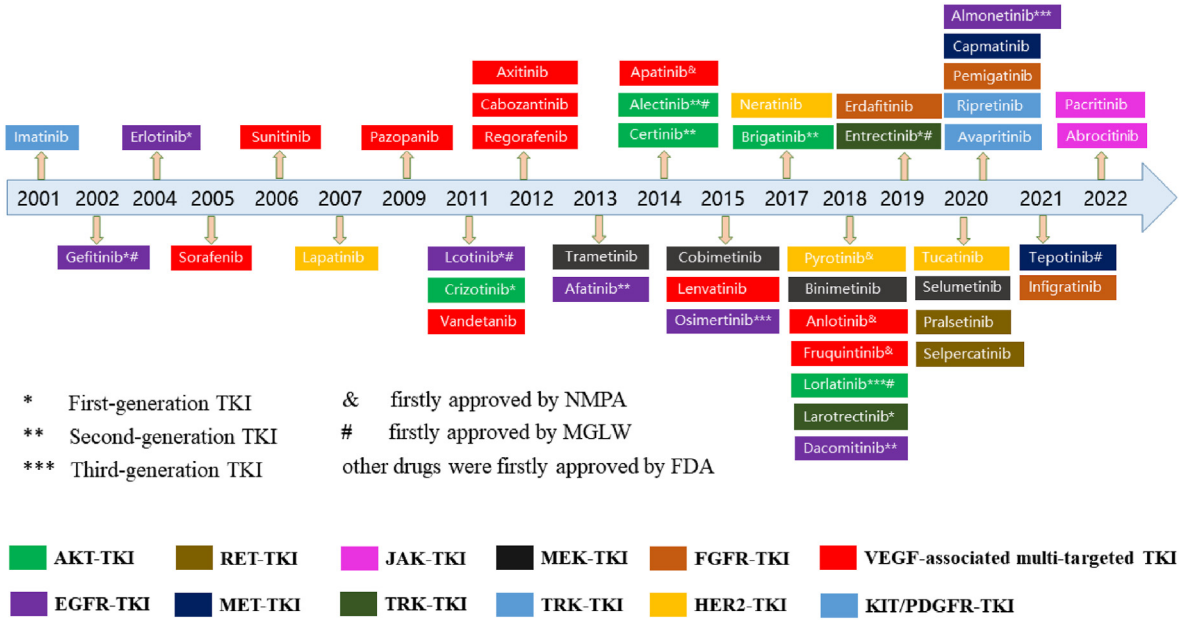

Fig. 2. Schematic summary of the approved TKIs in 2001–2022.

effects. Sunitinib's most frequent acceptable toxicity experienced by cancer patients includes cutaneous toxicities, fatigue, diarrhea, mucositis, etc. Among them, fatigue and asthenia are the most common and arduous side effects to manage. In addition, elevated blood pressure, cytopenia, liver enzyme disorders, and elevated serum creatinine levels are also common toxic undesirable effects [13]. Hence, it is indispensable to reduce the adverse effects of MTKIs through diversified approaches.

4. MTKIs anticancer mechanism

Kinase signaling is a rather complex network structure rather than a single linear pathway. If the damaged signal pathway is compensated by other pathways, tumor proliferation will resume. TKIs provide a novel targeted therapeutic intervention for tumors due to the overexpression of tyrosine kinase in some cancers. Most TKIs are multi-target drugs, while a few TKIs only have one target, such as bosutinib and gefitinib [40,41]. TKIs could inhibit signal transduction and regulate essential cellular biochemical functions by competitive inhibition of the adenosine triphosphate (ATP) binding pocket. The common targets include EGFR, HER2, FGFR1-4, IGFR, PDGF-α, c-KIT, VEGFR, TRK, RET, ALK, and so on. MTKIs mainly inhibit tumor cell proliferation and metastasis through four major signal pathways (JAK/STAT, RAS/RAF/MEK/ERK, PI3K/AKT/mTOR, PLC/PIP2/DAG/PLK) (Fig. 4). The inhibition of the cell signal transduction is capable of causing a range of antitumor effects, such as induction of cell apoptosis, antiangiogenesis, suppression of tumor invasion, and metastasis [42]. To illustrate, serving as a kind of multi-targeting MTKIs, sunitinib could inhibit members of the RTK families, including VEGFR, cKIT, FLT3, CSF-1R, PDGFR-A, PDGFR-B, and so on. For other classical multi-target MTKIs, sorafenib can inhibit tumor cell proliferation by blocking the Raf/MEK/ERK cell signaling pathway, meanwhile, hamper tumor angiogenesis by targeting VEGFR and PDGFR [43]. In summary, MTKIs can restrain the growth and metastasis of tumor cells, and induce tumor cell apoptosis and anti-tumor angiogenesis by acting on single or multiple targets to inhibit the activity of tyrosine kinase.

4.1. Directly inhibit tumor growth

MTKIs can be used as competitive inhibitors of ATP binding to tyrosine kinases, thus blocking the activity of tyrosine kinases and inhibiting tumor cell proliferation. MTKIs can inhibit the activity of multiple signal pathways or multiple tyrosine kinases in one signal pathway. The inhibition of kinase activity will activate a series of downstream pathways, which will directly affect the proliferation, metastasis, and survival of tumor cells. Recent studies have shown that ferroptosis is closely related to the mechanism of MTKIs [44–46]. Ferroptosis is a regulated process of cell death dependent on Fe. Ferroptosis has received considerable research interest due to the potential applications of cancer therapy [47]. As presented in Fig. 5a, sorafenib, as a typical drug of MTKIs, can directly inhibit the cystine/glutamate antiporter system X_c^-, indirectly inactivate glutathione peroxidase 4 (GPX4), and block cellular antioxidant defense. The system X_c^- can transfer glutamate to the outside of the cell while exchanging extracellular cystine for the intracellular environment. The conversion of cystine to cysteine for the synthesis of the antioxidant glutathione. Sorafenib inhibits glutathione generation associated with system X_c^-, leading to the accumulation of endogenous ROS and triggering ferroptosis. Additionally, GPX4 is a protease that inhibits lipid peroxidation, and glutathione is an indispensable cofactor for the activation of GPX4. Sorafenib can indirectly inhibit the activity of GPX4 via inhibiting the generation of glutathione, which results in the accumulation of lipid peroxides (LPO) in cells and then induce ferroptosis [48,49]. Li group used photosensitizer chlorin e6 (Ce6) to covalently connect hemoglobin (Hb) by the amido bond, and prepared Hb-Ce6 nanoplatforms to deliver sorafenib. The obtained micelles nanoparticles (SRF@Hb-Ce6) were obtained after decorating with a protein overexpressed in tumor cells (MMP2). The oxygen-carrying ability of Hb boosts PDT by relieving hypoxia, while Fe supplementation of Hb increases LPO generation. The enhanced PDT could induce tumor cell ferroptosis via recruiting T lymphocytes and increasing the secretion of IFN-γ. The increased IFN-γ could downregulate SLC3A2 and SLC7A11 (cystine/glutamate transporters), thereby further rendering cancer cells sensitized to ferroptosis (Fig. 5b) [50]. The progress of ferroptosis has been considered as a biologically regulated Fenton reaction dependent on Fe ions rather than other metal ions, especially Fe^{2+} (observably higher catalytic activity than Fe^{3+}). It is an exceedingly attractive strategy to enhance ferroptosis therapy by upregulating intracellular Fe^{2+} levels. The continuous Fe^{2+} supply can be obtained by cathodic reduction of the Fe^{3+} generated in the Fenton reaction (Fig. 5c). Previous studies have demonstrated that ferric chelates with tannic acid (TA) are more stable than ferrous chelates at neutral pH [51]. Researchers designed a

Table 1
The introduction of various MTKIs.

MTKIs	Molecular formula	Main target	Clinical application	adverse effect
Sorafenib	$C_{21}H_{16}ClF_3N_4O_3{\cdot}C_7H_8O_3S$	VEGFR1-3, PDGFRβ, c-KIT,FLT-3, RET, BRAF, c-RAF	Inoperable or distant metastatic hepatocellular carcinoma	Rashes, diarrhea, elevated blood pressure, redness, pain, swelling, or blisters on the palms or bottoms of the feet …
Lenvatinib	$C_{21}H_{19}ClN_4O_4$	VEGFR1-3, FGFR1-4, PDGFR-α, cKit, Ret	DITC	Hypertension, fatigue, diarrhea, arthralgia, loss of appetite, vomiting …
Sunitinib	$C_{22}H_{23}D_4FN_4O_2$	VEGFR1-3, PDGFRβ, c-KIT, FLT-3, RET	Gastrointestinal stromal tumors and	Cutaneous toxicities, fatigue, diarrhea, mucositis, asthenia …
Cabozantinib	$C_{28}H_{24}FN_3O_5$	MET, VEGFR1, VEGFR2, VEGFR3, ROS1, RET, AXL, NTRK, KIT	Local advanced or metastatic medullary thyroid cancer, advanced renal cancer, advanced NSCLC, Liver cancer, Advanced prostate cancer patients	Diarrhea, stomatitis, weight loss, loss of appetite, nausea, fatigue, dysgeusia, high blood pressure, abdominal pain, constipation …
Pazopanib	$C_{21}H_{23}N_7O_2S$	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, FGFR-1, FGFR-3, Kit, Itk, Lck, cFms	Advanced renal cell carcinoma, soft tissue sarcoma, epithelial ovarian cancer, NSCLC	Diarrhea, nausea, headache, difficulty breathing, weight loss, muscle pain …
Vandetanib	$C_{22}H_{24}BrFN_4O_2$	VEGFR2/3, EGFR, RET	Advanced medullary thyroid cancer	Diarrhea, rash, nausea, high blood pressure, headache, fatigue, decreased appetite …
Osimertinib	$C_{28}H_{33}N_7O_2$	EGFR, T790 M, HER2, HER3, HER4, ACK1, BLK	Local advanced or metastatic NSCLC	Mouth sores, rash, nausea, vomiting, dry skin, fatigue, nail toxicity, decreased appetite, diarrhea …
Regorafenib	$C_{21}H_{15}ClF_4N_4O_3$	VEGFR1/2/3, PDGFRβ, Kit, RET, Raf-1	Metastatic colorectal cancer	Fatigue, oral mucositis, diarrhea, weight loss, infection, high blood pressure, dysphonia …
Afatinib	$C_{24}H_{25}ClFN_5O_3$	HER2, sEGFR	NSCLC	Diarrhea, acne rash, mouth ulcers, paronychia …
Anlotinib	$C_{23}H_{22}FN_3O_3$	VEGFR, PDGFR, FGFR, c-Kit	Soft tissue sarcoma, medullary thyroid carcinoma, mRCC	Hypertension, skin reactions on hands and feet, peeling, gastrointestinal symptoms …
Alectinib	$C_{30}H_{29}D_5N_4O_2$	ALK, LTK, CHEK2, FLT3, RET	Anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic NSCLC	Visual disturbances, nausea, diarrhea, vomiting, muscle aches and swelling, fatigue …
Nilotinib	$C_{28}H_{22}F_3N_7O$	Bcr-Abl, PDGFR, c-Kit	Imatinib-resistant chronic myeloid leukemia	Bone marrow suppression, rash, itching, nausea, headache, fatigue, constipation …
Imatinib	$C_{29}H_{31}N_7O$	BCR/ABL1, KIT, RET, NTRK1, CSF1R, PDGFRA, PDGFRB, DDR1	Chronic myeloid leukemia and malignant gastrointestinal stromal tumors	Mild nausea, vomiting, diarrhea, myalgia, muscle cramps, rash …
Erlotinib	$C_{22}H_{23}N_3O_4$	EGFR, PDGFR, C-Kit	Local advanced or metastatic NSCLC	Rash, diarrhea, fatigue, nausea, anorexia, diarrhea …
Lapatinib	$C_{29}H_{26}ClFN_4O_4S$	EGFR, HER2	ErbB-2-overexpressing advanced or metastatic breast cancer	Nausea, diarrhea, stomatitis, indigestion, dry skin, rash …
Dasatinib	$C_{22}H_{26}ClN_7O_2S$	c-KIT, EPH, PDGFβ	Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia in chronic, accelerated, and blast phases (myeloid blast and lymphoma blast) that are resistant or intolerant to imatinib mesylate	Fluid retention, diarrhea, headache, nausea, rash, difficulty breathing, bleeding, fatigue …
Vandetanib	$C_{22}H_{24}BrFN_4O_2$	EGFR, RET, VEGFR2	Local advanced or metastatic symptomatic or progressive medullary thyroid cancer	Diarrhea, rash, acne, nausea, high blood pressure, headache, fatigue, loss of appetite, and abdominal pain …
Crizotinib	$C_{21}H_{22}Cl_2FN_5O$	ALK, MST1R, ROS, c-Met/HGFR	Anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic NSCLC	Abnormal vision, nausea, diarrhea, vomiting, constipation, edema, elevated transaminases and fatigue …

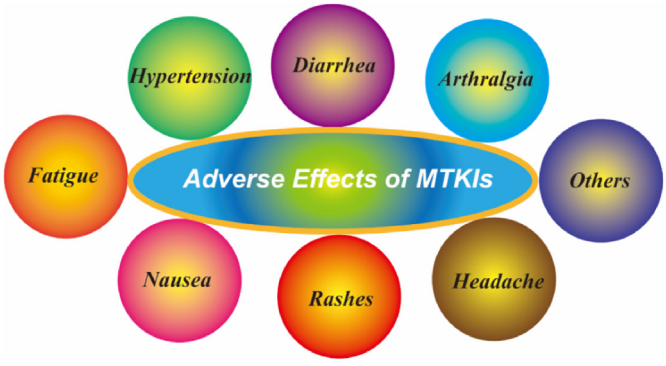

Fig. 3. The adverse effects summary of MTKIs.

ferrous-supply-regeneration nanotherapeutic to facilitate ferroptosis. In this protocol, sorafenib nanocrystal was first prepared as the core of nanoparticles. Subsequently, TA and Fe^{3+} were added to form the Fe^{3+} TA network which could attach to the crystal surface and interrupt the growth of sorafenib crystal. Finally, the above nanoparticle was mixed with methylene blue (photodynamic agent) to obtain SFT-MB nanoparticles. After SFT-MB is endocytosed by tumor cells, sorafenib was released for ferroptosis by the response of the lysosomal acid environment. TA was orchestrated to chemically reduce Fe^{3+} to Fe^{2+} which can be used for the generation of LPO involved in ferroptosis [52]. In another report, $ATB^{0,+}$-targeted (amino acid transporter $B^{0,+}$-targeted) liposome nanoparticles loaded with doxorubicin and sorafenib were constructed after modification with MMP2 (matrix metalloproteinase 2, a pharmacological target for cancer). MMP2 could stimulate the exposure of site-specific ligand (lysine) by PEG deshielding, and the exposed lysine combined with $ATB^{0,+}$ to realize the endocytosis of liposomes. The released sorafenib could block cystine/glutamate transporter to suppress GSH biosynthesis, which led to increased production of LPO. Meanwhile, DOX could generate more intracellular ROS to further disrupt redox homeostasis (Fig. 5d) [53]. MTKIs can inhibit the growth and metastasis of tumors by blocking multiple tyrosine kinase targets, and can also induce ferroptosis of tumor cells. However, the specific interaction

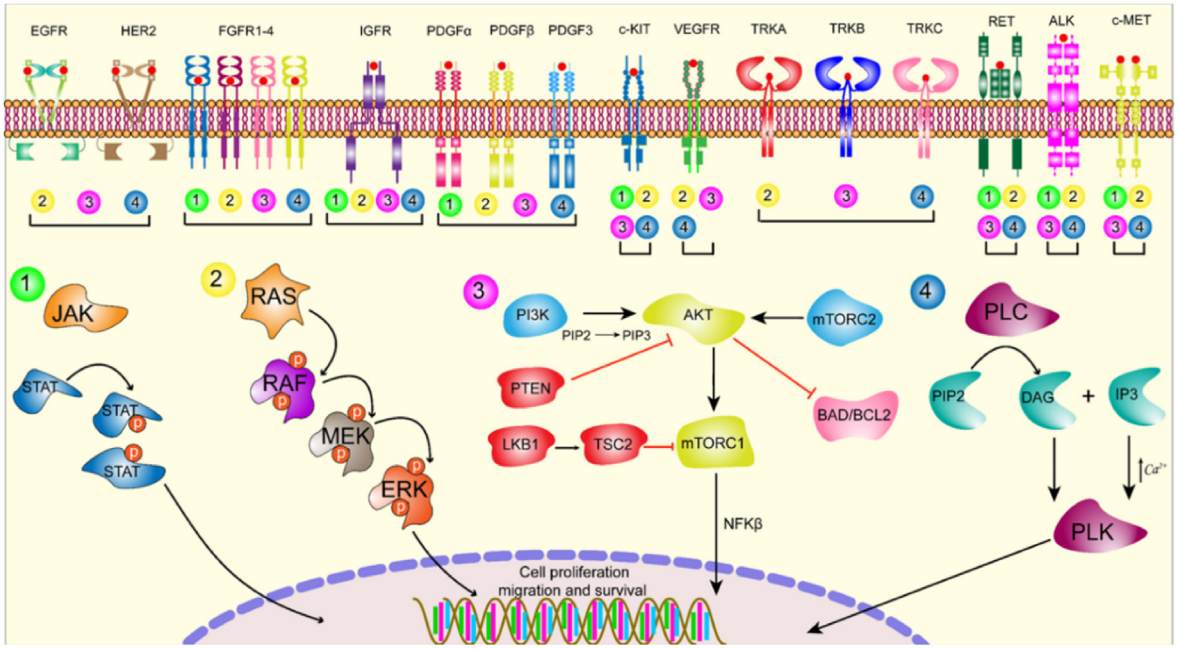

Fig. 4. The interaction between various signaling pathways is activated through TKIs and involved in tumor proliferation.

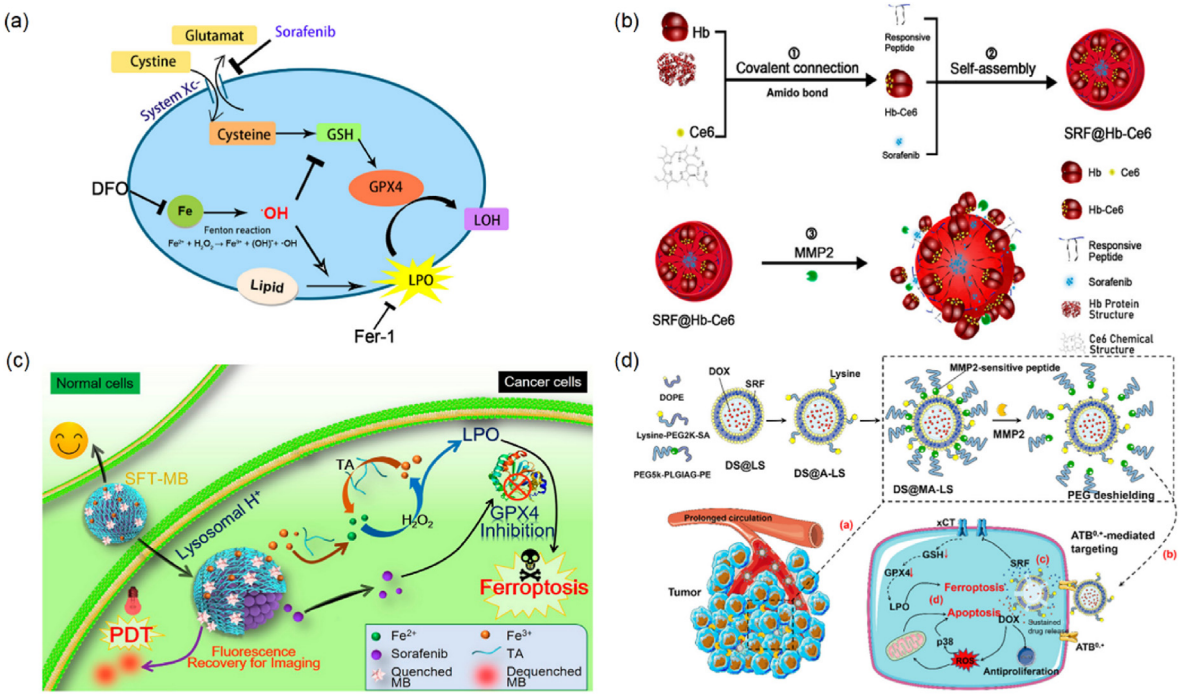

Fig. 5. (a) Schematic diagram displaying the simplified mechanism of ferroptosis. (b) Schematic illustration showing the components of SRF@Hb-Ce6, the synthesis process, and the dissociation. Reproduced with permission [50]. Copyright 2020, American Chemical Society. (c) Schematic Illustration of SFT-Mediated Combination of Ferroptosis and Image-Guided PDT. Reproduced with permission [52]. Copyright 2018, American Chemical Society. (d) Design and application of MMP2-Activated and $ATB^{0,+}$-Targeted Liposomes Incorporating Doxorubicin and Sorafenib (DS@MA-LS) for Cancer Therapy. Reproduced with permission [53]. Copyright 2020, American Chemical Society.

mechanism between MTKIs and ferroptosis still needs to be further explored.

4.2. Anti-angiogenesis

Tumor angiogenesis is an indispensable process for tumor development. As early as 1971, researchers proposed a novel breakthrough antitumor strategy to inhibit tumor growth by interfering with vessel proliferation [54,55]. In recent fifty years, the targeted antivascular strategy has experienced explosive growth as a potential technique for cancer treatment [56,57]. Anti-angiogenic schemes have been proved as a promising anti-tumor therapeutic strategy. The mechanism of angiogenesis is mostly modulated by chemical stimuli, for example, VEGF, FGF, PDGF, hypoxia-inducible factor (HIF), and so on [58]. The

overexpressed VEGF in tumors is associated with tumor progression, invasion, and metastasis. MTKIs can inhibit tumor angiogenesis by targeting the angiogenesis-related receptors. The antiangiogenic property of MTKIs is one of the major anti-cancer mechanisms for tumor growth [59]. Sun et al. designed a drug delivery system (Lip-IR780-Sunitinib) based on liposomes to optimize the therapeutic outcome. The group of Lip-IR780-Sunitinib under laser irradiation manifests the most significant inhibitory effect compared to other groups. Anti-CD31 immunohistochemical staining was conducted to assess the anti-angiogenic ability in vivo. And the microvessel density (MVD) of the Lip-IR780-Sunitinib/laser group possesses the lowest MVD value. The Lip-IR780-Sunitinib/laser demonstrated outstanding inhibit the migration performance of HUVEC cells, which was equivalent to that of free sunitinib [29]. As another commonly used anti-vascular small molecule targeted drug, sorafenib can not only inhibit the tumor cell proliferation by blocking the RAF/MEK/ERK pathways but also indirectly kill tumor cells via the down-regulated expression of VEGF and PDGF receptors [60]. Wei et al. fabricated versatile carrier-free nanoparticles (SC NPs) via assembling sorafenib and phototherapeutic reagent (Ce6). The SC NPs possess satisfactory water dispersity and anti-angiogenesis ability. The strategy for synergetic anti-angiogenic and phototherapy could effectively cut off the blood supply of tumors and kill cancer cells [28]. It is worth mentioning that researchers normalize the tumor vasculature and enhance the tumor perfusion with erlotinib, which could relieve tumor hypoxia and improve the efficacies of nanomedicine and immunotherapy [61]. Anti-angiogenesis is an important strategy for tumor therapy. As hypoxia can promote tumor angiogenesis, it provides a novel idea for us to explore the anti-tumor angiogenesis tactics of oxygen-producing nanocarriers delivering MTKIs in the future.

5. Delivery carriers of MTKIs

The low molecular weight MTKIs will accumulate off-target in healthy organs and tissues due to the influence of pharmacokinetics and biological distribution. The drug encapsulation through nanotechnology can effectively improve renal clearance threshold and blood half-life, reduce renal excretion, and promote the bioavailability of MTKIs [97]. It is crucial to explore one strategy that selectively kills tumor cells while preserving the essential host cells and their functions [98]. Relieving the toxic and side effects of chemotherapy drugs can also make patients

Table 2
The introduction of various MTKIs nanoparticles.

MTKIs	Nanoparticles	Carrier type	Average particle size (nm) (±S.D.)	Zeta potential (mV) (±S.D.)	PDI	Entrapment efficiency (EE%)	Drug loading (DL%)	Ref.
Sorafenib	Sorafenib-LNS	Liposomes	164.5(±4.5)	−11.0(±0.28)	0.202(±0.015)	–	10.55(±0.16)	[62]
Sorafenib	HA/SF	Liposomes	130.57(±14.06)	−18.1(±1.1)	0.261(±0.004)	–	6.8(±0.1)	[63]
Sorafenib	Resomer®RG 752H	PLGA	231.3(±30.1)	−22.2(±1.8)	0.19(±0.04)	76.6(±2.7)	11.2(±0.1)	[64]
Sorafenib	SRF@Hb-Ce6	Hemoglobin	175	−14.43	–	70%	–	[50]
Sorafenib	TPTN	Polymer	181.4(±3.4)	+14.95(±0.60)	0.236	95.02(±1.47)	2.38(±0.04)	[65]
Sorafenib	MMSNs@SO	MSNs	102.6(±3.06)	−25.43	0.119(±0.01)	5.36(±0.64)	2.68(±0.32)	[66]
Sorafenib	SO@MSN-CS-LA	MSNs	210.9(±2.8)	+7.7 (±2.6)	0.258(±0.022)	57.4(±2.1)	21.3(±0.9)	[67]
Sorafenib	SO/siVEGF@MSN-LA	MSNs	148.5(±3.5)	+8.3(±3.5)	0.153(±0.072)	55.3(±2.9)	55.3(±2.9)	[68]
Sorafenib	ADOPSor NPs	PLGA	175.25 ± 1.82	+19	0.148 ± 0.004	85%	–	[69]
Sorafenib	SCN	Polymer	84.97(±6.03)	–	0.176(±0.034)	98.16(±0.23)	6.54(±0.01)	[70]
Sorafenib	NAcGal-DOX/SOR LNPs	Lipid nanoparticles	121.2(±3.5)	−37.4(±3.6)	0.16(±0.03)	83.2(±3.3)	4.1(±0.4)	[71]
Sorafenib	PBB/sorafenib	Copolymer	240(±7.7)	−28.9(±5.7)	0.30(±0.07)	–	3.8(±0.48)	[72]
Sorafenib	mPEG-PDLLA	Polymeric	127.3(±2.0)	−3.35(±0.42)	–	95(±3.2)	6.5(±0.2)	[73]
Sorafenib	GAL-SSLN	Solid lipid nanoparticles	111.0(±6.99)	−19.8(±1.11)	0.354 (±0.024)	95(±1.8)	–	[74]
Sorafenib	DOX + SOR/ iRGDNPs	Lipid-polymer	126.3(±16.4)	−21.4(±4.6)	0.105(±0.016)	70.8(±2.8)	3.6(±0.05)	[75]
Sorafenib	LCC-DOX/miR-375	Lipid-coated calcium carbonate	100.7(±12.1)	+40.37(±3.38)	0.116 (±0.03)	–	35.2(±8.7)	[76]
Sorafenib	NP-TPGS-SFB	Polymeric	118.3(±5.1)	+3.3(±0.4)	0.15	86.5	15.5	[77]
Sorafenib	Gal-SLPs	Polyplexes	95.6 ± 5.2	−5.6 ± 0.8	–	74.5	3.6	[78]
Sorafenib	LD-SDN	Lipid-nanoparticles	126.5 (±1.33)	−25	0.135	94.5 (±1.62)	13.5(±0.85)	[79]
Sorafenib	GSI-Lip	Liposomes	100–150	−10-0	–	92.44 (±1.60)	0.1–0.2	[80]
Sunitinib	Lip-IR780-Sunitinib	Liposomes	150	–	–	90.12(±0.31)	–	[29]
Sunitinib	SU-MNC	Micelle	167.4(±2.4)	+5.4(±1.3)	0.19(±0.007)	77.1(±2.5)	12.9(±0.3)	[27]
Sunitinib	SU-PM	PEG-PLA	125.9(±4.2)	+7.7(±0.8)	0.20(±0.02)	82.7(±4.6)	13.7(±0.6)	[27]
Sunitinib	BSA-SPIOs	BSA	75.6(±4.6)	−32.1	–	99.8(±3.2)	7.0(±0.2)	[43]
Sunitinib	FA-Pt@Uio-66	MOFs	–	–6.33 ± 0.45	–	75.67 ± 5.57	2.52 ± 0.31	[81]
Afatinib	PSL	Liposomes	46–57	+48.4	< 0.2	52%	–	[82]
Afatinib	AFT-PLN@MAp	MSN	225	−5	–	–	15	[83]
Afatinib	A/D-PADP vesicle	Polymeride	130(±10)	–	–	–	1.73	[84]
Alectinib	DATAT-MNCA	Polymeride	122.0	–	–	44.9%	–	[85]
Osimertinib	OSI + SEL NP	Micelle	43	−30	0.581	–	13	[86]
Osimertinib	CP@NP-cRGD	CaP shell	123.4(±0.4)	−15.1(±1.4)	<0.25	84.6(±2.6)	0.3(±0.1)	[31]
Anlotinib	Anlotinib@IR820	Micelle	120	–	–	–	–	[87]
Anlotinib	cRGDyk-AnlotinibRM	Micelle	30	−15.6	–	98.64%	8.98	[88]
Erlotinib	DE-NPs	Polymer	84	−27.3	–	–	2.6	[89]
Erlotinib	EB@QSSQ	Micelle	112	–	–	50.3	–	[90]
Cabozantinib	PMILs	PLGA	150	–	0.15	50	1	[91]
Dasatinib	Core-shell nanomedicine	PLGA Albumin nano-shell	80	–	–	85	1.8	[92]
Lapatinib	T7-LP@LAP	Liposomes	144(±3)	−4.8(±0.6)	< 0.3	79.1(±5.1)	5.5(±0.4)	[93]
Lenvatinib	Bi/Se NPs	SeNPs	120	–	–	–	10	[94]
Regorafenib	t-LRR	Liposomes	187	−28.6	0.106	93.0	0.6	[95]
Imatinib	INPs	PLGA	250–300	−10.6	0.20	89.94	2.25	[96]

continue to receive drug treatment and avoid drug withdrawal caused by intolerable adverse reactions. Nanomedicine could realize controlled and continuous release of amphiphilic drugs, which reduces drug loss and adverse effects and increases drug action time. The therapeutic drugs can specifically actively and passively target tumor cells through targeted modification and EPR effect, respectively. Furthermore, nanoparticles can improve the solubility of MTKIs, and then improve the bioavailability of drugs. Therefore, it is imperative to potentiate the biosafety and water solubility of chemotherapeutic drugs through nano pharmaceutical technology (Table 2). MTKIs-loaded nanomedicines include liposomes, polymeric micelles, inorganic nanoparticles, polymers nanoparticles, and so on.

5.1. Liposomes

Liposomes are a category of microscopic phospholipid vesicles with a bilayered membrane structure similar to phospholipid bilayers in cells and can transport both hydrophilic and lipophilic drugs [99]. Both inside and outside the shell of liposomes are hydrophilic components, the central cavity can contain water-soluble substances. About 50 years ago, Alec Bangham first observed that phospholipids in aqueous systems could form closed bilayered structures [100]. Soon afterward, liposomes have become bioactive pharmaceutical carriers of great potential and received substantial attention for practical application in the field of cancer therapy. The liposomes are similar to physiological membranes, which makes it easier for liposomes to be endocytosed by neoplastic cells. Liposomes possess the unique advantages of superior bioavailability and low systemic toxicity [101]. Compared to the traditional free drug, liposomes can significantly reduce the adverse effects due to the poor extravasation into tissues with tight endothelial junctions. For example, liposome encapsulation can tremendously reduce the irreversible cardiotoxicity of free doxorubicin [102]. Hence, liposome-based drugs have been widely employed in anti-cancer research [100]. Yang et al. designed a liposomes nanoparticle to load IR780 and sunitinib by the film dispersion method. It should be pointed out in particular that the liposome shell not only prevents premature leakage of sunitinib but also effectively prevents hydration of IR780 [29]. In another study, the researcher successfully designed and synthesized sorafenib lipid-based nanosuspensions by the nanoprecipitation method to treat hepatocellular carcinoma. Compared with free sorafenib, the sorafenib-loaded lipid-based nanosuspensions possessed uniform size distribution and showed higher antitumor efficacy and higher biocompatibility [62]. In addition to the favorable therapeutic efficiency and enhanced biosafety of liposome delivery systems, the surface of liposomes can be modified to target molecules, thereby enhancing therapeutic targeting [103]. Zhang and cooperators fabricated hyaluronic acid (HA)/lipid hybrid nanoparticles to load sorafenib. The final synthesized nanoparticles (HA/SF-cLNS) displayed high drug-loading efficiency and excellent histological safety. Moreover, HA can specifically target to CD44 receptor overexpressed on the surface of the hepatocellular carcinoma (HCC) cytomembrane, which promotes the endocytosis of nanoparticles, enhancing their active targeting ability. In vivo experiment, the HA/SF-cLNS exhibited better therapeutic outcomes than free sorafenib [63]. Almurshedi and colleagues prepared pH-sensitive liposomes based on cationic to deliver afatinib to treat NSCLC. The drug release studies indicated that the obtained nanoparticles have pH-sensitive release behaviors [82]. Lipidic nanoparticles are the first nanoscale pharmaceuticals to realize the successful transition from a theoretical concept to clinical application. Most of the marketed nanomedicines are liposomes. However, liposomes still face imminent practical challenges and deserve further investigation thanks to the complexity of the biological milieu. It is well-known that breast cancer patients with positive human epidermal growth factor receptor 2 (HER2+) have a poorer prognosis [104]. Lapatinib can hamper tumor cell proliferation by inhibiting the expression of HER2. In a recent investigation, Zhang et al. encapsulated lapatinib with liposomes and subsequently used pH-sensitive T7 peptide to decorate the liposome. The obtained nanoparticles manifested superior targeting, pH sensitivity, and sustained release peculiarities [93]. Liposomes have shown great success in the pharmaceutical industry and have been recognized as effective drug delivery systems. Liposomes, have many advantages, including high biocompatibility, low immunogenicity, prolongation of drug halflife, low toxicity, etc. [105] However, nonselective distribution, low bloodbrain barrier penetration, instability, and cholesterol composition severely limited the application of traditional liposomes. For example, cholesterol can affects the particle size and thermodynamic parameters owing to the enhanced fluidity of the phospholipid bilayer [106]. In the future, many special liposomes, such as thermosensitive liposomes, pH sensitive liposomes, ultrasound sensitive liposomes, photosensitive liposomes and magnetic liposomes, will be further developed to overcome these disadvantages and improve the drug delivery capacity of MTKIs. Furthermore, the study of precursor liposomes can also overcome the instability of traditional liposomes. A good deal of novel and sophisticated lipid-based therapeutics will focus on the following exploration in the future.

5.2. Polymeride nanoparticles

Polymer nanoparticles may be defined as being colloidal systems. In the preparation of polymer nanoparticles, polymers can be divided into natural polymers (starch, polypeptides, albumin, sodium alginate, chitin, gelatin, cellulose. etc) and synthetic polymer materials (polyethylene glycol, poly-lactic-acid-co-glycolic-acid, polyvinyl alcohol, polyvinyl pyrrolidone, polyethylene, polyanhydrides, etc). Polymer nanoparticles can also be divided into polymer micelles and polymer nanospheres. Polymer micelles refer to the self-assembly of amphiphilic copolymers into specific supramolecular ordered aggregates in solution. Polymer nanospheres are matrix particles. Drugs can be adsorbed on the surface of polymer nanospheres or encapsulated in particles [107]. Polymer nanoparticles possess the advantages of high drug encapsulation efficiency, excellent cell uptake, superior stability, and satisfactory biocompatibility.

5.2.1. Polymeric micellar nanocomplex

Micelles are nanostructured materials generated by the self-assembly of amphiphilic molecules in water above a specific critical concentration. The micellar nanocomplex could deliver both hydrophilic and hydrophobic solute molecules with various structures and could substantially enhance the solubility of camptothecin and curcumin by factors of 25 and 10,000, respectively [108]. Polymeric micelles are nanoscale core-shell structures prepared by amphiphilic block copolymers [109,110]. Kurisawa et al. fabricated polymeric micellar nanocomplex (named SU-MNC) via utilizing poly (ethylene glycol)-conjugated epigallocatechin-3-O-gallate (PEG-EGCG) as nanocarrier to deliver sunitinib. The epigallocatechin-3-O-gallate is a primary ingredient of green tea, which has been proved to have potential anticancer effects. Compared to free sunitinib at equivalent concentrations, SU-MNC showed almost no cytotoxicity on human renal proximal tubule epithelial cells. In the renal cell carcinoma xenograft models, SU-MNC can obtain comparable efficacy with a 28-fold lower dose of sunitinib. Simultaneously, the group treated with SU-MNC did not show any abnormality, such as blood chemistry analysis, bodyweight loss, lethargy, diarrhea, rashes, discoloration, abnormal activity, and so forth. As a result, SU-MNC showed a greater therapeutic effect and reduced systemic toxicity than sunitinib monotherapy and traditional nanocarriers (SU-PM, SU-loaded polymeric micelle), which mainly benefit from the synergistic anticancer effects and tumor-targeted delivery of sunitinib nanoparticles [27]. Polymeric micelles can be easily surface-modified or stimuli-sensitized by using ligand conjugated amphiphilic polymer [111]. Compared to lipid constituted vesicles or other lipid carriers, polymeric micelles are smaller size, monodispersed, relatively stable and economical. However, polymeric micelles easily suffer from premature drug release, which is attributed to polymer fragments of various lengths. It is critical to find suitable

amphiphilic polymer to address this limitation.

5.2.2. Poly (lactic acid) and poly(lactic-co-glycolic acid) nanoparticles

Poly (lactic acid) (PLA) is well-known and commercially available biopolymer and it has been extensively used in the preparation of different polymer nanoparticles owing to its biodegradable, biocompatible, compostable, self-assembly, and magnetic resonance imaging properties [112]. The multi-block polymer PLA-PEG-poly(L-lysine)-diethylenetriamine pentaacetic acid (PLA-PEG-PLL-DTPA) was served as the delivery carrier ingredient of sorafenib. The PLA-PEG-PLL-DTPA reacts with the poly(L-histidine)-PEG-biotin (PLH-PEG-biotin) to form nanoparticles through self-assembly. The prepared nanoparticles loaded with sorafenib displayed satisfactory biocompatibility, high antitumor effect, and outstanding magnetic resonance imaging performance in H22 tumor-bearing mice [65]. In another work, researchers employed a clinically safe polymer PEG-b-PLA to deliver sorafenib. The sorafenib-loaded nanoparticles based on PEG-b-PLA showed satisfactory inhibitory efficacy for HCC cell lines. Conversely, the nanoparticles displayed low cytotoxicity to the normal hepatocyte with the same treatment conditions [113]. PLGA is one of the synthetic biodegradable polymers obtained from lactic and glycolic acid. PLGA has been approved by FDA because of its potential for drug encapsulation, excellent biocompatibility, and biodegradability [114]. PLGA is commonly used to encapsulate lipophilic drugs due to its hydrophobicity. Zhao et al. constructed PEG-PLGA-based nanoparticles via a dialysis method to deliver sorafenib. The nano encapsulation could reduce the dose of sorafenib to one-ninth and effectively reduce undesirable side effects. More importantly, the tumor growth inhibition effect of nanoparticles in B16–F10 bearing immunodeficient mice (Rag1/mice) is weaker than that of wild-type mice, which indicated that adaptive immune cell is indispensable for the antitumor effects of nano drugs based on sorafenib [115]. In another study, researchers encapsulated sorafenib and doxorubicin with PLGA and PLGA-PEG, respectively. The encapsulated efficiencies of the prepared PLGA and PEG-PLGA nanopolymers for sorafenib are 55% and 88%, respectively. The PEG-PLGA nanoparticles exhibited higher cytotoxicity than the PLGA nanocomposites, which may be attributed to the rapid sorafenib release of PLGA nanoparticles [116]. PLGA nanocarriers have the advantages of superior biocompatibility, biodegradability, long circulation time in vivo, sustained-release, and excellent encapsulation properties. However, PLGA still has many disadvantages. For example, both PLGA and PLA belong to high polymers, and the purification step in the synthesis process will affect the quality of the final product. This will lead to the high cost of the carrier's synthesis. In addition, the stability of PLGA nanoparticles also needs to be improved.

5.2.3. Chitosan polymeride nanoparticles

Chitosan is a natural biopolymer that is prepared by the deacetylation of chitin. Chitosan has been frequently used in drug delivery systems (DDS) because of its versatile physicochemical characteristics, for example, excellent biocompatibility and biodegradability, non-toxicity, and so on [117]. Mehdi and collaborators synthesized a pH-sensitive nano-core-shells magnetic nanocomposite based on chitosan to load sunitinib (mHPMC@Chitosan). The mHPMC@Chitosan manifests high encapsulation efficiency of sunitinib malate (above 86%) and excellent pH-responsive release performance. And further, achieve sustained release of sunitinib to optimize cancer therapeutics [118]. Gomathi et al. synthesized chitosan nanoparticles to deliver sunitinib via the ionic cross-linking method using sodium tripolyphosphate as a crosslinker. The sunitinib encapsulation efficiency of chitosan nanoparticles reaches up to 98.03%. The chitosan nanoparticles loading sunitinib are expected to acquire an anticancer outcome with minimal toxicity [119].

Chitosan can easily bind to nucleic acids, such as DNA and siRNA, through electrostatic interactions. In addition, chitosan also has many advantages, including easy accessibility, excellent biocompatibility, good biodegradability, and so on. However, chitosan has low solubility in physiological aqueous solutions, which restricted its further application. Although the water solubility of chitosan can be increased by hydrophilic modification, it may increase the additional biological toxicity. Further research is indespensible to reduce biological toxicity on the basis of ensuring hydrophilicity.

5.3. Bovine serum albumin (BSA)

Albumin is known as an endogenous protein and has been proven to be a natural and ideal drug vehicle because of its effective integration with various drugs [120–122]. BSA is a globulin found in bovine serum. As a commonly used nanocarrier, it has many certain benefits, such as minor toxicity, availability, scalability, low immunogenicity, and ease of synthesis and purification [123]. Gao et al. prepared lapatinib-incorporated core shell nanoparticles (LTNPs) based on BSA to evaluate the treatment effects of glioma. The LTNPs not only significantly improved the water solubility of lapatinib from 0.007 mg/mL to over 10 mg/mL but also showed superior antitumor effects and reduced dose of lapatinib. Mechanically, LTNPs may enhance anti-tumor proliferation effects by upregulating expression of secreted protein acidic and rich in cysteine (SPARC) in glioma cells [124]. In another study, bovine albumin stabilized by egg yolk lecithin was used to delivery lapatinib. The final synthesized nanoparticles possess higher water solubility and stronger anti-tumor effect compared to lapatinib (Tykerb®; GlaxoSmithKline, London, UK) [125].

Researchers used BSA as a nanocarrier to deliver sunitinib aimed at optimizing water solubility and biocompatibility of sunitinib. This nanoparticle (SPIO-SC) not only has a longer half-life in vivo and improves stability in vivo but also optimizes its drug loading capacity. After incubation for 72 h in H_2O and 1640 medium with or without 10% FBS, the dynamic light scattering size of the BSA nanoparticle showed a subtle change. The SPIO-SC is easier to be engulfed by tumor cells and presented satisfactory antitumor efficiency for Hela and MCF-7 cell lines. Meanwhile, the passive targeting capacity was augmented through the EPR effect [43]. More importantly, BSA can deliver two or more chemotherapeutic drugs at the same time to fulfill combined or synergistic therapy under the premise of reducing drug toxicity. However, BSA nanoparticles still have certain shortcomings, for example, BSA may induce unfavorable immunogenic reactions compared to human serum albumin (HSA).

5.4. Metal-organic frameworks (MOFs)

MOFs, with extremely high porosities, has drawn broad interest due to their well-defined pore aperture, tunable size, large surface areas, high agent loading, and so on [126]. MOFs in the nanoscale regime has displayed a wide range of potential biomedical applications, especially antitumor therapy. Zhang et al. prepared a suitable drug delivery platform by using folic acid (FA)-modified MOFs (Pt@Uio-66) to load sunitinib and indocyanine green (ICG). The final synthesized nanoparticles are denoted as ICG + Sunitinib@Pt@Uio-66. The loading rate and encapsulation percentage of sunitinib were 2.30% ± 0.28% and 72.67% ± 1.26%, respectively. The MOF-based nanocarrier displayed limited toxicity to HepG2 cells, which indicated that it possesses appreciable biocompatibility. Meanwhile, the ICG + Sunitinib@FPu NPs also showed a superior cytotoxic effect on cancer cells due to the combined therapy of sunitinib and ICG [81]. As a superior nanocarrier, MOFs have attracted increasing attention in recent years. However, only a few drug molecules containing unique functional groups (-COOH, $–SO_3H$, etc.) can bond with MOFs, which seriously limits the application of MOFs as effective drug carriers. Furthermore, researchs on the toxicity of MOFs and their biodegradation is still in its infancy. In the future, it is still necessary to explore non-toxic MOF carriers.

5.5. Mesoporous silica nanoparticles (MSNs)

MSNs have been widely applied as vehicles for cancer treatment due to their distinctive and stable pore structure. The drug delivery system

based on MSNs has shown significant advantages over conventional drug nanocarriers, such as high surface area, favorable biocompatibility, and easily modified surface [128]. MSNs offer a promising approach to delivering hydrophobic small molecule drugs [129,130]. Goel et al. prepared VEGFR targeted mesoporous silica nanostructures (named ^{64}Cu-NOTA-MSN-VEGF121) decorated with radioisotope 64Cu and VEGF121. In this system, the 64Cu-NOTA-MSN-VEGF121 was used for loading sunitinib (Fig. 6a). The loading efficiency of sunitinib in MSNs is approximately 10%, and the transmission electron microscopy (TEM) result demonstrated the successful synthesis of nanoparticles. The coronal PET images of the formed nanoparticles at various time points showed remarkably enhanced signals than the control group. At the same time, nanoparticles have also demonstrated excellent antitumor properties [127]. Near-infrared (NIR) persistent luminescence nanoparticles (PLN) have captured ever-increasing attention owing to their superior potential as new optical contrast agents for bioimaging [131]. In another study, MSNs were designed to limit the growth size of the PLN. As presented in Fig. 6b, the suitable pore radius of PLN nanoparticles can accommodate apatinib. Then, a specific SH-modified aptamer sequence (Map) was connected to PLN nanoparticles loaded with apatinib by a disulfide bond, which is of paramount importance for tumor targeting and tracking. The versatile PLN NPs (AFT-PLN@Map) not only minimize side effects, increase drug accumulation, and suppress tumor growth and metastasis but also be used for sustained fluorescence imaging under UV excitation (Fig. 6c) [83]. Zhao and co-workers designed and prepared a pH-sensitive MSN modified with pH-sensitive chitosan and lactic acid. The prepared MSN was responsible for loading hydrophobic chemotherapy drug sunitinib and ursolic acid by non-covalent interactions. The MSN encapsulation efficiency and the loading efficiency of sorafenib were >50% and >20%, respectively. The ingenious nanoparticles can elongate the blood circulation time, and inhibit cell proliferation and migration, which exhibit satisfactory angiogenesis inhibition capability (Fig. 6d) [67]. In conclusion, MSNs showed unique advantages in loading hydrophobic chemotherapy drug sunitinib. MSNs have been considered effective nanocarriers for anticancer drugs due to their superior drug delivery and endocytotic behaviors. However, the therapeutic benefits of MSNs-based systems in vivo should be rigorously and extensively demonstrated. At present, several silica nanoparticles are in phase I and II clinical trials, and preliminary data demonstrated the safety and viability of MSNs in humans.

5.6. Gold nanoparticles (AuNPs)

Gold nanoparticles (AuNPs) are superior drug delivery vehicles due to their plasmon absorption and scattering property. AuNPs have numerous intrinsic advantages, such as excellent biocompatibility, easy functional modification, and remarkable photothermal properties [132]. Accordingly, AuNPs have been extensively used in antitumor drug delivery. NSCLC is the predominant subtype of lung cancer. As a second-generation MTKIs, afatinib has been approved by FDA as the

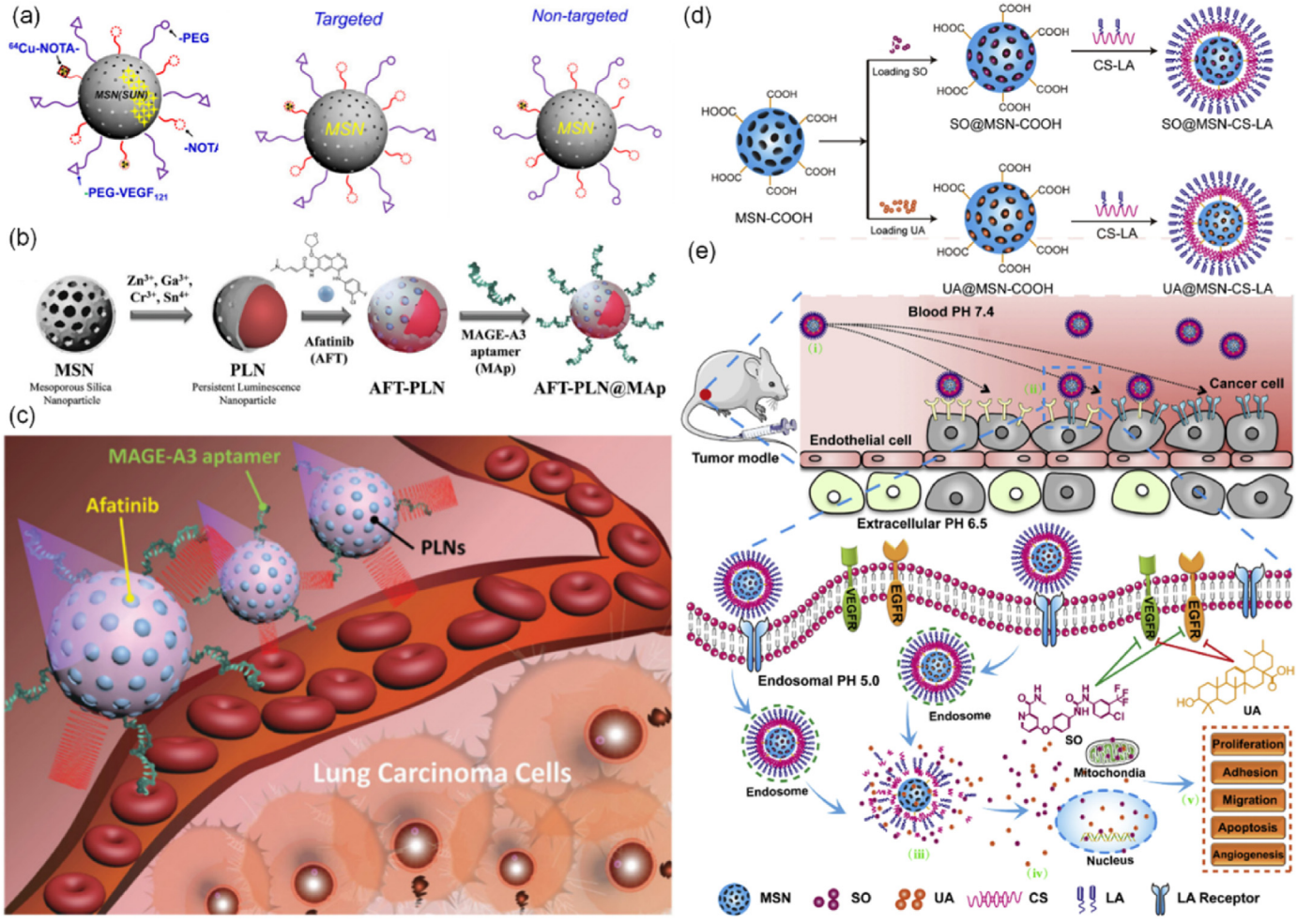

Fig. 6. (a) Schematic illustration of 64Cu-NOTA-MSN(SUN)-VEGF121 and 64Cu-NOTA-MSN-PEG. Reproduced with permission [127]. Copyright 2014, American Chemical Society. (b) Schematic diagram of the synthetic AFT-PLN@MAp procedure. (c) A targeting anticancer scheme of AFT-PLN@MAp nanoplatforms. Reproduced with permission [83]. Copyright 2020, Wiley-VCH. (d) Schematic diagram of the preparation of complex nanoparticles USMNs-CL. (e) Schematic illustration showing the co-delivery of ursolic acid and sorafenib by MSN-CS-LA for a synergistic effect in vitro. Reproduced with permission [67]. Copyright 2017, Elsevier Ltd.

first-line therapeutic scheme for metastatic NSCLC [133]. The researchers harnessed the thiolated afatinib analogs to the covalent attachment to the surface of citrate-capped AuNPs (Fig. 7a). The AuNPs were pegylated to obtain nanoparticles with favorable biocompatibility and colloidal stability. The resulting nanoparticle, designated as Afb-AuNPs, showed excellent cytotoxicity toward A549 cells (a kind of NSCLC cell lines) while maintaining not overtly cytotoxic to TT1 cells (a model cell of the healthy alveolar epithelium) when compared to free drug. At the same time, the release of proinflammatory cytokines is reduced during treatment, further demonstrating the excellent biocompatibility of Afb-AuNPs [134]. The toxicity of AuNPs to normal human system always is an issue of widespread concern. It is necessary to develop non-toxic AuNPs due to the controversy and inconsistency regarding the potential of AuNPs for clinical applications.

5.7. Others

5.7.1. Polymer covalent organic frameworks (COFs)

Strictly speaking, COFs are polymer nanoparticles, which are discussed separately here. COFs are porous organic polymeric materials that feature apparent advantages over other drug vehicles, such as high stability, abundant pore structure, large surface area, etc. [137,138] Zhang et al. designed and synthesized pazopanib-loaded amphiphilic nanocomposites based on COFs via a facile one-pot self-assembly strategy (Fig. 7b). The nanoparticle possesses the potential to penetrate the blood-brain barrier and could be decomposed to realize pazopanib release in an acidic tumor environment thanks to the presence of borate bonds. This provided a novel idea for treating renal cancer with brain metastasis [135]. The COFs have shown many advantages for drug delivery. However, the biodegradation and biocompatibility of COFs need to be improved to prevent the toxicity of the monomers used for generating COFs.

5.7.2. Bacillus cagulans spores

Spores are the dormant life modalities of probiotics. Bacillus cagulans is a probiotic approved by FDA, and they can produce spores and bacteriocin, which tremendously improve the microecology of the gastrointestinal tract. The dormant spores of bacillus cagulans encapsulated by a hydrophobic protein could resist a harsh external environment [143]. For the treatment of colon cancer, the nanotherapeutic reagent is administered intravenously, which is engaged in severe undesirable effects. To cope with these unsurmountable problems, Song and colleagues devised an autonomous nanoparticles generator (DOX/SOR/Spore-DA) modified with deoxycholic acid (DA) to potentiate the absorption efficiency of DOX and sorafenib. As displayed in Fig. 7c, the DOX/SOR/Spore-DA was decomposed by the germination effect of spores in the intestinal microenvironment. The generated probiotics colonized in the intestinal microenvironment, which acts as the regulator of the intestinal flora balance. The other ingredients (disintegrated hydrophobic protein, hydrophilic DA, sorafenib, and DOX) autonomously generate substantial nanoparticles by self-assembly in the intestine. Subsequently, the produced nanoparticles were endocytosed by intestinal epithelial cells by apical sodium-dependent bile acid transporter (ABST) mediated intracellular trafficking pathway. The ABST-mediated endocytosis realizes lysosome escape and increases the basolateral release of nanoparticles. This strategy observably improved the absorption efficiency of sorafenib and provided new guidance for the treatment of colon cancer [136]. Inevitably, the immune rejection of bacillus cagulans spores must be focused to achieve clinical translation.

6. Enhanced targeting performance of MTKIs nanoparticles

Targeting performance is the precise delivery of drugs to tumor tissues for preventing adverse effects on normal tissue. The current targeting strategies mainly include active targeting, passive targeting, and stimulation response release. Previous studies have proved that nanoparticles with a size range (10–200 nm) can enrich at the tumor site by EPR effects [145]. The surface of nanoparticles can also be modified with some specific targeting groups to actively target tumor cells by combining with receptors on the surface of tumor cells. Furthermore, the slow drug release via stimulus-responsive is also an important means to achieve tumor-targeted therapy (Fig. 8). The MTKIs nanoparticles are

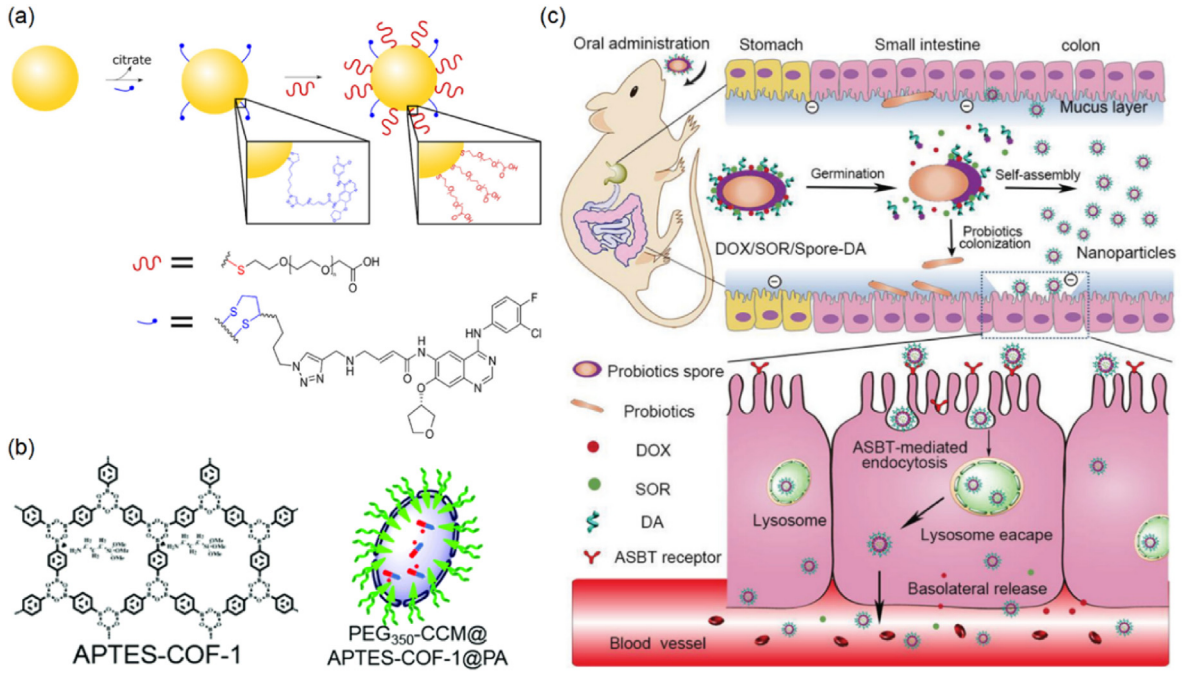

Fig. 7. (a) Schematic representation of the development of Afb-AuNPs. Reproduced with permission [134]. Copyright 2019, American Chemical Society. (b) Schematic illustration of the preparation of PEG350-CCM@APTES-COF-1@PA. Reproduced with permission [135]. Copyright 2020, The Royal Society of Chemistry. (c) Schematic illustration of the autonomous nanoparticles generator based on intestinal microenvironment control fabrication and the transepithelial transport mechanism of DOX/SOR/Spore-DA. Reproduced with permission [136]. Copyright 2019, Wiley-VCH.

enriched at the tumor site by the EPR effect. Some nanoparticles release MTKIs in the tumor microenvironment. The released MTKIs inhibit proliferation by targeting the over-expressed tyrosine-protein kinase receptor in tumor cells. The other nanoparticles combined with targeted receptors on the surface of the tumor cell membrane through surface-modified targeting groups and then were absorbed through the endocytosis of tumor cell.

6.1. Active targeting

Active targeting of nanoparticles refers to the specific binding of modified ligands on the surface of nanoparticles to receptors on the surface of tumor cells, thereby mediating the cytolysis of nanoparticles by tumor cells. The common surface modification ligands include peptides (1–2 nm), small molecules (0.3–1 nm) (folic acid, hyaluronan, etc.), proteins (5–10 nm), antibodies (10–20 nm), aptamers (5–20 nm), and so on (Fig. 8) [146].

6.1.1. Peptides targeting modification

Peptides have already been widely utilized in enhancing tumor targeting because of their small sizes, high affinity, excellent stability, and low immunogenicity [147]. Compared to antibodies, peptides (molecular weight <10 Kda) can be facile to penetrate solid tumors by overcoming the high interstitial fluid pressure of solid tumors [148]. The iRGD is a disulfide-based 9-amino acid cyclized peptide which can exclusively bind to integrin on tumor endothelial cells [149]. A typical peptide-functionalized porous silicon nanoparticle was developed by Wang group to deliver sorafenib by active targeting of peptides. Firstly, bicyclononyne was attached to the surface of porous silicon nanoparticles by a covalent bond. Secondly, RGD peptides were adopted to modify nanoparticles by strain-promoted azideealkyne cycloaddition click reaction. The peptide-functionalized nanoparticles could actively target sorafenib to the tumor tissue and showed a superior antitumor effect [150]. Glypican-3 (GPC3) is a heparan sulfate oncofetal proteoglycan located on the surface of cytomembrane via a glycophosphatidylinositol anchor. GPC3 is highly expressed on a series of tumors, particularly HCC [151]. A kind of GPC3-targeting peptide (G12) was harnessed to decorate liposomes co-loaded with sorafenib and IR780. In this specific-targeting functionalized system, targeting peptide G12 attached to the surface of nanoliposomes could recognize the GPC3 on the surface of GPC3-positive cancer cells and further promote endocytosis of nanoparticles [80]. In another report, FD7 peptide and cyclic (CD) peptide were leveraged to increase the permeability and perturb the tight junctions of the blood-brain barrier, which effectively deliver MTKIs into the site of tumor brain metastasis [152].

6.1.2. Folic acid (FA) targeting modification

FA is an essential micronutrient and plays an important role in one-carbon metabolism and nucleotide synthesis. The folate receptor (FR) is one of the primary mechanisms responsible for cellular uptake. FR has been proved to be highly expressive in up to 40% of human malignancies. It is reported that FR expression of tumor cells is 100–300 times higher than that in normal cells, especially in ovarian, colon cancer, epithelioid carcinoma of the uterine cervix, and epidermoid malignant tumor of the larynx [155–157]. The folate-modified nanoparticles have attracted broad interest because of their high affinity (Kd 0.01–1 nM) for FR. To illustrate, researchers prepared sorafenib-loaded BSA nanoparticles (SRF-BSA NPs) and further decorated them with FA by chemical coupling. The obtained nanoparticles (FA-SRF-BSA NPs) displayed higher tumor-targeting capability than SRF-BSANPs and free sorafenib in vivo experiments [158].

6.1.3. Hyaluronan (HA) targeting modification

HA is a natural non-branched heteropolysaccharide from the glycosamine glycan family, which can exclusively recognize receptors overexpressed by tumor cells. As one of the HA receptors, CD44, is usually highly expressed in many malignant tumors [159]. Chen et al. reported a novel multicomponent nano complex modified with HA to deliver afatinib and DOX. The multicomponent nanocomplex can be efficiently internalized into cells via the CD44-mediated pathway and showed more preferable anticancer effects over DOX + AFA [160].

6.1.4. Transferrin targeting modification

Transferrin is extremely important to maintain the balance of iron ions in the body, and it can bind to transferrin receptors and enter cells through endocytosis. Researchers synthesized a core-shell nanosystem to co-delivery DOX and sorafenib. The nano-core was composed of Poly(-vinyl alcohol) (PVA) and DOX, while the nano-shell was synthesized by human serum albumin and sorafenib. Subsequently, the surface of the obtained PVA-DOX/albumin-sorafenib nanoparticle was decorated with human serum transferrin to enhance the active targeting ability of nanoparticles. The nanoparticles displayed enhanced cellular endocytosis and excellent cytotoxicity for HepG2 cells, especially in the iron-deficient tumor microenvironment [153].

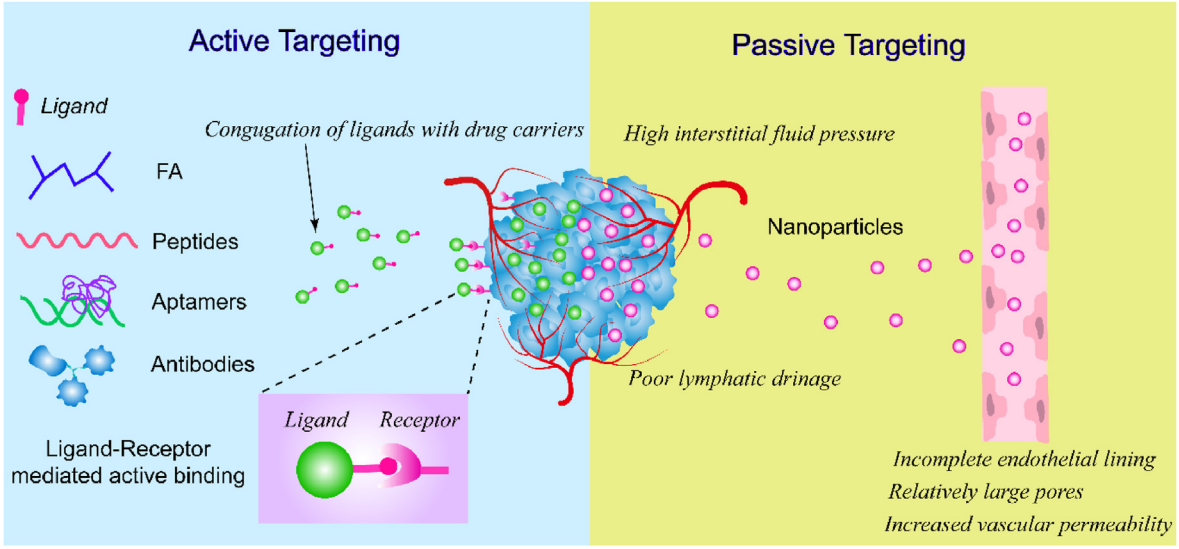

Fig. 8. The introduction of active and passive targeting.

6.1.5. Antibody targeting modification

Antibody targeting modification mainly relies on specific antigen binding and antibodies to endow nanoparticles with the active target characteristic. The antibody has become one of the most widely used targeting ligands in nanocarriers [161]. The glypican-3 (GPC3) is a cell membrane receptor overexpressed in HCC, and it can be used as a specific biomarker of HCC [162–164]. Cai et al. constructed a superparamagnetic iron oxide micellar nanodrug decorated with *anti*-glypican-3 antibody (AbGPC3) to deliver multikinase inhibitor sorafenib. The nanoparticles showed dual-sensitive sorafenib release, prominent anticancer effect, and minor toxic and side effects [154]. Even though the emerging strategies of antibody-modified nanocarriers effectively improve the active targeting of nanoparticles, a cascade of problems, such as low antibody modification coupling rate, are still worth exploring and overcoming.

6.1.6. Aptamer targeting modification

Aptamers are RNA/DNA oligonucleotide molecules with a specific affinity to the targeted complementary molecule. Aptamers have also been called chemical antibodies and possess some therapeutic advantages compared to monoclonal antibodies. These advantages include high reproducibility, high chemical stability, low molecular weight, and low cost [165]. For instance, pegaptanib, can bind VEGF and inhibit VEGF cellular interactions and has become the first aptamer approved by FDA to treat ocular vascular disease [166]. Researchers employed the specific targeting aptamer (MAGE-A3) to modify the infrared-persistent luminescence nanomaterials based on mesoporous silica, and then synthetic nanoparticles were leveraged to deliver afatinib. The MAGE-A3 on the surface of nanoparticles can recognize the MAGE-A3111-125 receptor on the surface of the cytomembrane, which mediates the endocytosis of nanoparticles by tumor cells. This regimen dramatically enhances the active targeting performance and anti-tumor efficiency of nanoparticles [83]. The aptamer targeting modification has main limitations, including fast degradation by nucleases in the blood and rapid renal clearance.

6.1.7. Protein corona

As we known that blood plasma contains roughly 3700 identified proteins and the protein concentration is approximately 60–80 g/L [167]. Once nanoparticles enter blood circulation system, the surafce of nanoparticles are inevitably encapsulated by proteins in the plasma to form the protein corona [168,169]. The impact of protein corona on the active targeting ability of nanoparticles is still controversial. Some studies reported that protein corona shielded the active part of the nanoparticle and inhibited the targeting ability of nanoparticle. For example, Mirshafiee et al. prepared fluorescent silica nanoparticles decorated with a strained cycloalkyne. Compared to bare nanoparticles, silica nanoparticles significantly decreased the targeting efficiencies by 94% and 99% after incubating with 10% or 100% serum, respectively [170]. Furthermore, small size targeting ligands such as aptamers are more easily shielded by the formed protein corona [171]. However, there are also many reports that the formation of protein corona did not affect the active targeting ability [172]. Even in the study of Caruso and collaborators, the protein corona was proven to facilitate specific targeting [173]. Gao group employed transferrin (Tf), a brain-targeting ligand, to modify nanoparticles to evaluate the specific targeting ability. The active targeting ability of Tf-modified nanoparticles is lost due to the formation of protein corona in vitro. Interestingly, despite protein corona was also formed in vivo, targeting ability of nanoparticles is partially preserved [174]. In conclusion, there is a huge different in the effects of protein corona on the active targeting ability. To overcome the issues of active targeting attenuation caused by the protein corona, researchers have explored many effective tactics, including reducing protein adsorption and recruiting specific proteins. Safavi-Sohi and colleagues prepared a novel silica nanoparticles decorated with biotin and cysteine. In this design, biotin served as the active targeting ligand while cysteine was used as a zwitterionic building block. Cysteine effectively reduced the adsorption of proteins on the nanoparticle surface and protected active targeting ligands [175]. Although great outcomes have been achieved, research in this area is still worthy of our vigorous exploration due to the complexity of the human physiological environment.

6.2. Passive targeting

The nanoparticles administrated by vein are usually distributed to the tumor site via capillaries. Characteristics of tumor vasculature, such as incomplete endothelial lining, relatively large pores, and increased vascular permeability, promote the enrichment of nanoparticles at the tumor site. In addition, high interstitial fluid pressure and poor lymphatic drainage facilitate the aggregation and penetration of nanoparticles (Fig. 8) [176]. These particular peculiarities enhanced the accumulation of nanoparticles into the tumor site, which is called the EPR effect. The size of nanoparticles is a vital factor to determine the efficiency of EPR effect. Nanoparticles below 10 nm are easily cleared by the kidneys while those above 100 nm will be recognized and eliminated by the reticuloendothelial system [177]. Therefore, the ideal passive targeting size of designed MTKIs nanoparticles is 10–100 nm.

7. Combination therapy of MTKIs nanoparticles

Combination therapy-based nanoparticles refer to these schemes that use two or more anticancer drugs to treat tumors. The advantages of combination therapy-based MTKIs nanoparticles lie in bypassing the MTKIs resistant mutation pathway and improving the therapeutic effect. Furthermore, it can reduce the dosage of a single drug and reduce the toxic and adverse effects of MTKIs (Table 3).

7.1. Combined photothermal therapy

Photothermal therapy (PTT) is an attractive therapeutic technique that has gained wide-ranging attention because of its apparent advantages, such as minimal invasiveness, high specificity, minor adverse effects, and excellent therapeutic efficacy [189–191]. Chemo-photothermal therapy (chemo-PTT) refers to a potential strategy for synergized efficacy in cancer therapy. The researchers used the liposome phospholipid bilayer to load the photothermal reagent IR780 and sunitinib. The formed liposome nanoparticles displayed a better photothermal effect than free IR780. The temperature increased from 31.5 °C to 73.8 °C in the nanoparticle groups, while reaching 43.5 °C in the free IR780 group after 240s of laser irradiation. Furthermore, the liposome nanoparticles showed a more stable photothermal effect than free IR780, which indicates that the nanoparticles are a prospective candidate material [29]. Similarly, He and colleagues fabricated a biodegradable/biocompatible nanoformulation with anlotinib and IR820 through facile self-assembling progress (Fig. 9a). The final synthetic nanomedicine (anlotinib@IR820) with pure drug ingredients achieved the superior synergistic therapeutic effect of NIR-activated PTT and a small molecule targeted therapy. The anlotinib@IR820 nanomedicine consisted of two pure therapeutic drugs without any vehicles and simultaneously conquered the defects of poor water solubility of anlotinib and the short lifespan of IR820. Under the lower power NIR laser irradiation, the anlotinib@IR820 can not only achieve mild PTT to reduce damage to surrounding normal tissues but also boost the permeability of the tumor cell membrane by the photothermal effect and increase the amount of anlotinib entering the tumor cells to kill tumor cells around healthy tissues (Fig. 9b). Anlotinib@IR820 nanomedicine can induce apoptosis and cell cycle blockade via targeting ERK, AKT, and STAT3 signal transduction pathways, to inhibit the growth of breast cancer [87]. MoS_2 is a two-dimensional transition metal dichalcogenide photothermal agent, and it is evidenced to have a higher loading ratio than that of graphene oxide in a research report [192]. Jia and co-workers used polyethylene glycol (PEG) as a linker to graft erlotinib onto MoS_2 nanosheets by click chemistry. Subsequently, nanocomposite synthesized in the previous step was employed to deliver DOX, forming

Table 3
The representative MTKIs nanoparticles for anti-tumor combination therapy.

Nanoparticles	Combination Therapy	Cell Lines	Cell Viability Rate (%)	Treatment Conditions	Method	Ref.
Anlotinib@IR820	PTT	MCF7	33	24 h([Anlotinib] = 0.8 ppm, [IR820] = 5 ppm, 808 nm, 0.8 W cm^{-2}, 3min)	CCK8	[87]
Lip-IR780-Sunitinib	PTT	4T1	50	24 h([IR780] = 0.2 μg/mL, 808 nm, 1 W cm^{-2}, 4min)	MTT	[29]
MoS_2-PEG-Er/DOX	PTT	A549	6.1	24 h([MoS_2-PEG] = 180 μg/mL,[Erlotinib] = 10 μg/mL, [DOX] = 20 μg/mL, 808 nm, 1 W cm^{-2}, 10min)	MTT	[182]
HPGBCA	PDT	A549	50	48 h([HPGBCA] = 0.41 mM, 660 nm, 50 mW cm^{-2}, 10min)	MTT	[183]
(ICG + S)@$mSiO_2$	PDT, Immunotherapy	H22	1	24 h([ICG] = 0.012 mg mL^{-1}, [Sorafenib] = 0.08 mg mL^{-1} S or [(ICG + S)@$mSiO_2$] = 0.1 mg mL^{-1})	MTT	[184]
NanoMnSor	Immunotherapy	JHH-7	≈30	72 h([sorafenib] = 4 μM,[MnO_2] = 40 μM, hypoxic = 1% O_2)	MTT	[179]
SEHPA	Gene therapy	Huh-7	≈25	24 h([sorafenib] = 8 μg/mL)	MTT	[185]
SF-PL/siGPC3	Gene therapy	Hep-G2	36.6	48 h([sorafenib] = 4 μM)	CCK8	[186]
EPC	Plant Extracts	BxPC-3	≈5	20 h([EPC] = 25 μM)	MTT	[187]
EB@QSSQ	Plant Extracts	A549	50	48 h([EB@QSSQ] = 4.1 × 10^{-6}M)	MTT	[188]

erlotinib/DOX loaded MoS_2 nanoparticles (MoS_2-PEG-Er/DOX). The MoS_2-PEG-Er/DOX achieved an efficient synergy therapy outcome between photothermal and small molecule targeted therapy for the therapy of malignant tumors (Fig. 9c) [182].

7.2. Combined photodynamic therapy

Photodynamic therapy (PDT) has emerged as an attractive therapeutic strategy because of many advantages, for instance, minimally invasive therapeutic procedures, early degradation, and selective cytotoxic activity [193,194]. In 1993, PDT was first clinically approved in Canada. The photosensitizer photofrin was also first used for the prophylactic treatment of bladder cancer [194]. With the continuous exploration of PDT for tumors, enormous combination therapy tactics have emerged in recent years. The researchers reported a photoactivable multi-inhibitor nanoliposome (PMIL) which could impair multiple and distinct molecular targets. The ingredients of PMIL include a benzoporphyrin derivative and cabozantinib encapsulated inside. Under NIR light-activated, the PMIL could induce tumor cell apoptotic signaling by the effect of PDT, and synergistically promote apoptosis with cabozantinib inhibition of anti-apoptotic signaling pathways. In addition, PDT-induced vascular damage combined with the sustained anti-vascular effect of cabozantinib can further effectively suppress tumor angiogenesis. It should be noted that the sustained inhibition of hepatocyte growth factor signaling could inhibit tumor cell invasion, metastasis, and metastatic escape [91]. Zhang et al. prepared active-targeting, enzyme, and ROS-dual responsive intelligent nanocarrier to deliver afatinib. The final nanoparticles (HPGBCA) synthesized by the self-assembly method can realize molecular targeted-photodynamic combinatorial therapy by sufficient intracellular ROS generation. The HPGBCA showed superior cellular uptake ability and good bioavailability due to the HA surface corona of the nanoparticle compared to free afatinib [183]. ICG is the only FDA-approved NIR PTT reagent, and it has been frequently used for the confirmation of surgical margins and real-time imaging [195]. Whereas the low targeting and short half-life severely limit its potential application. Yang et al. utilized a traditional MSN nanosystem to co-delivery the ICG and sorafenib to realize the collaborative PTT/immuno-enhanced therapy. The novel nanoparticles provide new possibilities for overcoming drawbacks in the clinical application of ICG. Meanwhile, the photothermal effect of nanoparticles can markedly induce cell apoptosis and produce cellular fragments. The generated fragments can activate the function of $CD8^+$ T cells. Apart from that, this synergistic system can also enhance the function of immune cells in the tumor and spleen, such as effector memory T cells, central memory T cells, and NK cells [184].

7.3. Combined immunotherapy

Previous works have demonstrated that sunitinib could remodel the immune-suppressive TME, block the accumulation of myeloid-derived suppressor cells (MDSCs), and reverse T cell suppression, which creates a favorable microenvironment depleted of MDSCs and improve the outcome of antitumor immunity [196]. As an arginine inhibitor, norvaline plays an indispensable role in correcting T-cell subpopulations and restoring immune imbalance [197]. Katopodi et al. employ copper sulfide as nanocarriers to enclose sunitinib and norvaline prodrug complexes. Subsequent surface modification with PLGA-PEG was used to increase the biocompatibility and stability of the nanoparticles. The nanoparticles could lead to the upregulation of $CD8^+$ T and $CD4^+$ T cell expression. Furthermore, the decreased MDSC infiltration prompted Treg inhibition and increased intratumoral CD8+/Treg ratio. The new MDSC-targeted nanoplatform effectively conquered MDSCs-mediated immunosuppression and presents a novel strategy for the therapy of metastatic tumors [198]. In a separate study report, researchers synthesized a self-assembled polymeric micelle based on poly (styrene-co-maleic anhydride) to load paclitaxel and sunitinib. The polymeric micelle reactivates antitumor immunity via inducing chemotherapy-induced immunogenic cell death and yields an enhanced synergistic apoptosis effect on tumor cells. In addition, the augmented dendritic cell maturation triggered by nano micelles efficaciously improves the tumor immunogenicity [199]. Remodeling the tumor immune microenvironment is an attractive strategy to activate the immunosuppression of tumor cells. Huang et al. developed a multi-target liposomal nanosystem with dual-modification (PD-L1 and mannose ligands) to deliver mTOR inhibitors (rapamycin) and regorafenib. The nanoparticles can target and repolarize tumor-associated macrophages (TAMs), reprogram immune cells, and inhibit tumor growth (Fig. 10a) [95]. Liu et al. prepared a novel Bi/Se nanoparticle to load lenvatinib to treat hepatocellular carcinoma. The loaded Bi quantum dots can serve as a CT contrast agent, and Se is vital for radiotherapy sensitization. Simultaneously, the prepared Bi/Se-Len nanoparticles re-educate and normalize the vascular structure of the tumor, which could alleviate tumor hypoxia. Eventually, the Bi/Se-Len nanoparticles elevated the response rate of immune checkpoints by upregulating $CD4^+$ and $CD8^+$ T lymphocytes and increasing the amount of NK cells (Fig. 10b) [94]. It is well known that manganese dioxide (MnO_2) nanoparticles could produce oxygen and attenuate hypoxia by the reaction with excess generated H_2O_2 and H^+ in the acidic TME [200]. Previous studies have proved that hypoxia could cause the homing of bone marrow-derived cells, which inhibits the antitumor immunity effect [201–203]. As presented in Fig. 10c, Chen et al. developed a tumor-targeted versatile MnO_2 nanoparticle to deliver sorafenib. The obtained nanoparticles, termed as NanoMnSor, can generate oxygen to mitigate hypoxia due to the existence of MnO_2. The

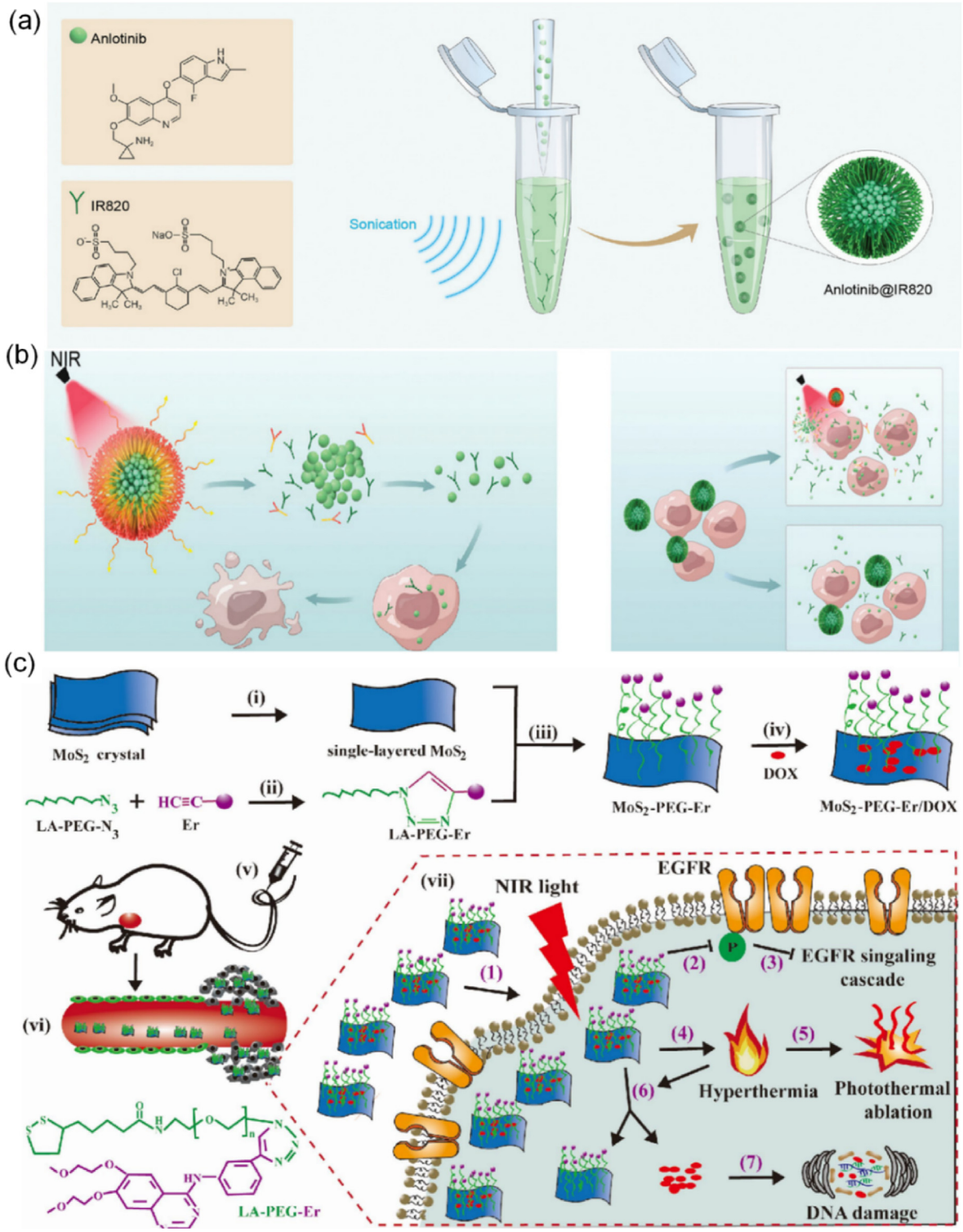

Fig. 9. (a) Schematic illustration of the fabrication process of Anlotinib@IR820 nanomedicine. (b) Scheme illustrating the photothermal-conversion performance and disassembly of Anlotinib@IR820 nanomedicine under laser irradiation at 808 nm. Scheme presenting the enhanced drug delivery exposed to mild heating. Reproduced with permission [87]. Copyright 2020, Wiley-VCH. (c) Synthesis and characterization of MoS_2-PEG-Er. Reproduced with permission [182]. Copyright 2020, Elsevier B·V.

hypoxia alleviation not only overcomes the resistance to sorafenib and suppresses primary tumor distal metastasis, but also ameliorates suppressive immunity and improves the effect of *anti*-PD-1 antibody immunotherapies by the macrophage polarization toward the immunostimulatory M1 phenotype [179].

7.4. Combined gene therapy

Gene therapy refers to a treatment strategy that transfers genetic material into the cells of the patients to provide therapeutic benefit. In most cases, engineered viruses are the main carrier form of gene therapy [204]. However, the immunogenicity, limited genetic load, and low

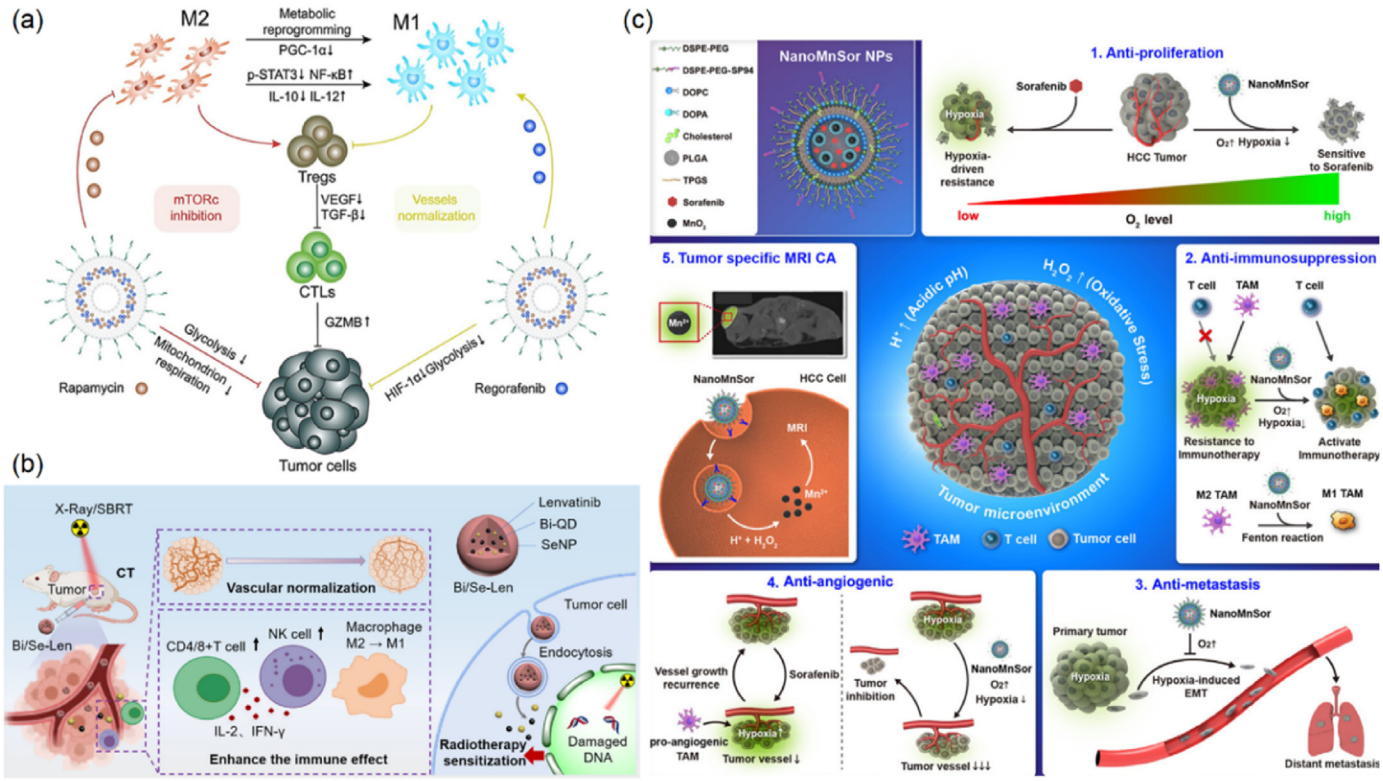

Fig. 10. (a) Anti-cancer schematic illustration of the dual-targeting delivery liposomal system. Reproduced with permission [95]. Copyright 2020, Elsevier. (b) Schematic Illustration of the Radiosensitization Mechanisms of Bi/Se-Len NPs in Imaging-Guided SBRT of Hepatocellular Carcinoma. Reproduced with permission [94]. Copyright 2021, American Chemical Society. (c) Schematic representation of the mechanism by which NanoMnSor can serve as a theranostic anticancer agent. Reproduced with permission [179]. Copyright 2020, American Chemical Society.

transfection efficiency restrict the applications of gene therapy with the virus as a vector. Accordingly, the development and engineering of non-viral vectors are crucial to overcoming application defects. The gene delivery of functionalized nanoparticles has attracted plentiful attention in recent years because of low immunogenicity and high transfection efficiency [205]. Sun et al. developed polyethyleneimine-modified liposomes to serve as the delivery carrier of sorafenib and siRNA targeting the GPC3 gene. The nanoparticles (SF-PL/siGPC3) showed high monodispersity and desirable stability and fulfilled the high codelivery efficiency of sorafenib and siRNA. The SF-PL/siGPC3 can downregulate the expression of GPC3 and cyclin D1 proteins, which significantly increases the tumorous sensitivity for sorafenib [186]. Autophagy has been proven to enhance cellular survival capability in a stressful milieu and facilitate sorafenib resistance [206,207]. Previous studies have shown that microRNA-375 (miR-375) can target the autophagy-related gene ATG7 to inhibit HCC cell autophagy [208]. Xiang group used lipid coating modified calcium carbonate nanoparticles to co-delivery miR-375 and sorafenib. The final synthesized miR-375/Sf-LCC nanoparticles displayed a higher uptake rate than free sorafenib, and dramatically ameliorated the therapeutic efficacy of sorafenib for the HCC [76]. CRISPR/Cas9 is a powerful gene-editing tool and has attracted wide attention in cancer therapies. It holds enormous potential for tumor therapy because of its excellent targeting function and gene silencing efficiency compared to siRNA [209]. In the work of Zhang and co-workers, a co-delivery platform (gene and drug) based on hollow MSNs (HMSNs) was developed to enhance HCC treatment efficiency (Fig. 11a). The recombinant CRISPR/Cas9 plasmids with single-guide RNA (sgRNAs) were constructed, and the sgRNAs inhibit the expression of the EGFR gene. The nanocomplex displayed high EGFR-editing efficiency (>60%) without off-target effects, regulating the EGFR-PI3K-Akt pathway to inhibit angiogenesis (Fig. 11b) [185]. Pigment epithelium-derived factor (PEDF) could promote apoptosis by suppressing blood vessel endothelial cell proliferation and migration [210]. As a powerful antiangiogenic gene, the PEGF gene therapy strategy has shown a superior therapeutic outcome on many tumors in previous works [211]. Chen et al. prepared sorafenib and PEDF gene co-encapsulated PEG-PLGA nanosystem (Sora@PEDF-NPs). The sora@PEDF-NPs not only showed lower toxicity than free sorafenib but also displayed excellent antitumor efficacy to solve mono-chemotherapy limitations in colorectal cancer (Fig. 11c) [212].

7.5. *The combined plant extracts therapy*

Plant extracts from natural plants have received considerable attention in cancer therapy [3]. For example, curcumin is a natural floristic yellow powder extracted from the rhizome of a turmeric plant [213]. Xu group prepared a carrier-free nanoparticle (EPC) composed of curcumin and erlotinib by the self-assembly strategy with the help of bifunctional PEG molecules. EPC shows superior cell killing ability and biocompatibility. In the pancreatic tumor mouse model, EPC can observably improve the median survival time of the tumor-bearing mice from 22 to 68 days [187]. Quercetin (QSSQ), as one of the flavonoids widely distributed in the plant kingdom, was evidenced to be adequate in inhibiting cell viability and inducing apoptosis and autophagy through the modulation of various signals transduction pathways [214]. Wu and coworkers prepared an EGFR-targeted nanoprodrug (EB@QSSQ) by disulfide-linked QSSQ and erlotinib. The EB@QSSQ showed excellent high drug loading and capacity (87.3%) due to the presence of a disulfide linker. Meanwhile, the GSH-triggered drug release can be implemented when overproduced glutathione at the tumor site breaks disulfide bonds. The combined therapy of erlotinib and QSSQ not only ameliorate drug bioavailability but also observably enhance the biocompatibility and antitumor efficiency [188].

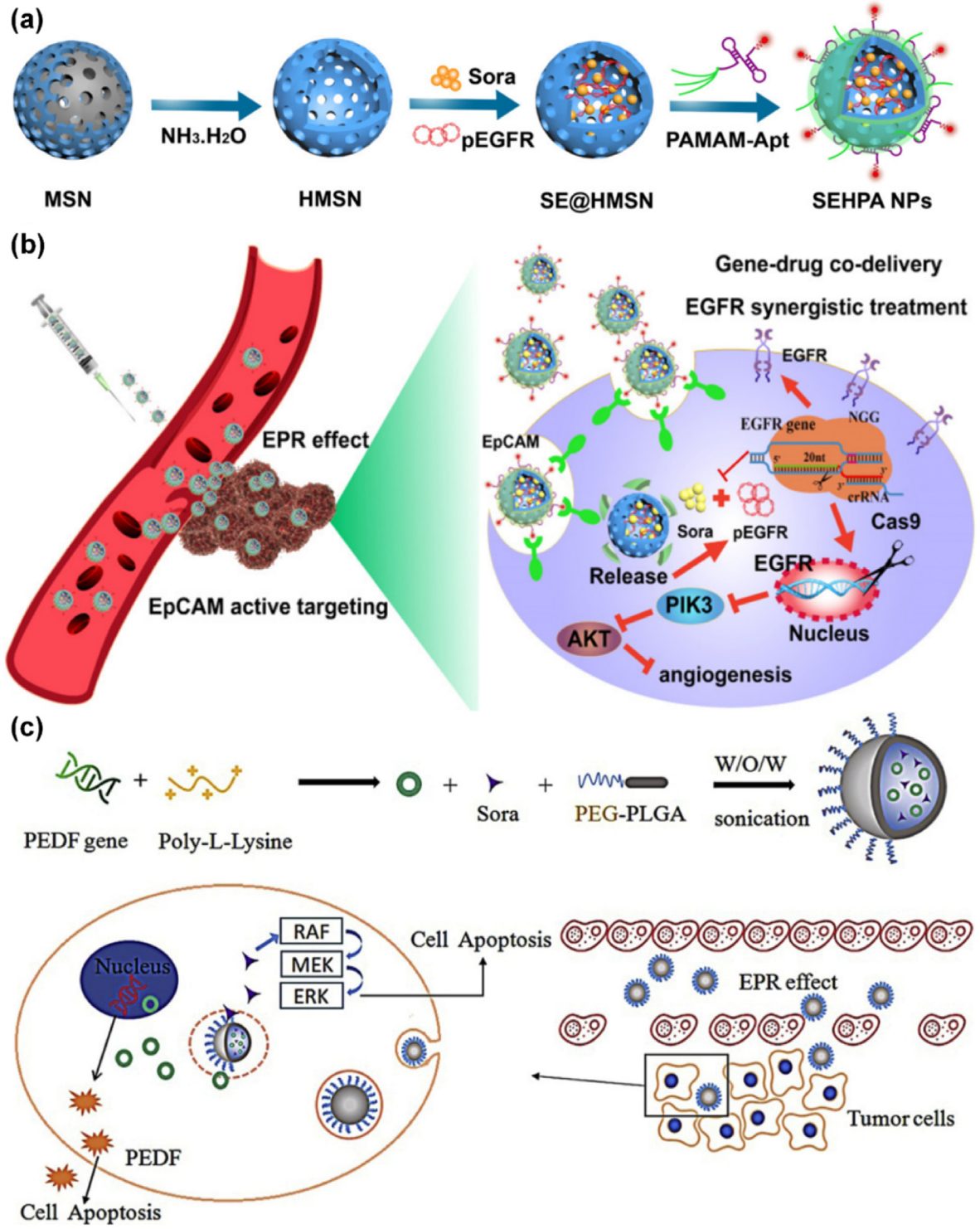

Fig. 11. (a) Schematic illustration of SEHPA NP preparation. (b) The mechanism of SEHPA NP on cancer cells. Reproduced with permission. Copyright 2020, American Chemical Society. (c) The mechanism of Sora@PEDF-NPs on C26 cells. Reproduced with permission [212]. Copyright 2019, Elsevier.

8. Nanotechnology fights MTKIs resistance

Drug resistance severely constrains the effectiveness of chemotherapies and is an inevitable problem faced by drug therapy for tumors. The intrinsic or acquired drug resistance is recognized as one of the main factors for treatment failure in over 90% of patients with metastatic cancer. The common mechanisms of drug resistance mainly include: (1) Impaired drug absorption of tumor cells. (2) Decrease intracellular drug concentration through overexpression of transporters (P-glycoprotein, multidrug resistance protein 1, breast cancer resistance protein, and so on). (3) Loss of proapoptotic factor function. (4) DNA repair pathways. (5) Changes in anticancer targets. (6) The conversion of anti-cancer drugs to non-active ingredients. (7) The drug is captured and degraded by lysosomes [215]. MTKIs resistance usually occurs within one year of treatment. The mutation and activation of the parallel signaling pathway may lead to MTKIs resistance during the treatment of malignancy. And

intratumoral heterogeneity is another main factor of resistance to MTKIs. The target receptors of MTKIs are usually overexpressed and over-activated in MTKIs-resistant tumors. There is no doubt that these various strategies of overcoming drugs can observably prolong the survival period of tumor patients. The common approaches to overcoming drug resistance include combination therapy, controlling drug levels in tumor cells (increasing or reducing the intracellular drug concentration), and affecting the tumor microenvironment [216]. Similarly, numerous nanomedicine technologies have been applied to overcome the problem of drug resistance to MTKIs effectively. In the previous section, we discussed current strategies for combination treatment based on MTKIs nanoparticles of tumors, which can not only aim at MTKIs sensitive tumors but also effectively treat MTKIs resistant tumors and reduce the adverse effects of drugs. However, it is interesting that MTKIs show significant differential effects on various tumors due to the heterogeneity of tumors and different targets. Therefore, in this section, we will summarize and discuss some common MTKIs resistance treatment strategies.

8.1. Sorafenib resistance

As a representative drug of MTKIs, sorafenib was approved by the FDA in 2007 to treat advanced HCC as the first-line drug [218]. Sorafenib could suppress tumor cell proliferation by inducing apoptosis and blockade of angiogenesis. Despite sorafenib possess the capacity that remarkably extends the median survival time (3–5 months) of HCC patients, sorafenib resistance usually occurs within six months of treatment which hinders its therapeutic efficacy [219]. The mechanisms of sorafenib resistance include tumor microenvironment, autophagy, the effect of cancer stem cells, epithelial-mesenchymal transition, etc. Studies have proved that tumor stemness is associated with sorafenib resistance [220]. Ubiquitin-specific protease 22 (USP22) plays a vital role in tumor stemness, and it can be acted as a therapeutic target for reversing tumor cell stemness. Xu group innovatively developed a self-activated cascade-responsive nanoplatform (Gal-SLP) by using galactose-decorated lipopolyplexes as a nanocarrier to deliver sorafenib and USP22 shRNA (shUSP22) (Fig. 12a). After Gal-SLP was endocytosed by tumor cells, the rapid release of sorafenib induced elevated intracellular reactive oxygen species (ROS), which triggered the rapid release of shUSP22 from nanoparticles by oxidizing ROS-responsive charge-reversal polymer shell. The released shUSP22 could inhibit USP22 expression by the degradation of USP22 RNA. The dramatical downregulation of USP22 not only enhances sorafenib chemosensitivity by hampering the potential activation of glycolysis but also gives rise to intracellular sorafenib accumulation by suppressing multidrug resistance-associated protein 1 (MRP1) (Fig. 12b). The enrichment of sorafenib effectively eradicates tumor cells, synchronously produce more cytotoxic ROS, and releases more RNA, forming a positive feedback treatment loop. This novel therapeutic strategy provides an inspiring idea for overcoming sorafenib resistance [78]. Hypoxia is also one of the exact mechanisms of sorafenib resistance [221]. The prolonged sorafenib treatment aggravates tumor hypoxia which upregulates the expression of C-X-C receptor type 4 (CXCR4) in HCC [222,223]. The CXCR4 overexpression is closely related to the therapeutic resistance of tumors [224]. Chen group prepared PLGA nanoparticles to encapsulate sorafenib and used D-a-tocopherol PEG-1000 succinate and an anionic lipid, dioleoylphosphatidic acid to stabilize the structure of nanoparticles. Subsequently, the CXCR4 inhibitor, AMD3100, not only modified sorafenib-loaded PLGA NPs, forming ADOPSor NPs but also endowed ADOPSor NPs with the CXCR4-targeted function. The ADOPSor NPs could continue to maintain the anti-vascular effect of sorafenib and dramatically aggravate tumor hypoxia. However, ADOPSor NPs overcome sorafenib resistance and reduce metastasis by blocking the infiltration of TAMs into the tumor microenvironment (Fig. 12c) [69]. In another study, the scientists developed sorafenib-gold nanoconjugate (SF-GNP) with an average size of ~8 nm in an aqueous medium. The SF-GNP efficaciously impeded the growth of HepG2 sorafenib resistance cells (inhibition ratio >80%), and the underlying mechanism of overcoming drug resistance was relevant to the down-regulated expression of ATP-binding cassette superfamily G member 2 (ABCG2) in SF-GNP treated sorafenib resistance HepG2 (Fig. 12d). The inhibition of ABCG2 caused by SF-GNP may prevent sorafenib efflux and reverse sorafenib resistance [217].

8.2. Osimertinib resistance

As the first FDA-approved third-generation MTKIs, the main target of osimertinib (OSI) is the EGFR. OSI shows intrinsic advantages in the therapy of NSCLC patients with activating EGFR mutation. Unfortunately, the inevitably acquired osimertinib resistance severely hampered its long-term benefits for patients [226,227]. To overcome OSI resistance and prolong the survival time of patients, Chen et al. designed a micelle nanoparticle that consisted of OSI and PEG-selumetinib conjugate. The PEG-selumetinib conjugate can self-assemble with OSI to form nanoparticles in an aqueous solution due to its hydrophobic and hydrophilic amphiphilic nature. The nanoparticle is capable of releasing precisely in ROS-excessive tumor microenviroenhacements. More importantly, the micelle nanoparticle showed an obvious inhibitory effect for OSI-resistant tumor cell lines in vitro and xenograft in nude mice. The mechanism of overcoming drug resistance can be indicated that the nanoparticle induces apoptosis by simultaneously inhibiting both EGFR and MEK [86]. As the third generation of MTKIs and first-line therapy for NSCLC, osimertinib show an intensely limited therapeutic effect for the NSCLC with brain metastases owing to the restricted penetration through the blood-brain barrier of most MTKIs [228]. Researchers developed an ingenious nanotherapeutic biomimetic codelivery system that could penetrate the blood-brain barrier to treat NSCLC with brain metastases. The regorafenib and disulfiram/copper ion chelate are encapsulated by albumin nanoparticles modified with T12 peptide. The synthesized nanoparticles conquered the osimertinib-resistant NSCLC with brain metastases in both the subcutaneous tumor model and the brain metastasized model [225]. As we all know, autophagy is an evolutionarily survival-promoting conserved mechanism [229]. Recent studies revealed that autophagic pathways could maintain mitochondrial function and energy homeostasis to promote the growth and proliferation of tumor cells [230]. Accordingly, it seems to be a potential regimen to overcome OSI resistance by the inhibition of autophagy. Gu et al. and cooperators reported that OSI-resistant tumor cells displayed higher autophagy expression levels in comparison with OSI-sensitive tumor cells, indicating a protective effect of autophagy in the progress of OSI treatment. Then, they designed multifunctional tumor-targeted nanoparticles (CP@NP-cRGD) to deliver chloroquine (the only clinically-approved autophagy inhibitor) and PD173074 (a selective FGFR1 inhibitor). The CP@NP-cRGD could target tumor tissue by EPR effects and the cRGD peptide on the nanoparticle's surface. The pH-responsive CaP shell can be decomposed in the acidic lysosomal environment and destroy the lysosomal membrane to protect drugs from degradation by lysosomes and achieve drug cascade release sustainably. The first released chloroquine can inhibit tumor autophagy, and then release PD173074 to block the FGFR1 pathway to induce apoptosis of OSI-resistance cells. The CP@NP-cRGD exhibited the enormous potential to replace free therapeutic pharmaceutical combinations in the treatment of NSCLC [31].

Reproduced with permission [231]. Copyright 2017, Published by Elsevier Ltd. (b) Schematic of a Lysosomal pH-Activatable Mitochondrial Targeting Polymer Nanoparticle (PKCF) and Its Application in Overcoming Drug Resistance by a Combination of Mitochondrial Delivery of DOX and Dual Inhibition of Drug Efflux. Reproduced with permission [89]. Copyright 2021, American Chemical Society. (c) Schematic illustration of multicomponent nanocomplex overcoming multidrug resistance. Reproduced with permission [160]. Copyright 2021, The Royal Society of Chemistry. (d) Schematic illustration of HA-TPD-CL-PTX/SOR liposome for co-delivery of PTX and SOR to overcome MDR in cancer cells. Reproduced with permission [232]. Copyright 2020, Wiley-VCH.

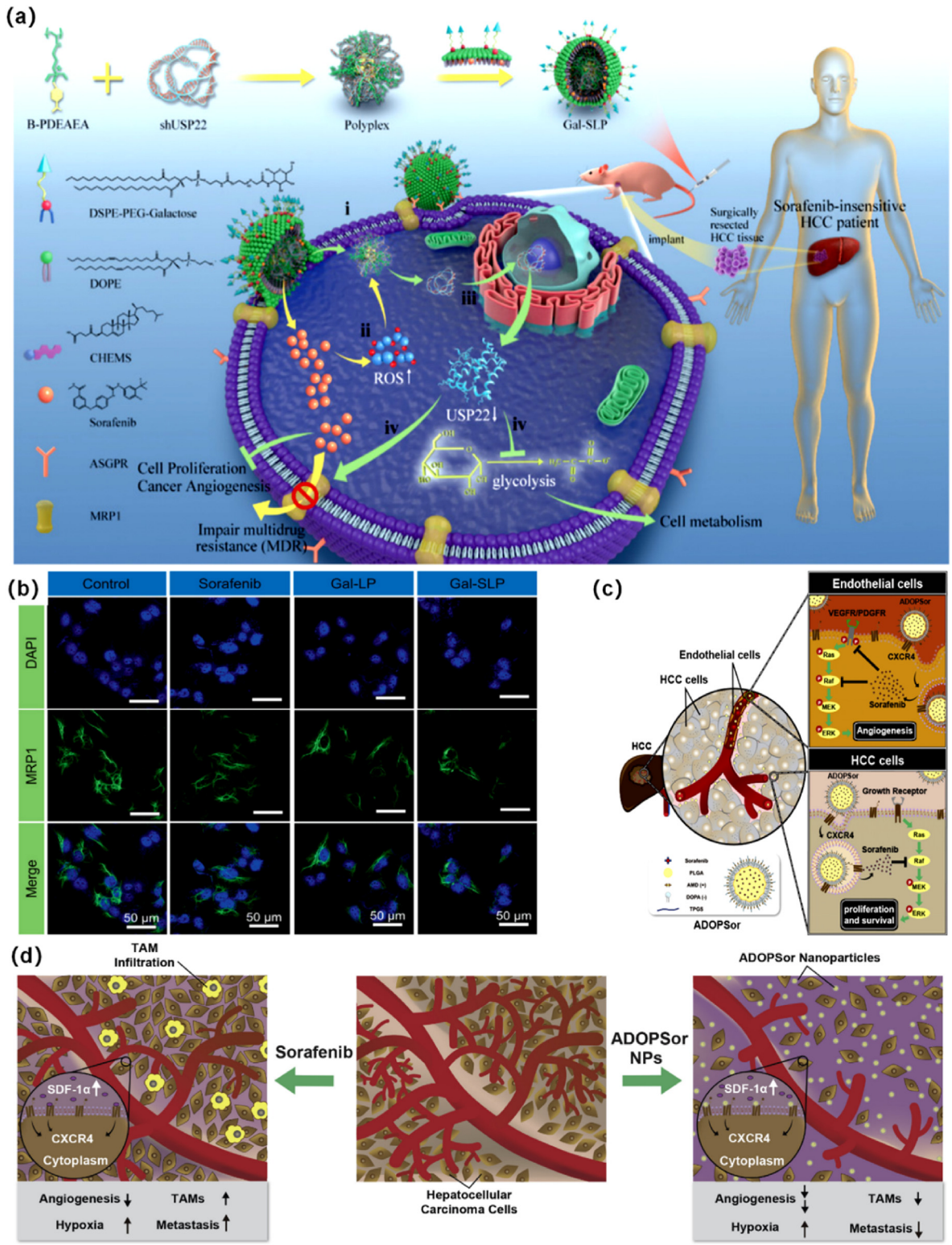

Fig. 12. (a) Schematic illustration of a self-activated cascade-responsive co-delivery system (Gal-SLP) for synergetic cancer therapy. (b) Immunofluorescence staining of MRP1 in Huh-7 cells treated with the indicated drugs for 48 h. The nuclei were stained with DAPI (blue) and MRP1 was labeled with CoraLite488 (green). Reproduced with permission [78]. Copyright 2020, Wiley-VCH. (c) Schematic illustration of the proposed structure and mechanisms of the anti-cancer actions of CXCR4-targeted lipid-coated PLGA NPs (ADOPSor NPs). Reproduced with permission [69]. Copyright 2015, Elsevier Ltd. (d) Schematic illustration of the mechanisms of the anti-cancer actions of sorafenib-loaded CXCR4-targeted NPs. Reproduced with permission [217]. Copyright 2020, Springer Nature.

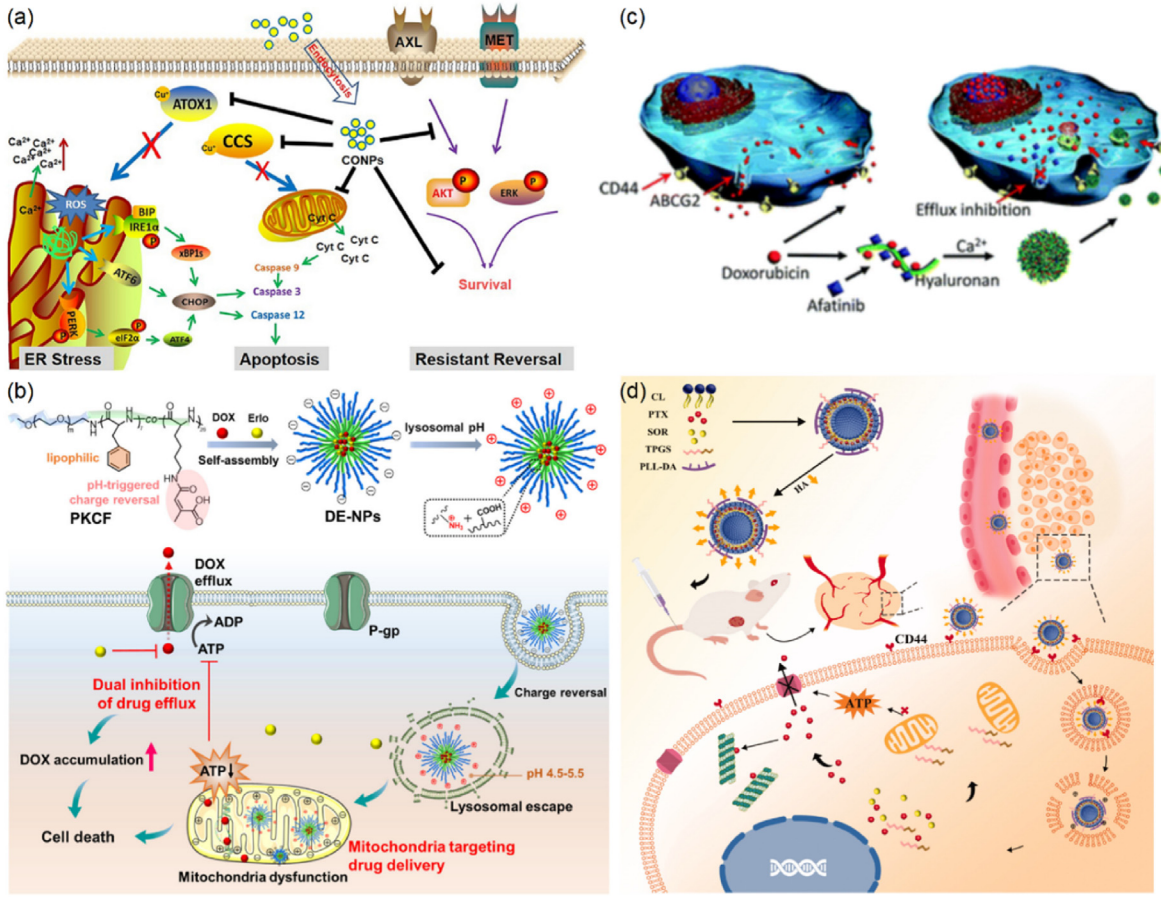

Fig. 13. (a) Schematic reversal sunitinib resistance illustration of CONPs nanoparticles.

8.3. Sunitinib resistance

Sunitinib treatment could significantly prolong progression-free survival and overall survival for metastasized RCC patients. However, drug resistance usually occurs after a period of sustained treatment of sunitinib (6–15 months). Some studies have shown that more than 80% of RCC patients ultimately develop resistance during sunitinib treatment [233]. Consequently, it is critical to explore emerging therapeutical strategies to overcome sunitinib resistance. The combination drug therapy using nanomedicine technology has become increasingly prosperous for anti-tumor drug resistance research in recent years. He et al. prepared bovine serum albumin (BSA)-stabilized super magnetic iron oxide (SPIO) nano-carriers to load sunitinib and curcumin (a drug-resistance depressor) via a co-precipitation strategy. The final product (SPIO-SC) not only shows superior magnetic resonance T2 contrast-enhancing outcome and potential drug loading capacity but also reduces the IC50 value of MCF7 calculated as the concentration of sunitinib (sunitinib and SPIO-SC were 6.15 mM and 2.43 mM, respectively). SPIO-SC exhibited significant tumor suppression with low toxicity compared with monotherapy [43]. Researchers found that the levels of AXL and MET were elevated after being chronically treated with sunitinib, which indicated inhibiting the expression of AXL and MET has become a promising therapeutic method of reversing sunitinib resistance [234]. Sun group prepared cuprous oxide nanoparticles (CONPs) to combat resistance to sunitinib therapy in renal cancer. As presented in Fig. 13a, CONPs can downregulate the expression of the copper chaperone proteins ATOX1 and CCS, which disrupt copper transportation in tumor cells. Subsequently, the release of cuprous ions can elevate the endogenous ROS generation and calcium levels in tumor cells by activating endoplasmic reticulum (ER) stress. The ER stress and mitochondrion-mediated apoptosis were activated in tumor cells to enhance the therapeutic effect. In addition, CONPs decrease the expression of AXL and MET, and inhibit their phosphorylation levels, making tumor cells resensitize to sunitinib [232].

8.4. Non-MTKIs resistance

The strategies based on MTKIs nanoparticle delivery systems not only solve their drug resistance but also demonstrate the ability to reverse the drug resistance of some commonly used chemotherapy drugs, such as doxorubicin (DOX). DOX is one of the most commonly used anthracycline chemotherapeutic agents in nano-drug delivery systems [235,236]. As a classical cytotoxic and DNA damaging agent, DOX is susceptible to developing drug resistance in the process of treatment [237]. The drug efflux by P-glycoprotein (P-gp) may be the primary cause of DOX resistance, and it can be restricted by P-gp inhibitors, for example, MTKIs [238,239]. Cheng et al. synthesized lysosomal pH-activatable mitochondrial targeting polymeric (PKCF) by conjugation of citraconic anhydride to the dangling amine groups of mPEG-block-poly. And then, PKCF was used to deliver DOX and erlotinib. The final synthesized nanoparticles, DE-NPs, not only maintain long blood circulation and reduce systemic toxicity but also show a significant inhibition effect on DOX-resistant MCF-7/ADR cells (a 17-fold decrease of IC50). The cationic and lipophilic poly segment of DE-NPs boost the lysosomal escape of erlotinib and DOX. Mechanistically, the erlotinib increases the concentration of intracellular DOX by inhibiting the P-gp, which realizes the reversal of drug resistance (Fig. 13b) [89]. Similarly, MTKIs nanoparticles can overcome the other wildly used chemotherapeutic agents by

inhibiting the P-gp or the other signaling pathways associated with drug resistance. The co-delivery of nano-formulations of different drugs provided a promising anti-resistance strategy.

8.5. Multidrug resistance (MDR)

MDR has emerged as the primary obstacle to the failure of clinical chemotherapy, which is mainly attributed to the overexpression of ATP-binding cassette (ABC) transporters superfamily, such as P-glycoprotein [240–242]. Among them, ABCG2 has been recognized as playing a vital role in drug resistance and proliferation in many solid tumors [243,244]. Fu et al. developed a novel multicomponent nanocomplex, which includes HA, ABCG2 inhibitor (afatinib), DOX, and biomimetic hyaluronan-based nano vehicles. The nanocomplex displayed a prominent therapeutic effect in overcoming ABCG2-mediated MDR by synchronously improving drug uptake and targeting capability (Fig. 13c) [160]. Lei et al. designed liposome nanoparticles decorated with HA. The nanoparticles were used to co-delivery paclitaxel and sorafenib, and the final synthetic nanoparticles possess a high tumor growth inhibition rate (78.52%). The novel nanoplatform not only realized lysosomal escape of the liposome but also increased the concentration of drugs in tumor cells by inhibiting the P-gp efflux, which is beneficial to fighting tumor multidrug resistance (Fig. 13d) [232].

9. Conclusions and perspectives

MTKIs have been widely leveraged in the treatment of malignancy tumors. Whereas MTKIs have a series of problems in clinical application, such as low bioavailability, high toxicity, and limited efficacy of drug-resistant treatment. To address these issues, the MTKIs nanomedicine delivery system has aroused intensive research interest in recent years. Given that there are few literature review reports on MTKIs nanoparticles, we provided a summary of advances in nanomedicine technology based on MTKIs for tumor therapy. Firstly, we elucidated the anticancer mechanism and adverse effects of MTKIs. Secondly, the carriers and targeting modification of MTKIs are summarized. Finally, the combination treatment on MKIs nanoparticles and overcoming MKIs resistance regimens are summarized and discussed. Despite the remarkable research progress of MTKIs-based nanoparticles being achieved due to their unparalleled characteristics, a multitude of questions deserves further exploration. (1) Considering some carriers have a low drug loading capacity and high cytotoxicity, the nano-vehicles with efficient delivery and highly biocompatibility should be further developed. (2) The low response rate to MTKIs in malignancies bring a bright prospect for combination therapy. It is worth noting that the combined therapeutic regimen can reduce the drug dose of MTKIs, to reduce the adverse effects of MTKIs. However, the interactions of various drugs or vehicles may generate new toxicity in patients or affect the overall efficacy. For example, nanoparticles based on heavy metal oxides are highly toxic to the human body. The strategies for co-delivery of MTKIs and photo-therapeutic agents may suffer the problems that the singlet oxygen produced during PDT inactivate the target receptors of MTKIs, thereby affecting the efficacy of MTKIs. (3) Many nanoparticles have poor stability in vivo. Toxicity and biocompatibility of nanoparticles are issues that must be paid attention to before their clinical application. The aggregation of nanoparticles in human blood may lead to embolism, especially pulmonary embolism and cerebral embolism, which seriously threaten the safety of human life. Nanoparticles are decomposed and metabolized during the transportation of nanoparticles to the tumor lesions, which will also affect the efficacy and increase the dosage of the drug, thereby increasing the toxicity. Besides, some nanocarriers, especially inorganic nanocarriers, are difficult to excrete through metabolism, resulting in persistent chronic toxicity. Hence, the stability and effective metabolism of nanoparticles in human plasma must be emphatically considered. Therefore, stable nano-carriers with superior biosafety should be further explored, and an effective toxicity monitoring strategy with a comprehensive deliberation should be established. (4) MTKIs-based nano-delivery systems have obtained breakthrough advances in animal models. However, only a few nanodrugs are successfully translated into clinical applications, which indicated that multi-center clinical trials should be conducted to accelerate the rate of translation and application. (5) Drug resistance is a serious problem of MTKIs treatment. It is still worthy of further exploration that reverses or overcome drug resistance by assembling various drugs or using specific nano-carriers. And the balance between efficacy and drug toxicity should also be focused on. (6) At present, most MTKIs are oral pharmaceutic preparations in clinical practice. However, most nanoparticles approved by FDA are administered by intravenous injection. Therefore, it is a valuable research direction to develop fascinating nanocarriers and improve the bioavailability of MTKIs for oral administration. (7) The therapeutic drugs and imaging agents can be integrated into nanocomplex to obtain multi-modal diagnosis and treatment of tumors. Current cancer treatment emphasizes comprehensive treatment including surgery, chemotherapy, radiotherapy, molecular targeted therapy, and so on. Nanotherapeutics can combine multiple treatment modalities, enable early diagnosis, and improve treatment efficiency through superior targeting ability. (8) MTKIs nanoparticles are injected into human circulatory system, the protein crown will be formed on the surface, which will affect the inherent characteristics of the nanoparticles. How to eliminate the protein crown in a complex physiological environment is another problem. (9) Although studies have demonstrated the high safety and efficacy of various MTKIs nanoparticles in vitro and in vivo, the process of translating them into clinical application is very slow. The main reason is that most preclinical studies focused on small animal models, such as rodents, while little studies have been conducted on larger and human-like animal models, such as pigs, sheep, or monkeys. Although few MTKIs nanoparticles are currently employed in clinical treatment, it is promising that versatile MTKIs nanoparticles will develop an effective strategy for clinical oncology treatment in the future with the tremendous improvement of nanotechnology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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