Review | Received 24 December 2024; Accepted 14 February 2025; Published 27 February 2025
https://doi.org/10.55092/bm20250003

Chiral materials in cancer therapy: insight into metabolic, apoptotic, and immune pathways

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Highlights:

- Review of some advance cancer therapies with latest chiral materials.
- Summary of 5 detailed mechanisms of cancer therapy with chiral materials.
- Different categories of chiral cytotoxicity against tumor cells.
- Summary of new strategy of cancer treatment: photothermal therapy, immunotherapy.

Abstract: Chirality, a fundamental property of biological systems, is intrinsic to numerous natural biosystems and plays a vital role in sustaining physiological processes. Leveraging their high specificity for biological targets, chiral nanomaterials have emerged as multifunctional tools in cancer therapy. These nanomaterials demonstrate superior biocompatibility, minimal cytotoxicity, and enhanced cellular penetration. Furthermore, the tunability of their surface structures enables precise chirality control, fostering the development of advanced biomaterials capable of targeting tumor metabolism, inducing apoptosis, and modulating immune responses. This review provides a comprehensive overview of recent advancements in the utilization of chiral materials for tumor-targeted therapies, metabolic modulation, apoptotic pathway intervention, photothermal applications, chiral cytotoxic effects, and immunomodulation. Moreover, we elucidate the mechanisms underlying these actions, examine the opportunities and challenges associated with employing chiral materials in oncology, and propose future directions for their advancement. Through the integration of these multifaceted strategies, chiral materials present considerable promise for improving the precision and efficacy of cancer therapeutics.

Keywords: chirality; chiral materials; cancer therapy; tumor targeting; cell metabolism; apoptosis; chiral cytotoxicity; immunotherapy

1. Introduction

Chirality, an intrinsic feature of biological systems, is present across various components of natural biosystems and plays a pivotal role in maintaining physiological processes within organisms [1]. Chiral characteristics are evident in amino acids, proteins, nucleic acids, organelles, and more complex tissues or organs [2]. The chiral properties exhibited by biomolecules and biological structures offer vast possibilities for interactions with engineered chiral materials [3,4]. Engineered chiral nanomaterials, therefore, can modulate various biological processes in organisms, including self-assembly [5,6], asymmetric reactions [7,8], enantioselective catalysis [9], polarization processes [10], and biochemical reactions [11,12]. For instance, chiral carbon dots (CDs) can mimic topoisomerase I (Topo I) and selectively mediate the topological rearrangement of superhelical DNA [13]. Similarly, gold nanoparticles (Au NPs) demonstrate chirality-dependent cell uptake behaviors [14].

Leveraging the inherent chirality of cells and the high specificity of organisms for chiral materials, chiral nanomaterials hold significant promise in biomedicine, particularly in the research and development of nanomedicines [15]. According to a recent report from the U.S. Food and Drug Administration (FDA), the FDA's Center for Drug Evaluation and Research (CDER) has approved a nanomedicine composed of chiral molecules [16]. The interaction between nanomedicines and cells exhibits a pronounced dependence on chirality [17]. Distinct enantiomers of the same drug can elicit varying or even opposite effects on cells. For instance, L-dopamine serves as an effective treatment for Parkinson's disease, whereas D-dopamine exhibits toxicity to the human body [18]. Consequently, chiral nanomedicines can be developed to specifically target a variety of tumor cells, leveraging their chirality to achieve precise recognition and treatment through advanced biochemical technologies.

In recent years, research on chiral nanomaterials has progressed from initial studies on inorganic materials to more sophisticated systems composed of organic compounds, metals, semiconductors, and their hybrids [8]. These chiral superstructures, consisting of hybrid complexes with chiral configurations, exhibit superior biocompatibility, minimal cytotoxicity, and enhanced cellular penetration [19]. Moreover, the tunability of their surface functionalities enables precise modulation of chirality, facilitating the design of novel biomaterials capable of coordinating disease treatments and regulating enantiomeric enzymatic reactions. Consequently, therapeutic strategies utilizing chiral nanomaterials are gaining increasing attention [20,21].

Malignant tumors represent one of the leading threats to human health [22–24]. They are characterized by unchecked proliferation, which manifests as the continuous growth of localized masses, destruction of normal tissue architecture, metastasis to other parts of the body, and late-stage cachexia symptoms such as wasting, anemia, and infection [25,26]. In 2020, approximately 19.3 million new cancer cases were diagnosed globally, with nearly 10 million deaths attributed to cancer—a figure that continues to rise annually [27]. By 2040, the annual incidence of new cancer cases is projected to reach 28.4 million globally [28].

Currently, comprehensive treatment strategies for malignant tumors integrate traditional therapies such as surgery, radiation therapy, and chemotherapy, with emerging approaches like biological therapy and immunotherapy to improve patient outcomes [29,30]. However, as understanding of cancer deepens, the limitations of conventional therapies have become increasingly evident [31]. For instance, surgical treatments are primarily confined to pathological biopsy and early tumor excision, which are often

ineffective for addressing metastases. Additionally, surgeries in critical anatomical regions pose significant challenges and risks. The associated trauma, including combined resection of essential endocrine glands, substantially impacts patient survival rates [32,33]. Similarly, chemotherapy drugs often lack specificity, causing significant damage to normal cells and exhibiting limited efficacy against certain tumors due to drug resistance. Radiotherapy is hindered by tumor radioresistance and unavoidable damage to surrounding tissues such as skin, glands, and nerves, with adverse effects that may persist for years [34]. These limitations have driven increasing interest in enantiomeric modification materials, which play pivotal roles in regulating biological processes and have emerged as promising strategies for malignant tumor treatment [20,35].

Chiral nanomaterials demonstrate unique advantages in oncology due to their chirality-dependent interactions with biological systems. Based on the differential affinity of chiral enantiomers for normal and tumor cells, optically active nanoparticles exhibit a remarkable ability to recognize tumor cells. Advances in chiral chemical and electrochemical sensors provide powerful tools for the early diagnosis of malignant tumors [36]. Furthermore, tumor cells display chiral-dependent biological behaviors such as adhesion and autophagy, and chiral nanomaterials can efficiently induce tumor cell apoptosis by activating exogenous cell death pathways [37]. The unique properties of chiral nanomaterials, including their nanoscale effects, spin-induced selectivity, and enantiomer-specific interactions, have garnered significant attention in the field of cancer therapy [38].

Additionally, chiral enantiomer ligands induce nanoparticles to self-assemble into intricate hierarchical structures such as nanospheres, nanorods, and nanoflowers, featuring complex morphologies and abundant chemical binding sites. These structures alter the electronic energy levels of the nanoparticles, enhancing electron-hole recombination and increasing fluorescence quantum yields. Their exceptional photothermal properties further enable efficient tumor cell ablation through photothermal conversion, presenting a novel avenue for cancer treatment [39].

Despite the substantial progress in leveraging chiral materials for malignant tumor therapy, the mechanisms underlying tumor recognition and cytotoxicity of left- and right-handed chiral isomers remain largely confined to foundational *in vivo* and *in vitro* studies. Therefore, a comprehensive review of recent advancements is imperative to consolidate the knowledge on chiral materials in tumor-targeted therapies, metabolic modulation, apoptosis induction, chiral cytotoxicity, and immunotherapy. This review also examines the self-assembled chiral structures of varying scales and geometries synthesized through diverse methods, highlighting their applications in tumor cell adhesion, surface protein interactions, and molecular probe recognition. Additionally, the review explores the impacts of chiral materials on tumor cell metabolism, immune responses, and cytotoxicity. Based on this synthesis, we identify the current limitations of chiral materials in oncology and the challenges in developing self-assembled chiral structures with enhanced therapeutic potential.

2. Classification of chiral materials

The advancement of nanoscale synthesis and assembly-related manufacturing technologies has catalyzed significant progress in the field of chiral materials [40]. Chiral ligands have evolved from natural organic molecules to a diverse array of materials, including metallic inorganic compounds [41] semiconductors [42], polymers [43], and ceramics [44]. Currently, the primary sources of chirality in nanomaterials are: (1) inherent chirality arising from constituent molecules or ligands, and (2)

chirality emerging from higher-order structures synthesized from achiral or racemic polymers or nanocrystals through nanoassembly techniques [45]. The first source often involves materials synthesized under chiral metal-organic frameworks (MOFs) or chiral covalent organic frameworks (COFs), whereas the second source predominantly relies on non-covalent forces such as hydrogen bonding for chiral formation [19,46].

Advanced chiral materials exhibit unique surface and chirality-dependent effects, offering immense potential in cancer therapy [47,48]. For example, chiral nanoparticles can efficiently traverse cell membranes and selectively target tumor cells due to the enantioselective interactions inherent to biological systems, enabling effective tumor treatment [49]. In recent years, various chiral nanomaterials have been synthesized for anti-tumor research. Cadmium telluride (CdTe) quantum dots functionalized with chiral glutathione, for instance, induce the formation of autophagic vacuoles within tumor cells, subsequently triggering autophagy and apoptosis [50]. Furthermore, chiral nanostructures derived from photosensitizers can generate reactive oxygen species and convert light energy into heat upon exposure to circularly polarized light, effectively killing tumor cells [51].

Chiral molecules conjugated with heavy metal ligands or radionuclides, such as chiral gold nanoclusters, serve as excellent radiosensitizers, enhancing the precision and efficacy of radiotherapy and chemotherapy [52,53]. Beyond small molecules, chiral supramolecular structural materials have also been developed for cancer therapy. For example, lysine-modified peptide dendrimers with natural chirality can rapidly activate autophagy in tumor cells [54]. Additionally, chiral-modified nanoenzymes are capable of targeting tumor cells via endocytosis, subsequently interfering with intracellular enzymatic reactions [55].

In summary, while anti-tumor strategies based on chiral nanomaterials remain in the experimental stage, the diversity and versatility of these materials offer unprecedented possibilities for advancing cancer therapy.

3. The pharmacodynamics and mechanisms of chiral materials or medicines in tumor treatment

The intrinsic mechanisms underlying the cytotoxic effects of chiral nanomedicines can be categorized as interference with oxygen metabolism, suppression of enzymatic activity, destruction of cellular structures, alteration of metabolic pathways, and modulation of immune function. Chiral nanomedicines disrupt the processes of oxygen absorption, transport, and utilization within cells, suppress enzymatic activity to mediate cellular damage, compromise cellular structures, and alter key metabolic pathways essential for cellular function. Additionally, they influence the immune system, potentially impairing its ability to respond effectively to tumor cells. The cytotoxicity of chiral materials upon entering cells is influenced by factors such as particle size, the nature of the chiral ligand, and the intrinsic toxicity of the inorganic core. Furthermore, apoptosis is modulated by changes in the physiological conditions necessary for cellular growth and survival, which are affected by the specific interactions of chiral materials with cellular components.

3.1. Chirality-enhanced targeting and aggregation in cancer therapy

Cancer tissues or cells exhibit a degree of stealth during early-stage formation, making their detection challenging. Traditional diagnostic methods such as physical examinations, imaging, biomarker-based

laboratory tests, and biopsies often fail to fully identify tumor formation, thereby affecting therapeutic outcomes and patient prognoses. However, enantiomers of chiral-modified nanomaterials can interact specifically with proteins within the organism [56,57], enabling the identification of early tumor cells and facilitating targeted drug delivery [58]. Furthermore, due to the organism's inherent and efficient selectivity for chiral enantiomers, the cellular uptake efficiency of chiral materials is significantly enhanced. This property allows for the increased accumulation of medicine particles in tumor cells and the tumor microenvironment, thereby amplifying the therapeutic effects mediated by the chirality of the medicine [19]. The table 1 displays some chiral materials that are used for anti-cancer therapy through chirality-enhanced targeting and aggregation in cancer therapy and their classification, proposed mechanism and biomedical applications.

Table 1. Classification, proposed mechanism and biomedical applications that are used for anti-cancer therapy through chirality-enhanced targeting and aggregation in cancer therapy of chiral materials.

Function of chiral medicines/materials	Medicine/materials type	Proposed mechanism	Reference
Cancer cells identification	Gold nanorod dimer	1.The dimer is engineered and endowed with chirality by a PSA-adaptive (prostate-specific antigen, PSA) mechanism. 2.The dimer manifests high specificity for PSA. 3.Bound and quantify PSA and its concentration.	[59]
	Plasma system with gold nanoparticles	1.The AFP-specific (alpha-fetoprotein, PSA) aptamer dimer with strong chiral reactivity is utilized with DNA-modified gold nanoparticles. 2.Quantify AFP levels in human tissues by through the reduction of the CD signal caused by disrupting of aptamer structure.	[60]
	Self-assemble Cys-CdTe/CdS structures	1.Weaken the CD signal in breast and hepatoma cells, while exhibiting minimal effects on normal cells. 2.Enable the differentiation of cancerous cells from healthy ones based on cellular CD signals.	[61]
Chiral enhancement of drug delivery system	Supramolecular hydrogel based on D-phenylalanine derivatives (DPFEG)	1.Loaded with the chiral anticancer drug oxaliplatin. 2.Undergo a helical transformation from left-handed to right-handed polarization under near-infrared irradiation (NIR). 3.Loaded with the chiral anticancer drug oxaliplatin, selectively released the drug under NIR control and demonstrating inhibitory effects on T47D breast cancer cells.	[71]
	Mesoporous silica with tetramethylethylenediamine phenylborate (PBAP) / hyaluronic acid-cyclodextrin complex (HA-CD)	1.pH- and H2O2-sensitive chiral nanorod system was loaded with doxorubicin (DOX) within the mesoporous silica. 2.Upon internalization by tumor cells, the acidic cytoplasmic environment shifted the supramolecular HA-CD switch, exposing the H_2O_2-sensitive region and triggering controlled DOX release.	[72]

Cont.

Function of chiral medicines/materials	Medicine/materials type	Proposed mechanism	Reference
Chiral enhancement of drug delivery system	Chiral mesoporous silica nanoparticles (CMSN) with chemically modified chitosan (CS), CS-CMSN	1.CS radicals rapidly degraded in the acidic tumor microenvironment. 2.Releasing the encapsulated anti-cancer drugs. 3.Demonstrated strong penetration into 4T1 tumor cells and effectively induced tumor cell apoptosis.	[73]
	L/D-cysteine surface modified GQD, L/D-GQDs	1.Incorporate Doxorubicin (DOX) through π-π stacking. 2.Deliver the drug into solid tumor-mimicking tissues.	[74]
Enhance Affinity with Tumor Cells by Chiral Modifications	Photosensitizers (PSs) with functional groups or chiral modifications	PSs with propyl-modified chiral centers showed enhanced tumor-targeting capabilities and greater accumulation within tumor cells.	[77]
	D- and L-type cysteine (Cys) modified black phosphorus nanosheets (BPNS)	1.D- and L-type cysteine (Cys) molecules are employed as chiral inducers to modify BPNS via non-covalent electrostatic interactions. 2.D-Cys-BPNS demonstrated cytotoxicity to tumor cells, a property closely linked to chirality. 3.D-Cys-BPNS effectively inhibited cytoplasmic decomposition, indicating higher cellular uptake and prolonged intracellular retention.	[83]

3.1.1. Chiral materials for cancer cell identification

Early cancer diagnosis predominantly relies on tumor markers such as alpha-fetoprotein (AFP) and prostate-specific antigen (PSA). However, traditional diagnostic methods for these markers exhibit low sensitivity during the early stages of cancer development. Chiral nanomaterials provide a more efficient alternative for early tumor detection. Tang *et al.* [59] engineered a gold nanorod dimer with strong chiral reactivity using a PSA-adaptive mechanism. When the dimer bound to PSA, the CD signal weakened significantly, demonstrating a high specificity for PSA and enabling the quantification of its concentration through a similar mechanism (Figure 1a-b). Similarly, Zhao *et al.* [60] developed a chiral plasma system assembled from gold nanoparticles to quantify AFP levels in human tissues. By utilizing DNA-modified gold nanoparticles to construct an AFP-specific aptamer dimer with strong chiral reactivity, the system demonstrated high sensitivity. Upon binding to AFP, the aptamer structure was disrupted, resulting in a reduction of the CD signal, which showed a log-linear correlation with AFP concentrations ranging from 0.02 to 5 ng/m L. This approach enabled precise quantification of AFP.

Beyond tumor marker detection in early cancer stages, chiral metamaterials facilitate the specific recognition of tumor cells. Folate receptors, which are overexpressed on the surface of tumor cell membranes, have become a promising target for cancer therapy. Li *et al.* [61] developed chiral nanosensors by inducing quantum dots to self-assemble into Cys-CdTe/CdS structures using folic acid and cysteine. These nanosensors caused a marked weakening of the CD signal in breast and hepatoma cells, while exhibiting minimal effects on normal cells. This enabled the differentiation of cancerous

cells from healthy ones based on cellular CD signals. This work establishes a novel method for cancer cell identification by leveraging the chirality of cellular CD signals.

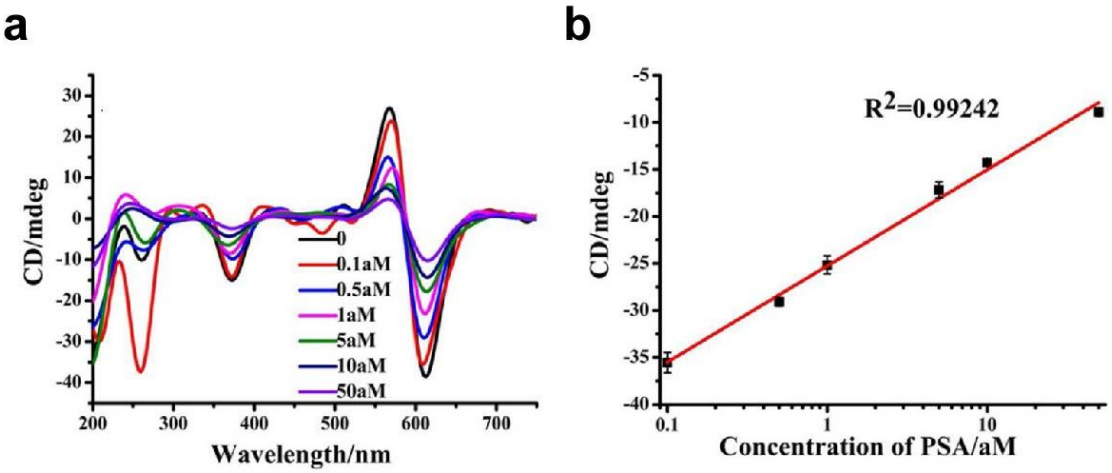

Figure 1. (a–b) The CD spectra various PSA concentrations of 0, 0.1, 0.5, 1, 5, 10, and 50 a M, and standard curve for the target PSA concentrations. Reprinted with permission. Copyright 2015, American Chemical Society [59].

3.1.2. Drug delivery systems with chiral enhancement

Early Most drugs used in tumor cell therapy possess chiral centers, and the pharmacokinetics of their enantiomers are highly dependent on chirality, which significantly influences their therapeutic efficacy [62,63]. Chiral metamaterials, such as supramolecular vesicles [64] and short peptide carriers [65], exhibit strong enantiomeric recognition and separation capabilities, enabling precise delivery of chiral drugs to specific locations. This greatly enhances drug release efficiency and accuracy, thereby improving therapeutic outcomes. As a result, chiral supramolecular structures hold immense potential in tumor therapy drug delivery systems [66,67].

Inspired by biomimetic helical structures, supramolecular hydrogels with non-covalent helical bonds have been introduced into chiral drug delivery system development. These supramolecular structures are highly responsive to environmental stimuli, particularly infrared light [68], and offer excellent controllability and adaptability [69,70]. For instance, Wang *et al.* [71] developed a supramolecular hydrogel based on D-phenylalanine derivatives (DPFEG) for the selective delivery of chiral anticancer drugs. By incorporating graphene oxide, they enabled the DPFEG to undergo a helical transformation from left-handed to right-handed polarization under near-infrared (NIR) irradiation. This delivery system, loaded with the chiral anticancer drug oxaliplatin, selectively released the drug under NIR control, demonstrating significant inhibitory effects on T47D breast cancer cells.

Wang *et al.* [72] designed a drug delivery system aimed at enhancing tumor targeting by modifying mesoporous silica with tetramethylethylenediamine phenylborate (PBAP) and a hyaluronic acid-cyclodextrin complex (HA-CD). This pH- and H_2O_2-sensitive chiral nanorod system was loaded with doxorubicin (DOX) within the mesoporous silica. Under normal physiological conditions, the system prevented premature DOX leakage, reducing side effects on healthy cells. Upon internalization by tumor cells, the acidic cytoplasmic environment shifted the supramolecular HA-CD switch, exposing the H_2O_2-sensitive region and triggering controlled DOX release. This release was further accelerated by

feedback-mediated H_2O_2 production, promoting rapid DOX accumulation in the tumor region and achieving excellent anti-tumor efficacy.

Gou *et al.* [73] synthesized a pH-responsive nanodrug delivery system by coupling chiral mesoporous silica nanoparticles (CMSN) with chemically modified chitosan (CS), creating CS-CMSN. This system exhibited high sensitivity to the acidic tumor microenvironment, where CS radicals rapidly degraded, releasing the encapsulated anti-cancer drugs. Furthermore, the CS-CMSN system demonstrated strong penetration into 4T1 tumor cells and effectively induced tumor cell apoptosis.

Jeon *et al.* used L/D-cysteine to surface modify GQD to obtain L/D-GQDs. Upon incorporating the widely used chemotherapeutic agent Doxorubicin (DOX) through π-π stacking, L-GQDs demonstrate superior efficacy as nanocarriers for delivering the drug into solid tumor-mimicking tissues. This approach yields a 25% increase in effectiveness against cancerous cellular spheroids compared to administering DOX without a carrier (Figure 2) [74].

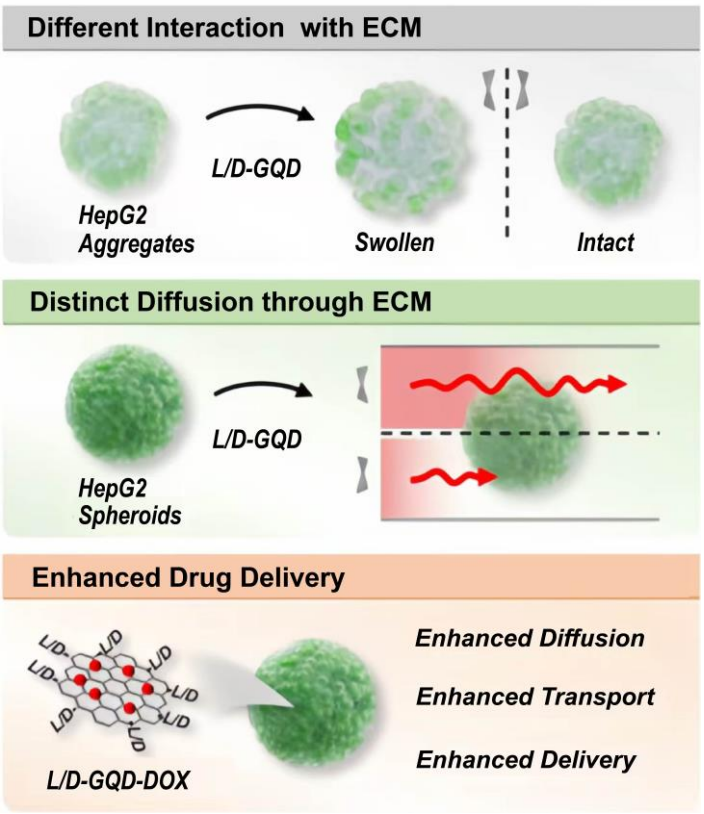

Figure 2. Schematic diagram of chiral GQDs testing in tumor-like cellular spheroids. The L-GQDs exhibited an apparent diffusion coefficient that was 1.7 times greater than that of the D-GQDs, suggesting that L-GQDs have an enhanced ability to transport into spheroids that mimic tumor cells. Reprinted with permission from Jeon, Zhu, Kim and Wang. Copyright 2023, under a Creative Commons Attribution License (CC-BY 4.0) [74].

3.1.3. Chiral modifications of anticancer drugs enhance affinity with tumor cells

With the advancement of asymmetric organocatalysis, the chiral modification of anticancer drugs has emerged as a key area of research [75]. Compared to chiral nanomedical drug delivery systems, direct chiral modification confers tumor-targeting capabilities to the drugs themselves, while also enhancing

their uptake by tumor cells [76]. Additionally, due to the smaller specific surface area of chiral drugs, rapid accumulation within tumor cells can be achieved, thereby improving their pharmacokinetic effects.

Cheruku *et al.* [77] investigated the impact of chiral centers at specific sites, such as 3 (1'), and functional group modifications on the tumor-targeting efficacy and photodynamic therapy (PDT) of pyropheophorbide-a. They synthesized a series of photosensitizers (PSs) with varying functional groups or chiral modifications and applied them to human lung cancer and head and neck cancer (NHC) cells. The study revealed that PSs lacking chiral centers or modified with alkyl or thioether groups exhibited limited uptake by tumor cells. In contrast, PSs with propyl-modified chiral centers showed enhanced tumor-targeting capabilities and greater accumulation within tumor cells. Interestingly, replacing the carboxyl group at site 172 of PSs with a methyl ester reduced both tumor cell uptake and PDT efficacy.

Phosphene, commonly referred to as black phosphorus nanosheets (BPNS), is a widely studied nano-anticancer agent known to induce cytoplasmic decomposition during tumor cell accumulation [78]. Initial applications of BPNS in chiral nanomedical drug delivery systems aimed to address these issues, but its anticancer efficacy and metabolic stability remained suboptimal [79,80]. Although direct passivation of BPNS improved its stability, it also diminished its reactivity [81,82]. To overcome these challenges, Chen *et al.* [83] employed D- and L-type cysteine (Cys) molecules, which are highly biocompatible and readily available, as chiral inducers to modify BPNS via non-covalent electrostatic interactions. The resulting Cys-BPNS nanomaterials exhibited comparable singlet oxygen yields and photothermal conversion efficiencies between the D- and L-forms. However, D-Cys-BPNS demonstrated greater cytotoxicity to tumor cells than L-Cys-BPNS, a property closely linked to chirality. In addition to accelerating intracellular accumulation, D-Cys-BPNS effectively inhibited cytoplasmic decomposition, indicating higher cellular uptake and prolonged intracellular retention.

3.2. Chiral materials alter the metabolism and physiological functions of tumor cells or tissues

Similar to normal cells, tumor cells rely on a series of metabolic processes to sustain life activities such as growth, proliferation, and metastasis [84,85]. In mature tumor tissues, the establishment of local blood circulation is essential to ensure a sufficient supply of nutrients for tumor cells. By altering the cellular metabolic pathways within tumor cells and inhibiting the formation of local blood circulation, the life activities of tumor cells can be effectively suppressed [86,87]. Dysregulated cellular metabolism not only contributes to cancer progression but also facilitates the formation of the tumor microenvironment (TME). This highlights metabolic reprogramming of tumor cells as a promising strategy for cancer treatment [88].

For example, chiral nanoparticles can attach to the surface of tumor cells through chiral specificity, then alter the metabolism of tumor cells [89]. A D-type chiral nanoparticles of which are created by altering the surface of nanoparticles with L/D phosphoserine (NP@-D-PYs) are dephosphorylated by alkaline phosphatase on the surface of tumor cells. And then, the nanoparticles strongly attach to the surface of tumor cells, which triggers the exogenous apoptotic pathway and leading to the death of cancer cells through apoptosis [90]. Additionally, Chiral nanomaterials or nanomaterials modified by chiral ligands possess distinct recognition abilities toward chiral enantiomers, while chirality is the basic property in nature, and many biomolecules are chiral, including amino acids, peptides, proteins, DNA, phospholipids sugars, *etc.* Therefore, chiral materials as artificially synthesised enzyme with chirality demonstrates high selectivity toward biomolecules inside the cells and then manifest high catalysis activity during biochemical reactions. Moreover, artificial chiral nanoenzymes not only showed tunable catalytic activity but also could

have well-catalytic behaviors in harsh acidic tumor microenvironments [91]. The table 2 displays some chiral materials that are used for anti-cancer therapy through altering the metabolism and physiological functions of tumor cells or tissues and their classification, proposed mechanism and biomedical applications.

Table 2. Classification, proposed mechanism and biomedical applications that are used for anti-cancer therapy through altering the metabolism and physiological functions of tumor cells or tissues of chiral materials.

Function of chiral medicines/materials	Medicine/materials type	Proposed mechanism	Reference
Alter the signaling pathways of tumor cells	Chiral polypeptide supramolecule (DPAICP) encapsulated within milk-derived extracellular vesicles (ME), DPAICP@ME	Upon accumulation in tumor tissues, DPAICP@ME exerted therapeutic effects by restoring the p53 and STAT3 signaling pathways.	[94]
	Novel chiral oxazoline copper (II)-based complex (Cu-A)	The downregulation of proteins ERK1/2, AKT, FAK, and VEGFR2, along with their phosphorylated forms p-ERK1/2, p-AKT, p-FAK, and p-VEGFR2 within the VEGF/VEGFR2 signaling pathway. This action leads to the inhibition of proliferation in SKOV3 and HUVEC cells.	[95]
	Chiral derivatives of ionone alkaloids	1.Compounds inhibited the HIF-1α/VEGF/VEGFR2/Akt signaling pathway. 2.This inhibition extended to downstream pathways, including Akt1/mTOR/p70S6K and Akt2/PKCζ/integrinβ1,	[96]
Disrupting enzyme reactions in tumor cells	Chiral D-/L-GOx	1.Combining glucose oxidase (GOx) with chiral carbon particles (CDs). 2.chiral carbon particles enhanced the enzymatic reactivity of GOx and improved the delivery efficiency of chiral GOx to tumor cells.	[100]
	Alkylgold (III) complex	1.Inhibited thioredoxin reductase activity in tumor cells under photo-induced conditions. 2.Exhibited strong cytotoxicity and effectively suppressed tumor angiogenesis	[101]
	Chiral phospho-ligand-modified Au (III) granule, (AuPhos-19)	The complex selectively disrupted mitochondrial metabolism in mouse and human TNBC cells without affecting normal cells	[102]
	Chiral isoxazole derivatives	1.Interacted with peroxidase 1 in HepG2 tumor cells, reducing its enzymatic activity. 2.Activated the ROS-mediated apoptosis pathway in HepG2 cells, ultimately inducing cell apoptosis	[103]
	D-type peptide particles	Acted as catalysts for cell self-ablation and synergistically induced anti-tumor immunity.	[104]
Increasing Reactive Oxygen Species (ROS) in Tumor Cells by Interfering with Tumor Cellular Metabolism	Bifunctionally modified chiral 1,4-diarylazetidin-2-ones.	1.The compounds inhibit tubulin polymerization. 2.Enhance intracellular ROS levels, reducing mitochondrial membrane potentia. 3.Inducing cell cycle arrest in the G2/M phases. 4.Leads to apoptosis of tumor cells and inhibits angiogenesis in tumor tissues.	[107]
	Chiral diaryl-substituted azetidin-2-one derivatives	1.The derivatives inhibit tubulin polymerization in tumor cells. 2.Disrupt angiogenesis, block the G2/M phases of the cell cycle. 3.Increase ROS levels in a dose-dependent manner, resulting in reduced mitochondrial membrane potential and tumor cell apoptosis	[108]

Zhang *et al.* [92] developed a multifunctional biomimetic nanoplatform, HM-BPT, which utilizes manganese dioxide particles encapsulated within a pH-sensitive, tumor-targeting hybrid membrane to deliver BPTES, a glutamine metabolism inhibitor, to tumor sites. This nanoplatform also depletes glutathione and supplies oxygen, providing synergistic effects that enhance its immunotherapeutic potential. Moreover, there are multiple additional strategies to disrupt the metabolic and physiological activities of tumor cells, making the metabolic manipulation of tumor cells a critical focus in cancer therapy.

3.2.1. Chiral materials alter the signaling pathways of tumor cells

Signal transduction is a fundamental physiological process in cells, and alterations in these pathways are often implicated in the pathogenesis of cancer. Consequently, targeting tumor cell signal transduction pathways has emerged as a viable strategy for cancer treatment [93]. He *et al.* [94] synthesized a chiral polypeptide supramolecule (DPAICP) encapsulated within milk-derived extracellular vesicles (ME), forming DPAICP@ME (Figure 3a-c). These vesicles demonstrated stability and maintained drug activity during gastrointestinal absorption and blood circulation. Upon accumulation in tumor tissues, DPAICP@ME exerted therapeutic effects by restoring the p53 and STAT3 signaling pathways.

Fan *et al.* synthesized a novel chiral oxazoline copper (II)-based complex (Cu-A) though an *in-situ* reaction. The proposed molecular mechanism behind its anti-ovarian cancer and anti-angiogenic effects involves the downregulation of proteins ERK1/2, AKT, FAK, and VEGFR2, along with their phosphorylated forms p-ERK1/2, p-AKT, p-FAK, and p-VEGFR2 within the VEGF/VEGFR2 signaling pathway. This action leads to the inhibition of proliferation in SKOV3 and HUVEC cells, the induction of apoptosis, the suppression of migration and metastasis, and the inhibition of angiogenesis. Furthermore, it promotes tumor cell apoptosis by inhibiting the expression of the anti-apoptotic protein Bcl-2 and by increasing the expression of the pro-apoptotic proteins Caspase-9 and Bax [95].

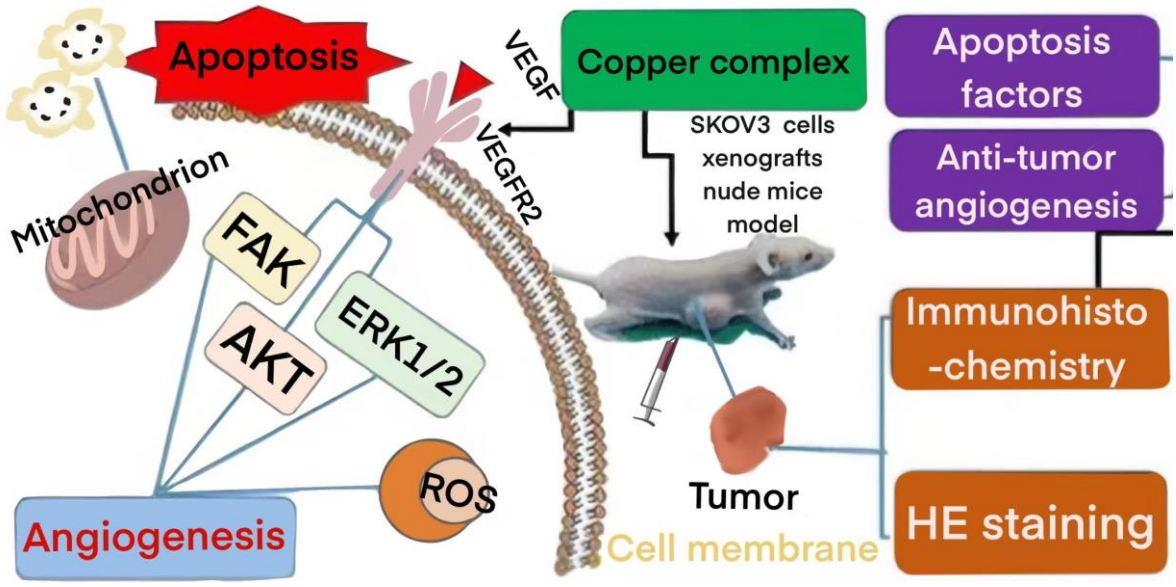

Figure 3. Schematic diagram of chiral oxazoline-copper (II)-based complex inhibiting ovarian cancer growth *in vitro* and *in vivo* by modulating the VEGF/VEGFR2 downstream signaling pathway and apoptotic factors. Reprinted with permission. Copyright 2023, Royal Society of Chemistry [95].

Additionally, Liu *et al.* [96] synthesized a series of chiral derivatives of ionone alkaloids and found that these compounds inhibited the HIF-1α/VEGF/VEGFR2/Akt signaling pathway. This inhibition extended to downstream pathways, including Akt1/mTOR/p70S6K and Akt2/PKCζ/integrinβ1, effectively preventing tumor metastasis.

It is a common misconception that tumor cells generate entirely new physiological responses to regulate their growth and differentiation. In reality, tumor cells utilize the same signaling pathway networks as normal cells, and disruption of a single pathway can lead to systemic failure [97]. Chiral materials, acting as selective modulators of cell signaling pathways, present a promising new strategy for tumor therapy by precisely targeting these critical pathways.

3.2.2. Inhibiting the physiological activity of tumor cells by disrupting enzyme reactions

Enzymes play a crucial role in cell metabolism, and altering metabolic pathways by disrupting enzyme reactivity in tumor cells or delivering specific enzymes directly to tumor cells represents a promising cancer treatment strategy. However, challenges such as the poor penetration of enzyme molecules across cell membranes and the loss of enzymatic activity after chemical modification remain significant. Therefore, developing chemically modified nano-elements capable of enhancing enzyme targeting and facilitating their cellular uptake without compromising activity is essential [98,99].

Bugaj *et al.* synthesized chiral D-/L-GOx by combining glucose oxidase (GOx) with chiral carbon particles (CDs). These chiral carbon particles enhanced the enzymatic reactivity of GOx and improved the delivery efficiency of chiral GOx to tumor cells. Notably, the enzymatic activity of D-GOx was higher than that of L-Gox [100]. Jiang *et al.* synthesized an alkylgold (III) complex that inhibited thioredoxin reductase activity in tumor cells under photo-induced conditions. This complex exhibited strong cytotoxicity and effectively suppressed tumor angiogenesis [101].

Oxidative phosphorylases (OXPHOS) play a pivotal role in maintaining and promoting the progression of human triple-negative breast cancer (TNBC) cells. Disrupting OXPHOS activity to inhibit cellular metabolism offers a potential therapeutic strategy for cancer treatment. Olelewe *et al.* reported that a chiral phospho-ligand-modified Au (III) granule, AuPhos-19, selectively disrupted mitochondrial metabolism in mouse and human TNBC cells without affecting normal cells [102]. Moreover, Wang *et al.* synthesized a series of chiral isoxazole derivatives that interacted with peroxidase 1 in HepG2 tumor cells, reducing its enzymatic activity. These derivatives also activated the ROS-mediated apoptosis pathway in HepG2 cells, ultimately inducing cell apoptosis [103]. Similarly, Yang *et al.* designed D-type peptide particles that acted as catalysts for cell self-ablation and synergistically induced anti-tumor immunity. Notably, the D-type peptides exhibited stronger effects than the L-type peptides [104].

The above studies demonstrate the widespread application of safe, efficient, mild, and straightforward self-assembly strategies in constructing chiral supramolecular nanomedicines with optimal drug properties and enzymatic activity, underscoring the significant advantages of chiral compounds in tumor therapy. These findings not only highlight the innovative applications of chiral compounds in cancer therapy but also pave the way for future research into the development of next-generation chiral nanomedicines with enhanced specificity and therapeutic efficacy.

3.2.3. Increasing reactive oxygen species (ROS) in tumor cells by interfering with tumor cellular metabolism

Reactive oxygen species (ROS) are integral to the normal physiological processes of eukaryotic cells, including signal transduction and apoptosis. Tumor cells are often characterized by increased ROS production and an imbalance in limiting factors that regulate ROS levels [105]. ROS can modulate the tumor microenvironment (TME), impacting tumor metabolism-related cells, local blood circulation in tumor tissues, and immune functions of tumor-associated immune cells [106]. Leveraging ROS production in tumor cells presents a promising strategy for cancer treatment.

Tang *et al.* synthesized bifunctionally modified chiral 1,4-diarylazetidin-2-ones. These compounds inhibit tubulin polymerization and enhance intracellular ROS levels, reducing mitochondrial membrane potential and inducing cell cycle arrest in the G2/M phases. This mechanism leads to apoptosis of tumor cells and inhibits angiogenesis in tumor tissues, effectively eliminating tumor cells [107]. Similarly, Liang *et al.* designed a series of chiral diaryl-substituted azetidin-2-one derivatives. These derivatives also inhibit tubulin polymerization in tumor cells, disrupt angiogenesis, block the G2/M phases of the cell cycle, and increase ROS levels in a dose-dependent manner, resulting in reduced mitochondrial membrane potential and tumor cell apoptosis [108].

Based on these studies, cytological research and *in vitro* experiments reveal that tumor cells exhibit differential chemoattractant and endocytic responses to chiral organic macromolecules, chiral electropolar nanoparticles, and chiral metal ligands. Proteomic studies further suggest that chiral materials interact with various levels of cell signaling pathways, driving biological processes in distinct directions [109].

Despite these advancements, exploring how chiral materials regulate the physiological activities of tumor cells remains a nascent field. Future research must focus on elucidating the mechanisms governing the affinity between chiral materials and tumor cells, minimizing their biological toxicity, and clarifying their roles in cellular metabolic pathways. Such efforts will pave the way for revealing the full potential of chiral materials in biological and clinical applications.

3.3. Chiral materials promote apoptosis of tumor cells

Every Apoptosis, a form of programmed cell death, ensures the orderly clearance of damaged or unwanted cells [110]. The uncontrolled growth of tumor cells is often linked to the inhibition of apoptosis, as the breakdown of apoptotic mechanisms and reduced expression of apoptosis-related proteins are key factors contributing to abnormal tumor proliferation [111]. Understanding the anti-apoptotic mechanisms of tumor cells and reactivating apoptosis are crucial strategies in cancer treatment [112].

Cisplatin is a widely used chemotherapy drug, but its effectiveness is limited in some tumor cells due to intracellular steric hindrance, which can lead to drug resistance. To address this, Xiong *et al.* synthesized chiral RuII-PtII complex nanoparticles (NPs) that function as stable and efficient drugs even in the presence of significant steric hindrance. These NPs effectively inhibited the telomerase activity of drug-resistant cancer cells, inducing apoptosis and reducing cisplatin resistance (Figure 4a) [113]. Additionally, Li *et al.* developed chiral folate-coupled Cys-CdTe/CdS quantum dots (QDs), which selectively identified and targeted breast cancer cells, inducing apoptosis with high accuracy (Figure 4b) [114].

Interestingly, metal-based chiral crystal substances have also demonstrated tumor-regulating capabilities. Fan *et al.* synthesized a chiral oxazoline compound with a Cu (II) ligand that induced apoptosis in SKOV3 ovarian cancer cells and human vascular endothelial cells. This compound

downregulated key signaling proteins, inhibited anti-apoptotic protein Bcl-2, and upregulated pro-apoptotic proteins such as Caspase-9 and Bax, promoting apoptosis [95]. Wang *et al.* explored chiral gold nanoparticles, finding that L-type nanoparticles activated NK cells and triggered NK and $CD8^+$ T cells to target tumor tissues, thereby enhancing tumor cell apoptosis through immunotherapy (Figure 4c) [115]. The table 3 displays some chiral materials that are used for anti-cancer therapy through promote apoptosis of tumor cells and their classification, proposed mechanism and biomedical applications.

Table 3. Classification, proposed mechanism and biomedical applications that are used for anti-cancer therapy through promote apoptosis of tumor cells of chiral materials.

Function of chiral medicines/materials	Medicine/materials type	Proposed mechanism	Reference
Promote apoptosis of tumor cells	Chiral RuII-PtII complex nanoparticles (NPs)	1.Function as stable and efficient drugs even in the presence of significant steric hindrance. 2.Inhibited the telomerase activity of drug-resistant cancer cells, inducing apoptosis and reducing cisplatin resistance	[113]
	Chiral folate-coupled Cys-CdTe/CdS quantum dots (QDs)	Selectively identified and targeted breast cancer cells, inducing apoptosis with high accuracy	[114]
	Chiral oxazoline compound with a Cu (II) ligand	1.Induced apoptosis in SKOV3 ovarian cancer cells and human vascular endothelial cells. 2.Downregulated key signaling proteins, inhibited anti-apoptotic protein Bcl-2, and upregulated pro-apoptotic proteins such as Caspase-9 and Bax, promoting apoptosis	[95]
	Chiral gold nanoparticles	Activated NK cells and triggered NK and $CD8^+$ T cells to target tumor tissues, thereby enhancing tumor cell apoptosis through immunotherapy	[115]
	Chiral dehydroabietic acid complexes with Cu (II)/Fe (III) ligands	1.Activated both intrinsic (mitochondria-mediated) and extrinsic (receptor-mediated) apoptosis pathways in MCF-7 cells. 2.Upregulated Bax, downregulated Bcl-2, released Cyt C, and induced DNA damage, as evidenced by increased γ-H2AX and p53 expression	[116]
	Λ-Ru chiral ruthenium complexes	Exhibited apoptosis induction in SGC-7901 tumor cells.	[117]
	Chiral enantiomeric particles (VOPs)	1.Mimicked cytolytic viral mechanisms 2.Existing clinical cytolysis agents by directly lysing tumor cells and inducing anti-tumor immunity	[118]

Further, Fei *et al.* synthesized chiral dehydroabietic acid complexes with Cu (II)/Fe (III) ligands, which activated both intrinsic (mitochondria-mediated) and extrinsic (receptor-mediated) apoptosis pathways in MCF-7 cells. These complexes upregulated Bax, downregulated Bcl-2, released Cyt C, and induced DNA damage, as evidenced by increased γ-H2AX and p53 expression [116]. Similarly, Zhang *et al.* designed chiral ruthenium complexes with different ligands, finding that Λ-Ru exhibited superior apoptosis induction in SGC-7901 tumor cells due to its selective localization in tumor tissues [117].

Inspired by viruses with cytolytic effects, Li *et al.* developed enantiomeric particles (D-VOPs and L-VOPs) that mimicked cytolytic viral mechanisms (Figure 4d). D-VOPs demonstrated superior therapeutic

effects compared to L-VOPs and existing clinical cytolysis agents by directly lysing tumor cells and inducing anti-tumor immunity [118].

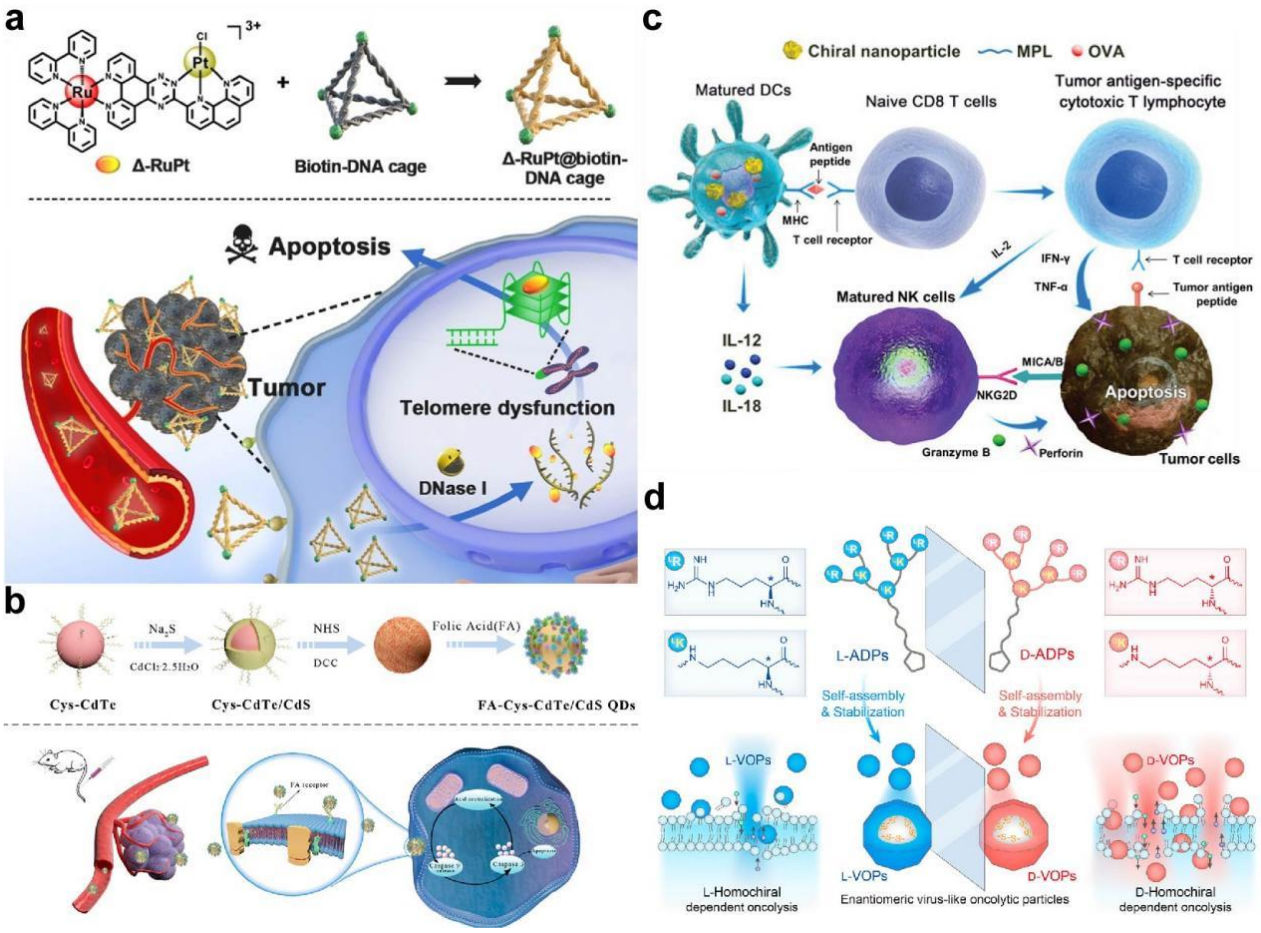

Figure 4. (a) Schematic representation of apoptosis induced by Δ-RuPt @biotin-DNA cage in cisplatin-resistant tumor cells. Reprinted with permission [113]. Copyright 2022 Wiley-VCH GmbH. **(b)** Synthesis process of chiral FA-Cys-CdTe/CdS quantum dots (QDs) and their synergistic effects on cancer therapy via the Caspase-dependent apoptosis pathway. Reprinted with permission. Reprinted with permission [114]. Copyright 2022, American Chemical Society Copyright 2021 Elsevier. **(c)** Mechanism of tumor growth inhibition and protection mediated by chiral nanoparticles. Reprinted with permission [115]. Copyright 2022 Wiley-VCH GmbH. (d) Structural illustration of L-ADP and D-ADP, biomimetic supramolecular assembly of L-VOP and D-VOP, and the chiral-dependent oncolytic mechanism of enantiomeric virus-like particles. Reprinted with permission. Copyright 2023, American Chemical Society [118].

These studies highlight the role of metal ions or compounds in enhancing the apoptosis-inducing ability of chiral enantiomers. Traditionally, D-chiral materials are believed to match the L-phospholipid molecular layer of tumor cell membranes, enabling better binding and uptake [119]. Additionally, D-isomers are less prone to enzymatic degradation, making them more effective in inducing apoptosis. However, recent findings indicate that some levorotatory materials can also effectively induce apoptosis in specific tumor cell types, suggesting the need for comparative studies on D- and L-chiral materials across different tumor

models. In summary, the development of novel chiral materials offers a promising avenue for inducing apoptosis in tumor cells more effectively, paving the way for advanced tumor-targeted therapies.

3.4. Chiral nanomaterials enhance tumor ablation via photothermal effects

Photothermal therapy (PTT) is an emerging cancer treatment strategy that utilizes heat generated under optical radiation to raise the local temperature of tumor cells, thereby destroying their protein structures or biomembranes to achieve cell death [120]. Recent advancements have incorporated chiral nanomaterials to enhance the efficacy of PTT. Specifically, chiral nanomaterials can enhance the effect of tumor phototherapy while minimizing damage to healthy cells, because of their ability to selectively absorb light waves based on their chirality during treatment [151]. Meanwhile, chiral nanomaterials can utilize the circularly polarized light (CPL), left or right CPL (LCP/RCP) to produce more hot electrons and reactive oxygen species (ROS), which accelerate the death of tumor cells with unique chiral responses [90]. The table 4 displays some chiral materials that are used for anti-cancer therapy through Enhancing Tumor Ablation via Photothermal Effects and their classification, proposed mechanism and biomedical applications.

Table 4. Classification, proposed mechanism and biomedical applications that are used for anti-cancer therapy through Enhancing Tumor Ablation via Photothermal Effects of chiral materials.

Function of chiral medicines/materials	Medicine/materials type	Proposed mechanism	Reference
Enhance Tumor Ablation via Photothermal Effects	Chiral penicillamine-modified $Cu_{2-x}Se$ nanoparticles (D/L-NPs)	Exhibited dual therapeutic effects through second near-infrared (NIR-II) activated photothermal therapy (PTT) and chemotherapy	[121]
	Supramolecular hydrogel system comprising L-phenylalaninyl (LPFEG) encapsulated in polydopamine nanoparticles (PDA-NPs)	PDA-NPs mediated NIR-stimulated photothermal therapy and scavenged free radicals at the wound site, while LPFEG mimicked the natural extracellular matrix to create a chiral microenvironment, therefore, facilitated fibroblast aggregation and tissue regeneration	[122]
	Cys-MoO_{3-x} nanoparticles	The strong absorption of nanoparticles at visible light frequencies, combined with the chirality of metal-to-ligand charge transfer, allows Cys-MoO_{3-x} nanoparticles to quickly generate hyperthermia for phototherapy.	[123]
	SirNA-PPA copolymer nanogel.	Induced tumor cell apoptosis through photodynamic pathways and enhanced immune responses as a synergistic effect.	[124]

Liu *et al.* constructed chiral penicillamine-modified $Cu_{2-x}Se$ nanoparticles (D/L-NPs) that exhibited dual therapeutic effects through second near-infrared (NIR-II) activated PTT and chemotherapy (Figure 5a). Notably, D-type NPs demonstrated superior efficacy compared to L-type. Furthermore, the photothermal synergy mediated by NIR-II irradiation enhanced the chemotherapy effects of hydroxyl free radicals released by the drug in D-type NPs [121].

To address tumor recurrence after surgical resection, Wang *et al.* developed a supramolecular hydrogel system comprising L-phenylalaninyl (LPFEG) encapsulated in polydopamine nanoparticles

(PDA-NPs). In this system, PDA-NPs mediated NIR-stimulated photothermal therapy and scavenged free radicals at the wound site, while LPFEG mimicked the natural extracellular matrix to create a chiral microenvironment. This facilitated fibroblast aggregation and tissue regeneration, effectively combining photothermal therapy with wound healing and preventing tumor recurrence [122].

Li *et al.* used chiral cysteine to reduce MoO_3 nanodots to obtain Cys-MoO_{3-x} nanoparticles with low cytotoxicity and feasible cell permeability, their strong absorption at visible light frequencies, combined with the chirality of metal-to-ligand charge transfer, allows Cys-MoO_{3-x} nanoparticles to quickly generate hyperthermia for phototherapy. This characteristic has the potential to transform the paradigm of PTT-based tumor cell treatments in a more cost-effective manner (Figure 5b) [123].

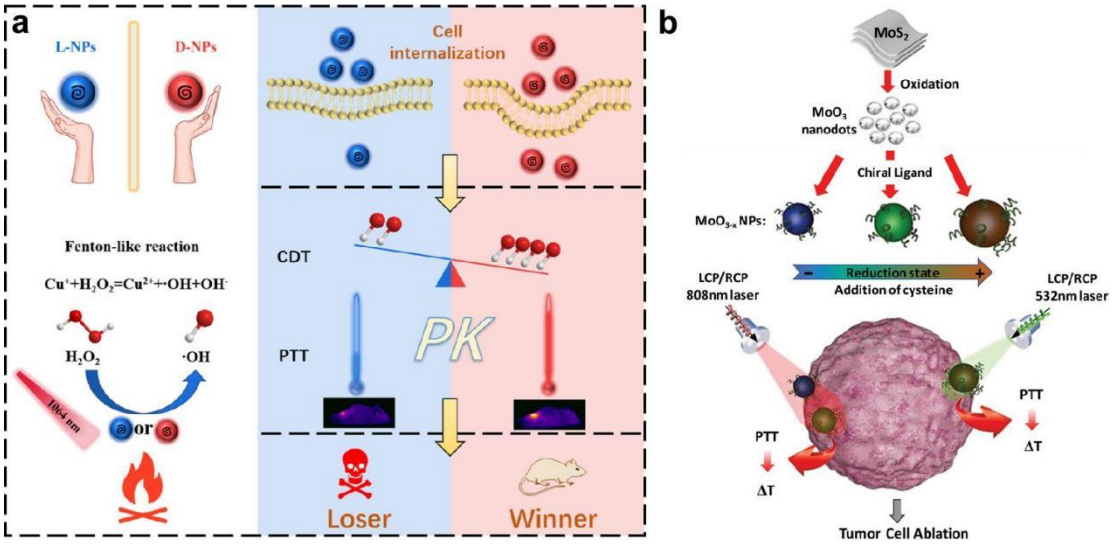

Figure 5. (a) Comparative schematic of the *in vivo* and *in vitro* synergistic efficacy of D-NP and L-NP in chemodynamic and photodynamic therapies. Reprinted with permission. Copyright 2021, American Chemical Society [121]. **(b)** Synthesis of Cys-MoO_{3-x} NPs and the applications for the ablation of tumor cell via CPL radiation. Reprinted with permission. Copyright 2019, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim [123].

Photoimmunotherapy, a newly proposed cancer treatment strategy, has also incorporated chiral nanotechnology. Guo *et al.* designed a nanogel system in which pheophorbide A (PPA) photosensitizer molecules were attached to specific sites on a DNA segment. Four such PPA-DNA molecules self-assembled into a tetrahedral structure, which was further complexed with siRNA to form a SirNA-PPA copolymer nanogel. This nanogel induced tumor cell apoptosis through photodynamic pathways and enhanced immune responses as a synergistic effect [124].

Based on these studies, chiral recognition is expected to play a pivotal role in enhancing the precision and efficiency of photothermal therapy [125,126]. Chiral nanomaterials exhibit unique properties such as near-infrared fluorescence, excellent biocompatibility, high chiral recognition potential, and stable photothermal conversion efficiency. These characteristics make chiral nanomaterials promising candidates for advanced photothermal therapy and near-infrared fluorescent probes.

3.5. Chiral material-mediated immunotherapy

Tumor immunotherapy primarily stimulates the body's immune system to generate a targeted immune response against tumor cells [127,128]. This approach requires a relatively robust immune system to be effective. Compared to traditional therapies, immunotherapy offers the advantage of inducing a long-term immune response [129,130], which can prevent tumor progression and reduce the risk of cancer recurrence [131]. However, the limited immune response within the body and the low immunogenicity of certain tumor types presents significant challenges to the broader application of immunotherapy. To address these limitations, recent advancements in chiral-modified nanomaterials have demonstrated their ability to specifically activate components of the immune system. These materials enhance anti-tumor immunotherapy by targeting and modulating immune-related pathways, garnering widespread attention for their potential in overcoming current immunotherapy limitations [132]. The table 5 displays some chiral materials that are used for anti-cancer therapy through material-mediated immunotherapy and their classification, proposed mechanism and biomedical applications.

Table 5. Classification, proposed mechanism and biomedical applications that are used for anti-cancer therapy through material-mediated immunotherapy of chiral materials.

Function of chiral medicines/materials	Medicine/materials type	Proposed mechanism	Reference
Enhance immune cell reactivity by promoting antigen uptake and presentation	Supramolecular chiral polymer micelle by complexing the tumor-associated antigen ovalbumin (OVA) with chiral histidine-modified polyethylenimine (PEI)	1.Reduced cationic cytotoxicity while promoting the uptake, processing, and presentation of tumor-specific antigens by DCs. 2.Promoting the rapid proliferation of antigen-specific T lymphocytes and effectively inhibiting tumor cell growth	[141]
	Chiral gold nanoparticles (Au NPs)	1.Chirality enhances the body's adaptive immune response by stimulating DCs. 2.Activate of CD8-positive T cells and CD69-positive NK cells, exert mechanical forces on bone marrow-derived DCs, promote cytokine production, and induce NK cells to release cytotoxins. 3.Enhanced antigen cross-presentation, enabling T lymphocytes to eliminate tumor cells.	[115]
Chiral nano-vaccine adjuvants in cancer prevention and treatment	Amphiphilic polypeptides poly(L-phenylalanine)-block-poly(L-lysine) (PL-K) / poly(L-phenylalanine)-block-poly(D-lysine) (PD-K)	1.The polypeptides are complexed with the model antigen chicken ovalbumin (OVA) to form nanovaccines PL-K-OVA and PD-K-OVA. 2.Promote DC maturation and type 1 T-helper cytokine secretion 3.induced stronger antigen cross-presentation and adaptive immune responses	[147]
	Chiral carbon dots (CDs) coupled with the model antigen OVA	Internalized by bone marrow dendritic cells (BMDCs), stimulating their maturation and enabling antigen cross-presentation to T lymphocytes	[148]

Cont.

Function of chiral medicines/materials	Medicine/materials type	Proposed mechanism	Reference
Chiral nano-vaccine adjuvants in cancer prevention and treatment	Chiral vidarabine monophosphate-gadolinium nanowires (aAGd-NWs)	1.A negative surface charge, ultrafine topography, and, notably, D-type chirality endow aAGd-NWs with the ability to penetrate deeply into tumor tissues, which forms the basis for their radiosensitization effect in damaging tumor cells located away from blood vessels. 2.aAGd-NWs exhibit efficient X-ray deposition, scattering, and emission capabilities, which enhance the generation of ROS, and then, endow aAGd-NWs with the ability to penetrate deeply into tumor tissues, which forms the basis for their radiosensitization effect in damaging tumor cells located away from blood vessels.	[149]
Therapy via tumor-associated macrophage regulation	Chiral MoS_2/COS_2-modified nanase particles with peroxidase (POD) and catalase (CAT)-like reactivity	1.Interact specifically with biological systems, effectively regulating Tumor-associated macrophage (TAM) polarization and reversing tumor immunosuppression. 2.Act as extracellular generators of hydroxyl radicals (*OH) and oxygen (O_2), then facilitated the repolarization of TAMs into the M1 phenotype.	[155]
	Chiral ruthenium-based nanase	1.Produces ROS and nitric oxide (NO) through an autocatalytic cascade reaction. 2.Exhibited dual oxidase and nitric oxide synthase activities under chiral control, rapidly generating singlet oxygen ($1O_2$) and O_2, which then reacted with arginine to produce sufficient NO. 3.The combined ROS and NO production induced M1 macrophage polarization while triggering tumor cell apoptosis and ferroptosis.	[156]
	Camptothecin(CPT) nanofibers (CNF) with a right-handed chiral property	1.Accumulates specifically in the mitochondria of cancer cells, leading to mitochondrial dysfunction and a 3.42-fold increase in reactive oxygen species (ROS) generation compared to the normal CPT molecule when exerting effects in tumor cells. 2.ROS amplification activates the caspase-1/gasdermin D (GSDMD) pathway, inducing pyroptosis that promotes M1 macrophage polarization and enhences $CD8^+$ T-cell-dependent antitumor immunity.	[157]

Almost all of biomolecules exist in only one form of enantiomer(L-type/D-type) in living organisms and the biological regulation of homeostasis relies on homochiral molecules, such as amino acids, sugars, and DNA, to function correctly, such as, sugars are represented by D-isomers, proteins composed of L-isomers, and DNA twists into right-handed helices[133]. Therefore, stereospecificity is essential for medicine to go into effect on specific biomolecule with natural chirality, and introducing proper chirality to medicine will significantly enhance the efficacy of medicine. As a result, chiral can be used to enhance the function of anti-tumor immune cells by accurately exerting and regulating biomolecules of them, such as Promoting Antigen Uptake and Presentation of Dendritic Cells (DC), macrophage and enhancing tumor-associated macrophage and lymphocytes. Additionally, formation of D-amino acid in

organism appears as a result of post-translational modification of an L-amino acid residue enzymatically converted into a D-amino acid residue in the peptide chain, and the amount of free D-amino acids in the organism is related with many diseases. D-amino and D-amino acids contain abnormal peptides or protein in some disease conditions [134]. Therefore, enhancement of chiral chemotaxis to those D-amino or abnormal peptides of immune cells makes it potential biomarkers and therapeutic targets for those diseases.

3.5.1. Chiral nanoparticles enhance immune cell reactivity by promoting antigen uptake and presentation

The ability of antigen-presenting cells (APCs) to absorb and cross-present tumor-specific antigens is critical for inducing a robust anti-tumor immune response [135–137]. Among APCs, dendritic cells (DCs) are the most important and effective, as they uptake tumor-specific antigens and activate lymphocytes. Activated T lymphocytes can then specifically recognize and eliminate tumor cells by secreting cytokines such as tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) [138,139]. Currently, the most common approach involves using nanomedicines developed via genetic engineering to stimulate DCs and initiate the immune response [140].

The chirality of nanomaterials has been shown to influence their interactions with cells and organisms. Jiang *et al.* [141] designed a supramolecular chiral polymer micelle by complexing the tumor-associated antigen ovalbumin (OVA) with chiral histidine-modified polyethylenimine (PEI). This design reduced cationic cytotoxicity while promoting the uptake, processing, and presentation of tumor-specific antigens by DCs. Furthermore, D-chiral supramolecular polymer micelles significantly increased the expression of co-stimulatory molecules on DCs, thereby promoting the rapid proliferation of antigen-specific T lymphocytes and effectively inhibiting tumor cell growth (Figure 6a).

Wang *et al.* [115] explored the impact of chiral gold nanoparticles (Au NPs) on the immune response to tumor cells and found that chirality enhances the body's adaptive immune response by stimulating DCs. This stimulation leads to the activation of CD8-positive T cells and CD69-positive NK cells. In experiments using the EG7.OVA tumor model, chiral NPs were observed to exert mechanical forces on bone marrow-derived DCs, promote cytokine production, and induce NK cells to release cytotoxins. Simultaneously, these nanoparticles enhanced antigen cross-presentation, enabling T lymphocytes to eliminate tumor cells. Notably, L-type NPs exhibited a higher affinity for DCs compared to D-type NPs, resulting in a stronger tumor apoptosis-inducing effect.

3.5.2. Chiral nano-vaccine adjuvants in cancer prevention and treatment

Cancer vaccines stimulate the immune system to recognize, suppress, and eliminate tumor cells by enhancing the adaptive immune response and improving tumor antigen presentation [142,143]. After injection, tumor-specific antigens in the vaccine induce the maturation of dendritic cells (DCs), which present antigens to T lymphocytes, thereby activating effector T lymphocytes. $CD8^+$ T lymphocytes subsequently migrate to tumor tissues and secrete cytokines such as tumor necrosis factor-α (TNF-α), leading to the destruction of cancer cells [144].

Recent advancements have introduced chiral biomaterials, such as chiral polypeptide thermogels [145], D-tetrapeptide hydrogels [146], and controllable chiral gold nanoparticles [132], into cancer vaccine development. However, effective chiral nanovaccines capable of inducing strong anti-tumor immune responses remain limited. To address this challenge, Su *et al.* [147] synthesized amphiphilic polypeptides

poly(L-phenylalanine)-block-poly(L-lysine) (PL-K) and poly(L-phenylalanine)-block-poly(D-lysine) (PD-K) by using L-phthalate ethyl ester (NCA) and lysine derivatives. These polypeptides were then complexed with the model antigen chicken ovalbumin (OVA) to form nanovaccines PL-K-OVA and PD-K-OVA. In their study, PD-K-OVA demonstrated superior ability to promote DC maturation and type 1 T-helper cytokine secretion compared to PL-K-OVA. Furthermore, PD-K-OVA induced stronger antigen cross-presentation and adaptive immune responses, as shown in experiments with a B16-OVA melanoma model. This highlights the potential of chiral peptides as effective vaccine adjuvants for cancer immunotherapy.

Liu *et al.* [148] further explored chiral carbon dots (CDs), which exhibit structural similarity to proteins and possess chiral properties, as well as functional versatility for antigen presentation. By coupling CDs with the model antigen OVA, they developed L/D-OVA nanovaccines. These chiral CDs were effectively internalized by mouse bone marrow dendritic cells (BMDCs), stimulating their maturation and enabling antigen cross-presentation to T lymphocytes. The resulting immune activation effectively inhibited B16-OVA melanoma growth, demonstrating the potential of chiral CDs as carriers and adjuvants in cancer vaccines (Figure 6b).

It can be used as situ tumor vaccines that directly administrate antigens to the tumor site to stimulate antitumor immune responses. Irradiated tumor itself as an intrinsic *in situ* vaccine. However, tumor cells have limited X-ray absorption capacity, and the tumor microenvironment lacks immune adjuvants necessary for effective phagocytosis and presentation of tumor antigens. Huang *et al.* [149] developed chiral vidarabine monophosphate-gadolinium nanowires (aAGd-NWs) through coordination-driven self-assembly based on vidarabine monophosphate (ara-AMP) and gadolinium (Gd), a clinical contrast agent. The aAGd-NWs exhibit a negative surface charge, ultrafine topography, and, notably, D-type chirality, and these features endow aAGd-NWs with the ability to penetrate deeply into tumor tissues, which forms the basis for their radiosensitization effect in damaging tumor cells located away from blood vessels. As a result of the presence of the high atomic number (high-Z) element Gd, aAGd-NWs exhibit efficient X-ray deposition, scattering, and emission capabilities, which enhance the generation of ROS. Then the process enhances the exposure of calreticulin (CRT) on the surface of tumor cells, which attract dendritic cells (DCs) for phagocytosis and antigen presentation. Simultaneously, aAGd-NWs causes DNA double-strand breaks while aAGd-NWs released ara-AMP, which acts as a DNA repair inhibitor, leading to the accumulation of DNA fragments within the cytoplasm, which promotes the activation of the cGAS/STING pathway and the subsequent secretion of interferon-beta (IFN-β) by surrounding immune cells. Consequently, the combined treatment of aAGd-NWs and radiation therapy synergistically induces *in situ* vaccination, facilitates immune priming, and potentiates the efficacy of checkpoint blockade immunotherapies (CBI) against both primary and metastatic tumors.

3.5.3. Chiral materials for cancer therapy via tumor-associated macrophage regulation

Tumor-associated macrophages (TAMs) are critical immune effector cells in the tumor microenvironment (TME) and are indicative of tumor immune infiltration. Their functional plasticity allows them to adopt either an immunostimulatory M1 phenotype with anti-tumor activity or an immunosuppressive M2 phenotype that supports tumor progression, depending on environmental signals [150]. M1-polarized macrophages enhance antigen processing and presentation, secrete co-stimulatory molecules, and activate T lymphocytes, thereby participating in the immune response against tumor cells [151].

Reactive oxygen species (ROS) are key regulators of TAM polarization, capable of activating signal transduction pathways that convert TAMs from the tumor-promoting M2 phenotype to the anti-tumor M1 phenotype, effectively inhibiting tumor development and progression [152]. However, this process depends on extracellular ROS, whereas most current nanotherapies produce intracellular ROS, which can lead to oxidative stress and macrophage death due to cellular refinement [153,154].

To address this challenge, Zhang *et al.* [155] synthesized chiral MoS2/COS2-modified nanase particles with peroxidase (POD) and catalase (CAT)-like reactivity. These chiral nanoparticles interact specifically with biological systems, effectively regulating TAM polarization and reversing tumor immunosuppression (Figure 6c). Their findings revealed that D-type nanoparticles (D-NPs) can evade macrophage uptake in the TME and act as extracellular generators of hydroxyl radicals (*OH) and oxygen (O_2). This extracellular ROS generation facilitated the repolarization of TAMs into the M1 phenotype. This groundbreaking approach demonstrated the potential of chiral nanases as extracellular ROS generators, providing a novel method for reprogramming TAMs in cancer immunotherapy.

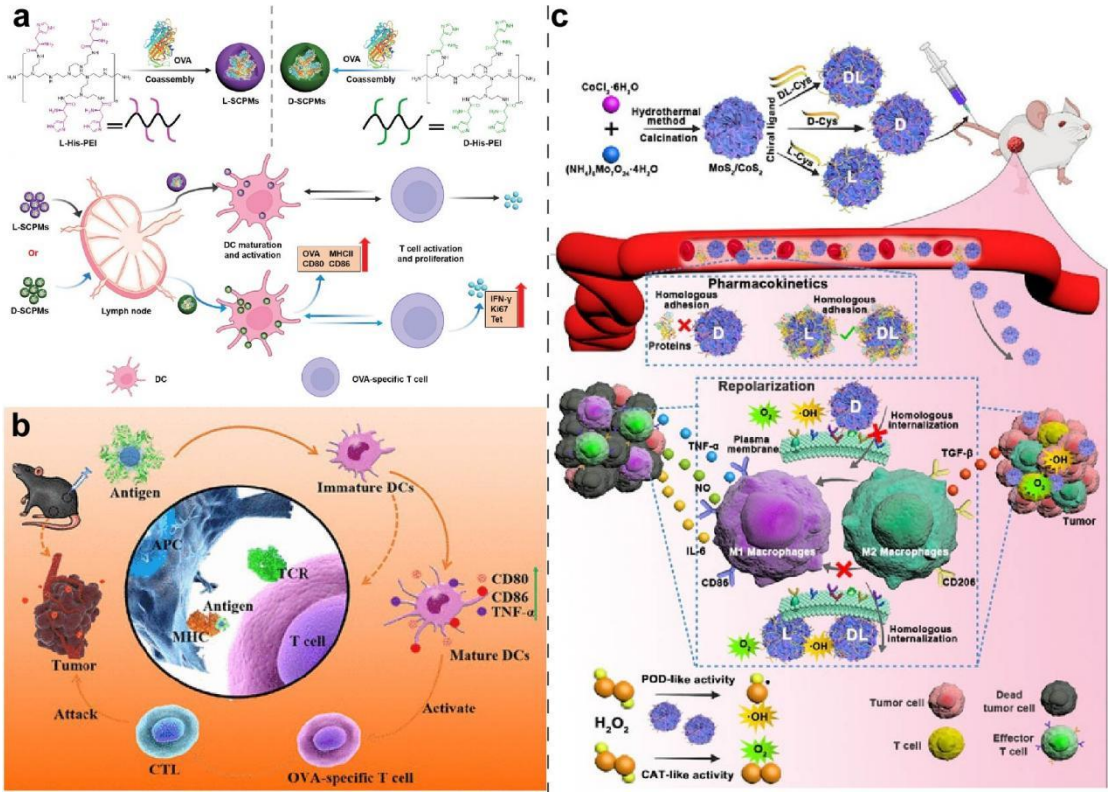

Figure 6. **(a)** Schematic diagram of SCPMs preparation and chiral-mediated antigen-specific immune activation. Reprinted with permission. Copyright 2022, Wiley-VCH GmbH [141]. **(b)** Procedures of L/D-OVA for Cancer Immunotherapy Subcutaneous injection of l/d-OVA nanovaccines allows them to be taken up by immature dendritic cells (DCs) and effectively stimulate their maturation, thereby inducing T cell proliferation and inhibiting the growth of B16-OVA melanoma [148]. Reprinted with permission. Copyright 2022, American Chemical Society. **(c)** Schematic diagram illustrating the use of chiral nanase to inhibit the growth of chiral-dependent tumors. Reprinted with permission. Copyright 2023, Wiley-VCH Verlag GmbH [155].

Building on this work, Chen *et al.* [156] developed a chiral ruthenium-based nanase that simultaneously produces ROS and nitric oxide (NO) through an autocatalytic cascade reaction. By integrating arginine into the nanase, they designed a system capable of promoting the endogenous

production of ROS and NO. This nanase exhibited dual oxidase and nitric oxide synthase activities under chiral control, rapidly generating singlet oxygen ($^1O_2$) and O_2, which then reacted with arginine to produce sufficient NO. The combined ROS and NO production induced M1 macrophage polarization while triggering tumor cell apoptosis and ferroptosis, presenting a highly effective catalytic strategy for cancer therapy.

Feng *et al.* [157] constructed Camptothecin (CPT) nanofibers (CNF) with a right-handed chiral property via supramolecular self-assembly, which significantly overcomes the solubility barriers associated with bioavailability and improves tumor immune prognosis. Through formulating chiral CNF with mitochondrial-targeted DSPE-PEG-TPP, CNF accumulates specifically in the mitochondria of cancer cells, leading to mitochondrial dysfunction and a 3.42-fold increase in reactive oxygen species (ROS) generation compared to the normal CPT molecule when exerting effects in tumor cells. This ROS amplification activates the caspase-1/gasdermin D (GSDMD) pathway, inducing pyroptosis that promotes M1 macrophage polarization and enhences $CD8^+$ T-cell-dependent antitumor immunity. Consequently, CNF achieves 1.8-fold greater growth inhibition of distant tumor and reduces tumor metastasis compared to the CPT molecule. Our innovative platform, assembling CPT molecules into chiral CNF structure, is highly anticipated to overcome the current clinical limitations of CPT molecules and offer a new direction for the development of next-generation immunotherapy strategies.

4. Conclusion and prospect

The development of novel chiral nanomaterials and their application in biomedical fields, particularly in tumor therapy, has seen significant progress in recent years. This review explores the synthetic pathways and classification of chiral materials, including chiral self-assembled nanostructures and supramolecular structures, and highlights their important contributions to tumor-targeted therapies. These therapies encompass key principles such as cell metabolism, apoptosis, cytotoxicity, and immunotherapy. It has been demonstrated that introducing chirality can induce autophagy and apoptosis in tumor cells, as well as modulate the immune response *in vivo*, presenting broad prospects for anti-tumor applications.

However, several challenges remain to be addressed. Non-chiral nanomaterials inevitably cause cytotoxicity when introduced into the human body, leading to side effects on healthy cells. Moreover, the specific mechanisms through which chiral nanomaterials influence the body's immune response have not been fully elucidated. Therefore, exploring proper chirality is significant for application of chiral materials for cancer therapy. This is not only a potential opportunity to enhance treatment of tumor, but also a challenge, which perhaps to consume a large amount of resources, and medical or research institution need to conduct long-term development with persistent perseverance. Additionally, proposed mechanism to be clarified clearly because of the differ between each enantiomer, it is manifested as that one isomer demonstrate therapeutic to tumor cells while another isomer being toxic for organism.

Although chiral nanomaterials show promising tumor-targeting abilities and accumulation within the tumor microenvironment, their hydrolysis performance is often suboptimal, and their strong immunogenicity further limits clinical application. Thus, it is crucial to explore methods for controlling these nanomaterials within the body.

Recent research indicates that the chirality of nanomaterials can significantly influence their properties, sometimes even producing opposing effects. This raises critical questions, such as: How can we precisely obtain a specific chiral nanomaterial through adjustments in synthesis methods?

Additionally, it remains unclear whether chiral nanomaterials undergo changes upon entering the human body. Moreover, the potential long-term radiation damage to healthy cells from using chiral nanomaterials as photosensitizers in photothermal therapy warrants further investigation. Meanwhile, the supervision system of chiral medicine need to be constructed to ensure the continuous standardized development of chiral medicine, such as setting a standard optically purity of different kind of chiral medicine, developing guidelines of toxicity or therapeutic which belong to different enantiomers of the same or different molecules.

In conclusion, advancing our understanding of the basic mechanisms and theoretical foundations of chiral nanomaterials in nanotherapy, clarifying the pharmacokinetics and molecular effects of chiral therapy, and developing safer and more stable chiral nanomaterials for clinical use will be key directions for future research.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 81970976), the Key research and development plan of Gansu Province (No. 23YFGA0009, 22YF7GA007), the Joint Research Foundation of Gansu Province (No. 24JRRA950), the Basic Research expenses of Central Universities (No. lzujbky-2024-23), the Research Start-up Fee for Talents Introduced by "Double First-class Guidance Special Program" (No. 561119203), and the Youth Science and Technology Talent Innovation Project of Lanzhou (No. 2024-QN-84).

Conflicts of interests

The authors declare that there are no conflicts of interest.

Authors' contribution

Investigation, data management, and writing of the original draft, Qicheng Li and A-xue Jiang; investigation, data management, and writing work, Mengya Zhang and Lili Yang; setting up the overarching structure of the article, blueprint for its organization and layout, Shanchuan Guo and Shengjie Xiao; support in resource provision, and contribution to the writing process through involvement in reviewing, editing, visualization, and supervision, Yu Ma and Rong Wei. All authors have read and agreed to the published version of the manuscript.

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