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REVIEW

Research Progress of SN38 Drug Delivery System in Cancer Treatment

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Abstract: The active metabolite of irinotecan (CPT-11), 7-ethyl-10-hydroxycamptothecin (SN38), is 100–1000 times more active than CPT-11 and has shown inhibitory effects on a range of cancer cells, including those from the rectal, small cell lung, breast, esophageal, uterine, and ovarian malignancies. Despite SN38's potent anticancer properties, its hydrophobicity and pH instability have caused substantial side effects and anticancer activity loss, which make it difficult to use in clinical settings. To solve the above problems, the construction of SN38-based drug delivery systems is one of the most feasible methods to improve drug solubility, enhance drug stability, increase drug targeting ability, improve drug bioavailability, enhance therapeutic efficacy and reduce adverse drug reactions. Therefore, based on the targeting mechanism of drug delivery systems, this paper reviews SN38 drug delivery systems, including polymeric micelles, liposomal nanoparticles, polymeric nanoparticles, protein nanoparticles, conjugated drug delivery systems targeted by aptamers and ligands, antibody-drug couplings, magnetic targeting, photosensitive targeting, redox-sensitive and multi-stimulus-responsive drug delivery systems, and co-loaded drug delivery systems. The focus of this review is on nanocarrier-based SN38 drug delivery systems. We hope to provide a reference for the clinical translation and application of novel SN38 medications.

Keywords: SN38, drug delivery system, cancer

Introduction

Camptothecin, a pentacyclic alkaloid isolated by Well et al from the Chinese dove plant Camptotheca acuminata in 1966,[1] has drawn considerable interest from academics. More research has revealed that topoisomerase I (Topo I) inhibitors such as camptothecin and its derivatives bind to Topo I to create a CPT-Topo I-DNA ternary complex, which prevents DNA synthesis and ultimately causes cancer cells to die.[2] The first comedogenic derivatives to receive FDA approval were topotecan (TPT) and irinotecan (CPT-11), which are now frequently used as chemotherapeutic medicines. For the treatment of small-cell lung and ovarian cancers, TPT has been licensed as a second-line agent, and CPT-11 has been approved as a first-line agent for the treatment of metastatic colorectal malignancies.[3] However, CPT-11 is an inactive prodrug, which needs to be converted to its active metabolite SN38 by hepatic carboxylesterase activation, and carboxylesterase has inter-individual variability and low activity. Meanwhile, only 2~8% of CPT-11 is converted to SN38 in vivo,[4] which is converted to the water-soluble inactive metabolite SN38 glucuronide (SN38G) in the liver by ureidoside diphosphate glucuronosyltransferase (UGT1A1), and SN38G excreted in the intestine is converted to SN38 by the bacterial enzyme β-Glucosidase (β-Glu). Free SN38 directly affects healthy cells like the intestinal epithelium, which can have negative effects including delayed-onset diarrhea.[5,6]

7-Ethyl-10-hydroxycamptothecin (SN38) is the main active metabolite of CPT-11, which has been shown to be effective against a variety of tumor cells, including those from colorectal, small cell lung, lymphoma, breast, esophageal, and uterine cancers, as well as in the treatment of many types of tumors, such as colorectal, small cell lung, and lymphatic carcinoma, breast, esophageal, uterine and ovarian cancers.[7] The biological activity is 100–1000 times more

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than that of CPT-11[8] and it does not require hepatic carboxylesterase for metabolization, which eliminates the drug's individual variations.

However, the relatively high hydrophobicity and instability of SN38 at physiological pH limit its clinical translation. SN38 has a molecular weight of 392.4 g/moL, an ionization constant of pKa of 2.01 and an oil-water partition coefficient of logP of 2.65 at 25°C, and is virtually insoluble in water as well as in most medical solvents and oils, but only in 0.5% dimethyl sulfoxide, formic acid, and acetic acid. So the direct production of liquid formulations are limited. In addition, the E-ring lactone structure of SN38 is subject to reversible PH-dependent hydrolysis, which is shown in (Figure S1). When SN38 is exposed to a physiological environment at pH = 7.4, the lactone ring partially hydrolyzes to a carboxylate form without having any therapeutic effect; when pH 9.0, the lactone ring is hydrolyzed and SN38 only exists in the carboxylate form.[9] At pH 4.5, the E-ring maintains a stable lactone ring structure. Therefore, a variety of drug delivery strategies, including drug delivery systems and the creation of prodrugs, have been studied and developed to overcome the shortcomings of SN38, which is difficult to be soluble and susceptible to ring-opening and inactivation in physiological environments.

Currently, some SN38 prodrugs such as DTS-108,[10] EZN-2208,[11] and SN38 antibody-drug coupling (ADC) IMMU-132[12] and IMMU-130[13] are in clinical trials. These prodrugs have structural modifications and antibody coupling to C_{10} and C_{20} of SN38, which improves the solubility of the drug, the stability of the lactone ring, and the ability of the drug to target tumors.[14] Aside from the prodrug approach, the construction of an SN38-based drug delivery system has distinct advantages in terms of enhancing SN38 solubility, stability, and targeting. In recent years, drug delivery system for tumor therapy has attracted great interest, and many nano-formulations of anticancer drugs, such as Doxil and Abraxane, have been used in clinical trials.[15] Drug delivery systems show great potential in antitumor. Therefore, the aim of this paper is to provide a review of SN38-based drug delivery systems including passive-targeted drug delivery systems, active-targeted drug delivery systems, physicochemical-targeted drug delivery systems and co-loaded drug delivery systems (Figure S2).

Passive Targeted Drug Delivery System

Passive targeting refers to the natural in vivo enrichment of drugs in cancer tissues through the enhanced permeability and retention (EPR) effect due to the large number of immature neovascularization in cancer tissues, the high perfusion and high permeability of the tumor, and the imperfect drainage of the lymphatic system in the tumor distribution characteristics.[16] Passive targeting delivery systems can improve the pharmacokinetic properties of drugs, increase drug efficacy and reduce drug toxicities.[17] Usually, passive targeting systems utilize biodegradable, safe, non-toxic, biocompatible and non-immunogenic carrier materials, such as liposomes, solid lipid nanoparticles, polymeric micelles, and dendrimers (Table S1).

Polymeric Micelles

Polymer micelles are self-assembled encapsulations of insoluble pharmaceuticals by blocking copolymers in water by hydrophobic interaction, electrostatic interaction, and other driving forces to create micellar solutions with nanostructures that range in size from 10 to 100 nm.[18] It is characterized by small particle size, stable structure, solubility, and low toxicity. Polymer micelles encapsulating a large number of hydrophobic drugs have better water solubility, which greatly improves drug solubility, while polymer micelles show improved pharmacokinetic properties in preclinical animal models, as well as increased efficacy with a higher safety profile for medicinal medicines.[19] Zhang et al[20] linked the OEG chain as a hydrophilic part on the C_{20} ester bond of SN38 to obtain the amphiphilic molecule OEG-SN38 and self-assembled it into OEG-SN38 nanomicelles in water [Figure S3(A)]. The nanomicelles were highly stable in PBS, and the release rate was only 4.71% after 35 h. In vitro cellular assays showed that OEG-SN38 micelles had stronger blocking effects on G2/M stage tumor cells than CPT-11, with IC_{50} values of 0.032, 0.27, 0.30, 1.61, and 1.61 μg/mL in SKOV-3, MCF-7, BCap37, HT-29, and KB cell lines, respectively, which were significantly higher than the antitumor activity of CPT-11 on the above mentioned cell lines (IC_{50} values of 6.53, 4.41, 21.65, 49.65 and 18.29 μg/mL, respectively). In addition, in vivo experiments conducted in SKOV-3 human ovarian xenograft tumor model and BCap37 human breast xenograft tumor model both showed significant differences in the anti-tumor effect of OEG-SN38 micelles compared to CPT-11, which were (70.03±6.30)% vs (84.95±6.54)% and (72.51%±4.97)% vs (8form micelles [Figure S3(B)]. In vitro

cellular assays showed that $mPEG_{2K}$-$PLA_{1.5K}$-SN38 possessed stronger cytotoxicity (IC_{50}=0.25 μg/mL) and apoptosis-inducing ability than CPT-11 and $mPEG_{2K}$-SN38, which might be related to the stronger cellular uptake of $mPEG_{2K}$-$PLA_{1.5K}$-SN38 into BEL-7402 human hepatocellular carcinoma cells. Meanwhile, the in vivo distribution study in nude mice BEL-7402 cell transplantation model demonstrated that DiR-labeled $mPEG_{2K}$-$PLA_{1.5K}$-SN38 was distributed in all organs throughout the body within 2 h and concentrated in the tumor site within 24 h, whereas $mPEG_{2K}$-SN38 was mainly concentrated in the liver. Therefore, at the same dose, $mPEG_{2K}$-$PLA_{1.5K}$-SN38 (1042 mM) showed a significant tumor inhibition rate compared to $mPEG_{2K}$-SN38 (1837 mM) at 30 days. Duan et al[22] synthesized CS-g-PCL copolymers with different grafting ratios as carriers using methanesulfonic acid as a solvent and catalyst to incorporate SN38 into micelles. As the content of grafted PCL increased, the encapsulation rate and drug loading increased. In vitro release assays confirmed by HPLC showed that after 12 h of PBS incubation, only 22.4% of SN38 remained in the lactone ring form and more than 88% of the lactone ring was preserved when SN38 was incorporated into CS-g-PCL. In vitro cellular experiments with the L929 cell line revealed that the formulation was less cytotoxic in vitro than free SN38.

Sadat et al[23] developed mPEO-b-PCCL/SN38 and mPEO-b-PBCL/SN38 polymeric micelles to improve the solubility of SN38. The IC_{50} values of the self-assembled mPEO-b-PBCL/SN38 and mPEO-b-PCCL/SN38 micelles against the human colorectal cancer cell lines HCT-116, HT-29 and SW620 were (0.11 ± 0.04) μM, (0.04±0.02) μM (HCT-116); (0.39 ± 0.16) μM, (0.08±0.04) μM (HT-29); (0.10 ± 0.04) μM, (0.02±0.01) μM (SW620), which were significantly more toxic than irinotecan (6.94±2.51) μM (HCT-116), (11.35±4.04) μM (HT-29) and (6.63±3.64) μM (SW620). In addition, hemolytic assay showed that mPEO-b-PBCL/SN38 micelles did not cause hemolysis and mPEO-b-PCCL/SN38 had some hemolytic effect (Figure S4). Djurdjic et al[24] prepared PAA_{13}-PCL_{35}-PAA_{13} loaded SN38 self-assembled polymer micelles by nanoprecipitation. Growth inhibition studies and DNA fragmentation analysis of SW480 cells line clearly showed that the micelles increased the growth inhibitory effect and the DNA fragments compared to the free SN38 solution. Liu et al[25] created two SN38 macromolecular prodrugs with different coupling locations, CS-(10s)SN38 and CS-(20s)SN38, which were able to self-assemble into micelles in an aqueous solution to increase SN38's solubility in water. The half-inhibitory concentrations of CS-(20s)SN38 and CS-(10s)SN38 on CT26 cells were (1.8±0.4) × 10^3 nmol/L and (3.5±0.2) × 10^3 nmol/L, and were 25.9-fold and 13.3-fold greater than those of CPT-11. The in vivo assay also revealed that, at the same dose, CS-(20s)SN38 significantly decreased tumor growth in CT26 xenografted BALB/c mice by 64.7%, compared to CPT-11 and CS-(10s)SN38.

Lipid Nanoparticles

Liposomes

Liposomes are vesicle-like substances made of cholesterol and phospholipids that are similar to the bilayer of biological membranes, and they have been regarded as the most popular nanocarrier material since their discovery due to their unique advantages.[26] Liposomes are less immunogenic and histocompatible, making them safer to utilize as carriers for targeted drug delivery. They can also improve medication water solubility, increase drug stability, and play a role in controlled release.[27] They can also readily be functionalized by different parties to increase the circulating half-life, hit a specific target, encourage cellular uptake, and even trigger responsive drug release. And the FDA has approved a variety of liposomes containing small-molecule drugs for clinical applications.[28–30] Wu et al[31] combined palmitic acid with the C10 ester bond of SN38 to produce SN38's lipophilic prodrug, SN38-PA. It was then encapsulated into a long-circulating liposome carrier by a film dispersion technique [Figure S3(C)]. Compared to CPT-11, SN38-PA has a more reliable closed-lactone structure, and it can be converted to SN38 more efficiently in rat plasma, so compared with CPT-11, it showed stronger cytotoxicity in S180, MCF-7, LLC, and HCT-116 cells, which was 16.18–328.39 times of CPT-11 toxicity. Pharmacokinetics showed that SN38-PA liposomes prolonged the half-life of SN38, resulting in a 9.7-fold decrease in its clearance, and the mean area under the curve was 7.5-fold than that of CPT-11, while SN38-PA liposomes were able to release free SN38 in various tissues. Pharmacodynamic assays demonstrated that the tumor inhibitory rate of SN38-PA on S180 loaded mice was 1.61-fold than that of CPT-11, and there was no obvious toxicity. Fang et al[32] prepared a precursor drug (LA-SN38) by linking the unsaturated fatty acid linoleic acid (LA) with lipophilic SN38 and encapsulated it into PEG-modified liposomes (LipoNP). Cellular uptake assays showed that LipoNP was able to promote more SN38 into HCT-116 than supramolecular nanoparticles

(SNP 1), and decreased cellular uptake by RAW264.7 macrophages, suggesting that PEG-encapsulated liposomes can accelerate tumor cells' absorption of chemotherapy medicines while slowing macrophage clearance. Thus, in vitro cytotoxicity showed that LipoNP exhibited stronger cytotoxicity than SNP and CPT-11 in several colon cancer cell lines. In addition, in vivo assays in the human colorectal HCT-116 tumor model demonstrated that intravenous LipoNP inhibited tumors at a rate of 81.1%, which was higher than CPT-11 (57.9%) and SNP 1 (68.3%). Du et al[33] developed liposomes based on SN38 phospholipid concatenated (Di-SN38-PC) prodrugs [Figure S3(D)]. The cytotoxic effect of Di-SN38-PC liposomes on MCF-7 and HBL-100 was comparable to that of SN38. In addition, pharmacokinetic assays demonstrated that Di-SN38-PC liposomes have a longer blood circulation time compared to the parent drug. Shirazi et al[34] prepared a nanostructured lipid carrier containing SN38 (NLC-SN38). NLC-SN38 showed significant cytotoxicity against U87MG glioblastoma cells compared with the free drug; after 24 h of incubation, the IC_{50} value of NLC-SN38 was about 2.12 μg/mL, and that of free SN38 was 8.44 μg/mL; when the incubation time was prolonged to 72 h, the IC_{50} value of NLC-SN38 was 0.06 μg/mL, while the free drug was 0.38 μg/mL, indicating that NLC-SN38 was more effective than the free drug SN38. Liu et al[35] prepared SN38-phospholipid complex (SN38-PC) and loaded it into lipid nanoparticles using high-pressure homogenization to form SN38-phospholipid nanoparticles (SN38-PC-LNs). SN38-PC-LNs exhibited cytotoxicity against HT-29, HepG2, A549, and MCF-7 tumor cell lines relative to SN38, the formulation decreased the IC_{50} value of HT-29 from (1.54±0.05) μg/mL to (0.34±0.16) μg/mL, the IC_{50} value of HepG2 from (8.54±0.36) μg/mL to (0.34±0.07) μg/mL, and the IC_{50} value of A549 from (5.28±0.97) μg/mL to (0.24 ±0.01) μg/mL for A549, IC_{50} value from (6.89±1.04) μg/mL to (0.70±0.04) μg/mL for MCF-7, and the cytotoxicity effect of SN38-PC-LNs on these tumor cell lines was significantly higher than that of CPT-11 in all of them. In vivo experiments showed that, at the same concentration (8 mg/kg), the tumor inhibition rates of SN38-PC-LNs, SN38, and CPT-11 treatment groups were 71.80%, 62.13%, and 48.56%, respectively. Moreover, Xing et al[36] designed a moeixitecan-loaded liposomal nanoparticles (MLP) by loading a lipophilic SN38 prodrug moexitecan into liposome nanoparticles via ethanol injection. Nanoliposomes have the advantage of high biocompatibility and the ability to increase solubility and bioavailability and utilized to deliver hydrophilic and lipophilic medications. In vitro cellular assays showed that MLP had significant cytotoxicity compared with CPT-11, and the apoptosis rate of HT-29 cells after 48 h of MLP incubation was 46.4%, which was higher than that of the CPT-11 group (29.4%). The in vivo test showed that the tumor inhibition rates of MLP and CPT-11 on HT-29 colorectal transplantation tumor model mice were (66.86±6.54)% and (46.06±6.30)%, respectively.

Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLN) are solid natural or synthetic lipids (eg lecithin, triacylglycerol, etc.) used as carriers for pharmaceuticals, with the medications enclosed in the lipid cores to form a solid pellet drug delivery system with particle sizes ranging from 50 to 1000 nm.[37] SLN has several benefits, including excellent biocompatibility, stable physicochemical properties, low toxicity, and high safety. Meanwhile, SLN has the potential to be a drug carrier that can reduce discomfort in the gastrointestinal tract, enhance drug loading, stop drug efflux, and adjust drug release.[38] Mosallaei et al[39] prepared solid lipid nanoparticles SLN-SN38 and PEG-SLN-SN38 containing SN38 using ultrasound technology. Compared with the SN38 solution (SOL-SN38), the cytotoxicity of SLN-SN38 and PEG-SLN-SN38 on C-26 and HT-116 cell lines was significantly increased after 48 hours of exposure, with IC_{50} values of (10,167.7 nM vs 1148.0 nM vs 886.4 nM in C-26 cell lines) and (282.7 nM vs 220.6 nM vs 217.3 nM in HCT-116 cell lines), respectively. In addition, comparing the survival rates of C-26 xenograft tumor mice models for 60 days, all mice died after 46 days of treatment with 5% glucose and irinotecan, the blank group and PEG-SLN-SN38 (20 mg/kg) died after 50 days and the SLN-SN38 (20 mg/kg) group had a 14% survival rate at 60 days.

Polymer Nanoparticles

Biodegradable polymer nanoparticles are frequently utilized in the field of pharmaceuticals due to the excellent properties such as non-toxic small molecules for the explained products and the obvious slow and controlled release effect of drugs.[40] The widely used biodegradable materials mainly include dextran, chitosan, alginate, polylactic acid (PLA), polylactic acid-hydroxyglycolic acid copolymer (PLGA) and so on. Cheng et al[41] developed linoleic acid coupled SN38 (LA-SN38) nanoparticles (EBNPs) using

biodegradable polyethylene oxide polyoxybutane (PEO-PBO). EBNP was able to efficiently manage the release, with just 34.93% of the SN38 released after 24 hours, but 61.79% of the (LA-SN38 NPs) SNPs were released at the same time. The IC_{50} values of EBNP on human colon cancer cells, HT-29 and HCT-116, were 0.63 and 5.56 μg/mL, respectively, which were significantly lower than SNPs and CPT-11. EBNP may evade macrophage phagocytosis and boost tumor cell uptake, increasing tumor targeting. The in vivo imaging results revealed that EBNP had the highest fluorescence intensity in tumor tissues, outperforming CPT-11 and SNPs. Following EBNP treatment, the maximum degree of tumor necrosis was seen.

Protein Nanoparticles

Protein nanoparticles are highly structured nanoparticles self-assembled from protein molecules with a nanoscale, and protein-based nanoparticles have more advantages than other nanocarriers, including biocompatibility, bifunctionality, biomolecular recognition, abundant renewable sources, and the ability to biodegrade into small-molecule amino acids. More importantly, protein nanoparticles can be precisely genetically engineered to use functional sites with specific locations for specific cell targeting and protein delivery.[42,43] Currently, a variety of proteins extracted from animals and plants have been used to construct protein nanoparticles, including collagen, albumin, casein, and soy protein. In recent years, the study of albumin as a nanomedicine carrier has received great attention. The most prevalent protein in plasma is albumin, and it plays a crucial function in controlling blood homeostasis and transporting related lipophilic substances within the blood. Albumin has a strong binding capacity to many drugs and is non-immunogenic, highly stable, and has good drug-carrying properties,[44] and has excellent biological properties in nano delivery system. Sepehri et al[45] created human serum albumin (HSA) couplings of SN38 by derivatizing the SN38 20-hydroxyl group with glycine and adding succinyl groups to covalently connect HAS [Figure S3(E)], resulting in two conjugates with distinct molar ratios (SN38: HSA 15:1 and 60:1). Comparing the IC_{50} values of SN38-HSA-15, SN38-HSA-60 and irinotecan in HT-29 human colon cancer cells, the lower molar ratio SN38 coupling was the most cytotoxic, being 5.16-fold more potent than that of the higher molar ratio SN38 coupling and 3- to 14-fold more potent than that of irinotecan. Biodistribution showed higher plasma levels of SN38-HSA (5.2 ± 2.25)% compared to free SN38 (1.9 ± 0.65)%, and the coupling accumulated more in the liver and spleen, but blood cytotoxicity assays showed no toxic effects on the liver and spleen. Yao et al[46] covalently attached SN38 to the free cysteine-34 of bovine serum albumin (BSA)'s sulfhydryl group of bovine serum albumin to obtain a prodrug BSA-SN38 conjugate (BSA: SN38=1: 1) [Figure S3(F)], which improved the solubility and antitumor effect of the drug. In vivo study showed that BSA-SN38 conjugate group (0.21 ± 0.15 g) could reduce the average tumor weight of CT-26 Balb/c colon cancer model mice compared with the untreated control group (4.74 ± 0.73 g).

Active Targeted Drug Delivery Systems

Active targeting refers to giving drugs or their carriers the ability to actively bind to their targets, which mainly involves attaching probe molecules such as antibodies, peptides, glycoconjugates, nucleic acid aptamers, etc. It can bind specifically to target molecules to the surface of the drug or its carrier, thereby enabling the drug to be directed to a specific tissue or organ.[47] This targeting strategy can evade the action of the mononuclear phagocytosis system and allow the maximum accumulation of the drug at the target site, improving the anti-cancer effect of the drug while reducing off-target toxicity (Table S2).

Aptamer and Ligand

Active targeted drug delivery systems that rely on ligand/aptamer specific binding can induce receptor-mediated endocytosis, greatly facilitating selective accumulation of drugs in target cells and organelles while improving in vivo circulation time, tissue distribution, and uptake by tumor cells with nano delivery systems.[48]

Folate Receptors

Receptors for folate, sometimes called folate-binding proteins are one of the three main types of folate transporters. It has been shown[49,50] that folate receptors $FOLR_1$ and $FOLR_2$ are overexpressed in a variety of cancers, while their expression is restricted in healthy tissues, therefore preparation of folate-coupled nanodrug systems that bind and internalize into cells through folate receptor-mediated endocytosis can achieve cell-specific targeting. Fang et al[51] prepared folate-

modified SN38-targeted liposomes. Cellular uptake studies showed that SN38-targeted liposomes were efficiently taken up into MCF7 breast cancer cells with significantly higher cytotoxicity (IC_{50}=0.11 μM) than free SN38 solution (IC_{50} =0.37 μM). Imaging analysis suggested that the targeted liposomes were equally capable of selectively targeting MCF7 tumors in vivo. In addition, in vivo toxicity tests showed that SN38 liposomes were able to significantly increase platelet levels in BALB/c mice to (347.00 ± 23.59) × 10^9/L, ameliorating the reduction in platelets, and no adverse effects such as diarrhea were observed (Figure S5). Ebrahimnejad et al[52] used poly-lactide-co-glycolide-polyethylene glycol-folate (PLGA-PEG-FOL) conjugate to prepare SN38 nanoparticles. PLGA-PEG-FOL could prolong drug release in vivo and was able to sustain release up to (23.1 ± 2.01)% of the drug loading. The targeting nanoparticles were modified with folic acid to enhance the cytosolic uptake of HT-29 cells as well as their cytotoxicity, with IC_{50} values of (30 ± 1.1)% for folic acid-modified nanoparticles, (51.5 ± 2.3)% for unmodified nanoparticles, and (90.1 ± 3.2)% for free SN38 in 48 hours.

Integrin Receptors

Integrins, or integrins, are a class of heterodimeric transmembrane glycoprotein receptors that mediate mammalian cell adhesion and signal transduction, consisting of α and β subunits, and are involved in the regulation of various cellular processes such as cell migration, invasion, and proliferation and intercellular signaling, cell adhesion and the process of vascular neogenesis. Integrins are highly expressed in all tumor tissues and neovascular endothelial cell membranes, and their expression is associated with tumor migration and angiogenesis. Among them, integrin $\alpha v\beta_3$ is the most widely studied. Alibolandiet et al[53] loaded SN38 on chitosan coated PLGA nanoparticles and achieved targeted delivery of integrin receptor $\alpha_v\beta_3$ on tumor vascular surface by tetrac (tetraiodothyroacetic acid) modification, which in turn downregulated vascular supply to tumor tissue by blocking the binding of $\alpha v\beta_3$ to its agonist thyroid hormone. Tetrac modification increased the uptake and cytotoxicity of $\alpha v\beta_3$ high-expression Caco-2, C26 cell lines to Tetrac-CS-PLAG-SN38, with no significant difference in integrin-negative control cell lines. The cytotoxicity assay showed that the survival of Caco-2 (0.95 μg/mL) and C26 cells (1.61 μg/mL). In C26 tumour-bearing mice, Tetrac-CS-PLGA-SN38 showed strongest anti-tumor effect while significantly improved survival rate of mice. In addition, an in vivo angiogenic CAM model showed that free tetrac inhibited FCF2-induced angiogenesis by 31%, Tet-CS-PLAG-SN38 by 100%, and CS-PLAG-SN38 by no inhibition, indicating that Tet-CS-PLAG-SN38 could enhance anti-angiogenic effect. Li et al[54] prepared an RGD modified sub-5 nm ultrafine iron oxide nanoparticles (uIONP) coated with amphiphilic poly(ethylene glycol)-*block*-allyl glycidyl ether (PEG-*b*-AGE) polymer for delivering SN38 (RGD-uIONP/SN38), in which RGD peptide was able to target $\alpha_v\beta_3$ integrin receptors highly expressed in U87MG cells and enhance the EPR effect, which in turn enhanced the targeting of SN38 to glioblastoma. Cell confocal fluorescence imaging and blocking assays showed that U87MG cells could specific uptake of RGD-uIONP/SN38, and thus the cytotoxicity of RGD-uIONP/SN38 on U87MG glioblastoma cells (IC_{50}=30.9 ± 2.2) nM was significantly higher than that of free SN38 (IC_{50}=1770 ± 148) nM. According to an in vivo study conducted on an orthotopic mouse model of GBM, 11.5% injected RGD-uIONP/SN38 (10 mg Fe/kg) is delivered to the tumor specifically, resulting in a substantial 41% increase in animal survival over those treated with SN38 alone.

IGF-1R

The insulin-like growth factor 1 receptor (IGF-1R) is a transmembrane receptor discovered on human cell surfaces that is activated by the hormone insulin-like growth factor 1 (IGF-1) and another related hormone, insulin-like growth factor 2 (IGF-2). IGF-1 primarily promotes mitosis, regulates hormone production and secretion in the body, and influences cell chemotaxis, immunity, and migration.[55] It is widely believed that IGF-1R has a significant impact on cancer and is highly expressed in a variety of malignancies. uLONP/SN38, an SN38 loading amphiphilic polymeric ultrafine iron oxide nanoparticle with a particle size of 3.5 nM, was prepared by Xue et al[56] and a targeting ligand (IGF-1) for targeting the surface of pancreatic cancer cells with highly expressing IGF1R was used as a modifier (IGF1-uLONP/SN38). The resulting uIONP/SN38 exhibited stable drug loading and release in tumor mesenchymal and lysosomal settings. Imaging assays demonstrated that IGF1-uLONP/SN38 enhanced the NIR signal of IGF-1R high-expression cell lines, indicating that IGF1 enhanced the specific targeting ability of uLONP/SN38, and thus the IC_{50} values of IGF-1-uLONP/SN38 on MiaPaCa-2 and panc02 cells [(11.8±2.3) nM, (20.8±3.5) nM] were also significantly lower than those of free SN38.

CD133 Receptor

CD133 is one of the classical surface markers of tumor stem cells (CSC), which are associated with self-renewal and hyper-differentiation potential of tumor cells and can mediate tumor growth, heterogeneity and drug resistance.[57] Targeting CSC is a novel anticancer tool, and CD133 has been shown to be high expression in a wide range of solid tumors.[58] Therefore, CD133 is expected to be a new candidate as a therapeutic target for tumor cells or CSCs. Alibolandi et al[59] coupled free SN38 to a poly ethyleneglycolated acetylated carboxymethylcellulose backbone to form self-assembled nanoparticles (PEG-AcCMC-SN38), subsequently, the self-assembled NPs were covalently bounded to an RNA aptamer against CD133-expressing HT29 cells. Targeting self-assembled nanoparticles significantly increased cellular uptake in HT-29 cell lines overexpressing CD133, as demonstrated by fluorescence microscopy and flow cytometry. Therefore, aptamer-modified PEG-AcCMC-SN38 boosted SN38 cytotoxicity on HT-29 cells much more than non-targeted PEG-AcCMC-SN38, while exhibited no significant difference on CHO cells.

MUC1

It was discovered that MUC1 expression was substantially connected with tumor differentiation and that it increased with increasing malignancy. MUC1 is a glycoprotein that is overexpressed in tumor cells.[60] MUC1 has the effects of promoting adhesion of tumor cells to normal cells and reducing adhesion between tumor cells, promoting tumor cell genesis, and inhibiting tumor cell apoptosis in tumor cells.[61] Sayari et al[62] developed a targeted drug delivery system (CS-SN38-Apt NPs) with n-carboxyethyl chitosan ester (CS-EA) as a carrier and MUC1 DNA aptamer as a targeting agent. Confocal microscopy confirmed that CS-SN38-Apt NPs were able to be effectively taken up by MUC1-positive HT-29 cells than non-targeted drugs. MTT assay results further confirmed that the viability of HT-29 cells lines treated with free SN38, CS-SN38 NPs and CS-SN38-Apt NPs were 57.59%, 73.23%, and 55.32%, indicating that the toxicity of CS-SN38-Apt NPs on HT-29 cells was greater than that of non-targeted NPs and comparable to that of the free drug.

Glucose Transporter

Glucose transporter subtype I (GLUT1) and lectin receptor are the two glycosyl targeting receptors and transporters that have received the most research. GLUT1 is a potential tumor target since it is aberrantly produced in a variety of cancers to support the basal metabolism of glucose in tumor cells and to control glucose absorption by tumor cells.[63] For this purpose, a glucosamine-modified SN38 precursor drug (PLA-SN38) delivery nanoplatform (Glu-SNP) for orienting "Sweet Tooth" was developed by targeting GLUT1,[64] a potential therapeutic target overexpressed in gastric cancer cells. The nanoparticles exhibited slow-release properties with (33.00 ± 2.20)% drug release at day 14. In vitro assays showed that the IC_{50} of SN38, nontargeted PLA-SN38-loaded nanoparticles (SNP) and Glu-SNP in MKN45 was (68.36 ± 3.826), (167.7 ± 9.321) and (125.8 ± 8.684) nM, respectively, and in SGC-7902 cells was (63.48 ± 5.936), (208.82 ± 20.34) and (154.3 ± 16.33) nM, suggesting that glycosylation modification enhanced the in vitro antitumor activity of Glu-SNP. Moreover, Glu-SNP was found to enhance the specific intracellular uptake and targeting ability of nanoparticles to gastric cancer, and in vivo distribution imaging in MKN45 transplanted nude mouse model showed that Glu-SNP detected higher fluorescence signal at the tumor site than SNP. In addition, Glu-SNP and SNP inhibited tumor growth in MKN45 transplanted nude mice by (91.5 ± 1.49)% and (93.9 ± 1.08)%, respectively, which was markedly greater than CPT-11 (20.6 ± 13.2)% (Figure S6). Yang et al[65] prepared three SN38-glucose couples by modifying the 20-hydroxyl group of SN38 (Glu-SN38) [Figure S7(A)] for targeting overexpressing GLUTs in tumor cells. Adding 100 mM glucose to the medium caused, the IC_{50} values of the most active of these SN38-glucose couplers, 5b and irinotecan, were altered 8.3-fold and 1.3-fold, respectively, while 5b showed a higher selectivity for the human colorectal cancer cell-line HCT-116 compared to other negative control cells. Thus, 5b (31.7%) exhibited a stronger ability to induce apoptosis in HCT-116 cells compared to irinotecan (11.7%). Additionally, in vivo tests revealed that 5b dramatically slowed the growth of HCT-116 tumor transplantation BALB/c nude mouse model.

EDB Receptor

It has been demonstrated that the matrix glycoprotein fibronectin (FN) goes through alternative splicing specifically during carcinogenesis and organ development. Ectodomain-B (EDB) FN, one of the splice variants, is not typically seen in healthy adult tissues and is regarded to be a sign of tumor angiogenesis. Additionally, it has been discovered that the

density of tumor microvessels correlates with the expression of ED-B FN, which is specifically localized to tumor cells.[66] Kim et al[67] prepared a cancer-targeted self-assembled nanoparticle (APT_{EDB}-SN38 NPs) via conjugating fibronectin extra domain B-specific peptide (APT_{EDB}) and SN38. In vitro assays showed that the cytotoxicity of free SN38 was far greater than that of APT_{EDB}-SN38 NPs, with IC_{50} values of 135.4 nM and 472.6 nM in LLC mouse lung cancer cells and 20.32 nM and 318.3 nM in U87MG, respectively. According to in vivo pharmacokinetic findings, the half-lives of ATP_{EDB}-SN38 NPs and CPT-11 were 1.877 h and 0.44 h, respectively, with AUC values of 109 ng/h/mL and 85.3 ng/h/mL. According to in vivo tests performed on C57BL/6 mice bearing EDB-positive tumors, APT_{EDB}-SN38 NPs demonstrated greater tumor suppression (34%) than non-relevant aptide (APT_{SCR})-SN38 NPs (9%) and CPT-11(8%).

Antibody-Drug Conjugate

Antibody-drug conjugate (ADC) is an emerging class of drug candidates developed by fusing or coupling monoclonal antibodies with cytotoxic drugs.[68] They can deliver cytotoxic drugs directly into target tumor cells, exploiting both the specificity of monoclonal antibodies and the high activity and lethality of small-molecule oncology drugs, an approach that reduces systemic exposure to cytotoxic payloads compared to other delivery modalities.[69] Among them, the DNA topoisomerase of camptothecin class I Inhibitors are currently the most promising payload that can cleave single stranded DNA, inhibit topoisomerase repair mechanisms, and cause DNA damage and cell apoptosis. At present, this type of toxin has been approved as an SN38-based ADC, IMMU-132.[70] In addition, IMMU-130, IMMU-140, and others are currently in the development stage (Table S3).

IMMU-132

Sacituzumab govitecan (IMMU-132) is an ADC that consists of a hydrolyzable linker CL2A connecting SN38 to a humanized monoclonal antibody against trophoblast cell surface antigen 2 (Trop-2) (hRS7). Trop-2, as a transmembrane calcium signal transducer, is highly expressed in a variety of tumor types including breast triple-negative breast cancer (TNBC) and HR+/HER2- advanced breast cancer, while its expression in normal tissues is limited, and it has been found in more than 85% of epithelial tumors,[71] which has a wide range of applications. In April 2021, IMMU-132 was approved as the first ADC for the treatment of patients with TNBC for adult patients with unresectable locally advanced or metastatic TNBC who have received at least 2 therapies (at least one of which was for metastatic disease) with significant efficacy. This approval is based primarily on the clinical trials of IMMU-132-01 and ASCEN, which demonstrated a favorable objective remission rate (ORR) of 33.3%, a clinical benefit rate (45.4%)[72] and a significantly improved progression-free survival (PFS) relative to the monotherapy group (5.6 months vs 1.7 months) and median overall survival (OS) (12.1 months vs 6.7 months).[73] On February 3, 2023, the FDA approved IMMU-132 for patients with HR+/HER2-advanced breast cancer who have received prior endocrine therapy and ≥2 lines of systemic therapy for metastatic disease. The approval was based on a global, multicenter, open-label Phase III clinical trial, TROPiCS-02, which demonstrated a higher median PFS (5.5 months vs 4 months) and median OS (14.4 months vs 11.2 months) in the IMMU-132 group compared to the chemotherapy groups.[74,75] Meanwhile clinical trials of IMMU-132 in the treatment of locally advanced or metastatic urothelial carcinoma,[76] metastatic non-small cell lung cancer (NSCLC),[77] and small cell lung cancer (SCLC)[78] are advancing. In addition, IMMU-132 has demonstrated significant activity against endometrial cancer including endometrial cancer, prostate cancer, brain metastases and glioblastoma.[79]

IMMU-130

IMMU-130 is an ADC consisting of humanized anti-carcinoembryonic antigen (CEACAM5) antibodies hMN-14 and SN38 linked by CL2A.CEACAM5 is expressed in a wide range of solid tumors, especially in 80% of metastatic colorectal cancers (MCRC) and is now widely used as a prognostic marker for CRC. Sharkey et al[13] conducted preclinical trials and showed that in LS174T or GW-39 human colon tumor xenograft model mice, the IMMU-130 group of mice had AUC values 11–16 times higher than those of CPT-11, and that this delivery advantage was amplified by at least 30-fold when standardized for the SN38 equivalents injected against each product. Meanwhile, Dotan et al[80] conducted a phase I/II clinical trial of this drug in patients with refractory or recurrent metastatic colorectal cancer, which showed that 1 out of 86 patients achieved partial remission and again after the second course of treatment after treatment

interruption, with a sustained remission time of 2.7 years, the best overall remission for 42 patients was stable disease, and 27 patients had a tumor size and plasma carcinoembryonic antigen concentration were significantly reduced after treatment. In addition, the CBR was 29% and the median PFS and OS were 3.6 (95% CI 2.0–4.0) and 6.9 months (95% CI 5.7–7.8), respectively.

IMMU-140

As a member of the MHC class II antigens, HLA-DR is expressed in a wide range of hematological malignancies and solid tumors. Preclinical trials conducted by Cardillo et al[81] demonstrated significant efficacy of IMMU-140 compared to controls in seven models of human disease: acute lymphoblastic leukemia (ALL), chronic lymphoblastic leukemia (CLL), multiple myeloma (MM), acute myeloid leukemia (AML), diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma (HL) and melanoma. Furthermore, IMMU-140 demonstrated two distinct mechanisms of action in vitro: classical double-stranded DNA breaks and apoptosis via SN38, and non-classical apoptotic signaling by IMMU-114. These findings suggest that this medication may have advantages in therapeutic applications.

Trastuzumab-SN38 Antibody Drug Couple

Trastuzumab, developed for targeting the HER2 receptor in human breast cancer, was approved by the FDA in 1998 for the treatment of HER 2+ metastatic breast cancer (MBC) becoming the first HER2-targeted drug approved.[82,83] In recent years, with the deepening of research, trastuzumab-based ADCs targeting HER 2 have important applications in anti-breast cancer, ovarian cancer, and other cancer treatments. Yao et al[84] coupled SN38 with trastuzumab through three different linkers (more stable ester chain, pH-sensitive carbonate bond, and water-soluble PEG and carbonate bond) to prepare three ADC couplers (T-SN38 A, T-SN38 B, and T-SN38 C) and evaluated their efficacies for the treatment of ovarian cancer in vitro and in vivo. The drug-antibody ratios of the three couplers were 3.7, 3.2, and 3.4, respectively. In vitro cellular experiments showed that after exposing the SKOV3 cell line to each drug group for 72 h, the IC_{50} values of T-SN38 A, T-SN38 B, and T-SN38 C were (5.2 ± 0.3), (4.4 ± 0.7), and (5.1 ± 0.4) nM, respectively, which were stronger than those of free SN38 (IC_{50}=11.3±1.3 nM) and free trastuzumab (IC_{50}>1200 nM). In vivo experiments demonstrated that all three T-SN38 couplings inhibited tumors in Her2-positive human ovarian cancer xenograft model mice. Kobzev et al[85] synthesized a trastuzumab-SN38 antibody coupling (Cy5-Ab-ss-SN38) labeled by the near-infrared fluorescent dye Cy5 using a glutathione-responsive self-immolative disulfide carbamate as a linker, antibody coupling (Cy5-Ab-ss-SN38) labeled with the near-infrared fluorescent dye Cy5. The drug-antibody ratio was 2.0, and the fuel-antibody ratio was 0.7. Cytotoxicity experiments showed that the ADC increased the cytotoxicity of SKBR3 and BT474 by 8.5-fold and 4.1-fold compared with the free drug treatment, respectively, and showed no effect on MDA-MB-231 cells. Meanwhile, in vivo experiments showed that Cy5-Ab-SS-SN38 reduced the tumor volume in SKBR3-loaded mice from about 30 mm^3 to (10±1) mm^3 in 29 days, while it had no significant effect on tumors in MDA-MB-231-loaded mice in vivo.

Physio-Chemical Targeted Drug Delivery Systems

Tumor microenvironment is an ecological environment conducive to the growth of tumors formed during the process of tumor development, exhibiting biological features such as hypoxia, acidosis, high interstitial pressure, and high expression of specific enzymes or receptors, which are significantly different from normal tissues.[86] These specific tumor microenvironments provide more opportunities for precise treatment of tumors. For example, designing drug delivery systems that can mimic biological responsiveness based on the microenvironment at the tumor site enables on-demand responsive release of drugs.[87] Drugs can be released from these delivery systems in response to particular physical situations (eg magnetic response, light response) or chemical conditions (eg redox response, PH response), and are therefore also referred to as physiochemically targeted delivery systems (Table S4).

Magnetic Targeting

Magnetic targeting refers to the use of different properties of magnetic field response to achieve magnetic-targeting transportation of drugs with permanent magnetism, or magnetic thermotherapy that generates warming when an alternating magnetic field with high frequency is used, or magnetic resonance imaging to construct an integrated system

for diagnosis and treatment by using metal ions (iron, manganese, or gadolinium) with paramagnetism or superparamagnetism.[88] For example, Wang et al[89] attached SN38 to the surface of nuclear/shell-type Fe/Fe_3O_4 magnetic nanoparticles (MNPs) via a carboxylesterase cleavable linker (MNP-SN38) and loaded them into tumor-targeting dual-stable RAW264.7 cells [mouse monocyte/macrophage-like cells (Mo/Ma)]. The Tet-On Advanced system for intracellular carboxylesterase (InCE) expression in these cells caused the release of SN38 from the nanoplatform in response to the injection of doxycycline, as evidenced by HPLC analysis. When 2.0 mg of nanoparticles were dispersed in an alternating magnetic field, the MNP-SN38 nanoplatform demonstrated effective heating ability (SAR = 522 ± 40 W/g), with the temperature rising above 30 °C in just 5 minutes, which could trigger thermochemotherapy. In addition, the MTT assay revealed that the MNP-SN38 had low toxicity even at 320 μg/mL in Mo/Ma dual stable model cells.

Photosensitive Targeting

Due to UV-visible light sources, conventional light medication delivery methods have weak penetration depth and high dispersion to soft tissues. Near-infrared (NIR)-responsive systems are the latest generation of light-responsive nanomedicines, where tissue penetration deepens and scattering qualities decline with increasing wavelength.[90] For example, a brand-new, multipurpose NIR nano-agent ($_{cRGD}^{IR}NANO_{SN38}$) was created by Tsai et al[91] by combining the NIR anabolic dye IR780, PEG, and cRGD peptide with the chemotherapy agent SN38 for treating colorectal cancer. With the aid of the photosensitizer, $_{cRGD}^{IR}NANO_{SN38}$ was able to produce enough heat when exposed to NIR light to kill tumor cells. Modification of cRGD peptides enables nanomedicines to bind specifically to tumor vessels expressing αvβ3, thus facilitating targeted uptake. Cellular-release experiments showed that $_{cRGD}^{IR}NANO_{SN38}$ had long-term stability below 45 °C, with a release rate of 10% at 24 h in the presence of PTT. In vitro cytotoxicity showed that the IC_{50} values of $_{cRGD}^{IR}NANO_{SN38}$, $^{IR}NANO_{SN38}$ and free SN38 on DLD-1 cells were (3.1 ± 0.6), (5.8 ± 1.1) and (11.1 ± 1.2) μg/mL, respectively, which may be related to the targeting of tumor vasculature by cRGD and thus increasing the uptake of DLD-1 cells. Moreover, the $_{cRGD}^{IR}NANO_{SN38}$ showed strongest tumor inhibition effect on HCT116 tumor-bearing mice model under NIR light irradiation.

Redox-Sensitive

The tumor microenvironment typically exhibits increased redox levels in comparison to normal tissues. When compared to normal cells, the quantity of ROS in tumor cells can reach 100 M, which is a 100-fold increase[92]; GSH levels in tumor cells range from 1 to 10 mM, which is approximately 100 times more than that in blood and healthy cells;[93] therefore, both overexpressed GSH and ROS can be used as stimulatory factors for smart response nanodrug carriers to design redox-sensitive small-molecule prodrug nanoparticles. Common redox-sensitive linker arms include disulfide, thioether, diselenium, selenium ether, sulfur ketone, and succinimide-thioether bonds.

GSH Response

Glutathione (GSH), which consists of glutamate, cysteine, and glycine, is an important redox regulator that has a significant impact on the scavenging of free radicals, the preservation of biofilm integrity, and the activity of sulfhydryl-containing enzymes.[94] Since the expression of GSH is much higher in tumors than in normal cells, when the drug delivery system reaches the tumor cells, the redox-sensitive linker bonds introduced within the drug carrier are broken by the high concentration of GSH, which leads to the breakage and rapid release of the drug, thus enabling the targeted drug transport. Zheng et al[95] designed an SN38 hydrophobic precursor, SN38-oleic acid (SN38-etcSS-OA), using disulfonyl-ethyl carbonate (etcSS) as a linker [Figure S7(B)]. SN38-etcSS-OA may self-assemble into rod-like nanocluster aggregates (SEONPS) with significant redox sensitivity and reduction reactivity, releasing more than 80% of SN38 after 0.5 h in a high redox environment (10 mM DTT). Because of the EPR effect, this nano-aggregate targeted tumor cells, and the increased intracellular reduced GSH environment was able to activate SN38 prodrugs, releasing SN38 sufficiently to exert anti-tumor activity. Furthermore, the nano-aggregate generated 29.5% apoptosis in CT26 cells, which was significantly greater than CPT-11 (2.6%), but slightly lower than free SN38 (39.6%), and it was also shown considerable anti-tumor effect in CT26 tumor-bearing BALB/C mice model, with a tumor inhibition rate of 60.2%. He[96] created an SN38-lysophospholipid concatenation (SN38-SS-PC) by conjugating SN38 with lysophospholipid via

a cleavable disulfide bond linker, and assembling the SN38-SS-PC into redox-responsive liposomes utilizing the thin-film approach. The in vitro release profiles revealed that roughly 93.65% of SN38 was released 24 hours after glutathione (GSH) administration. Meanwhile, the lactone form of SN38-SS-PC liposomes was more stable than free drug under simulated physiological environment, with a content of the SN38 lactone ring more than 85% in SN38-SS-PC liposomes while less than 10% in free SN38 after 12 hours of incubation. SN38-SS-PC liposomes demonstrated the highest cytotoxic effects on MCF-7 and A549 cells, with IC_{50} values of 5.4 μg/mL and 9.6 μg/mL, respectively, when compared to free SN38 and irinotecan. After 6 hours of cell culture, the SN38 fluorescence intensities increased, indicating increased cellular uptake. In vivo experiments in 4T1 tumor-bearing model revealed that the tumor weight was significantly lower in the administration group mice than in the saline group, and the SN38-SS-PC liposome group had the lowest tumor weight with a tumor inhibition rate (TIR) of approximately 53.3%, which was significantly higher than that of irinotecan at 11.7%. Zhong et al[97] inserted disulfide bonds into SN38 and used it to prepare GSH responsive nanoassemblies (SNSS NAs). SNSS NAs were able to increase the absorption of Panc-2 and BxPC-3 cells when compared to free SN38, and in vitro cellular uptake demonstrated that SNSS NAs were internalized via a clathrin-mediated exocytosis pathway. According to in vitro cytotoxicity studies, the IC_{50} values of CPT-11, SN38 and SNSS NAs were (9.769±0.362) μM, (0.0066±0.001) μM, (0.170±0.027) μM in Panc-2 and (0.388±0.012) μM, (0.011±0.001) μM, (0.049±0.003) μM in BxPC-3, respectively, which may be related to the slowed release effect of SNSS NAs. Additionally, the GSH inhibitor BSO was added to the cell lines, and this resulted in a decrease in the cytotoxicity of glutathione sensitive SNSS NAs, indicating that SN38 release and cytotoxicity were dependent on GSH concentration. Targeting tests using Cy7-labeled SNSS NAs in mice with Panc-1 tumors showed that the SNSS NAs were able to increase the accumulation at the tumor site. Moreover, the SNSS NAs (39.6 mg/kg) had a tumor inhibition rate of 74.7% in nude mice bearing Panc-1 tumors, and mice receiving SNSS NAs did not exhibit any hazardous side effects (Figure S8). Hao et al[98] selected an E-selectin-conjugated peptide as a targeting ligand and metastasis inhibitor, and conjugated the peptide with SN38 and PEG to generate an amphiphilic PEGylated peptide–drug conjugate (PDC). Then, the amphiphilic conjugate formed self-assembled nanoparticles (PEG-Pep-SN38) in aqueous conditions. The PEG-Pep-SN38 could specifically target the tumor vascular endothelium cells and break and release SN38 in the tumor microenvironment due to high GSH concentrations. In vivo tests revealed that PEG-Pep-SN38 had a tumor growth inhibition impact similar to irinotecan, with an in vivo tumor inhibition rate of 76.01%, while 70.48% in the irinotecan group, and 45.86% in the PEG-SN38 group. Furthermore, PEG-Pep-SN38 was discovered to effectively extend the survival time of mice bearing B16-F10 tumors. Mauro et al[99] developed a redox-sensitive amphiphilic polysaccharide linking thiocholesterol and inulin (INU-Cys-TC) via disulfide and INU-Cys-TC was sufficiently self-assembled to form micelles to deliver SN38. Because cancer cells have high levels of reduced glutathione, SN38 incorporated into micelles releases its payload in the tumor, enhancing its tumor selectivity while reducing negative effects on healthy cells. According to the drug release test, the drug in the INU-Cys-TC@SN38 was released 32% in the first hour and 100% in the following 48 h in pH=7.4 HSA PBS solution. INU-Cys-TC@SN38 had IC_{50} values of (3.3 ± 0.3), (47 ± 3.1) mM in the HCT-116 and MCF-7 cells, respectively, after 24 hours of incubation, according to in vitro tests, and the IC_{50} values of the drug-loaded micelles were 8-fold higher than those of the free drug on normal cells (16-HBE).

ROS Response

ROS are a class of oxygen-derived chemicals produced by the human body that are closely associated with the progression of multiple cancer cells. ROS-responsive nano delivery strategy is to make the nano delivery system react with the highly expressed ROS in tumor cells, thus achieving better therapeutic effects by reducing the level of ROS in the microenvironment while achieving tumor-targeted release of the drug.[100] Gong et al[101] created a ROS-responsive hydrogel, covalently cross-linked by phenylboronic acid-modified SN38 (SN38-SA-BA) with poly(vinyl alcohol) (PVA) for delivering anti-programmed cell death protein ligand 1 antibodies (aPDL1). In the presence of endogenous ROS in tumors, SN38-SA-BA can be oxidized and hydrolyzed to release SN38, which promotes ROS generation and triggers the self-accelerating release of SN38, with the enhanced release of aPDL1. The results demonstrated that the SN38 prodrug hydrogel could induce immunogenic cell death (ICD) in cancer cells while also eliciting anti-tumor immunological responses and increasing immune cell infiltration. Meanwhile, the released aPDL1 may inhibit the interaction of PD1 and

PDL1 and increase the population of homoreactive T cells, hence suppressing tumor progression. Moreover, PVA-SN38 hydrogel-loaded aPDL1 dramatically reduced tumor development in B16F10 melanoma tumor model.

Multi-Stimulus Responses

Response-based drug delivery systems have made some progress in the construction of intelligent drug delivery systems, but most of them are single-responsive, the design of dual-responsive or multi-responsive nanomedicines, which can achieve the purpose of meeting different requirements in a drug delivery system at the same time, has become an important development direction of drug delivery systems.[102] Lin et al[103] prepared a stepwise stimulation response strategy for a tumor-penetrating peptide iRGD combined with GSH-responsive SN38-dimer (d-SN38) nanoparticles (d-SN38@NPs/iRGD). After intravenous injection, d-SN38@NPs could effectively accumulate and penetrate into the deep region of tumor sites with the assistance of iRGD. The gathered nanoparticles simultaneously transformed into nanofibers upon 650 nm laser irradiation at tumor sites to promote their retention in the tumor and burst release of reactive oxygen species for photodynamic therapy. The loaded d-SN38 with disulfide bond responded to the high level of GSH in tumor cytoplasm, which consequently resulted in SN38 release and excellent chemo-photodynamic effect on tumor. After co-administration of iRGD with d-SN38, the cellular uptake was 2.08 times higher than that of d-SN38NPs, and the cell permeability was 2.93 times higher than that of d-SN38NPs. Compared to d-SN38NPs (IC_{50}=1.33 μg/mL), d-SN38@NPs/iRGD had a 2.7-fold greater cytotoxic effect on 4T1 cells (IC_{50}=0.48 μg/mL). In vivo assay in 4T1 tumor-bearing mouse model demonstrated that the tumor inhibition rate of the laser irradiation group was 7.42 times higher than that of the tumor inhibition rate of the no-laser irradiation group. Thus, iRGD combined with photodynamic force can synergistically exert anti-tumor effects (Figure S9). Liu et al[104] synthesized multiple stimuli-responsive SN38 prodrug, PEG-S-S-SN38, by combining PEG with SN38 with disulfide bonds and carbonic ester linkages as linkers [Figure S7(C)], which could self-assemble into nanoparticles (PEG-S-S-SN38 NPs). PEG-S-S-SN38 NPs were released slowly in the physiological environment, with a release rate of 11.3% after 48 h. Rapid release was achieved in the tumor cytoplasmic environment, with a release rate of 91.3% in the presence of 10 mM GSH, and 85% in the presence of esterase for 26 h. Meanwhile, PEG-S-S-SN38 NPs were rapidly absorbed into tumor cells and had equivalent in vitro cytotoxicity and cell cycle effects as SN38. Furthermore, the inhibition rate of PEG-S-S-SN38 NPs in BCap37 xenograft tumor model was (72.49 ± 6.26)%, which was twice as high as CPT-11 (38.64 ± 13.04)%. Chen et al[105] designed a multifunctional SN38-conjugated nanosystem FA-PPSM (FA-PDA@PZM/SN38@BSA-MnO_2) for synergistic chemotherapy, photodynamic therapy (PDT) and photothermal therapy (PTT). Due to the conjugation of FA which could enhance the transport of nanoparticles into tumor cells through folate receptor-mediated endocytosis, 7.45% of FA-PPSM was internalized by Eca-109 cancer cells after 6 h of incubation, whereas only 40.33% of non-targeted PPSM was taken up. After irradiation with 808 nm laser for 5 min, the temperature of 200 μg/mL FA-PPSM suspension increased, which could kill the tumor cells by converting the light energy into heat energy. In the acidic environment of tumors, BSA-MnO_2 nanoparticles decompose to generate O_2 and Mn^{2+}. The released O_2 can alleviate the efficiency of tumor hypoxia-dependent PDT, and the generated Mn^{2+} is used for tumor magnetic resonance imaging and detection. The percentage of late apoptosis or cell death in the FA-PPSM synergistic PDT/PTT treatment group was higher than that in the blank group and single laser-induced PDT or PTT and showed significant tumor suppression in Eca-109 mice. In addition, the toxicity of FA-PPSM was evaluated, and the results showed that FA-PPSM nanocomposites were effective in suppressing myelosuppression and diarrhea compared to irinotecan. Furthermore, Hosseinzadeh et al[106] design a MUC1 modified SN38-HA conjugated gold nanoparticle which is against metastatic colon cancer cells. In vitro release experiments showed that the release of the nanoparticles was faster under acidic (pH 5.2) conditions and LED light radiation. The aptamer-modified nanoparticles increased the degree of cellular internalization by 1.5–2.2-fold, thus enhancing the cytotoxicity against HT-29 and SW480, with the cytotoxicity IC_{50} values of aptamer-modified nanoparticles being (16.72 ± 1.18) and (34.18 ± 5.53) μM for HT-29 and SW480, respectively, and that of the no-modified SN38-HA gold NPs being (27.62 ± 0.88) and (46.86 ± 4.07) μM for HT-29 and SW480, respectively, and there was no difference in cytotoxicity on CHO-negative cell lines, which was related to the overexpression of MUC1 glycoprotein on the surface of colon cancer cell lines. Furthermore, the combination of SN38-HA gold NPs and LED light reduced the migratory potential of the HT-29 and SW480 cell lines. According to antiproliferative research, the cell viability of SW480, HT29, and CHO treated with MUC1 modified SN38-HA gold NPs was (16.5 ± 1.16)%, (17.04 ± 3.20)%, and (9.15 ± 1.18)%, respectively, and the viability after LED irradiation was (8.95 ± 1.54)%, (3.31 ± 0.65)%, and (1.35 ± 0.27)%, respectively. The use of LED can increase local cell temperature through the SPR characteristics of SN38-HA gold NPs.

Co-Delivery Drug Delivery System

Due to the complexity of tumor pathology, there is an increasing demand for multi-drug combinations in clinical treatment. Multi-drug combination can act on multiple pathways and targets simultaneously to exert synergistic effects; however, there is still much room for optimization of current clinical multi-drug combination delivery strategies.[107] Nanomedicine delivery system can precisely regulate the multi-component flexible loading of drugs and carry the drugs to overcome the physiological and pathological barriers to achieve effective enrichment of tumor tissues and cells, and complete sustained, controlled and targeted delivery to achieve anti-tumor efficacy and toxicity reduction, which has shown a broad prospect in the field of tumor multidrug combination therapy and become one of the new directions of drug development (Table S5).

Co-Loaded Drug Delivery System for Chemotherapeutic Agents and SN38

Due to the single target and limited therapeutic effect of chemotherapy drugs when used alone, they cannot meet clinical needs. Therefore, currently, most first-line chemotherapy regimens for colorectal cancer in clinical practice use a combination of different drugs. However, the simple combination use of drugs has problems such as uncontrollable release and overlapping toxic and side effects.[108] Therefore, the establishment of SN38 co-carrier drug delivery systems based on the combination of chemotherapy drugs has attracted people's attention. Simultaneously encapsulating two chemotherapy drugs in nanocarriers can further enhance the therapeutic effect and reduce the toxicity of single drugs while maintaining their drug activity. Sun et al[109] fabricate a cargo-free and pH-responsive nano-medicine (PEG-DOX /SN38 NPs), which was self-assembled from prodrug (PEG-CH=N-DOX) and SN38. In vitro experiments showed that the IC_{50} values of PEG-DOX/SN38 NPs were 0.2 mg/mL (DOX) and 0.08 mg/mL (SN38), respectively, which were lower than those of the other groups. Additionally, compared with other drug formulations, PEG-DOX/SN 38 NPs reduced the percentage of CD44+/CD24-cells, which have been used as the specific markers for breast cancer stem cells (bCSCs). The tumor volume in the PEG-DOX/SN38 NPs group was 7.8, 7.1, 2.8, and 2.3 times less than the tumor volumes in the groups that received 0.9% NaCl, free PEG-DOX, free SN38, and free PEG-DOX+SN38, respectively (Figure S10). A hydrophilic oxaliplatin (OxPt) prodrug core with a lipid shell containing a hydrophobic cholesterol-conjugated SN38 prodrug (Chol-SN38) were used to create a two-stage release mechanism by Jiang et al[110] to enhance the drug deposition and antitumor efficacy of OxPt/SN38 core-shell nanoparticles [Figure S7(D)]. In vitro cytotoxicity tests showed that Chol-SN38 exhibited a 9-fold higher cytotoxicity on MC38 murine colon carcinoma cells than irinotecan. The IC_{50} values of Chol-SN38, irinotecan were (10.75 ± 1.73) μM, (93.32 ± 8.75) μM, respectively. In vivo experiments have shown a strong synergistic effect between OxPt/SN38 and immune checkpoint blockade, which can significantly impede prostate cancer models with spontaneous tumor development and invasion and colorectal cancer liver metastasis models. Among them, the MC38, CT26, and KPC mouse tumor models showed cure rates of 50%, 33.3%, and 40%, respectively. Mechanism research suggests that OxPt/SN38 may play an important role in the tumor immune microenvironment by enhancing immunogenic cell death and upregulating PD-L1 expression.

Co-Loaded Drug Delivery System for Reversal of Drug Resistance Inhibitors and SN38

Tumor MDR is an important cause of chemotherapy failure in clinical practice, which can adversely affect chemotherapy efforts by reducing intracellular drug accumulation and altering the distribution of drugs within cells, thereby reducing the efficacy of chemotherapy. Therefore, the preparation of drug delivery systems for co-loading chemotherapeutic drugs with drug reversal resistance agents to achieve the combination of chemotherapeutic drugs and multidrug resistance inhibitors can enhance the antitumor effects. Nagheh et al[111] loaded the MDR reversal drug verapamil and SN38 in PEG-PLGA copolymers, and prepared SN38-PEG-PLGA-Ver nanoparticles. Cytotoxicity assay showed that SN38-PEG-PLGA-Ver nanoparticles were able to change the nucleus morphology of HT-29 cells, which significantly reduced the cell activity. ABCG2 is a transport protein linked to irinotecan resistance, and the expression of BAX/BCL2 is linked to apoptosis. The expression of ABCG2 was significantly reduced after nanoparticle treatment compared to free SN38, while the expression of BAX and the BAX/BCL2 ratio increased.

Co-Loaded Drug Delivery System for siRNA and SN38

In recent years, RNA interference technology represented by siRNA (Small interfering RNA, siRNA) has shown great potential in the treatment of human diseases, providing new ideas for the precise treatment of tumor. When siRNA enters the cell, it can specifically bind to relevant mRNAs, selectively block pathological pathways, and significantly reduce the off-target effects of anticancer drug.[112] siRNA combined with chemotherapeutic drugs will become a new strategy for efficient tumor treatment, with good prospects for clinical translation. Bi et al[113] prepared transferrin (Tf) liposomes co-loaded with TAT-PEG-SN38 and survivin siRNA (Tf-L-SN38/P/siRNA). This liposome was able to increase endocytosis and consequently cytotoxicity in HeLa cells, and the results of in vitro cellular experiments revealed that Tf-L-SN38/P/siRNA (IC_{50}=175 nM) exhibited stronger cytotoxicity compared with Tf-L-SN38 (IC_{50}=2.03 μM) and SN38 (IC_{50}=2.55 μM) in HeLa cells. Meanwhile, pharmacodynamic experiments indicated that Tf-L-SN38/P/siRNA exhibited the strongest tumor inhibition of 76.8% in HeLa cell xenograft tumor nude mice compared with the Tf-L-SN38 group (inhibition rate = 43%) and SN38/P/siRNA group (inhibition rate = 37.7%).

Co-Loaded Drug Delivery System for Vitamin E and SN38

Vitamin E is frequently used to prevent cardiovascular disease, slow the aging process, and control reproductive function due to its antioxidant qualities. And some research has supported that. Immunotherapy may benefit from vitamin E's immunomodulatory function, which affects a range of immune cells.[114] Additionally, vitamin E and its derivatives have potent antitumor properties. They can inhibit the growth of tumor cells both in vitro and in vivo, leading to the death of the tumor cells, while at the same time lowering the negative side effects and boosting the effectiveness of anticancer medications. These properties have a promising clinical future.[115] Iyer et al[116] formulated biodegradable poly(propylene glycol)-poly(ethylene glycol) (PLA-PEG) based nanoparticles (NPs) containing SN38 coupled to tocopherol succinate (SN38-TS). In vivo experiments in xenograft models revealed that all SN38-TS NPs regimens were considerably superior to irinotecan, and "cures" were obtained in all NP arms. At 4 hours after SN38-TS NP delivery, the level of SN38 in neuroblastoma, tumors was 200-fold higher than in the irinotecan group. In addition, Nguyen et al[117] prepared SN38-TOA NPs by combining tocopheryloxyacetate (TOA) with SN38 and encapsulated it into polymer nanoparticles. TOA, a hydrophobic mitogen, is able to improve SN38 hydrophobicity while enhancing SN38 hydrophobicity while enhancing the anti-tumor effect. The 110-day survival rate of BR6 neuroblastoma model mice treated with SN38-TOA NPs reached 100%. In addition, the efficacy of SN38-TOA NPs in a subgroup of high-risk neuroblastoma, the IMR-32 neuroblastoma line, demonstrated that SN38-TOA-NPs led to complete regression of tumors in all the mice with no recurrence after 180 days. In vivo distribution assays showed that the concentration of SN38-TOA NPs in the blood was more than 400 times than that of CPT-11 and the concentration of the drug in tumors was 3 times than that of CPT-11 after 4 h of administration, suggesting a long retention of SN38-TOA NPs in the body as well as their accumulation in tumors.

Discussion

SN38 continues to receive extensive attention by virtue of its significant cytotoxic effects. In order to overcome its limitations in clinical applications, this paper presents a review based on SN38 drug delivery systems. Four main delivery modes are included: passive targeted delivery system, active targeted delivery system, physicochemical targeted delivery system, and co-loaded drug delivery system. (1) The passive targeted delivery system based on the EPR effect exploits the advantageous accumulation of nanomedicines in the tumor tissue mesenchyme. It is generally believed that macromolecules with molecular weights above 40 kDa and nanoparticles with diameters of 10 ~ 200 nm are ideal for exploiting the EPR effect, and therefore a large number of antitumor drugs have been used in the form of nanocarrier loading.[118] The passive targeting nanocarriers reviewed in this paper mainly include polymeric micelles, liposomal nanoparticles, protein nanoparticles, and polymeric nanoparticles. All of the above carriers can use their own properties to improve the water solubility of SN38 and avoid the hydrolytic inactivation of the E-cyclolactone structure. At the same time, they can improve the pharmacokinetic and biodistribution characteristics, thus reducing the toxicity and immunogenicity of SN38 and improving the bioavailability. (2) Generally speaking, in order to achieve high selectivity of nanoparticles, the receptors on the surface of target cells need to be highly specific, and the expression level is generally

higher than 10^5.[119] So as to achieve the enrichment of the drug in the tumor and improve the therapeutic effect, and at the same time, reduce the total dose of the drug and the toxic side effects on normal tissues. The SN38 active targeted delivery system based on ligand-receptor specific binding mainly includes various ligand molecules such as folate receptor, integrin receptor, IGF-1R, CD133, glucose transporter, EDB receptor and other ligand molecules capable of binding specifically to tumor cells. The ligands are used as drug carriers, and through the mediating effect of the receptors, the drug concentration in the lesion area can be increased, the therapeutic efficacy can be improved, and the toxic side effects can be reduced, so as to achieve the purpose of targeted therapy. Meanwhile, SN38 ADC based on the specific combination of antigen and antibody has made certain achievements, and a variety of ADCs are currently in the clinical research stage. (3) In order to further improve the efficiency of nano drug delivery, some scholars have designed a delivery system based on the triggering of specific stimulation sources in vivo and ex vivo, as well as based on the differences of the internal environment of the tumor to complete the intelligent and controllable release of the drug, which is the physicochemical targeting delivery system. The targeting and precise release of drugs can be achieved through exogenous signals such as light, heat, magnetic field, electric field, etc., and endogenous physiological characteristics such as weak acidity and high reducibility, etc., which are different from those of normal tissues in the abnormal proliferation of tumor cells. In addition, the multi-stimulus-responsive drug delivery system can respond to two or more external stimuli at the same time, in order to give full play to its intelligent advantages in the process of tumor treatment, reduce the pain caused by the adverse reactions of drugs to the patients, and provide a new way of thinking for the research of targeted drug delivery. (4) Due to the complex pathogenesis of cancer, the use of single-drug chemotherapy can usually only block one signaling pathway in the tumor growth process, making it difficult to achieve a sustained and complete anti-tumor effect. Combining two drugs and using nanocarriers to simultaneously transport them to the tumor lesion site can effectively inhibit tumor MDR, reduce the dose of drugs, inhibit the growth of tumor tissues, improve the therapeutic effect, and reduce the toxic side effects caused by single-drug high-dose therapy, which has a good prospect for development.

The development of SN38-based drug delivery systems for tumor treatment has been more researched and has made some progress, but the only drug approved and applied in the clinic is the SN38-based ADC, IMMU-132. There is still a lack of nano drug delivery systems that have entered clinical applications. There are many reasons for this phenomenon. (1) Nanocarrier-based passive-targeted drug delivery systems enhance drug enrichment in tumor tissues mainly through the EPR effect, whereas a single passive targeting has a very limited role in increasing the drug enrichment rate within tumor tissues. Meanwhile, the safety of long-term use of nanocarriers is still unknown, especially the possibility of toxicity at the cellular level, where nanomaterials can damage cells to varying degrees after cellular exposure.[120–122] (2) Many targeting ligands in active targeted drug delivery systems are susceptible to denaturation and inactivation, which cannot ensure the stability of their targeting function. Moreover, when the delivery system interacts with blood, plasma proteins may adsorb on the surface of nanoparticles to form protein crowns, thus reducing or even eliminating the specific recognition ability of ligands and corresponding receptors.[123] (2) Physicochemical targeting is based on the design of the human body environment, which is complex, with biological proteins in the blood, pH environment, etc., constantly changing,[124] so the stability of the SN38 drug delivery system designed based on physicochemical targeting is poor. At the same time, the inherent heterogeneity and complexity of tumors can also interfere with the tissue penetration of drugs and reduce the delivery efficiency. (4) Co-loaded drug delivery system is a promising strategy, but there are still many shortcomings, for example, how to precisely control the proportion of two drugs with different physicochemical properties, pharmacokinetics and tissue distribution. There is a lack of research on how to better control the release of drugs and how to realize the temporal sequencing of drug delivery.[125]

The development of SN38 drug delivery systems presents both opportunities and challenges. From the perspective of clinical translation, passive-targeted drug delivery systems have the advantages of strong stability, simple structure and preparation process, easy industrial mass production, and lower price compared to active-targeting drug delivery systems, physicochemical-targeting drug delivery systems, and co-loaded drug delivery systems, and have good application prospects. In subsequent research, in-depth studies on the safety, biocompatibility, and pharmacokinetics of nanocarriers will help further promote the clinical translation of passive targeted drug delivery systems. Based on the five-step cascade of nanomedicines (CAPIR) proposed by Sun et al,[126] nanomedicines undergo multiple-cascade processes in vivo after

intravenous injection to exert therapeutic effects, including long blood circulation, tumor accumulation, tumor infiltration, tumor cell internalization, and drug release. Any inefficient step will reduce the overall delivery effect. Therefore, active targeted drug delivery systems that can significantly improve tumor targeting and enhance drug accumulation at the tumor site, as well as Physio-chemical targeted drug delivery systems that can achieve intelligent controlled drug release, are important strategies for enhancing the bioavailability of nanomedicines. In subsequent research, it is of great significance to conduct in-depth research on how to overcome the complex biological barriers in the tumor microenvironment and improve ligand stability. In addition, co-loaded drug delivery systems are a new approach in the process of tumor chemotherapy. Conducting in-depth research on the differences in pharmacokinetics between drugs to achieve a reasonable ratio of two drugs, effective co-loading and ordered release, can promote the application of co-loaded drug delivery systems in tumor treatment. In addition, the significant difference between mouse tumor models and clinical patient tumors is an important reason for the low clinical conversion success rate of nanomedicine delivery systems. Therefore, it is crucial to construct in vitro and in vivo models that can indicate clinical features. Overall, it is believed that with further in-depth research, the clinical translation of the SN38 drug delivery system will be achieved.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no potential conflicts of interest in this work.

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