Crosslinked nanogel for cancer theranostics

Subjects: Polymer Science

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Crosslinked nanogels the structures of which are covalently crosslinked have better physiological stability than micelles and liposomes, making them more suitable for cancer theranostics. The applications of nanogels in drug and gene delivery as well as development of novel cancer therapeutic methods are first introduced, followed by the introduction of applications in optical and multimodal imaging, and imaging-guided cancer therapy.

crosslinked nanogel optical imaging cancer therapy

1. Introductio

Cancer is one of the major threats to human lives all over the world [1]. Traditional cancer treatment process divides diagnosis and therapy into different procedures, which is time consuming and requires high cost [2][3]. In contrast, cancer theranostics which combines diagnosis and therapy into one system can overcome such disadvantages, and has shown great potential in the field of cancer treatment [4][5][6]. Recently, phototheranostics, which based on optical imaging, have been widely studied because of their unique advantages such as high safety and sensitivity, low cost and capability of multi-channel imaging [7][8][9][10][11]. Numerous phototheranostic systems based on variety of materials such as small molecular dyes [12][13], anti-cancer drugs [14][15] and biomacromolecules [16] have been developed. However, as theranostics require the combination of multiple functionalities including imaging and therapy, complicated synthetic procedures are usually inevitable [17][18]. Therefore, developing phototheranostic systems based on multifunctional and facile synthesized materials is in high demand.

Among numerous materials for phototheranostics, nanomaterials have shown great promise and been widely applied in the field of cancer imaging and therapy [19][20]. Compared with small molecular dyes or drugs, nanomaterials can be easily prepared via nano-based preparation methods such as nanoprecipitation and nanoemulsion [21][22][23]. Some inorganic nanoparticles or 2D nanomaterials have unique optical properties, which can be used as phototheranostics directly [24][25][26][27]. In addition, different functionalities can be integrated into nanomaterials by simply doping or linking different moieties [28][29]. Anti-cancer drugs can also be absorbed or covalently linked onto such nanomaterials, endowing them with the capability for chemotherapy [30][31]. For organic nanomaterials, hydrophobic anti-cancer drugs or photosensitizers as well as optical imaging contrast agents can be encapsulated into micelles or liposomes simultaneously, which is a conventional way to construct phototheranostic platforms [32][33][34][35]. Owing to their relatively good biocompatibility, organic nanoparticles have gained increasing attention in the field of phototheranostics.

Although organic nanoparticles have been widely applied in cancer imaging and therapy, some drawbacks of conventional nanoparticles should be overcome. As most organic nanoparticles are micelles and liposomes, they may dissociate when their concentration decrease lower than the critical micelle concentration [36]. Such a feature makes nanoparticles unstable in harsh conditions such as blood circulation, which further leads to the burst release of encapsulated drugs or contrast agents [37][38]. To overcome such drawbacks, crosslinked nanogels have been chosen in the development of phototheranostic systems. Compared with micelles or liposomes, a crosslinked structure can stabilize the nanogels, leading to the non-dissociable nanostructure [39][40][41][42]. Such structure makes nanogels keep intact in the circulation, thus resulting in improved biodistribution and better tumor accumulation [43][44].

2. Crosslinked Nanogels for Cancer Therapy

Nanomaterials have been widely used as carriers for drug and gene delivery in the field of cancer therapy [45]. As crosslinked nanogels have the advantages including good stability and environmental responsiveness, nanogels can be good candidates for nanocarriers [46]. The crosslinked structure may prevent the burst release of loaded drugs. In addition, an activatable drug- or gene-delivery system can be developed by nanogels with environmental responsiveness [47]. In this section, we summarize applications of nanogels for cancer therapy including chemotherapy, gene therapy and enzyme dynamic therapy. The properties of these nanogels introduced in this section are summarized in Table 1. The most commonly used anti-cancer drug was doxorubicin (DOX), and it can be loaded via electrostatic interaction with nanogels. Drugs can be released under specific responsiveness such as pH, glutathione (GSH) and esterase. However, such method sometimes led to low drug loading capacity. To improve the drug-loading capacity, drug-crosslinked nanogels were designed, and the drug loading capacity can reach as high as 60.8%. For gene therapy, therapeutic RNAs were commonly loaded by ionic interaction, and can be released in a tumor-associated microenvironment.

Table 1. Summary of the nanogels for cancer therapy by loaded drug, loading capacity, responsiveness and animal study.

Type	Loaded Drug	Loading Capacity	Responsiveness	Animal Study	References
Chemotherapy	DOX/GL	1.2% (DOX)	pH	Yes	[48]
	DOX	5.7%	-	No	[49]
	DOX	54.1%	pH/GSH/trypsin	Yes	[50]
	DOX	18.2%	pH/GSH	Yes	[51]
	TAX	20–30%	pH/esterase	Yes	[52]
	Pt(IV)	60.8%	GSH/ascorbic acid	Yes	[53]

Type	Loaded Drug	Loading Capacity	Responsiveness	Animal Study	References
	Pt(IV)/TPZ	8.06% (Pt)/9.12% (TPZ)	GSH	Yes	[54]
Gene therapy	siRNA	-	RNase H	Yes	[55]
	siRNA	-	pH/RNase H	Yes	[56]
	siBcl2	-	DTT	Yes	[57]
	RNase	23.5%	NTR	Yes	[58]
Enzyme dynamic therapy	-	-	$\cdot O_2^-/H_2O_2$	Yes	[59]
	-	-	H_2O_2	Yes	[57]

DOX: doxorubicin; GL: glycyrrhizin; DTT: dithiothreitol; NTR: nitroreductase.

3. Crosslinked Nanogels for Cancer Diagnosis and Imaging-Guided Cancer Therapy

Precise and personalized treatment can provide better therapeutic efficiency than traditional therapy, and are the trends in the field of cancer treatment [60]. To achieve such a goal, powerful diagnostic methods are in high demand as real-time monitoring of the therapeutic process is a fundamental requirement. Thus, development of imaging-guided cancer therapeutic systems has gained increasing attention in recent years [61]. By virtue of the advantages of crosslinked nanogels, they have been utilized for constructing variety of nanotheranostic systems. In this section, we summarized the applications of nanogels for cancer imaging and imaging-guided therapy. The general properties of nanogels discussed in this section were summarized in Table 2.

Table 2. Summary of the nanogels for cancer imaging and imaging-guided therapy by imaging modality, therapeutic method, responsiveness and animal study.

Type	Imaging Modality	Therapeutic Method	Responsiveness	Animal Study	References
Imaging	CT	-	-	Yes	[62]
	T_1-MRI	-	-	Yes	[63]
	T_1-MRI/CT	-	-	Yes	[64]
	FL	-	-	No	[65]
	FL	-	pH/caspases	Yes	[66]

Type	Imaging Modality	Therapeutic Method	Responsiveness	Animal Study	References
Imaging-guided therapy	FL	PDT/PTT	-	Yes	[67]
	FL	PDT	-	Yes	[68]
	FL	Chemotherapy	Temperature	Yes	[69]
	T_1-MRI/PA	PTT	-	Yes	[70]
	T_1-MRI	Chemotherapy	pH	Yes	[71]
	PA/FL/PT	PDT/chemotherapy	Laser	Yes	[72]
	Fluorescence/T_2-MRI	PDT/chemotherapy	pH/GSH	Yes	[73]

CT: X-ray computed tomography; MRI: magnetic resonance imaging; FL: fluorescence; PDT: photodynamic therapy; PTT: photothermal therapy; PA: photoacoustic.

4. Conclusions and Outlook

In recent years, crosslinked nanogels have shown great promise in the field of cancer imaging and therapy. Compared with traditional micelles and liposomes, nanogels have a covalently crosslinked nanostructure, endowing nanogels with better physiological stability, multifunctionality and improved drug-release profile. The nanogels usually have a hydrodynamic size of tens to hundreds of nanometers, making them effectively accumulate in tumor sites. In addition, nanogels show good biocompatibility both in vitro and in vivo, indicating their potential in clinical translation. The nanogels can be used for anti-cancer drug and gene delivery. Such drug or gene-loaded nanogels have an improved release profile. In addition, novel therapeutic methods such as EDT can be designed based on the structure of nanogels, providing good therapeutic efficacy with minimized side effect. In addition to drugs, contrast agents can be conjugated or loaded onto nanogels. Such nanogels have been widely applied for imaging-guided cancer therapy. Nanogels loaded with photosensitizers can be used for phototheranostics, while Fe_3O_4-coated or Gd-conjugated nanogels are good candidates for MRI. Owing to the multifunctionality of nanogels, activatable chemotherapy-based nanotheranostic systems may also be developed.

In the field of cancer imaging, numerous advantages have been shown from these crosslinked nanogels. Crosslinked nanogels have better stability than micelles and liposomes, which can prevent burst release during circulation, thus improving the tumor accumulation and drug-delivery efficiency. Some nanogels were reported to had higher accumulation in a tumor site compared with other major organs including liver and spleen [57][73], which was seldom reported for micelles and liposomes [74]. In addition, fluorophores can be easily conjugated onto the surface of nanogels by virtue of their multifunctionality. Such a design was superior to encapsulation of fluorophores within nanoparticles as their fluorescence signal may be quenched due to aggregation [75]. Gd

complexes are usually conjugated onto the nanogels for T_1-weighted MRI. Compared with Gd-conjugated micelles, nanogels may retain their MRI signal better in the circulation owing to their higher physiological stability [70].

In the aspect of cancer therapy, higher tumor accumulation leads to higher drug-delivery efficiency and lower toxicity towards normal tissues. Compared with other surface engineered nanomaterials such as silica nanoparticles [76], nanogels may have better biodegradability, and are easier to develop on-demand DDS. These features make loaded drugs be easily released from nanogels. On the other hand, compared with other biodegradable nanomaterials such as polyester nanoparticles, nanogels usually have higher stability [77]. Thus, the flexibility of structures makes nanogels not only have good physiological stability, but also can release drugs in the desired site.

Although crosslinked nanogels have shown great potential in the field of cancer theranostics, several issues need to be resolved to further push forward the clinical translation of nanogels. As nanogels have a crosslinked structure, they usually have poor biodegradability compared with micelles and liposomes. Thus, the metabolic period may be much longer than micelles or liposomes. Such a process may cause long-term toxicity which hinders the clinical translation of nanogels. To improve such an issue, nanogels constructed by biodegradable materials or crosslinkers can be a rational choice to prepare biodegradable nanogels. Therefore, preparing nanogels with such a feature can be one of the research focuses in future study. Another critical issue for clinical translation is the productivity and reproducibility of nanogel preparation.

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