Polyethyleneimine-Based Drug Delivery Systems for Cancer Theranostics

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With the development of nanotechnology, various types of polymer-based drug delivery systems have been designed for biomedical applications. Polymer-based drug delivery systems with desirable biocompatibility can be efficiently delivered to tumor sites with passive or targeted effects and combined with other therapeutic and imaging agents for cancer theranostics. As an effective vehicle for drug and gene delivery, polyethyleneimine (PEI) has been extensively studied due to its rich surface amines and excellent water solubility.

polyethylenimine drug delivery cancer treatment cancer imaging cancer theranostics

1. Introduction

Cancer is a human disease characterized by abnormal cell proliferation and metastasis and poses a very significant threat to human health. Its occurrence is closely related to harmful environment, bad lifestyle, and heredity. Early diagnosis and treatment of cancer is the most important strategy to improve survival rates. Recently, nanotechnology has attracted extensive attention in the biomedical field, particularly in the early diagnosis and treatment of cancer [1][2].

The development of novel multifunctional nanoparticles (NPs) for cancer theranostics is one of the most important trends in the development of nanomedicine [3][4][5][6]. Compared with traditional drug delivery systems, NP-based drug delivery systems can not only improve the water solubility and stability of drugs, but also influence the distribution of drugs in vivo owing to the nanosized effects of NPs [7]. In addition, the kinetics of drug release can be controlled through material design and surface modifications. More importantly, targeted molecules can be modified on the surface of NPs to specifically target tumor sites, thereby improving the bioavailability of drugs and reducing toxicity to off-target tissues [8]. To date, various NPs have been developed for construction of NP-based drug delivery systems including liposomes [9][10], micelles [11], nanogels [12][13], radionuclide-labeled NPs [14][15], and metal NPs [16][17][18][19].

Polyethyleneimine (PEI) is a cationic polymer molecule composed of abundant amine groups and two aliphatic carbons, and because of its specific structure and properties it has been widely used to stabilize or modify various inorganic hybrid NPs [20]. As a cationic polyamine, PEI can interact with or bind to anionic residues of DNA templates and polymerase through electrostatic interaction, thus significantly improving their transfection efficiency [21]. In addition, the strong positive surface potential of PEI presents obvious cytotoxicity to cells because of its abundant amine groups [21]. Therefore, neutralizing the surface potential of PEI through various chemical or

physical modifications can effectively reduce its cytotoxicity and improve biocompatibility. It is worth noting that these surface modifications not only improve the biocompatibility of PEI, but also enable it to acquire other functions, such as biomarker and targeting.

2. Overview of PEI

PEI is a commercially widely used cationic polymer containing primary, secondary, and tertiary amino groups in a ratio of 1:2:1 with strong positive charges [22]. PEI can be synthesized as linear PEI (**Figure 1**a) or branched PEI (**Figure 1**b) with a molecular weight ranging from 700 Da to 1000 kDa according to the degree of polymerization [23]. PEI can be easily prepared using an AB-type monomer via a simple one-step reaction [24]. In addition, PEI can be considered a low-cost option compared to dendrimers with the same molecular weight [25]. PEI has been widely used in different fields because of its unique structure and abundant amino groups. For example, in industry, PEI can be used as a flocculant to remove oil present in synthetically produced water, or as a wet strength agent in paper-making and the manufacture of shampoo [26][27]. In biomedicine, PEI is widely used in enzyme immobilization [28], virus immobilization on cellulose [29], cell adhesion [30], gene transfection [31], and the synthesis of NPs to enhance their stability and anticancer efficacy [32].

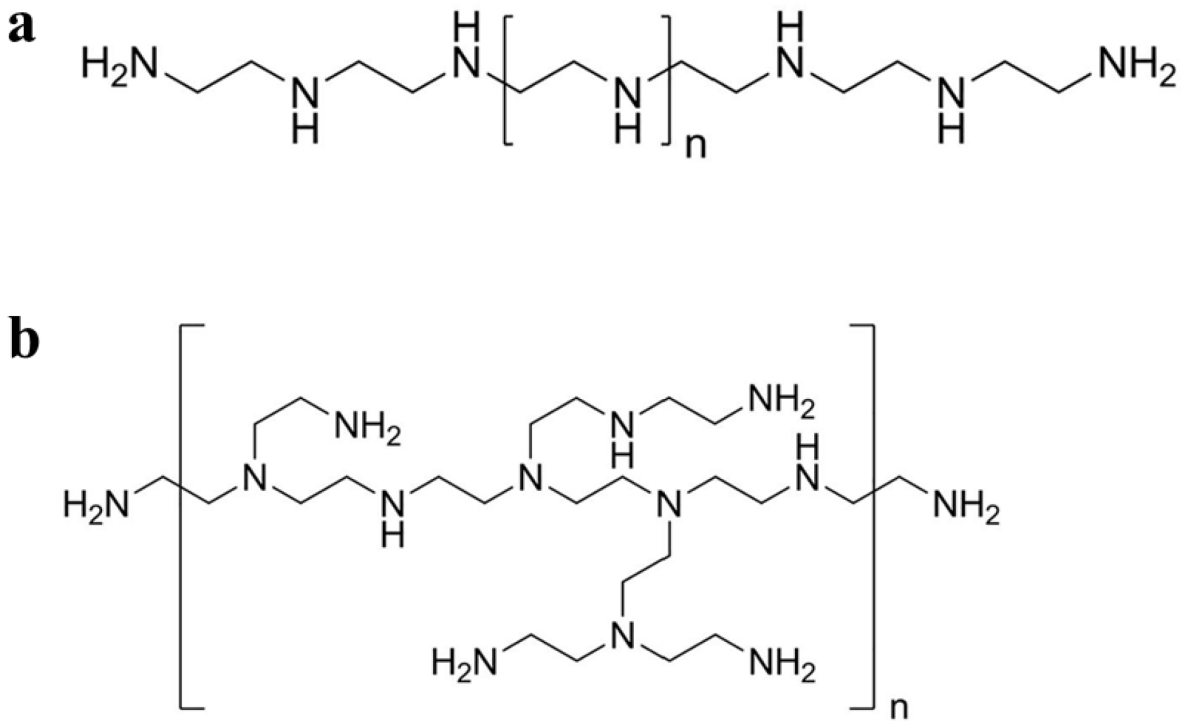

Figure 1. Schematic diagram of the chemical structures of (**a**) linear and (**b**) branched PEI.

Branched PEI is a hyperbranched polymer synthesized using the monomer method; that is, the cationic polymer is obtained by acid-catalyzed ring-opening polymerization of aziridine monomers [33]. Each branch of secondary amines in the branched chain of hyperbranched PEI has 3–35 nitrogen atoms on average. This branch distribution can form a spherical internal structure, which can encapsulate NPs, drug molecules, and other small molecules.

Furthermore, the lone pair electrons of nitrogen atoms in branched PEI can stabilize metal ions via coordination interaction. Therefore, branched PEI has a wide range of applications in gene transfection [34][35][36], drug delivery [37][38], and molecular imaging [25][39].

Linear PEI contains only secondary amines, whereas branched PEI contains various types of amines, i.e., primary, secondary, and tertiary. Linear PEI is solid at room temperature, in contrast to branched PEI which is liquid at all molecular weights [20]. Linear PEI is a high-charge cationic polymer and has been widely used in biomedical fields. For example, linear PEI has antibacterial properties against various pathogens and can therefore be used as a bacteriostatic agent [40][41]. Additionally, as a cationic polymer, linear PEI can form a polymer with nucleotides for gene transfer [42]. Compared with branched PEI, linear PEI is an effective nonviral gene vector with higher cell viability and transfection efficiency [43]. A balanced picture of the PEI studies including advantages and limits has been presented in **Figure 2**.

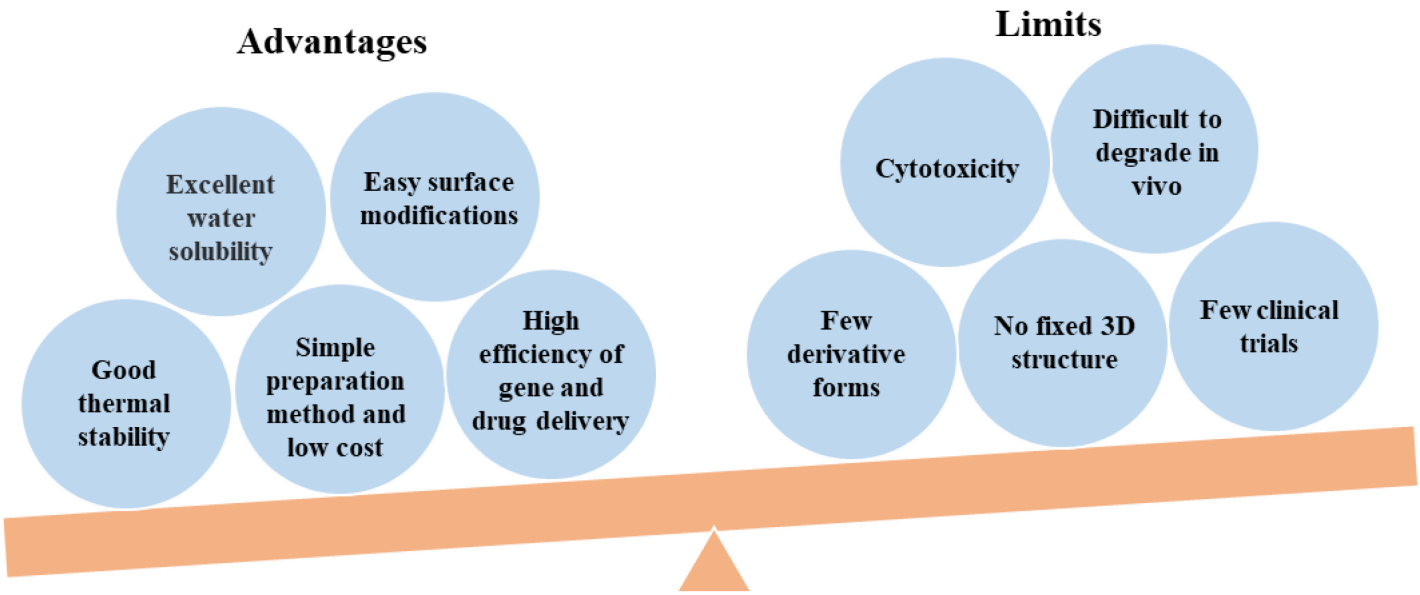

Figure 2. A balanced picture of PEI studies including advantages and limits.

3. PEI Modifications

As a cationic polymer, PEI contains abundant amino groups and as a result has a certain degree of cytotoxicity. Cationic PEI enters cells by adhering to negatively charged transmembrane heparanproteoglycans, which can cause cell damage through membrane destabilization [44]. Additionally, the internalized PEI causes apoptotic cell death by forming pores in the mitochondrial membrane [45][46]. PEI is not well-degraded in organisms, and its cytotoxicity is closely related to its molecular weight and branching degree [47]. Branched PEI with a higher molecular weight has a higher cytotoxicity. The surface amines of PEI can be shielded with simple modifications, thus significantly improving the biocompatibility of PEI [21]. At present, the surface amines of PEI are mainly shielded with covalent bonds such as carboxylation, acetylation, and hydroxylation, or with electrostatic modification of negatively charged proteins. However, currently, there is a lack of systematic research to contrast

the benefits and challenges of these approaches for the surface modifications of PEI. For example, Wen et al. improved the biocompatibility of PEI through carboxylation, acetylation, hydroxylation, and PEGylation [21]. These methods effectively reduced or shielded the positive charge of the PEI, thus reducing cytotoxicity. Various functional groups including polyethylene glycol (PEG), folic acid (FA), hyaluronic acid (HA), fluorescent tags, and protein can be modified with PEI for biomedical applications [24][25][48][49][50][51][52][53][54][55][56][57][58]. PEI modifications for biomedical applications in recent years are summarized in **Table 1**.

Table 1. Summary of PEI modifications carried out in recent years.

Modification Types	Aims	Ref.
Carboxylation modification	Gene delivery, absorption of heavy metals in sewage.	[59][60][61][62]
Acetylation modification	Gene delivery efficiency improvement, cytotoxicity reduction.	[62][63][64]
Hydroxylation modification	Biocompatibility enhancement, gene delivery, transformation improvement of NPs.	[65][66][67]
PEG modification	Stability and transfection efficiency improvement.	[68][69][70]
FA modification	Tumor-targeted delivery.	[71][72]
HA modification	Tumor-targeted gene delivery, stability improvement.	[73][74]
Protein modification	Gene delivery, protein transduction.	[75][76][77]
FI modification	Fluorescence imaging.	[57]

4. Synthesis of PEI-Based NPs

NP-based drug delivery systems with high biostability, targeting, and biodegradation have significantly improved clinical efficacy [78][79][80][81]. Compared with traditional drug delivery systems, NP-based drug delivery systems can not only improve the water dispersibility and stability of drugs, but also significantly change the distribution and

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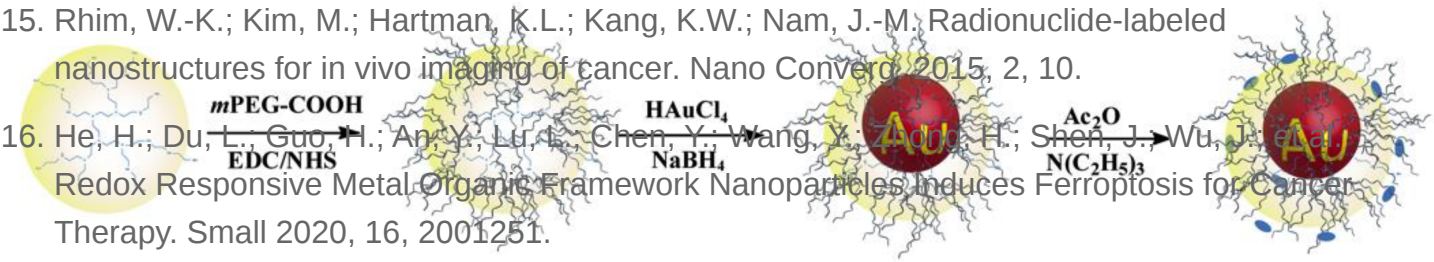

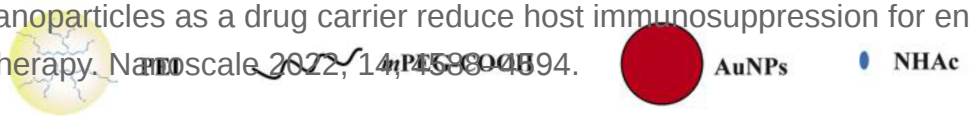

Figure 3. Schematic illustration of the synthesis of PP–AuNPs.

5. PEI-Based Drug Delivery Systems

Since the FDA first approved liposomal doxorubicin as a delivery system in 1995, various drug delivery systems have been developed for the treatment of different diseases [101]. The development of nanotechnology provides more options for the design of drug delivery systems.

As a cationic polymer, PEI can not only ingest foreign agents and numerous PEGylation groups on its surface can be modified with various functional modifications [102]. For example, targeting agents [103][104], biomacromolecules [105][106], lactic acid [107][108], transactivating protein [109], and antibodies [110][111], modify PEI to target specific cancer cells; fluorescent labeling molecules, such as fluorescein isothiocyanate (FI), modify PEI for cell marking [57]; and biocompatible agents, such as PEG and oligosaccharides, can improve the biocompatibility of PEI [56][112][113][114][115]. The internal cavity of hyperbranched PEI and the large number of amino groups on the surface can be readily constructed as a nanoplatform, which can effectively stabilize or entrap small biological molecules (e.g., DNA, siRNA, drugs) or metal ions. The unique physicochemical properties and low price of PEI promote its wide application in biomedicine.

5.1. PEI-Based Drug Delivery Systems for Cancer Treatment

PEI is a class of large-molecular-weight polymers, among which hyperbranched PEI has a hydrophobic cavity, dendritic three-dimensional structure, and plentiful positively charged amino groups on the surface, which provide the conditions for further chemical modifications [21][116][117][118]. PEI is an effective drug carrier for cancer treatments such as chemotherapy and gene therapy because of its unique structure, commercial availability, and low price. **Table 2** provides a detailed summary of PEI-based drug delivery systems for cancer therapy.

Table 2. PEI-based drug delivery system for cancer treatment.

Therapeutic Modalities	Therapeutic Agents	Cell Line Models	In Vivo Models	Ref.
Chemotherapy	DOX	HeLa	HeLa	[57]
	MTX	HCT 116	/	[119]
	PTX	HepG2	/	[120]
	DOX	C6	/	[121]
	DOX	HeLa	HeLa	[122]
	DOX	4T1, HepG2	/	[123]
	DOX	A549	/	[124]
	DOX, siRNA	MDA-MB-231, HeLa, EAT	EAT	[125]
	DOX	SKBR3	SKBR3	[126]
Gene therapy	pDNA	HeLa, 16HBE14o−, HepG2	/	[127]
	pDNA	Huh7	Huh7	[128]
	DNA	NIH/3T3	/	[45]
	pDNA	HeLa	/	[51]

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Therapeutic Modalities	Therapeutic Agents	Cell Line Models	In Vivo Models	Ref.
Gene therapies	DNA	HeLa, CT26	CT26	[129]
	mRNA	B16-OVA	B16-OVA	[130]
	RNase A	MDA-MB-231	/	[131]
	Oxidized mesoporous carbon nanospheres, pDNA	MCF-7	MCF-7	[132]
Other therapies	CAT-Ce6	T24	T24	[133]
	GO, DTX, anti-miRNA21	MDA-MB-231	/	[134]
	CuS, DTX, CpG	4T1	4T1	[135]
	pDNA, 9B9 mAb	SMMC-7721	SMMC-7721	[136]

Table 3. PEI-based imaging or imaging-guided cancer therapy.

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5.2. PEI-Based Drug Delivery System for Cancer Imaging

Contrast agents are widely used in molecular imaging to enhance imaging resolution. Owing to its unique physicochemical structure, PEI can effectively stabilize or encapsulate various agents for cancer imaging applications. A variety of imaging contrast agents can be constructed based on PEI including computed tomography (CT), magnetic resonance (MR), and single-photon emission CT (SPECT) imaging [137][138]. This section summarizes the progress of research concerning the use of PEI to construct multifunctional nanosystems as contrast agents for single-modal and multimodal molecular imaging. **Table 3** summarizes PEI-based imaging or

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Imaging Types	Imaging Agents	Cell Line Models	In Vivo Models	Ref.
CT	AuNPs	A549	A549	[53]
	AuNPs	MCF-7	MCF-7	[139]
	AuNPs	HeLa	HeLa	[140] [141]
	Bi_2Se_3 NPs	A549, U14	U14	[142]
	Gd ions	KB	KB	[143]
MR	Superparamagnetic iron oxide nanocrystals	MCF-7/Adr	/	[144]
	Superparamagnetic iron oxide NPs	Chondrolyte cells	/	[145]
	Ultrasmall iron oxide NPs	4T1	4T1	[85]
	Gd(OH)(3)-doped Fe_3O_4 NPs	KB	/	[146]
	Fe_3O_4 NPs	HepG2	HepG2	[147]
	Fe_3O_4 NPs	U87MG, HeLa	U87MG, HeLa	[148]
SPECT	^{131}I	4T1	4T1	[149]
	^{99m}Tc	C6	C6	[150]

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Imaging Types	Imaging Agents	Cell Line Models	In Vivo Models	Ref.
MR/CT	AuNPs, Gd_2O_3	HeLa	HeLa	[151]
	Fe_3O_4@Au nanostars	HeLa	HeLa	[152]
	Fe_3O_4@Au nanocomposites	KB	/	[49]
	Au-Gd NPs	HeLa	HeLa	[54] [153]
MR/PA	Gd/CuS	KB	KB	[154]
SPECT/CT	^{99m}Tc, AuNPs	HCC-LM3	HCC-LM3	[58]
	^{99m}Tc, AuNPs	SKOV-3	/	[86]
	AuNPs, ^{131}I	C6	C6	[102]
MR/CT/PA	Fe_3O_4 NPs, Au nanostars	HeLa	HeLa	[155]
MR/SPECT/PA	^{19}F,^{99m}Tc, ICG	HepG2	HepG2	[156]
CT/MR/upconversion luminescence	Yb^{3+}- and Gd^{3+}-doped UCNPs	A2780	A2780	[157]

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5.3. PEI-Based Drug Delivery Systems for Cancer Theranostics

The development of nanotechnology provides new strategies with regard to the combination of therapeutic drugs and imaging agents for imaging-guided cancer therapy, namely cancer theranostics [18][158][159]. As a highly cationic polymer, PEI has the advantages of low cost, easy surface functionalization, stable chemical properties, and high loading of small molecules and NPs, enabling it to be used to construct PEI-based drug delivery systems for cancer theranostics. As an example, Shi et al. used an inverse mini-emulsion method to prepare PEI-based hybrid

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nanogels for incorporation with ultrasmall iron oxide NPs and the anticancer drug DOX for T_1 MR imaging-guided chemotherapy of tumors [85]. The nanogels displayed excellent water solubility and colloidal stability, high DOX loading efficiency (51.4%), and a pH-dependent release of the DOX with an accelerated release rate under acidic pH. Compared to free ultrasmall iron oxide NPs, the nanogels showed a much higher r_1 relaxivity at 2.29 mM^{-1} s^{-1}. Additionally, under the guidance of T_1-weighted MR imaging, the nanogels effectively inhibited tumor growth. HA-modified PEI stable Fe_3O_4@Au core–shell nanostars (NSs) were used for trimodal CT-, MR-, and photothermal-imaging-guided PTT of tumors [152]. Here, HA-modified PEI provided the NSs with desirable colloidal stability, biocompatibility, and targeted specificity to cancer cells overexpressing CD44 receptors. With the Fe_3O_4 core NPs and Au star shell, the NSs could be used as a contrast agent for efficient MR and CT imaging of tumors in vivo. Furthermore, because of the NIR absorption property, the NSs could also be used as a nanoprobe for thermal imaging and PTT of tumors.

Laponite (LAP) is a synthetic biodegradable nanoclay with a large specific surface area and cation exchange capacity [100]. Combining LAP with PEI not only can improve the drug loading rate of the complex, but also produce good stability. Zhuang and colleagues created PEI-modified LAP using a polylactic acid-PEG-COOH spacer. The PEI-LAP was used as a nanoplatform to embed AuNPs and load DOX for targeted CT imaging and chemotherapy of tumors [140]. The formed nanocomplexes displayed excellent colloidal stability and a high drug loading efficiency of up to 91.0 ± 1.8%, which significantly inhibited the growth of tumors and reduced the side effects of DOX. Alkoxyphenyl acylsulfonamide (APAS) as a zwitterionic polymer can enhance the cellular uptake of NPs at the pH of tumor microenvironment [161]. Zhu et al. used APAS-linked PEI as a vehicle to entrap AuNPs and labeled it with radioactive ^{131}I to enhanced trimodal SPECT/CT imaging-guided radiotherapy of tumors [102]. Because of the charge conversion property of APAS, the AuNPs can change from neutral to positively charged in a weak acid environment, thus promoting cellular uptake. In addition, after ^{131}I labeling, the therapeutic agents can enhance SPECT/CT dual mode imaging and radiotherapy of tumors in vivo.

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