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Recent advances in the development of poly(ester amide)s-based carriers for drug delivery

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ABSTRACT

Biodegradable and biocompatible biomaterials have several important applications in drug delivery. The biomaterial family known as poly(ester amide)s (PEAs) has garnered considerable interest because it exhibits the benefits of both polyester and polyamide, as well as production from readily available raw ingredients and sophisticated synthesis techniques. Specifically, α-amino acid-based PEAs (AA-PEAs) are promising carriers because of their structural flexibility, biocompatibility, and biodegradability. Herein, we summarize the latest applications of PEAs in drug delivery systems, including antitumor, gene therapy, and protein drugs, and discuss the prospects of drug delivery based on PEAs, which provides a reference for designing safe and efficient drug delivery carriers.

1. Introduction

Drug delivery in the body is crucial for therapeutic efficacy, and delivery technology is indispensable, ranging from common small-molecule drugs to today's popular immunotherapeutic agents, which has an important significance in controlled-release and targeted drug delivery, enhancing drug stability and promoting drug absorption (Park et al., 2022). In recent years, the rapid development of pharmacology, materials science, and biomedicine has led to emergence of new delivery strategies that have quickly been adapted to the ever-changing needs of drug delivery, making it possible to develop many drugs into dosage forms (Allen and Cullis, 2004). Despite this, with the advent of new-generation therapeutics such as peptides, monoclonal antibodies, nucleic acids, and living cells, new challenges have arisen, especially with stability (peptides), efficiency of intracellular delivery (nucleic acids), and survivability and expansion (living cells) (Vargason et al., 2021). These limitations make it challenging for conventional formulations to effectively fulfill their therapeutic roles. Therefore, drug delivery technologies must evolve to address these shortcomings (see Fig. 1).

The physicochemical properties of drugs, delivery carriers, and delivery devices are all included in the scope of drug delivery systems. Drug delivery carriers are a class of biomedical materials that have gradually emerged with the development of material science. Among them, polymer-based carriers have been extensively studied, particularly in antitumor therapeutics (Beck-Broichsitter et al., 2015; Kamaly et al., 2016). They can improve tumor cell recognition and destruction through surface modification or co-administration strategies, and also can be engineered with functional groups or linkages that respond to the intelligent release of drugs based on the tumor microenvironment (Jiang et al., 2017; Lou et al., 2019).

Both natural and synthetic polymers, such as cyclodextrins, dextran, chitosan, cellulose, polylactic acid, and polyhydroxyacetic acid, are often utilized as drug delivery carriers. Their application is largely influenced by their mechanical, physicochemical, and biological characteristics (Schmaljohann, 2006; Qiu and Park, 2012; Rehfeldt et al., 2007). Aliphatic polyesters, represented by polylactic acid (PLA) and polyglycolic acid (PGA), are widely used in the biomedical fields owing to their adequate biodegradability and biocompatibility (Tang et al., 2016). However, their single chemical structure lacks extensively tunable physicochemical features, as well as weak mechanical and thermal qualities limit their applicability. Polyamides are a very important class of polymers with high tensile strength, insulating properties, heat resistance, and abrasion resistance. Compared to polyesters, the amide bonds and strong intermolecular hydrogen bonding interactions of polyamides significantly improve their thermal and mechanical properties. Meanwhile, polyamides have the disadvantage of slower biodegradation rate (Winnacker and Rieger, 2016). To obtain

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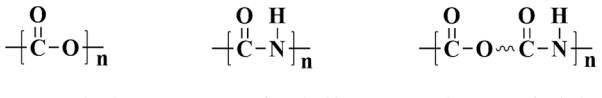

Fig. 1. Structure of polyester (PE), polyamide (PA), and poly(ester amide) (PEA).

polymers with excellent overall properties, Carothers and Hill (1932) developed a new type of aliphatic copolymer, "poly(ester amide)" (PEA), by melt polycondensation using monomers with 1,3-propanediol, adipic acid, and aminocaproic acid. Their main chain contains both ester and amide bonds. The ester bonds allow PEA to degrade under physiological conditions, resulting in good solubility. Strong hydrogen bonds among the amide groups enable PEA to exhibit superior thermal and mechanical properties. With the deepening research on such materials, various PEA polymers have been synthesized, and their applications have continuously expanded (Lips et al., 2006; Rodriguez-Galan et al., 2011; Sun et al., 2011).

1.1. Amino acid-based PEAs (AA-PEAs)

Poly(amino acid)s are another widely used class of polymeric materials. Structurally analyzed, they have a similar chemical structure to proteins and have the same degradation product, α-amino acids. Poly (amino acid)s exhibit good biodegradability and biocompatibility, and can facilitate tissue repair and cell growth, leding to extensive applications in the biomedical fields, including use as drug release carriers and surgical sewing lines (Hu et al., 2018). Additionally, these polymeric materials can be functionalized because of their unique functional groups. However, their drawbacks such as high crystallinity, slow degradation, poor mechanical properties, and antigenicity (Katsarava, 2003), preventing them from being widely used in clinical settings. Researchers have shown interest in natural amino acid-based polymers that are capable of fully utilizing the special biological properties of amino acids while avoiding the drawbacks of poly(amino acid)s. To this end, a class of novel biodegradable polymers known as poly(ester amide)s with α-amino acid structural units were gradually developed in the 1990 s. Three units (natural α-amino acid, aliphatic dicarboxylic acid, and aliphatic diol) were polycondensed to produce PEAs (Fig. 2). By rationally changing the chemical structures of the three units, products with different physicochemical, mechanical, and thermal properties, can be obtained and applied in different fields (Pang and Chu, 2010; Yuan et al., 2021; Wu et al., 2011). Amino acid units not only confer biodegradability and biocompatibility but also serve as functional groups for chemical coupling with some drugs, expanding the applications of PEAs (Barrera et al., 1993). Additionally, the pendent chains of amino acids can be futher modified to adjust the structures of PEAs, thereby altering their physicochemical properties, including hydrophobicity, biodegradability, affinity for drugs, charge properties, and optical properties, making it a promising drug delivery carrier (see Fig. 3).

1.2. Structure-property relationships

The physicochemical properties of PEAs can be adjusted by structural modifications without compromising their excellent biocompatibility. AA-PEAs not only have a chemical structure similar to that of proteins, but can also participate in normal physiological metabolism as pseudo-proteins. After simple hydrolysis or enzymatic degradation, the natural amino acids will be released into the circulation and absorbed. Due to the structural diversity, especially the multiple stereospecific information on different functional groups and amino acids, AA-PEA becomes a promising biomaterial, and some preliminary studies on its structure–property relationships have been conducted.

It has been demonstrated that the ratio of amide to ester directly affects polymer properties (Chromcová et al., 2008). Futher, differences in the chemical structure of the monomers (e.g., isomers, residues, or chain segmenters) have an equally important effect on PEA properties. Fan et al. (2002) synthesized stereoisomeric L- and D- Phe-PEAs and evaluated their enzymatic biodegradation properties. As expected, L-Phe-PEAs exhibited better enzymatic degradability than D-Phe-PEAs. A possible explanation is that the natural α-amino acids in proteins are almost L-type, and L-amino acid residues are more protease specific. Accordingly, the libraries of AA-PEAs are all based on L-type amino acids. Armelin et al. (2001) explored the hydrolytic and enzymatic degradation properties of AA-PEAs based on L-glycine and L-alanine with different ester/amide ratios. The proportion of the α-amino acid residues in the repeating unit were found to have a strong influence on the degradation rate. Natarajan et al. (2017) synthesized PEAs with different chain lengths and hydroxyl positions using different aliphatic and aromatic diols. The results indicated that biodegradability, release kinetics, and cytocompatibility can be adjusted by controlling the chain length of the diol and the position of hydroxyl groups.

The charge properties of side chain residues will have a crucial impact on the interactions to the carried drugs and the supported cells. PEAs with positive charges, especially anionic L-Arg- or L-Lys-PEAs, can interact electrostatically with negatively charged cell membranes, thereby promoting cell internalization. In addition, the positive charge

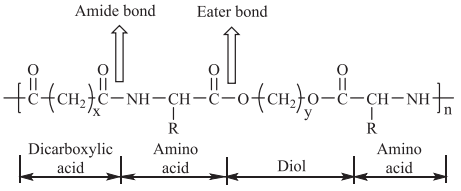

Fig. 3. Chemical structure of AA-PEA (reproduced with permission from Wu et al., 2011).

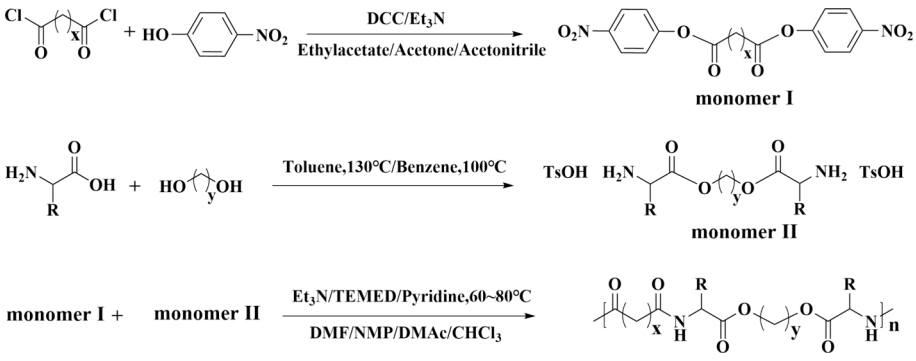

Fig. 2. Solution polycondensation for AA-PEA synthesis (reproduced with permission from Han and Wu, 2022).

of cationic polymers is more conducive to directly loading negatively charged drugs, such as nucleic acids and proteins, through electrostatic adsorption. Wu et al. (2012) systematically investigated the structure–function relationship of arginine-based poly(ether ester amide) gene vectors. You et al. (2018) also attempted to synthesize a series of structurally tunable Arg-PEAs as nucleic acid delivery vectors, and studied the effects of their different structures on siRNA transfection efficiency. The detailed discussions will be listed at "3. Gene delivery vector".

The study of structure–property relationships has provided support for obtaining PEAs with excellent biological properties, such as satisfactory drug delivery carriers. However, there are still many unrevealed structural characteristics and variations, or mechanisms affecting some other properties that need to be further investigated. To satisfy the needs of biomedical applications, researchers have developed a variety of forms based on PEAs, such as nanoparticles, microspheres, liposomes, hyperbranched structures, three-dimensional (3D) micropore hydrogels, and scaffolds (Han and Wu, 2022). In this review, we primarily summarize the applications of PEAs in drug delivery systems, including antitumor, gene therapy, and protein drugs, and elaborate on the prospects of PEA-based drug delivery, providing a reference for the design of safe and efficient drug delivery carriers.

2. Targeted delivery carriers for tumor therapy

Cancer is a major obstacle to extending human life expectancy in the 21st century. International research organizations estimated that by 2030, there will be 21.4 million new cancer-related cases and 13.2 million new cancer-related deaths annually worldwide (Sung et al., 2021). Chemotherapy is one of the most commonly used treatments for cancer, with the goal of delivering drug molecules into tumor cells to inhibit their growth or kill them (Sun et al., 2017). Although chemotherapeutic drugs can reach various organs through blood circulation, there are still many challenges, including short circulation time, poor water solubility of small molecules, low bioavailability, poor tumor specificity, and multidrug resistance (Chen et al., 2017). Therefore, the need for clinically targeted delivery technologies for antitumor drugs has considerably increased. Synthetic polymers have attracted significant attention for the controlled release of drugs, and smart nanoscale drug delivery platforms derived from PEAs offer an effective strategy for high precision tumor therapy. Guo and Chu (2007) were the first to investigate the possibility of using PEAs as drug delivery carriers. Biodegradable hydrogels (FPBe-G) were created by photopolymerizing two precursors: FPBe, an unsaturated PEA (UPEA) based on fumarate, and poly(ethylene glycol)diacrylate (PEG-DA). This hydrogel had a porous cross-linked network structure, and paclitaxel (PTX) was loaded into it, which exhibited sustained and near-linear release characteristics within 2 months, demonstrating the feasibility of PEA in drug delivery applications. Ghaffar et al. (2011) conducted an in-depth research on the biodegradation process of PEA by LC-ToF-MS technique and monitored the enzyme (α-chymotrypsin)-mediated surface erosion degradation mechanism. This continuous linear degradation process further supports the potential of PEA for drug delivery applications.

Guo and Chu (2009) produced novel biodegradable submicron microspheres of phenylalanine-based PEA using an oil-in-water (O/W) emulsion/solvent evaporation technique. Their biodegradation behaviors at 37℃were examined in relation to the concentration and duration of the enzyme (α-chymotrypsin). The result revealed a surface erosion degradation mechanism that was comparable to earlier reports. Without having a marked impact on size and surface morphology, the PTX-loaded microspheres showed high encapsulation efficiency, indicating the possibility of injectable delivery of hydrophobic antitumor drugs by AA-PEA microspheres. To develop a novel therapeutic approach for non-small cell lung cancer, a library of phenylalanine based PEAs were combined with docetaxel (Dtxl) to produce nanoparticles (NPs) (Chen et al., 2018). The screened Dtxl-8P4 NPs showed persistent drug release and a mild burst action, together with the advantages of small size and high drug loading capacity. In addition, Dtxl-8P4 NPs had prolonged blood circulation, effectively escaping lysosomal degradation and delivering Dtxl to the tumor site. It follows that AA-PEA nanoparticles are capable of loading large amounts of hydrophobic drugs and may be a potential method for antitumor drug delivery.

2.1. Smart-responsive PEA drug carriers

Over the past 30 years, nanotechnology has achieved great success in the targeted delivery of antitumor drugs. Combining drug molecules with nanocarriers through embedding, encapsulation, adsorption, or covalent bonding to form a "nano-delivery system" can improve the solubility of the drug molecules, prolong the circulation time of the encapsulated drugs *in vivo*, and reduce drug toxicity (Wang et al., 2014; Cun et al., 2016). Simultaneously, the abnormal tumor vascular system allows drugs to accumulate passively at the tumor site through the enhanced permeability and retention (EPR) effect (Gerlowski and Jain, 1986; Maeda, 2015). Various nanodrugs, such as doxorubicin liposomes and paclitaxel micelles, have been used in clinical treatment based on this effect. However, owing to the existence of multiple drug delivery barriers in the body, traditional nanodelivery systems cannot achieve the desired therapeutic effect. The heterogeneity of the EPR effect in different tumors and the complex tumor microenvironment (TME) also limit the delivery efficiency of nano-delivery systems (Bertrand et al., 2014; Khawar et al., 2015). Therefore, it is extremely important to enhance drug permeability, cellular uptake and intracellular release efficiency, or to endow nanodrugs with more functionalities for higher antitumor activity.

The complex TME at the tumor site is a significant obstacle to drug delivery that cannot be ignored (Overchuk and Zheng, 2018). The extracellular microenvironment of tumors is characterized by microacidity, hypoxia, and high levels of enzymes secreted by the tumor cells. Tumor cells also have many biochemical indicators that are different from normal cells, such as high concentrations of reactive oxygen species (ROS) and glutathione (GSH) (Mo and Gu, 2016). These characteristics have been widely used as endogenous stimulation sources to mediate smart-responsive drug delivery systems to achieve activation of target molecules and controlled drug release. Based on these properties, responsive nanodrug delivery systems provide new opportunities for tumor therapy. In the following section, we summarize PEA-based TME-responsive drug delivery strategies developed in recent years.

2.1.1. pH-responsive nanodrug delivery systems

Changes in pH are one of the characteristics of diseased tissues in the body. In a normal physiological state, the pH of extracellular fluid and blood is close to 7.4, whereas the pH of pathological sites of inflammation, infection, or tumors is less. The rapid proliferation of tumor tissues leads to the lack of nutrients and oxygen at the tumor site, and a high glycolysis rate causes acidic metabolites to accumulate in the tumor mesenchyme, causing a reduction in the pH of the extracellular environment (6.5–7.2) (Stubbs et al., 2000). In addition, the pH of intracellular endosomes and lysosomes can be lower (4.0–6.0) (Zou et al., 2014). Therefore, the significant pH value difference between tumor and normal tissues can be exploited for designing polymeric nanodelivery systems, with the main design strategies including conformational or solubility changes, charge inversion, protonation effects, or chemical bond breaking.

Certain groups are deprotonated at physiological pH but can be protonated in an acidic environment, causing the drug carriers to deform or degrade. Based on this, introducing protonated groups on the surface of the polymers by physical or chemical methods to design pH-sensitive nanodelivery systems can achieve desirable effects, such as nanoparticle disintegration, enhanced cell uptake, and deep tumor infiltration (Wang et al., 2014). Yuan et al. (2021) synthesized an *in vivo* metabolizable branched PEA (BPEA) using arginine, phenylalanine, and

inositol. Arginine and phenylalanine serve as the hydrophilic and hydrophobic chain segments, respectively, which can regulate the properties of the BPEA such as hydrophilicity, hydrophobicity and solubility. PTX was encapsulated into BPEA carriers to prepare nanoparticles, which can exploit the EPR effect to deliver drugs to tumor cells; the protonation of arginine's guanidine group occurred when the pH dropped, which increased the hydrophilicity of BPEA, diminished the stability of the nanoparticles, and speeds up the release of PTX.

Introducing pH-triggered broken chemical bonds is one of the most widely used strategies for pH-responsive nanodelivery systems. The commonly used chemical bonds include hydrazones, Schiff bases, *cis*-maleic acid monoamides, and acetals (Kanamala et al., 2016). They are stable under normal physiological conditions and break under acidic conditions, degrading the carriers and in turn increasing their uptake or accelerating drug release from tumor cells. Chen et al. (2018) created a core–shell nanoparticle platform using PEAs with different amino acids, diols, and dicarboxylic acids. The core of the preferred APP1i@eNP nanoparticle was loaded with both the paclitaxel/human serum albumin (PTX/HSA) complex and free PTX, whereas the shell was only consisted of the PTX/HSA complex and surface-modified with PEG for better biosafety, longer body circulation, and higher tumor enrichment. Desorption of the outer shell of APP1i@eNP occurred at a lower pH with an increase in particle size, indicating decomposition of the nanoparticles, which supports the inherent acid-sensitive nature of PEAs containing ester bonds.

2.1.2. *Reduction-sensitive drug delivery systems*

GSH is the main reducing substance in cells and mainly plays a role in preventing the oxidation of hemoglobin and scavenging free radicals, as well as protecting cell membranes in cells (Schafer and Buettner, 2001). It has been found that the intracellular GSH concentration is 100–1000 times higher than the extracellular one (Cheng et al., 2011). Owing to the extremely fast proliferation and vigorous metabolism of tumor cells, the intracellular GSH concentration is significantly increased and is approximately 7–10 times higher than that in normal cells (Chen et al., 2018). Based on the difference in GSH concentration between tumor and normal cells, nanodrug delivery systems with redox sensitivity can be designed. Disulfide bond (S-S) is a commonly used structure for constructing reduction responsive carriers. It can remain stable in an extracellular environment with low GSH concentrations, whereas in an intracellular environment with high GSH concentrations, it will be rapidly cleaved by the GSH-mediated thiol-disulfide exchange reaction, causing the carrier to crack and release drugs (Sun et al., 2009). Sun et al. (2015) used the disulfide-containing di-*p*-toluenesulfonate of bis-L-phenylalanine diester (SS-Phe-2TsOH) and di-*p*-nitrophenyl adipate (NA) for solution polycondensation to prepare a class of enzymatically and reductively degradable α-amino acid-based PEA (SS-PEA) containing disulfide bonds. DOX-loaded SS-PEA nanoparticles were shown to enter tumor cells through endocytosis and release a large amount of DOX under the action of α-chymotrypsin and GSH (Fig. 4A). The same team coupled SS-PEA with thiol-functionalized galactose (Gal-SH) via the Michael addition process to create a novel reductively degradable PEA-grafted galactose (SS-PEA-Gal) copolymer (Lv et al., 2015). β-D-galactose (Gal), a specific targeting ligand for the ascending salivary acid glycoprotein receptor (ASGP-R) in mammalian hepatocytes, is a useful tool for targeted chemotherapy of hepatocellular carcinoma. The copolymer-derived nanoparticles have good drug-loading capacity, in which Gal acts as a hydrophilic shell and SS-PEA as a hydrophobic core. Experiments showed that DOX-loaded nanoparticles demonstrated strong targeting of hepatocellular carcinoma cells, resulting in highly selective antitumor effects *in vitro* (Fig. 4B). This work proposes a new method for preparing tumor-targeting nanoparticles by grafting hydrophilic targeting ligands onto a stimulus-sensitive polymer skeleton.

2.1.3. *Enzyme-responsive nanodrug delivery systems*

Various enzymes exist in the microenvironment of tumor tissues,

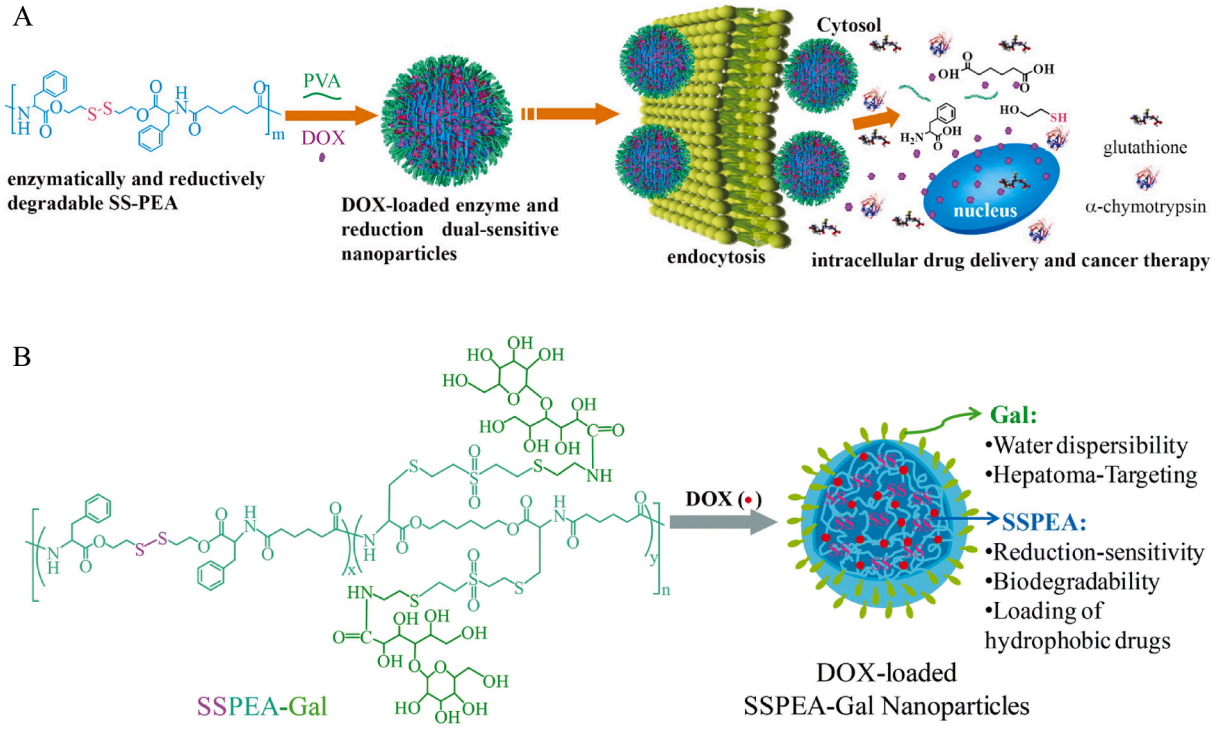

Fig. 4. Reduction-sensitive drug delivery based on disulfide bond. (A) Schematic illustration of DOX-loaded SS-PEA nanoparticles for antitumor drug delivery (reproduced with permission from Sun et al., 2015). (B) Schematic illustration of DOX-loaded SSPEA-Gal nanoparticles for antitumor drug delivery (reproduced with permission from Lv et al., 2015).

with concentrations and activities much higher than those of normal tissues, playing an important role in the growth, invasion, and metastasis of tumors (Li et al., 2017). Due to the high concentration of enzymes in tumor tissues, such as histone protease, glycosidase, matrix metalloproteinase, and hyaluronidase, enzyme-responsive polymer nanodelivery systems can be designed to achieve tumor-specific drug release and controlled morphology changes (Sun et al., 2014; Hu et al., 2012). Ji et al. (2017) prepared a biodegradable nanocomplex (HA(CD)-4Phe4) based on β-cyclodextrin-grafted hyaluronic acid and phenylalanine-based PEA for loading a naturally sourced chemotherapeutic drug, garcinic acid (GA). Hyaluronic acid (HA) can actively target over-expressed CD44 receptors in multiple tumor cells and improve the delivery efficiency. Under the action of hyaluronidase, the carrier underwent enzymatic biodegradation in tumor tissues and accelerated the release of GA from the nanocomplexes. Results showed that the GA-loaded nanocomplexes exhibited better cytotoxicity in MDA-MB-435 multidrug-resistant melanoma cells than free GA. Moreover, inhibition of matrix metalloproteinase activity was also detected in these cells, demonstrating potency of the nanocomplex in inhibiting tumor metastasis.

2.1.4. Reactive oxygen-responsive nanodrug delivery systems

ROS are a class of highly oxidizing single-electron reduction products produced by the mitochondria, and they are involved in regulating various physiological and pathological processes. Excess ROS are produced at focal sites in many pathological states such as cardiovascular disease, inflammation, and cancer (Tan and Suda, 2018), which can cause some cytotoxicity from oxidative stress in cells. Tumor cells have greater ROS levels compared to normal cells, and designing ROS-responsive carriers can help release therapeutic agents precisely and rapidly to the target cells through this difference (Saravanakumar et al., 2017). H_2O_2 is the main component of ROS with a concentration of approximately 100 times in TME than that in normal tissues, which makes it an effective endogenous stimulant as a major marker of oxidative stress (Hsu and Almutairi, 2021). Xu and Chu (2021) synthesized a L-methionine-based PEA (Met-PEA) and coupled PEG to the end of the chain. The Met-PEA-PEG polymer could be self-assembled into nanoparticles for antitumor drug delivery. Met-PEA was the core of the nanoparticles for loading hydrophobic antitumor drugs, and PEG prolonged the circulation time and reduced the adsorption of proteins and enzymes on their surfaces, slowing down the biodegradation rate of Met-PEA. Methionine is an important antioxidant *in vivo*, and the Met residues of Met-PEA-PEG can be oxidized by ROS to form methionine sulfoxide, which makes the polymer more hydrophilic. At high concentrations of H_2O_2, the structure and morphology of the self-assembled nanoparticles were sensitive to the oxidizing environment, their size became inhomogeneous, and stability decreased. Loading Nile Red into Met-PEA-PEG-NPs exhibited a time-dependent release behavior induced by H_2O_2. Moreover, these NPs were sensitive to high levels of intracellular ROS levels in PC3 prostate cancer cells. This oxidative reactivity enabled Met-PEA-PEG-NPs to accelerate drug release under oxidative stress conditions and promoted effective drug delivery at localized oxidative disease sites.

2.2. PEA-based photochemical internalization and photodynamic therapy

Tumor cells internalize nanodrugs through a process called endocytosis that is mediated by transporter protein (Sahay et al., 2010), in which the plasma membrane encloses the nanoparticles, forming a closed vesicle structure that eventually merges with endolysosomes (Albanese et al., 2012). However, endolysosomal chelation may delay drug release and affect therapeutic efficacy (Kou et al., 2013; Austin et al., 2005). Photochemical internalization (PCI) is an effective technique for endosomal escape and cytoplasmic release of drugs through the photoinduced cleavage of endolysosomes (Cho et al., 2003). Currently, photosensitizers and therapeutic agents are administered separately, and differences in their biodistribution and pharmacokinetic profiles may affect the efficiency in facilitating drug therapy. Ji et al. (2019) prepared a reduction-sensitive nanocomplex ArgPEA-ss-HA via disulfide bonding, and the PCI photosensitizer AlPcS2a was coupled to the surface of the nanocomplex by PEG. The nanocomplex enabled the co-delivery of the photosensitizer and the therapeutic drug, eliminating differences in biological distribution caused by separation administration. AlPcS2a induced endolysosomal rupture of MDA-MB-231 cells upon light irradiation, and DOX-loaded nanocomplexes were translocated into the cytoplasm, where GSH severed the disulfide bonds of the polymers and accelerated drug release (Fig. 5). The PCI effect and DOX-loaded nanocomplexes synergistically inhibited MDA-MB-231 cells, and a light-enhanced antitumor effect was observed at a well-tolerated dosage.

Photodynamic therapy (PDT) is a tumor treatment technology that was introduced in the late 1970s, its mechanism involves using specific wavelengths of light to activate photosensitizers that are selectively retained in tumor tissues, interacting with the oxygen to produce chemically active singlet oxygen and a number of active free radicals. These radicals futher interact with biological macromolecules to destroy cellular organelle structures and selectively kill tumor cells (Dolmans et al., 2003). Currently, PDT still faces challenges that affect its efficacy. Similar to PCI technology, PDT therapeutic efficacy depends on the photosensitizers, most of which are poorly water-soluble and difficult to administer directly via intravenous injections. Additionally, accumulation of photosensitizers in normal tissues has been observed (Allison et al., 2004), and non-targeted distribution of photosensitizers not only affects the efficacy but also leads to cutaneous photosensitization; therefore, patients undergoing PDT are usually advised to avoid sunlight exposure to minimize side effects (O'Connor et al., 2009). Considering the drawbacks of the direct administration of free photosensitizers, targeted delivery of photosensitizers to the action site with suitable carriers is a feasible strategy. Many polymeric nanocarriers have been reported for photosensitizers that can protect them from degradation, improve their circulation time in the blood, selectively target tumor tissues, and control their release (Mastera et al., 2013). Arg-PEA and HA were combined to create a biodegradable nanocomplex HA-Arg-PEA as the carrier for chlorin e6 (Ce6), a new type of photosensitizer (Ji et al., 2017). HA can promote tumor-specific endocytosis mediated by the overexpression of the CD44 receptor and achieve targeted delivery of Ce6. Arg-PEA not only provided electrostatic interactions with HA to form self-assembled nanostructures but also improved the monomerization of Ce6 at physiological and mildly acidic pH. The carrier entered the cell and underwent enzymatic degradation in the presence of hyaluronidase, rapidly released Ce6 and generated singlet oxygen. *In vitro* studies showed that the HA-Arg-PEA nanocomplexes significantly increased the level of Ce6 in MDA-MB-435 multidrug-resistant tumor cells in a short time, and the efficiency of PDT was enhanced.

2.3. PEA-based tumor vaccine immunotherapy

Tumor immunotherapy is a therapeutic method that utilizes the immune system to specifically kill tumor cells and induce immune memory in the body, inhibiting the proliferation, metastasis, and recurrence of tumors (Klevorn and Teague, 2016). More effective techniques need to be researched because current immunotherapy has drawbacks such as unreliable response rates, toxic side effects, and intrinsic tumor immunity resistance (De Miguel and Calvo, 2020; Sharma and Allison, 2015). Unlike ordinary preventive vaccines, nanotechnology-based tumor vaccines and tumor-specific neoantigens can produce durable and specific antitumor responses in patients and are expected to be the next generation of immunotherapy (Morse et al., 2021). Tumor vaccines can use tumor-associated antigens such as DNA, RNA, proteins, or peptides to modulate the immune system. After the vaccine enters the body, the antigen is recognized by pattern recognition receptors (PRRs) on the surface of antigen-presenting cells (APCs), such

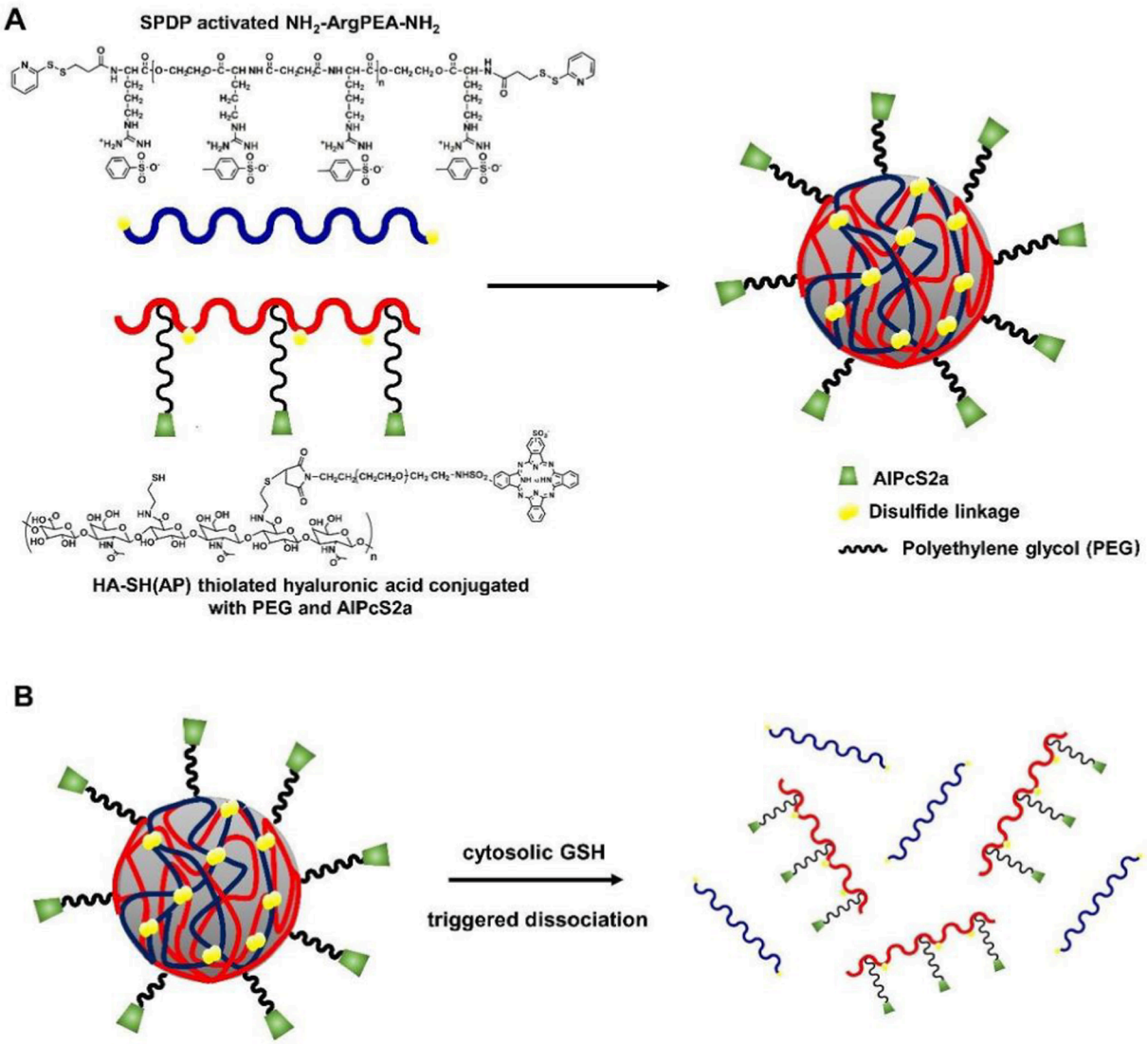

Fig. 5. Co-delivery of photosensitizers and therapeutic drugs. (A) The formation of reduction-sensitive nanocomplex ArgPEA-ss-HA(AP) via disulfide linkage. (B) Dissociation of ArgPEA-ss-HA(AP) nanocomplex triggered by GSH (reproduced with permission from Ji et al., 2019).

as peripheral dendritic cells (DCs), and transported to immune organs, where it is ultimately presented to T cells through major histocompatibility complex (MHC) molecules, initiating a unique tumor-killing process (Sahin and Türeci, 2018). Nanovaccines can localize tumor-specific antigens and adjuvants on the same particles to simultaneously present peptides and be in an activated state, which is the key to activating antigen-specific T cells to kill tumor cells and achieve an immune response. Additionally, nanocarriers can effectively protect the antigens and adjuvants from the external environment during delivery. Some studies have shown that, compared with traditional subcutaneous immunization with bare peptides, loading antigen peptides and adjuvants with nanoparticles before subcutaneous inoculation can increase the number of new antigen-responsive T cells by approximately 30 times (Kuai et al., 2017).

The carrier is a warehouse that controls the release of antigens and adjuvants and is the main skeleton of the vaccine. Various materials such as metal nanoparticles, silica nanoparticles, liposomes, and polymers have been used in antigen delivery (Meng et al., 2016). Ji et al. (2018) developed an Arg-Phe-PEA-based therapeutic carrier containing antigenic proteins for tumor immunotherapy. This carrier adopted a PCI strategy to form an electrostatic complex with the photosensitizer AlPcS2a, and the photochemical blockade of the endocytosis region by AlPcS2a enabled the model antigen ovalbumin (OVA) to achieve endosomal escape. OVA stimulation elicited MHC-I presentation and a cytotoxic T cell response, and the intensity of the stimulation response was dependent on the doses of the photosensitizers and light. High doses of the photosensitizers and light enhanced the antigen-specific $CD8^+$ T cell responses *in vivo*, demonstrating potential adjuvant effects. Xie et al. (2023) investigated the adjuvant properties of FK-13, a core peptide derived from the antimicrobial peptide LL-37. To ensure co-delivery of the antigen and FK-13, the investigator fused the antigenic epitope with FK-13 to obtain a fusion peptide, FK-33, and used a Phe-PEA polymer (8p4) as a delivery carrier. *In vivo* inoculation of 8p4 + FK-33 nanoparticles (8FNs) induced dendritic cell activation in lymph nodes and produced strong tumor antigen-specific $CD8^+$ T cell responses (Fig. 6). The 8FNs nanovaccine had noteworthy therapeutic and preventative effects on the growth of tumors in situ, as well as an efficient inhibition of tumor spread. Moreover, 8FNs can bind to different tumor antigens and show synergistic therapeutic effects with anti-programmed cell death protein 1 (PD-1) therapies. 8FNs are a promising option for personalized tumor vaccines and could be applied as a combinatorial method to enhance existing immunotherapies.

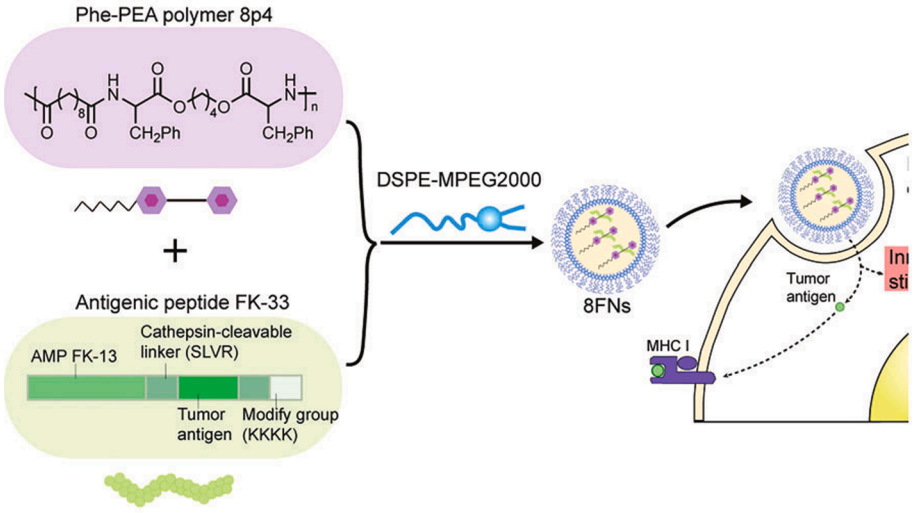

Fig. 6. Schematic illustration of the vaccine design, tumor antigen presentation, and innate stimulation in dendritic cells by 8FNs nanovaccine (reproduced with permission from Xie et al., 2023).

3. Gene delivery vector

Gene therapy has recently become a popular topic in medicine, it refers broadly to treatments that use genes as drugs. In the process, functional exogenous genes are introduced into recipient cells, which can express products or inhibit the transcription and translation of certain genes to achieve therapeutic purposes. In 1972, Neufeld et al. (1972) first proposed gene therapy to treat human genetic diseases, and FDA approved the first trial of genetic therapy for adrenal acid deficiency in 1990 (Sheridan, 2011); thus, gene therapy was introduced in clinics. At the beginning of the 21st century, with the rapid development of genome sequencing, progress in vector technology, and improvements in the safety, gene therapy began to gradually make breakthroughs and enter a stage of rapid development.

Currently, gene therapy is divided into two main categories: *in vitro* and *in vivo*. Intravenous injection is a direct means of delivering exogenous genes to the target, making *in vivo* therapy more straightforward and practical than *in vitro* therapy. However, owing to the poor stability, genes are vulnerable to nuclease degradation during *in vivo* transmission. To achieve a more effective *in vivo* gene therapy, selecting safe and efficient gene vectors is necessary. Vectors for gene delivery are usually divided into viral and non-viral delivery systems. Viral vectors such as adenoviruses, adeno-associated viruses, and lentiviruses are used in research for their efficient gene transmission capabilities, but the potential for mutation, immunogenicity and other safety problems restrict them from use in clinical applications (Mizuguchi and Hayakawa, 2004). Compared with viral vectors, non-viral vectors such as cationic polymers, liposomes, and dendrimers have various advantages, including high production, simple and controllable structures, easy modification, and low immunogenicity (Pérez-Martínez et al., 2011). These vectors generally need to form complexes with genes to protect them from degradation, simultaneously facilitating cellular uptake and promoting their endosome escape during gene delivery (Lungwitz et al., 2005). Cationic polymers are of great interest owing to these properties. Commonly used cationic polymer vectors include polyethyleneimine (PEI), poly-l-lysine (PLL), chitosan and dendrimers (He et al., 2010). Ideal gene vectors should have both low toxicity and high transfection efficiency (Shim and Kwon, 2010); however, there are currently no vectors with either feature. PEI, dendritic polymers, and high-molecular-weight PLL with high transfection efficiency have a certain degree of cytotoxicity, whereas chitosan with good biocompatibility only dissolves in dilute acid. Therefore, the development of vectors with low toxicity and high transfection efficiency is important for gene delivery.

AA-PEAs have drawn the interest of scientists as gene delivery vectors (Chu, 2012), and their properties are related to the type of amino acid introduced. Those who synthesized from hydrophobic nonpolar amino acids are typically neutral and water-insoluble, whereas the use of polar amino acids such as lysine, arginine, and histidine yields AA-PEAs with cationic or anionic charges. AA-PEAs containing lysine or arginine were expected to be excellent vectors for gene delivery because of their good water solubility and cationic nature under physiological conditions (Chu, 2012; Wu, 2011). Yamanouchi et al. (2008) used Arg-PEAs as vectors for plasmid DNA, and *in vitro* cellular experiments demonstrated that their transfection efficiency was comparable to that of the commercially available transfection reagent. Owing to the limitations of Arg-PEAs in transfecting primary and stem cells, Wu et al. (2012) developed a new family of arginine-based poly(ether ester amide)s (Arg-PEEAs). Certain members of the Arg-PEEA family have shown reduced cytotoxicity compared to PEI and improved transfection efficiency compared to Lipofectamine 2000. You et al. (2018) developed a class of finely structured Arg-PEA libraries via polycondensation, the authors regulated their structures by adjusting the the glycol chain segment during the preparation process and studied the influence of the different structures on siRNA transfection effects. Research results showed that the longer the CH2 segment of the diol or the presence of pendent groups, the stronger the hydrophobicity and the worse the transfection efficiency of Arg-PEAs. When the diol contains unsaturated bonds, Arg-PEAs have the strongest hydrophobicity and the lowest transfection efficiency, while when they contain ether bonds, presenting high hydrophilicity and transfection efficiency. Moreover, the particle size and zeta potential of the Arg-PEA/siRNA nanoparticles were directly correlated with the chemical structure of Arg-PEA (Fig. 7). Lancelot et al. (2018) studied on the PEA dendritic polymers, which were fully biocompatible and degradable in aqueous media at physiological and acidic pH. The presence of a large number of peripheral cationic groups allowed these dendritic macromolecules to spontaneously form dendritic complexes with pDNA and siRNA, showing efficient *in vitro* siRNA transfection in both tumor and non-tumor cell lines.

4. Protein drug delivery systems

Proteins are involved in various biochemical reactions in organisms and are the main bearers of life activities. Many human diseases are closely related to the functional regulation of proteins. In 1982, the introduction of recombinant human insulin marked the birth of

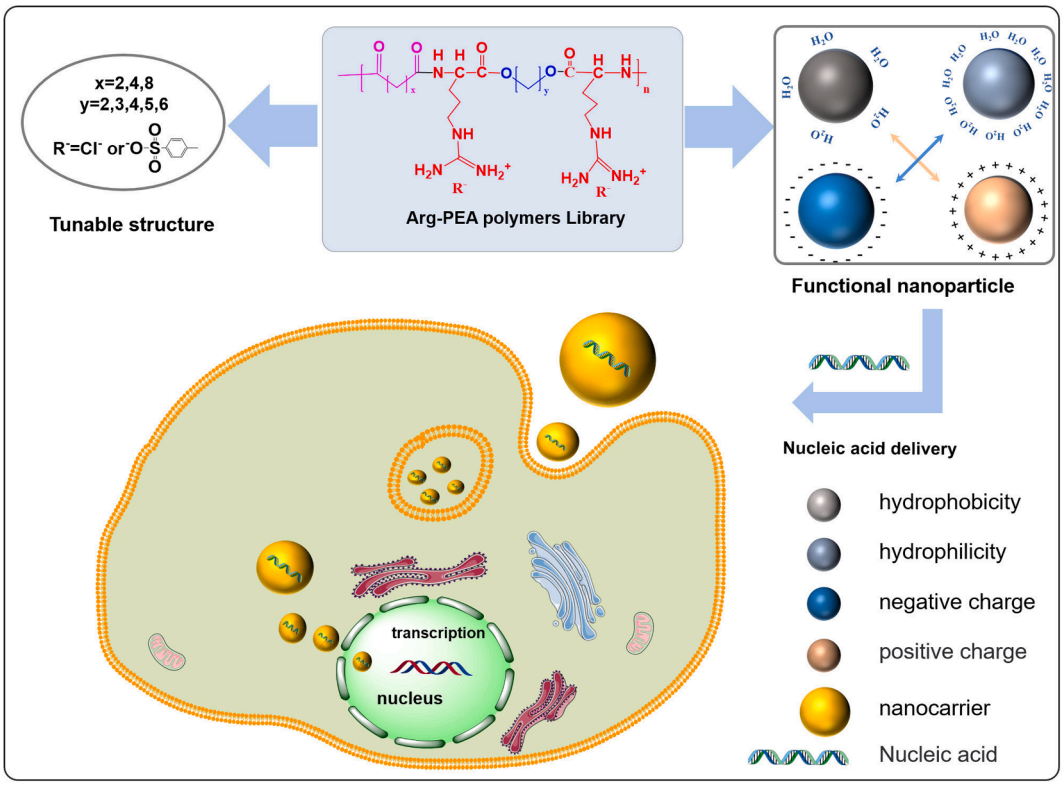

Fig. 7. Arg-PEA polymer-based nanoplatform for nucleic acid delivery (reproduced with permission from You et al., 2018).

recombinant protein-based drugs. Subsequently, with the development of biotechnology and molecular biology, an increasing number of protein drugs such as cytokines, antibodies, and enzymes have emerged and are widely used in medicine. Compared with small-molecule drugs, protein drugs have many advantages and have become an important component of pharmaceutical products (Tiwari et al., 2012). Although protein drugs have been widely used to treat many diseases, including malignant tumors, autoimmune diseases and genetic diseases, they still suffer from drawbacks such as high preparation difficulty, poor stability, and immunogenicity. Additionally, the natural characteristics of proteins with high molecular weight, hydrophilicity and easy destruction of tertiary structures, make it difficult for them to cross the cell membrane into the cytoplasm, which seriously limits their development into dosage forms (Yu et al., 2016). To overcome these limitations and improve therapeutic effects, researchers have developed a lot of nanomaterial-based protein delivery systems (Yang et al., 2014; Yuan et al., 2017). By selecting different delivery materials and modifying them appropriately, carriers can be endowed with specific release mechanisms and targeting capabilities to accurately regulate the release of protein drugs and realize highly efficient delivery.

Diabetes is one of the most common metabolic and chronic diseases worldwide. The number of people who have diabetes is increasing and trending towards younger age groups. The subcutaneous administration of insulin is a effective therapeutic approaches for treating diabetes. However, this administration method is invasive, which may lead to some side effects (Khafagy et al., 2007). Therefore, researchers have gradually turned their attention to new modes of insulin administration, such as oral and transdermal administration (Babu et al., 2008; Chaturvedi et al., 2013; Chen et al., 2017b; Lopes et al., 2015). Compared with subcutaneous injections, these methods are more convenient, comfortable and easily accepted by patients. Designing insulin delivery carriers to overcome multiple physiological and biochemical barriers for the non-injection treatment of diabetes has been a popular topic in research on protein drug delivery, and novel insulin delivery carriers based on PEAs have also received increasing attention.

4.1. *Oral administration of insulin*

Oral administration faces multiple biological challenges that greatly limit insulin absorption due to the physiological barriers in gastrointestinal tract (Abramson et al., 2019; Marizza et al., 2014). Polymeric carriers are effective means of encapsulating, protecting and ultimately enhancing the oral bioavailability of insulin, and their promise for oral insulin administration has been demonstrated by numerous investigations (Chaturvedi et al., 2013; Chen et al., 2011). These carriers can offer prolonged and controlled release characteristics, protect the drugs from external conditions, and even aid in intestinal drug absorption. He et al. (2012) developed a biodegradable L-lysine-/L-leucine-based PEA with pendent carboxylic acid groups (PEA-COOH), insulin can be loaded into the PEA microspheres using a solid-in-oil-in-oil technique with high encapsulation efficiency. This PEA could be biodegraded under the influence of specific enzymes such as α-chymotrypsin and elastase, the latter being the main proteolytic enzyme in the small intestine (Pang and Chu, 2010). In this work, the pH-sensitive PEA was intended to shield insulin from acidic stomach environments and release insulin into the intestines. To improve the membrane permeability of the drug protein and regulate its pH-dependent release, lysine was introduced to PEA to make it more hydrophobic (Ding et al., 2010). Insulin-loaded PEA microspheres produced a dose-dependent hypoglycemic effect in STZ-induced diabetic rats when given oral doses; the activity curve indicated a relative bioavailability of 4.44 ± 0.71 %. Drug delivery has seen an increase in interest in arginine-containing polymers because they can enter cells more effectively than other cationic polymers (Holowka et al., 2007). Research has shown that oligoarginine significantly enhances intestinal uptake of insulin without inducing cellular damage (Morishita et al., 2007), suggesting that arginine-rich polymers may overcome the low permeability of intestinal epithelial membranes, a major barrier for oral insulin administration. Based on these studies, He et al. (2013) conducted a more in-depth research using PEA-COOH and Arg-PEA, followed by the preparation of insulin-loaded blend microspheres. Arg-PEA was added to improve insulin absorption

in the intestines, whereas PEA-COOH served as a pH-responsive material. For up to 10 h, oral PEA blend microspheres containing insulin dramatically lowered blood glucose levels in diabetic rats, and oral bioavailability rose to 5.89 ± 1.84 %, according to *in vivo* tests.

Han and Wu (2022) developed a class of lysine-based PEAs (Lys-PEAs) that can interact with proteins and encapsulate them into nanocomplexes via electrostatic interactions. By changing the monomer type and molar ratio, the chemical structure of Lys-PEA can be adjusted. Studies of structure–function relationships demonstrated that the length of the carbon chain, hydrophilicity, and their electrical properties of the diacid/diol chain segments can affect the interactions between polymers and proteins, and ultimately, the outcome of protein delivery. Natural polysaccharides represented by HA can counteract acid denaturation and enzymatic digestion in the stomach, as well as promote absorption, enhance transmucosal delivery and overcome the intestinal epithelial barrier (Meneguin et al., 2021; Lee et al., 2021). Thus, HA was used for the surface modification to prepare Lys-PEA@Protein@HA nanocomplexes (Han et al., 2023). Using insulin as a model protein, the nanocomplexes not only protected its structural integrity in gastrointestinal tract but also overcame the restriction from the lumen of the canaliculus to the outside of the basement, allowing for the safe and efficient transport of insulin through the intestinal epithelial layer into the systemic circulation, followed by a controlled release in the physiological environment. This multifunctional Lys-PEA@Protein@HA nanocomplex can be considered a versatile carrier for oral biomolecule delivery, offering more possibilities for treating various diseases.

4.2. Transdermal administration of insulin

Transdermal administration refers to a type of delivery method in which drugs pass through the skin and are absorbed through capillaries, then enter the body's circulation to produce effects (Ma and Wu, 2017). It can avoid first-pass effect and has advantages with stable blood concentration and convenient administration, thus reducing adverse reactions, as well as improving drug therapeutic index and compliance (Mitragotri et al., 1995). The stratum corneum is the main barrier for transdermal drugs, and its dense "brick wall structure" makes it difficult for macromolecules to cross it by passive diffusion (Smith, 2007). As a typical protein drug, the transdermal delivery of insulin is one of the most challenging directions for non-injectable drug delivery techniques (Khafagy et al., 2007). Zhang et al. (2018) developed a new kind of Arg-PEA and PEG-DA based blend hydrogel for the transdermal delivery of insulin. Arg-PEA is cationic under physiological conditions and adsorbs anion-containing proteins via electrostatic interactions. As a highly cationic network, the blend hydrogel futher promoted the adsorption of proteins and transdermal peptides; the latter is a potent osmotic facilitator that improves transdermal drug delivery and promotes the diffusion and distribution of drugs in the skin. The results showed that insulin and transdermal peptides released from the hydrogel maintained their activity, achieved transdermal drug delivery, and effectively regulated blood glucose levels.

5. Drug delivery studies for other diseases

In addition to antitumor and biomacromolecule drugs, some amphiphilic PEA nanoparticles and microspheres have been investigated for loading antimicrobial or anti-inflammatory drugs to treat infectious diseases and certain inflammatory conditions. Zhu et al. (2019) developed a series of PEA random copolymers by varying the type of amino acids and feed ratio. The copolymers self-assembled into micelles with average diameters of 150–200 nm. Interestingly, the degraded random block micelles could reassemble into smaller micelles with diameters < 20 nm, which is promising for drug delivery. Owing to the pendent groups in the lysine- and arginine-based portions, the PEA micellar nanocarriers exhibited inherent antimicrobial properties against *Escherichia coli* and *Staphylococcus aureus*, and this bactericidal ability was further enhanced by grafting levofloxacin. Currently, most drug treatments for osteoarthritis are administered systemically, which may lead to some side effects. Therefore, drugs delivered directly to the joints are becoming a desirable substitute. Villamagna et al. (2019) prepared and characterized two different PEA particles. Small structural differences between the two polymers caused significant changes in particle properties, and loaded celecoxib showed different release rates simultaneously. Andrés-Guerrero et al. (2015) created an AA-PEA microsphere that macrophages and retinal pigment epithelial cells could tolerate *in vitro*. The dexamethasone-loaded PEA microspheres showed a high drug encapsulation rate (85 %), and the pharmacokinetic simulations suggested that these microspheres could release drugs in rabbit eyes for as long as 3 months.

Additionally, new forms of drug delivery have emerged based on the wider application of PEA. Aslankoohi and Mequanint (2020) synthesized a PEA-bioactive glasses hybrid material by a sol–gel process and combined it with drug-carrying mesoporous silica nanoparticles (MSNs) to prepare a 3D porous scaffold for bone tissue engineering applications. The resultant homogeneous single-phase material presented hydroxyapatite deposition on its surface, facilitated the adhesion and growth of mesenchymal stem cells, and promoted the steady release of the model drug. This biomaterial can potentially serve as a bifunctional platform for bone regeneration via ion release and biomolecular delivery. Nose-to-brain delivery is a promising route for drugs, it refers to the use of the unique anatomical structure connecting the brain to the nasal cavity to achieve the delivery of drugs directly to the central nervous system by passing the blood–brain barrier, which provides a safer, effective and convenient route of drug delivery for the treatment of brain or central nervous system diseases. Al-Baldawi et al. (2023) prepared carbamazepine-loaded arginine poly (ester amide) nanocapsules [(CBZ/Arg-PEA) NCs] using interfacial polycondensation method for direct delivery of CBZ to the brain via the nose-brain transport pathway. Process optimization was carried out using Quality by Design to determine the optimal process parameters to produce NCs with critical quality attributes. *In vivo* studies in mice demonstrated that the NCs were able to deliver CBZ directly to the brain and obtained a sustained increase in brain concentration at 2, 5 and 10 min after administration. AA-PEA seems to be a promising drug delivery carrier via the nose-brain transport pathway.

6. Concluding remarks

Current research trends in drug delivery focus on developing safe and effective carriers that can be used in clinical practice. As summarized in this review, a lot of work has gone into creating novel drug delivery systems based on PEAs during the past few decades, and some progress has been achieved. AA-PEAs have been extensively studied because of their good biocompatibility, biodegradability, and structural flexibility. Compared with other monomers, amino acid components have special advantages that can greatly improve the biocompatibility of PEAs and limit immune or toxic side effects. Some functional groups of specific amino acids can achieve the stimuli-responsiveness of the carriers or serve as side-responsive sites for further modification of drugs. Therefore, PEAs have been increasingly used in drug delivery, especially for cancer, gene, and protein drugs. However, they still require further structural modifications to achieve more precise drug release, higher delivery efficiency, and reduced cytotoxicity. The length of the backbone of PEAs, the feed ratio of the monomers, and the molecular weight of the polymers may have significant impacts on their physicochemical and biological properties. Additionally, the side chains provide reaction sites for further modification, which can greatly expand the functionality of PEAs. Therefore, elucidation of the structure–activity relationship is necessary to optimize the design of the materials and is essential for clinical translation.

Owing to the biological barriers that exist during *in vivo* delivery, there are still great challenges in applying PEAs in clinical settings. Good

carriers should have a high drug loading rate, high gene transfection rate, low toxicity, and the ability to overcome multiple biological barriers. PEAs can usually be rationally modified with different functionalized fragments so that they can exhibit various biological activities to meet the requirements of drug delivery. Hyaluronic acid, with its good biocompatibility, biodegradability, and special CD44 receptor binding ability, can be used as a surface modification material for nanoparticles, which not only improves the targeting of the nanoformulations but also prolongs the circulation time of drugs *in vivo*. PEGylation is another common strategy to prolong the circulation time; it reduces protein adsorption and immunogenicity of polymer nanocarriers in the blood. In conclusion, modifying PEAs from different perspectives is a direction for further research.

During drug delivery, the carriers must remain stable in somatic circulation and release drugs rapidly after selective uptake into the target cells, thus maximizing drug efficacy and minimizing side effects. Stimulus-responsive delivery systems are attractive strategies for achieving spatiotemporally controlled drug release. Many of the frequently used stimuli in nanocarriers, such as certain properties of the tumor microenvironment (microacidity, redox properties, and overexpression of specific enzymes), have been extensively investigated as endogenous sources of stimulation in the development of PEAs. In recent years, great attention has been paid to designing stimuli-responsive drug carriers using external conditions as stimulation signals, such as light, electricity, magnetic field, and ultrasound. These stimuli-responsive carriers can undergo changes in chemical structure or physical properties in response to stimulation signals. Generally speaking, exogenous stimulus signals are more controllable than endogenous stimulus, and the combination of dual or multiple stimulus-sensitizing features appears to be more promising than single stimulus-responsive carriers, as carriers are more sensitive to dynamic pathological microenvironments.

Overall, PEAs are being developed as attractive candidates for highly diverse and versatile biomaterials. Drug carriers based on PEAs seem to be getting more and more feasible, despite a few challenges that still needing to be addressed. We believe that PEA-based drug therapies will have additional clinical applications in the future.

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CRediT authorship contribution statement

Rui Xie: Writing – original draft, Investigation, Formal analysis. **Jiang Li:** Writing – review & editing. **Min Zhao:** Visualization, Supervision. **Fan Wu:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization.

Declaration of Competing Interest

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

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