Review

Macromolecular therapeutics

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ABSTRACT

This review covers water-soluble polymer–drug conjugates and macromolecules that possess biological activity without attached low molecular weight drugs. The main design principles of traditional and backbone degradable polymer–drug conjugates as well as the development of a new paradigm in nanomedicines — (low molecular weight) drug-free macromolecular therapeutics are discussed. To address the biological features of cancer, macromolecular therapeutics directed to stem/progenitor cells and the tumor microenvironment are deliberated. Finally, the future perspectives of the field are briefly debated.

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1. Introduction

Macromolecular therapeutics (polymeric nanomedicines, polymer–drug conjugates) are a group of compounds that are characterized by their large molecular weight. There is no clear definition of the term in the literature; some authors use it in the broadest sense, including any macromolecular system with biological activity. In this review, we shall restrict our discussion to water-soluble polymer–drug conjugates and macromolecules that possess biological activity without attached low molecular weight drugs. We shall discuss the main design principles, and the novel approaches that aim to speed up the translation into clinical practice. Finally, we will provide an outlook into the future of this important scientific field.

2. Water-soluble polymers with biological activity

Water-soluble polymers may possess intrinsic biological activity that relates to their structure, molecular weight, charge density, charge distribution, conformation, and stability [1]. Macromolecules such as dextran, poly(N-vinylpyrrolidone), and hydroxyethylstarch have been used as blood plasma expanders to restore the blood volume following trauma or shock [2]. Poly(2-vinylpyridine-N-oxide) has demonstrated activity against silicosis; its effect has been explained by adsorption of the weakly basic polymer on the weakly acidic surface of silica [1]. Polyelectrolytes stimulate interferon production in cells and living organisms [3,4]. Stereochemistry may have an impact on activity: isotactic poly(acrylic acid) possesses antiviral properties whereas atactic poly(acrylic acid) does not [5].

Water-soluble polymers, PEG [6–13], poly[N-(2-hydroxypropyl)methacrylamide] (polyHPMA) [14–18], polyoxazolines [19,20], poly(N-vinylpyrrolidone) [21], polyacryloylmorpholine [21], and poly(N,N-dimethylacrylamide) [21] have been used to modify proteins and increase their resistance to proteolysis, reduce their antigenicity, and prolong their intravascular half-life [22]. In addition, modification of liposomes, and nanoparticles with semitelechelic (ST) polymers is a widely used method to avoid recognition by the reticuloendothelial system [21,23–26]. These topics are covered in a recent review [27].

3. Water-soluble polymer–drug conjugates

3.1. Historical perspective

The conjugation of drugs to synthetic and natural macromolecules was initiated about sixty years ago — for reviews of the early work see refs. [1,28]. Jatzkewitz used a dipeptide (GL) spacer to attach a drug (mescaline) to polyvinylpyrrolidone in the early fifties [29] and Ushakov's group in Leningrad (now St. Petersburg) synthesized conjugates of poly(N-vinylpyrrolidone) with various antibiotics in the sixties and seventies [30–32]. Mathé et al. pioneered conjugation of drugs to immunoglobulins, setting the stage for targeted delivery [33]. DeDuve discovered (Nobel Prize 1974) that many enzymes are localized in the lysosomal compartment of the cell and the lysosomotropism of macromolecules [34], important phenomena for the design of polymer–drug conjugates. Finally, Ringsdorf analyzed the research results of the field and presented a clear concept of the use of polymers as targetable drug carriers [35].

The research on the use of HPMA copolymers as drug carriers commenced in the early 70s in the Kopeček laboratory in Prague. The choice of HPMA for development as a drug carrier was not random. Based on the detailed studies of the relationship between the structure of hydrophilic polymers and their biocompatibility [28,36–45], N-substituted methacrylamides were chosen as the target because the α-carbon substitution and the N-substituted amide bond ensured hydrolytic stability of the side-chains. We synthesized a series of compounds trying to identify a crystalline monomer for easy purification and reproducible synthesis. The first crystalline N-substituted methacrylamide we

succeeded in synthesizing was HPMA, and it was chosen for future development [46,47]. In April of 1974, we filed two patent applications [48,49] which covered the synthesis of N-substituted (meth)acrylamides containing oligopeptide sequences and their application as drug (and other biologically active compounds) carriers. The amazing development of this polymer in the scientific community is summarized in Table 1 and Fig. 1. We designed oligopeptide spacers stable in the bloodstream [50] and susceptible to enzymatically catalyzed hydrolysis in the lysosomal compartment [51], demonstrated the targetability of the HPMA copolymer system [52,53], and revealed numerous advantages of polymer–drug conjugates over free drugs as will be described below.

3.2. Design principles

3.2.1. Water-soluble polymer carriers

There are numerous reviews that describe the design of macromolecular therapeutics [1,35,54–60]; thus we shall briefly review the important design principles. The water-soluble polymer carrier has to be biocompatible; hence it needs to be either degradable or have a molecular weight below the renal threshold (about 50 kDa for a random coil) to permit elimination from the organism by glomerular filtration. To prevent nonspecific reuptake of the macromolecule after being released into the bloodstream following cell death, its structure should warrant that internalization occurs by fluid-phase pinocytosis. The absence of nonspecific interactions with plasma membranes will minimize the accumulation of the carrier in non-targeted cells thus increasing the biocompatibility of the carrier. In addition, its structure should provide drug attachment/release sites for the incorporation of drugs. Different structures have been used and conjugates based on dextran [61], carboxymethyldextran [62], poly(glutamic acid) [63–65], poly(malic acid) [66,67], polyacetals [68,69], poly(vinyl alcohol) [70,71], PEG [72–74], poly(L-γ-glutamyl-glutamine) [75], and polyHPMA [76–78] have been successfully evaluated.

3.2.2. Spacers

The drug is bound to the carrier via a spacer that is stable in the bloodstream [50] and interstitial space but enzymatically or chemically cleavable in the lysosomal compartment of the cell. The lysosomal membrane is not permeable to macromolecules [79]. Consequently, the drug needs to be released from the carriers inside lysosomes. One option is to use the pH difference between blood and lysosomes and bind the drug via pH-sensitive bonds [80,81], using hydrazo [82], cis-aconityl [83], or maleic [84] spacers.

The other option is to design spacers that match the specificity of lysosomal enzymes. Based on detailed degradation studies of oligopeptide sequences attached to HPMA copolymers [85,86] with model enzymes [87–91] and lysosomal enzymes [92,93], the sequence GFLG, specific for cathepsin B, was identified [51]; it has been widely used in preclinical [94–96] and clinical settings [76,77]. Another widely used lysosomally degradable sequence is valine–citruline [97,98].

3.2.3. Self-immolative spacers

Elongated spacers, where the enzymatically cleavable bond is separated from the drug by a self-eliminating group, have been designed by several groups [99–101]. Such an approach was used for the design of oral drug delivery systems based on HPMA copolymer–9-aminocamptothecin conjugates [102] and for binding prostaglandin to HPMA copolymer via a cathepsin K sensitive terapeptide (GGPNle) and a self-eliminating 4-aminobenzylalcohol structure [103] (Fig. 2).

3.2.4. Targeting

Optionally, a targeting moiety is used that enhances the accumulation of the conjugate in target cells [52,53]. Active targeting of polymer–drug conjugates can be achieved by the incorporation of target cell specific ligands, such as peptides, carbohydrates, lectins,