Biomaterials 134 (2017) 91–116

Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

Review

Protein based therapeutic delivery agents: Contemporary developments and challenges

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ARTICLE INFO

Article history:
Received 13 February 2017
Received in revised form
18 April 2017
Accepted 21 April 2017
Available online 21 April 2017

Keywords:
Drug delivery
Gene therapy
Cell therapy
Structural proteins
Protein engineering
Biomaterials

ABSTRACT

As unique biopolymers, proteins can be employed for therapeutic delivery. They bear important features such as bioavailability, biocompatibility, and biodegradability with low toxicity serving as a platform for delivery of various small molecule therapeutics, gene therapies, protein biologics and cells. Depending on size and characteristic of the therapeutic, a variety of natural and engineered proteins or peptides have been developed. This, coupled to recent advances in synthetic and chemical biology, has led to the creation of tailor-made protein materials for delivery. This review highlights strategies employing proteins to facilitate the delivery of therapeutic matter, addressing the challenges for small molecule, gene, protein and cell transport.

1. Introduction

Research efforts toward the controlled administration of pharmaceuticals have evolved over the last half century. First realized in 1952 [1] Dexedrine® formulated in Spansule® (Smith, Kline & Fench Laboratories, now merged into GlaxoSmithKline) exhibited a gradual release [2]. This historical milestone aroused the significance of sustained release systems followed by the development of controllable drug delivery. In addition, the delocalized effects from free drug compounds that were systemically administrated by either enteral (digestive tract, *i.e.* orally) or parenteral (non-digestive tract, *i.e.* subcutaneously, intramuscularly or intravenously) routes greatly hindered therapeutic efficacy [3,4].

Despite advancements in conventional polymeric and liposomal delivery agents including drug protection, site targeting, and toxicity reduction, these approaches are still plagued by issues of instability of drug storage and release [5]. These ever-present challenges motivate the development protein-based drug delivery vehicles. Compared to synthetic polymers, natural proteins possess inherent advantages – better bioavailability, biocompatibility, biodegradability with low toxicity – and have thus been the focus as a platform for delivery of various small molecule therapeutics, gene therapies, and protein biologics [6]. Protein-based delivery vehicles may provide a more efficacious approach to delivering therapeutics by virtue of the ability to refine the compositional sequence and structure of proteins [7–12].

In general, an optimal protein-based carrier would possess several qualities [13] among: 1) stability to adapt environmental factors such as temperature, pH, ionic strength, and the presence of proteases; 2) appropriate scale for administration routes; 3) reasonable complexity for modification; 4) interior and/or exterior to associate with therapeutics; 5) proper interaction to bind therapeutics; 6) capacity to release therapeutics in controlled manner; 7) specificity to target treated cells or tissues; 8) protection from therapeutic degradation; and 9) efficiency of cellular and/or nuclear internalization. Therefore, certain proteins may not be considered suitable as delivery systems. Enzymes, for example, are commonly structured with high level of complexity in order to generate a catalytic site specifically for the substrate, intermediate, product,

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http://dx.doi.org/10.1016/j.biomaterials.2017.04.036
0142-9612/

byproduct, and any applicable cofactor; thus, they are limited in how they can be modified. Due to their sophisticated structure and function, enzymes are often delicate to produce and to preserve, restricting their capability to serve as a therapeutic delivery agent.

To expand the availability of protein-based carriers that meet the aforementioned criteria, recombinant proteins that are genetically designed, engineered and biosynthesized in a host organism are being developed for designated therapeutic payloads. With well-established databases and innovations in synthetic and chemical biology, custom-made protein engineered delivery systems are emerging. In addition, further modifications such as conjugation with chemicals, *e.g.* PEGylation and/or hybridization with inorganic materials [14] are positioning engineered proteins as more versatile and responsive by improving solubility, specificity, and traceability.

Herein, we review current strategies employing proteins to facilitate the delivery of therapeutic matter for small molecules, nucleic acids, protein therapeutics, and cells (Fig. 1). As demonstrated, these classes of therapeutics span a variety of clinical applications, and are restricted in their efficacy and/or application due to challenges in delivery.

2. Small molecule therapeutics

Small molecule chemistries have been employed to address most clinical indications [15]. Advancements in computational chemistry and high-throughput formulation have produced more efficacious compounds [16]. Despite these efforts however, several characteristic flaws, including low solubility and high toxicity, compromise the efficacy of many pharmaceutical compounds [4]. They are also relatively unstable and easily degraded in physiologic conditions. This is due in part to clearance facilitated by the reticuloendothelial system, renal clearance, and chemical/enzymatic deactivation [3,4,17–20]. Pharmacokinetics and pharmacodynamics continue to be a technical hurdle for many of these basic

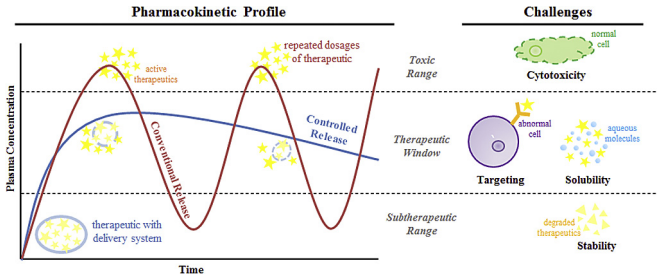

Fig. 2. Challenges associated with the delivery of small molecule therapeutics. The pharmacokinetic profile of a drug compound is reflective of its time-dependent distribution upon administration. Various delivery methods may tailor the distribution profile accordingly, modified significantly from conventional release profiles, by which challenges pertaining to unintended toxicity (top boundary) or sub-therapeutic efficacy (bottom boundary) may be overcome. In addition, challenges such as cytotoxicity, targeting, solubility and stability may also affect the pharmacokinetic profile.

formulations (Fig. 2). The physicochemical properties of small molecules may not yield ideal pharmacokinetic profiles. In addition, issues of solubility, non-specific degradation or binding, and unintended toxicity are barriers confronting the efficacy of a small molecule therapeutic. However, these shortcomings of physicochemical properties may be decoupled by way of a delivery vehicle of significantly different character, *e.g.* biomacromolecules.

This overarching challenge of multi-faceted clearance may be overcome with proteins, specific to certain indications. In oncology, for example, chemotherapeutic drugs have been drawing extensive attention to the field of drug delivery because the enhanced permeability and retention (EPR) effect presented by the support of a delivery system lessens the damage and toxicity toward normal cells [21]. The EPR effect first reported in 1986 by Matsumura and Maeda is a unique phenomenon of tumors largely producing vascular permeability factors owing to its defective blood vessels to ensure tumor tissues are supplied with sufficient nutrients and

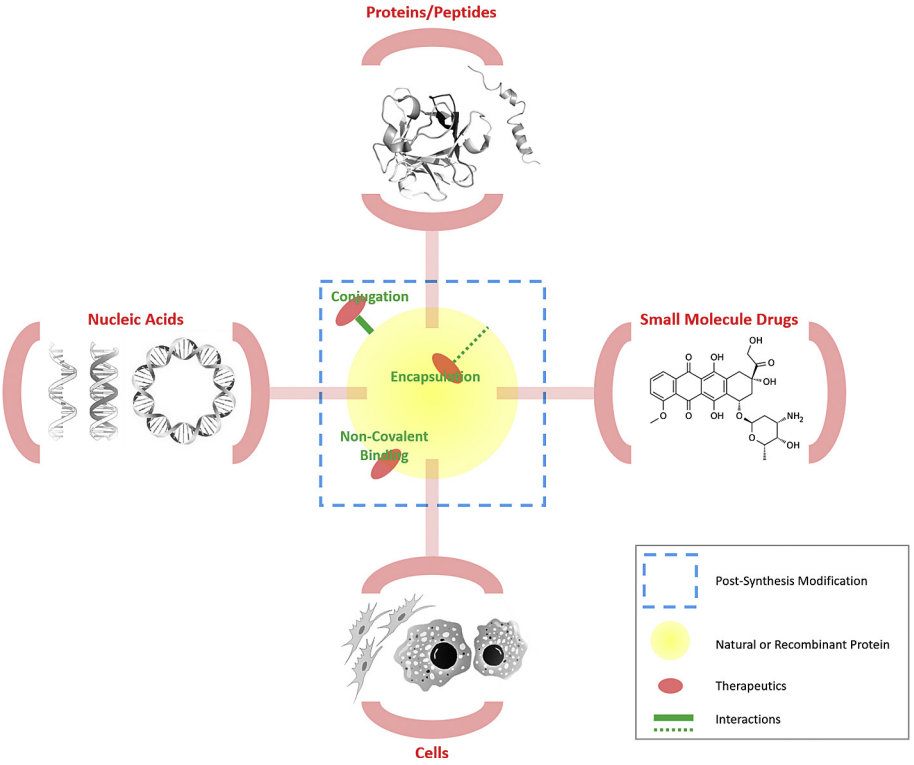

Fig. 1. Illustration of protein-based drug delivery systems and available therapeutic payloads: small molecule drugs, nucleic acids, proteins/peptides and cells.