Advanced Drug Delivery Reviews 106 (2016) 63–72

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

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

Drug delivery with living cells☆

Lies A.L. Fliervoet, Enrico Mastrobattista [1]

Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht University, P.O. Box 80082, 3508 TB Utrecht, The Netherlands

ARTICLE INFO

Article history:
Received 1 January 2016
Received in revised form 18 April 2016
Accepted 19 April 2016
Available online 27 April 2016

Keywords:
Nanomedicine
Synthetic biology
Cell engineering
Biopharmaceutics
Cell therapy

ABSTRACT

The field of drug delivery has grown tremendously in the past few decades by developing a wide range of advanced drug delivery systems. An interesting category is cell-based drug delivery, which includes encapsulation of drugs inside cells or attached to the surface and subsequent transportation through the body. Another approach involves genetic engineering of cells to secrete therapeutic molecules in a controlled way. The next-generation systems integrate expertise from synthetic biology to generate therapeutic gene networks for highly advanced sensory and output devices. These developments are very exciting for the drug delivery field and could radically change the way we administer biological medicines to chronically ill patients. This review is covering the use of living cells, either as transport system or production-unit, to deliver therapeutic molecules and bioactive proteins inside the body. It describes a wide range of approaches in cell-based drug delivery and highlights exceptional examples.

Contents

1. Introduction . . . 64
2. Cell-based drug carriers . . . 64
 2.1. Red blood cells . . . 64
  2.1.1. Prodrug approach . . . 64
  2.1.2. Loading of active substances . . . 64
  2.1.3. Drug-binding proteins or protein domains . . . 64
  2.1.4. Coupling of drugs to the surface of RBCs . . . 65
 2.2. Macrophages . . . 65
 2.3. Dendritic cells . . . 66
 2.4. Challenges and limitations . . . 66
3. Transduced cells: constant therapeutic producers . . . 66
 3.1. Bacteria . . . 66
 3.2. Stem cells . . . 67
 3.3. Tumor cells . . . 67
 3.4. T lymphocytes . . . 67
 3.5. Challenges and limitations . . . 68
4. Transduced cells: highly advanced sensory and output devices using synthetic circuits . . . 68
 4.1. External trigger-induced genetic devices . . . 68
  4.1.1. Drugs and biochemical substances . . . 68
  4.1.2. Light and γ-irradiation . . . 68
  4.1.3. Physiologically inert molecules . . . 68
 4.2. Advanced therapeutic and prosthetic networks . . . 69
  4.2.1. Identifying cancer cells . . . 69
  4.2.2. Blood glucose homeostasis . . . 69
  4.2.3. Synthetic interfaces between brain activities and peripheral circulation . . . 69
  4.2.4. The metabolic syndrome . . . 69
  4.2.5. Prosthetic networks . . . 70

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Biologically-inspired drug delivery systems".

E-mail address: E.Mastrobattista@uu.nl (E. Mastrobattista).
[1] Mailing address: Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands. Tel.: +31 622 736 567.

http://dx.doi.org/10.1016/j.addr.2016.04.021
0169-409X/

4.3. Challenges and limitations . . . 70
5. Conclusions . . . 70
References . . . 71

1. Introduction

The field of drug delivery has grown tremendously in the past few decades by the development of a wide range of nano-sized advanced drug delivery systems for systemic drug delivery. Lipid nanoparticles, such as liposomes, micelles and extracellular vesicles along with virus-inspired vectors and polymeric particles have been studied to deliver bioactive compounds into targeted tissues. However, such nanomedicines have several limitations. Mainly due to their size, they have difficulties in passing the endothelial lining, which restricts targeting to tissues with a naturally enhanced vascular permeability, such as the liver and spleen, or tissues with an inflammation-mediated induced permeability [1]. In addition, nanoparticles can be cleared rapidly from the circulation by phagocytic uptake and hepatic filtration which shorten their blood circulation half-lives. Moreover, when reaching the target cells, intracellular delivery may be limited due to inefficient endosomal escape of the particle and its cargo [2,3]. Finally, also toxicity may play a role in the failure of nanomedicine therapy. To address these challenges, cell-based drug delivery could offer a number of advantages. Encapsulation inside cells could improve pharmacokinetic profiles of drugs or significantly increase drug targeting toward pathological conditions [4]. Microorganisms and immune cells are known to home toward sites of inflammation, including cancer and are therefore considered to be perfect candidates to function as transporters for cytostatic agents or enzymes that can locally convert a prodrug into its cytotoxic counterpart [5,6]. Another approach involves a cell-based system that can sense the environment and if necessary respond to changes in an appropriate way. This system would have a huge potential in treating metabolic disorders by restoring homeostasis and the first proof-of-concepts have already been successfully demonstrated in animal models [7,8]. These developments are very exciting for the drug delivery field and could have an enormous impact on pharmaceutical technology. This review is covering the use of living cells, either as transport system or production-unit, to deliver therapeutic molecules and bioactive proteins inside the body.

2. Cell-based drug carriers

One application of the use of living cells for drug delivery is by utilizing the circulation capacity of blood cells to prolong the circulation time of drugs or the capacity of certain immune cells to home into inflamed tissues for targeted drug delivery. To this end, drugs can be loaded inside the cells or attached to the cell surface and in this way the therapeutic cargo is transported through the circulation.

2.1. Red blood cells

The idea of using red blood cells (RBCs) as drug delivery systems was first described in the 1970s [9] and recently re-discussed as an alternative for polymer-based drug vehicles. RBCs have various characteristics, such as long circulation-time, high drug-loading capacity and good biocompatibility, which make them interesting for the delivery of drugs in the circulation [4]. Furthermore, several techniques allow easy processing of RBCs and because of their large volume a reasonable amount of drugs can be loaded [10]. Dependent on the type of drug and the desired effect (e.g. slow delivery or stabilization of the drug in the circulation) different approaches can be applied which are discussed below and a schematic representation is presented in Fig. 1.

2.1.1. Prodrug approach

Encapsulation of drugs into RBCs can be used to develop a slow-releasing depot of active compounds in the circulation [11]. Therefore, a prodrug is loaded inside RBCs where internal enzymes convert the drug to its active form followed by release in the circulation. The non-diffusible prodrug is loaded into autologous RBCs by temporary opening the cell membrane pores under hypotonic conditions. The pores are then re-sealed once normal osmosis had been restored [12]. The release process is usually based on phosphorylation, whereby dephosphorylation of the non-diffusible prodrug results in a diffusible active molecule [4]. However, not every drug is suitable for this approach since the dephosphorylated compound has to be able to pass the RBC membrane by passive diffusion or by transporter-mediated mechanisms [13]. Furthermore, the prodrug needs to contain a certain degree of hydrophilic properties to enable encapsulation. Several types of prodrugs, including anti-inflammatory, antiviral and anti-cancer drugs have been used for this purpose [4,10,11]. Magnani et al. showed that dexamethasone 21-phosphate could be efficiently loaded into RBCs in a wide concentration range [10]. Subsequently, dexamethasone is released in the circulation by passive diffusion (Fig. 1A). This advanced dexamethasone drug delivery system has been further developed to finds its application in the clinic for the treatment of chronic inflammatory diseases (e.g. cystic fibrosis, inflammatory bowel disease and ataxia telangiectasia). In a recent finished trial in ataxia telangiectasia patients, treatment with the EryDex system (i.e. autologous loaded RBCs) resulted in significant neurological improvement, as well as the system proved to be safe and well tolerated [14].

2.1.2. Loading of active substances

In contrast to the prodrug approach, active pharmaceutics can also be directly encapsulated into RBCs to increase the circulation time [15]. In addition, protein-based drugs are protected by clearance in different organs and from circulating proteases and antibodies leading to a more stable pharmaceutical product [4,10]. This approach finds its best implementation in therapies using enzymes. Enzymes are rapidly cleared by the liver and after repeated administration antibodies are produced that can inactivate the protein [16]. However, when encapsulated into RBCs the enzyme benefits from the above described properties without impairing its catalytic function. The (toxic) substrate can enter the RBC where it is converted into a (nontoxic) product which is subsequently released in the circulation (Fig. 1B) [4,17]. The most advanced example is the encapsulation of asparaginase in RBCs, known as ERY-ASP, for the treatment of acute lymphoblastic leukemia and acute myeloid leukemia [18]. Phase IIb/III clinical studies are currently ongoing using this product.

2.1.3. Drug-binding proteins or protein domains

Encapsulation of drugs that diffuse rapidly through the RBC membrane is of no use, because no advantages in pharmacokinetic properties are obtained compared to conventional delivery. In order to retain the diffusible drug inside the RBC, Biagiotti et al. proposed a new strategy in which specific drug-binding substances can be used to bind the drug in a reversible way inside the RBC [10]. It was demonstrated that encapsulated phenytoin in human RBCs with bovine serum albumin showed an 8-times higher drug loading compared with normal RBCs [19]. Other researchers have focused on using recombinant immunophilins, which are proteins that can bind immunosuppressive drugs [12]. Tacrolimus possesses a poor pharmacokinetic profile (i.e. low oral bioavailability, narrow therapeutic window), which can be improved when encapsulated in RBCs with the corresponding