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Review article

Therapeutic targeting strategies using endogenous cells and proteins

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ABSTRACT

Targeted drug delivery has become extremely important in enhancing efficacy and reducing the toxicity of therapeutics in the treatment of various disease conditions. Current approaches include passive targeting, which relies on naturally occurring differences between healthy and diseased tissues, and active targeting, which utilizes various ligands that can recognize targets expressed preferentially at the diseased site. Clinical translation of these mechanisms faces many challenges including the immunogenic and toxic effects of these non-natural systems. Thus, use of endogenous targeting systems is increasingly gaining momentum. This review is focused on strategies for employing endogenous moieties, which could serve as safe and efficient carriers for targeted drug delivery. The first part of the review involves cells and cellular components as endogenous carriers for therapeutics in multiple disease states, while the second part discusses the use of endogenous plasma components as endogenous carriers. Further understanding of the biological tropism with cells and proteins and the newer generation of delivery strategies that exploits these endogenous approaches promises to provide better solutions for site-specific delivery and could further facilitate clinical translations.

1. Introduction

Although there is ample scientific literature dedicated to improving the diagnostic procedures and identifying novel drugs for the treatment of debilitating diseases conditions, many of the research approaches do not lead to an efficacious treatment against the disease conditions. Interestingly, the major hurdle in developing a successful treatment option lies in the effective targeting of the drugs to their site of action as per the requirement of the treatment [1]. This issue becomes even more critical in case of delivery of highly potent and specific, yet labile and complex, therapeutically active agents [2]. Strategies designed to achieve this objective include the use of drug delivery systems. The use of carrier systems assures to augment the specificity and safety of therapeutic, diagnostic or prophylactic agents thereby improving their efficacy [2]. The key functions of these carriers include enhancing the drug half-life, effectively targeting the therapeutic agents to the site of action, thereby minimizing the effects in non-target tissues [3].

Biological delivery agents such as viral vectors have been used effectively in gene therapy due to their high transfection efficiency [4]. However, encapsulation of a variety of drugs, initiation of undesired immune responses and cytotoxicity are the limiting factors associated with clinical applications of virus-based carrier systems [5]. Alternatively, to enhance the delivery efficiency, various strategies such as the use of organic, inorganic, synthetic, and biological or hybrid nanomaterials have been evaluated. The use of nanocarrier systems is based on the concept that nano-sized carriers can target diseased/inflamed tissue based on the characteristic leaky vascular of the diseased tissue [6]. Doxil®, a poly(ethylene glycol) (PEG) modified liposomal formulation of doxorubicin is an excellent example of a United States Food and Drug Administration-approved nanocarrier system which significantly helped overcome the cardiac toxicity associated with doxorubicin [7]. However, this passive targeting is associated with limitations such as low vascular density in the diseased core and lack of cellular specificity [8]. To overcome these issues, nano-formulations have explored active targeting strategies for enhancing site specific drug action while limiting the unwanted toxicity to healthy tissue. Active targeting generally involves ligand-receptor interactions. However, these interactions are possible only when the two components are in close proximity [9]. Additionally, it has been observed that the use of active drug targeting strategies, does not essentially translate into efficacious delivery systems, as even with active drug targeting ligand, the drugs tend to accumulate in non-targeted organs, reducing the distribution of the drug to the targeted tissue [9].

Thus, the effectiveness of these platforms to overcome barriers

Abbreviations: Apo-E, Apolipoprotein-E; DSPE, 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine; IL-6, Interlukin-6; INF-α/INFγ, Interferon-α/γ; MSC, Mesenchymal stem cells; PEG, Polyethylene glycol; PLGA, Poly(lactic-*co*-glycolic acid); RBC, Reb blood cell; RES, Reticular endothelial system; TAM, Tumor-associated macrophages; Tfr, Transferrin receptor; TGF- β1, Transforming growth factor -β1; TNF-α, Tumor necrosis factor

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involved in drug transport in a human body, such as reaching the target tissue and engaging intracellular targets, is still sub-standard. Furthermore, the immunogenic and toxic effects of the non-natural delivery systems form a major obstacle in clinical translations [10]. With the intention of circumventing the hindrances imposed by these carrier systems composed of exogenous materials, exploiting the endogenous molecules for delivery is of pronounced interest. Endogenous carriers are not recognized as foreign and thus are not susceptible to degradation and do not elicit an immune response when used autologously [11]. Additionally, these agents use endogenous mechanisms for uptake, intracellular trafficking and subsequent delivery of their cargo to the recipient cells [11]. Thus, a better understanding of the biology of these endogenous targeting moieties and exploring strategies to conjugate to these endogenous moieties would help in enhancing the efficacy of the drug delivery systems.

In this review, we discuss different cell types which are exploited as carriers for various therapeutic agents. Cellular components such as exosomes which are harnessed as endogenous carriers are deliberated in detail. We have also included various plasma components which can be used as escort molecules by nano-formulation based drugs or drug alone to reach their site of action. Each endogenous targeting strategy discussed here includes a specific method of conjugation with a therapeutic agent and relevant studies are highlighted. Furthermore, the review discusses in detail the endogenous targeting moieties which have made it to the clinical applications.

2. Cells and cellular components as drug carriers

The effectiveness of most drugs is determined by the ratio of their distribution to the target and non-target tissue or cells. Therapeutic agents can interact with cells and cellular components, which can act as carriers for these agents to reach their site of action. Table 1 lists multiple cell types which can be harnessed as drug carriers. These cellular drug carriers are broadly classified by the therapeutic agent they interact with and their targeting strategy.

2.1. Red blood cells (RBCs) and RBC ghosts

Once inside the biological system, drugs predominantly rely on the vascular system for their distribution to the desired tissue. RBCs are the most abundant cells in the human blood and constitute > 99% of the total blood cells with an average lifespan of 100–120 days (which extraordinarily exceeds the life span of synthetic carriers such as PEGylated liposomes which are about 10 h) [12]. Furthermore, human blood has a total of $3 * 10^{13}$ RBCs in circulation with approximately $5 * 10^{6}$ per microliter of blood [12]. The major function of erythrocytes is transporting oxygen carrying hemoglobin throughout the body and they travel about 250 km through the cardiovascular system [12]. Thus, RBCs confine the unintended extravasation as well as extend the time in the systemic circulation, thereby representing ideal drug carriers. Additionally, RBCs generally do not attach to the endothelial lining of the vasculatures due to the presence of endothelial glycocalyx and are driven into the circulatory system by the hydrodynamic forces [13]. RBCs do not extravasate into any organs other than the liver sinusoidal spaces and the site of erythropoiesis in the spleen [12]. Thus RBCs, inadvertently act as carriers for drugs, in turn having an effect on their pharmacokinetic profile and biodistribution. A prolonged time in the circulation, availability, high biocompatibility and large surface and volume are the significant features of RBC as a drug carrier. The plasma membrane of the RBCs is composed of the phospholipid bilayer. The outer layer is formed of glycoproteins and glycocalyx, resulting in negative charge [14], while the inner layer is composed of phosphatidylserine [14]. Thus, taking advantage of these features of RBCs, they can be exploited as drug carriers for which multiple strategies listed below are researched.

2.1.1. Strategies for drug delivery by RBCs

2.1.1.1. Drug encapsulation in RBCs. Various methods have been established for loading RBCs with the desired drug molecules (Fig. 1). The most frequently used methods include endocytosis of the drug [15], electroporation [16] and hypo-osmotic pre-swelling [15] which is followed by resealing. These techniques have resulted in loading efficiencies from 10 to 77% with the drug retaining its activity [15,16]. However, it is important to note that, to harness the ability of RBC as an endogenous carrier with enhanced time in systemic circulation, it is essential that RBCs retain their structural and functional integrity. Thus, in this context, all the above methods harbor certain shortcomings, regardless of their reported success.

Disruption of the RBC cell membrane leads to loss of the structural integrity and morphology. As a result, the RBCs are recognized as foreign bodies by the immune cells which lead to their elimination from the systemic circulation. Furthermore, hemoglobin which is an important component of RBC escapes out (reduction in hemoglobin count and pinkish coloration of RBCs) when RBCs lose their structural properties due to harsh drug loading methods [17–19]. This, in turn, results in damaging the oxygen transport system which is a major function of the RBCs.

Another method recently developed for RBC loading is to use cell penetrating peptides. The advantage of this method is that it does not result in perturbation of the cell membrane and hence could maintain the functionality of the RBCs [17]. He et al. showed that there was no hemoglobin escape and RBCs retained their physical properties when

Table 1
Cells as drug carriers for different pathophysiological conditions.

Cell type	Nanoformulation/vector	Pathophysiological condition	Therapeutic agent	Ref
RBC	Protamine conjugate	Lymphoma	L-asparaginase	[17]
RBC	–	Acute leukemia	Daunorubicin	[20]
RBC		Lymphoma	Doxorubicin	[21]
RBC ghost	–	HIV	Azidothymidine	[23,27,28]
RBC	–	Cystic fibrosis	Dexamethasone	[31]
RBC	–	Cardiovascular disorders	Plasminogen activators	[36,39,40,45]
RBC	–	Immunization	Immunoglobulins	[37]
RBC	–	Endotoxemia, ischemia-reperfusion injury	Thrombomodulin	[42]
RBC	–	Malarial infection	chloroquine	[43]
Macrophages	Gold nanoshells	Hypoxic tumor core	Photothermal ablation therapy	[48,49]
Macrophages	Cyclodextrin nanoparticles	Brain metastasis	Model dye rhodamine	[53]
Macrophages	PLGA nanoparticles	Brain metastasis	Model dye coumarin	[52]
Macrophages	Microspheres	Brain metastasis	Red fluorescent label	[51]
Macrophages	Solid lipid nanoparticles	HIV-infected areas of brain	Indinavir	[54,55]
Platelets	cRGD modified liposomes	Cardiovascular diseases	Streptokinase	[63]
Mesenchymal stem cells	Adenoviral viral vector	Glioma	Human interleukin-2	[67]
Mesenchymal stem cells	Recombinant adeno-associated viral vector	Lung metastasis	Interferon-β	[68]