

Nanomedicine in the future of HIV treatment

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Although highly active antiretroviral therapy (HAART) has resulted in remarkable decline in the morbidity and mortality in AIDS patients, controlling HIV infections still remain a global health priority. In particular approaches, which offer site-specific, effective and safe drug delivery can be helpful in global elimination of AIDS progression. Currently, several nanoscaled vehicles such as polymeric nanoparticles, micelles, liposomes, dendrimers are intensively explored. Moreover, paramagnetic or magnetic nanoparticles or monocytes/macrophages based delivery can be employed to improve the delivery of drugs across the blood - brain barrier. The presented study describes the possibilities of nanomedicine in controlling HIV.

Keywords: AIDS; blood-brain barrier; dendrimers; liposomes; micelles; nanoparticles

1. Introduction

The human immunodeficiency virus (HIV) is a lentivirus, causing acquired immunodeficiency syndrome (AIDS) [1]. HIV is still responsible for more than 25 million deaths worldwide and estimated 34 million people are infected with HIV across the globe [2]. From development of nucleoside analog reverse-transcriptase inhibitor zidovudine (AZT) in 1987 [3] significant advances in HIV therapy have been achieved. Moreover, subsequent development of highly active antiretroviral therapy (HAART), using a cocktail of antiretroviral drugs significantly improved the life expectancy and quality of patients suffering from HIV [4]. Despite the striking successes in disease management, HAART is still associated with disadvantages such as inability to inhibit the drug-resistant viral strains, serious adverse effects, high costs and inability to eradicate HIV from its reservoirs [5]. As such, killing HIV in cellular and tissue reservoirs represents a major challenge for eradicating HIV infection. The infection of a relatively few cell types makes it desirable to direct drug therapy only to infected

cells. Moreover latently infected cells do not show any signs of infection on their surface. Thus, active targeting of HIV drugs to HIV-infected cells has been difficult to achieve [6].

The recent advances in the development of nanomaterials have shown promises to revolutionize diagnosis, treatment and prevention of many diseases/pathogens, including HIV.

The present study discusses particularly the possibilities and advantages of nanoscaled materials and technologies in control of HIV.

2. Nanomedicine in HIV treatment

The use of nanomaterials in medicine raises high expectations for human health and nanotechnology is already contributing to the development of new drugs, biologics, and medical devices [7]. The improvement of existing therapeutics has the potential to give promising solutions to many illnesses, aiming for a better, more efficient and affordable healthcare [8]. The larger surface to volume ratio of nanoparticles allows much higher loading and dissolution rates, which significantly influences the biological half-life of employed drugs. Further, nano-based drugs exhibit advantages in sen-

se of drug release kinetics. Higher amount of drug in nanoparticle results in an initial burst release, followed by a constant slow release [6]. The increased blood circulation time prolongs the associated release of drug and hydrophilic coating can reduce the dose frequency of poor soluble drugs [9]. Finally, by selective targeting, the side effects can be minimized. Several nanoscaled systems such as liposomes, dendrimers, different nanoparticles, micelles and others have gained considerable interest for the treatment of AIDS, as is shown below.

2.1 Superparamagnetic iron oxide nanoparticles

Superparamagnetic iron oxide nanoparticles (SPIONs) comprise magnetite (Fe_3O_4) and maghemite ($\gamma\text{-Fe}_2\text{O}_3$) are the most commonly employed nanoparticles in biomedicine. Their superparamagnetic behavior makes them superior and offers possibilities as targeting using external magnetic field ("remote control" to move the drug-loaded on SPIONs to specific site) or observation of their distribution by magnetic resonance imaging (MRI) [10]. Moreover, synthesis of SPIONs is quite easy, low-cost and highly monodispersed suspension can be synthesized easily [11]. Combination with other nanoparticles, such as liposomes (forming magnetosomes) or quantum dots offers multifunctional particles, suitable for broad spectrum of applications [12]. It is general fact that numerous molecules such as drugs, enzymes or proteins can be immobilized on the SPIONs surface [13], nevertheless application in HIV/AIDS is limited. Saiyed et al. (2009) showed that AZT can be immobilized on SPIONs surface; however the inhibition effect on nanoformulation remains comparable with free drug [14]. The same group further formulated magnetosomes bearing AZT and observed their transport across BBB and it was demonstrated that magnetosomes-AZT permeability was enhanced by threefold in comparison with free AZT [15]. It can be stated that modified formulas of SPIONs can reduce drug clearance, metabolism and entrapment by reticuloendothelial system (RES).

2.2 Liposomes

Liposomes are usually small (80 - 100 nm), using variety of encapsulation methods [16]. Surface of liposomes can be easily modified to improve its properties [17], while incorporation of hydrophilic polyethylene glycol (PEG) can prevent interactions with plasma proteins, thus retarding recognition and removal by RES. Liposomes utilized for delivery of anti-HIV/AIDS drugs can be classified as ionic-stabilized, immune-stabilized or sterically-stabilized [18]. It was demonstrated that half-life of lipo-zalcitabine in the brain of Sprague-Dawley rats can be prolonged to 23 h as compared with 1.1 h for non-encapsulated drug [19]. Jin et al. revealed that encapsulation of AZT-myristate (prodrug of AZT) can lead to longer half-life and higher concentrations of AZT in brain and other organs [20]. In elimination of HIV-related infections, several fold increase in the concentration of amphotericin B was observed when BBB was crossed by liposomes with amphotericin B tethered with RMP-7 (bradykinin B2 receptor agonist) [21]. Freeling and colleagues suggested lipid nanoparticles, containing triple-drug-cocktail of lopinavir (LPV), zidovudine (ZDV) and zalcitabine (ZC) [22]. In primates their nanoparticles produced over 50-fold higher intracellular concentrations of LPV and ZDV in lymph nodes, when compared to free drug and these levels were enhanced and sustained up to 7 days. Despite the demonstrations that liposomal drugs can be highly effective in increasing of successes of treatment of HIV/AIDS, few disadvantageous issues such as low drug entrapment ability for water-soluble drugs, still exist.

2.3 Dendrimers

Dendrimers are a class of monodisperse polymers distinguished by their repeated branching structure emanating from a central core [23]. They can be engineered in the size range of 10 - 100 nm and may contain many reactive functional end groups and internal void spaces, which make them potent for drug delivery systems [24]. The nature of dendrimers thus offers both possibilities - encapsulation and surface bioconjugation. In HIV research, dendrimers

are mostly studied for drug delivery to brain across the BBB. Dendrimers can be employed for delivery of anti-HIV siRNA as was demonstrated by Jimenez et al. [25]. Dendrimer/siRNA complex exhibited good permeability across the BBB and resulted in significant inhibition of the viral replication. Further, carbosilane dendrimers bearing sulfonate or carboxylate groups achieved 85 - 90% HIV inhibition without inducing inflammation or vaginal irritation in mice [26]. The limited application of dendrimers is associated with complicated production and their polycationic nature, which is toxic for negatively charged membranes.

2.4 Micelles

Micelles are aggregates of surfactant molecules dispersed in a liquid colloid, formed from hydrophilic head and hydrophobic single-tail regions in the micelle centre with diameter varying from 1-50 nm [27]. The inner cavity can be utilized as the encapsulation space. Currently there are three types molecules - micelles, block copolymers, surfactants and polymer-lipid conjugates used for preparation of micelles [28]. It was demonstrated that administration of P85 micelles with zidovudine, lamivudine and nevirapin resulted in 78-92% down-regulation of p24 expressing monocyte-derived macrophages [29], whereas application without dendrimer resulted only in 62% inhibition during 2 weeks postinoculation of HIV. The largest disadvantages of all types of micelles is their significant instability, however they are still matter of concern, due to their exceptional ability to reduce premature drug release.

2.5 Bioconjugates

The drug-polymer bioconjugate-based nanocarriers can significantly influence HIV therapy by specific localization to viral reservoir sites. The most studied polymers for CNS delivery are currently acrylic, polyesters and poly(butyl cyanoacrylate) (PBCA) [30], however there are concerns about their degradation (toxic degradation products, as formaldehyde byproducts in case of PBCA) or ability to permeate the BBB. It was shown that PBCA nanoparticles are able to deliver an improved amount of drug, and the

permeability of zidovudine and lamivudine can be increased by 8-20 fold or 10-18 fold, respectively [31]. Further, BBB permeability of acrylic polymers through receptor-mediated endocytosis can be enhanced by adsorption of apolipoproteins on surface of polymer [32]. The group of polymeric bioconjugates contains broad spectrum of applicable substances, however further experiments in vitro and in vivo are required to understand the phenomenon of metabolic degradation, transport across BBB and their undesired toxicity.

3. Conclusions

Insufficient concentration and short retention of anti-HIV drugs are the major causes, leading to failure of eradicating HIV from reservoirs and development of multi-drug resistance against anti-HIV drugs. Recently, some novel nanocarrier-based drug delivery systems shown remarkable properties to overcome many of the problems connected with HIV treatment. Possibility of targeting, elevation of drug residence and ability to cross BBB makes nanoscaled carriers promising platforms for treatment HIV/AIDS; however further research to resolve other issues such as immunogenicity, unwanted drug leakage and carrier metabolism will be required.

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Conflicts of Interest

The authors declare they have no potential conflicts of interests concerning drugs, products, services or another research outputs in this study. The Editorial Board declares that the manuscript met the ICMJE „uniform requirements“ for biomedical papers.

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