

Active Targeted Drug Delivery for Microbes Using Nano-Carriers

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Abstract: Although vaccines and antibiotics could kill or inhibit microbes, many infectious diseases remain difficult to treat because of acquired resistance and adverse side effects. Nano-carriers-based technology has made significant progress for a long time and is introducing a new paradigm in drug delivery. However, it still has some challenges like lack of specificity toward targeting the infectious site. Nano-carriers utilized targeting ligands on their surface called ‘active target’ provide the promising way to solve the problems like accelerating drug delivery to infectious areas and preventing toxicity or side-effects. In this mini review, we demonstrate the recent studies using the active targeted strategy to kill or inhibit microbes. The four common nano-carriers (e.g. liposomes, nanoparticles, dendrimers and carbon nanotubes) delivering encapsulated drugs are introduced.

Keywords: Active target, Ligands, Microbe, Nano-carrier.

1. INTRODUCTION

In modern life, human are always threaten by infectious diseases [1-6]. Bacteria, virus and fungi are the critical reasons to infectious diseases [7-11]. Bacteria served many diseases by the food route [12]. In Germany, *Escherichia coli* in Fenugreek sprouts exported from Egypt caused 48 deaths from 2011 to 2012 [13]. Virus could cause various diseases including human immunodeficiency virus (HIV) [14, 15] and influenza [16, 17]. Fungi like *Cryptococcus neoformans* could lead to chronic liver disease [18]. Luckily, with the development of safe vaccines and antibiotics, the infectious diseases seemed to be totally cured by these therapies [19]. However, there are some adverse drug effects if patients take these drugs at common dose or overdose such as insomnia [20], osteoporosis [21], headache [22] and liver failure [23]. Furthermore, these pathogens with a very fast doubling cycle develop a mechanism for becoming resistant to a specific drug at a glance [24]. In hence, scientists are trying to find new approaches to solve aforementioned problem urgently.

The nanotechnology is an emerging science [25, 26] and the nano-carriers have been used for medical applications for a long time [27-34]. Nano-carriers containing drug have emerged as an innovative and promising alternative for drug delivery to the targeted site [35]. They also greatly improve free drug safety and drug efficacy [36]. Drug-laden nano-carriers could be designed and tailored to reach the intended site. Thus, the pathogenic area could be precisely cured by the drug, elevating the therapeutic effectiveness [37]. There is a lot of significant proof that nano-carriers are superior in biocompatibility, targeting, and tissue penetration [38].

Compared to a free drug, the advantages of a nano-scale drug delivery system include increasing bioavailability, reduced drug amount and frequency and reduced systemic side effects [39]. In hence, active targeted drug delivery combined nano-technological carrier platforms is a better way to prolong, localize, target with the pathogenic sites and reduction of drug side-effects [40].

2. ACTIVE TARGETING STRATEGIES

One of the important prerequisites of a drug delivery system is to send a therapeutic agent effectively to the pathologic site as soon as it can [41]. Active targeted strategy is the prospective approach for drug delivery [32, 40]. Active strategies have introduced by Paul Ehrlich and known for ‘magic bullet’ to describe this system [42]. This system can reach the intended site in higher concentrations in the short period of time. Active targeted delivery is believed that it can improve efficacy while reducing unpleased side-effects. Some certain bacteria, fungi and all viruses are intracellular parasites [43]. As they are growing and reproducing inside the special host cells, scientists could create an active targeted drug delivery system that copied cells infected by those parasites [44]. Active targeted strategies used curtained ligands such as antibodies, peptides, nano-bodies, sugar molecules and aptamers on surface of nano-carriers to improve therapeutic efficacy [45, 46]. Most common seen nano-carriers are liposomes [47-51], nanoparticles [52-56], dendrimers [57-59] and carbon nanotubes [60-62], and the others..

3. ACTIVE TARGETED NANO-CARRIERS

3.1. Liposomes

Liposomes are self-assembling spherical vesicles composed of amphiphilic lipid bilayers with an inner aqueous

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core frequently used as platforms in pharmaceuticals and cosmetics for drug release [63-65]. This unique dual release capability makes the delivery of two types of substances in the same time [66]. The first FDA-approved liposomal drug, doxorubicin-encapsulated PEGylated liposomes for curing AIDS connected Kaposi's sarcoma, begun production in 1995 [67]. Composed of natural lipids, liposomes are low toxicity, ease of preparation and high biodegradability [68]. In hence, it works well with a wide range of agents to facilitate a targeted delivery by means of abovementioned characteristics from liposomes [69]. Liposomes binding different specific ligands on their surface such as glycerolipids of Archaea (Archaeosomes) or virus glycoprotein/antigens (viroosomes) could display immunoadjuvant potential for a vaccine and higher affinity to the targeted sites than the free drug [66]. The details of references connected with binding ligands for treatment of diseases resulted from microbes are summarized in (Table 1).

3.2. Nanoparticles

Nanoparticles including metal and non-metal nanoparticle were systematized by our previous review [80]. Both of them have many unique physicochemical properties including extremely small size [81, 82], huge surface to mass ratio [83], high reactivity and a distinctive interaction with biological systems [84]. Nanoparticles have been demonstrated to elevate drug stability, bioavailability, targeting and uptake [85]. Particles less than 5 nm are rapidly expelled from the circulation by extravasation and larger particles have limited diffusion in the extracellular space [86]. In hence, the development of nanoparticles containing medicines has made it possible to increase the therapeutic index of many compo-

nents using suited ligand to arrive the intention site [87]. Nanoparticles binding ligands could enhance antiviral activity and improve cytotoxicity, low water solubility, and rapid clearance from circulation of the free drug [88]. The details of studies to treat microbes by nanoparticles with binding ligands are summarized in (Table 2).

3.3. Dendrimers

Dendrimers were synthesized by Buhleier *et al.* and Tomalia *et al.* during 1970–1990 [96]. Dendrimers are synthetic, highly branched, spherical polymers [97, 98]. Compared to traditional linear polymers, dendrimers are much superior as a drug carrier [99]. Also, they have different kinds of dendrimers; polyamidoamine dendrimer is the first one to be created [80]. There are many outstanding properties of dendrimers such as monodispersity, nano-sizes and shapes, biocompatibility, low toxicity, good pharmacokinetics and can easily provide the active targeted drug delivery [96]. Dendrimers binding ligands result in reducing cytotoxicity, hemolytic bioactives and increasing biocompatibility than the free drug [96]. The details of references related to binding ligands to treat diseases caused by microbes are summarized in (Table 3).

3.4. Carbon Nanotubes

Carbon nanotubes are cylindrical nanostructures consisted of pure carbon atoms covalently bonded in hexagonal arrays [108]. They have two kinds of nanotube such as single-walled carbon nanotubes or multi-walled carbon nanotubes [109]. Carbon nanotubes showed the efficacy as drug delivery vehicles since they can be easily internalized into cells [110]. Moreover, single-walled carbon nanotubes have

Table 1. Liposomes binding ligands for microbes.

Ligands	Target	Remarks	Ref.
Human monoclonal single chain antibodies	H5N1	10 times reduction in the viral titer	[70]
<i>T. cruzi</i> protein antigens	<i>T. cruzi</i>	All infected animals were survived after 30 days.	[71]
Toll-like receptor 4	Respiratory syncytial virus	Decreasing lung viral titers upon live virus challenge in mice	[72]
MPER-specific antibody 10E8	HIV-1 (envelope glycoprotein gp41)	Constructing mimicking the fusion intermediate of gp41	[73]
MPER-specific single chain antibody, 2H10	HIV-1 (envelope glycoprotein)	Preventing HIV-1 from infecting cells	[74]
Wheat germ agglutinin	MRSA	Eradicating all MRSA at 1.25 μ M (90 min)	[75]
Hepatitis A antigens	Hepatitis A virus	Achieving 100% seroprotection in infants and children	[76]
HA	B-strain influenza	Providing good immunogenicity, safety and tolerability on children	[77]
HA	A-strain Influenza	Preventing 75% of influenza- like illnesses	[78]
Sendai virus F protein	Hepatitis C virus	Inhibiting the Hepatitis C virus RNA functions.	[79]

**T. cruzi*: *Trypanosoma cruzi*; MPER: Membrane-proximal external region; MRSA: Methicillin-resistant *Staphylococcus aureus*; HA: Hemagglutinin antigens; HIV: Human immunodeficiency virus

Table 2. Nanoparticles binding ligands for microbes.

Ligands	Target	Remarks	Ref.
CD4-BP4 peptide	HIV-2	Providing selective binding and efficient delivery of Indinavir to CD4 ⁺ -HIV host cells	[89]
Ulex europaeus agglutinin I	<i>S. aureus</i>	Promoting clearance of an acute <i>S. aureus</i> systemic infection	[90]
Nucleic acid	HBV	Halting HBV replication	[91]
Bacitracin A and Polymyxin E	<i>S. aureus</i> , <i>B. amyloliquefaciens</i> , <i>E. coli</i> and <i>P. aeruginosa</i>	Resulting in up to 10-fold antibacterial activity and no bacterial resistance	[92]
Polyoxometalate and tyrosine	<i>E. coli</i>	Causing pore formation, cell wall cleavage and cell lysis of <i>E. coli</i>	[93]
HPV protein	HPV	Reducing HPV-related disease including cervical cancer	[94]
Cell-penetrating peptides	HPV	Providing 8 times cellular uptake	[95]
Integrin-binding peptide	HBV	Delivering siRNA to the cytosol of the targeted cells	[88]

**S. aureus*: Staphylococcus aureus; *B. amyloliquefaciens*: Bacillus amyloliquefaciens; *E. coli*: Escherichia coli; *P. aeruginosa*: Pseudomonas aeruginosa; HPV: Human papilloma virus; HBV: Hepatitis B virus

Table 3. Dendrimers binding ligands for microbes.

Ligands	Target	Remarks	Ref.
DC-SIGN lectin receptor	HIV(P24 capsid protein)	Reducing the infection by 100% at 10 μ M	[100, 101]
SB105-A10 peptide	HIV(Gp41 and gp120 envelope protein)	Inhibiting the HIV-1 _{ada} R5 strain infection without altering the tissue viability	[102]
Anti-HIV nucleic acids	HIV	Having 10 times less cytotoxic	[103]
GalAG2 tripeptides	<i>P. aeruginosa</i>	Inducing biofilm dispersal <i>in vitro</i>	[104]
G2KPY tripeptide	<i>P. aeruginosa</i>	Inhibiting <i>P. aeruginosa</i> biofilm <i>in vitro</i>	[105]
SB105 and SB105 A10 peptides	Human cytomegalovirus	Enhancing antiviral activity	[106]
Gatifloxacin	MRSA	Increasing antimicrobial activity	[106]
(RW) _{4D} peptides	<i>E. coli</i>	Inhibiting biofilm formation of <i>E. coli</i>	[107]

*HIV: Human immunodeficiency virus; MRSA: Methicillin-resistant Staphylococcus aureus; *E. coli*: Escherichia coli; *P. aeruginosa*: Pseudomonas aeruginosa

high chemical stability and easy functionalization than multi-walled carbon nanotubes [80]. single-atomic layer walled carbon nanotubes through surface modification have been continuously used in active targeted drug delivery [111]. Because of its large surface area, they have been bound numerous ligands on their surface to the targeted sites [111]. Although the carbon nanotubes are widely used for treatments of cancer, they are still few publications used in curing diseases caused by microbes. Compared to the free drug, carbon nanotubes binding different ligands provide promising outcomes like reducing adverse effects, controlling drug delivery and improving patient compliance [112]. The details of references associated with binding ligands to inhibit microbes are summarized in (Table 4).

4. CHALLENGES AND FUTURE DEVELOPMENTS

Although the active targeted strategy using nano-carriers has been solved many concerns from the conventional drug strategy, there is still a challenge reported by some researchers [117]. Active targeted strategy was a notable and efficient approach to send drug toward the pathogenic organs, however, Kunjachan *et al.* reported active targeted strategy should not be overestimated because the drug retention time using the active targeted approach would be diminished easily in the animal model [46]. Besides, active targeted delivery needs highly specific target recognition and great deal of target binding affinity. In hence, length of branches carrying a ligand and the number of ligands per

Table 4. Carbon nanotubes binding ligands for microbes.

Ligands	Target	Remarks	Ref.
siRNA	HIV(CXCR4 co-receptor)	Blocking HIV viral entry and reducing infection	[113]
siRNA	HIV(CXCR4 co-receptors)	Reducing 60% expression levels of CXCR4	[114]
FMDV peptides	FMDV (Protein VP1)	Showing immunogenicity and eliciting antibody response	[115]
FMDV peptides	FMDV(B cell epitope)	Enhancing significantly the virus neutralizing antibody titers	[116]

*HIV: Human immunodeficiency virus; FMDV: Foot-and-mouth disease virus

nano-carriers should be considered [112]. Besides, the most of papers about active targeted drug delivery for microbes we collected are *in vitro*, scientists could further use *in vivo* model to determine the efficacy of active targeted strategy in the future.

CONCLUSION

Because of the site specific targeting of drugs and lots of other advantages, active targeted drug delivery system is gaining popularity in present scenario. By specific targeted ligands, drugs can be directly targeted to their site of action to prevent toxicity and undesired effects to other sites. These can be used for bioavailability enhancement of the drugs, having poor bioavailability, to reduce the dose of drug administered. Consequently, active targeted drug delivery using nano-carriers provide a guarantee to cure infectious diseases precisely and efficiently.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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