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Short Communication

Stimuli responsive lipid coated mesoporous silica nanoparticles for drug delivery

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Abstract

Immediate relinquishment of the drug from the drug distribution carrier after cellular uptake is a sizably voluminous challenge. Premature leakage of the chemotherapeutics during circulation, causing side effects to salubrious tissue, is even more germane. Stimuli responsive drug distribution systems have addressed these issues and have become more alluring in last few years. Physical stimuli including ultrasound (US) due to its non- invasive nature are considered very safe and efficacious. Mesoporous silica nanoparticles due to their salient features are very felicitous for drug distribution to tumor cells. These features include more sizably voluminous surface area, hydrophilic and hydrophobic nature, tailorable pore size and pore volume, inner and outer surface for affixment, mechanical vigor and non-toxic nature. By cumulating distinguishing features of liposomes to mesoporous silica nanoparticles very copacetic results can be achieved. We have developed an US responsive drug distribution system where we have utilized mesoporous silica nanoparticles as a drug carrier, doxorubicin as a model drug, perfluoropentane (PFP) as an US responsive material and liposomes as gatekeeper. The relinquishment of the drug was prosperously triggered by US due to the disruption of low boiling point PFP inside pores, building up pressure and causing the immediate release. This immediate release was additionally visually examined in cell culture experiments where our system has engendered more cytotoxic effects to tumor cells as compared to non- US carriers. Lipid coating to MSNPs not only provided the gate keeping effects but additionally enhanced the cellular uptake of the carrier.

Introduction

Incipient World alphaviruses affect North, South, and Central America and pose a major public health threat as they are highly infectious and can result in fatal encephalitis in humans. One of these alphaviruses, the Venezuelan equine encephalitis virus (VEEV), is relegated as a Category B Agent by the CDC and NIAID due to facilitate of aerosolization of highly infectious virions and the lack of controlled vaccines and antivirals against the virus3. Because of its potentially debilitating health consequences, low infectious dose in humans, and stability in storage, VEEV is a potential bioterrorism agent and has been anteriorly stockpiled in the US and USSR. In additament to its utilize as a bioterrorism agent, natural VEEV outbreaks have resulted in equine and human infections in North and South America, causing high rates of fatality in equines (85%) and chronic neurological complications in humans. The virus causes influenza-like symptoms in humans with 14% of infections resulting in neurological complications and sequelae, including disorientation, ataxia, melancholy, and convulsions. With one percent of human infections resulting in mortality4,5, the development of incipient strategies to inhibit VEEV infection is critical to minimizing fatalities and complications of infection from both bioterrorism and natural outbreaks.

MSNs coated with fortified lipid bilayers (lipid-coated MSNs (LC-MSNs)) have been employed in drug and protein distribution applications to ameliorate colloidal stability and subsequent circulation time, biocompatibility, cargo loading and relinquish, and tissue-concrete targeting. Encapsulation of the MSN within a conformal fortified lipid bilayer via liposome fusion can amend colloidal stability in physiological solutionsand avert cargo release prior to cell internalization or some other external trigger21. Furthermore, a lipid bilayer coating offers a supplemental surface that can be functionalized independently of the MSN surface for tissue-categorical targeting. Conclusively, the intrinsical instability and broad size distribution of liposomes is overcome by adhesion to the MSNs to compose LC-MSNs. Thus, LC-MSNs harness the advantages and overcome the obstacles associated with MSNs and liposomes in one multifarious platform for minute molecule distribution.

In this work, we highlight the utilization of LC-MSNs for ML336 distribution to inhibit VEEV. LC-MSN characterization revealed uniformly sized particles coated with a lipid bilayer that maintained colloidal stability. The distribution conveyance was able to load and relinquish ML336 in a manner that inhibited virus in vitro. Cell internalization studies suggest a clathrin-mediated endocytosis pathway is involved in uptake of LC-MSNs. Determinately, ML336 loaded LC-MSNs showed in vivo viral inhibition in a murine model of VEEV infection. Overall, this work demonstrates the first utilization of a nanoparticle-predicated system for the distribution of ML336. The prosperous inhibition of virus achieved with this platform could have widespread benefit in combatting VEEV and other viral infections resulting from bioterrorism or natural causes.

LC-MSN cellular entry mechanism

To commence to understand the dependency of LC-MSN cellular internalization on lipid bilayer disruption and consummate drug cargo release, we first investigated whether LC-MSNs enter cells through endocytosis. LC-MSNs conjugated with affinity ligands are kenned to enter cells utilizing trafficking pathways of the targeting receptor. For example, cholera toxin B conjugated LC-

MSNs use lipid raft endocytosis for internalization after binding the GM1 ganglioside20. LC-MSNs have additionally been formulated to evade non-concrete uptake in blood circulation19. However, LC-MSN uptake in static conditions represented in these studies is not well understood. To determine whether LC-MSNs undergo cellular internalization through endocytosis, fluorescent LC-MSNs containing Cy3-labeled MSN cores were habituated to facilitate visualization and quantitation of ingression into HeLa cells while in the presence of sundry endocytosis inhibitors. HeLa cells were treated with a pH dependent endocytosis inhibitor (BAF), clathrin-mediated endocytosis inhibitors (CPZ, DYN), caveolae-medicated endocytosis inhibitors (PMA, DYN) or macropinocytosis inhibitors (wort and IPA-3), for 1 h prior to the integration of Cy3-labeled LC-MSNs. Cells were vigorously washed to abstract free particles and then examined by microscopy methods. Cy3-labeled LC-MSNs were yarely internalized by HeLa cells under untreated (no inhibitor (NI)) conditions and in the presence of wort, IPA-3, and PMA. On the other hand, in the presence of BAF, CPZ and DYN the cellular uptake of LC-MSNs was pellucidly inhibited suggesting the role of clathrin-mediated endocytosis in cellular internalization of LC-MSNs

Conclusion

In this work, we presented the first utilization of LC-MSNs to distribute ML336 for TC-83 VEEV inhibition both in vitro and in vivo. ML336 loaded LC-MSNs were prosperously coated with a lipid bilayer, which significantly amended colloidal stability, and enabled sustained relinquishment of cargo over the course of 4 hours. Viral loads were minimized by 4–6 orders of magnitude in TC-83 VEEV infected HeLa cells treated with ML336 loaded LC-MSNs, which was repeatable across several particle batches in different studies. Furthermore, in vitro studies betokened the possibility of supplemental relinquishment of ML336 after cellular internalization via clathrin-mediated endocytosis and enhanced ML336 stability when loaded in LC-MSNs. Safety studies denoted that LC-MSNs were not toxic in mice at the doses administered in this study. In mice infected with TC-83 VEEV, treatment with ML336-loaded LC-MSNs resulted in a consequential minimization of viral load in the encephalon after four days of treatment. Overall, these studies highlight the utility of LC-MSNs for drug distribution in antiviral applications, and provide a supplemental bulwark against VEEV and other alphaviruses in the cases of natural infection or bioterrorism.