Mesoporous silica nanoparticles as diagnostic and therapeutic tools: how can they combat bacterial infection?

Sen Karaman, Didem; Manner, Suvi; Rosenholm, Jessica

Published in:
Therapeutic Delivery

DOI:
10.4155/tde-2017-0111

Published: 01/01/2018

For reprint orders, please contact: reprints@future-science.com

Therapeutic Delivery

Mesoporous silica nanoparticles as diagnostic and therapeutic tools: how can they combat bacterial infection?

Didem Şen Karaman*,[1], Suvi Manner[1] & Jessica M Rosenholm[1]

[1]Pharmaceutical Sciences Laboratory, Faculty of Science & Engineering, Åbo Akademi University, Turku, Finland

* Author for correspondence: dsen@abo.fi

First draft submitted: 16 November 2017; Accepted for publication: 30 January 2018; Published online: 2 March 2018

Keywords: antibacterial • antimicrobial resistance • bacterial biofilms • bacterial infections • drug delivery • mesoporous silica nanoparticles • multifunctional nanoparticles • nanoantibiotics • nanotherapeutics

Nanoparticle-based drug delivery is one of the most promising approaches to overcome the challenges in the delivery of therapeutic compounds to the site of interest. The size of particles on the nanoscale provides them access to many otherwise inaccessible areas in the body. With the aid of nanoparticle-based drug-delivery systems, the drug of interest can be accumulated at the necessary site whereby the penetration of the drug through the target cells is improved. The essential aim of drug delivery is not only to improve efficacy, safety and/or patient comfort but also the personalization of therapies tailoring the design of the drug-delivery systems. With the sophisticated design of nanoparticles, prominent therapeutic and diagnostic functionalities can be obtained that are quite distinctive from those obtainable by conventional approaches.

An increasing number of bacterial infections are caused by antibiotic-resistant strains and persistent biofilms, which are structured communities of bacterial cells embedded in a self-produced matrix, and attributed to a variety of chronic infections [1]. Implementation of nanoparticle-based antibacterial treatments and diagnosis is currently considered one of the most promising strategies to overcome the challenges of bacterial infections, such as the increasing treatment failures caused by antimicrobial resistance and the persistent nature of biofilms in the treatments; as well as the declined investments in antimicrobial drug discovery during the past few decades [2]. The groundbreaking approaches in combating bacterial infections has been devoted to the utilization of nanoparticles as versatile tools for the diagnosis as well as prevention (e.g., vaccination and medical devices) and treatment of bacterial infections [3].

Antibacterial applications of nanomaterials

The utilization of nanomaterials has gained ground in the treatment of bacterial infections, especially making use of the knowledge generated from research on oncology-related nanomedicine. Different types of nanomaterials have been reported to offer advantages in reducing acute toxicity, overcoming resistance and reducing the cost, when compared with conventional antibiotics [4,5]. Most studies to date have focused on inorganic nanoparticles containing silver [6], gold [7], copper oxide [8], zinc oxide [9], titanium oxide [10] and cerium oxide [11] as antibacterial constructs. These materials can inherently exert antibacterial activity through multiple modes of action, and can further, similarly as for imaging agents, be used as building blocks in systems additionally utilized for efficient delivery of antibacterial compounds [12]. These strategies enable bacterial attacks on many fronts [13], making it palpably more difficult for bacteria to develop resistance simultaneously toward all modes of action. Further, the ability of so-called 'prickly' nanoparticles [14] or star-shaped molecular assemblies [15] to combat antibacterial resistance via physical methods, by inducing physical disruption of the bacterial cell wall, was recently portrayed in the media as a promising means of 'winning the war against superbugs' [16]. Importantly, these physically acting nanomaterials can further be combined with chemical strategies, in other words, loading of drugs to the same nanosystems or used in combinatorial therapy, thereby synergistically increasing their effect.

newlands press

Mesoporous silica-based approaches to combat bacterial infections

Among the nanomaterials of interest for pharmaceutical development, mesoporous silica nanoparticles (MSNs) provide an ideal platform to invest more research efforts for providing different strategies to combat bacterial infections. The functional advantages and flexible design options of MSNs make them attractive tools for the treatment of infectious diseases.

To date, a vast array of successful methods has been developed whereby the physicochemical properties of silica nanoparticles can been tailored for specific applications and needs by employing versatile sol–gel synthetic methods and elaborated surface functionalization strategies [17]. In recent years, scientists have pointed out the unique conceptual similarities between biofilms and tumor microenvironments, which can be exploited to design novel and selective treatments [18]. By keeping the employed strategies in mind for the preparation of MSNs in cancer nanomedicine, similar approaches can be followed for the development of MSN-based nanoantibiotics for combating both acute and chronic bacterial infections.

MSNs can be constructed as antibacterial nanocomposites to be utilized either as inherent antibacterial nanoparticles, and/or as delivery systems for molecular antibacterial agents. In addition, the size and the surface functionalities of MSNs can be tuned to improve their interactions with both planktonic and biofilm bacteria, as well as enhance the penetration through the biofilm matrix. Moreover, MSNs can interfere with the bacterial cell-to-cell communication (quorum sensing) to prevent biofilm formation. Consequently, MSNs can function as a promising platform to overcome the challenges associated with combating bacterial infections. In this commentary, we discuss the strengths of MSNs as diagnostic and therapeutic tools to combat infectious diseases by considering the upsurge of interest in the literature.

MSNs for the identification of bacterial infections

Precise and rapid diagnosis of bacterial infections is important in order to avoid the unnecessary use of antibiotics, which is a key driver of antibacterial resistance. A variety of diagnostic approaches have been used with varying sensitivity, specificity, cost and efficacy. Among the existing diagnostic approaches, polymerase chain reaction sequencing is known to be highly sensitive. However, polymerase chain reaction-based systems lack practicalities and can be costly for limited patient care environments [19]. In the case of biofilm-associated infections, routine microbiological testing assists with the diagnosis of a clinical infection; as there is no 'gold standard' available to reveal the presence of biofilm from samples collected within clinical settings [20].

Lots of efforts have been devoted toward the identification and monitoring of diseases by incorporating imaging agents and affinity ligands in/on nanoparticle matrices. In this context, MSNs represent a powerful nanoparticle-based platform for the identification and monitoring of bacterial infections. With the aid of the flexible design options of MSNs, multimodal imaging modalities can be incorporated into a single MSN system, and the detection specificity can be introduced by appropriate surface modifications. Similar approaches have already been employed with different types of nanoparticles (e.g., magnetic nanoparticles, gold nanoparticles, quantum dots) for specific, selective and fast bacterial detection and labeling by modifying nanoparticles' surfaces with antibiotics, antibodies, aptamers, peptides and carbohydrates [21].

MSN-based antibacterial nanocomposites

MSN-based antibacterial nanocomposites can be designed by tuning the MSN matrix to exert antibacterial properties by depositing metal ions or ultrasmall nanoparticles onto the silica matrix or by encapsulating metal/metal oxide nanoparticles into shells of mesoporous silica. By this way, the most frequently proposed antibacterial modes of action provided with pristine metal/metal oxide nanoparticles, such as oxidative stress, metal ion release and non-oxidative mechanisms, can be imparted on the MSN-based nanocomposites. Employing different design strategies, such as porous silica shell coating on metal/metal oxide nanoparticles, simultaneously overcomes the very common problems with aggregation of metal oxide particles that hampers their performance. Further, the increased surface area imparted by the porous silica shell can be employed as cavities for delivering therapeutic agents in order to provide synergetic effects in the treatment regime.

MSNs as a carrier for antibacterial compounds & targeted delivery

Utilization of MSNs as effective drug-delivery systems has been thoroughly documented for slightly over a decade, especially for anticancer therapeutics. Recently, the delivery of antibacterial agents has been investigated by employing similar strategies as those employed in cancer therapeutics by loading the drug molecules into the pores

of MSNs [22], *in situ* incorporation of the drug molecules into the MSN matrix [23] or conjugating them onto the surfaces of MSNs [24]. In the use of MSNs as the carrier for antibacterial drug compounds, their surface functionality along with their size and shape are critical parameters to be optimized to tune the drug release profiles [25]. In this context, the features of MSNs (e.g., high specific surface areas, large pore volumes and tunable pore sizes), the possibility of diverse surface functionalization strategies and controlled drug release, as well as the penetration ability of MSNs through biological barriers make them powerful candidates for the design of effective drug-delivery systems.

Conventional antibiotic therapy can be toxic and harmful to healthy tissues as well as for beneficial, commensal bacterial species. However, especially when treating biofilm infections, long-term therapy with high doses of antibiotics is typically needed due to the tolerance associated with biofilm-growing bacteria. This, in turn, triggers resistance development. In the literature, very few studies exist regarding the utilization of MSNs in biofilm control, even though they have all the required features to design efficient antibiofilm agents, such as the aforementioned high drug loading capacity and tunable surface chemistry. For instance, MSNs can be employed in the immobilization of enzyme-based quorum sensing inhibitors to enhance their stability and efficacy. In addition, the particle surface of MSNs can be tuned with cationic, anionic or hydrophilic functional groups in order to control their penetration through the biofilm for providing efficient drug delivery and biofilm eradication.

Furthermore, MSNs can potentially offer the possibility of delivering antibiotics in a targeted fashion for specific bacterial species in order to achieve an adequate antibiotic concentration at the site of infection. Therefore, by constructing species-selective MSN designs, the excessive use of antibiotics, as well as the toxic effects to commensal bacteria and healthy cells could be reduced.

Future perspective

In addition to the use of MSNs with single modality for either the treatment or identification of bacterial infections, they also possess great potential as nanoparticle-based theranostic systems in combating bacterial infections by combining therapeutic and diagnostic modalities in the same nanosystem [26]. The abilities of MSNs as carriers for multiple drug molecules as cargo, while efficiently protecting the incorporated cargo from harsh conditions in the environment, offers a solution for the treatment and prevention of polymicrobial biofilms and simultaneous tracking of the therapeutic process. Since the treatment of biofilms remains the obstacle in bacterial infections, MSNs with the ability to penetrate through biological barriers can provide effective killing of persistent bacterial cells located in the deepest layers of the biofilms. Typically, two antibiotics with distinct mechanisms of action are required for the treatment of biofilm infections, as monotherapy alone is not sufficient. Therefore, multidrug-carrying MSNs could offer an efficient solution for the treatment of biofilm infections or one antibiotic and one adjunctive agent could be combined to enhance the efficacy of the antibiotic agent. Further, the major current problems associated with the use of quorum sensing inhibitors *in vivo* are related to inefficient stability and efficacy, which are features that have been shown multiple times to be improved by MSNs. Given the proven potential of MSNs accumulated during the last decade and this still relatively unexplored application area, we foresee an upsurge in the research on MSNs for combating bacterial infections in the near future.

Financial & competing interests disclosure

The authors wish to acknowledge the Magnus Ehrnrooth Foundation for funding our project, '*Development of species-selective nanoparticles for the treatment of biofilms*' for supporting us in our quest to address the above-discussed topic, as well as the members of the COST Action TD1305, '*Improved Protection of Medical Devices Against Infection*' for fruitful insights and discussions. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1. Bjarnsholt T. The role of bacterial biofilms in chronic infections. *APMIS* 121(136), 1–58 (2013).
2. şen Karaman D, Manner S, Fallarero A, Rosenholm JM. Current approaches for exploration of nanoparticles as antibacterial agents. In: *Antibacterial Agents.* Ranjith N Kumavath (Ed.). InTech, Croatia (2017).
3. Zhu X, Radovic-Moreno AF, Wu J, Langer R, Shi J. Nanomedicine in the management of microbial infection – overview and perspectives. *Nano Today* 9(4), 478–498 (2014).

4. Weir E, Lawlor A, Whelan A, Regan F. The use of nanoparticles in antimicrobial materials and their characterization. *Analyst* 133(7), 835–845 (2008).
5. Beyth N, Houri-Haddad Y, Domb A, Khan W, Hazan R. Alternative antimicrobial approach: nano-antimicrobial materials. *Evid. Based Complement. Alternat. Med.* 2015, 1–16 (2015).
6. Pal S, Tak YK, Song JM. Does the antibacterial activity of silver nanoparticles depend on the shape of the nanoparticle? A study of the Gram-negative bacterium, *Escherichia coli*. *Appl. Environ. Microbiol.* 73(6), 1712–1720 (2007).
7. Li X, Robinson SM, Gupta A, Saha K *et al.* Functional gold nanoparticles as potent antimicrobial agents against multi-drug-resistant bacteria. *ACS Nano* 8(10), 10682–10686 (2014).
8. El Zowalaty M, Ibrahim NA, Salama M, Shameli K, Usman M, Zainuddin N. Synthesis, characterization, and antimicrobial properties of copper nanoparticles. *Int. J. Nanomed.* 8, 4467–4479 (2013).
9. Sirelkhatim A, Mahmud S, Seeni A *et al.* Review on zinc oxide nanoparticles: antibacterial activity and toxicity mechanism. *Nano Micro Lett.* 7(3), 219–242 (2015).
10. Kubacka A, Diez MS, Rojo D *et al.* Understanding the antimicrobial mechanism of TiO2-based nanocomposite films in a pathogenic bacterium. *Sci. Rep.* 4, 4134 (2014).
11. Reshma P, Ashwini K. Cerium oxide nanoparticles: synthesis, characterization and study of antimicrobial activity. *J. Nanomater. Mol. Nanotechnol.* 6(3), 1–5 (2017).
12. Sahlgren C, Meinander A, Zhang H *et al.* Tailored approaches in drug development and diagnostics: from molecular design to biological model systems. *Adv. Healthc. Mater.* 6(21), 1–34 (2017).
13. Sen Karaman D, Sarwar S, Desai D *et al.* Shape engineering boosts antibacterial activity of chitosan coated mesoporous silica nanoparticle doped with silver: a mechanistic investigation. *J. Mater. Chem. B* 4(19), 3292–3304 (2016).
14. Wu R, Zhang H, Pan J *et al.* Spatio-design of multidimensional prickly Zn-doped CuO nanoparticle for efficient bacterial killing. *Adv. Mater. Interfaces* 3(18), 1600472 (2016).
15. Lam SJ, O'Brien-Simpson NM, Pantarat N *et al.* Combating multidrug-resistant Gram-negative bacteria with structurally nanoengineered antimicrobial peptide polymers. *Nat. Microbiol.* 16162, 1–11 (2016).
16. Smith N. Does this 25 year-old hold the key to winning the war against superbugs? *Telegraph* (2016). www.telegraph.co.uk/health-fitness/body/does-this-25-year-old-hold-the-key-to-winning-the-war-against-th
17. Sen Karaman D. Physicochemical characteristics of silica nanoparticles tailored for nanomedicine, Åbo Akademi University, Turku, Finland (2016).
18. Koo H, Allan RN, Howlin RP, Stoodley P, Hall-Stoodley L. Targeting microbial biofilms: current and prospective therapeutic strategies. *Nat. Rev. Microbiol.* 15(12), 740–755 (2017).
19. Gao W, Thamphiwatana S, Angsantikul P, Zhang L. Nanoparticle approaches against bacterial infections: nanoparticle against bacterial infections. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* 6(6), 532–547 (2014).
20. Percival SL, Suleman L, Vuotto C, Donelli G. Healthcare-associated infections, medical devices and biofilms: risk, tolerance and control. *J. Med. Microbiol.* 64(4), 323–334 (2015).
21. Chen L, Zhang J. Bioconjugated magnetic nanoparticles for rapid capture of Gram-positive bacteria. *J. Biosens. Bioelectron.* 1(S11), 1–5 (2012).
22 . Khan MA, Wallace WT, Islam SZ *et al.* Adsorption and recovery of polyphenolic flavonoids using TiO_2-functionalized mesoporous silica nanoparticles. *ACS Appl. Mater. Interfaces* 9(37), 32114–32125 (2017).
23. de Oliveira L, Bouchmella K, Picco A *et al.* Tailored silica nanoparticles surface to increase drug load and enhance bactericidal response. *J. Braz. Chem. Soc.* 28(9), 1715–1724 (2017).
24. Mosselhy D, Ge Y, Gasik M *et al.* Silica-gentamicin nanohybrids: synthesis and antimicrobial action. *Materials* 9(3), 1–16 (2016).
25. Maleki A, Kettiger H, Schoubben A *et al.* Mesoporous silica materials: from physico-chemical properties to enhanced dissolution of poorly water-soluble drugs. *J. Control. Rel.* 262, 329–347 (2017).
26. Choi KY, Liu G, Lee S, Chen X. Theranostic nanoplatforms for simultaneous cancer imaging and therapy: current approaches and future perspectives. *Nanoscale* 4(2), 330–342 (2012).