Tailored Silica Nanomaterials for Immunotherapy

Luo Gu

Department of Materials Science and Engineering, Institute for NanoBioTechnology, Johns Hopkins University, Baltimore, Maryland 21218, United States

Mesoporous silica nanoparticles with extra-large pores show promise as a nanomaterial adjuvant for cancer vaccines.

The renowned immunologist Charles Janeway called vaccine adjuvants “the immunologists’ dirty little secret.” This whimsical expression is also quite accurate because these immunological agents are critical for inducing effective immune response to vaccines, yet they are often poorly characterized, and the exact mechanisms of how they work are not well understood. A good example of a widely used adjuvant is aluminum salts (e.g., aluminum hydroxide), which mainly promote antibody responses. However, in recent years, new types of biomaterials-based adjuvant with rationally designed chemical and physical features are being developed thanks to innovative materials engineering strategies and advances in our understanding of the immune system. Now, Jaeyun Kim and colleagues have developed silica nanoparticles with extra-large pores as a promising material system and adjuvant for cancer vaccines.2

Mesoporous silica nanoparticles (MSNs) were first developed in the 1990s, later becoming one of the most studied nanomaterials for controlled drug release and delivery. They have attracted significant research attention for various drug delivery applications because of their low toxicity, tunable particle size, high porosity, versatile surface chemistry, good chemical stability, low cost, etc.3,4 However, previous studies have mainly focused on the delivery of small molecular drugs due to the small pore size of the material (typically 2–6 nm). MSNs’ small pore size prevents efficient loading of macromolecules such as proteins, which has limited their utility in immunotherapy as many antigens and immunostimulatory factors are macromolecules (e.g., proteins, nucleic acids).

In their study, Cha et al. synthesized MSNs with 20–30 nm pores and demonstrated the advantage of using large-pore nanoparticles to incorporate antigens and immunological “danger signal” molecules to design more effective cancer vaccines (Figure 1).2 The large-pore structure was achieved by using a substantial quantity of ethyl acetate as a pore expansion agent together with surfactant-stabilized iron oxide seed nanoparticles in the silica sol–gel reaction. Unlike the block copolymer method of large-pore MSNs synthesis, this method resulted in an irregular porous structure with more accessible pores.5 These extra-large pore MSNs show significantly higher loading of both protein antigen and short single-stranded synthetic DNA molecules (the “danger signal”) than conventional small-pore MSNs. In addition, the flexible surface silane modification of MSNs allows for increased loading capacity by optimizing the electrostatic interactions between the nanoparticles and the payloads.

The extra-large pore antigen-containing MSNs effectively activated dendritic cells (DCs) in culture, while the antigen alone failed to induce such activation. The mechanism of how these nanoparticles activate immune cells is not fully understood, as multiple factors likely contribute to their adjuvant effects. For example, previous studies on other types of MSNs have shown that both the surface chemistry and the physical structure of MSNs can affect their immunostimulatory potency.

Published: April 24, 2018

Figure 1. Silica nanoparticles with extra-large pores as both a delivery system and an adjuvant for cancer vaccines. Mesoporous silica nanoparticles (MSNs) target dendritic cells (DCs) in lymph nodes and deliver tumor antigens and “danger signals” to activate DCs, which then leads to a cytotoxic T lymphocyte (CTL) antitumor response. Figure is adapted from ref 2 (Copyright 2018 American Chemical Society) and ref 10 (Copyright 2016 Nature).
mediated through their activation of inflammatory response proteins (e.g., inflammasomes). 6,7 Since surface ligand distribution of nanoparticles regulates their interactions with DCs, it would be interesting to investigate whether the irregular porous structure of extra-large pore MSNs contributes to their adjuvant properties.

Cha et al. tested the prophylactic efficacy of the nanoparticle vaccine against melanoma using a model tumor antigen. Mice vaccinated with extra-large pore MSNs containing both antigen and “danger signal” molecules showed significant tumor growth inhibition, while vaccination with soluble antigen and “danger signal” molecules showed little effect. More importantly, the mice that survived from the first tumor challenge in the nanovaccine group also established immunological memory against the melanoma cells. This immunological memory protected the animals from cancer reoccurrence when rechallenged with the tumor cells, which demonstrated one of the most important advantages of cancer immunotherapy. Consistent with these results, significantly higher numbers of memory T cells were detected in mice inoculated with the nanovaccine than in the control group.

More importantly, the mice that survived from the first tumor challenge in the nanovaccine group also established immunological memory against the melanoma cells. This immunological memory protected the animals from cancer reoccurrence when rechallenged with the tumor cells, which demonstrated one of the most important advantages of cancer immunotherapy.

Because of the strong adjuvant effect and other interesting chemical and physical properties of porous silica nanomaterials, they have attracted significant attention and are becoming a very important class of materials for immunotherapy. The detailed mechanism of MSNs’ adjuvant function needs to be further investigated. Fortunately, recent studies have advanced our understanding of the interactions between MSNs and the immune system (inflammasome activation, depot effect, etc.), and demonstrated the advantages of MSNs over conventional adjuvants. 6,7,9 Therefore, rationally designed MSNs are increasingly being developed as more potent adjuvants. The work by Kim and colleagues is an example of such progress. In addition to the intrinsic adjuvant effect of MSNs, the extra-large pores of the nanoparticles provide a means to effectively deliver high molecular weight antigens and immunostimulatory molecules, promoting antigen presentation on the surface of immune cells through desired pathways. This feature is especially appealing when protein or complex antigens need to be incorporated in the vaccines. For example, in many cases tumor-associated antigens are not well-defined, so tumor extracts are sometimes used as the source of antigen to capture the unidentified mutations. The complex composition of tumor extracts would require a vaccine system that can incorporate various types of protein antigens. Such flexibility is also an important design parameter to consider for the development of personalized therapeutic vaccines using patient tumor samples as the source of antigen.

In addition to the intrinsic adjuvant effect of MSNs, the extra-large pores of the nanoparticles provide a means to effectively deliver high molecular weight antigens and immunostimulatory molecules, promoting antigen presentation on the surface of immune cells through desired pathways. This feature is especially appealing when protein or complex antigens need to be incorporated in the vaccines.

Continued progress on porous silica nanomaterials and other new types of biomaterials-based adjuvants will certainly lead to a paradigm shift in vaccine development. Rationally designed or even personalized adjuvants will not only replace those used conventionally in vaccines but may even enable new types of immunotherapy. 10 The unflattering name of adjuvants, the immunologists’ dirty little secret, will soon be history.

Author Information
E-mail: luogu@jhu.edu.

ORCID
Luo Gu: 0000-0002-9813-7202

Notes
The author declares no competing financial interest.

REFERENCES
(1) Marrack, P.; McKee, A. S.; Munks, M. W. Towards an understanding of the adjuvant action of aluminium. Nat. Rev. Immunol. 2009, 9, 287−293.
(2) Cha, B. G.; Jeong, J. H.; Kim, J. Extra-Large Pore Mesoporous Silica Nanoparticles Enabling Co-delivery of High Amounts of Protein Antigen and Toll-like Receptor 9 Agonist for Enhanced Cancer Vaccine Efficacy. ACS Cent. Sci. 2018, DOI: 10.1021/acscentsci.8b00035.
(3) Slowing, I. I.; Vivero-Escoto, J. L.; Wu, C.-W.; Lin, V. S.-Y. Mesoporous silica nanoparticles as controlled release drug delivery and gene transfection carriers. Adv. Drug Delivery Rev. 2008, 60, 1278−1288.
(4) Li, Z.; Barnes, J. C.; Bosoy, A.; Stoddart, J. F.; Zink, J. I. Mesoporous silica nanoparticles in biomedical applications. Chem. Soc. Rev. 2012, 41, 2590–2605.

(5) Zhao, D.; et al. Triblock Copolymer Syntheses of Mesoporous Silica with Periodic 50 to 300 Angstrom Pores. Science 1998, 279, 548–552.

(6) Kim, J.; et al. Injectable, spontaneously assembling, inorganic scaffolds modulate immune cells in vivo and increase vaccine efficacy. Nat. Biotechnol. 2015, 33, 64.

(7) Li, W. A.; et al. The effect of surface modification of mesoporous silica micro-rod scaffold on immune cell activation and infiltration. Biomaterials 2016, 83, 249–256.

(8) Verma, A.; et al. Surface-structure-regulated cell-membrane penetration by monolayer-protected nanoparticles. Nat. Mater. 2008, 7, 588–595.

(9) Wang, X.; Li, X.; Yoshiyuki, K.; Watanabe, Y.; sogo, Y.; Ohno, T.; Tsuji, N. M.; Ito, A. Comprehensive Mechanism Analysis of Mesoporous-Silica-Nanoparticle-Induced Cancer Immunotherapy. Adv. Healthcare Mater. 2016, 5, 1169–1176.

(10) Gu, L.; Mooney, D. J. Biomaterials and emerging anticancer therapeutics: engineering the microenvironment. Nat. Rev. Cancer 2016, 16, 56–66.