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Enhancing immunogenicity of antigens through sustained intradermal delivery using chitosan microneedles with a patch-dissolvable design

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Microneedles (MNs) enable painless and efficient delivery of vaccines to the skin with the objective of targeting epidermal and dermal antigen-presenting cells (APCs) to induce an efficient immune response [1,2]. In this study, we report a patch-dissolvable embeddable MN system, composed of biodegradable chitosan MNs and a dissolvable supporting array patch, for complete and sustained delivery of encapsulated antigens to the skin **(Fig. 1)**. The supporting array can provide mechanical strength to fully insert chitosan MNs into the skin and then rapidly dissolve in skin interstitial fluid. After insertion, MNs could be directly implanted in the dermal layer as an intradermal (ID) depot to allow extended release of the model antigen ovalbumin (OVA) for up to 28 days. Using this system for sustained transdermal delivery minimizes patch wearing time, thus reducing skin irritation caused by long-term contact with transdermal adhesive or patches.

Targeted antigen delivery to the dermal layer that contains numerous APCs can induce stronger immunogenicity than can an intramuscular injection [3,4]. We found that rats immunized with MNs containing low-dose OVA (approximately 200 μg) had persistently high antibody levels for 18 weeks **(Fig. 2)**, which were significantly higher than those observed after an intramuscular injection of full-dose OVA (approximately 500 μg), demonstrating at least 2.5-fold dose sparing. Moreover, OVA-encapsulated chitosan MNs had superior immunogenicity to OVA plus chitosan solution, indicating that MN-based delivery and prolonged skin exposure can further enhance chitosan's adjuvanticity.

This is the first study to demonstrate the antigen dose-sparing potential of chitosan MNs. The use of low-dose vaccines is cost-effective and important for the safety of vaccine recipients because it can alleviate concerns associated with some adverse events caused by immunization. We expect that the patch-dissolvable MN system may serve as a new generation of transdermal vaccine delivery system to provide sustained immune stimulation and improve vaccine immunogenicity.

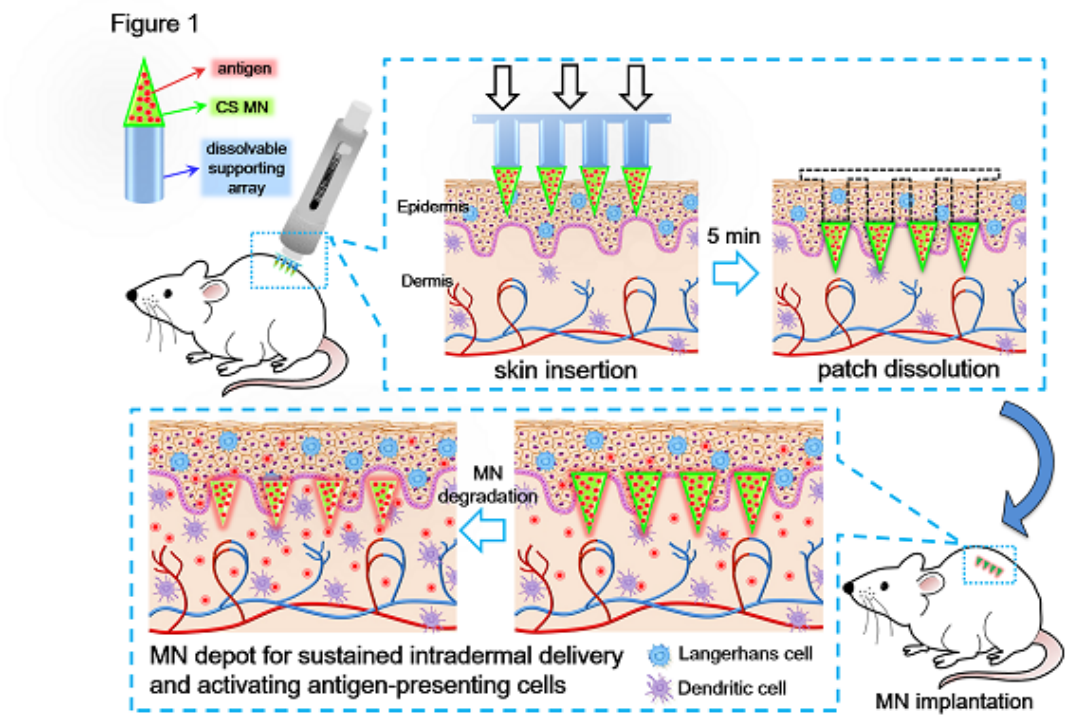

Fig. 1. Schematic illustrations of chitosan microneedles (MNs) with a patch-dissolvable design, consisting of antigen-loaded chitosan MNs and a dissolvable polyvinyl alcohol/polyvinyl pyrrolidone supporting array patch. After insertion, the supporting array can be quickly dissolved in the skin, thus implanting the MNs in the dermal layer as an intradermal (ID) depot to allow sustained release of the antigen and activating antigen-presenting cells.

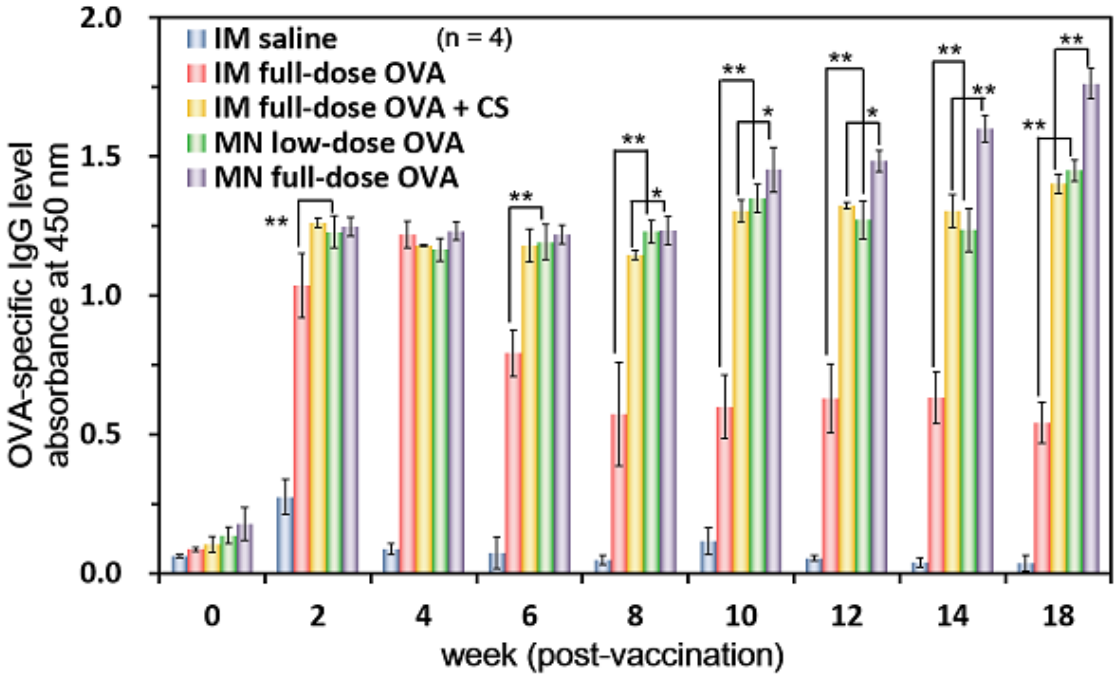

Fig. 2. OVA-specific IgG levels of rats after administration of a single dose of OVA on day 0: rats were intramuscularly injected with saline only (IM saline), or saline containing 500μg OVA (IM full-dose OVA), or 500μg OVA+1mg chitosan+0.1mg trehalose (IM full-dose OVA+CS); rats were received with MNs containing 200μg (MN low-dose OVA) or 500μg OVA (MN full-dose OVA) (n=4 rats for each group).

Reference

1. J.M. Arya, L. Dewitt, M. Scott-Garrard, Y.W. Chiang, M.R. Prausnitz. Rabies vaccination in dogs using a dissolving microneedle patch J. Control. Release, 10 (2016), pp. 19-26.
2. E.S. Esser, A. Romanyuk, E.V. Vassilieva, J. Jacob, M.R. Prausnitz, R.W. Compans, I. Skountzou. Tetanus vaccination with a dissolving microneedle patch confers protective immune responses in pregnancy. J. Control. Release, 236 (2016), pp. 47-56.
3. Y.M. Vasiliev. Chitosan-based vaccine adjuvants: incomplete characterization complicates preclinical and clinical evaluation. Expert Rev. Vaccines, 14 (1) (2015), pp. 37-53.
4. E.C. Carroll, L. Jin, A. Mori, N. Muñoz-Wolf, E. Oleszycka, H.B. Moran, S. Mansouri, C.P. McEntee, E. Lambe, E.M. Agger, P. Andersen, C. Cunningham, P. Hertzog, K.A. Fitzgerald, A.G. Bowie, E.C. Lavelle. The vaccine adjuvant chitosan promotes cellular immunity via DNA sensor cGAS-STING-dependent induction of type I interferons. Immunity, 44 (3) (2016), pp. 597-608.