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ARTICLE

Enhanced Cancer Vaccination by *In Situ* Nanomicelle-Generating Dissolving Microneedles

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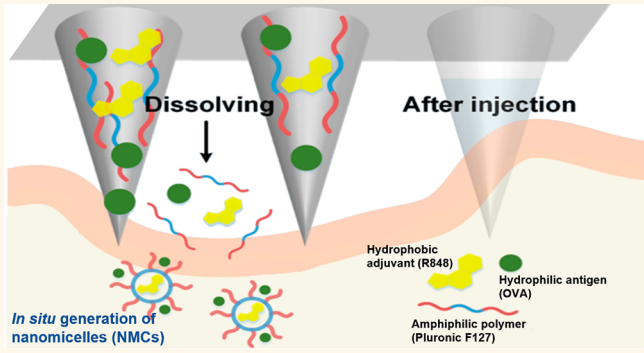
Supporting Information

ABSTRACT: **Efficient delivery of tumor antigens and immunostimulatory adjuvants into lymph nodes is crucial for the maturation and activation of antigen-presenting cells (APCs), which subsequently induce adaptive antitumor immunity. A dissolving microneedle (MN) has been considered as an attractive method for transcutaneous immunization due to its superior ability to deliver vaccines through the stratum corneum in a minimally invasive manner. However, because dissolving MNs are mostly prepared using water-soluble sugars or polymers for their rapid dissolution in intradermal fluid after administration, they are often difficult to formulate with poorly water-soluble vaccine components. Here, we develop amphiphilic triblock copolymer-based dissolving MNs *in situ* that generate nanomicelles (NMCs) upon their dissolution after cutaneous application, which facilitate the efficient encapsulation of poorly water-soluble Toll-like receptor 7/8 agonist (R848) and the delivery of hydrophilic antigens. The sizes of NMCs range from 30 to 40 nm, which is suitable for the efficient delivery of R848 and antigens to lymph nodes and promotion of cellular uptake by APCs, minimizing systemic exposure of the R848. Application of MNs containing tumor model antigen (OVA) and R848 to the skin of EG7-OVA tumor-bearing mice induced a significant level of antigen-specific humoral and cellular immunity, resulting in significant antitumor activity.**



KEYWORDS: *cancer vaccine, dissolving microneedle, nanomicelle, Toll-like receptor agonist, lymphatic delivery*

Vaccines have been considered one of the first-line treatments for the control of cancer as well as infectious disease. Antigen-presenting cells (APCs), such as dendritic cells (DCs), macrophages, and B cells, are known to play a central role in inducing efficient antitumor or antiviral immune responses after vaccination. For maturation and activation of APCs, the efficient delivery of antigens and immunomodulators called adjuvants is critical. Microneedles (MNs) have emerged as an attractive way to overcome the skin barrier for cutaneous drug delivery in a minimally invasive manner.[1,2] MNs represent an array of needles of several hundred microns in length, which can achieve efficient transdermal delivery of biomacromolecules, such as protein or DNA, across the stratum corneum.[3−9] MNs can avoid unnecessary pain as the length of the MN is long enough to pierce skin but does not stimulate dermal nerves and may not require professional training for administration.[10−12] MNs are especially useful for the delivery of vaccines as transdermal vaccine delivery has advantages over intramuscular or subcutaneous administrations due to a relative abundance of resident Langerhans cells and APCs, including DCs and macrophages, in the epidermis and dermis of skin.[13−17] Among various types of MNs, dissolving MNs have attracted much attention due to their ease of preparation and improved safety.[18,19] Unlike solid and hollow MNs that pose the risk of breakage in the skin, dissolving MNs do not leave the debris of needles underneath the skin, minimizing the risk of

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