Smart Transdermal Vaccine Delivery Systems Using Hyaluronic Acid Derivatives

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Statement of Purpose: A variety of vaccine delivery systems have been investigated for efficient immunization via easy administration. Transdermal vaccine delivery was thought to be attractive due to the strong immune responses at a low dose by Langerhans and dendritic cells in the skin tissues [1]. We previously reported smart transdermal delivery systems of human growth hormone (hGH) using hyaluronic acid (HA) derivatives [2]. After hydration of stratum corneum by hygroscopic HA, HA-hGH conjugates could be delivered transdermally by the facilitation via HA receptors in the epidermis and dermis. In this work, we developed smart transdermal vaccine delivery systems using HA-ovalbumin (HA-OVA) conjugates as a model system. After transdermal delivery, we assessed the immunization by HA-OVA conjugates.

Methods: HA-OVA conjugates were synthesized by site-specific reaction between HA-aldehyde (HA-ALD) and N-terminal amine group of OVA as described elsewhere [2]. HA-ALD was prepared by the treatment of HA with sodium periodate. The resulting HA-OVA conjugate was characterized by GPC analysis and ELISA. To visualize the transdermal delivery, HA-OVA conjugates were labeled with rhodamine B (RhoB) for intravital confocal microscopy. In addition, after HA-OVA conjugate was topically administered on the back skin of Balb/c mice, *in vivo* immunization efficiency was evaluated by measuring the concentration of anti-OVA IgG in cardiac blood.

Results: Figure 1 shows the schematic representation for smart trandermal vaccine delivery systems using HA-OVA conjugates. The successful synthesis of HA-OVA conjugate was confirmed by GPC. The peak of OVA was shifted to an earlier retention time after conjugation. The HA-OVA conjugate was analyzed by Bradford assay and ELISA to measure the concentration of OVA in the conjugate and to confirm the maintenance of its binding affinity to anti-OVA antibody.

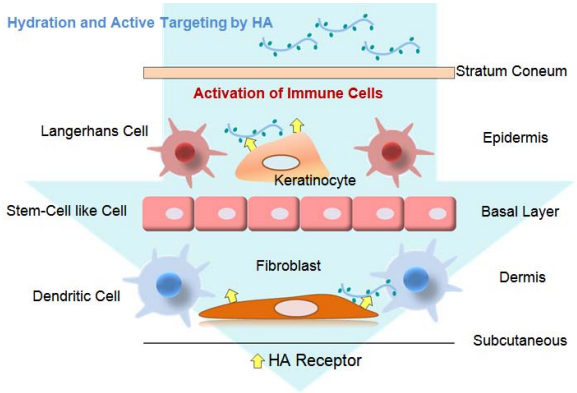

Figure 1. Schematic representation of smart transdermal vaccine delivery system of HA-OVA conjugates.

As shown in Figure 2, intravital confocal microscopy clearly visualized the effective transdermal delivery of HA-OVA-RhoB conjugates. When topically applied to the back skin of mice, RhoB and OVA-RhoB remained mainly on the stratum corneum without penetration into deep dermal tissues. However, HA-RhoB and HA-OVA-RhoB conjugates were well delivered through the skin, being distributed even to the dermis.

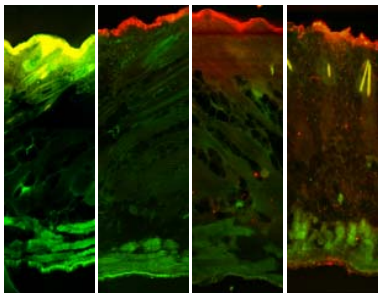

Figure 2. Intravital confocal microscopic images of cross-sectioned skin tissues (×20) after transdermal delivery of RhoB, OVA-RhoB, HA-RhoB, and HA-OVA-RhoB conjugates (from left to right).

Finally, *in vivo* immunization was assessed after transdermal delvery of HA-OVA conjugates (Figure 3). The HA-OVA conjugate resulted in more significant production of OVA-specific antibody than OVA 4 weeks post-administration, which might be ascribed to the efficient transdermal delivery of HA-OVA conjugates into deep skin tissues stimulating Langerhans cells and dermal dendritic cells.

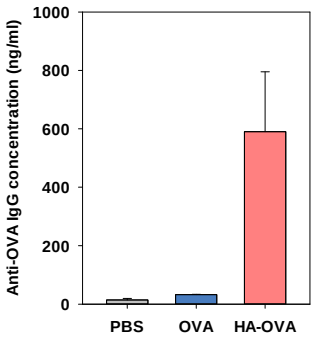

Figure 3. Immune responses induced by OVA and HA-OVA 4 weeks post-treatments.

Conclusions: A smart transdermal vaccine delivery system was successfully developed using HA-vaccine conjugates. As a model system, HA-OVA conjugates could be delivered to the epidermal and dermal tissues, and significantly enhanced the immune responses induced by OVA. These results demonstrated the feasibility of HA-based transdermal vaccine delivery systems for further development.

References:

1) Kenney RT et al. New Engl J Med, 2004;351:2295-2301.
2) Yang JA et al. Biomaterials, 2012;33:5947-5954.