Non-invasive and effective intradermal delivery of macromolecules by iontophoresis, weak electric current technology

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Skin is the versatile target for macromolecular medicines. However, since stratum corneum is tight barrier of skin, non-invasive transdermal delivery of macromolecules is difficult. Recently, iontophoresis (ItP) has been recognized as a non-invasive intradermal delivery technology. ItP can deliver ionic molecules by using weak electricity (0.3-0.5 mA/cm^2). Although it has been considered that ItP delivers only small ionic molecules, we have succeeded in the delivery of macromolecules such as siRNA and CpG-oligoDNA by ItP (*Int J Pharm* 2010, *J Control Release* 2011). In addition, we found that weak electricity opens intercellular junction via activation of cell signaling pathways (*J Biol Chem* 2014). Based on these findings, we have challenged the non-invasive intradermal delivery of various macromolecules by ItP. We tried the intradermal delivery of antibody IgG (Molecular weight: 150,000) by ItP [1]. Fluorescence of FITC-labeled IgG antibody was broadly observed in the skin after ItP administration and extended from the epidermis to the dermis layer of rats. In imiquimod-induced psoriasis model rats, antibodies were also delivered via ItP into inflamed skin tissue. Additionally, upregulation of interleukin-6 mRNA levels, which is related to pathological progression of psoriasis, was significantly inhibited by ItP of the anti-tumor necrosis factor-α drug etanercept, but not by its subcutaneous injection. On the other hand, we succeeded in the intradermal delivery of mRNA encoding antigen, a tumor associated antigen human gp10025-33 peptide (KVPRNQDWL), as a potential treatment for melanoma [2]. Following ItP-mediated intradermal delivery of a mRNA, an immune response is elicited resulting in activation of skin resident immune cells. Tumor growth was prevented significantly by ItP of mRNA in mice bearing melanoma. Additionally, there was an elevation in mRNA expression levels of various cytokines, mainly interferon (IFN)-γ, as well as infiltration of cytotoxic $CD8^+$ T cells in the tumor tissue. Furthermore, we succeeded in the ItP-mediated direct delivery of nucleic acid therapeutics, without use of carriers, to internal organs liver and spleen [3].

[1] Fukuta T, et al., *J Control Release*. 323, 323-332 (2020).
[2] Husseini RA, et al., *Biol Pharm Bull*. 46, 301-308 (2023).
[3] Hasan M, et al., *J Control Release*. 343, 392-399 (2022).