International Vaccine Design Center

Division of Mucosal Vaccines (New Dimensional Vaccine Design Team)

新次元ワクチンデザイン系・粘膜ワクチン分野

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To explore new avenues for mucosal vaccine development and immune-regulation, investigators have begun to employ novel adjuvants and targeting mucosal tissues and immune cells for vaccine delivery and elucidate the mechanisms of immune-regulation in the mucosal tissues. Despite recent advanced sciences, it remains to develop effective mucosal vaccines for human use. To this end, our main task is to define the effectiveness and safety of novel mucosal vaccines including adjuvant- and delivery system-development, and bring them from bench-top to practical applications.

1. Cationic nanogel-based nasal therapeutic HPV vaccine prevents the development of cervical cancer

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Therapeutic vaccines against cervical cancer caused by human papillomavirus (HPV) are still an unmet medical need, despite a prophylactic HPV vaccine being available, and the now-licensed systemic vaccines may have a limited effect on the reproductive tract. To specifically inhibit cervical cancer development, the concept of mucosal immunity based on the reproductive-respiratory axis was adopted to develop a nasal HPV therapeutic vaccine. We used a cationic nanogel for the nasal vaccine delivery system and targeted HPV16 E7, an oncoprotein in HPV-driven cervical cancer to demonstrate the feasibility of a nasal therapeutic vaccine. The vaccine was combined with cyclic di-adenosine monophosphate as a cell-mediated immunity-inducing adjuvant. Intranasal immunization with the nanogel vaccine induced E7-specific $CD4^+$ and $CD8^+$ T cells in mouse cervicovaginal tissue. An antitumor effect due to the infiltration of vaccine-induced E7-specific T cells was also observed in an orthotopic tumor model in mice. Furthermore, intranasal immunization of nonhuman primates with the nanogel vaccine using a spray device that is also applicable to humans induced E7-specific T cells in the reproductive tissues. Our findings demonstrated that this nasal therapeutic vaccine effectively controlled cervical cancer and will contribute to preclinical evidence for clinical testing in the near future.

2. Novel mucosal vaccine development for the induction of mucosal immunity in the aero-, digestive- and reproductive mucosa.

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It has been shown that oral antigen (Ag) plus adjuvant delivery for induction of immunity, as opposed to nasal delivery, is an effective non-invasive route. Further, it is well-tolerated and avoids the possibility of Ag and /or adjuvant uptake into the olfactory tissues with subsequent entry into the central nervous system (CNS). However, oral vaccines require relatively large amounts of Ag and adjuvant and are exposed to the proteolytic enzymes and lower pH of the stomach. Considerably, their efficacy limits the mainly gastrointestinal mucosa. In this regard, it is essential to develop a new generation of oral adjuvants which elicit mucosal immunity in the entire mucosal surfaces including respiratory and reproductive tracts. In order to accomplish this goal, we planned to discover novel molecules which could use potential oral adjuvant for inducing global protective mucosal immunity by using a single-cell mRNA sequencing approach. We have successfully established several DNA libraries from nasopharyngeal-associated lymphoid tissues and Peyer's patches of naïve mice as well as mice given either oral or nasal vaccine. The sequence data have been analyzed using SHIROKANE supercomputer system and we have identified several unique molecules which preferentially upregulated in the NALT of mice given nasal vaccine when compared with those in Peyer's patches of mice given an oral vaccine. Our results showed that one of these molecules, X is indeed up-regulated in NALT and the reproductive tract. We showed that mice deficient with this molecule X resulted in reduced levels of antigen-specific IgA antibody responses in the vaginal washes despite intact levels of serum IgG titers. Further, mononuclear cells isolated from the uterus of molecule X-deficient mice contained reduced numbers of IgA antibody-producing cells when compared with those of wild-type and heterogygous littermates. When we have assessed chemokine receptor expression which involved for the regulation of antigen-specific IgA responses, none of these receptors are essential for the regulation of mucosal IgA antibody responses.

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