International Research and Development Center for Mucosal Vaccines

Division of Mucosal Vaccines
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Mucosal vaccine is a prospective strategy for the vaccine development against pathogens invading through mucosal tissues. We have examined the immunological functions of commensal and pathogenic microorganisms as well as diets and applied them to the development of adjuvants and antigen delivery for the efficient immune responses against mucosal vaccines. These findings also could be extended to the development of mucosal immunotherapy against allergic, inflammatory, and infectious diseases.

1. Emerging roles of dietary lipids and vitamin B1 for the regulation of allergic inflammatory diseases and immune system development

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Immune system is regulated by dietary materials and their metabolites. We previously found that dietary intake of linseed oil, rich in $\omega 3$ α-linolenic acid, led to the amelioration of allergic responses in the gut and nasal mucosa through the metabolic conversion of α-linolenic acid into anti-allergy and anti-inflammatory lipid mediators of 17,18-epoxyeicosatetraenoic acid and 15-hydroxyeicosapentaenoic acid. Here, we extended our view by showing the evidence that

maternal intake of linseed oil led to the alleviation of allergic symptoms in the offspring skin. Lipidomic analysis revealed that breast milk contained much amount of 14-hydroxydocosapentaenoic acid (14-HDPA) when mouse dams were fed with linseed oil in comparison to conventional soybean oil. We found that 14-HDPA exhibited potent bioactivity in the induction of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) on plasmacytoid dendritic cells in offspring, which led to the inhibition of inflammatory cytokines production from T cells in the skin. Our another course of study revealed that vitamin B1-deficiency resulted in thymic involution with remarkable reduction of the number of CD4 and CD8 α double positive thymocytes. We further found that vitamin B1 deficient mice showed enhanced maturation phenotype of $\gamma\delta$ thymocytes by increased expression of TGFβ superfamily cytokines due to the vitamin B1-mediated metabolic impairment and accumulation of branched-chain α-keto acids in thymic stromal cells. These results collectively demonstrate that dietary lipid and vitamin B1 plays key roles in the control of immune systems, which can be applied to the development and optimization of vaccine against infectious and allergic diseases.

2. The mechanism for a commensal bacterium *Alcaligenes* to cohabit inside intestinal lymphoid tissue and application as a vaccine adjuvant

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Lymphoid-tissue–resident commensal bacteria (LRCs), including *Alcaligenes faecalis*, colonize within dendritic cells (DCs) in intestinal lymphoid tissue including the Peyer's patches (PPs) of mammals. LRCs modulate the host immune system to promote intestinal IgA antibody responses. Indeed, we previously demonstrated that *A. faecalis* activates DCs to produce IL-6, an IgA production-enhancing cytokine, through the weak agonistic activity of its lipopolysaccharide (LPS) against toll-like receptor (TLR) 4 together with low inflammatory activity, indicating that *Alcaligenes* spp. maintain their homeostatic environment in PPs without inducing an excessive inflammatory response. Here, we show an intracellular symbiotic system in which the LRC *Alcaligenes* creates a unique energy shift in DCs. Whereas DCs showed low mitochondrial respiration when they were co-cultured with non-symbiotic *Escherichia coli*, DCs carrying *A. faecalis* maintained increased mitochondrial respiration. Furthermore, *E. coli* induced apoptosis of DCs but *A. faecalis* did not. Regarding an underlying mechanism, *A. faecalis*—unlike *E. coli*—did not induce intracellular nitric oxide (NO) production in DCs due to the low activity of its LPS. Therefore, *A. faecalis*, an example of LRCs, may persist within intestinal lymphoid tissue because they elicit little NO production in DCs. In addition, the symbiotic DCs exhibit characteristic physiologic changes, including a low rate of apoptosis and increased mitochondrial respiration.

Unique characteristics of *Alcaligenes* LPS, which moderately activate host immune responses, promoted us to be examined for application as a vaccine adjuvant. Indeed, we previously reported that *Alcaligenes* LPS promoted antigen-specific immune responses including IgG antibody and Th17 responses without excessive inflammation. Here, we chemically synthesized *Alcaligenes* lipid A, an active part of LPS, and examined its efficacies as a vaccine adjuvant. In both systemic and nasal vaccination, *Alcaligenes* lipid A enhanced antigen-specific IgG/IgA antibody and Th17 responses. Further, in nasal vaccination with pneumococcal surface protein A (PspA) as a vaccine candidate antigen, *Alcaligenes* lipid A induced the protective immunity against *Streptococcus pneumoniae* infection. These findings suggest that *Alcaligenes* lipid A is a useful and applicable synthetic adjuvant for both systemic and nasal vaccine development including *S. pneumoniae* vaccine.

3. A Nanogel-based trivalent PspA nasal vaccine protects macaques from intratracheal challenge with pneumococci.

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Current polysaccharide-based pneumococcal vaccines are effective but not compatible with all serotypes of *Streptococcus pneumoniae*. We previously developed an adjuvant-free cationic nanogel nasal vaccine containing pneumococcal surface protein A (PspA) which is expressed on the surfaces of all pneumococcal serotypes. Because PspA proteins have sequence diversity, we formulated and tested a nanogel-based trivalent pneumococcal nasal vaccine to demonstrate the vaccine's immunogenicity and protective efficacy in macaques. Nasal vaccination of macaques with cationic cholesteryl pullulan nanogel (cCHP)-trivalent PspA vaccine effectively induced PspA-specific IgGs that bound to pneumococcal surfaces and triggered complement C3 deposition. The immunized macaques were protected from pneumococcal intratracheal challenge through both inhibition of lung inflammation and elimination of the bacteria from the lungs. These results demonstrated that the cCHP-trivalent PspA vaccine is an effective candidate vaccine for broad protection against pneumococcal infections.

4. Comparative whole-genome and proteomics analyses of the next seed bank and the original master seed bank of MucoRice-CTB 51A line, a rice-based oral cholera vaccine

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We have previously developed a rice-based oral vaccine against cholera diarrhea, MucoRice-CTB. Using Agrobacterium-mediated co-transformation, we produced the selection marker–free MucoRice-CTB line 51A, which has three copies of the cholera toxin B subunit (CTB) gene and two copies of an RNAi cassette inserted into the rice genome. We determined the sequence and location of the transgenes on rice chromosomes 3 and 12. The expression of alpha-amylase/trypsin inhibitor, a major allergen protein in rice, is lower in this line than in wild-type rice. Line 51A was self-pollinated for five generations to fix the transgenes, and the seeds of the sixth generation produced by T5 plants were defined as the master seed bank (MSB). T6 plants were grown from part of the MSB seeds and were self-pollinated to produce T7 seeds (next seed bank; NSB). NSB was examined and its whole genome and proteome were compared with those of MSB. First, we re-sequenced the transgenes of NSB and MSB and confirmed the positions of the three CTB genes inserted into chromosomes 3 and 12. The DNA sequences of the transgenes were identical between NSB and MSB. Next, using whole-genome sequencing, we compared the genome sequences of three NSB with three MSB samples, and evaluated the effects of SNPs and genomic structural variants by clustering. No functionally important mutations (SNPs, translocations, deletions, or inversions of genic regions on chromosomes) between NSB and MSB samples were detected. Analysis of salt-soluble proteins from NSB and MSB samples by shot-gun MS/MS detected no considerable differences in protein abundance. No difference in the expression pattern of storage proteins and CTB in mature seeds of NSB and MSB was detected by immuno-fluorescence microscopy.

In Conclusions, all analyses revealed no considerable differences between NSB and MSB samples. Therefore, NSB can be used to replace MSB in the near future.

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