International Research and Development Center for Mucosal Vaccines

Division of Mucosal Barriology
粘膜バリア学分野

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The goal of our research is to explore antigen uptake receptors on specialized epithelial M cells to identify potential targets for mucosal vaccine delivery. Thus, this division aims to develop novel mucosal vaccines by taking advantage of the conjugation of M-cell-receptor ligands with various vaccine antigens.

1. Human norovirus propagation in human induced pluripotent stem cell-derived intestinal epithelial cells.

Shintaro Sato[1–5], Kota Hisaie[1,3], Shiho Kurokawa[4], Akio Suzuki[2], Naomi Sakon[6], Yohei Uchida[4], Yoshikazu Yuki[4], and Hiroshi Kiyono[4,5,7–9]: [1]Mucosal Vaccine Project, BIKEN Innovative Vaccine Research Alliance Laboratories, Research Institute for Microbial Diseases, Osaka University, [2]Mucosal Vaccine Project, BIKEN Center for Innovative Vaccine Research and Development, The Research Foundation for Microbial Diseases of Osaka University, [3]Graduate School of Medicine, Osaka University, [4]Division of Mucosal Vaccine, Research and Development Center for Mucosal Vaccines, The Institute of Medical Science, The University of Tokyo, [5]Division of Mucosal Barriology, Research and Development Center for Mucosal Vaccines, The Institute of Medical Science, The University of Tokyo, [6]Department of Microbiology, Osaka Institute of Public Health, [7]Division of Mucosal Immunology, IMSUT Distinguished Professor Unit, The Institute of Medical Science, The University of Tokyo, [8]Mucosal Immunology and Allergy Therapeutics, Institute for Global Prominent Research, Chiba University, [9]Division of Gastroenterology, Department of Medicine, School of Medicine, CU-UCSD Center for Mucosal Immunology, Allergy and Vaccines, University of California, San Diego.

Worldwide, human norovirus (HuNoV) is a major cause of intestinal infectious gastroenteritis leading to morbidity and mortality in children and the elderly, and thus having major social and economic influences. Neither an effective vaccine nor an effective treatment is currently available. One of the biggest reasons for the lack of an appropriate prevention or treatment strategy is the unavailability of methods for culturing HuNoV. Therefore, the recent development of a HuNoV replication system in human primary intestinal epithelial cells (IECs) has spawned advances in HuNoV characterization and opened up new strategies for HuNoV vaccine development. However, this technique currently requires human tissue cells and supplementation with bile, which contains unidentified components. Here, we report the replication of HuNoV in human induced pluripotent stem cell-derived IECs without bile. Furthermore, we provide evidence that vaccination with not only GII.4 but also GII.17 virus-like particles can induce neutralization anti-

bodies against the predominant type of HuNoV, GII.4.

2. Therapeutic effect of vitamin D3-containing nanostructured lipid carriers on inflammatory bowel disease.

Zai K[1], Hirota M[2], Yamada T[2], Ishihara N[2], Mori T[1,3,4], Kishimura A[1,3,4,5], Suzuki K[2], Hase K[2,6], Katayama Y[1,3,4,5,7,8]: [1]Department of Applied Chemistry, Faculty of Engineering, Kyushu University. [2]Division of Biochemistry, Faculty of Pharmacy, Keio University. [3]Graduate School of Systems Life Sciences, Kyushu University. [4]Center for Future Chemistry, Kyushu University. [5]International Research Center for Molecular Systems, Kyushu University. [6]Division of Mucosal Barriology, International Research and Development Center for Mucosal Vaccines, The Institute of Medical Science the University of Tokyo. [7]Centre for Advanced Medicine Innovation, Kyushu University. [8]Department of Biomedical Engineering, Chung Yuan Christian University.

The active form of vitamin D_3, $1,25(OH)_2D_3$ has been found to exert multiple effects on the suppression of progression of inflammatory bowel disease (IBD). Vitamin D_3 has been gathering attention as a therapy for IBD. However, the clinical trials conducted to date revealed that a relatively high dosage of vitamin D_3 was required to see a significant therapeutic effect. Thus, effective formulation and delivery of vitamin D_3 to colonic inflammatory lesions will be required. Herein we describe the preparation of a nanostructured lipid carrier (NLC) for the encapsulation of $1,25(OH)_2D_3$ for colonic delivery via oral administration. The optimized fabrication procedure enabled the incorporation of $1,25(OH)_2D_3$ in the NLC by minimizing the destruction of chemically unstable $1,25(OH)_2D_3$. The obtained NLCs orally delivered $1,25(OH)_2D_3$ to the colon in mice and maintained a high concentration of $1,25(OH)_2D_3$ in the colonic tissue for at least 12 h. The NLC showed multiple effects on the suppression of symptoms of colitis induced by dextran sodium sulfate, namely maintaining crypt structure, reducing the tissue concentration of inflammatory cytokines, suppressing the infiltration of polymorphonuclear leukocytes, and augmenting anti-inflammatory CX_3CR1^{high} macrophages. Our NLCs containing $1,25(OH)_2D_3$ may be an alternative treatment for IBD therapy.

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International Research and Development Center for Mucosal Vaccines

Division of Innate Immune Recognition
自然免疫制御分野

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Innate immunity is the `gateway' of immune response. By controlling innate immunity, it is thought that the whole immunity is controllable. Our major focus is the elucidation and understanding of molecular function of the innate immune cells in small intestine for the development of mucosal vaccine against infectious diseases and mucosal immune therapy for inflammatory bowel diseases, food allergy and cancer. We also analyze intestinal microbiome by developing new informatics method. We will develop new therapeutic strategies against various dysbiosis-related diseases targeting on intestinal microbiota.

1. Development of next-generation vaccine targeting on DCs in small intestinal lamina propira (LP)

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CD103$^+$ DCs are the major conventional DC population in the intestinal lamina propria (LP). Our previous report showed that low density cells in the LP could be classified into four subsets based on the difference in CD11c/CD11b expression patterns: CD11c^{hi}CD11b^{lo} DCs, CD11c^{hi}CD11b^{hi} DCs, CD11c^{int}CD11b^{int} macrophages and CD11c^{int}CD11b^{hi} eosinophils. The CD11c^{hi}CD11b^{hi} DCs, which are CD103$^+$, specifically express Toll-like receptor (TLR) 5 and TLR9, and induce the differentiation of naïve B cells into IgA$^+$ plasma cells. These DCs also mediate the differentiation of Ag-specific Th17 and Th1 cells in response to flagellin. Intraperitoneal injection of activated antigen(Ag)-loaded CD11c^{hi}CD11b^{hi} DCs induced Ag-specific IgG in serum and IgA in stool samples, Th1 and Th17 responses and strong CTL activity. Thus, CD11c^{hi}CD11b^{hi} DCs are suitable targets for oral vaccines in the intestine. CD11c^{hi}CD11b^{hi} LPDCs but not conventional DCs in other tissues specifically express Raldh2, which catalyzes retinal to retinoic acid. Recent report showed that Raldh2 is essential for the induction of IgA. On the basis of analysis of CD11c^{hi}CD11b^{hi} DCs, we developed a new mucosal adjuvant, which can induce Ag-specific mucosal immune responses even by parenteral immunization. By using this method, we are now trying to regulate mucosal infection as well as dysbiosis-related diseases.

2. Analysis of resident macrophages in small intestinal LP

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$CD11c^{int}CD11b^{int}$ cells in small intestinal LP are resident macrophages. They specifically express chemokine receptor CX3CR1 in intestinal LP. Their phagocytotic activity is very strong. Although they express MHC class II, they cannot move from LP to draining lymph nodes effectively, suggesting that they may be involved in local immune responses in intestine. They express TLR4, TLR7 and TLR9 and produce TNF-α and IL-10 by TLR stimulation. We performed microarray analysis in the $CD11c^{int}CD11b^{int}$ cells, $CD11c^{hi}CD11b^{hi}$ cells, splenic $CD11c^{+}$ DCs and peritoneal macrophages with or without stimulation of TLR ligand and compared signaling pathways among them. We found several candidate genes which specifically express in $CD11c^{int}CD11b^{int}$ cells. We generated gene-targeting mice and are examining the *in vivo* function of them in $CD11c^{int}CD11b^{int}$ cells.

3. Development a new therapy for acute radiation injury in mucosa.

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High-dose ionizing radiation induces severe DNA damage in the epithelial stem cells in small intestinal crypts and causes gastrointestinal syndrome (GIS). Although the tumor suppressor p53 is a primary factor inducing death of crypt cells with DNA damage, its essential role in maintaining genome stability means inhibiting p53 to prevent GIS is not a viable strategy. Here, we show that the innate immune receptor Toll-like receptor 3 (TLR3) is critical for the pathogenesis of GIS. $Tlr3^{-/-}$ mice show substantial resistance to GIS owing to significantly reduced radiation-induced crypt cell death. Despite showing reduced crypt cell death, p53-dependent crypt cell death is not impaired in $Tlr3^{-/-}$ mice. p53-dependent crypt cell death causes leakage of cellular RNA, which induces extensive cell death via TLR3. An inhibitor of TLR3-RNA binding ameliorates GIS by reducing crypt cell death. Thus, we propose blocking TLR3 activation as a novel and preferable approach to treat GIS. We further analyzed the role of TLR3 in radiation-induced oral mucositis.

4. Analysis of intestinal microbiota.

Kosuke Fujimoto[1], Satoru Miyano[2], Hiroshi Kiyono[3−6], Seiya Imoto[7] and Satoshi Uematsu[1]: [1]Division of Innate Immune regulation, International Research and Development Center for Mucosal Vaccines, The Institute of Medical Science, The University of Tokyo. [2]Laboratory of DNA Information Analysis, Human Genome Center, The Institute of Medical Science, The University of Tokyo. [3]International Research and Development Center for Mucosal Vaccine, The Institute of Medical Science, The University of Tokyo, [4]Mucosal Immunology and Allergy Therapeutics, Institute for Global Prominent Research, Chiba University, [5]Division of Gastroenterology, Department of Medicine, School of Medicine, CU-UCSD Center for Mucosal Immunology, Allergy and Vaccines, University of California, San Diego, [6]Division of Mucosal Immunology, IMSUT Distinguished Professor Unit, The Institute of Medical Science, The University of Tokyo, [7]Division of Health Medical Data Science, Health Intelligence Center, The Institute of Medical Science, The University of Tokyo.

Our intestinal tract carries a lot of bacteria in the lumen as the resident microorganism. In addition to resident bacteria, viruses are also present in our intestinal tract, most of which are bacteriophages. However, it is still unclear what kind of bacteriophage exist in our intestinal tract, and what kind of bacteria they infect with. As one of the reasons, isolation of viral nucleic acids and preparation of libraries have not been established. Since conserved sequence such as 16s rRNA gene do not exist in virus, whole genome analysis is necessary. Even if comprehensive whole genome analysis of intestinal viruses were performed, most of the sequence fragments couldn't be classified by homology search due to the insufficient public databases. Thus, virome analysis is relatively difficult compared with bacteiome analysis and this situation is expressed by the word "vral dark matter". We are now developing the isolation method of intestinal viruses and are generating analysis pipeline of metagenome analysis of them. We also generating the method to analyze host-parasite association identified based on the shotgun sequencing data of the bacterial flora and viral plexus.

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International Research and Development Center for Mucosal Vaccines

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To explore new avenues for mucosal vaccine development, investigators have begun to employ novel adjuvants and targeting mucosal tissues and immune cells for vaccine delivery. Despite recent advanced sciences, it still 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. Mast cells orchestrate pathological event for the renal fibrotic disease via induction of collagen expressing unique myeloid cell population

Yosuke Kurashima[1–6], Sho Watarai[2], Sayuri Murasaki[1,2], Akie Inami[2], Seiichi Matsumura[3], Kaoru Shimada[2], Fujimi Arai[2], Yuta Kogure[2], Takaaki Kigoshi[2], Hiroshi Kiyono[1,2,5,7]: [1]International Research and Development Center for Mucosal Vaccines, The Institute of Medical Science, The University of Tokyo, [2]Department of Mucosal Immunology, IMSUT Distinguished Professor Unit, The Institute of Medical Science, The University of Tokyo, [3]Department of Innovative Medicine, Graduate School of Medicine, Chiba University, [4]Laboratory of Vaccine Materials, National Institute of Biomedical Innovation, Health and Nutrition, [5]Division of Gastroenterology, Department of Medicine, CU-UCSD Center for Mucosal Immunology, Allergy and Vaccines, University of California, [6]Institute for Global Prominent Research, Chiba University, [7]Mucosal Immunology and Allergy Therapeutics, Institute for Global Prominent Research, Chiba University.

Excessive accumulation of extracellular matrix such as type I collagen induced fibrosis and eventually causing organ failure. In kidney, renal interstitial fibrosis can be seen as a common pathology when chronic kidney disease was aggravated. Adequate preventive methods and novel treatments for fibrosis are required and desired. However, the underlined mechanisms of kidney fibrosis especially interstitial fibrosis have not been well elucidated. To address this issue, we have examined the involvement of various innate immune cells [e.g., lymphocytes, innate lymphoid cells (ILCs), basophils, and mast cells] which are shown to participate in fibrogenesis of various organs by the use of unilateral ureteral obstruction (UUO) model. Our data showed that depletion of neither basophils nor ILCs showed reduction of collagen deposition. On the contrary, mast cells induced increase of collagen-expressing activated fibroblasts in UUO; thereby, mice with deficiency of mast cells showed reduction of collagen deposition as well as the number of activated fibroblasts. In addition, unique M2-like macrophage populations expressing collagen, are reduced in mast cell-deficient mice. Those M2-like macrophages are induced by fibrogenic fibroblasts *in vitro*. Taken together, these results suggested that mast cells are a key initiator for the kidney fibrosis by the direct stimulation of fibroblasts and indirect induction of fibrogenic myeloid cell populations by mast cell-stimulated fibroblasts. The

triangular interaction of mast cells, fibroblasts and fibrogenic myeloid cells could be a major pathological event for renal fibrotic disease and considered as a new drug target.

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 tolerant 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 relative large amounts of Ag and adjuvant and are exposed to the proteolytic enzymes and lower pH of the stomach. Considerably, their efficacy limits to mainly gastrointestinal mucosa. In this regard, it is essential to develop 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 single cell mRNA sequencing approach. We have successfully established the RNA library from nasopharyngeal associated lymphoid tissues and Peyer's patches of mice given either oral or nasal vaccine and obtained the sequence data. We are currently analyzing this sequence data using SHIROKANE super computer system in order to find novel mucosal imprinting molecules.

Recently, the sublingual (SL) mucosa has been targeted to deliver immunotherapy to treat allergic hypersensitivities in addition to oral and nasal immunization routes. Indeed, SL vaccine delivery has been shown to be a novel and effective route for induction of Ag-specific secretory (S) IgA antibody (Ab) responses, including those in the other mucosa. The SL delivery of Ags, as opposed to nasal or oral immunization, is a non-invasive route which avoids the olfactory region and the CNS and requires lower doses of Ag than the oral route, thus avoiding the proteolytic enzymes and lower pH of the stomach. We have shown that mice SL immunized with pneumococcal surface protein A (PspA) plus poly (I:C) resulted in the enhancement of PspA-specific mucosal SIgA and systemic IgG Ab responses and provided protection against *Streptococcus pneumoniae* infection. These results show that SL immunization may be a potent strategy for the induction of Ag-specific immunity in the entire mucosal surfaces.

Publications

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International Research and Development Center for Mucosal Vaccines

Division of Mucosal Vaccines
粘膜ワクチン学分野

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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. Development of a bivalent food poisoning vaccine: augmented antigenicity of the C-terminus of Clostridium perfringens enterotoxin by fusion with the other food-poisoning toxin antigen

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Food poisonings caused by Clostridium perfringens, Shiga toxin (Stx)-producing Escherichia coli (STEC), and cholera occur frequently worldwide; however, no vaccine is currently available. Therefore, we aimed to develop a bivalent vaccine against C. perfringens, STEC, or cholera infections. Although it has been considered that C-terminal region of C. perfringens enterotoxin (C-CPE) could be a good vaccine antigen to block the binding to its receptor, it was insufficient for induction of protective immune response due to the low antigenicity. However, the fusion of C-CPE with Stx2 B subunit (Stx2B) or cholera toxin B subunit (CTB) augmented antigenicity of C-CPE without affecting antigenicity of fused antigens. Indeed, high levels of C-CPE-specific neutralizing IgG were found in the serum of mice immunized with the fusion protein Stx2B-C-CPE or CTB-C-CPE. Additionally, comparable and substantial levels of Stx2B- and CTB-specific neutralizing IgG were induced in mice receiving Stx2B-C-CPE or Stx2B alone and CTB-C-CPE, or CTB, respectively. These antibody responses against toxins were sufficient for protective immunity in vitro and in vivo, indicating that C-CPE-based fusion protein could induce protective immunity. As underlying mechanism, ex vivo stimulation with fused antigen,

but not C-CPE, induced cytokine production from splenic T cells, suggesting that fused antigen, but not C-CPE, -specific T cells were induced and plausibly promoted Ig-class switching of each toxin-specific B cells from IgM to IgG. These findings collectively indicate that C-CPE-based fusion protein is a T cell-antigen-supplement-type bivalent vaccine, which could be an efficient against C. perfringens, STEC, and cholera infections.

2. Development of cationic nanogel-based nasal vaccines for various infectious diseases

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Nasal vaccines not only induce an antigen-specific systemic immune response, but induce antigen-specific secretory IgA at the mucosal site to which the vaccine is administered, thereby blocking the invasion of foreign microorganisms into the host. Furthermore, it induces an antigen-specific immune response also at the mucosal surface distant from the administration site such as genital tract. Based on the advantages of such a nasal vaccine, we are promoting the development of a novel nasal vaccination system using cholesteryl group-containing pullulan (CHP) nanogel. A cationic types of CHP nanogels, cCHP nanogel have been developed as a novel drug delivery system which adhere to the epithelial layer of the nasal cavity after nasal immunization and elicit the effective immunity by sustained antigen release. In addition, the vaccine antigens incorporated into cCHP nanogels did not show brain deposition after intranasal administration in mice and non-human primates, so this vaccine appears to be safe and could be a promising new delivery system. Recently, we have been establishing a cCHP nanogel vaccine for various respiratory infectious diseases such as Pneumonia or sexually transmitted disease such as cervical cancer caused by human papilloma viruses. In any cases, the antigen specific antibody responses or cellular immune responses are effectively induced after nasal vaccine administration and the efficacy of vaccination is confirmed by bacterial infection model in mice. Thus, a cCHP nanogel-based nasal vaccination system provides a promising approach to various infectious diseases.

3. Analysis of miRNA candidates as biomarkers for prediction and evaluation of mucosal vaccination

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MucoRice-CTB is an oral vaccine against cholera that incorporates a cholera toxin B subunit (CTB) which does not have toxicity into rice as a vaccine antigen by genetic engineering technologies. The advantage of this rice-based oral vaccine is 1) enzyme resistance, 2) long-term stable at room temperature, and 3) not cause physiological or physical discomfort. In addition, oral vaccination can induce both systemic and mucosal immune responses in the body. Indeed, when the MucoRice-CTB is administered orally to mice, pigs and macaques, cholera toxin-induced diarrhea is inhibited by antigen-specific secretory IgA with its neutralizing activity and provides protective immunity over a long period of time. Based on the animal experiments, we have further investigated the safety and efficacy of the MucoRice-CTB in human. We conducted a doctor-led Phase I clinical trial using MucoRice-CTB at the Hospital of Institute of Medical Science, the University of Tokyo since 2015 to 2016. In the Phase I clinical trial, the dose of MucoRice-CTB was performed by 3 cohorts of 1 g (CTB 3 mg), 3 g (CTB 9 mg), 6 g (CTB 18 mg), with a double blind test on 20-40 years old healthy adult male who have no allergic reaction to rice. MucoRice-CTB was administered every two weeks, four times, and CTB-specific antibody titer in serum and feces in each subject was confirmed by ELISA assay. In parallel, we proceeded with the search of serum miRNA biomarkers using microarray analysis. In recent years, several miRNAs have been identified as biomarkers for disease discrimination. In this study, we aim to investigate the miRNA biomarkers from two aspects, 1) evaluating the effect of mucosal vaccine by identifying serum miRNA that are specifically induced by administration of MucoRice-CTB, and 2) predicting the vaccine responsive-

ness. We hope that the identification of these MucoRice-CTB specific miRNAs will lead to the discovery of common biomarkers in mucosal vaccines in the future.

4. Development of antibody-producing MucoRice against norovirus gastroenteritis

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Human norovirus (HuNoV) usually infect by transmitted via the fecal-oral route, through contaminated food or water as aerosolized vomitus. Norovirus gastroenteritis with vomiting and diarrhea can occur in all age, but it may become severe if it infects elderly people, infants and immunocompromised humans. But there is no vaccine for norovirus gastroenteritis, since Takeda Phama prepares HuNoV GII.4 Virus-like particle (VLP) vaccine for phase III study in development.

We have developed a novel therapy against norovirus gastroenteritis with transgenic rice-producing neutralizing antibody, MucoRice. Recently we could selected several antibodies to HuNoV VLP, which inhibited Norovirus proliferation using human induced pluripotent stem cells(iPSCs) established in our lab. (Sato et al., CMGH 2018, DOI: 10.1016/j.jcmgh.2018.11.001)

To introduce antibody gene in rice gene, we advanced the MucoRice system by using RNA interference (RNAi) technology to suppress the production of the two major endogenous storage proteins, prolamin and glutelin, to increase vaccine protein or antibody expression (Tokuhara et al., JCI 2013, 123: 3829-3838). In present, the DNA sequence of the antibody was introduced into the rice by the *Agrobacterium*-mediated method. Then, the first generation of MucoRice introduced transgene of the antibody was harvested and the accumulation of the antibody was confirmed by SDS-PAGE and immunoblot analysis.

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International Research and Development Center for Mucosal Vaccines

Division of Mucosal Symbiosis
粘膜共生学分野

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Gastrointestinal tract is a unique organ which is constitutively exposed by various antigens including commensal microbiota. In order to create symbiotic environment to non-pathogenic luminal microorganisms, epithelial cells (ECs) and immune cells cooperatively establish homeostasis of intestinal microenvironment. We aim to identify the mechanisms of epithelial α1, 2-fucosylation, one of symbiotic factors between host and microbiota, and uncover the role of ECs-immune cell network in the establishment of intestinal homeostasis.

1. Innate lymphoid cells govern intestinal epithelial α1, 2-fucosylation

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α1, 2-fucosyl linkages located to terminal carbohydrate moiety expressed on intestinal epithelial cells is catalyzed by fucosyltransferase 2 (Fut2). Epithelial α1, 2-fucose is one of symbiotic factors which mediate host-microbiota interaction. For example, epithelial α1, 2-fucose is utilized as a dietary carbohydrate by various symbiotic bacteria such as *Bacteroides*. Therefore, disruption of Fut2 leads to dysbiosis both in mice and human and predisposed to the development of inflammatory diseases such as Crohn's disease. Despite of the importance for intestinal and systemic homeostasis, the molecular and cellular mechanisms of the induction of epithelial Fut2 and subsequent α1, 2-fucosylation remain unknown. We found that group 3 innate lymphoid cells (ILC3) are critical inducers of intestinal epithelial Fut2 expression and fucosylation that is mediated by the production of interleukin 22 and lymphotoxin from ILC3 in a commensal bacteria-dependent and -independent manner, respectively. Fut2-deificient mice are susceptible to the infection by pathogenic microorganisms. These data unveil a novel function of ILC3 in creating the appropriate symbiotic environment and protective platform against pathogenic microorganisms through regulating the epithelial α1, 2-fucosylation.

2. Pathogenic fungi induce epithelial α1, 2-fucosylation in the gut

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Intestinal epithelial cells are first line of defense against infection by pathogenic microorganisms. *Candida albicans* are one of commensal fungi reside in the mucosal surface including gastrointestinal tract. However, *C. albicans* also have been reported to exert pathogenic effects in the immunocompromised host and expand to the systemic comopartments, which is called invasive candidasis. Invasive candidiasis triggered by *C. albicans* triggered by colonization in the gut is one of the serious infectious disease in the world. So far, it is unclear how *C. albicans* colonize and affect epithelial physiology in the gut. To investigate this, we established *C. albicans* colonizing model by using several antibiotics treated mice and found that *C. albicans* colonization induce epithelial α1, 2-fucosylation in the gut. Because epithelial α1, 2-fucose is one of symbiotic factor between host and commensal bacteria, this data suggests that *C. albicans* affect epithelial glycosylation and host epithelial cells may protect *C. albicans* infection by modulating commensal microbiota.

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