International Research and Development Center for Mucosal Vaccines

Division of Innate Immune Regulation
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. 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 inducing both antigen-specific systemic and mucosal immunity

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A next-generation vaccine strategy capable of inducing both systemic and mucosal immunity is awaited. We showed that intramuscular vaccination with a combination of CpG oligodeoxynucleotides and curdlan as adjuvants systemically induced antigen-specific IgA and IgG production in mice. After priming, markedly high titers and long-lasting antigen-specific IgA and helper T-cell responses were acquired by antigen boosting of the target organs. This immunization effectively regulated *Streptococcus pneumoniae* infection. Moreover, vaccination for *Clostridium ramosum* (*C. ramosum*), a representative causative commensal microbiota for obesity and diabetes, alleviated high-fat diet-induced obesity in mice by controlling the number of *C. ramosum* in the mucosa. Collectively, this vaccine strategy induces strong antigen-specific mucosal and systemic immunity and has the potential to prevent infections and commensal microbiota-associated diseases. The patent of this new vaccine strategy was granted in 2019 in Japan and in 2020 in US. We are currently conducting monkey experiments for formulation in human on the basis of collaboration with Mitsubishi Tanabe Pharmaceutical company. We started collaboration with Medicago in Canada and are developing an IgA-inducing mucosal vaccine with this system by using SARS-CoV-2 Viral-like particle as an antigen which have been developed by Medicago.

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 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 are analyzing the role of TLR3 in radiation-induced oral mucositis.

Publications

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