International Symposium 1-1

Commensal bacteria-derived metabolites shape the intestinal immune system through epigenetic modifications

○ Koji Hase[1], Yukihiro Furusawa[1], Yuuki Obata[1], Shinji Fukuda[2], Hiroshi Ohno[3]
[1]International R&D Center for Mucosal Vaccines, The Institute of Medical Science, The University of Tokyo,
[2]Institute for Advanced Biosciences, Keio University,
[3]RIKEN Center for Integrative Medical Sciences (IMS-RCAI)

Gut commensal microbes shape the mucosal immune system by regulating differentiation and expansion of several types of T cells (*1*). *Clostridia*, a dominant class of commensal microbe, can induce colonic regulatory T (Treg) cells, which play a central role in the suppression of inflammatory and allergic responses (*2*). However, the molecular mechanisms by which commensal microbes induce colonic Treg cells have been unclear. Here we show that a large bowel microbial fermentation product, butyrate, induces the differentiation of colonic Treg cells. A comparative NMR-based metabolome analysis suggested that the luminal concentrations of short-chain fatty acids (SCFAs) positively correlated with the number of Treg cells in the colon. Among SCFAs, butyrate induced the differentiation of Treg cells *in vitro* and *in vivo* and ameliorated the development of colitis induced by adoptive transfer of $CD4^{+}CD45RB^{hi}$T cells in $Rag1^{-/-}$ mice. Treatment of naïve T cells under the Treg-polarizing conditions with butyrate enhanced histone H3 acetylation in the promoter and conserved non-coding sequence (CNS) regions of the *Foxp3* locus. These data indicate that the microbial-derived butyrate can regulate differentiation of Treg cells by epigenetic changes. Our findings provide new insight into the mechanisms by which host-microbe interactions establish immunological homeostasis in the gut (*3*).

【References】

(*1*) Chung H, et al. 2012. Gut Immune Maturation Depends on Colonization with a Host-Specific Microbiota. Cell **149**, 1578–1593.
(*2*) Atarashi K, et al. 2013. Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. Nature **500**, 232–236.
(*3*) Furusawa Y, et al. 2013. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature **504**, 446–450.