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Role of DC and chemokines for the induction of gut-homing CD4⁺CD25⁺ regulatory T cells in Peyer's patches

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Mucosal exposure to an antigen leads to three potential outcomes. (1) The induction of local secretory IgA specific to the antigen, (2) systemic priming, and (3) the induction of systemic hyporesponsiveness to the antigen (mucosal-induced tolerance). It has been reported the DCs in the MALT have an essential role for what outcome is induced. For the induction of oral tolerance, antigen specific regulatory T cells are likely to be generated in the GALT including Peyer's patch (PP) and DCs are also important for this induction. However, how these regulatory T cells are induced by mucosal antigen administration and how chemokines are involved in the interaction between Ag specific T cells and DCs are still unclear. Furthermore, although there has been reports that CD4⁺CD25⁺ regulatory T cell (T_{reg}) is involved in the tolerance induction, the role of CD4⁺CD25⁺ T_{reg} in the mucosal immune system has remained controversial.

To clarify these issues, we transferred naive T cells from ovalbumin (OVA)-TCR transgenic mice (DO11.10) into Balb/c mice, and 24 hrs later, we fed FITC conjugated OVA (FITC-OVA) to Balb/c mice. Kinetics of FITC positive cells and KJ1.26 positive OVA specific T cells in PP after the feeding of FITC-OVA were checked by immunofluorescein staining. To examine the phenotype of OVA specific T cells accumulated in PP after OVA feeding, the gene expressions of these T cells were checked by real time PCR.

FITC positive cells appeared in subepithelial dome (SED) of PP as soon as 3 hrs after the feeding of FITC-OVA. FITC positive cells in SED were CD11c positive DCs. 24 hrs after the feeding of FITC-OVA, DCs capturing FITC-OVA migrated from SED to interfollicular region (IFR) and interacted with OVA specific T cells accumulated in IFR of PP. In contrast, OVA specific T cells were not detected in IFR in non-fed mice. Furthermore, the gene expression levels of CD25, forkhead transcription factor Foxp3, chemokine receptors such as CCR4, CCR8, CCR9 and CXCR3 were substantially high in OVA specific T cells accumulated in PP after OVA feeding. Immunofluorescein staining showed that thymus and activation-regulated chemokine (TARC: CCL17) was expressed in IFR of PP. More detailed results will be shown and discussed.

Previous reports show that CD4⁺CD25⁺ T_{reg} selectively expresses CCR4, CCR8, CXCR3 and Foxp3, and TARC is a ligand for CCR4. These results suggest that PP DCs capturing oral antigen interact with antigen specific T cells attracted by TARC in IFR of PP and induce CCR9 positive gut-homing CD4⁺CD25⁺ T_{reg} in PP.