［課程－２］

審査の結果の要旨

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In this dissertation, I demonstrated the specific mucosal cytokine and chemokine signaling pathways are involved in the induction of antigen (Ag)-specific immune response after nasal vaccination including Ag-specific IgA antibody responses and mucosal crosstalk between nasal and reproductive compartments. Firstly a new immunological role of TSLP (thymic stromal lymphopoietin), an epithelial cytokine, following nasal immunization was investigated. I further expanded my investigation to determine the role of the specific chemokine signaling for the mucosal crosstalk between nasal and female genital tissues. Finally, I discussed their implications on nasal vaccination against respiratory and sexually-transmitted diseases, such as pneumococcal infection and genital herpes. The important findings of this study are as follows:

1. Thymic stromal lymphopoietin (TSLP) expressions in respiratory tissues were increased in mice nasally immunized with pneumococcal surface protein A (PspA) plus CT. Moreover, TSLP receptor (TSLPR) expressions were elevated in mucosal DCs in mice nasally immunized with pneumococcal surface protein A (PspA) plus CT.
2. PspA-specific IgA Ab responses were impaired in TSLPR-KO mice after nasal immunization with PspA plus CT.
3. Mucosal $CD11c^+$ cells (DCs and macrophages) and from nasally immunized TSLPR-KO, compared with WT mice, were less activated and exhibited remarkably reduced IgA enhancing cytokine expressions (e.g., IL-6) whereas non-mucosal $CD11c^+$ cells (DCs and macrophages) were not affected.
4. In a DC–B cell co-culture system, TSLP treatment augmented IgA production in an IL-6-dependent manner.
5. Nasal immunization with HSV-2 TK^- could induce the upregulation of expressions of CCR5 and CXCR3 in $CD4^+$ T cells in the antigen priming sites (e.g., CLNs) and vagina tissue. However, deficiency of CCR5, but not CXCR3, impairs the migration of nasally primed antigen-specific effector cells from nasal mucosa to the vagina.
6. Expressions of ligands of CCR5, CCL3, CCL4 and CCL5 expressions were all

upregulated in vaginal tissue and especially CCL5 expression was highly enhanced in stromal cells of vaginal tissue after nasal immunization. Moreover, intravaginal blockade of CCL5 using neutralizing antibody treatment diminished the number of HSV-2-specific effector cells in the vagina.

7. Using adoptive transfer model, I found that donor mice who received CLN cells from CCR5-knock out mice were susceptible to HSV-2 lethal virus infection.

8. Induction of CCL5 in vagina tissue is largely dependent on IFN-γ-producing migrated cells from secondary lymph nodes (e.g., CLN). The underlying mechanism needs further investigation.

On the basis of these findings, I conclude that TSLP–TSLPR cascade-dependent mucosal $CD11c^{+}$ cells (DCs and macrophages) are critical for the induction of pneumococcal vaccine antigen-specific IgA response, but not IgG responses, after nasal immunization. Furthermore, it was demonstrated that CCR5-CCL5 interaction is important for Ag-specific IFN-γ production is essential in vaginal mucosa upon intranasal vaccination with HSV-2 TK^{-} to confer protection against lethal HSV-2 infection. I expect that new knowledge from this doctoral dissertation will facilitate the development of more effective nasal vaccine and adjuvant treatments. This study therefore deserves the award of Ph.D. degree.