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論文の要旨
Abstract of thesis

In this doctoral dissertation, Yu-Hsien Lin describes the role of Allergin-1in the maintenance of intestinal homeostasis. The summary is as follows:

Background:

Allergin-1 is a transmembrane protein; the extracellular region contains an immunoglobulin-like domain, and the intracellular region contains two immunoreceptor tyrosine-based inhibitory motifs (ITIM). Upon phosphorylation of the tyrosine residues in the ITIM, Allergin-1 can recruit Src-homology 2 domain (SH2)-containing protein tyrosine phosphatases such as SHP-1 and SHP-2 and evoke further downstream signaling. Allergin-1 is expressed in a wide variety of immune cells including dendritic cells, mast cells, macrophages, neutrophils and basophils. By repressing FcεRI-mediated signaling, Allergin-1 suppresses passive cutaneous and systemic anaphylaxis. In addition, by repressing toll-like receptor 2 (TLR2)-mediated signaling in mast cells,Allergin-1 suppresses TLR2 ligand-induceddermatitis. However, the role of Allergin-1 in the maintenance of intestinal homeostasis remains unclear.

Purpose:

The author aimed to clarify the functional role of Allergin-1 in the maintenance of intestinal homeostasis.

Results:

The author first examined whether mice deficient in Allergin-1 expression exhibit any phenotypes related to intestinal functions. Whether the permeability of the intestinal barriers in Allergin-1-deficient mice was different from wild-type mice was tested by an assay using FITC-dextran. Four hours after oral administration of FITC-dextran, the concentration of FITC-dextran in the serum was measured. As a result, Allergin-1-deficient mice exhibited significantly higher serum concentration of FITC-dextran compared to wild-type mice, suggesting that these Allergin-1-deficient mice have increased intestinal permeability. In addition, the colon length of Allergin-1-deficient mice were shorter than wild-type mice, which implicated increased inflammatory responses in the Allergin-1-deficient mice.Notably, the author found that the increased permeability of the intestine (but not the reduced colon length) of the Allergin-1-deficient mice could be improved by oral administration of antibiotics.

To further investigate this point, the authorcarried out fecal microbiota transplantation experiments. Upon fecal transplantation from Allergin-1-deficient mice to wild-type mice, wild-type mice also showed a tendency for defective barrier functions.Next, the compositions of the microbiota were compared between Allergin-1-deficient mice and wild-type mice. As a result, the author showed that the composition of several kinds of bacteria were altered in Allergin-1-deficient mice. The proportions of *Allobaculu*, *Turicibacter*, and*Bifidobacterium* were significantly increased in Allergin-1-deficient mice compared to wild-type mice, whereas the proportion of *CandidatusArthromitus* was decreased. Interestingly,*Allobaculum* and *Bifidobacterium*were increased in aged mice, which have higher intestinal permeabilitycompared to young mice. However, cautious interpretations were required because *Bifidobacterium* also exerted protective effectsunder lipopolysaccharides (LPS) stimulation-induced barrier dysfunctions during treatment with dextran sulfate sodium, which is a model for inflammatory bowel diseases.

During the analyses of the compositions of the microbiota, the author showed that wild-type miceinitially exhibit compositions of the microbiota similar to Allergin-1-deficient mice upon receiving fecal transplantation from Allergin-1-deficient mice. However,the microbiota composition within a couple of weeks after decal transferreturned tothose of the original wild-type mice. Thus, Allergin-1-deficient intestinal environment was necessary for maintaining the characteristic compositions of the microbiota that were observed in Allergin-1-deficient mice. One possible mechanism might be that the physical barrier function was altered in the Allergin-1-deficient mice, considering the finding that the colon expression level of *mucin1*was reduced.

In addition, the author showed that Allergin-1-deficient mice exhibited increased susceptibility to treatment with dextran sulfate sodium, which is a model forinflammatory bowel diseases. Following oral treatment with dextran sulfate sodium indrinking water, body weight and mortality rate were monitored. In comparison with wild-type mice, Allergin-1-deficient mice showed significantly increased weight loss as well asmortality rate. By conducting histological analyses, the author showed that Allergin-1-deficient mice have more crypt loss and inflammatory cell infiltration compared to wild-type mice on day3, but not on day 7, after treatment with dextran sulfate sodium. Thus, Allergin-1-deficient mice showed enhanced inflammation in the early phase of dextran sulfate sodium-induced colitis.

Discussion:

These findings suggested that Allergin-1-deficient mice have deficient intestinal barrier functions, the underlying mechanism of which might be dysbiosis, i.e. alterations in the intestinal flora. To clarify which bacteria is responsible for the phenotypes related to intestinal barrier functions in the Allergin-1-deficient mice or wild-type mice that received fecal transplantation from Allergin-1-deficient mice, the generation of gnotobiotic mice transferred with a specific kind of bacteria is necessary.

Conclusion:

Altogether, the authordemonstrated the importance of Allergin-1 in maintenance of the intestinal barrier function and microbiota composition.

審査の要旨
Abstract of assessment result

【批評 Review】

The applicant successfully showed that Allergin-1 plays an important role in the maintenance of the intestinal barrier function. Moreover, careful observation by the applicant led to the finding that Allergin-1 exerts its function on intestinal barriers via regulating the compositions of the intestinal flora. Alteration of intestinal barrier function has been reported to increase the severity of inflammatory bowel diseases including Crohn's disease and ulcerative colitis. Thus, the successful identification of a transmembrane protein that is involved in inflammatory bowel diseases and subsequent elucidation of the underlying mechanism in this dissertation are very valuable in that it is expected to contribute to future developments of novel therapeutics.

【最終試験の結果 Result】

The final examination committee conducted a meeting as a final examination on 3 February, 2020. The applicant provided an overview of dissertation, addressed questions and comments raised during Q&A session. All of the committee members reached a final decision that the applicant has passed the final examination.

【結論 Conclusion】

Therefore, the final examination committee approved that the applicant is qualified to be awarded a Doctor of Philosophy in Human Biology.