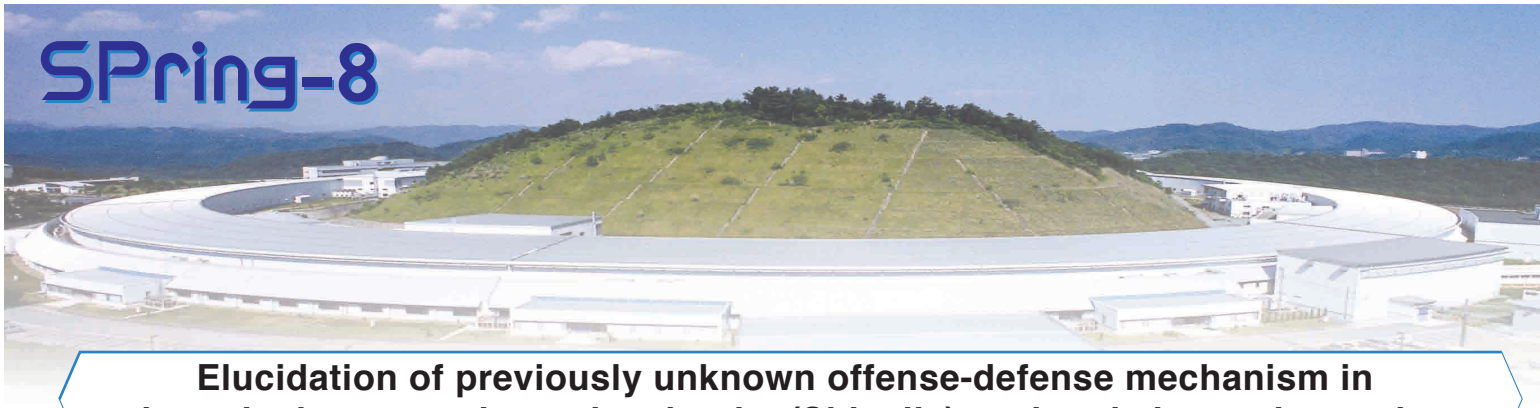

Elucidation of previously unknown offense-defense mechanism in intestinal tract: pathogenic microbe (Shigella) vs. host's innate immunity

Every year, approximately 15 million people lose their lives due to infectious diseases, and around 2 million out of them are caused by enteral infections. Although the intestinal tract is constantly exposed to numerous microbes, it has layers of protective barriers centered on innate immunity to guard the living system from microbial invasion. On the other hand, the enteropathogenic species Shigella and the allied pathogenic E-coli (typically 157) possess a highly sophisticated mechanism to worm their way into the living body, tactically eluding the protective systems. However, the details of these mechanisms-the innate immunity mechanism blocking pathogenic microbial invasion into intestinal mucosa, and the strategy employed by pathogenic microbes to circumvent them-have been a complete mystery.

Researchers at the Institute of Medical Science of Tokyo University (Prof. Chihiro Sasagawa, Dr.Masato Sanada, et al.) conducted a study, in collaboration with Prof. Tsunehiro Mizushima (University of Hyogo) and the large-scale synchronous radiation facility "SPring-8," on this issue, using Shigella as a model microbe. They elucidated the following mechanisms: (i) the recognition mechanism to detect the invasion of pathogenic microbes into mucosal epithelia, and (ii) the methods Shigella takes to counter the recognition and protection measures taken by the host.

In more specific terms, the results are summarized as below.

(i) A leaf-like protrusion (or, ruffle membrane) is formed when a pathogenic microbe invades a cell. The study demonstrated the importance of the inflammation signal pathway that depends on the diacylglycerol (DAG)-TRAF6-NF-kB pathway localized in the leaf-like protrusion, which provides a mechanism to recognize the leaf-like protrusion as a warning signal.

(ii) The study identified that Shigella secretes OspI as the countermeasure, and clarified the steric structure (Fig. 2) and biochemical properties of the protein.

The researchers discovered, in conducting the study summarized in (i) and (ii), that OspI is a "new deamidating enzyme" that makes a specific binding to UBC13 and deamidates its 100-th glutamine, resulting in the inhibition of TRAF6 activation, and thereby plays an important role in the proper control of the above-described inflammation signal pathway. This study discovered a previously unknown defense mechanism in place in mucosal epithelia that produces an effect against the pathogenic microbes, especially in the early stage of infection, and it also clarified the hidden strategy on the side of pathogenic microbes to evade the mechanism. Such knowledge should provide targets for future research, in view of developing new drugs and vaccines.

Reference: "The Shigella effector OspI deamidates Ubc13 to dampen the inflammatory response"
Takahito Sanada, Minsoo Kim, Hitomi Mimuro, Masato Suzuki, Michinaga Ogawa, Akiho Oyama, Hiroshi Ashida, Taira Kobayashi, Tomohiro Koyama, Shinya Nagai, Yuri Shibata, Jin Gohda, Jun-ichiro Inoue, Tsunehiro Mizushima, and Chihiro Sasakawa.
Nature **483** , 623-626 published online 11 March 2012

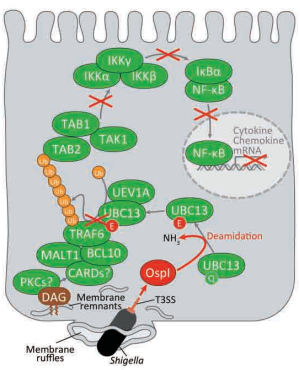

Fig.1. Inflammatory suppression mechanism of Shigella through OspI

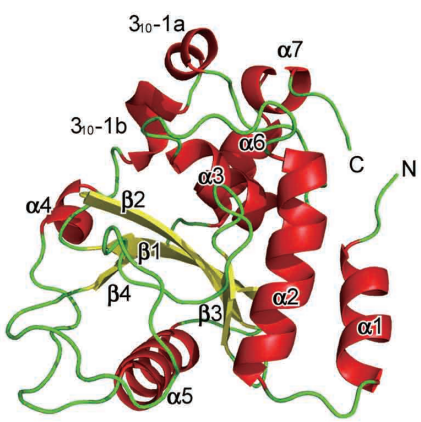

Fig.2. β-strands (yellow), seven α-helixes (red), and one 310 helix (red).