【Grant-in-Aid for Specially Promoted Research】
Biological Sciences

Title of Project : Study of bacterial stratagem to circumvent host innate immune system and its application

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Research Area : Medicine, dentistry, and pharmacy

Keyword : Barrier, Gut, Innate Immunity, *Shigella*

【Purpose and Background of the Research】

The gut epithelium deploys multiple innate defense mechanisms to fight microbial intruders, those are composed of two distinctive barriers, one is intrinsic mucosal barrier, and the other one is innate immune barrier. Current our studies have indicated that mucosal bacterial pathogens have evolved mechanisms to circumvent these gut innate defense barriers and exploit host cells as the replicative niches. Notably, gastrointestinal bacterial pathogens such as *Shigella* are equipped with highly evolved infectious mechanisms as the diverged array of executioners, called "effectors" delivered via their type III secretion system (T3SS). Whereby the bacterial pathogens are capable of manipulating host factors and signaling pathways involved in various cellular events related to actin dynamics, cell-cell junction, cell polarity, cell proliferation, cell death, membrane trafficking, and innate immune response. In-depth and comprehensive analyses of *Shigella* pathogenesis and its interaction with intestinal mucosa will provide not only important insights into understanding bacterial infectious stratagem and host innate defense responses, but also molecular and cellular bases towards development of mouse infection model and identification of small compounds to control bacterial infection.

【Research Methods】

In this project, we wish to elucidate the role of the bacterial effectors in promoting bacterial infection and circumventing the mucosal innate immune barriers at molecular, cellular, tissues, and whole body levels. To attain our research goal, as the first subject, we focus our special concern on yet-uncharacterized *Shgiella* effectors and elucidate their dynamic interplays between the bacterial effectors and their target host factors. As the second subject, we develop mice natural infection model for bacillary dysentery with *Shigella*, and wish to define the host factor(s) that protect mice from the natural infection. As the final subject, we perform high-through-put screening for identifying small compounds to inhibit *Shigella* IpaH effector, since the IpaH family effectors are highly conserved among many other bacterial pathogens.

【Expected Research Achievements and Scientific Significance】

The expected output of our project will shed further light into understanding basic bacterial infectious stratagems as well as that specific to *Shigella*, and provide new paradigm in 'Infection Biology' by strengthening the molecular basis in developing animal models, vaccines, and drugs.

【Publications Relevant to the Project】

1. Ogawa, M., Yoshikawa, Y, Kobayashi, T, Mimuro, H, Fukumatsu, M, Kiga, K, Piao, Z, Ashida, H, Yoshida, M, Kakuta, S, Koyama, T, Goto, Y, Nagatake, T, Nagai, S, Kiyono, H, Kawalec, M, Reichhart, J.-M, Sasakawa, C. A tecpr1-dependent selective autophagy pathway targets bacterial pathogens. ***Cell Host Microbe*** 9, 376-389, 2011
2. Kim M, Ogawa M, Fujita Y, Yoshikawa Y, Nagai T, Koyama T, Nagai S, Lange A, Fässler R, Sasakawa C. Bacteria hijack integrin-linked kinase to stabilize focal adhesions and block cell detachment. ***Nature*** 459, 578-82, 2009

【Term of Project】 FY2011-2015

【Budget Allocation】 407, 500 Thousand Yen

【 Homepage Address and Other Contact Information】

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