Centers of Advanced Medicine
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General Summary

Arthropod vectors are organisms that play a role in the transmission of a pathogen between humans or from animals to humans. Vectors tend to be blood-sucking insects that ingest the disease-causing organism with the blood from an infected host and then inject it into a new host at the time of their next blood-meal. New strategy to control the vector should absolutely be developed and involved in integrated vector management (IVM), because it is one of the most effective means of dealing with the problem while waiting for a vaccine or another effective dengue control strategy. In this center, based on collaboration between our center and institutions in endemic countries such as Burkina Faso, Nigeria, and Taiwan, entomological studies promoting multilateral approaches have been performed to gather fine knowledge of diagnosis, ethology, immunity, and epidemiology of vector species on effective vector control.

Research Activities

Symbiotic bacteria Wolbachia *manipulate host germline stem cells by targeting host RNAs*

Wolbachia are the most abundant intracellular bacteria, infecting >65% insect species. The global *Wolbachia* pandemic is maintained by their ability to manipulate host biology in diverse ways such as feminization, parthenogenesis, male killing, cytoplasmic incompatibility and viral protection. *Wolbachia* have received attention for use in controlling insect pests and disease vectors by applying their biology. However, contrary to the advances in their practical use, the mechanisms how *Wolbachia* manipulate host cellular functions are largely unknown. To elucidate the interactions between *Wolbachia* and hosts at the molecular level, we aimed to identify *Wolbachia* factors controlling host cells and reveal their functions. To achieve this goal, we adopted a novel strategy employing a heterologous expression system using *Drosophila* genetics. As a result, we identified one *Wolbachia* gene named *TomO* (*TOxic Manipulator of Oogenesis*) which recapitulated some of the *Wolbachia*'s effects on *Sex-lethal* (*Sxl*) mutants of *D. melanogaster*. The Sxl is the master regulator of the sex determination system in *D. melanogaster* females. In *Sxl* mutant females, the germline stem cells (GSCs) were masculinized and lost, otherwise *Wolbachia* infection rescued the aberration. The heterologous expression of TomO in *Drosophila* GSCs also prevented the loss of the mutants GSCs. We revealed that TomO targets host *nanos* mRNAs, which are responsible for the maintenance of GSCs, and enhances their translation. Considering that the regulation of specific RNAs could mediate the diverse *Wolbachia*-induced phenomena, it will be of great interest to examine the

involvement of TomO.

Genetic dissection of mosquitoes adaptation to different hosts

Zoophilic mosquitoes bite animals and maintain infectious diseases in the sylvatic cycle. However, humans are occasionally bitten by zoophilic mosquitoes and receive causal agents of infectious diseases from animals. This shift in biting is responsible for occasional outbreaks in humans. Mosquito olfaction plays a significant part in host-seeking behavior of mosquitoes. An evolutionary adaptation of *Ae. aegypti* to human odors which was driven by single nucleotide polymorphisms in the gene encoding an odorant receptor has been presented in a past study. However, genetic alteration in mosquito genome would take longer time, and other possible mechanism of instability and plasticity in host preference of mosquito is to be investigated for prevention of mosquito-borne diseases. We developed genetically modified strains of yellow fever mosquito (*Aedes aegypti*) lacking either odorant-binding proteins 34 or 39 gene by CRISPR/Cas9 system. These mosquitos showed impaired host-seeking activity. It has been known that several species of mosquitoes can experimentally adapt to a new host animal by repeated blood-sucking in a transgenerational manner. For artificially inducing mosquito adaptation to different host species, we are currently establishing *Ae. aegypti* strains reared with mice, rabbits, chickens, common marmosets, and horses as sources of blood meal.

Publications

Chinuki Y*[1]*, Ishiwata K, Yamaji K, Takahashi H*[1]*, Morita E*[1] *(*[1]Shimane Univ).*** Haemaphysalis longicornis tick bites are a possible cause of red meat allergy in Japan. *Allergy.* 2016; **71:** 421-5.