

(Form 1)

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| Kyoto University | Doctor of Philosophy in Life Sciences | Name | Jung Hyun Im |
| Thesis Title | Regulation of antiviral responses by RIG-I dissociation from dsRNA | | |
| <p>(Thesis Summary)</p> <p>RIG-I and MDA5 are DExD/H-box helicases and function as critical sensors for double-stranded RNA (dsRNA) produced in virus-infected cells to induce antiviral innate immune responses, including the production of type I interferon. It has been shown that RIG-I and MDA5 sense distinct dsRNA types. For example, RIG-I and MDA5 sense short and long dsRNA, respectively. Previous studies elucidated that MDA5 binds to long dsRNA to form fiber-like polymer, which is a critical intermediate for processing into the “activated” MDA5. On the other hand, RIG-I can bind to dsRNA irrespective of its size, therefore the molecular mechanism by which RIG-I is selectively activated by short dsRNA was unknown. Particularly, the reason why RIG-I is not activated by long dsRNA was unexplained. This study revealed the precise mechanism how RIG-I recognizes different sizes of dsRNA to conform to active structure for antiviral signaling. RIG-I binds to short dsRNA and efficiently dissociates through ATP hydrolysis thereby forming “active” molecular conformation. However, RIG-I binds to long dsRNA by forming indissociable non-fiber aggregates. The dissociated RIG-I from short dsRNA forms homo oligomers as well as hetero oligomers with the adaptor protein MAVS to facilitate intracellular antiviral signaling. In summary, this study revealed for the first time how RIG-I is selectively activated by short dsRNA.</p> | | | |

(Form 2)

(Thesis Evaluation Summary)

During the thesis defense on June 13th, the committee pointed out that the doctoral thesis bore a striking resemblance to the original paper published in Scientific Report. As a result, the committee requested substantial revisions for the thesis. Additionally, we raised concerns regarding the sample sizes, the number of experimental trials, and statistical analyses presented in several figures within the doctoral thesis (These concerns included results with N=1 potentially showing no reproducibility, results with an N=2 sample size showing statistical significance, and the use of a *t*-test to analyze multiple samples). Similar concerns were also found in the original paper. Consequently, the committee asked questions to the applicant about the sample sizes and the number of experimental trials in certain experiments, revealing a lack of sufficient understanding of the applicant's approach to sample sizes, trial numbers, and statistical analyses.

Then, the committee requested the applicant to study about sample sizes and experimental trials and improve her understanding. In addition, we also requested the applicant to study statistical analyses. Upon completion of these studies, the committee requested that the applicant revised the content of the doctoral thesis accordingly. Furthermore, for experiments where reproducibility was not be confirmed and for experiments that would affect the conclusions of this study, the committee requested to conduct the experiments to confirm the reproducibility.

In October, the review committee conducted individual interviews, during which they confirmed that the applicant had gained a better understanding of sample sizes, experimental trials, and statistical analyses. Furthermore, in the revised doctoral thesis, new data were added, the descriptions related to sample sizes, experimental trials and statistical analyses were accurately revised, and the issues of similarity with the original paper were resolved. As a result, the committee determined that the doctoral thesis had reached a sufficient level.

This thesis now substantiates the candidate's enough knowledge of life sciences, demonstrates expert research capability in the field of immunology, and presents new discoveries and concepts that contribute to further development of the candidate's research field. Moreover, the thesis is written logically and coherently, which satisfies the degree requirement that the thesis shall serve as a valuable document for future reference. Therefore, the thesis examination committee hereby concludes that the candidate has passed all of the requirements for the degree of Doctor of Philosophy in Life Sciences.

The thesis, thesis summary, and thesis evaluation summary will be published through the Kyoto University Research Information Repository. If the thesis cannot be published on the website immediately after the degree is awarded, due to patent application, journal publication constraints, or other reasons, please indicate the earliest date that the thesis can be published. (Please note, however, based on Article 8 of the Degree Regulations, that the thesis must be published within three months of the date that the degree is awarded.)

Thesis publication date : _____