(Form 1)

Kyoto University	Doctor of Philosophy in Life Sciences	Name	AHMED S.A. ABU TAYEH
Thesis Title	Constitutive RIG-I activation causes skin lesion resembling psoriasis in transgenic mice		

(Thesis Summary)

RIG-I, an RNA helicase functioning as a critical sensor for invading and replicating viral RNA, triggers antiviral responses including type I interferon (IFN) production. It was reported that a mutation of *DDX58* gene encoding human RIG-I is associated with rare autoimmune diseases including Singleton-Merten syndrome (SMS). A mutation found in a SMS patient caused single amino acid substitution (E373A) of RIG-I and conferred its constitutive activity, hence chronic IFN production. However, its relationship with autoimmune phenotype in vivo was not demonstrated. The applicant analyzed transgenic mice harboring a human chromosomal fragment encompassing entire *DDX58* locus. The mice exhibited systemic inflammation with reduced body weight and survival. CD11c positive dendritic cells were major source of IFN production. Splenomegaly associated with activated splenocytes was observed. T cells with effector marker were also increased. A notable phenotype was skin pathology resembling psoriasis, which is one of the symptoms of SMS. In the skin, hyper proliferation with expression of keratin 5 was observed (acantosis and parakaratosis). Genetic deletion of *MAVS*, a critical signaling adaptor for virus-induced signaling by RIG-I, abolished the phenotype, indicating that constitutive signaling of RIG-I is responsible for the phenotype. Also genetic deletion of IL-17 greatly ameliorated the skin phenotype, suggesting Th17 involvement. Further, deletion of *Rag2* partially attenuated the skin phenotype indicating involvement of acquired immunity. Because it was reported that gut microbiota promotes IL-17 production, the applicant removed gut bacteria by antibiotics treatment. The treatment reduced IL-17 production and significantly attenuated the skin phenotype. Finally to explore development for prophylaxis and treatment, the mice were treated with tofacitinib, a clinically utilized medicine for blocking IFN action. Prophylactic tofacitinib prevented the development of skin phenotype and it facilitated recovery of existing skin lesion.

In summary, the study demonstrated that RIG-I E373A causes systemic inflammation and psoriasis in the skin. The skin phenotype is dependent on production of IFN, Th17 and acquired immunity. Finally the study suggested tofacitinib treatment for possible prophylaxis and treatment of the psoriasis associated with constitutive IFN signature.

(Form 2)

(Thesis Evaluation Summary)

Following issues were discussed during the thesis defense.

Although genetically identical, one third of the transgenic mice developed skin phenotype. This may be due to environmental trigger including infections and mechanical stress. Why transgenesis of *DDX58* rather than gene editing strategy (or knock in) to alter mouse *Ddx58* gene was chosen? It was practical reason that BAC transgenesis was commercially available rather than knock in, which takes longer time. What is the advantage of this model system over imiquimod-induced psoriasis? Both animal models have similar phenotypes and represent certain types of human diseases. The transgenesis model is based on the finding that the *DDX58* mutation was identified in SMS patient and psoriasis is one of the symptoms of SMS. Therefore this mouse model is more relevant to mutation-mediated, chronic interferonopathies. In addition to initial activation of IFN and downstream pathways, there may be secondary danger signal, such as DNA signal released from the dead cells, may amplify the inflammatory cycle to establish the pathology. A few modifications of the thesis were requested by the reviewers, including an addition of a model figure for the antiviral innate immunity, which were revised properly.

In summary, the applicant's conclusions that RIG-I E373A causes systemic inflammation and psoriasis in the skin in mouse model and that the skin phenotype is dependent on production of IFN, Th17 and acquired immunity are novel and scientifically significant. Moreover the study suggested tofacitinib treatment for possible prophylaxis and treatment of the psoriasis associated with constitutive IFN signature.

This thesis substantiates the candidate's extensive and wide knowledge of life sciences, demonstrates expert research capability in the field of immunology, and presents new discoveries and concepts that contribute to the profound understanding and 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. On January 26th, 2021, the PhD thesis oral examination was held. Pursuant to this oral examination, 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 :