(Form 1)

Kyoto University	Doctor of Philosophy in Life Sciences	Name	Lee Sumin
Thesis Title	Constitutively active signaling of MDA5 in Treg cells causes apoptosis of Treg cells and results in autoimmune diseases		

(Thesis Summary)

MDA5 is the critical viral RNA sensor for the induction of innate antiviral responses. A missense mutation, MDA5 G821S, was identified in mouse with severe autoimmune phenotypes. G821S substitution causes conformational change of MDA5 protein and confers constitutive signaling without viral RNA. Thus, MDA5 G821S is a gain-of-function mutation and causes constitutive production of antiviral cytokines including type I IFN (IFN-I) and contributes to the pathology. Recently, human genome analyses revealed that gain-of-function mutations of MDA5 cause autoimmune diseases, including Aicardi-Goutières Syndrome (AGS) and Singleton-Merten Syndrome (SMS). Because these diseases are commonly triggered by constitutive production of IFN-I, these are collectively termed as interferonopathy. However, the involvement of Treg cells in the pathogenesis of MDA5 G821S interferonopathy remains unclear. This study aimed to delineate the mechanism between the expression of constitutively active MDA5 in Treg cells and autoimmune diseases. To address this question, mice expressing MDA5 G821S in Treg cells were generated (Treg G821S mice). Treg G821S mice showed a reduction of peripheral Treg cell number due to elevated apoptosis and resulted in scurfy-like phenotypes, including lupus-like nephritis and high lethality. Interestingly, the number of activated Tregs was significantly reduced in AGS patients, suggesting Treg abnormality is a common mechanism for human and mouse interferonopathies. Furthermore, adaptive transfer of wild-type Treg cells into the mice with systemic expression of MDA5 G821S, improved their autoimmune symptoms and lethality. Taken together, this study demonstrates that constitutively active MDA5-mediated signaling disturbs the homeostatic function and activation of Tregs and may contribute to the pathology of interferonopathy.

(Form 2)

(Thesis Evaluation Summary)

Because MDA5G821S results in constitutive activation of acquired immune responses, the applicant aimed to elucidate the role of Treg cells in the autoimmune phenotypes. The applicant made mice expressing MDA5 G821S in a Treg-specific manner (Treg G821S mice) and analyzed Treg population and Treg functions. Treg G821S mice showed a reduction of peripheral Treg cell numbers due to elevated apoptosis. Treg cells from Treg G821S mice failed to suppress in an experimental colitis model, suggesting that G821S disturbs the function of Treg. Treg G821S mice exhibits lupus-like nephritis and high lethality. Examination of Treg G821S mice revealed inflammation in lung, small intestine, colon and kidney, as well as production of auto-antibodies. These were consistent with the results that activated Treg is reduced in AGS patients. Furthermore, adaptive transfer of wild-type Treg cells into systemic G821S mice ameliorated the autoimmune phenotypes and survival. In summary, this study demonstrates that constitutively active MDA5-mediated signaling in Treg cells disturbs Treg cell functions, thereby contributing to the pathology of interferonopathy.

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 November 8th, 2022, 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.

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Thesis publication date :