論　文　内　容　の　要　旨
Synopsis of Thesis

氏　名 Name	國吉　佳奈子
論文題名 Title	**Pivotal role of RNA-binding E3 ubiquitin ligase MEX3C in RIG-I-mediated antiviral innate immunity** **（RNA結合性E3リガーゼMEX3Cの抗ウイルス応答における役割）**

論文内容の要旨

〔目　的(Purpose)〕

The RIG-I-like receptors, RIG-I, MDA5, and LGP2, are cytoplasmic sensors for RNA viruses that mediate the antiviral innate immune responses. They sense RNAs derived from different RNA viruses. Then RIG-I and MDA5 trigger intracellular signaling pathways via an adaptor, IPS-1. Recent studies demonstrated that RLRs accumulate in cytoplasmic granules containing stress granule (SG) markers following viral infection. These granules, called "antiviral stress granules" (avSGs), are distinguishable from canonical SGs and contain viral RNA, viral nucleocapsid protein, and RNA-dependent protein kinase (PKR). AvSGs are reported to be a platform for the detection of viruses. However, the relationship between RLR-mediated antiviral responses and the formation of avSGs is poorly understood. Here, we identified the RNA-binding and RING-containing protein MEX3C, that localizes to SGs and triggers RIG-I-dependent antiviral responses by ubiquitination of RIG-I.

〔方法ならびに成績(Methods/Results)〕

To determine the roles of MEX3C in the antiviral innate immune responses, we overexpressed MEX3C and RIG-I together with an *IFNB* promoter-driven reporter plasmid in HEK293 cells and measured the reporter gene expression. Notably, the overexpression of Flag–MEX3C enhance the RIG-I-mediated *IFNB* promoter activity. We determined cellular localization of MEX3C. In unstimulated murine bone-marrow-derived macrophages (BMDM), MEX3C localized to cytoplasmic puncta. After NDV infection, MEX3C accumulated in enlarged cytoplasmic structures, where it colocalized with TIA-1, a marker of SGs. Furthermore after NDV infection, both RIG-I and MEX3C accumulated in cytoplasmic puncta. To examine the physiological contribution of MEX3C to antiviral immune responses, we generated *Mex3c*-deficient mice. We examined the production of cytokines in response to RNA virus infection. The production of IFN-β, IL-6, and IL-12p40 after infection with NDV or VSV was abrogated by *Mex3c*-deficient PECs. In contrast, the production of these cytokines after infection with EMCV, which is recognized by MDA5, or stimulation with lipopolysaccharide (LPS), a ligand for TLR4, was not impaired in the *Mex3c*-deficient PECs.

〔総　括(Conclusion)〕

Our data shows that MEX3C mediates the ubiquitination and activation of RIG-I and colocalizes with RIG-I in avSGs after viral infection. And MEX3C is critical for innate immune responses against RNA virus infections.

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

國吉佳奈子さんは、入学以来自然免疫学に関与する新規分子の探索およびその解析を行い、立派な成果を挙げてきました。特に、抗ウイルス応答に関与する新規分子ＭＥＸ３Ｃの研究ではそのマウスにおける機能を検討し、自然免疫応答、特に抗ウイルス応答制御するあらたな分子とその制御機構を明らかにしました。本研究はＲＩＧ－Ｉを介した抗ウイルス応答の全容を解明する一助となりました。本研究は今後の自然免疫学の発展に寄与する価値ある研究成果であったと考えております。実際、本研究成果はＰＮＡＳ紙に掲載される予定で、さらに2014年キーストンで開催された国際学会で口頭発表題目として抜擢され国際的なインパクトも大きいと思われます。したがって、本研究成果は國吉さんに学位を授与するに足りるものであると考えております。