Elucidation of molecular mechanisms of immune cell migration and their application to medicine

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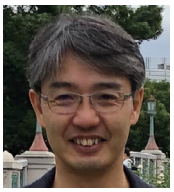

Abstract

Immune cells use the actin and myosin-mediated cellular contractility (actomyosin contraction) to move through confined spaces in vivo, but the detailed regulatory mechanisms are unknown. When Lamtor1, a component of the lysosomal membrane-tethered Ragulator complex was specifically deleted in immune cells, the induction of the acquired immune system was impaired due to the impaired migration of dendritic cells. In the confined space, dendritic cells were unable to move forward due to impaired contraction in the rear of cell. Furthermore, the Ragulator complex regulates actomyosin contraction by altering the localization of MLCP through interacting with MPRIP, which anchors myosin light chain phosphatase (MLCP) to actin.

Background & Results

Immune cells migrate throughout the body to monitor invading pathogens. Among immune cells, dendritic cells are highly motile and are responsible for capturing invading pathogens, migrating to lymph nodes and spleen, and presenting antigens to lymphocytes, resulting in inducing antigen-specific immune responses to protect the host from pathogens. Dendritic cells migrate in an elongation-contraction pattern in response to chemokines, in which the anterior region of the cell elongates and the posterior region contracts by actomyosin contraction. However, the regulatory mechanism of actomyosin contraction is unknown. It has been reported that the Ragulator complex, which anchors mTORC1 on the lysosomal membrane for metabolism, is involved in cell motility, but the mechanism of its involvement in actomyosin contraction is unknown.

We generated mice lacking dendritic cell-specific Lamtor1, a component of the Ragulator complex, and examined the function of Lamtor1 in dendritic cells and found that Lamtor1 is involved in actomyosin contraction. Dendritic cell-specific Lamtor1-deficient mice had a reduced number of dendritic cells migrating from peripheral tissues to lymph nodes and a markedly reduced induction of the acquired immune system. Furthermore, observation of dendritic cell migration in an experimental system that recapitulated dendritic cell migration in vivo revealed that Lamtor1-deficient dendritic cells were unable to advance due to impaired actomyosin contraction in the posterior region of the cell. Investigating the mechanism of this defect, we found that the Ragulator complex interacts with actin-anchored MPRIP (myosin phosphatase Rho-interacting protein), which leads to competitively interfere the binding between MPRIP and MYPT1, a component of myosin light chain phosphatase complex (MLCP), a brake on actomyosin contraction. The sequestration of MLCP from actin leads to the phosphorylation of MLC, promoting the actomyosin contraction. In this study, we elucidated the detailed mechanism of immune cell migration, by which the Ragulator complex regulates actomyosin contraction through its interaction with MPRIP.

Significance of the research and Future perspective

This study revealed that when chemokine signaling induces anterior-posterior cell polarity, lysosomes localize to the posterior of the cell, and the Ragulator complex on the lysosomal membrane associates with MPRIP to inhibit the binding of MPRIP with MYPT1, which divert MLCP, from the actomyosin contractile site. Since mutations in Ragulator complex components are known to cause human immunodeficiency diseases and cancer cells also utilize actomyosin contraction during cancer metastasis, the interaction between the Ragulator complex and MPRIP may provide a new therapeutic target against human diseases such as an inflammation, autoimmune diseases, anti-tumor immune responses, and cancer metastasis caused by cell migration.

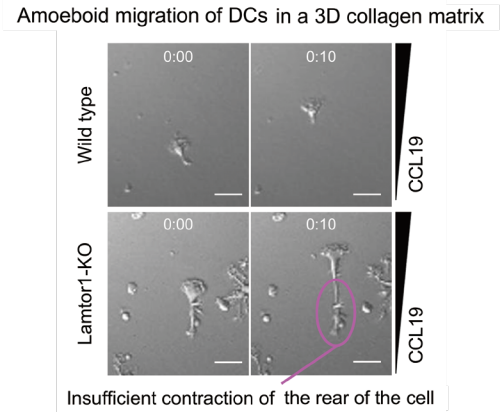

Figure 1

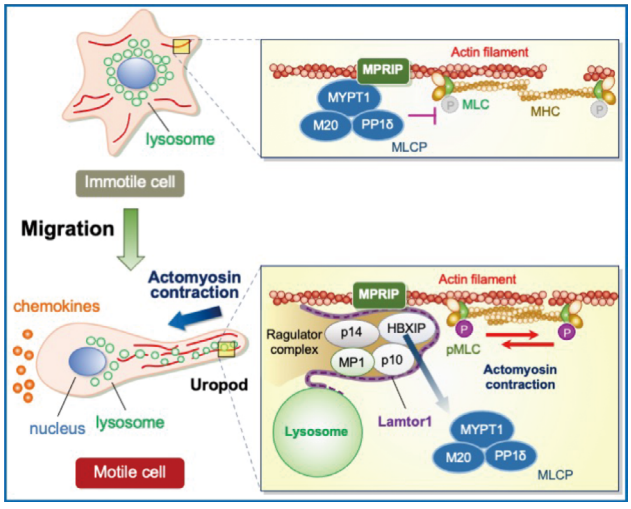

Figure 2

Patent

Treatise Nakatani, Takeshi; Tsujimoto, Kohei; Park JeongHoon; et al. The lysosomal Ragulator complex plays an essential role in leukocyte trafficking by activating myosin II. Nature Communications. 2021, 12(1): 3333, doi: 10.1038/s41467-021-23654-3

URL

Keyword immune cell migration, actomyosin contraction, the ragulator complex, lamtor1, MPRIP