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論　文　要　旨

学　位　論　文（要約）

表　　題　乱流下で血小板を産生する巨核球におけるミトコンドリアの断片化

Mitochondrial fragmentation in thrombopoietic megakaryocytes under turbulent flow

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表題

乱流下で血小板を産生する巨核球におけるミトコンドリアの断片化

１　研究目的

Platelet transfusion is a crucial lifesaving treatment to stop for bleeding and patients who suffer various disease conditions. Currently, platelet resource is donor dependent in clinics. However, strategies with induced pluripotent stem cells (iPSCs) have emerged for a promising resource of platelets. Understanding the biological machinery of platelets biogenesis is key to achieve a supply of fully functional platelets for clinics. Mitochondria are an indispensable organelle to maintain cellular activities. However, the functions of mitochondria in platelet biogenesis are largely unknown. To this end, a major bottleneck is the lack of platforms to recapitulate the cellular processes of *in vivo* platelet biogenesis for *in vitro* multifaceted studies using various biochemical and biophysical analytical techniques. In this study, we developed an easy-to-use turbulence generator system (TGS) that recapitulates the cellular process of *in vivo* platelet biogenesis in typical cell culture dishes.

２　研究方法

In vivo, using two-photon microscopy, bone marrow megakaryocyte (MK) is visualized in CAG-GFP mice. Mitoctracker red FM dye possible to label mitochondria morphology either *in vivo* and *in vitro*. Superior imaging technique combine with particle imaging velocity (PIV) analysis enable to measure fluid force and direction in *in vitro* and *in vivo*. Analyzing bone marrow physiological thrombopoietic condition, newly turbulence flow in cell culture scale. Taking this advantage, we cultured MKs from fetal liver and iPSC-derived MKs under turbulence stimulation in *vitro*.

３　研究成果

Previously, we have revealed that not laminar, turbulent flow accelerated platelet release from MKs in living mice bone marrow. In this study, our intravital imaging visualized that turbulent flow triggered mitochondria fragmentation in thromobopietic MKs in murine bone marrow. We further showed that fragmented mitochondria in platelets are crucial to maintain activation capitates of circulating platelets in mice. To link these findings, we developed the turbulent generator system (TGS) that is inspired with native setting of platelet biogenesis in MKs under turbulent blood flow. The TGS can be attached to typical cell culture dishes and efficiently trigger platelet biogenesis from isolated murine MKs. By using TGS, we successfully visualized dynamics of mitochondrial fragmentation in iPSC-derived MKs and active transfer processes of fragmented mitochondria from MKs to platelets.

４　考察

On the conventional cultured conditions, turbulent and laminar flows are difficult to be analyzed and controlled. However, our TGS system is enable to visualize response of cell to each mechanical factor, and regulate fore determination independently. We reproduced similar flow conditions to physiological ones in living bone marrow, and under such turbulence stimulation, thrombopoietic process was physically and genetically upregulated. This study would provide turther opportunities to understand biological machinery of platelet biogenesis toward archieving improved quality of platelets in clinical applications.

５　結論

In this study, we revealed that mitochondrial dynamic is a key player in production of fully functional platelets from MKs stimulated with the turbulent flow. High spatiotemporal intravital imaging evidenced mitochondrial fragmentation in thrombopoietic MKs in bone marrow of mice. We observed detailed process of mitochondria fragmentation in proplatelet production in MKs under turbulent flow stimulation in cell culture system with turbulence generator. These findings suggested a feedback loop for promoting platelet biogenesis via mechano-stimulated mechanism and transportation of fragmented mitochondria for functional platelets.