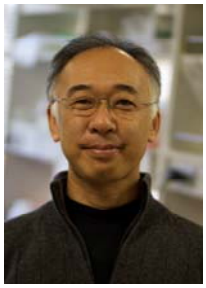
【Grant-in-Aid for Scientific Research (S)】

Biological Sciences (Medicine, Dentistry, and Pharmacy)



Title of Project： Mechanisms and physiological functions of intercellular communication by cell death

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Research Project Number：16H06385　Researcher Number：50202338
Research Area：Developmental Genetics
Keyword：Inflammation, Cellular Proliferation and cell death, Intercellular communication

【Purpose and Background of the Research】

Function of cell death was thought to be required to get rid of unwanted cells. However, recent genetic study revealed that dying cells release signal molecules and act as a signal center. Our research goal is to reveal the molecular mechanisms and physiological functions of cell-death coupled secretion. Our study will provide the new type of intercellular communication and the novel strategy for diagnosis and treatment of diseases.

【Research Methods】

We have generated FRET sensor for activated caspase-1, named SCAT1. By using SCAT1, the spatial and temporal activation of caspase-1 occurred as the manner of all-or-none (digital) at the single-cell level. Caspase-1 activated macrophage die immediately and real-time concurrent detection of caspase-1 activation and IL-1β release demonstrated that dead macrophages release a local burst of IL-1β in a digital manner. Thus, dying macrophages as the main source of IL-1β within cell populations. To study the molecular mechanisms of caspase-1 mediated active secretion, identification of caspase-1 substrates by Gel-enhanced LC-MS/MS and chemical library screening for IL-1 β secretion will be conducted. We also study the apoptosis- and necrosis-coupled secretion by using *Drosophila* genetics and bioimaging. Three different types of cell death will be focused in our study.

1. Caspase-1 mediated pyroptosis
2. Caspase-3-mediated apoptosis
3. Caspase-independent necrosis

【Expected Research Achievements and Scientific Significance】

Capase-1 activity is required for pyroptosis of macrophage but also for IL-1 β secretion. Identification of the mechanisms of active secretion of signal molecules from three different types of dying cells will provide the novel concept of intercellular communication and contribute for understanding of active participation of cell death for development, tissue homeostasis and diseases.

【Publications Relevant to the Project】

・Kashio, S., Obata, F., Zhang, L., Katsuyama, T., Chihara, T., and Miura, M.: Tissue non-autonomous effects of fat body methionine metabolism on imaginal disc repair in *Drosophila*. Proc. Natl. Acad. Sci. USA., 113, 1835-1840, 2016.

・Yamaguchi, Y., and Miura, M.: Programmed cell death in neurodevelopment.
Dev. Cell 32, 478-490, 2015

・Liu, T., Yamaguchi, Y., Shirasaki, Y., Shikada, K., Yamagishi, M., Hoshino, K., Kaisho, T., Takemoto, K., Suzuki, T., Kuranaga, E., Ohara, O., and Miura, M.: Single-cell imaging of caspase-1 dynamics reveals an all-or-none inflammasome signaling response.
Cell Rep. 8, 974-982, 2014,

【Term of Project】FY2016-2020

【Budget Allocation】140,900 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.f.u-tokyo.ac.jp/~genetics/index.html