Associate Professor Takeda Tetsuya
Group research activities

Project: Membrane remodeling in health and disease

(1) Elucidating membrane fission mechanisms by Dynamin

Endocytosis is required for incorporation of molecules from extracellular environment into cells across membrane barrier. Endocytosis is required for essential biological processes including differentiation, neuronal transduction and signal transduction. In contrast, aberrant endocytosis is tightly linked to various congenital diseases and cancers. Thus, studying endocytosis is important for both physiological and pathological perspectives. In endocytosis, a small area of cell membrane is invaginated and severed to form endocytic vesicles. Dynamin, a large GTPase, plays essential roles in the membrane invagination and fission (membrane remodeling) in endocytosis. Dynamin assembles into an higher ordered "helical" structure at the neck of invaginating endocytic pits and structural changes of the helices coupled with GTP hydrolysis drives membrane fission. However, precise mechanisms of the dyamin-mediated membrane fission remain to be elucidated. We are analyzing mechanism of the dynamin-mediated membrane fission using High Speed Atomic Force Microscopy (HS-AFM) to tackle this fundamental question (Fig.1).

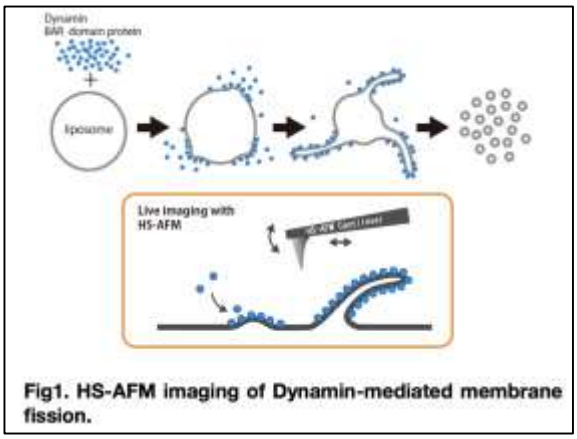

Fig1. HS-AFM imaging of Dynamin-mediated membrane fission.

(2) Pathogenesis of congenital myopathy caused by aberrant membrane remodeling

Congenital myopathies are a group of muscle diseases causing muscular weakness. Although frequency of congenital myopathies is relatively low (e.g. 1000 patients in Japan), its pathogenesis is poorly understood thus designated as one of rare intractable diseases by Japanese Ministry of

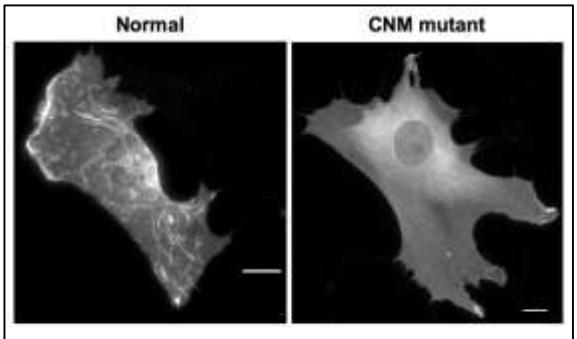

Fig2. Membrane tubulation by normal and CNM mutant form of human BIN1 in mouse myoblast (C2C12). CNM mutant lacks membrane tubulation activity.

Health, Labour and Welfare. Centronuclear myopathy (CNM) is one of congenital myopathies and membrane remodeling proteins, Dynamin2 and BIN1, are among causal genes of CNM. We hypothesize that membrane remodeling defects caused by mutations of Dynamin2 and BIN1 leads to pathogenesis of CNM. To elucidate pathogenesis of CNM, we are taking multidisciplinary approaches including cell biology, genetics, biochemistry and biophysics using muscle cell lines and in vitro reconstituted system (Fig.2).

(3) Membrane remodeling in cytokinesis

Cytokinesis is the final step in cell division that physically separates one mother cell into two daughter cells. Regulated cytokinesis is crucial to guarantee proper inheritance of genomic materials into daughter cells. In the development of animals and plants, asymmetrical separation of cell fate determinants is essential for cell differentiation. In contrast, aberrant cytokinesis causes various diseases such as cancer, infertility and developmental defects. Cytokinesis is accompanied by a dynamic morphological changes of cell shape, which is caused by cooperative function of cytoskeleton (actin and microtubules) and membrane. Although function and regulation of cytoskeleton in cytokinesis is relatively well understood, membrane function remains to be elucidated. We have demonstrated membrane remodeling machineries, BAR domain proteins and ESCRT, play essential roles in membrane function in cytokinesis (Takeda *et al*., *Nat. Cell Biol.* 2004; Takeda *et al.*, *Open Biol.* 2013; Capalbo *et al.*, *Open Biol.* 2012). We are taking multiple approaches including cell biology, in vitro reconstitution and live imaging to elucidate function and regulation of membrane remodeling in cytokinesis.

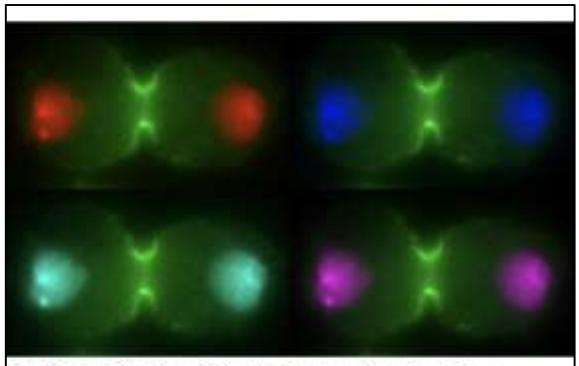

Fig3. Localization of Syndapin (green) and nucleus (pseudo colors) in cytokinesis of fruit fly cells (*D.Mel-2*).

Selected Pub lications

Takeda, T., Robinson, I.M., Savoian, M.M., Griffiths, J.R., Whetton, A.D., McMahon, H.T. and Glover, D.M. (2013) *Drosophila* F-BAR protein Syndapin contributes to coupling the plasma membrane and contractile ring in Cytokinesis. *Open Biol.* 7;3(8):130081. (http://rsob.royalsocietypublishing.org/content/3/8/130081/suppl/DC2)

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Other publicatoins

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Yamada, H., **Takeda, T.**, Michiue, H., Abe, T. and Takei, K. Actin bundling by dynamin 2 and cortactin is implicated in cell migration by stabilizing filopodia in human non-small lung caricinoma cells. *Int J Oncol.,* 2016; 49(3):877-886.

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Shibasaki M. (2003) The promoter polymorphism in the eosinophil cationic protein gene and its influence on the serum eosinophil cationic protein level. *Am J Respir Crit Care Med.*, 167(2):180-4.

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