

先端研究開発室

Advanced Research Initiative

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■研究概要

エンドサイトーシスや細胞遊走などの生命現象は細胞膜の変形や細胞骨格の再編成を伴うダイナミックな生命現象であり、外界からの刺激を細胞の形態変化につなげるシグナル伝達経路によって制御されている。我々はこれまでX線結晶構造解析や生化学的手法を用いて経路の構成タンパク質の構造や機能を解明することで、真核細胞の活動を支えるこれらの生命現象の巧妙な仕組みの理解を目指して研究を進めてきた。最近、電子顕微鏡を用いた脂質二重膜中の膜タンパク質の新規イメージング/構造解析技術の開発と、創薬標的を含む様々な膜タンパク質への応用を集中的に進めている。

■Research Projects

Endocytosis and cell migration are dynamic physiological processes of eukaryotic cells accompanied by membrane and/or actin cytoskeletal remodeling. These processes are regulated by cellular signaling pathways, which link extracellular signals to corresponding morphological changes of the cell. We have been investigating the mechanisms underlying the functions exerted by these proteins with mainly X-ray crystallography and various biochemical techniques. We are currently intensively working on the development of a novel imaging/structure determination technology using electron microscopy for the visualization of membrane proteins in the lipid bilayer and its application to a variety of membrane proteins, including drug targets.

■Major Recent Publications:

1. Kong S.G., Yamazaki Y., Shimada A., et al. CHLOROPLAST UNUSUAL POSITIONING 1 is a plant-specific actin polymerization factor regulating chloroplast movement. *Plant Cell* 36: 1159-81, 2023.
2. Hanawa-Suetsugu K., Itoh Y., Ab Fatah M., et al. Phagocytosis is mediated by two-dimensional assemblies of the F-BAR protein GAS7. *Nat. Commun.* 10: 4763, 2019.
3. Shimada A., Yamaguchi A., Kohda D. Structural basis for the recognition of two consecutive mutually interacting DPF motifs by the SGIP1 μ homology domain. *Sci. Rep.* 6: 19565, 2016.

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■研究概要

アデノシン三リン酸の損傷体であるイノシン三リン酸 (ITP) は通常は生体内では特異的分解酵素ITPAにより検出レベル以下に抑制されているが、ITPAの欠損により細胞内へ蓄積すると拡張型心筋症様の心機能異常を伴う発達性およびてんかん性脳症35 (DEE35)を引き起こす。我々は遺伝子改変マウスを用いた研究によりDEE35における心臓の異常の原因はITPによるミオシン機能阻害であり、てんかん発作の原因は膜電位脱分極による神経細胞易興奮性獲得であることを明らかにした。現在は、さらにITPによる膜電位脱分極の分子メカニズムの解明とDEE35治療薬探索を行っている。

■Research Projects

Inosine triphosphate (ITP) is a non-canonical nucleotide formed by oxidative deamination of ATP. ITP is undetectable in normal cells because it is efficiently hydrolyzed by a specific enzyme, ITPA. In human, ITPA-deficiency causes Developmental and Epileptic Encephalopathy 35 (DEE35) with epileptic seizure and cardiac abnormality. Our research with gene modified mice showed that increased ITP causes cardiac abnormality by inhibiting myosin function, and ITPA deficiency results in epileptic seizure through membrane depolarization and increased firing in neurons. Now, we are trying to clarify a molecular mechanism of the depolarization and to develop a screening system for drugs to treat DEE35.

■Major Recent Publications:

1. Schrader C.E., Williams T., Pechhold K., et al. APE2 Promotes AID-Dependent Somatic Hypermutation in Primary B Cell Cultures That Is Suppressed by APE1. *J. Immunol.* 210(11): 1804-14, 2023.
2. Koga Y., Tsuchimoto D., Hayashi Y., et al. Neural stem cell-specific ITPA deficiency causes neural depolarization and epilepsy. *JCI Insight* 5: e140229, 2020.
3. Haruyama N., Sakumi K., Katogi A., et al. 8-Oxoguanine accumulation in aged female brain impairs neurogenesis in the dentate gyrus and major island of Calleja, causing sexually dimorphic phenotypes. *Prog. Neurobiol.* 180: 101613, 2019.