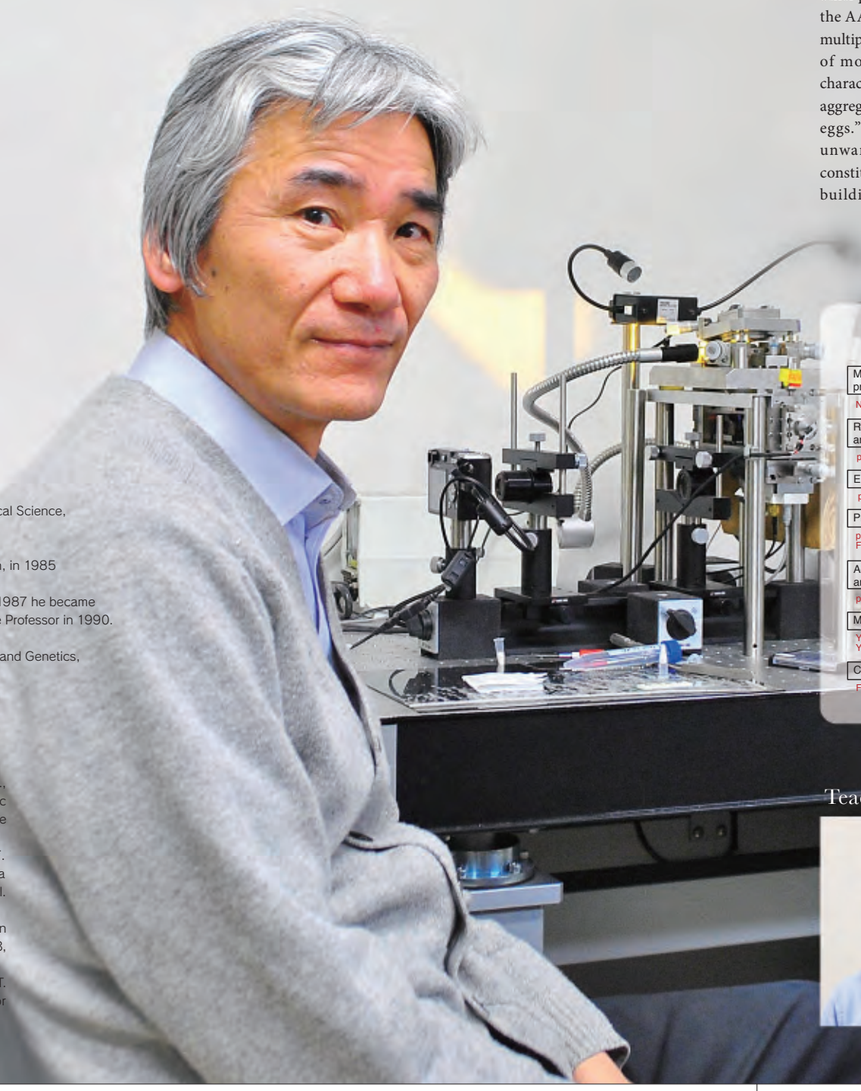
Division of Developmental Regulation
Medical Cell Biology

Molecular chaperones Focusing on the diverse functionality of the AAA family of proteins

Molecular chaperones work to monitor and assist the life of proteins.
In particular, AAA proteins function to disaggregate protein aggregates,
and this family of proteins is the focus of Dr. Teru Ogura's research.
Elucidating the mechanism of AAA proteins will help
our further understanding of neurodegenerative diseases.



Professor
Teru Ogura
ogura@gpo.kumamoto-u.ac.jp

Profile

Obtained a Bachelor' s degree from the Department of Biological Science, Hiroshima University, then went on to receive a Ph.D. from the Graduate School of Science of Kyoto University.
After working as a researcher at the National Institute of Health, in 1985 Dr. Ogura became Assistant Professor at the Institute for Medical Genetics at Kumamoto University Medical School. In 1987 he became Senior Assistant Professor at the same institute, and Associate Professor in 1990.
1990 Research fellow, Edinburgh University, UK
2000 Associate Professor, Institute of Molecular Embryology and Genetics, Kumamoto University
2002 Professor, IMEG.
2008-2009Director, IMEG

References

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AAA proteins mediate protein recycling in cells

Proteins, which are vital to maintaining human life, consist of genetically defined sequences of amino acids that must fold into three-dimensional shapes in order to perform their functions. Professor Ogura says, "According to specific physical and chemical rules, the linear sequence of amino acids determines the 3D structure, which is crucial for proper protein function. However, proteins are very fragile and readily denatured by heat and other physicochemical stresses, which cause them to aggregate with other proteins." Here enters the molecular chaperone, the key subject of Dr. Ogura's research. Molecular chaperones monitor the formation of abnormal or damaged proteins resulting from aberrant cellular responses. They also assist refolding of denatured proteins and disaggregate proteins aggregates formed upon heat shock. "Literally, a chaperone means a caretaker, and molecular chaperones are proteins that take care of other proteins," Dr. Ogura continues. "We focus on the AAA (triple-A) family of proteins, which have multiple functions distinct from those of other types of molecular chaperones. AAA proteins are characterized by their ability to disaggregate protein aggregates, such that they could theoretically unboil eggs." In addition, some AAA proteins degrade unwanted proteins and reduce them into their constituent amino acids, which can then be used as building blocks to make new proteins. In other words, these molecules scavenge and recycle protein waste, serving as effective and efficient housekeepers for the cell.

AAA family proteins are ubiquitous, found in organisms from bacteria to humans. Similar sets of AAA family proteins are present in a wide range of species, from unicellular yeast to multicellular mammals. In order to elucidate the functions of AAA family proteins, Dr. Ogura's laboratory uses C. elegans, one of the simplest multicellular organisms, as well as unicellular yeast as model organisms.

Working towards elucidation and treatment of neurodegenerative disorders

Recent research evidence shows that many neurodegenerative diseases including Alzheimer's and Parkinson's diseases arise from aggregation of abnormal proteins. "These diseases are caused by amyloid fibrils, which are accumulation of misfolded proteins, and molecular chaperones are capable of disassembling them," Dr. Ogura says. "In patients with neurodegenerative disorders, pathogenic proteins tend to form amyloid fibrils and the activities of molecular chaperones are altered. However, no detailed underlying mechanisms have been clarified." Depositions of abnormal proteins are commonly found in Alzheimer's and Parkinson's disease patients. Dr. Ogura emphasizes that research must be pursued from various perspectives, because causative proteins differ by the types of disease.

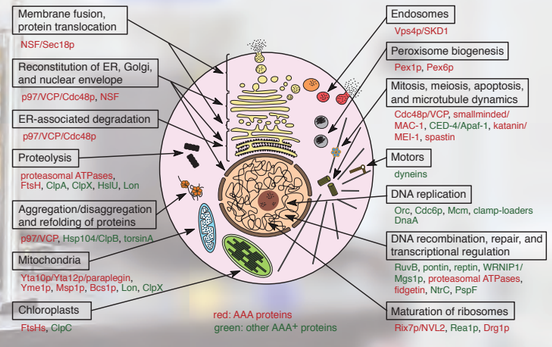
The pathogenesis of amyotrophic lateral sclerosis (ALS) may possibly involve an AAA protein, p97. "In ALS patients, the activity of p97 is altered, although its ATPase activity, which generates the energy for chaperone function, is not reduced. We do not even know yet whether we should activate or suppress this AAA protein to prevent and treat ALS."

Increasing attention is focused on the research on molecular chaperones, which play a key role in the development of neurodegenerative diseases. Dr. Ogura is investigating the mechanisms of molecular chaperones as a basis for understanding pathogenesis.

High-speed atomic force microscopy accelerates analytical research

Recently, Dr. Ogura's laboratory has introduced a state-of-the-art analytical device—high-speed atomic force microscope. "This apparatus can visualize the movements of proteins and other molecules. We are excited that this device has significantly advanced analysis of AAA proteins providing new data that were not available through conventional approaches," said Dr. Ogura, beaming with hopes for the future.

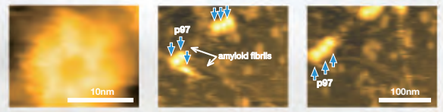
Various cellular functions of AAA proteins



Human diseases caused by mutations of AAA/AAA+ proteins

AAA proteins	
Pex1p, Pex6p	Peroxisome disorders (Zellweger syndrome, neonatal adrenoleukodystrophy, infantile Refsum disease)
Paraplegin	Hereditary spastic paraplegia (AR-HSP)
Spastin	Hereditary spastic paraplegia (AD-HSP)
p97/VCP	Familial inclusion body myopathy with Paget disease of bone and frontotemporal dementia (IBMPFD), Amyotrophic lateral sclerosis (ALS)
BCS1L	Mitochondrial compex III deficiency, GRACILE syndrome, Björnstad syndrome
AFG3L2	Spinocerebellar ataxia type 28 (SCA28), Spastic ataxia neuropathy syndrome
AAA+ proteins	
Torsin A	Early onset torsin dystonia
Axonemal dynein	Primary ciliary dyskinesia (PCD), Kartagener syndrome
Cytoplasmic dynein	Lissencephaly (Miller-Dieker lissencephaly)
Mysterin/RNF213	Moyamoya disease
ORC1, ORC4, CDC6	Meier-Gorlin syndrome

Structure of the AAA protein p97 and its binding to amyloid fibrils revealed by high-speed atomic force microscopy



Teaching Staff

Associate Professor

Kunitoshi Yamanaka

My research is focused on the analysis of the functions performed by AAA family chaperones, as well as the mechanisms by which neurodegenerative diseases can occur as a result of the malfunction of AAA chaperones. My approach to research is that there is always a need to come up with new ideas in order to discover new things, and that determination is key to achieving your research objectives.

Assistant Professor

Masatoshi Esaki

Recently, my interest has been focused on how cellular organelles such as mitochondria are constructed and maintained. I would like to explain the phenomena observe by microscopy in terms of the activity of molecules such as proteins. I am particularly interested in the functions of Cdc48/p97, a cytosolic AAA chaperone.