A Subdomain of the Endoplasmic Reticulum Forms a Cradle for Autophagosome Formation

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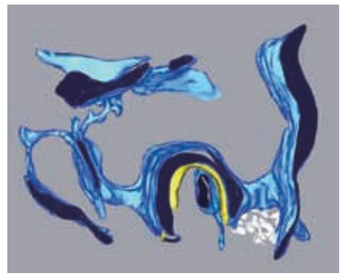
Nature Cell Biology, **11**, 1433-1437 (2009)

Autophagy is a bulk degradation process in eukaryotic cells and plays fundamental roles in cellular homeostasis. Despite much progress in identifying autophagy-related genes, the origin and the source of autophagosomal membranes are long-standing questions in the field. By electron microscopy, we show that the endoplasmic reticulum (ER) associates with early autophagic structures called isolation membranes (IM) in mammalian culture cells. Overexpression of a mutant of Atg4B, which causes defects in autophagosome formation, caused accumulation of ER-IM complexes. Electron tomography revealed the ER-IM complex as a subdomain of the ER cradling the IM, and showed that both ER and isolation membranes are interconnected.



Therapeutic Activation of Signal Transducer and Activator of Transcription 3 by Interleukin-11 Ameliorates Cardiac Fibrosis After Myocardial Infarction

Obana, M.[*1]; Maeda, M.; ***Takeda, K.***[*2]; ***Hayama, A.***[*1]; ***Mohri, T.***[*1]; ***Yamashita, T.***[*1]; ***Nakaoka, Y.***[*2]; ***Komuro, I.***[*2]; ***Takeda, K.***[*2]; ***Matsumiya, G.***[*2]; ***Azuma, J.***[*1]; ***Fujio, Y.***[*1]
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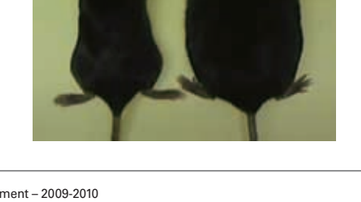
Circulation, **121**, 684-691 (2010)

Cardiac remodeling after myocardial infarction (MI) results in heart failure. Clinically, the prevention of cardiac remodeling improves the survival rate; however, the prognosis of heart failure is not satisfactory. So far, We have demonstrated that STAT3, a signaling molecule downstream of IL-6 family cytokines, plays an important role in cardioprotection. Here, we revealed that administration of IL-11, a member of IL-6 family, ameliorates cardiac fibrosis after MI. (Figure; Blue areas indicate cardiac fibrosis). The cardioprotection by IL-11 was abrogated in cardiomyocyte-specific STAT3 knockout (STAT3CKO) mice. Cardiac activation of STAT3 by IL-11 could be a novel therapeutic strategy against heat failure.



Functionality of the Voltage-gated Proton Channel Truncated in S4

Sakata, S.; ***Kurokawa, T.***; Nørholm, M. H. H.; Takagi, M.; ***Okochi, Y.***; Heijne, G.; ***Okamura, Y.***
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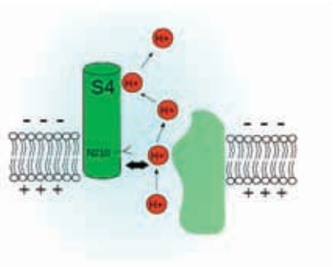
Proceedings of the National Academy of Sciences of the United States of America, **107**, 2313-2318 (2010)

Voltage-gated ion channels are responsible for electric signals in brain and muscle and consist of the two distinct domains: the voltage sensor domain for voltage sensing and the pore domain for ion conduction. The voltage-gated proton channel, VSOP/Hv1, is involved in regulation of membrane potential and pH homeostasis in phagocytes. Unlike conventional voltage-gated ion channels, VSOP/Hv1 does not contain pore domain. To understand operating mechanisms of VSOP/Hv1, a series of deletions were made in the 4th transmembrane segment (S4), which is critical for sensing voltage in conventional voltage-gated channels. VSOP/Hv1 exhibited channel activities even when the half of the S4 is deleted, suggesting different mechanisms from conventional voltage-gated channels.



Diabetes Accelerated Memory Dysfunction via Cerebrovascular Inflammation and Aβ Deposition in an Alzheimer Mouse Model with Diabetes.

Takeda, S.; ***Sato, N.***; Uchio-Yamada K.; Sawada, K; Kunieda, T.; ***Takeuchi, D.***; ***Kurinami, H.***; ***Shinohara, M.***; ***Rakugi, H. and Morishita, R.***
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Proceedings of the National Academy of Sciences of the United States of America, **107**, 7036-7041 (2010)

Diabetes mellitus (DM) is one of the major non-genetic risk factors for Alzheimer disease (AD). However, the mechanism by which DM increases the risk of AD has not been elucidated. In this study, we generated animal models that reflect the pathologic conditions of both diseases. This study showed that a vicious cycle underlies the interaction between AD and DM. The onset of diabetes exacerbated cognitive dysfunction in ADxDM mice. Notably, these mice showed cerebrovascular inflammation and severe amyloid angiopathy. Conversely, the cross-bred mice showed an accelerated diabetic phenotype compared with DM mice, suggesting that AD amyloid pathology could aggravate diabetes.

High cGMP synthetic activity in carp cones.

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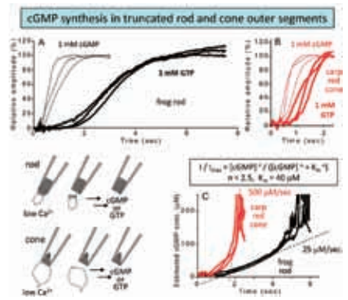
Proceeding of the National Academy of Sciences of the United States of America, **106**, 11788-11793 (2009)

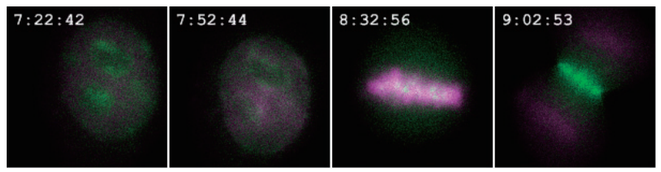
Our visual system consists of two components, rods functioning in twilight and cones functioning in daylight. Cones show briefer light responses than rods, which ensures higher time resolution of our daylight vision. The briefer response in cones is partly because of rapid recovery of a response attained by the synthesis of cGMP. Using purified rod and cone homogenates, we measured the activity of guanylate cyclase (GC), an enzyme responsible for cGMP synthesis. Our results showed both biochemically and electrophysiologically that the GC activity is >10 times higher in cones than in rods. This estimation of the GC activity reasonably explained the rapid recovery of a light response in cones.



Visualizing Histone Modifications in Living Cells: Spatiotemporal Dynamics of H3 Phosphorylation during Interphase

Hayashi-Takanaka, Y.; Yamagata, K.; Nozaki, N.; ***Kimura, H.***
(Graduate School of Frontier Biosciences)

The Journal of Cell Biology, **187**, 781-790 (2009)



We developed a powerful and straightforward method for visualizing the endogenous proteins and their modifications in living cultured cells and mouse preimplantation embryos, by loading fluorescently labeled specific Fab antibody fragments. Live cell imaging of histone H3 phosphorylation led to a discovery of differential regulation of phospho-dephospho cycle in normal and cancerous cells. The technology developed here is applicable to any post-translational modifications when specific antibodies are available, and will prove useful in understanding the roles of histone modifications in regulating the life of the cell.

A Single Polymorphic Amino Acid on Toxoplasma gondii Kinase ROP16 Determines the Direct and Strain-Specific Activation of Stat3.

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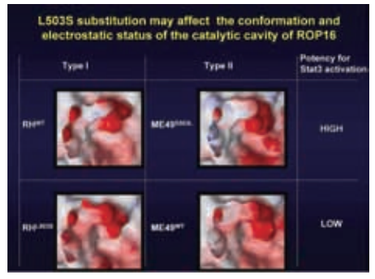
[*1] (Graduate School of Medicine)
[*2](Immunology Frontier Research Center)

The Journal of Experimental Medicine, **206**, 2747-2760 (2009)



Infection by Toxoplasma gondii down-regulates the host innate immune responses, such as proinflammatory cytokine production, in a Stat3-dependent manner. A forward genetic approach recently demonstrated that the type II strain fails to suppress immune responses because of a potential defect in a highly polymorphic parasite-derived kinase, ROP16.
Here we generated ROP16-deficient parasites by reverse genetics and found essential and direct requirement of ROP16 in parasite-induced Stat3 activation and the significance of a single amino acid replacement in the function of type II ROP16.

The 28-Amino Acid Form of an APLP1-Derived Aβ-Like Peptide Is a Surrogate Marker for Aβ42 Production in the Central Nervous System

Yanagida, K.; ***Okochi, M (C.A.).***; ***Tagami, S.***; ***Nakayama, T.***; ***Kodama, TS.***; ***Nishitomi K.***; ***Jiang J.***; ***Mori K.***; ***Tatsumi, S.***; Arai, T.; Ikeuchi, T.; Kasuga, K.; Tokuda, T.; Kondo, M.; Ikeda, M.; Deguchi, K.; ***Kazui, K.***; ***Tanaka, T.***; ***Morihara, T.***; ***Hashimoto, R.***; ***Kudo, T.***; Steiner, H.; Haass, C.; Tsuchiya, K.; Akiyama, H.; Kuwano, R.; ***Takeda, M.***
(Graduate School of Medicine)

EMBO Molecular Medicine, **1**, 223-235 (2009)

We discovered that human CSF, indeed, contains "Aβ-like peptides" which we formerly hypothesized. The brain APLP1-derived APL1β25,27 and 28 are generated by β- and γ-cleavages. In contrast to Aβ, the APL1β are not amyloidogenic and do not accumulate in the Alzheimer brains. Up-regulation of the relative Aβ42 production causes a parallel increase in the production of APL1β28 *in vitro* and *in vivo*. Importantly, the relative APL1β28 levels are higher in CSF from sporadic Alzheimer patients than in CSF from controls. Thus, (i) the novel APL1β28 peptide is a long-sought surrogate marker for Alzheimer Aβ42 and (ii) the relative APL1β28 level in CSF is a prodromal marker for Alzheimer's.