BIOGRAPHICAL SKETCH

NAME: Yasushi Okamura

POSITION TITLE: Professor, Department of Physiology, Osaka University, Japan

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
University of Tokyo, Tokyo, Japan	B.S.	04/1979	03/1985	Medicine
University of Tokyo, Tokyo, Japan	Ph.D.	04/1985	03/1989	Neurobiology
University of Tokyo, Tokyo, Japan	Post-doc	04/1989	03/1990	Neurobiology
State University of New York at Stony Brook, Stony Brook, NY	Post-doc	03/1990	07/1991	Neurobiology

A. Personal Statement

Research in my lab concerns the molecular mechanisms and physiological roles of voltage-sensing proteins, including voltage-sensing phosphatase and voltage-gated ion channels. Our work has focused mainly on how enzyme activity (VSP) and proton permeation (Hv1/VSOP) are regulated by voltage sensor and on novel roles of electrochemical signals mediated by these membrane proteins. We have also been investigating regulation of axonal distribution of ion channels in neurons.

B. Positions, Scientific Appointments and Honors

Positions

2007 – Present Professor, Department of Physiology, Graduate School of Medicine, Osaka University, Suita, Japan
2001–2008 Professor, Okazaki Institute for Integrative Bioscience, National Institute of Natural Science, Okazaki, Japan
2000 Visiting scientist in Bioengineering Department, Case Western Reserve University
1995 – 2001 Senior researcher, National Institute of Bioscience and Human-technology, Agency of Industrial Sciences and Technology, Tsukuba, Japan
1990 – 1995 Lecturer, University of Tokyo, Tokyo, Japan

Scientific Appointments

2007 – Present Editorial Board, Journal of Physiological Sciences
2010 – 2015, 2017 – 2020 Editorial Board, The Journal of Physiology
2015 Guest Editor, Frontiers in Pharmacology of Ion Channels and Channelopathies
2015 – Present Editorial Board, The Journal of General Physiology
2015 Chair, 95th annual meeting of the Physiological Society of Japan
2008 – Present Committee member, Japan-US Brain Research Cooperative Program (NIH-JSPS)
2006 – 2008, 2018 – 2023 Associate member of Science Council of Japan (SCJ)
2023-2029 Member of Science Council of Japan (SCJ)
2020 – Present Program Officer, Research Center for Science System, Japan Society for the Promotion of Science (JSPS)

2022 – Present Council member, International Union of Physiological Sciences (IUPS)

Honors

1994−1997	Human Frontier Science Program Award
2007−2010	Human Frontier Science Program Award
2014	President's honors of Osaka University
2018	Commendation for review for Research fellowship for young scientists (JSPS)

C. Contributions to Science

1. **Biodiversity and biophysical principle of voltage sensor domain.** Voltage sensor domain has long been thought as a domain unique to voltage-gated ion channels which have the pore gate domain. I found two unique membrane proteins that have voltage sensor domain but lack pore gate domain. Voltage-sensing phosphatase, VSP, has PTEN-like phosphoinositide phosphatase domain instead of pore gate domain. This provided the first example where voltage sensor domain regulates function other than ion permeation (Murata, Y., et al, 2005). Using state-of-the art techniques of electrophysiology, fluorometry with fluorescent unnatural amino acid (Sakata, S., et al, 2016) and structural biology, we revealed basic molecular mechanisms of coupling between the voltage sensor domain and cytoplasmic enzyme region of VSP. We also identified Hv1/VSOP, voltage-gated proton channel, which contains the voltage sensor domain but lacks pore gate domain. In Hv1, voltage sensor domain plays dual role of voltage sensing and proton permeation (Sasaki, M. et al., 2006). We revealed dimer stoichiometry, membrane topology and 3D atomic structure of Hv1. Our recent findings of X-ray crystal structure (Fujiwara, Y., et al, 2012; Takeshita, K. et al, 2014), together with its compact size (polypeptide length in about 230 amino acids), have provided basis for atomic level in silico studies on proton permeation and gating to mathematics researchers. These two proteins have provided novel opportunities for understanding basic principles of voltage sensor domain and ion permeation, which have been the central questions in ion channel research.

   a. Murata, Y., Iwasaki, H.,Sasaki, M., Inaba, K. and ***Okamura, Y.** (2005). Phosphoinositide phosphatase activity coupled to an intrinsic voltage sensor. Nature, 435:1239-1243.
   b. Sasaki, M., Takagi, M. and ***Okamura, Y.** A voltage sensor-domain protein is a voltage-gated proton channel, Science, 312(5773), 589-92.
   c. *Fujiwara, Y., Kurokawa, T., Takeshita, K., Kobayashi, M., Okochi, Y., Nakagawa, A. and ***Okamura, Y.** (2012). The cytoplasmic coiled-coil mediates cooperative gating temperature sensitivity in the voltage-gated H+ channel Hv1. Nat. Communi, 3:816
   d. Takeshita, K., Sakata, S., Yamashita, E., Fujiwara, Y., Kawanabe, A., Kurokawa, T., Okochi, Y., Matsuda, M., Narita, H. ***Okamura, Y.** and *Nakagawa A (2014). X-ray crystal structure of voltage-gated proton channel. Nat. Struct. & Mol. Biol. (4):352-7.
   e. *Sakata, S., Jinno, Y., Kawanabe, A. and ***Okamura, Y.** (2016). Voltage-dependent motion of the catalytic region of voltage-sensing phosphatase monitored by a fluorescent amino acid. Proc. Natl. Acad. Sci. U. S. A. 113(27):7521-7526.
   f. Mizutani, N., Kawanabe, A., Jinno, Y., Narita, H., Yonezawa, T., Nakagawa, A. and ***Okamura, Y.** (2022). Interaction between S4 and the phosphatase domain mediates electrochemical coupling in voltage-sensing phosphatase, VSP**.** Proc. Natl. Acad. Sci. U. S. A. 119(26):e2200364119.

2. **Roles of voltage-gated proton channel, Hv1/VSOP, in immune cells.** Over the past 30 years since the first description of outward currents from invertebrate neurons, molecular identity of voltage-gated proton channel has been unclear. Voltage-gated proton channel had been studied in granulocytes as the important pathway for charge compensation during respiratory burst of granulocytes. Identification of the gene encoding voltage-gated proton channel (the same gene was identified by David Clapham's group) has enabled to study biological functions of voltage-gated proton channels at the whole animal level. We showed that phagosomes of neutrophils contain Hv1 protein (Okochi, Y. et al., 2009) and respiratory burst was abnormal in neutrophils from mouse lacking Hv1 (El Chemaly, A., et al., 2010). Hv1 was shown by

other groups to be expressed in nonimmune cells including human sperm, human airway epithelium, human oocytes and human cancer cells. We showed HV1 knockout mice exhibit hyperinflammation through Hv1's defect in T-lymphocytes and neutrophils, and abnormal glucose metabolism through Hv1's defect in Kupffer cell in liver. We also showed that microglia in different regions of mouse brain express different level of Hv1 and knockout mice show milder ageing-related behavior phenotypes than the wild-type animal accompanied by altering gene expression patterns of neurotransmitter receptors (Kawai et al, 2021).

a. Okochi, Y., Sasaki, M., Iwasaki, H. and ***Okamura, Y.** (2009), Voltage-gated proton channel is expressed on phagosomes Biochem. Biophys. Res. Commun. 382(2):274-9.
b. El Chemaly, A., Okochi, Y., Sasaki, M., Arnaudeau, S., **Okamura, Y.** and *Demaurex, N. (2010), VSOP/Hv1 proton channels sustain calcium entry, neutrophil migration, and superoxide production by limiting cell depolarization and acidification J. Exp. Med. 207(1):129-39.
c. *Kawai, T., Takao, K.. Akter, S., Abe, M., Sakimura, K., Miyakawa, T. and ***Okamura, Y.** (2021) Heterogeneity of microglial proton channel in different brain regions and its relationship with aging. J Neurochem. 157(3):624-641.DOI: 10.1111/jnc.15292.

3. **Biological roles of voltage-sensing phosphatase, VSP, in sperm and epithelium.** VSP expression is commonly found in testis from marine invertebrate to human. We found that knockout mice of VSP exhibits defect of *in vitro* fertilization and abnormal motility pattern of matured sperm. This was accompanied by upregulation of $PI(4,5)P_2$ sensitive sperm specific K+ channel, Slo3. Electron microscopic analysis showed biased distribution of $PI(4,5)P_2$ with head-high and tail-low pattern dependent on the 5-phosphatase activity of VSP. Loss of VSP leads to excess $PI(4,5)P_2$ in the tail membrane activating more number of Slo3 channels in sperm tail (Kawai, T. et al, 2019). This is the first discovery of biological role of $PI(4,5)P_2$ in mature mammalian sperm as well as the first identification of in vivo function of VSP. Recently, it was shown that VSP plays role in endocytosis in a class of specialized epithelial cell, called lysosome-rich enterocyte, of zebrafish, and larvae of zebrafish with defect of VSP gene exhibits higher lethality during development with defect of endocytosis of nutrients (Ratanayotha, A. et al, 2022).

a. Kawai, T., Miyata, H., Nakanishi, H., Sakata, S., Morioka, S., Sasaki, J., Watanabe, M., Sakimura, K., Fujimoto, T., Sasaki, T., Ikawa, M. and ***Okamura, Y.** (2019) Polarized PtdIns(4,5)P2 distribution mediated by a voltage-sensing phosphatase (VSP) regulates sperm motility. Proc. Natl. Acad. Sci. U. S. A.116(51), 26020-26028
b. Ratanayotha, A., Matsuda, M., Kimura, Y., Takenaga, F., Mizuno, T., Md. Israil Hossain, Higashijima, S., *Kawai, T., Ogasawara, M. and ***Okamura, Y.** (2022) Voltage-Sensing Phosphatase (VSP) Regulates Endocytosis-Dependent Nutrient Absorption in Chordate Enterocytes. Communi. Biol. 2022 Sep 10;5(1):948. doi: 10.1038/s42003-022-03916-6.
c. *Kawai T, Morioka S, Miyata H, Andriani RT, Akter S, Toma G, Nakagawa T, Oyama Y, Iida-Norita R, Sasaki J, Watanabe M, Sakimura K, Ikawa M, Sasaki T, **Okamura Y**.(2024) Nat Commun. 15(1):7289. doi: 10.1038/s41467-024-51755-2.PMID: 39181879

4. **Development of molecular tools based on VSP for neuroscience and cell biology.** Based on transportability and self-contained nature of the voltage sensor domain of VSP, we have developed protein-based voltage indicator which can visualize individual spikes in mammalian neurons (Tsutsui, H. et al, 2008; 2013). Currently, about half of recent studies of optical measurement of neuronal networks in cultured neuron or *in vivo* brain have utilized genetically-encoded voltage indicators (GEVIs) which were designed from the voltage sensor domain of VSP. Voltage-sensing phosphatase also provides important material to transiently alter plasma membrane phosphoinositides. VSP has advantages of irreversibility and rapid speed of manipulation of $PI(4,5)P_2$ of plasma membranes over other tools. We engineered VSP to better optimized tool based on biophysical mechanisms of domain-to-domain coupling of Ci-VSP (Kawanabe, A. et al., 2020). So far more than 50 types of membrane proteins (mostly ion channels plus several transporters) have been studied for their phosphoinositide dependence (Mizutani, N. et al, 2019) using VSP or modified VSPs in heterologous expression cell system, cell lines and primary cultured cells (Okamura, Y. et al,

2018). These tools are deposited in Addgene and more than 65 requests of sending plasmids have been made.

a. Tsutsui, H., Karasawa, S., **Okamura, Y.** and *Miyawaki, A. (2008). Improving membrane voltage measurements using FRET with new fluorescent proteins. Nature Methods, 8,683-5.
b. *Tsutsui, H., Jinno, Y., Tomita, A., Niino, Y., Yamada, Y., Mikoshiba, K., Miyawaki, A. and **Okamura, Y.** (2013) Improved detection of electrical activity with a voltage probe based on a voltage-sensing phosphatase. J. Physiol. 591(18):4427-37.
c. ***Okamura, Y.**,Kawanabe, A. and Kawai, T. (2018) Voltage-Sensing Phosphatases: Biophysics, Physiology and Engineering. Physiol. Rev. 8(4), 2097-2131.
d. Kawanabe, A., Mizutani, N., Polat Onur, K., Yonezawa, T., Kawai, T., Mori, M.X. and ***Okamura, Y.** (2020) Engineering an enhanced voltage-sensing phosphatase. J Gen Physiol.152(5):e201912491.

5. **Phylogenetic approach to vertebrate-specific neuronal traits of membrane excitability.** CNS of vertebrates show highly populated neurons with rapid conduction. This depends on myelination with clustered localization of voltage-gated ion channels in two specific membrane domains of neurons, axon initial segments and node of Ranvier. Clustering of several membrane proteins, mainly voltage-gated sodium channels and voltage-gated K^+ channels are regulated by their binding to adaptor protein, ankyrinG. We showed that in lamprey, the most primitive vertebrate that lacks myelin, CNS neurons show clustered Nav channels as found in the axon initial segments of mammalian neurons (Hill, A.S. et al, 2008). Further, ascidian, which belongs to the protochordate, has an ancestral Nav gene (Okamura, Y.. et al, 1994) closely related to a clade of ten vertebrate Nav alpha subunit genes. This ascidian Nav has conserved ankyrin binding motif which has an ability of targeting to axon initial segments of mammalian neurons despite the absence of myelin in ascidians(Kawai, T. et al, 2021). Therefore traits for rapid conduction in vertebrate axons were acquired through multiple steps during chordate evolution.

a. ***Okamura, Y.** and Tsukita, S. (1986) Morphology of freeze-substituted myelinated axon in mouse peripheral nerves. Brain Res. 383(1-2):146-58.
b. ***Okamura, Y.**, Ono, F., Okagaki, R., Chong, A. and Mandel G. Neural expression of a sodium channel gene requires cell specific interaction. Neuron, 13: 937-948.(1994).
c. Shirahata, E., Iwasaki, H., Takagi, M., Lin, C., Bennett, V.,***Okamura, Y.** and Hayasaka K (2006) Ankyrin-G regulates inactivation gating of the neuronal sodium channel, Nav1.6. J. Neurophysiol. 96(3):1347-57.
d. Hill, A.S., Nishino, A., Nakajo, K., Zhang G, Fineman JR, Selzer ME, **Okamura, Y.** and *Cooper. E.C. (2008), Ion channel clustering at the axon initial segment and node of Ranvier evolved sequentially in early chordates. PLoS Genetics, (12):e1000317.
e. Kawai, T., Hashimoto, M., Eguchi, N., Nishino, J..M, Jinno, Y., Mori-Kreiner, R., Aspaker, M., Chiba, D., Ohtsuka, Y., Kawanabe, A., Nishino, A.S. and ***Okamura, Y.** (2021) Heterologous functional expression of ascidian Nav1 channels and close relationship with the evolutionary ancestor of vertebrate Nav channels. J. Biol. Chem. 296:100783.

Bibliography (main 50 papers):

Original Papers

1. * **Okamura, Y.** and Tsukita, S. (1986) Morphology of freeze-substituted myelinated axon in mouse peripheral nerves. Brain Res. 383(1-2):146-58.
2. * **Okamura, Y.** and Shidara, M. (1987) Kinetic differences between Na channels in the egg and in the neurally differentiated blastomere in the tunicate. Proc Natl Acad Sci U S A. Dec;84(23):8702-6.
3. * **Okamura, Y.** and Shidara, M. (1990) Changes in sodium channels during neural differentiation in the isolated blastomeres of the ascidian embryo. J. Physiol., 431:39-74.
4. * **Okamura, Y.**, Ono, F., Okagaki, R., Chong, A. and Mandel, G. (1994) Neural expression of a sodium channel gene requires cell specific interaction. Neuron, 13: 937-948.

5. Ono, F., Katsuyama, Y., Nakajo, K. and ***Okamura, Y.** (1999) Subfamily-specific posttranscriptional regulation underlies K^+ channel expression in a developing neuronal blastomere. J. Neurosci., 19(16): 6874-6886
6. Miyamoto T, Morita K, Takemoto D, Takeuchi K, Kitano Y, Miyakawa T, Nakayama K, **Okamura, Y.**, Sasaki H, Miyachi Y, Furuse M and *Tsukita, S. (2005) Tight junctions in Schwann cells of peripheral myelinated axons: a lesson from claudin-19-deficient mice. J. Cell Biol., 169(3):527-38.
7. Murata, Y., Iwasaki, H., Sasaki, M., Inaba, K. and ***Okamura, Y.** (2005) Phosphoinositide phosphatase activity coupled to an intrinsic voltage sensor. Nature, 435:1239-1243.
8. Sasaki M, Takagi M and ***Okamura, Y.** (2006) A voltage sensor-domain protein is a voltage-gated proton channel, Science, 312(5773), 589-92.
9. Shirahata E, Iwasaki H, Takagi M, Lin C, Bennett V, ***Okamura, Y.** and Hayasaka, K. (2006) Ankyrin-G regulates inactivation gating of the neuronal sodium channel, Nav1.6. J. Neurophysiol. 96(3):1347-57.
10. Hill, A.S., Nishino, A., Nakajo, K., Zhang, G., Fineman, J.R., Selzer, M.E., **Okamura, Y.** and *Cooper, E.C. (2008). Ion channel clustering at the axon initial segment and node of Ranvier evolved sequentially in early chordates. PLoS Genetics, (12):e1000317.
11. Koch HP, Kurokawa T, Okochi Y, Sasaki M, ***Okamura, Y.** and *Larsson HP (2008). Multimeric nature of voltage-gated proton channels. Proc. Natl. Acad. Sci. U.S.A., 105(26):9111-6.
12. Iwasaki H, Murata Y, Kim Y, Hossain MI, Worby, CA, Dixon, JE, McCormack, T, Sasaki, T and ***Okamura, Y.** (2008). A voltage-sensing phosphatase, Ci-VSP, which shares sequence identity with PTEN, dephosphorylates phosphatidylinositol 4,5-bisphosphate. Proc Natl Acad Sci U S A 105, 7970-7975.
13. Tsutsui, H., Karasawa, S., **Okamura, Y** and *Miyawaki A (2008). Improving membrane voltage measurements using FRET with new fluorescent proteins. Nature Methods, 8,683-5.
14. Murata Y, ***Okamura, Y**. (2007) Depolarization activates the phosphoinositide phosphatase Ci-VSP, as detected in Xenopus oocytes coexpressing sensors of PIP2. J. Physiol. , 583:875-889.
15. Okochi Y, Sasaki M, Iwasaki H and * **Okamura, Y.** (2009). Voltage-gated proton channel is expressed on phagosomes. Biochem. Biophys. Res. Commun. 382(2):274-9.
16. El Chemaly A, Okochi Y, Sasaki M, Arnaudeau S, **Okamura, Y.** and *Demaurex N (2010). VSOP/Hv1 proton channels sustain calcium entry, neutrophil migration, and superoxide production by limiting cell depolarization and acidification. J. Exp. Med. 207(1):129-39.
17. Sakata, S., Kurokawa, T., Norholm, M.H., Takagi, M., Okochi, Y., von Heijne, G. and ***Okamura, Y.** (2010). Functionality of the voltage-gated proton channel truncated in S4. Proc. Natl. Acad. Sci. U. S. A. 107(5):2313-8.
18. Ratzan, W.J., Evsikov, A.V., **Okamura, Y.**, *Jaffe, L.A. (2011). Voltage sensitive phosphoinositide phosphatases of Xenopus: their tissue distribution and voltage dependence. J Cell Physiol. 226(11):2740-6.
19. Matsuda M, Takeshita K, Kurokawa T, Sakata S, Suzuki M, Yamashita E, ***Okamura, Y.**, *Nakagawa A (2011). Crystal structure of the cytoplasmic PTEN-like region of Ci-VSP provides insight into substrate specificity and redox regulation of the phosphoinositide phosphatase activity. J. Biol. Chem., 286(26):23368-77.
20. *Nishino A, Baba SA, * **Okamura, Y.** (2011). A mechanism for graded motor control encoded in the channel properties of the muscle ACh receptor. Proc. Natl. Acad. Sci. U. S. A., 108(6): 2599-2604.
21. Kurokawa T, Takasuga S, Sakata S, Yamaguchi S, Horie S, Homma KJ, Sasaki T, ***Okamura, Y.** (2012). 3' phosphatase activity toward PI(3,4)P2 by voltage-sensing phosphatase, VSP. Proc. Natl. Acad. Sci. U. S. A., 109(25):10089-94.
22. *Fujiwara Y, Kurokawa T, Takeshita K, Kobayashi M, Okochi Y, Nakagawa A, ***Okamura, Y.** (2012). The cytoplasmic coiled-coil mediates cooperative gating temperature sensitivity in the voltage-gated H+ channel Hv1., Nat. Communi., 3:816. doi: 10.1038/ncomms1823.
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28. Kawanabe A and ***Okamura, Y.** (2016) Effects of unsaturated fatty acids on the kinetics of voltage-gated proton channels heterologously expressed in cultured cells. J. Physiol. 594(3)595-610 doi:10.1113/JP271274
29. *Okochi Y, Aratani Y, Adissu HA, Miyawaki N, Sasaki M, Suzuki K and ***Okamura, Y.** (2016) The voltage-gated proton channel Hv1/VSOP inhibits neutrophil granule release. J. Leukoc. Biol. 99(1)7-19. doi:10.1189/jlb.3HI0814-393R.
30. Inagaki S, Tsutsui H, Suzuki K, Agetsuma M, Arai Y, Jinno Y, Bai G, Daniels M, **Okamura, Y.**, Matsuda M. and *Nagai T (2017) Genetically encoded bioluminescent voltage indicator for multi-purpose use in wide range of bioimaging. Sci. Rep. 7:42398.
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32. Kawai T, Okochi Y, Ozaki T, Imura Y, Koizumi S, Yamazaki M, Abe M, Sakimura K, Yamashita T and ***Okamura, Y.** (2017) Unconventional role of voltage-gated proton channels (VSOP/Hv1) in regulation of microglial ROS production. J. Neurochem. 142(5), 686-699.
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34. Mizutani N, Okochi Y and ***Okamura, Y**. (2019) Distinct functional properties of two electrogenic isoforms of the SLC34 Na-Pi cotransporter. Physiol. Rep. 7(14), e14156.
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Reviews

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Book Chapters
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