

BIOGRAPHICAL SKETCH

NAME: Yoshifumi Okochi

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

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
Hokkaido University, Sapporo, Japan	B.S.	04/1992	03/1998	Agriculture (Milk)
Nagoya University, Nagoya, Japan	M.S.	04/1998	03/2000	Molecular Biology (<i>C.elegans</i>)
Nagoya University, Nagoya, Japan	Ph.D.	04/2000	11/2005	Molecular Biology (<i>C.elegans</i>)
National Institute for Physiological Sciences & Integrative Bioscience Center, Okazaki, Japan	Post-doc	12/2005	03/2008	Ion channel
Osaka University, Suita, Japan	Post-doc	04/2008	07/2008	Ion channel

A. Personal Statement

My research interest is how ion channels (e.g. Hv1/VSOP) regulate cellular functions.

B. Positions

Positions

2020 – Present Associate Professor, Department of Physiology, Graduate School of Medicine, Osaka University, Suita, Japan

2012 - 2013 Research fellow in Sergio Grinstein Lab, Department of Biochemistry, University of Toronto and Cell Biology Program Hospital for Sick Children in Toronto

2008 – 2020 Assistant Professor, Department of Physiology, Graduate School of Medicine, Osaka University, Suita, Japan

C. Contributions to Science

1. **Voltage-gated proton channel, Hv1/VSOP, in neutrophils.** Voltage-gated proton channels Hv1/VSOP were discovered in Okamura lab. We demonstrated that Hv1/VSOP helps ROS production mediated by NADPH oxidase using Hv1/VSOP-KO mice (Okochi et al., BBRC 2009). We also found two novel functions of Hv1/VSOP in addition to ROS regulation; One is the inhibition of granule secretion by Hv1/VSOP in neutrophils, which leads to less HOCl production (Okochi et al., JLB 2016). We also found that Hv1/VSOP-KO mice challenged by fungi exhibit severe inflammation in the lung (Okochi et al., JLB 2016), which is probably mediated by excess granule secretion. These findings were introduced in the Editorial of JLB (Robert A. Clark. Proton pathway paradox: Hv1 H⁺ channel sustains neutrophil Nox2 activity, yet suppresses HOCl formation. JLB 2016 99:1-4). The second is the inhibition of chemotaxis by Hv1/VSOP in neutrophils. We found that Hv1/VSOP inhibits the migration to lower concentrations of fMLF through the regulation of ERK activity (Okochi et al., JLB 2020). While Hv1/VSOP maintains ROS production to eliminate pathogens in neutrophils, the channel plays a role in avoiding excess inflammation through the inhibition of granule secretion and chemotaxis in neutrophils.

1. **Okochi Y**, Sasaki M, Iwasaki H, Okamura Y (2009) Voltage-gated proton channel is expressed on phagosomes. *Biochem. Biophys. Res. Commun.* 382(2):274-9.
 2. **Okochi Y***, Aratani Y, Adissu HA, Miyawaki N, Sasaki M, Suzuki K, Okamura Y* (2016) The voltage-gated proton channel Hv1/VSOP inhibits neutrophil granule release. *Journal of Leukocyte Biology.* 99(1):7-19.
 3. **Okochi Y***, Umemoto E, Okamura Y* (2020) Hv1/VSOP regulates neutrophil directional migration and ERK activity by tuning ROS production. *Journal of Leukocyte Biology.* 107(5):819-831.
2. **Significance of Hv1/VSOP dimerization in ER.** Hv1/VSOP forms dimer, which is necessary for cooperative gating and steeper voltage dependency. We found another role of dimerization of Hv1/VSOP; dimerization of Hv1/VSOP takes place in the ER, which leads to the retention of the protein in the ER (Okochi et al., *Biophys J* 2024).
1. **Okochi Y***, Jinno Y, Okamura Y*. Dimerization is required for the glycosylation of S1-S2 linker of sea urchin voltage-gated proton channel Hv1. *Biophys. J.* 2024 Jul 31:S0006-3495(24)00493-4. doi: 10.1016/j.bpj.2024.07.034.
3. **Establishment of phagosomal membrane potential imaging in phagocytes.** To understand the role of membrane potential in the endomembrane, we are trying to measure the membrane potential on phagosomes using a fluorescent voltage probe. (no references).
4. **Molecular mechanisms of thermotaxis in *C. elegans* (doctoral thesis).** To understand the mechanisms of thermotaxis behavior in *C. elegans*, we screened thermotaxis-defective mutants by the EMS method and obtained many mutants. We found that nPKC-epsilon/eta TTX-4 regulates sensory signals, thermosensation, olfaction, and osmosensation in *C. elegans* (Okochi et al., *EMBO J* 2005).
1. **Okochi Y**, Kimura KD, Ohta A, Mori I (2005) Diverse Regulation Of Sensory Signaling By *C. elegans* nPKC-epsilon/eta TTX-4 *EMBO J* 24(12) 2127-2137.

Bibliography:

Original Papers

2. **Okochi Y**, Kimura KD, Ohta A, Mori I. (2005) Diverse regulation of sensory signaling by *C. elegans* nPKC-epsilon/eta TTX-4. *EMBO J.* 24:2127-37. doi: 10.1038/sj.emboj.7600697.
3. Hossain MI, Iwasaki H, **Okochi Y**, Chahine M, Higashijima S, Nagayama K, Okamura Y. (2008) Enzyme domain affects the movement of the voltage sensor in ascidian and zebrafish voltage-sensing phosphatases. *J Biol Chem* 283:18248-59. doi: 10.1074/jbc.M706184200.
4. Koch HP, Kurokawa T, **Okochi Y**, Sasaki M, Okamura Y, Larsson HP. (2009) Multimeric nature of voltage-gated proton channels. *Proc Natl Acad Sci U S A.* 105:9111-6. doi: 10.1073/pnas.0801553105.
5. **Okochi Y**, Sasaki M, Iwasaki H, Okamura Y. (2009) Voltage-gated proton channel is expressed on phagosomes. *Biochem Biophys Res Commun.* 82:274-9. doi: 10.1016/j.bbrc.2009.03.036.
6. Sakata S, Kurokawa T, Nørholm MH, Takagi M, **Okochi Y**, von Heijne G, Okamura Y. (2010) Functionality of the voltage-gated proton channel truncated in S4. *Proc Natl Acad Sci U S A.* 107:2313-8. doi: 10.1073/pnas.0911868107.
7. El Chemaly A, **Okochi Y**, Sasaki M, Arnaudeau S, Okamura Y, Demaurex N. (2010) VSOP/Hv1 proton channels sustain calcium entry, neutrophil migration, and superoxide production by limiting cell depolarization and acidification. *J Exp Med.* 207:129-39. doi: 10.1084/jem.20091837.
8. Adachi T, Kunitomo H, Tomioka M, Ohno H, **Okochi Y**, Mori I, Iino Y. (2010) Reversal of salt preference is directed by the insulin/PI3K and Gq/PKC signaling in *Caenorhabditis elegans*. *Genetics.* 186:1309-19. doi: 10.1534/genetics.110.119768.
9. Ohnishi N, Kuhara A, Nakamura F, **Okochi Y**, Mori I. (2011) Bidirectional regulation of thermotaxis by glutamate transmissions in *Caenorhabditis elegans*. *EMBO J.* 30:1376-88. doi: 10.1038/emboj.2011.13.
10. Miyara A, Ohta A, **Okochi Y**, Tsukada Y, Kuhara A, Mori I. (2011) Novel and conserved protein macoilin is required for diverse neuronal functions in *Caenorhabditis elegans*. *PLoS Genet.* 5:e1001384. doi:

- 10.1371/journal.pgen.1001384.
11. 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 Commun.** 3:816. doi: 10.1038/ncomms1823.
 12. Sasaki M, Tojo A, **Okochi Y**, Miyawaki N, Kamimura D, Yamaguchi A, Murakami M, Okamura Y. (2013) Autoimmune disorder phenotypes in Hvcn1-deficient mice. **Biochem J.** 450:295-301. doi: 10.1042/BJ20121188.
 13. Takeshita K, Sakata S, Yamashita E, Fujiwara Y, Kawanabe A, Kurokawa T, **Okochi Y**, Matsuda M, Narita H, Okamura Y, Nakagawa A. (2014) X-ray crystal structure of voltage-gated proton channel. **Nat Struct Mol Biol.** 21:352-7. doi: 10.1038/nsmb.2783.
 14. Mutua J, Jinno Y, Sakata S, **Okochi Y**, Ueno S, Tsutsui H, Kawai T, Iwao Y, Okamura Y. (2014) Functional diversity of voltage-sensing phosphatases in two urodele amphibians. **Physiol Rep.** 2:e12061. doi: 10.14814/phy2.12061.
 15. **Okochi Y***, Aratani Y, Adissu HA, Miyawaki N, Sasaki M, Suzuki K, Okamura Y*. (2016) The voltage-gated proton channel Hv1/VSOP inhibits neutrophil granule release. **J Leukoc Biol.** 99:7-19. doi: 10.1189/jlb.3HI0814-393R. * equal corresponding author
 16. Mizutani N, **Okochi Y**, Okamura Y. (2019) Distinct functional properties of two electrogenic isoforms of the SLC34 Na-Pi cotransporter. **Physiol Rep.** 7:e14156. doi: 10.14814/phy2.14156.
 17. **Okochi Y***, Umemoto E, Okamura Y. (2020) Hv1/VSOP regulates neutrophil directional migration and ERK activity by tuning ROS production. **J Leukoc Biol.** 107:819-831. doi: 10.1002/JLB.2A0320-110RR. * corresponding author
 18. Paixao IC, Mizutani N, Matsuda M, Andriani RT, Kawai T, Nakagawa A, **Okochi Y***, Okamura Y*. (2023) Role of K364 next to the active site cysteine in voltage-dependent phosphatase activity of Ci-VSP. **Biophys J.** Jan 19:S0006-3495(23)00038-3. doi: 10.1016/j.bpj.2023.01.022. * equal corresponding author
 19. **Okochi Y***, Jinno Y, Okamura Y*. Dimerization is required for the glycosylation of S1-S2 linker of sea urchin voltage-gated proton channel Hv1. **Biophys. J.** 2024 Jul 31:S0006-3495(24)00493-4. doi: 10.1016/j.bpj.2024.07.034. Epub ahead of print. PMID: 39086135. * equal corresponding author

Reviews

1. Okamura Y, **Okochi Y**. (2019) Molecular mechanisms of coupling to voltage sensors in voltage-evoked cellular signals. *Proc Jpn Acad Ser B Phys Biol Sci.* 95:111-135, 2019. DOI: 10.2183/pjab.95.010
2. **Okochi Y***, Okamura Y. (2021) Regulation of neutrophil functions by Hv1/VSOP voltage-gated proton channels. **International Journal of Molecular Sciences**10.3390/ijms22052620