BIOGRAPHICAL SKETCH

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NAME: XIANGMING ZHA

eRA COMMONS USER NAME (credential, e.g., agency login): ZXIANGMING

POSITION TITLE: ASSOCIATE PROFESSOR

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Shanghai Jiao Tong University, Shanghai, China	B.Sc.	1991	Biochem. Engineering
Shanghai Brain Research Inst., Shanghai, China	M.Sc.	1994	Neurobiology
University of Iowa, Iowa City, IA	Ph.D.	2000	Biology
Cell Signaling Technology, Beverly, MA		2002	Proteomics
Univ. of Iowa and Howard Hughes Med. Inst.		2007	Neurosience

A. Personal Statement

I have been working on brain acid signaling since 2004. My work on acid-sensitive ion channels (ASICs) includes their role in spine remodeling and signaling, channel trafficking and stoichiometry, acidotoxicity, and ischemic brain injury. In recent years, I started to investigate signaling mediated by proton-sensitive GPCRs. Our recent work showed that GPR68 mediates neuronal acid signaling, contributes to hippocampal LTP, and GPR68 activation offers protection in brain ischemia. These studies on ASIC and GPR68 emphasize acid signaling in neurons. In addition, we are also examining brain acid signaling on cerebrovascular functions.

B. Positions and Honors

Positions and Employment

1991-1994 Graduate Research Assistant, Shanghai Brain Res. Institute, Chinese Academy of Sciences
1994-1995 Research Assistant, Shanghai Brain Research Institute, Chinese Academy of Sciences
1996-2000 Graduate Research Assistant, Dept. of Biological Sciences, University of Iowa, Iowa City, IA
2000-2002 Postdoctoral scientist, Cell Signaling Technology, Beverly, MA
2002-2004 Postdoctoral scholar, Department of Biology, University of Iowa, Iowa City, IA
2004-2007 Postdoctoral Fellow, Howard Hughes Medical Institute & Univ. of Iowa, Iowa City, IA
2007-2009 Research Specialist I, Howard Hughes Medical Institute & Univ. of Iowa, Iowa City, IA
2009-2014 Assistant Professor, Dept. of Cell Biology & Neuroscience, Univ. S. Alabama, Mobile, AL
2014-2016 Assistant Professor, Dept. of Physiology & Cell Biology, Univ. S. Alabama, Mobile, AL
2016-2021 Associate Professor, Dept. of Physiology & Cell Biology, Univ. S. Alabama, Mobile, AL
2021- Associate Professor, Division of Pharmacology & Pharmaceutical Sciences, Univ. Missouri-Kansas City, Kansas City, MO

Other experience and professional services

Grant review:

NIH: NTRC (6/2021, 6/2019)
AHA: CDA (2021, 2018-19); TPA (2020); Brain/Stroke II (2013-16)

Other ad hoc: Action on Hearing Loss International Project Grant (2017)
Morehouse School of Medicine RCMI G12 Pilot grant (2014)

Editorial board:

2012- Editor, PLoS One
2014-20 Review Editor (2014-20), Frontiers Cell Dev Bio & Frontiers Mol Biosci
2015- Editor, Molecular Brain
2021- Associate editor (2021-), Frontiers Cell Dev Bio & Frontiers Mol Biosci

Ad hoc Journal Review:

Nat Commun, Mol Therapy; J Neurosci, Sci Signal, JBC, Neurobio of Disease, Sci. Rpt., Neuroscience, PLoS One, J Alz Dis, Trans Stroke Res, FEBS J, J Neurosci Res., Current Drug Targets, Int J Biochem Cell Bio., Aging, Mol Neurobio., Neursci. Bull., Mol Brain, Frontier Pharm., Mol Psychiatry.

C. Contributions to Science

1. Signaling underlying dendritic spine remodeling.

I have investigated signaling mechanisms underlying the remodeling of dendritic spines in multiple studies. Using time-lapse and quantitative confocal imaging, I investigated how epileptiform activity (EA)-induced calcium signaling induces the remodeling dendritic spines. Our result shows that EA , and found that EA shifts the balance of synapse gain and loss, leading to a net loss of spine synapses but inducing the formation of filopodia which has abnormally slow motility. With two-photon microscopy and fluorescence resonance energy transfer (FRET), we determined the mechanism by which ASICs regulate spine calcium signaling (Ref 2a, 4b). Other than Besides the CaMKII signaling, we have also investigated the role of PKA signaling in spine remodeling. We found that chronic increase in PKA activity reduces spine number while inhibiting PKA has the opposite effect.

a. **Zha XM**, Green SH, and Dailey ME. (2005) Regulation of hippocampal synapse remodeling by epileptiform activity. ***Mol. Cell. Neurosci.*** 29(4): 494-506. (***Journal cover**)

b. **Zha XM**, Dailey ME, and Green SH. (2009) Role of Ca^{2+}/calmodulin-dependent protein kinase II in dendritic spine remodeling during epileptiform activity in vitro. ***J Neurosci.Res.*** 87:1969–1979. PMCID PMC2694514.

c. Lu Y, **Zha XM**, Kim EY, Schachtele S, Dailey ME, Hall DD, Strack S, Green SH, Hoffman DA, and Hell JW. (2011) A kinase anchor protein150-associated protein kinase A limits dendritic spine density. ***J Biol Chem.*** 286:26496-506. PMCID: PMC3143614.

2. Define the role of ASICs as a postsynaptic proton receptor.

One main area that I have contributed to is defining the role of ASICs at synaptic sites. My work on this topic is summarized below in three categories: *A) Define the synaptic localization of ASICs in brain neurons*. We showed a preferential somatodendritic distribution of ASIC1a and ASIC2, and a preferential targeting of ASIC1a to dendritic spines. *B) Define the mechanism responsible for ASIC-induced Ca^{2+} increase.* We showed that ASIC1a is required for the Ca^{2+} rise. However, as opposed to the previous assumption that Ca^{2+} is mainly through Ca^{2+} permeable ASIC1a homomers, our data indicate that the main effect of ASICs is through its depolarizing effect and the secondary activation of voltage-gated calcium channels. *C) Define the functional impact of ASICs on synaptic sites.* We showed that ASICs mediate H^+-induced calcium increase in dendrites and spines. In addition, acidosis reduced the density and length of dendritic spines in an ASIC1a-dependent manner. Together, these data demonstrate that ASICs function as a proton receptor in dendritic spines.

a. **Zha XM**, Wemmie JA, Green SH, and Welsh MJ. (2006) ASIC1a is a postsynaptic proton receptor that affects the density of dendritic spines. ***Proc. Natl. Acad. Sci.*** 103: 16556-16561. PMCID: PMC1621052.

b. Jing L, Chu XP, Jiang YQ, Collier DM, Wang B, Jiang Q, Snyder PM and **Zha XM**. (2012) *N*-Glycosylation of acid-sensing ion channel 1a regulates its trafficking and acidosis-induced spine remodeling. ***J Neurosci.*** 32: 4080-91. PMCID: PMC3322463.

3. ASIC in acidotoxicity and ischemic brain injury.

To link the biology of proton receptors to functional outcome, we have investigated acidosis- and ischemia-induced neuronal injury. Since ASIC2 is one of the main ASIC subunits expressed in the brain, we have explored the role of ASIC2 deletion in various brain regions in mouse. Our data revealed that deleting ASIC2 is protective against acidosis- and ischemia-induced neuronal injury in hippocampus, cortex and striatum. As one step towards exploring the contribution of ASICs to neuronal injury in human brain, we recently presented evidence for increased trafficking of human ASIC1a, which led to increased acidosis-induced injuries.

a. Jiang N*, Wu J*, Leng T*, Yang T, Zhou Y, Jiang Q, Wang B, Hu Y, Ji YH, Simon RP, Chu XP, Xiong ZG#, and **Zha XM**#. (2017) Region specific contribution of ASIC2 to acidosis- and ischemia-induced neuronal injury. ***J Cereb Blood Flow Metab***. 37: 528-40. PMCID: PMC5381448. (# co-corresponding author)

b. Xu Y*, Jiang YQ*, Li C, He M, Rusyniak WG, Annamdevula N, Ochoa J, Leavesley SJ, Xu J#, Rich TC, Lin MT, and **Zha XM**#. (2018) Human ASIC1a mediates stronger acid-induced responses as compared to mouse ASIC1a. ***FASEB J*** 32: 3832-43. PMCID: PMC5998965.

4. ASIC trafficking and stoichiometry.

Another area that I have been working on is the basic mechanism underlying ASIC trafficking and function. In a recent study, we performed a semi-quantitative analysis of ASIC subunit ratio in the brain. Our results implicate that the main functional ASICs in the mouse brain are ASIC1a homomers and ASIC1a/2a heteromers. We further compared the expression of ASICs in acutely resected human cortical tissue. Human cortical tissue mainly expresses ASIC1a and 2a but has little 2b, and exhibit a higher membrane:total ratio of ASIC1a. To get into the mechanism, we have also investigated how *N*-glycosylation, channel heteromerization, and protein motifs regulate ASIC trafficking and function.

a. **Zha XM**, Wang R, Collier DM, Wemmie JA, Snyder P, and Welsh MJ. (2009) Oxidant regulated intersubunit disulfide bond formation between ASIC1a subunits. ***Proc. Natl. Acad. Sci.*** 106: 3573–3578. PMCID: PMC2642663.

b. **Zha XM**, Costa V, Harding A, Reznikov L, Price MP, Benson CJ, and Welsh MJ. (2009) ASIC2 subunits target acid-sensing ion channels to the synapse via an association with PSD-95. ***J Neurosci.*** 29: 8839-46. PMCID: PMC2734339.

c. Jing L, Chu XP, Jiang YQ, Collier DM, Wang B, Jiang Q, Snyder PM and **Zha XM**. (2012) *N*-Glycosylation of acid-sensing ion channel 1a regulates its trafficking and acidosis-induced spine remodeling. ***J Neurosci.*** 32: 4080-91. PMCID: PMC3322463.

5. Define the role of GPR68 as a metabotropic proton receptor in brain neurons.

To determine whether protons signal through metabotropic pathways in neurons, we examined the expression of proton-sensitive GPCRs in the brain. In a series of studies, we showed that GPR68 is primarily present in neurons in hippocampus, cortex, and striatum, and mediates acid-induced PKC activation in cortical neurons. GPR68 deletion reduced hippocampal LTP. GPR68-/- mice further exhibited deficits in a step-through passive avoidance test. These data demonstrate that GPR68 contributes to synaptic plasticity and fear-related memory. Further, we investigated GPR68 function in neuronal injury. GPR68 deletion worsened both acidosis- and ischemia-induced neuronal injury, both in organotypic slices and in a rodent model of focal ischemia. The effect on ischemic brain injury correlates with a rise in post-stroke hemorrhagic transformation. Conversely, GPR68 overexpression protected the mice against middle cerebral artery occlusion-induced brain injury. We further performed RNA-Seq analysis on GPR68-/- and found that GPR68 regulates pathways involving misfolded protein responses and ER stress. Together, these data establish the importance of GPR68 in synaptic physiology and neuronal injury.

a. Wang T*, Zhou G*, He M, Xu Y, Rusyniak GW, Xu Y, Ji Y, Simon RP, Xiong ZG, and **Zha XM**. (2020) GPR68 is a neuroprotective proton receptor in brain ischemia. ***Stroke*** 51:3690-700. PMCID: PMC7678672.

b. Xu Y, Lin MT, and **Zha XM**. (2020) GPR68 deletion impairs hippocampal long-term potentiation and passive avoidance behavior. ***Molecular Brain*** 13:132. PMCID: PMC7526169.

c. Zhou G*, Wang T*, and **Zha XM**. (2021) RNA-Seq analysis of knocking out the neuroprotective proton-sensitive GPR68 on basal and acute ischemia-induced transcriptome changes and signaling in mouse brain. ***FASEB J.*** 35(4):e21461. PMCID: PMC7970445.

A full list of my published work:
https://www.ncbi.nlm.nih.gov/myncbi/xiangming.zha.1/bibliography/public/

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing research support:

Extramural support:

NIH/NINDS R01NS102495 (Zha) 08/15/2017-06/30/2022
Neuroprotective role of OGR1 in brain ischemia.
This grant will investigate the role of GPR68/OGR1 in neuronal acid signaling and brain ischemia in mouse.
Role: PI

Intramural support:

Startup funds from UMKC. 08/01/2021-09/30/2029
The startup package provides support for both personnel and experimental needs to my lab.