BIOGRAPHICAL SKETCH

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NAME: Lin, Mike T.

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

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
University of British Columbia, BC, Canada	B.S.	07/1996	Biochemistry
Loma Linda University, CA, USA	M.S.	06/1999	Physiology
Loma Linda University, CA, USA	Ph.D.	09/2004	Physiology
Oregon Health Science University, OR, USA	Postdoctoral	03/2012	Synaptic Physiology

A. Personal Statement

My independent research, established at the University of South Alabama, applies electrophysiology, biochemistry, molecular biology, cell physiology, and animal behavior strategies to basic science and clinical investigations that address a mechanism that impairs cognition in critically ill patients. I began my career as an electrophysiologist under Dr. Lawrence D. Longo's guidance, and with extramural visits and training at the City of Hope (Dr. Michael Barish), Cal Tech (Dr. Henry Lester), UCLA (Dr. Andy Charles), and the University of Vermont (Dr. Mark Nelson), I characterized the large-conductance calcium-activated potassium (BK) channels in sheep cerebral arteries and found differential Ca^{2+} sensitivity during animal development. I then joined Drs. John Adelman and James Maylie laboratories at the Vollum Institute at OHSU and focused on potassium channels at the synapse. I showed that small-conductance K_{Ca} (SK2) channels reside in dendritic spines where they are activated by synaptically evoked Ca^{2+} influx, forming a Ca^{2+}-mediated feedback loop with NMDA receptors. Supported by an NSRA grant (F32MH080480), my work found an unexpected role for SK2 channels in modulating long-term potentiation and intrinsic excitability. During my tenure at OHSU and supported by the Pathway-to-Independence grant (K99HL102056), I additionally worked with several researchers (e.g., Drs. Alkayed, Herson, Hurn, Ronnekleiv, Stenzel-Poore, and Stackman) in vascular injury, ischemic stroke, and animal behavior.

At the University of South Alabama, I studied how vascular endothelial microdomains and barrier integrity are modulated by potassium and calcium channels. This line of work, supported by R00HL102056, was conducted in collaboration with Drs. Mark Taylor, David Weber, and Mary Townsley. I have further developed a new niche in vascular biology and neuroscience. Through collaboration with Drs. Ron Balczon and Troy Stevens at the University of South Alabama, and with Drs. Jean-Francois Pittet and Brant Wagener at the University of Alabama, Birmingham, our work shows that cerebrospinal fluid and plasma collected from bacterial pneumonia ICU patients also contain neurotoxic amyloid and tau variants. These neurotoxic species in the circulation and in the central nervous system induce secondary injury leading to a cognitive deficit.

Looking back at my training and career, I am amazed that I have been so fortunate to have the opportunity to work with many prominent mentors/sponsors and scientists. And I am both delighted to have the opportunity to train the next generation of scientists and the privilege to work in a new area that is clinically significant.

Ongoing and recently completed projects that I would like to highlight include:

R01 HL140182 Lin (PI) 04/01/2018 – 8/31/2027
"Nosocomial pneumonias impair cognitive function"
The overall goal of the grant is to explore the mechanism of pneumonia-induced cytotoxic supernatant generation, its propagation in endothelium, its transmissibility from humans-to-rodents and rodents-to-rodents, and its level in rodents and in patient specimens, including BALF, plasma, and CSF. This application supports ICU patient enrollment and specimen collection.
Role: PI

1R01HL155288-01A1 Taylor(PI) 09/01/2021 - 07/31/2025
NIH/NHLBI
"Network signature of low-flow endothelial dysfunction"
We hypothesize that disruption of TRPV4-KCa2.3 signaling under conditions of low FSS causes a progressive, highly restricted endothelial Ca2+ signature that promotes endothelial dysfunction and vascular remodeling.
Role: Co-Investigator

Citations:

a. **Lin MT**, Lujan R, Watanabe M, Adelman JP, Maylie J. SK2 channel plasticity contributes to LTP at Schaffer collateral-CA1 synapses. *Nat Neurosci*. 2008; 2:170-7. PMCID: PMC2613806.
b. **Lin MT**, Adelman JP, Maylie J. Modulation of Endothelial SK3 channel activity by Ca^{2+}-dependent caveolar trafficking. *Am J Physiol Cell Physiol.* 2012; 303:C318-27. PMCID: PMC3423019.
c. Yap FC, Weber DS, Taylor MS, Townsley MI, Comer BS, Maylie J, Adelman JP, **Lin MT**. Endothelial SK3 channel-associated Ca^{2+} microdomains modulate blood pressure. *Am J Physiol Heart Circ Physiol.* 2016; 310:H1151-63. PMCID: PMC4867388.
d. **Lin MT**, Balczon R, Jean-Francois P, Wagener B, Moser S, Morrow KA, Voth S, Francis CM, Leavesley S, Bell J, Alvarez DF, Stevens T. Nosocomial pneumonia elicits an endothelial proteinopathy. *Am J Respir Crit Care Med.* 198:1575-1578, 2018. With an editorial correspondence. PMCID: PMC6298632.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2019- Associate Professor, Dept. of Physiology and Cell Biology, U. South Alabama, Mobile, AL
2012-2019 Assistant Professor, Dept. of Physiology and Cell Biology, U. South Alabama, Mobile, AL
2005-2012 Postdoctoral Fellow, Vollum Institute, Oregon Health Science University, Portland, OR
2002-2004 Animal Care Assistant, Hypoxic Animal Care, Loma Linda University, Loma Linda, CA
1997-2004 Graduate Research Assistant, Physiology, Loma Linda University, Loma Linda, CA
1996-1997 Lab Assistant, Physiology and Pharmacology, University of British Columbia, Vancouver, BC
1996 Summer Intern, Biochemistry, Cal-Tech Inc., Diamond Bar, CA

Professional Memberships

2014- American Heart Association
2007- Society for Neuroscience
2003- American Physiological Society

Honors and Professional Service (selected examples)

2021- Ad hoc Reviewer, NIH: ZRG1 F03B-R L (20)
2018-2022 Recipient of my first NIH Research Project Grant (R01)
2018 Ad hoc Reviewer, NIH/NHLBI: HLBP 1 Workgroup
2017-2018 Recipient of a COM Intramural Grant
2016- Member, Center for Lung Biology
2015-2019 Member, Editorial Board, *Scientific Reports*
2010-2016 Recipient of a Pathway to Independence Award (K99/R00)
2008-2010 Recipient of an Individual Postdoctoral Fellowship (F32)
2006-2007 Recipient of an Institutional Postdoctoral Training Grant (T32)

Reviewer for: *American Journal of Physiology, Anesthesiology, Arteriosclerosis Thrombosis and Vascular Biology, Circulation Research, FASEB Journal, Journal of Cerebral Blood Flow & Metabolism, Journal of Molecular and Cellular Cardiology, Journal of Neuroscience, Journal of Vascular Research, JOVE*, *Life Sciences, Microbes and Infection*, *PLoS One, Scientific Reports,* etc.

C. Contributions to Science

1 **Lung infection elicits endothelial derived amyloids that impair neural function.** Collaborative efforts among members in the Center for Lung Biology discovered that *P. aeruginosa* ExoY expression in endothelium causes cells to release factor(s) that impair their recovery from infection. In particular, ExoY induces endothelial production and release of cytotoxic proteins with amyloid characteristics, including oligomeric τ and amyloid beta (Aβ). These endothelial cell amyloids share characteristics of prion disease, in that they are transmissible among cells and self-replicating. These findings indicate infection elicits lung endothelial cell production of cytotoxic amyloids that may contribute to end organ dysfunction. In our ongoing work we have tested this principle and found intensive care unit patients with nosocomial pneumonia have amyloids present in the bronchoalveolar lavage fluid, plasma and cerebrospinal fluid. The amyloids present in the cerebrospinal fluid are sufficient to impair long term potentiation in the hippocampus. We are examining the nature of these endothelial amyloids, mechanisms leading to their production and release, and their biodistribution during critical illness.

a. **Lin MT**, Balczon R, Jean-Francois P, Wagener B, Moser S, Morrow KA, Voth S, Francis CM, Leavesley S, Bell J, Alvarez DF, Stevens T. Nosocomial pneumonia elicits an endothelial proteinopathy. *Am J Respir Crit Care Med.* 2018; 198:1575-1578. [see also the editorial correspondence: Amyloidosis by bacterial infection in critically ill patients? *Am J Respir Crit Care Med.* 2018; 198:1475-1476.] PMCID: PMC6298632.
b. Scott AM, Jager AC, Gwin M, Voth S, Balczon R, Stevens T, **Lin MT**. Pneumonia-induced endothelial amyloids reduce dendritic spine density in brain neurons. *Sci Rep*. 2020; 10:9327. PMCID: PMC7283224.
c. Balczon R, **Lin MT**, Lee JY, Abbasi A, Renema P, Voth SB, Zhou C, Koloteva A, Francis CM, Sodha NR, Pittet JF, Wagener BM, Bell J, Choi C, Ventetuolo CE, Stevens T. Pneumonia initiates a tauopathy. *FASEB J*. 2021; 35:e21807. PMID:34384141. PMCID: PMC8443149.
d. Choi C, Gwin M, Voth S, Kolb C, Zhou C, Nelson AR, deWeever A, Koloteva A, Annamdevula NS, Murphy JM, Wagener BM, Pittet JF, Lim SS, Balczon R, Stevens T, and **Lin MT***. Cytotoxic tau released from lung microvascular endothelial cells upon infection with *P. aeruginosa* promotes neuronal tauopathy. *J Biol Chem.* 2021; 298:101482. PMCID: PMC8718960.

2 **SK2 channel activity in neurons contributes to synaptic transmission.** It has long been established that 1) glutamatergic AMPAR and NMDAR directly modulates excitatory neural signal, and 2) an increase in synaptic strength is an underlying cellular mechanism for learning and memory. Thus, scientists have been striving toward understanding the means that contribute to synaptic transmission, AMPAR and NMDAR signaling, and neural plasticity. At about the time that I joined Dr. John Adelman's laboratory, we uncovered the involvement of SK2 channels in shunting synaptic transmission current, dampening excitatory potentials (EPSPs), in hippocampal CA1 neuron. An important message from this line of research is that SK2 channels, acting as a Ca^{2+} sensor in postsynaptic spine to detect NMDAR-mediated Ca^{2+} influx, modulate postsynaptic potentials. Following high frequency stimulation that induces LTP, the removal of SK2 channels from postsynaptic density is both Ca^{2+} and PKA dependent; removal of synaptic SK2 channels enhances potentiation. Furthermore, SK2 endocytosis is mechanistically linked to exocytosis of AMPARs. A similar mechanism involving SK2 channels has also been demonstrated in ischemia-reperfusion condition (eg. cardiac arrest and stroke). Ischemia-induced glutamate overload, via an NMDAR-dependent Ca^{2+} signaling, causes SK2 channel endocytosis which leads to further potentiation and excitotoxicity. As the blockade of NMDAR as a neuroprotective strategy has failed in human trials due to side effects, perhaps activating synaptic SK2 channels is a feasible therapy for neuroprotection.

a. **Lin MT**, Lujan R, Watanabe M, Adelman JP, Maylie J. SK2 channel plasticity contributes to LTP at Schaffer collateral-CA1 synapses. *Nat Neurosci*. 2008; 2:170-7. PMCID: PMC2613806.
b. **Lin MT**, Lujan R, Frerking M, Maylie J, Adelman JP. Coupled activity-dependent trafficking of synaptic SK2 channels and AMPA receptors. *J Neurosci.* 2010; 30:11726-34. PMCID: PMC2952431.

c. Allen D, Bond C, Lujan R, Ballesteros-Merino C, **Lin MT**, Wang K, Klett N, Watanabe M, Shigemoto R, Stackman RW, Maylie J, Adelman JP. The SK2-long isoform directs synaptic localization and function of SK2-containing channels. *Nat Neurosci.* 2011; 6:744-49. PMCID: PMC3417338.
d. Wang K, **Lin MT**, Adelman JP, Maylie J. Distinct Ca^{2+} microdomains in dendritic spines couple to SK and K_V4 channels. *Neuron.* 2014; 81:379-87. PMCID: PMC3904135.

3 **SK3 channels contribute to vascular function and blood pressure regulation.** Post-menopause, aging, and hypertension are all major risk factors for cardiovascular disease morbidity and mortality: the leading cause of death in the United States. Recent estimates show that while 30% of adults have high blood pressure, normotensive individuals at age 55 have a 90% lifetime risk of developing hypertension. Hypertension, the so-called 'silent killer', usually does not present clinical symptoms until complications emerge. Physiological changes including menopause and aging induce irreversible changes in the cardiovascular system that frequently result in diminished endothelium-dependent regulation of vascular tone and can lead to hypertension. Ca^{2+} signaling in vascular endothelium is a key regulator for many of the endothelium-derived vasoactive factors, including endothelins, prostaglandins, nitric oxide, and endothelium-derived hyperpolarization (EDH). Recent advances have demonstrated unequivocally that SK3 and IK (intermediate conductance) channels play a crucial role in EDHF-mediated vasorelaxation, due in large part to their characteristic biophysical properties and sub-cellular localizations. My work showed differential trafficking of SK3 and IK channels in aortic endothelial cells—trafficking of SK3 requires intact caveolae, whereas IK channels do not undergo active trafficking. We further showed that the contribution of SK3 to EDH and vasorelaxation is upregulated by estrogen, suggesting that estrogen's protective role in cardiovascular system may due, in part, to the upregulation of endothelial SK3 channels. Genetic deletion of these channels results in a hypertensive mouse. The scientific community now focuses on characterization of SK3 and IK channel mediated signaling.

a. Qian X, Francis, M, Kohler R, Solodushko V, **Lin M**, Taylor MS. Positive feedback regulation of agonist-stimulated endothelial Ca^{2+} dynamics by $K_{Ca}3.1$ channels in mouse mesenteric arteries. *Arterioscler Thromb Vasc Biol.* 2014; 34:127-35. PMCID: PMC4181598.
b. **Lin MT**, Adelman JP, Maylie J. Modulation of endothelial SK3 channel activity by Ca^{2+}-dependent caveolar trafficking. *Am J Physiol Cell Physiol.* 2012; 303:C318-27. PMCID: PMC3423019.
c. Yap FC, Taylor MS, **Lin MT**. Ovariectomy-induced reductions in endothelial SK3 channel activity and endothelium-dependent vasorelaxation in murine mesenteric arteries. *PLOS ONE.* 2014; 9:e104686. PMCID: PMC4126749.
d. Yap FC, Weber DS, Taylor MS, Townsley MI, Comer BS, Maylie J, Adelman JP, **Lin MT**. Endothelial SK3 channel-associated Ca^{2+} microdomains modulate blood pressure. *Am J Physiol Heart Circ Physiol.* 2016; 310:H1151-63. PMCID: PMC4867388.

4 **Functional coupling of TRPV4-IK-SK3 channels contributes to endothelial permeability.** Vascular endothelium is a monolayer of cells that lines our entire blood circulation. Thus, in addition to their contribution to vascular tone regulation, ECs also control endothelial barrier integrity—disruption of EC integrity leads to edema. It has been shown that activation of pulmonary vanilloid transient receptor potential subtype 4 (TRPV4) cation channels induces Ca^{2+} influx into alveolar septal endothelium and results in an increased endothelial permeability. In systemic vessels, other and our group have shown that endothelial TRPV4 are functionally coupled to IK and SK3 channels; however, less is known about the signaling coupling of TRPV4 and K_{Ca} channels in pulmonary endothelium. We showed that in pulmonary microvascular endothelial cells TRPV4 channels are functionally, yet differentially, coupled to SK3 and IK channels. Activation of TRPV4-IK-SK3 positive feedback pathway leads to increased lung permeability. Currently we are utilizing endothelium-specific knockout mouse models to examine specific and differential couplings between TRPV4-SK3 and TRPV4-IK channels.

a. **Lin MT**, Adelman JP, Maylie J. Modulation of endothelial SK3 channel activity by Ca^{2+}-dependent caveolar trafficking. *Am J Physiol Cell Physiol.* 2012; 303:C318-27. PMCID: PMC3423019.
b. Yap FC, Weber DS, Taylor MS, Townsley MI, Comer BS, Maylie J, Adelman JP, **Lin MT**. Endothelial SK3 channel-associated Ca^{2+} microdomains modulate blood pressure. *Am J Physiol Heart Circ Physiol.* 2016; 310:H1151-63. PMCID: PMC4867388.

c. **Lin MT**, Jian MY, Taylor MS, Cioffi DL, Yap FC, Liedtke W, Townsley MI. Functional coupling of TRPV4, IK, and SK channels contribute to Ca^{2+}-dependent endothelial injury in rodent lung. *Pulm Circ*. 2015; 5:279-90. PMCID: PMC4449238.
d. McFarland S, Weber DS, Choi C, **Lin MT**, and Taylor MS. Ablation of endothelial TRPV4 channels alters and dynamic Ca^{2+} signaling profile in mouse carotid arteries. *Int. J. Mol. Sci.* 2020; 21:2179. PMCID: PMC7139994

5 **Ion channels contribute to vascular response to hypoxia.** The human brain represents 2% of total body weight, yet, for its proper function, requires 15% of cardiac output, and consumes 20% of total oxygen (O_2) and 25% of total glucose. Because of its high metabolic activity and O_2 requirement, the brain is particularly vulnerable to hypoxia. For example, to meet the demand for O_2, acute hypoxia can develop into cerebral palsy in fetuses and cerebral edema in adults, respectively, due to dysregulation of cerebral blood flow. The large conductance K_{Ca} (BK) channels have been implicated to play important roles in vascular smooth muscle contractility. In addition to their capability to sense intracellular $[Ca^{2+}]_i$, BK channels in vascular smooth muscle cells are sensitive to changes in hypoxia, plasma membrane composition, protein phosphorylation, splices variation, and pH etc. They are pivotal to the regulation of smooth muscle contractility, and global deletion of BK channel leads to hypertension. Taken these together, we studied developmental changes in BK channel Ca^{2+} sensitivity, phosphorylation, and following long-term hypoxia. We found that increased BK channel activity in basilar arteries occur in association with both increased Ca^{2+} affinity and voltage activation following hypoxia. This could be a novel mechanism by which sheep easily acclimatize to long-term high altitude hypoxia. In a related line of work, we showed that acidosis in the brain after insult, e.g., ischemic stroke, activates the acid-sensing ion channels. Activation of these channels contribute to neuronal damage, leading to reduced long-term potentiation and animal learning.

a. **Lin MT**, Hessinger DA, Pearce WJ, Longo LD. Developmental differences in Ca^{2+}–activated K^+ (BK_{Ca}) channel activity in ovine basilar artery. *Am J Physiol Heart Circ Physiol.* 2003; 285:H701-9. PMID: 12689856.
b. Tao X, **Lin MT**, Thorington GU, Wilson SM, Longo LD, Hessinger DA. Long-term hypoxia increases calcium affinity of BK channels in ovine fetal and adult cerebral artery smooth muscle. *Am J Physiol Heart Circ Physiol.* 2015; 308:H707-22. PMCID: PMC4385992.
c. 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. Human ASIC1a mediates stronger acid-induced responses as compared with mouse ASIC1a. *FASEB J.* 32:3832-3843, 2018. PMCID: PMC5998965.
d. Xu Y, **Lin MT**, and Zha XM. GPR68 deletion impairs hippocampal long-term potentiation and passive avoidance behavior. *Mol Brain.* 13:132, 2020. PMCID: PMC7526169.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/mike.lin.1/bibliography/40831692/public/?sort=date&direction=ascending