Choosing Fuel for Cardiac Activity Following Ischemia/Reperfusion after VF Resuscitation

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My name is M. Ali Azam and I am a former member of the Physiological Society of Japan while I was a graduate student in Japan. On this occasion, I would like to describe my exciting experiences that started in Japan and is going on in Canada. After graduation as a MD and participating in clinical research in ICDDR, B which is the world famous research centre for infectious diseases in Bangladesh, I became interested in studying abroad. I applied for and won the Japanese Government Monbukagakusho Scholarship to study the molecular mechanism for regulation of vascular smooth muscle contraction in depth in Professor Takuwa sensei’s Lab. When I arrived at Kanazawa in October 2003, it was just after their publication of an epoc making paper showing Ca\(^{2+}\)-dependent activation of Rho and Rho kinase and resultant inhibition of myosin light chain phosphatase (MLCP) as the mechanism for Ca\(^{2+}\) sensitization of vascular smooth muscle contraction [1], which turned out to be closely related to my thesis work to be done in Kanazawa. Here I have to say that before coming to Prof. Takuwa sensei’s lab, I had no experience in smooth muscle physiology and molecular biology. Six months after my arrival, my wife and daughter joined me to make my life in Kanazawa very much enjoyable personally as well and also more productive. Two years later, my son Atyah was born in Japan and my daughter Aniqa started going to hoikyuen. Aniqa could speak in Japanese. By this time, my wife made some Japanese friends. We miss Kanazawa, cherry blossoms, tulip festival, natsu matsuri, Kenrokuen, Kanazawa castle, Sai gawa river and so on.

Gradually, I learned all the necessary techniques needed for my project and became familiar to the signal transduction field through bountiful journal clubs and lab meetings. I am really grateful to my Professor and his lab members. During my PhD training, I was involved in Prof. Takuwa’s innovative project to determine the role of class II phosphoinositide 3-kinase \(\alpha\)-isoform (PI3K C2\(\alpha\)) in vascular smooth muscle contraction. I could make contributions to the discovery that PI3K C2\(\alpha\) is located upstream of Rho activation [2], and that the Ca\(^{2+}\)-PI3K C2\(\alpha\)-Rho kinase-MLCP inhibition axis is enhanced in spontaneously hypertensive rats [3]. I disclosed, in my thesis work, that the action of cAMP in relaxation of vascular smooth muscle involves inhi-
bition of this very signaling axis [4]. Since PI3K C2a has been so familiar to me as a molecule involved in Rho activation and Ca^{2+} sensitization of smooth muscle contraction, it was a big surprise to me when I found that recent Nature Med paper by Prof. Takuwa’s group, who discovered that PI3K C2a is desperately required for embryonic vascular development and vascular barrier function, with the mechanism involving intracellular vesicular trafficking and Rho activation on the vesicles inside of cells [5].

After completion of my PhD in Japan, I started working as a post doctoral fellow at the University of Toronto, Canada, where my research topic was to determine the molecular mechanism for increased myogenic response (pressure induced vasoconstriction) in heart failure (HF) following myocardial infarction. In a mouse model of HF, I found in mesenteric artery that myosin light chain (MLC) phosphorylation is increased and myosin light chain phosphatase (MLCP) is deactivtated. In this model the MLCP regulator GTP-Rho was reduced, however, activation of p38 MAPK and ERK1/2 were increased. Inhibition of p38 MAPK normalized the increased myogenic tone in HF following MI [6].

After successful completion of post doctoral training, I started working at Dr. Nanthakumar’s research lab, The Hull Family Cardiac Fibrillation Management Laboratory, Toronto General Hospital. Dr. Nanthakumar is one of the pioneers in cardiac electrophysiology and pathophysiology of arrhythmias. Here I worked in a research project addressing pharmacological deffribillation of ventricular fibrillation (VF) in human heart. We studied electrical mapping and K_{ATP} channel expression pattern in human heart in a Langendorff setup, demonstrating that treatment with K_{ATP} channel blocker glibenclamide spontaneously terminates VF [7]. At present, I am working to determine the effects of modulation of cardiac energy sources for the management of cardiac contractility following ischemia/reperfusion (I/R) after VF resuscitation. As everyone knows, in a normal healthy heart, the major energy for the cardiac activity is derived from oxidation of fatty acid (FA) with only a minor part derived from oxidation of glucose and lactate. In ischemic condition, oxidation of FA is inefficient as it requires more oxygen to produce the same amount of ATP compared to glucose, whereas glucose could serve as an alternative energy source as the substrate for anaerobic glycolysis, which however could result in production of harmful molecules such as lactic acid and proton, leading to accumulation of intracellular Ca^{2+}. In this context, my research focus is to figure out the effects of increasing glucose oxidation and decreasing of FA oxidation in the mitochondria in I/R injured heart. My results so far are quite exciting and shed light towards unexplored pathways of modulating mitochondrial function, showing that enhancing glucose oxidation is associated with increased cardiac contractility following I/R after VF resuscitation in rat heart in a Langendorff setup, which led me to win the American Heart Association Young Investigator Award 2012 [8]. I believe that in near future improving mitochondrial function will play an important role in the treatment of cardiovascular diseases.

I am enjoying research that started in Kanazawa and is going on in Toronto, and my career goal is to establish myself as an independent biomedical scientist who could contribute to patients’ better prognosis through better understanding of pathophysiology. If I get an opportunity, I’d like to work in Japan again.

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A handkerchief with the map of Kagoshima

Department of Cell Biology, University of Oklahoma Health Sciences Center
Hongguang Nie (聂宏光)

I am Hongguang Nie, now a teacher of Pharma-
cology in China Medical University and I used to be
an exchange student in Professor Kameyama’s lab at Kagoshima University from 2003 to
2004. It was a precious chance for me to study
in Professor Kameyama’s lab. During my one-
year stay in Japan, I liked the place and people
there very much, most importantly, the abroad
experience and knowledge in the electrophysiol-
yogy field helped me a lot in my present research
work. Professor Kameyama and his group have
been studying the detailed mechanisms for regu-
lation of cardiac Cav1.2 Ca2+ channels using elec
trophysiological and molecular biological meth-
ods, and made much progress in this field. I feel
that I have studied a lot in Professor Kameyama’s
lab and the staff in his lab were all very warm-
hearted and helped me a lot. I enjoyed my life
very much in Japan, we visited famous places to-
gether in Japan, which is a very sweet memory
for me. Also I could make a lot of progress in my
research work and our paper done in Professor
Kameyama’s lab at Kagoshima University, pub-
lished in JPS[1], received the Hiroshi Irisawa Me-
memorial JPS Award 2007. It was a great honor for
me. I thank the reviewers of JPS for helpful and
critical review of the manuscript.

After this stay in Japan, I became a postdoc-
toral fellow in the University of Texas Health Sci-
cence Center at Tyler in USA for one year. My
major there was to study the electrolyte and fluid
transport in epithelial and mesothelial cells, espe-
cially in human lung mesothelial cells. The expe-
rience and technique I studied in Professor Ka-
meyama’s lab helped me so much to address the
research topic that I could contribute to several
papers published during these years. When I
came back to China in 2009, I was promoted to an
Associate Professor and now I have enrolled my
own graduates in China Medical University.

At the beginning of this year, I was assigned
by China Scholarship Council to have another chance to come to USA, again for the previous excellent works in Japan and USA. Now I am a Research Scholar in University of Oklahoma Health Sciences Center. Especially noted to say, when I contacted with the present lab, I asked Professor Kameyama to write a recommendation letter for me, which moved my present boss, knowing that I had studied in Japan for one year and had so many publications based on this, to accept my application nearly instantaneously. I have been here for more than 3 months to try to find the mechanism about the TRPP2 channels using patch-clamp method, recording the currents both in the whole-cell and single-channel mode, which I had studied in Japan. I always keep the notebooks that I used in Japan for the details of several key points with me, which help me a lot also in my present work. Also a few days ago, when we talked about the patch-clamp machine and software we were using, I told my present boss that I studied this technique in Japan and my Professor in Japan was very skilled in this field, so many years ago he designed the program and analysis software for the recorded currents, and the Professor here deepened his recognition on Professor Kameyama.

When I think about the experience in Japan, I can’t help reminding so many sweet memories and also I remember the special time when the Professor Kameyama’s group celebrated my birthday in his lab. They presented me beautiful flowers and I still keep the photo Professor Kameyama took himself using the instant camera on that day. Although 10 years have passed, I feel that the scene just happened yesterday. When Professor Kameyama saw me off at the airport, he gave me a handkerchief with the map of Kagoshima, which is my favorite until now. After coming back to China and I had my new baby, the first thing I did was to send the newborn’s photo to Professor Kameyama and share my happiness with his staff. They told me that he printed this baby’s photo and pasted it in the lab meeting room, which made me very moved. Also when I had any achievements in the research work these years, I’d like to tell Professor Kameyama and I am very happy to have a chance to share my happiness with him together.

At last, thank you all for giving me a chance to review my study life in Japan here and I think the impressive memories in Japan will always be held in the rest of my life.