BIOGRAPHICAL SKETCH

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NAME: Chen, Guoxun

eRA COMMONS USER NAME (agency login): GCHEN6

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.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Wuhan University, Wuhan, Hubei	BS	07/1986	Virology and Molecular Biology
Wuhan University, Wuhan, Hubei	MS	07/1989	Virology and Molecular Biology
University of Texas Southwestern Medical Center at Dallas (UTSW), Dallas, Texas	PHD	06/2001	Biochemistry and Molecular Biology
UTSW, Dallas, Texas	Postdoctoral Fellow	07/2006	Postdoctoral training in the Department of Molecular Genetics and Biophysics at

A. PERSONAL STATEMENT

My long-term research goal is to understand the roles of vitamin A (VA) in glucose and lipid metabolism, and in the development of metabolic diseases, such as obesity and diabetes. Our lab has shown that VA status affects the obesity development in Zucker fatty (ZF) rats, and retinoids regulate the expression of hepatic genes involved in the control of the hepatic glucose and lipid homeostasis. Recently, we reported that insulin-regulated gene expression was impaired in hepatocytes isolated from Zucker lean (ZL) rats experiencing a short-term over-eating condition, a phenomenon that we named as the hepatic insulin resistance at gene expression (HIRAGE). I was the PI of a projected funded by American Heart Association National Program to investigate the mechanism by which retinoids synergized with insulin to induce the hepatic glucokinase gene (*Gck*) expression. Recently, my proposal to study the role of VA in the development of type 2 diabetes using Zucker diabetic fatty (ZDF) rats was funded by the Diabetes Education and Research Foundation. My future career plan is to continue my research program and try to understand the roles of VA in the regulation of hepatic glucose and lipid metabolism, and in the development of insulin resistance and type 2 diabetes.

B. POSITIONS AND HONORS

Positions and Employment

2006 - 2012 Assistant Professor, The University of Tennessee at Knoxville, Knoxville, TN
2012 - Associate Professor, The University of Tennessee at Knoxville, Knoxville, TN

Other Experience and Professional Memberships

2006 - Member, American Diabetes Association (ADA)
2006 - Member, American Society of Nutrition
2007- Member, American Heart Association (AHA)
2011- Permanent member, Chinese American Diabetes Association
2016- Member, Council on Undergraduate Research
2016- Permanent member, North America Chinese Society for Nutrition
2018- Chair-elect, Nutritional Science and Metabolism Research Interest Section of ADA
2019- President of North America Chinese Society for Nutrition

Honors

1987 Excellent Graduate Student at Wuhan University, Wuhan University
1998 Outstanding scientific poster of GSO, UTSW, Dallas
1999 Sigma-Xi, UTSW, Dallas
1999 Trainee of NIH Training Grant, UTSW, Dallas
2009 NPAM Young Investigator Award, AHA Scientific Sessions 2009

2016 Service Excellence and Leadership Award at University of Tennessee, Knoxville (UTK)
2020 Jacquelyn Orlando DeJonge Award, College of Education, Health and Human Sciences, UTK

C. CONTRIBUTION TO SCIENCES

(The complete and publicly available publication list of the PI can be found: http://www.ncbi.nlm.nih.gov/sites/myncbi/16wKJLieasBAx/bibliography/47358785/public/?sort=date&direction=ascending. * or **for students as co-authors or the first authors, respectively)

1. My first research publication in the United States was about the physiological functions of leptin, a cytokine derived from adipocytes. Under the guidance of Dr. Roger Unger at UTSW, I made recombinant adenovirus (Ad-leptin) containing rat *Lep* cDNA, which induced hyperleptinemia in rats. The results from experiments using this Ad-leptin have revealed that leptin not only suppresses feeding behavior, but also regulates energy expenditure in rats. This Ad-leptin construct has become a valuable tool for the field to study leptin's physiological functions ever since.
   a. **Chen G,** Koyama K, Yuan X, Lee Y, Zhou YT, O'Doherty R, Newgard CB, Unger RH. Disappearance of body fat in normal rats induced by adenovirus-mediated leptin gene therapy. Proc Natl Acad Sci U S A. 1996 Dec 10;93(25):14795-9.
   b. Koyama K, **Chen G**, Wang MY, Lee Y, Shimabukuro M, Newgard CB, Unger RH. Beta-cell function in normal rats made chronically hyperleptinemic by adenovirus-leptin gene therapy. Diabetes. 1997 Aug;46(8):1276-80.
   c. Shimabukuro M, Koyama K, **Chen G**, Wang MY, Trieu F, Lee Y, Newgard CB, Unger RH. Direct antidiabetic effect of leptin through triglyceride depletion of tissues. Proc Natl Acad Sci U S A. 1997 Apr 29;94(9):4637-41.

2. The islets isolated from animals have been the major tools to study the regulation of insulin secretion and β-cell functions. Therefore, a pancreatic β-cell line with robust glucose-stimulated insulin secretion is very important. In addition, it had been thought that the immune system destroys the pancreatic β-cells via cytotoxicity mediated by cytokines such as interleukin 1β and γ-interferon. As a PhD student under Dr. Christopher Newgard, I originated a novel idea to select cytokine-resistant INS-1 cells in media with increasing doses of these two cytokines. I designed, performed, and accomplished the research work by myself. Moreover, we found that the parental INS-1 cell line contained cells with different glucose-stimulated insulin secretion responses. This led to the identification of clonal INS-1 cells with high glucose-stimulated insulin secretion responses (high responders). These cell lines have been useful tools to study physiology of pancreatic β-cells.
   a. **Chen G**, Hohmeier HE, Gasa R, Tran VV, Newgard CB. Selection of insulinoma cell lines with resistance to interleukin-1beta- and gamma-interferon-induced cytotoxicity. Diabetes. 2000 Apr;49(4):562-70.
   b. Hohmeier HE, Mulder H, **Chen G**, Henkel-Rieger R, Prentki M, Newgard CB. Isolation of INS-1-derived cell lines with robust ATP-sensitive K+ channel-dependent and -independent glucose-stimulated insulin secretion. Diabetes. 2000 Mar;49(3):424-30.
   c. **Chen G**, Hohmeier HE, Newgard CB. Expression of the transcription factor STAT-1 alpha in insulinoma cells protects against cytotoxic effects of multiple cytokines. J Biol Chem. 2001 Jan 5;276(1):766-72.

3. Hyperlipidemia is commonly associated with metabolic diseases such as obesity and type 2 diabetes. Insulin is needed for the induction of hepatic lipogenesis during refeeding, a process mediated by sterol regulatory element-binding protein 1c (SREBP-1c), a major transcription factor to induce lipogenesis in the liver. As a postdoc fellow in the lab of Drs. Michael Brown and Joseph Goldstein at UTSW, I was assigned to identify the insulin responsive element in the promoter SREBP-1c gene (*Srebp-1c*). The challenge then was to develop a reporter gene assay in primary rat hepatocytes, which are only cells with insulin-induced *Srebp-1c* expression. I systemically tested transfection conditions such as the medium pH, and finally optimized the reporter gene assay, and identified the insulin responsive elements of *Srebp-1c* gene. Here, the challenge became an opportunity to learn and grow independently. Later on, it has helped me to identify retinoic acid responsive element (RARE) in the promoters of the cytosolic form of phosphoenolpyruvate carboxykinase gene (*Pck1*), *Gck*, and *Srebp-1c*. These RAREs demonstrate the convergence of a hormone (insulin) and a nutrient (VA) in the control of metabolism.
   a. **Chen G**, Liang G, Ou J, Goldstein JL, Brown MS. Central role for liver X receptor in insulin-mediated activation of *Srebp-1c* transcription and stimulation of fatty acid synthesis in liver. Proc Natl Acad Sci U S A. 2004 Aug 3;101(31):11245-50.

b. **Li R, Chen W, Li Y, Zhang Y, **Chen G.** Retinoids synergized with insulin to induce *Srebp-1c* expression and activated its promoter via the two liver X receptor binding sites that mediate insulin action. Biochem Biophys Res Commun. 2011 Mar 11;406(2):268-72.

c. **Howell M, Li R, Zhang R, Li Y, Chen W, **Chen G.** The expression of *Apoc3* mRNA is regulated by HNF4α and COUP-TFII, but not acute retinoid treatments, in primary rat hepatocytes and hepatoma cells. Mol Cell Biochem. 2014 Feb;387(1-2):241-50.

d. **Kuang, H., Wei, CH., Wang, T., Eastep, J., Li, Y., **Chen, G.** Vitamin A Status Affects Weight Gain and Hepatic Glucose Metabolism in Rats Fed a High-Fat Diet. Mol Cell Biochem. 2019 (Epub ahead of print)

4. The interactions of hormones and nutrients contribute to the development of metabolic diseases. However, how nutrient and hormone pathways converge to regulate the hepatic gene expression is still an open question. To understand this, I examined the liver-derived lipophilic molecules that can positively or negatively affect the insulin-regulated hepatic gene expression in primary rat hepatocytes. Opportunities arrived when the rat liver lipophilic extract affected the insulin-regulated expression levels of *Pck1*, *Gck*, and *Srebp-1c* in primary rat hepatocytes. This allowed me to purify and identify the active molecules as retinoids. I established collaboration with Dr. Catherine Ross at Penn State University to study the effect of reinoids and VA deficiency on the hepatic *Gck* expression. This finding allowed me to secure the Scientist Development Grant from American Heart Association to study the mechanism. Later on, we identified a RARE in the promoter of hepatic *Gck* promoter. This RARE interacts with multiple transcription factors including retinoic acid receptor (RAR), retinoid X receptor (RXR), hepatocyte nuclear factor 4α (HNF4α), and chicken ovalbumin upstream transcription factor II (COUP-TFII) in the rat liver nuclear extract. It suggests that both hormonal and nutritional signals work together to regulate the dynamic associations of these transcription factors with the *Gck* RARE, and in turn, control its expression in the liver.

a. **Chen G.** Liver lipid molecules induce PEPCK-C gene transcription and attenuate insulin action. Biochem Biophys Res Commun. 2007 Sep 28;361(3):805-10.

b. **Chen G**, Zhang Y, Lu D, Li NQ, Ross AC. Retinoids synergize with insulin to induce hepatic *Gck* expression. Biochem J. 2009 May 1;419(3):645-53.

c. *Zhang Y, Li R, Chen W, Li Y, **Chen G.** Retinoids induced *Pck1* expression and attenuated insulin-mediated suppression of its expression via activation of retinoic acid receptor in primary rat hepatocytes. Mol Cell Biochem. 2011 Sep;355(1-2):1-8.

d. **Li R, Zhang R, Li Y, Zhu B, Chen W, Zhang Y, **Chen G.** A RARE of hepatic *Gck* promoter interacts with RARα, HNF4α and COUP-TFII that affect retinoic acid- and insulin-induced *Gck* expression. J Nutr Biochem. 2014 Sep;25(9):964-76.

5. Insulin regulates metabolic homeostasis, at least partially, through the control of the hepatic gene expression. My lab has compared the insulin-regulated gene expression in primary hepatocytes isolated from Zucker fatty (ZF) and Zucker lean (ZL) rats. We found that the insulin-regulated *Srebp-1c* and *Pck1* expressions are impaired in hepatocytes from ZF rats fed ad libitum, but not those from ZF rats fasted for overnight or ZL rats. We named this phenomenon as the HIRAGE (hepatic insulin resistance at gene expression). This impairment is partially corrected in hepatocytes in ZF rats fed a VA deficient diet for eight weeks. More importantly, this impairment was observed in hepatocytes from ZL rats after a transition over-eating. We also observed that the expression level of retinal dehydrogenase 1 (RALDH1), an enzyme responsible of the hepatic retinoic acid production, in hepatocytes of ZF rats is higher than that of ZL rats. This suggests a potential linkage between HIRAGE and vitamin A metabolism. My lab has independently established a system to investigate the dietary energy intake and nutrient compositions on the HIRAGE. This nutritional study will help us to reveal the underlying mechanisms of the hepatic insulin resistance.

a. *Zhang Y, Chen W, Li R, Li Y, Ge Y, **Chen G.** Insulin-regulated *Srebp-1c* and *Pck1* mRNA expression in primary hepatocytes from Zucker fatty but not lean rats is affected by feeding conditions. PLoS One. 2011;6(6):e21342.

b. **Li Y, Zhang Y, Li R, Chen W, Howell M, Zhang R, **Chen G.** The hepatic *Raldh1* expression is elevated in Zucker fatty rats and its over-expression introduced the retinal-induced *Srebp-1c* expression in INS-1 cells. PLoS One. 2012;7(9):e45210.

c. **Chen W, Howell ML, Li Y, Li R, Chen G. Vitamin A and feeding statuses modulate the insulin-regulated gene expression in Zucker lean and fatty primary rat hepatocytes. PLoS One. 2014 Aug 8;9(8):e100868.

d. **Li, Y., Liu, Y. and Chen, G. Vitamin A Status Affects the Plasma Parameters and Regulation of Hepatic Genes in Streptozotocin-Induced Diabetic Rats. Biochimie. 2017; 137:1-11.

D. RESEARCH SUPPORT

Funded and in Progress

Time: 2019/01/01-2019/12/31 (No cost extension to 2020/06/30)
Agency: Diabetes Action Research and Education Foundation
Name (Role): Guoxun Chen (Principal Investigator)
Title: Determine the role of vitamin A in the development of type 2 diabetes in Zucker diabetic fatty rats
Description: We hypothesize that variations of dietary intake of vitamin A (VA) will modulate the obesity development and onset of type 2 diabetes in Zucker diabetes fatty rats (ZDF) rats. The purpose of this design is to find out whether dietary VA amount will be able to correct the development of type 2 diabetes and whether this correction is associated with changes of energy expenditures.

Time: 2018/05/01-2020/04/30 (No cost extension to 2020/08/31)
Agency: Zestern Biotechnology LLC
Name (Role): Guoxun Chen (Principal Investigator)
Title: Analysis of insulin-regulated glucose transporter 4 protein expression using a novel quantitative dot blot method and traditional western-blot
Description: Quantitative dot blot (QDB) is a novel method developed by Zestern Biotechnology LCC to quantify the protein levels in biological samples. Here, we hypothesize that long-term insulin treatment (> 48 hours) regulates the GLUT4 protein level in L6 cells. This proposal is to investigate the expression level of glucose transporter 4 (GLUT4) in L6 cells using both QDB and Western-blot.

Completed Research Support

Time: 2015/10/01-2017/09/30
Agency: Zestern Biotechnology LLC
Name (Role): Guoxun Chen (Principal Investigator)
Title: Regulation of Raldh1 mRNA and protein levels in the liver of rats in the cycle of fasting and refeeding
Description: This proposal is to determine whether the expression levels of retinaldehydrogenase 1 (Raldh1 for gene and RALDH1 for protein) are altered during normal cycle of fasting and refeeding. The traditional Western Blot and a novel technique for antibody-based protein detection will be used to determine the hepatic RALDH1 protein levels in Zucker lean rats in the cycle of fasting and refeeding.

Time: 2009/07/01-2013/06/30
Agency: 09SDG2140003, American Heart Association National Program
Name (Role): Guoxun Chen (Principal Investigator)
Title: Determining the Mechanism by Which Retinoids Synergize with Insulin to Stimulate Hepatic *Gck* Expression
Description: The overall goal of the project was to identify the mechanism by which retinoids synergize with insulin to induce the hepatic glucokinase expression. Glucokinase is essential for glucose homeostasis. We have identified a retinoid acid response element (RARE) in the promoter of hepatic *Gck* expression. This RARE interacts with RARα, RXRα, HNF4α and COUP-TFII.