BIOGRAPHICAL SKETCH

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NAME: Huang, Yingqun

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

POSITION TITLE: 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
Fudan University School of Medicine, China	B.S., M.D.	05/88	Medicine
Fudan University School of Medicine, China	M.S.	05/91	Pathophysiology
University of Connecticut Health Center	Ph.D.	05/97	Biomedical Sciences
University of Connecticut Health Center	Postdoctoral	07/99	Molecular Biology
Yale University School of Medicine	Postdoctoral	07/03	Molecular Biology
Yale University	Master of Art	07/20	Honorary Degree

A. Personal Statement

As a graduate student and postdoctoral fellow, I was interested in the rules and mechanisms governing the nucleocytoplasmic transport of mRNAs. I discovered a subset of SR proteins as a new class of mRNA nuclear export factors. These were originally thought to act solely as mRNA splicing factors, but I showed that they also interact with the mRNA export protein NXF1 to promote export. This work changed basic conceptions of mRNA export and my model has become the most widely accepted one for the role of SR proteins in mRNA export. As an independent investigator, I first studied the RNA-binding protein LIN28, which was among four factors shown to reprogram somatic cells to induced pluripotent stem cells. The field once believed that blocking the biogenesis of miRNA let-7 was the only function of LIN28, but my research showed that LIN28 is also a master posttranscriptional regulator of a subset of mRNAs involved in regulating growth and metabolism in human embryonic stem cells. In recent years, we have used cell and mouse models and an interdisciplinary approach to demonstrate the potential of noncoding RNAs, such as lncRNA H19 and miRNA let-7, as targets and/or therapeutics for type-2 diabetes and tumors. In the last few years, I have extended my research to the epigenetic factor TET3 and was the first to unmask its role in glucose metabolism and energy homeostasis. Most recently, while testing a small molecule inhibitor of TET in mice for treating diabetes I unexpectedly found that it induces hyperphagia. This serendipitous finding has led to my recent discovery of TET3 in central control of feeding and energy balance as well as other complex behaviors. Results from these studies (part of which have been published in the *Journal of Clinical Investigation*) have contributed to the conceptual framework and preliminary data of the current proposal. Thinking “out-of-box” and perseverance are additional strengths that I believe have characterized my scientific career. My interdisciplinary experience and expertise have positioned me perfectly for successful completion of the proposed project.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

1997-1999 Postdoctoral Fellow, Department of Microbiology, University of Connecticut Health Center
1999-2003 Postdoctoral Fellow, Department of Molecular Biophysics & Biochemistry, Yale University School of Medicine

2003-2010 Assistant Professor, Department of Obstetrics, Gynecology & Reproductive Sciences, Yale University School of Medicine
2010-2020 Associate Professor, Department of Obstetrics, Gynecology & Reproductive Sciences, Yale University School of Medicine
2020- Professor, Department of Obstetrics, Gynecology & Reproductive Sciences, Yale University School of Medicine

Honors, Awards, and Patents

1988 Rong-Ling's Award for Graduation with Distinction in Medicine
1997 Edward G. Henderson Memorial Prize for outstanding Ph.D. thesis in Biomedical Sciences
1999 US Patent No. 5,990,298, "Cis-acting Cellular Nucleic Acid Molecules"
2000-2003 Ruth L. Kirschstein National Research Service Award
2005-2006 Fannie E. Rippel Foundation Award
2006 Technology licensing, "Development of a polyclonal antibody specific for the mouse NXF2"
2013 Harold Behrman Teaching Award
2015-2016 Bennack-Polan Foundation Award
2020- International Patent No. PCT/US20/26290, "Methods of treatment of diseases and disorders associated with increased TET level, increased H19 level, increased level of TGF signaling, or any combination thereof"
2022- Provisional Patent No. 63/378.121, "Compositions and methods of treating or preventing endometriosis and other diseases or disorders"

C. Contributions to Science

1. The RNA binding protein Lin28 is highly expressed in human embryonic stem cells and is among four factors shown to reprogram somatic cells to induced pluripotent stem cells. The field had once believed that blocking the biogenesis of microRNA let-7 was the only function of Lin28. Studies from my lab however has shifted the field to accept that Lin28 is also a master posttranscriptional regulator of a subset of mRNAs involved in regulating cell growth and metabolism.

a. Qiu C, Ma Y, Wang J, Peng S, **Huang Y**. (2010) Lin28-mediated post-transcriptional regulation of Oct4 expression in human embryonic stem cells. ***Nucleic Acids Res.*** 38:1240-8. PMID: 1996627
b. Peng S, Chen LL, Lei XX, Yang L, Lin H, Carmichael GG, **Huang Y**. (2011) Genome-wide studies reveal that Lin28 enhances the translation of genes important for growth and survival of human embryonic stem cells. ***Stem Cells****.* 29:496-504. PMID: 21425412
c. Jin J, Jing W, Lei XX, Feng C, Peng S, Boris-Lawrie K, **Huang Y.** (2011) Evidence that Lin28 stimulates translation by recruiting RNA helicase A to polysomes. ***Nucleic Acids Res****.* 39:3724-34. PMID: 21247876
d. **Huang Y**. (2012) A mirror of two faces: Lin28 as a master regulator of both miRNA and mRNA. ***Wiley Interdiscip Rev RNA****.* 3:483-94. PMID: 22467269

2. The developmentally regulated, imprinted H19 lncRNA has long been implicated in human genetic disorders and cancer. However, the physiological function and mode of action of this conserved lncRNA have remained elusive. Using gene knockdown and overexpression, combined with genome-wide transcriptome analysis, we show that H19 inhibits microRNA let-7 function by acting as a molecular "sponge". We highlight the physiological significance of this finding by showing that depletion of H19 causes precocious muscle differentiation, a phenotype recapitulated by let-7 overexpression *in vitro*. As let-7s comprise a major microRNA family known to play important roles in development, cancer, and metabolism, this discovery has far-reaching impact on all of these areas. Recently, we discovered yet another function of H19: it interacts with adenosylhomocysteine hydrolase (SAHH), the only mammalian enzyme capable of hydrolyzing S-adenosylhomocysteine (SAH), which is a potent feedback inhibitor of SAM-dependent methyltransferases including DNA methyltransferases. H19 binds to SAHH and inactivates its enzymatic activity, thereby altering DNA methylation in a genome-wide fashion.

a. Kallen AN, Zhou XB, Xu J, Qiao C, Ma J, Yan L, Lu L, Liu C, Yi JS, Zhang H, Min W, Bennett AM, Gregory RI, Ding Y, **Huang Y**. (2013) The imprinted H19 lncRNA antagonizes let-7 microRNAs. ***Mol Cell****.* 52:101-12. PMID: 2405534

b. Zhou J, Yang L, Zhong T, Mueller M, Men Y, Zhang N, Xie J, Giang K, Chung H, Sun X, Lu L, Carmichael GG, Taylor HS, **Huang Y**. (2015) H19 lncRNA alters DNA methylation genome-wide by regulating S-adenosylhomocysteine hydrolase. ***Nat Commun.*** 6:10221. PMID: 26687445
c. Zhang N, Geng T, Wang Z, Zhang R, Cao T, Camporez JP, Cai SY, Liu Y, Dandolo L, Shulman GI, Carmichael GG, Taylor HS, **Huang Y**. (2018) Elevated hepatic expression of H19 long noncoding RNA contributes to diabetic hyperglycemia. ***JCI Insight.*** 3:e120304. PMID: 29769440
d. Geng T, Liu Y, Xu Y, Jiang Y, Zhang N, Wang Z, Carmichael GG, Taylor HS, Li D, **Huang Y.** (2018) H19 lncRNA promotes skeletal muscle insulin sensitivity in part by targeting AMPK. ***Diabetes***. 67:2183-2198. PMID: 30201684

3. The evolutionarily conserved, liver-enriched transcription factor HNF4α has been extensively studied for its role in hepatic differentiation and function. The gene contains two promoters, P2 and P1, which drive multiple HNF4a isoforms in a development- and tissue-specific manner. It was long thought that the P2-derived isoform predominates during fetal development, however after birth the P1-derived isoform takes over, directing a wide range of liver functions including hepatic glucose production (HGP). In contrast to the long-standing dogma in the field, we discovered epigenetic P2 promoter reactivation in adult liver with an essential role in control of HGP both under physiological and pathological conditions. Using mouse and human primary hepatocytes and mouse models, we demonstrated that this regulation involves H19 lncRNA and an epigenetic mechanism mediated by TET3 not previously shown to have a role in glucose regulation. Importantly, we showed that inhibition of TET3 or only the P2-specific isoform alleviated type-2 diabetes in both dietary and genetic mouse models. We concluded that the TET3-mediated reactivation of HNF4α P2 promoter and its derived isoform reflect a previously unexpected regulatory mechanism of HGP in adult liver. More recently, we discovered that let-7 mediates metformin-induced inhibition of HGP via targeting the TET3/HNF4α P2 axis and that liver-specific delivery of let-7 ameliorated hyperglycemia and improved glucose homeostasis in mouse models of diabetes.

a. Da Li, Cao T, Sun X, Jin S, Di Xie, Huang X, Yang X, Carmichael GG, Taylor HS, Diano S, **Huang Y**. (2020) Hepatic TET3 contributes to type-2 diabetes by inducing the HNF4a fetal isoform. ***Nat Commun.*** 11:342. PMID: 31953394
b. Xie D, Chen F, Zhang Y, Shi B, Song J, Chaudhari K, Yang S-H, Zhang GJ, Sun X, Taylor HS, Li D, **Huang Y**. (2022) Let-7 underlies metformin-induced inhibition of hepatic glucose production. ***Pro Natl Aca Sci USA.*** 119(14):e2122217119. PMID: 35344434

4. The TET family of proteins have been well studied in the areas of development, stem cells, and cancer, but their central role in regulation of feeding and energy metabolism had never been documented. We were the first to report that CRISPR-mediated genetic ablation of *Tet3* specifically in hypothalamic AGRP induces hyperphagia, obesity and diabetes, in addition to reduction of stress-like behaviors. Mechanistically, TET3 deficiency activates AGRP neurons, simultaneously upregulates the expressions of *Agrp*, *Npy* and vesicular GABA transporter *Slc32a1*, and impedes leptin signaling. In particular, we uncovered a dynamic association of TET3 with the *Agrp* promoter in response to leptin signaling, which induces association of a chromatin-modifying complex leading to transcription inhibition, and that this regulation occurs both in mouse models and human cells. Our results unmasked TET3 as a critical central regulator of appetite and energy metabolism while revealing its unexpected dual role in control of feeding and other complex behaviors through AGRP neurons.

a. Xie D, Stutz B, Li F, Chen F, Lv H, Sestan-Pesa M, Catarino J, Gu J, Zhao H, Stoddard C, Carmichael GG, Shanabrough M, Taylor HS, Liu ZW, Gao XB, Horvath TL, **Huang Y.** (2022) TET3 epigenetically controls feeding and stress response behavior via AGRP neurons. ***J Clin Invest***. 132:e162365

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