Shu-Hao Hsu, Ph.D.

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Education

THE OHIO STATE UNIVERSITY | Columbus, OH

Ph.D. in Molecular, Cellular and Developmental Biology, 2006-2012

- Mentor: Dr. Samson Jacob; Co-advisor: Dr. Kalpana Ghoshal.
- Area of specialization: microRNA (miR)-oriented study in hepatocarcinogenesis.
- Thesis: *The Biological Functions of miR-122 and its Therapeutic Application in Liver Cancer.*

NATIONAL TAIWAN UNIVERSITY | Taipei, Taiwan

M.S. in Anatomy and Cell Biology, 2001-2003

- Mentor: Dr. Sung-Tsang Hsieh.
- Area of specialization: morphological study of cutaneous nerve innervation; human gross anatomy, histology, and neuroanatomy.
- Thesis: *Cutaneous Innervation in mf Rats.*

B.S. in Zoology, 1997-2001

Research Interests

- Molecular mechanism involved in the liver polyploidy and aneuploidy.
- microRNA-mediated differentiation of embryonic stem cells.
- Generation and phenotypic analysis of animal models of human liver diseases.
- Development of microRNA based cancer therapeutics.

Work Experience

2015-present **Assistant Professor, Dept. of Anatomy and Cell Biology, National Taiwan University, Taipei, Taiwan.**

2013-2015 **Postdoctoral Associate, Dept. of Pathology, University of Pittsburgh, Pittsburgh, PA.**

2005-2006 **Research Associate, Dept. of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan.**

2003-2005 **Teaching Associate, Dept. of Anatomy and Cell Biology, College of**

Medicine, National Taiwan University, Taipei, Taiwan.

Awards

- **Oral presentation, FASEB SRC- Liver Biology: Fundamental Mechanisms and Translational Applications (2014).**
- **Oral presentation, Department of Pathology 14th Annual Retreat (2014).**
- **Scholar-in-Training Award in American Association for Cancer Research (AACR) 102th annual meeting (2011).**
- **Poster Award in OSU Comprehensive Cancer Center -James 12th Annual Scientific Meeting (2011).**
- **Poster Award in OSU Molecular Life Sciences Interdisciplinary Graduate Programs Symposium (2011)**.
- **Dean's award of the college of science, (2001)**
- **Dr. Da-qui Chei and Song-yen Fong Memorial Scholarship (2001)**

Publications

1. **Hsu SH**, Delgado ER, Otero PA, Teng KY, Kutay H, Meehan KM, Moroney JB, Monga JK, Hand NJ, Friedman JR, Ghoshal K, Duncan AW. (2016) MicroRNA-122 Regulates Polyploidization in the Murine Liver. ***Hepatology***. Mar 26. doi: 10.1002/hep.28573. [Epub ahead of print.]
2. **Hsu SH**, Duncan AW (2015). Pathological polyploidy in liver disease. ***Hepatology***, Sep; 62(3):968-70.
3. Wang X, He H, Lu Y, Ren W, Teng KY, Chiang CL, Yang Z, Yu B, **Hsu S**, Jacob ST, Ghoshal K, Lee LJ. (2015). Indole-3-carbinol inhibits tumorigenicity of hepatocellular carcinoma cells via suppression of microRNA-21 and upregulation of phosphatase and tensin homolog. ***Biochim Biophys Acta***. Jan; 1853(1):244-53.
4. Eichhorn SW, Guo H, McGeary SE, Rodriguez-Mias RA, Shin C, Baek D, **Hsu SH**, Ghoshal K, Villén J, Bartel DP. (2014) mRNA Destabilization Is the Dominant Effect of Mammalian MicroRNAs by the Time Substantial Repression Ensues. ***Mol Cell.*** Oct 2;56(1):104-15.
5. Wang B, **Hsu SH,** Wang X, Kutay H, Bid HK, Yu J, Ganju R, Jacob S, Yuneva M, Ghoshal K. (2014) Reciprocal regulation of miR-122 and c-Myc in hepatocellular cancer: Role of E2F1 and TFDP2. ***Hepatology***. Feb;59(2):555-66.
6. **Hsu SH**, Wang B, Kutay H, Bid H, Shreve J, Zhang X, Costinean S, Bratasz A, Houghton P, Ghoshal K. (2013) Hepatic loss of miR-122 predisposes mice to hepatobiliary cyst and HCC upon diethylnitrosamine exposure. ***Am J Pathol*** . Dec;183(6):1719-30.
7. **Hsu SH**, Yu B, Wang X, Lu Y, Schmidt CR, Lee RJ, Lee LJ, Jacob ST, Ghoshal K. (2013) Cationic lipid nanoparticles for therapeutic delivery of siRNA and miRNA to murine liver tumor. ***Nanomedicine***. Nov;9(8):1169-80.
8. **Hsu SH**, Ghoshal K. (2013) MicroRNAs in Liver Health and Disease. ***Curr Pathobiol Rep.*** Mar;1(1):53-62.

9. **Hsu SH,** Motiwala T, Roy S, Claus R, Mustafa M, Plass C, Freitas MA, Ghoshal K, Jacob ST. (2013) Methylation of gene encoding the growth suppressor protein tyrosine phosphatase receptor-type O (PTPRO) in human hepatocellular carcinoma and identification of VCP as its bona fide substrate. ***J Cell Biochem***. Mar 26. Aug;114(8):1810-8.
10. **Hsu SH**, Wang B, Kota J, Yu J, Costinean S, Kutay H, Yu L, Bai S, La Perle K, Chivukula RR, Mao H, Wei M, Clark KR, Mendell JR, Caligiuri MA, Jacob ST, Mendell JT, Ghoshal K. (2012) Essential metabolic, anti-inflammatory and anti-tumorigenic functions for miR-122 in mouse liver. ***J Clin Invest.*** Aug; 122 (8).
11. Yu B, **Hsu SH**, Zhou C, Wang X, Terp MC, Wu Y, Teng L, Mao Y, Wang F, Xue W, Jacob ST, Ghoshal K, Lee RJ, Lee LJ. (2012) Lipid nanoparticles for hepatic delivery of small interfering RNA. ***Biomaterials***, Sep; 33 (25).
12. Kutay H, Klepper Corie, Wang B, **Hsu SH**, Datta J, Yu L, Zhang X, Majumder S, Motiwala T, Kahn N, Belury M, McClain C, Jacob ST, Ghoshal K. (2012) Reduced susceptibility of DNA methyltransferase 1 hypomorphic (Dnmt1N/+) mice to hepatic steatosis upon feeding liquid alcohol diet. ***Plos One***. (E-pub, **co-first author**)
13. Wang B, **Hsu SH**, Frankel W, Ghoshal K, Jacob ST. (2012) Stat3-mediated activation of miR-23a suppresses gluconeogenesis in hepatocellular carcinoma by downregulating G6PC and PGC-1α. ***Hepatology*****,** Jul; 56 (1).
14. Tsuei DJ, Lee PH, Peng HY, Lu SL, Su DS, Jeng YM, Hsu HC, **Hsu SH**, Wu JF, Ni YH, Chang MH. (2011) Male germ cell-specific RNA binding protein RBMY: a new oncogene explaining male predominance in liver cancer. ***PLoS One***, Nov; 6 (11).
15. Wang B, **Hsu SH**, Majumder S, Kutay H, Huang W, Jacob ST, Ghoshal K. (2010) TGFbeta-mediated upregulation of hepatic miR-181b promotes hepatocarcinogenesis by targeting TIMP3. ***Oncogene***, Mar; 29 (12).
16. Bai S, Nasser MW, Wang B, **Hsu SH**, Datta J, Kutay H, Yadav A, Nuovo G, Kumar P, Ghoshal K. (2009) MicroRNA-122 inhibits tumorigenic properties of hepatocellular carcinoma cells and sensitizes these cells to sorafenib. ***J Biol Chem*****.**, Nov; 284 (46).
17. **Hsu SH**, Lee MJ, Hsieh SC, Scaravilli F, Hsieh ST. (2004) Cutaneous and sympathetic denervation in neonatal rats with a mutation in the delta subunit of the cytosolic chaperonin-containing t-complex peptide-1 gene. ***Neurobiol Dis*****.**, Jul;16 (2).

miR-122, the most abundant liver-specific microRNA (miRNA), was known as a key regulators in cholesterol metabolism and hepatitis C virus (HCV) replication. In patients with hepatocellular carcinoma (HCC), reduced miR-122 expression frequently correlates with metastasis and poor prognosis. However, it is not clear if sustained miR-122 loss may directly cause HCC development. To address this, we generated a germ-line and liver specific miR-122 knockout mice to evaluate the biological function of miR-122 *in vivo.* As a result, the deletion of mouse Mir122 promoted hepato-steatosis, hepatitis, and the development of tumors resembling human HCC. These pathologic manifestations were associated with hyperactivity of oncogenic pathways and hepatic infiltration of inflammatory cells that produce pro-tumorigenic cytokines, including IL-6 and TNF. Moreover, delivery of miR-122 to a MYC-driven mouse model of HCC strongly inhibited tumorigenesis, further supporting the tumor suppressor activity of this miRNA. Lastly, we observed profound, lifelong depletion of polyploid hepatocytes, proving that miR-122 is required for complete hepatic polyploidization. The connection between this impaired polyploidization and tumorigenesis remains to be elucidated.

To establish further the tumor suppressor role of miR-122, we tested the feasibility of the therapeutic delivery of miR-122 to the liver and tumor cells by lipid-based nanoparticles, which is recognized as a safe delivery method due to its biocompatibility. LNP-DP1, a novel DODMA based cationic lipid nanoparticle formulation, was thus developed as a vehicle to deliver miR-122. *In vitro*, LNP-DP1-mediated transfection of a miR-122 mimic to HCC cells down-regulated miR-122 target genes by >95%. *In vivo*, siRNAs/miRNAs encapsulated in LNP-DP1 were preferentially taken up by hepatocytes and tumor cells in miR-122 KO mice without causing systemic toxicity. Moreover, we intratumorally injected LNP-DP1 encapsulating miR-122 mimic to HCC xenograft and resulted in ~50% growth suppression of cancer cells within 30 days, which correlated well with suppression of target genes and impairment of angiogenesis. Taken together, these findings revealed critical biological functions of miR-122 and suggested potential utility of nanoparticles-based miR-122 therapy for HCC patients.