Symposium 13

Obesity Related Comorbidity-Fatty Liver

Chairpersons

Chang Beom Lee
Hanyang University, Korea

Geeta Appannah
University Putra Malaysia, Malaysia

Speakers

Seung-Jin Kim
Kangwon National University, Korea

Hua Wang
The First Affiliated Hospital of Anhui Medical University, China

Jun Hwa Hong
Eulji University, Korea

Panel Discussion

Bo Kyung Koo
Seoul National University, Korea

Youn Huh
Eulji University, Korea

Seung-Jin Kim

Kangwon National University, Korea

Education

Period	Affiliation	Position
– **2008-2013**	Chonnam National University	Ph.D.
– **2006-2008**	Chonnam National University	M.S.
– **2000-2006**	Chonnam National University	B.S.

Affiliations / Experience

Period	Affiliation	Position
– **2024-Present**	Kangwon National University	Associate Professor
– **2019-2024**	Kangwon National University	Assistant Professor
– **2015-2019**	NIAAA/NIH	Post-Doc Fellow
– **2014-2015**	NIDDK/NIH	Post-Doc Fellow

Committee Memberships

- American Association for the Study of Liver Diseases (AASLD, USA)
- American Association for Cancer Research (AACR, USA)
- Korean Society for Biochemistry and Molecular Biology (KSBMB, Korea)
- Korean Society for Molecular and Cellular Biology (KSMCB, Korea)
- Review Editor: Frontiers in Immunology

Publications

- Alcohol, adipose tissue and liver disease: mechanistic links and clinical considerations. Nature Reviews Gastroenterol. & Hepatol
- Adipocyte death preferentially induces liver injury and inflammation through the activation of chemokine (C-C Motif) receptor 2-positive macrophages and lipolysis. Hepatology
- Obesity increases morbidity and mortality in alcoholic hepatitis. EBioMedicine
- Deletion of adipocyte prohibitin 1 exacerbates high-fat diet-induced steatosis but not liver inflammation and fibrosis. Hepatol. Commun
- BRCA1 function in the intra-S checkpoint is activated by acetylation via a pCAF/SIRT1 axis. Oncogene

Symposium 13

Impact of Adipocyte Death on Steatotic Liver Disease (SLD)

Seung-Jin Kim (Kangwon National University, Korea)

The current presentation discusses mouse models which focus on metabolic diseases. Adipocyte death occurs under various pathophysiological conditions, including obesity and alcohol drinking, and can trigger organ damage particularly in the liver, but the underlying mechanisms remain obscure. To explore these mechanisms, we developed a mouse model of inducible adipocyte death by overexpressing the human CD59 (hCD59) on adipocytes (adipocyte-specific hCD59 transgenic mice). Injection of these mice with intermedilysin (ILY), which rapidly lyses hCD59 expressing cells exclusively by binding to the hCD59 but not mouse CD59, resulted in the acute selective death of adipocytes, adipose macrophage infiltration, and elevation of serum free fatty acid (FFA) levels. ILY injection also resulted in the secondary damage to multiple organs with the strongest injury observed in the liver, with inflammation and hepatic macrophage activation. Mechanistically, acute adipocyte death elevated epinephrine and norepinephrine levels and activated lipolysis pathways in adipose tissue in a chemokine (C-C motif) receptor 2-positive (CCR2+) macrophage-dependent manner, which was followed by FFA release and lipotoxicity in the liver. Additionally, acute adipocyte death caused hepatic CCR2+ macrophage activation and infiltration, further exacerbating liver injury. Our findings suggest that adipocyte death predominantly induces liver injury and inflammation, which is probably due to the superior sensitivity of hepatocytes to lipotoxicity and the abundance of macrophages in the liver.

Hua Wang

The First Affiliated Hospital of Anhui Medical University, China

• Education

Period	Affiliation	Position
– **2007-2014**	Laboratory of Liver Diseases, NIAAA, NIH. (Liver Biology)	Postdoctoral
– **1994-1999**	Department of Clinical Medicine, Anhui Medical University	M.D.
– **1999-2005**	Institute of Clinical Pharmacology, Anhui Medical University	Ph..D.

• Affiliations / Experience

Period	Affiliation	Position
– **2019-Present**	Research Office of Anhui Medical University	Deputy Director
– **2014-2018**	Laboratory of Liver Diseases, NIAAA, NIH	Guest Researcher
– **2014-Present**	Department of Oncology, The First Affiliated Hospital of Anhui Medical University	Oncologist
– **2012-Present**	Deputy Director, Institute for Liver Disease, Anhui Medical University	Professor
– **2012-Present**	School of Pharmacy, Anhui Medical University, China	Professor

• Committee Memberships

- Chinese Association for Pharmacology
- The American Association of Immunologists (AAI)
- American Association for the Studies of Liver Disease (AASLD)

• Publications

- Dai H#, Zhu C#, Huai Q#, Xu W, Zhu J, Zhang X, Zhang X, Sun B, Xu H, Zheng M, Li X*, Wang H*. Chimeric antigen receptor-modified macrophages ameliorate liver fibrosis in preclinical models. J Hepatol. 2024 Jun;80(6):913-927
- Wang J#, Wang X#, Peng H, Dong Z, Liangpunsakul S, Zuo L*, Wang H*. Platelets in Alcohol-Associated Liver Disease: Interaction With Neutrophils. Cell Mol Gastroenterol Hepatol. 2024 Mar 8;18(1):41-52. doi: 10.1016/j.jcmgh.2024.03.001
- Fu S#, Liu M#, Zhu C, Zhang H, Zhao C, Xie Y, Chen G, Sheng D, Pan J, He Z, Dai Y, Gao Y, Li X, Chen L, Qian Y, Jin T, Sun C, Tian Z, Wang H*, Bai L*. Regulatory mucosa-associated invariant T cells controlled by β1 adrenergic receptor signaling contribute to hepatocellular carcinoma progression. Hepatology. 2023 Jul 1;78(1):72-87. doi: 10.1097/HEP.0000000000000014
- Xu L#,Yang Y#,Wen X, Jeong J, Emontzpohl C, Atkins C, Sun Z, Poulsen K, Hall D, Bynon J, Gao B, Lee W, Rule J, Jacobsen E, Wang H*, Ju C*. Hepatic recruitment of eosinophils and their protective function during acute liver injury. J of Hepatol. 2022 Aug;77(2):344-352
- Wei X#, Yin F#, Wu M#, Xie Q, Zhao X, Zhu C, Xie R, Chen C, Liu M, Wang X, Ren R, Kang G, Zhu C, Cong J, Wang H*, Wang X*. G protein-coupled receptor 35 attenuates nonalcoholic steatohepatitis by reprogramming cholesterol homeostasis in hepatocytes. Acta Pharm Sin B. 2023 Mar;13(3):1128-1144. doi: 10.1016/j.apsb.2022.10.011

Symposium 13

GDF15 and Fatty Liver

Hua Wang (The First Affiliated Hospital of Anhui Medical University, China)

Background and aims: liver fibrosis/cirrhosis is significant health burden worldwide, resulting resulting in liver failure or cancer and accounting for many deaths each year. The pathogenesis of liver fibrosis is very complex, which makes treatment challenging. Growth differentiation factor 15 (GDF15), a cysteine knot protein belonging to the transforming growth factor b (TGF-β) superfamily, has been shown to play a protective role after tissue injury and to promote a negative energy balance during obesity and diabetes. However, paucity of literature is available about GDF15 function in liver fibrosis. This study aimed to investigate the immunomodulatory role and therapeutic potential of GDF15 in progression of hepatic fibrosis.
METHODS: GDF15 expression was studied in patients with fibrosis/cirrhosis and in 2 murine models of liver fibrosis, including mice treated with CCl4 or DDC diet. GDF15 involvement in the pathogenesis of liver fibrosis was assessed in Gdf15 knockout mouse using both CCl4 and DDC diet experimental models. We used the CCl4 and/or DDC diet–induced liver fibrosis model to examine the antifibrotic and antiinflammatory effects of AAV8-mediated GDF15.
RESULTS: GDF15 expression is decreased in the liver of animal models and patients with liver fibrosis/cirrhosis compared with those without liver disease. In vivo studies showed that GDF15 deficiency aggravated CCl4 and DDC diet–induced liver fibrosis, while GDF15 overexpression mediated by AAV8 or its recombinant protein alleviated CCl4 and/or DDC diet–induced liver fibrosis. In Gdf15 knockout mice, the intrahepatic microenvironment that developed during fibrosis showed relatively more inflammation, as demonstrated by enhanced infiltration of monocytes and neutrophils and increased expression of proinflammatory factors, which could be diminished by AAV8-mediated GDF15 overexpression in hepatocytes. Intriguingly, GDF15 exerts its effects by reprogramming the metabolic pathways of macrophages to acquire an oxidative phosphorylation–dependent antiinflammatory functional fate. Furthermore, adoptive transfer of GDF15-preprogrammed macrophages to mouse models of liver fibrosis induced by CCl4 attenuatted inflammation and alleviated the progression of liver fibrosis.
CONCLUSION: GDF15 ameliorates liver fibrosis via modulation of liver macrophages. Our data implicate the importance of the liver microenvironment in macrophage programming during liver fibrosis and suggest that GDF15 is a potentially attractive therapeutic target for the treatment of patients with liver fibrosis.

Jun Hwa Hong

Eulji University, Korea

• Education

Period	Affiliation	Position
– **2015**	Eulji University	Ph.D.
– **2008**	Eulji University	M.Sc.
– **2004**	Eulji University	M.D.

• Affiliations / Experience

Period	Affiliation	Position
– **Present**	Eulji University Hospital, Korea	Associate Professor
– **2023**	Eulji University Hospital, Korea	Assistant Professor
– **2017**	Kyungpook National University Hospital, Korea	Clinical Assistant Professor
– **2015**	Chungnam National University Hospital	Fellowship

• Committee Memberships

- The Korean Society for the Study of Obesity
- The Korean Endocrine Society
- The Korean Diabetes Association
- The Daejeon Chungcheong Division of Korean Endocrine Society

• Publications

- Comparison of therapeutic efficacy and safety of sitagliptin, dapagliflozin, or lobeglitazone adjunct therapy in patients with type 2 diabetes mellitus inadequately controlled on sulfonylurea and metformin: third agent study. Diabetes Res Clin Pract. 2023 Aug 11;110872. doi: 10.1016/j.diabres.2023.110872
- Comparison of the effects of gemigliptin versus glimepiride on cardiac function in patients with type 2 diabetes uncontrolled with metformin: The gemi-heart study. Diabetes Obes Metab. 2023 Aug;25(8):2181-2190. doi: 10.1111/dom.15095. Epub 2023 May 3
- A randomized, active-controlled, parallel, open-label, multicenter, phase 4 study to compare the efficacy and safety of pregabalin sustained release tablet and pregabalin immediate release capsule in type II diabetic patients with peripheral neuropathic pain. Medicine (Baltimore). 2023 Apr 25;102(17):e33701
- Effects of Virtual Reality Exercise Program on Blood Glucose, Body Composition, and Exercise Immersion in Patients with Type 2 Diabetes. Int. J. Environ. Res. Public Health 2023, 20(5), 4178
- SGLT-2 inhibitors and GLP-1 receptor agonists in metabolic dysfunction-associated fatty liver disease: Trends Endocrinol Metab. 2022 Jun;33(6):424-442. doi: 10.1016/j.tem.2022.03.005. Epub 2022 Apr 28

Symposium 13

TZD and SGLT2i Combination for Fatty Liver Management

Jun Hwa Hong (Eulji University, Korea)

Fatty liver has become a leading cause of liver disease, affecting 30% of the global population. Fatty liver is particularly high in obese individuals and patients with type 2 diabetes mellitus (T2DM). Simple fat deposition in the liver to inflammation and fibrosis are variably expressed in patients. Thiazolidinedione (TZD) is representative improvement of insulin resistance and hepatic steatosis. However, there is some barriers to maintain the TZD by peripheral edema, weight gain and contraindicated to patients with heart failure. Sodium Glucose Co-Transporter 2 inhibitor (SGLT2i) also showed improvement of fatty liver with weight loss, alleviation of edema, and beneficial effect to wide spectrum of heart failure. Thus, we anticipated the synergistic improvement of fatty liver with combination treatment of TZD and SGLT2i. In this session, I will present the clinical data of TZD and SGLT2 combination therapy on fatty liver.