27O-ISMS03 **Translational Research in Drug Development for NASH Using a Cell-based Chemical Screening**

○Yusuke HIRATA[1], Atsushi MATSUZAWA[1]
[1]Laboratory of Health Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University

Non-alcoholic steatohepatitis (NASH) is characterized by hepatic damage, inflammation, and fibrosis, eventually leading to liver cirrhosis and cancer. Although the number of NASH patients has increased in recent years, which is estimated to be more than a million in Japan, effective therapies for NASH have not been established. Compelling evidence has revealed that saturated fatty acids accumulation in the liver, accompanied by fat storage, cause liver cell death and inflammation, which consequently contribute to NASH development and progression. A compound that can effectively inhibit saturated fatty acid-induced cell death will be a potential candidate of therapeutic drug against NASH. However, no such compound has been discovered yet.

Here, we identified a compound (hereafter named as compound X) that strongly suppresses palmitic acid (PA, the dominant saturated fatty acid in the liver)-induced cell death by using a cell-based chemical screening. PA accumulation induces various stresses such as oxidative stress and endoplasmic reticulum (ER) stress in liver cells, resulting in the activation of JNK (the stress-responsive MAP kinase) and ultimately apoptosis. We found that compound X-treatment diminished PA-induced JNK activation and cleavage of caspase-3, a hallmark of apoptosis, in liver cell lines HepG2 and Hepa1-6. Moreover, PA-induced reactive oxygen species (ROS) generation and XBP1 mRNA splicing (an ER stress marker) were significantly inhibited by compound X-treatment. These results collectively suggest that compound X suppresses PA-induced oxidative stress and ER stress, thereby inhibiting JNK activation and apoptosis. This study provides a candidate therapeutic drug against NASH. In this meeting, we discuss the molecular mechanisms by which compound X inhibits PA-induced apoptosis.