Bench to bedside : the novel mechanism of SCM-198 for treating metabolic dysfunction–associated steatohepatitis

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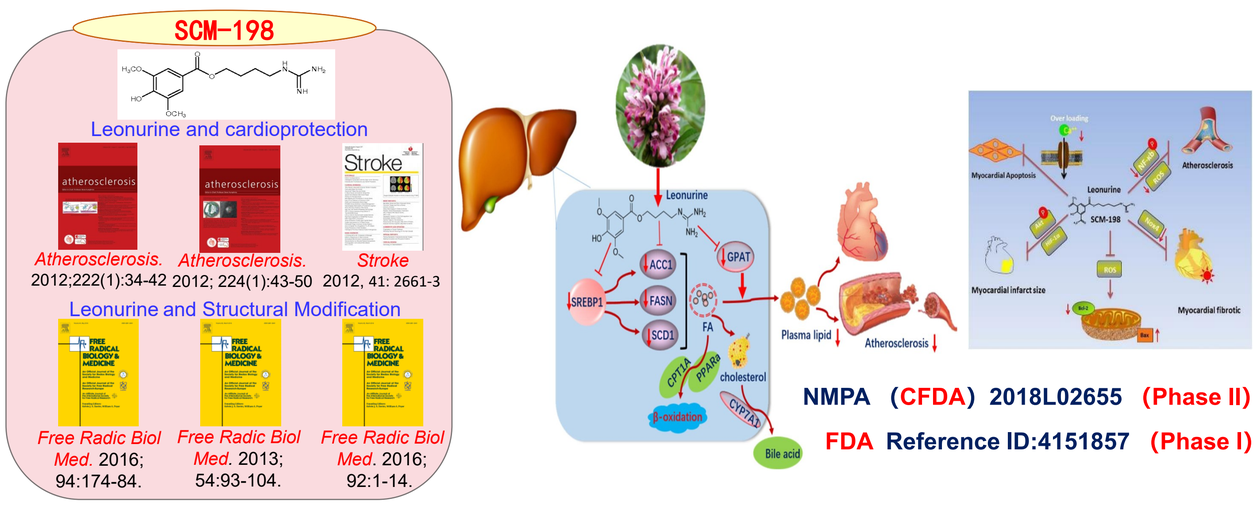
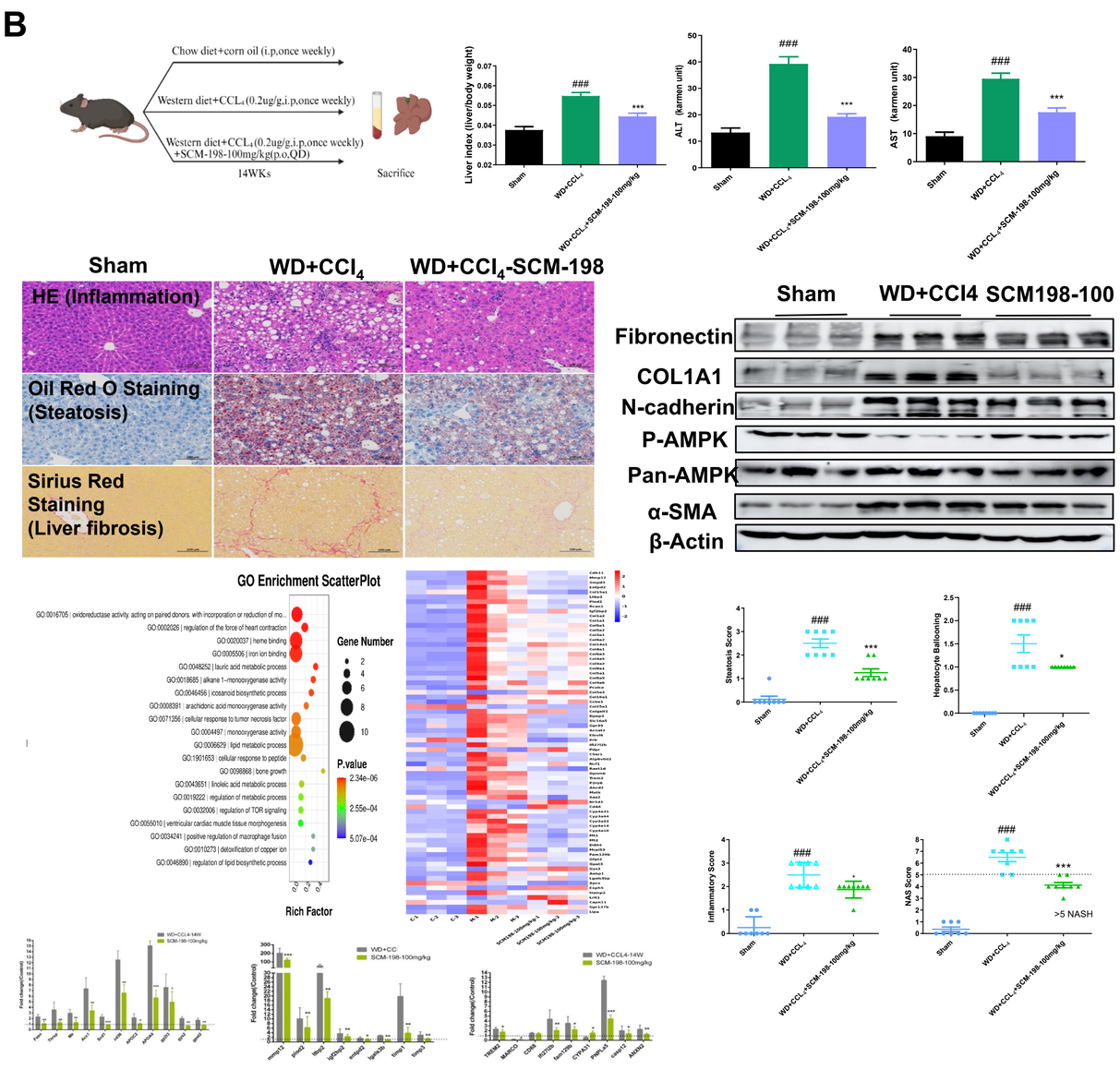
Metabolic dysfunction–associated steatohepatitis (MASH) is the serious type of metabolic dysfunction-associated steatotic liver disease (MASLD) lacking clinical drugs. If left untreated, it can advance to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). MASH is strongly associated with metabolic disorders such as obesity, insulin resistance, type 2 diabetes, and hyperlipidemia. Thus, it is imperative to pursue treatment from a comprehensive viewpoint. Leonurine (SCM-198, 4-guanidino-n-butyl syringate), a multi-target small molecule medication, is an active alkaloid extracted from traditional Chinese herbal medicine leonuri with significant cardiovascular protective effects discovered and synthesized by our research group earlier. It demonstrates effectiveness in reducing inflammation and lipid metabolism disorders, indicating its potential to mitigate the advancement of MASH. Extracellular vesicles (exosomes, EVs) could be detected in body fluids and are closely associated with the onset and progression of MASH, which makes EVs likely to become reliable biomarkers and targets for therapeutic interventions. Our previous research has demonstrated that SCM-198 could improve MASH in several *in vivo* models. Mechanistically, this effect may be associated with the regulation of EVs secreted from hepatic cells. Hence, our study not only investigates the effectiveness and specific mechanism of SCM-198 in treating MASH, but also aids in utilizing Western medical technology to identify non-invasive clinical indicators of MASH. This facilitate the integration of traditional Chinese and Western medicine in order to effectively prevent and improve MASH.

A



A. The structure of SCM-198 and reported pharmacodynamics and targets. Leonurus alkaloid (SCM-198) is an active ingredient of traditional Chinese medicine with significant cardiovascular protective effects discovered and synthesized by our research group earlier. It has multiple pharmacological effects (anti-inflammation, antioxidation, lipid metabolism regulation, stroke treatment, etc.).
Zhu et al. 2018, Pharmacol Ther, 188: 26-35.
Zhu et al. fphar,2018, 1663-9812

B



B. Pharmacodynamic validation of SCM-198 in WD+CCL4 induced MASH model.
Biochemical indicators and pathological results shows that SCM-198 could significantly improve steatosis, inflammation and fibrosis caused by WD+CCL_4 diet. Liver transcriptomics results of WD+CCL_4 diet induced MASH demonstrated that SCM-198 differentially regulated genes associated with lipid metabolism, inflammatory signaling, and fibrogenesis

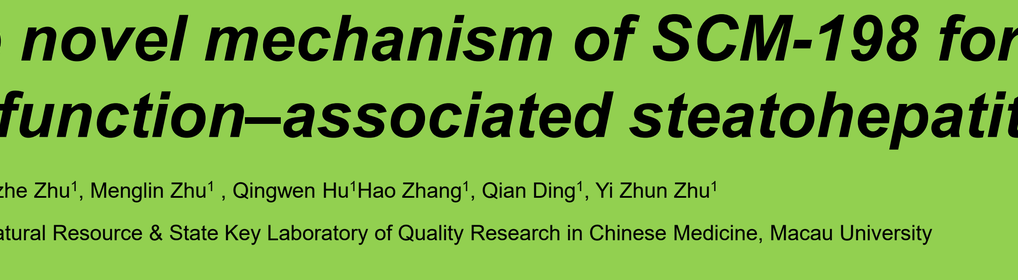
C

C. Pharmacodynamic validation of SCM-198 in FFC diet induced MASH model.
Biochemical indicators and pathological results shows that SCM-198 could significantly improve steatosis, inflammation and fibrosis caused by FFC diet.

C

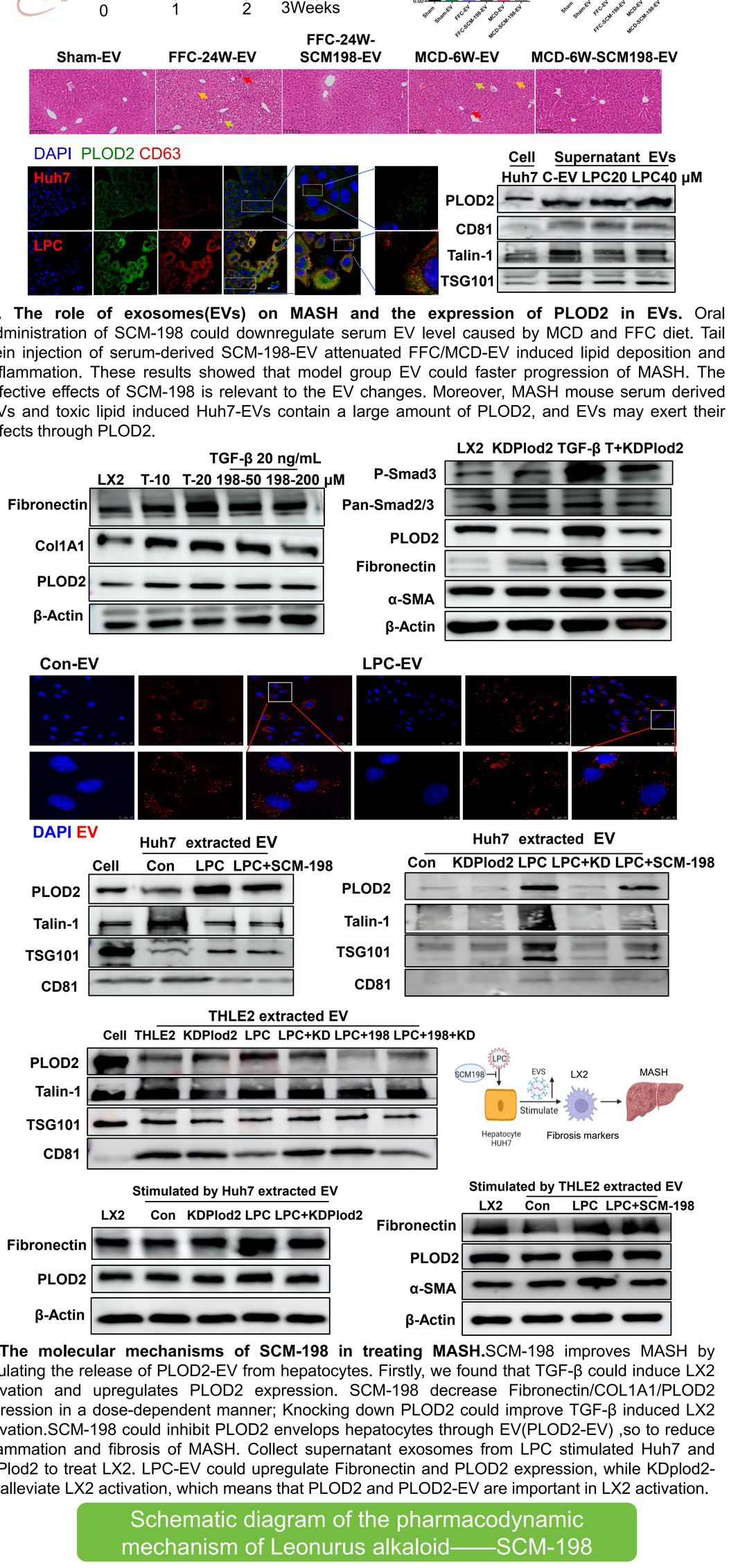
D. Pharmacodynamic validation of SCM-198 *in vitro* and PLod2 validation.SCM-198 could ameliorate OA+PA induced lipid accumulation in hepatocyte HepG2 and LO2; SCM-198 could not downregulate pro-fibrosis markers expression caused by TGF-β in LX2. Plod2 is upregulated in MASH liver.

D



D. The role of exosomes(EVs) on MASH and the expression of PLOD2 in EVs. Oral administration of SCM-198 could downregulate serum EV level caused by MCD and FFC diet. Tail vein injection of serum-derived SCM-198-EV attenuated FFC/MCD-EV induced lipid deposition and inflammation. These results showed that model group EV could faster progression of MASH. The effective effects of SCM-198 is relevant to the EV changes. Moreover, MASH mouse serum derived EVs and toxic lipid induced Huh7-EVs contain a large amount of PLOD2, and EVs may exert their effects through PLOD2.

E



E. The molecular mechanisms of SCM-198 in treating MASH.SCM-198 improves MASH by regulating the release of PLOD2-EV from hepatocytes. Firstly, we found that TGF-β could induce LX2 activation and upregulates PLOD2 expression. SCM-198 decrease Fibronectin/COL1A1/PLOD2 expression in a dose-dependent manner; Knocking down PLOD2 could improve TGF-β induced LX2 activation.SCM-198 could inhibit PLOD2 envelops hepatocytes through EV(PLOD2-EV) ,so to reduce inflammation and fibrosis of MASH. Collect supernatant exosomes from LPC stimulated Huh7 and KDPlod2 to treat LX2. LPC-EV could upregulate Fibronectin and PLOD2 expression, while KDplod2-EV alleviate LX2 activation, which means that PLOD2 and PLOD2-EV are important in LX2 activation.

Schematic diagram of the pharmacodynamic mechanism of Leonurus alkaloid——SCM-198

Conclusion

In summary, currently, we have discovered that the therapeutic effect of SCM-198 maybe relevant to the regulation of exosome secreted from hepatocytes to improve liver microenvironment so to alleviate MASH. Our work could help to investigate the enhancement impact and precise molecular mechanism of SCM-198 on MASH, endeavor to achieve the translation of scientific and technical advancements and facilitate the integration of traditional Chinese and Western medicine in order to effectively prevent and improve MASH.

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