S33-3 Serine palmitoyltransferase inhibitor suppresses HCV replication in a mouse model

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Serine palmitoyltransferase (SPT) is a first-step enzyme in the sphingolipid biosynthetic pathway. NA255 and Myriocin is an inhibitor of SPT and suppresses replication of the hepatitis C virus (HCV) replicon. However, it is still unknown whether this SPT inhibitor suppresses HCV replication *in vivo*. We investigated the anti-HCV effect of SPT inhibitor against intact HCV using chimeric mice with humanized liver infected with HCV genotype 1a or 1b. We administered myriocin into HCV infected chimeric mice and succeeded in reducing the HCV RNA levels in serum and liver to 1/10–1/100 of the levels prior to the 8 day treatment. Furthermore, combined treatment with pegylated interferon reduced the HCV RNA levels to less than 1/10000 of the control levels. In conclusion, we elucidated the inhibitory mechanism of HCV replication by SPT inhibitor *in vitro* and determined that SPT inhibitor inhibits HCV replication in a chimeric mouse model with humanized liver. Our results suggest that SPT may be an effective target of drugs designed to inhibit HCV replication, and that SPT inhibitor has the potential to be a lead compound in the development of new anti-HCV drugs.