中文題目：Sirolimus 對於肝硬化大鼠之肝性腦病變的作用
英文題目：Effect of sirolimus on hepatic encephalopathy of cirrhotic rats
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Background: Cirrhosis is often associated with portal hypertension and portal-systemic shunts formation, which leads to hepatic encephalopathy. Emerging evidence shows that sirolimus can improve liver fibrosis in cirrhotic rats. Herein, we investigate the therapeutic effect of hepatic encephalopathy by sirolimus treatment in common bile duct ligation-induced cirrhotic rats.

Methods: Common bile duct ligated-rats were intraperitoneally administered with 0.5 and 2 mg/kg/day sirolimus or vehicle for 2 weeks. Four weeks post common bile duct ligation, motor activities, body weight, biochemistry and hemodynamic data were measured. The liver was dissected for histopathology, immunohistochemical stains and protein analysis. On the parallel groups, the portal-systemic shunts of cirrhotic rats were determined.

Results: Body weight gain was significantly lower in sirolimus-treated rats compared to the control group. Meanwhile, sirolimus reduced portal pressure and the plasma levels of alanine aminotransferase, aspartate aminotransferase and ammonia, and attenuated the intrahepatic inflammation and fibrosis in cirrhotic rats. In addition, the phosphorylation of mammalian target of rapamycin (mTOR) and P70S6K protein expressions were significantly down-regulated and endothelial nitric oxide synthase (eNOS) expression up-regulated by sirolimus in the liver. Sirolimus did not influence portal-systemic shunts and motor activities of cirrhotic rats.

Conclusions: Sirolimus significantly improved hepatic inflammation and fibrosis accompanied by portal pressure reduction in cirrhotic rats, in which down-regulated mTOR/P70S6K and up-regulated eNOS protein phosphorylation might play a role. However, sirolimus did not significantly change the severity of portal-systemic shunts and influence motor activities, suggesting that the multifactorial pathogenesis of hepatic encephalopathy cannot be fully overcome by sirolimus.

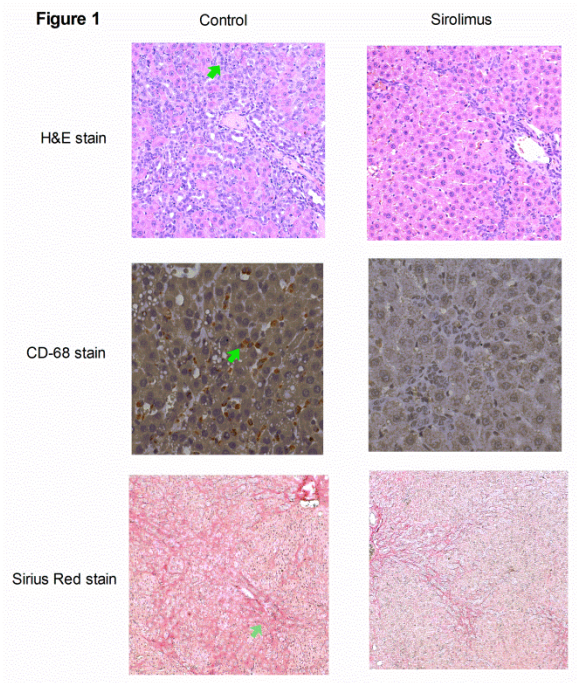

Fig. 1. Liver histology of cirrhotic rats with or without sirolimus treatment. The representative hepatic H&E stain showed (upper panel, magnification 100x) lymphocyte accumulation (green arrow) with disruption of hepatic lobules in control rats, which was improved by sirolimus. The CD68-stained image of liver reveals that the extent of CD68-stained macrophage (middle panel, brown cells indicated by green arrow) was attenuated by sirolimus (magnification 200x). Under Sirius Red staining (lower panel), the control liver showed significant fibrotic change (red color), which was ameliorated by sirolimus (green arrow, magnification 40x)

Figure 2

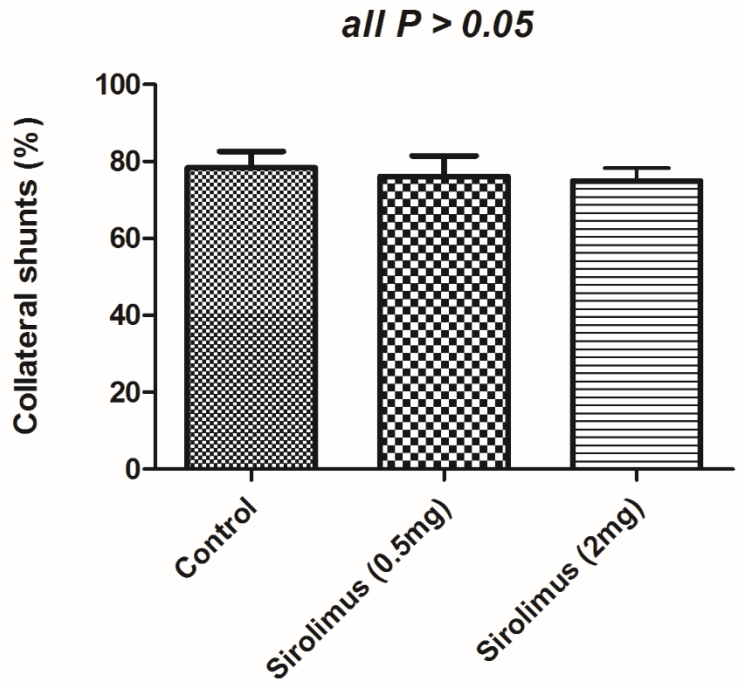

Fig. 2. Portal-systemic collateral shunting degree in cirrhotic rats treated by differently dosed sirolimus. The collateral shunts were not significantly different among 0.5 mg, 2 mg sirolimus-treated and control groups.

Figure 3

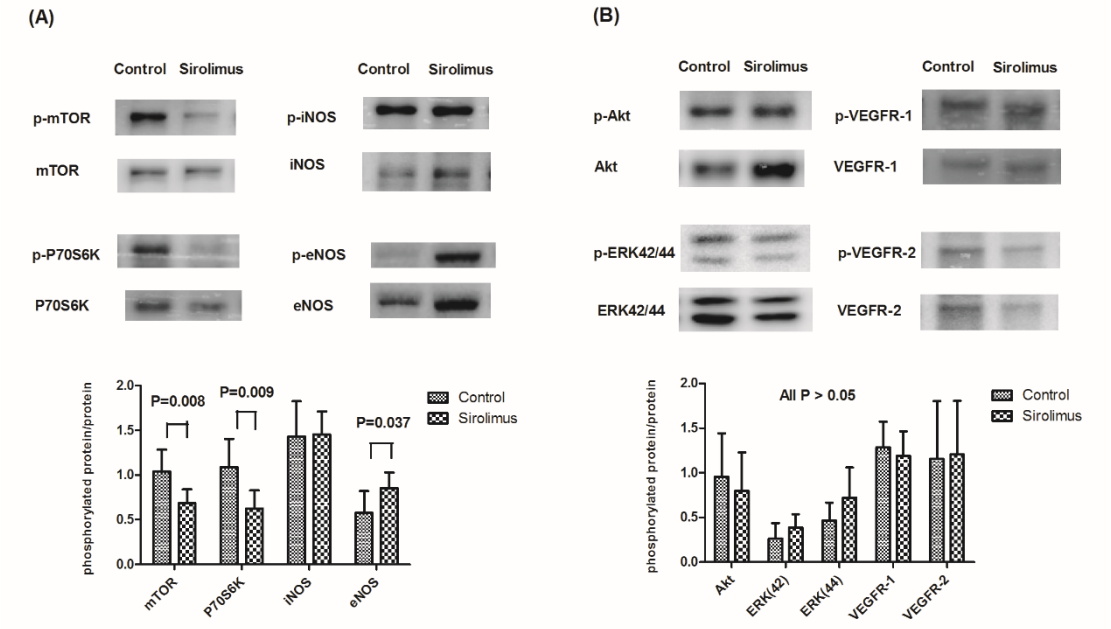

Fig. 3. Hepatic protein expressions in cirrhotic rats treated by sirolimus or vehicle. (A) The phosphorylated mTOR and P70S6K protein expressions were significantly down-regulated and eNOS was up-regulated by sirolimus. (B) The phosphorylated Akt, ERK (42/44), VEGFR-1 and VEGFR-2 protein expressions were not significantly influenced by sirolimus.