**THE HYDROGEL-ENCAPSULATED T0901317 REDUCES ATHEROSCLEROSIS WITHOUT EFFECT ON LIPOGENESIS IN APOE DEFICIENT MICE**

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Activation of LXR by ligand (e.g., T0901317 or T317) induces macrophage ABCA1/ABCG1 expression to enhance cholesterol efflux, thereby inhibiting foam cell formation and atherosclerosis. However, LXR activation in hepatocytes induces fatty acid synthesis to result in fatty liver and hypertriglyceridemia. Targeting macrophage LXR selectively can avoid the adverse effects of T317 occur to the liver. The peptide hydrogel can be taken up by monocyte/macrophages, but not by hepatocytes. In this study, we treated apoE deficient (apoE-/-) mice with the hydrogel-encapsulated T317 (GFFY-T317) and determined if GFFY-317 can inhibit atherosclerosis without activation of lipogenesis. ApoE-/- mice received the following treatment for 16 weeks. Group 1 (Control): high-fat diet (HFD); Group 2 (TF group): HFD containing T317; Group 3 (THI group): HFD and s.c. injection of GFFY-T317. Compared with control group, *en face* lesions were decreased by ~37.4 and ~33.17% by TF and THI. The collagen content was increased while necrotic cores, macrophages accumulation and inflammation were decreased in fibrous cap of lesions by TF and THI. The inhibition of foam cell formation by TF and THI was attributed to LXR-induced ABCA1/G1 expression. Interestingly, in contrast to severe liver steatosis induced by TF, THI had little effect on lipid content in the liver. Levels of serum total cholesterol, triglyceride (TG) and ALT/ALP, and liver TG accumulation induced by LXR were also decreased by THI. Mechanistically, GFFY-T317 was only taken up by monocyte/macrophages *via* a receptor-mediated endocytosis, and the drug-loaded macrophages were recruited to the lesion areas. Thus, hepatic LXR and LXR-targeted genes expression (SREBP1, ACC1 and FASN) were not activated, and the LXR ligand-induced fatty liver was eliminated. The GFFY-T317 also reduced established advanced lesions indicating its therapeutic effects. Taken together, our study demonstrates that GFFY-T317 can reduce atherosclerosis without effect on lipogenesis, indicating this system might be a novel therapy for atherosclerosis treatment.