NYU School of Medicine

Effect of Lipoprotein Lipase Deletion on Atherosclerosis Regression

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Introduction & objective

Elevated levels of circulating triglyceride (TGs) associate with more coronary vascular disease (CVD). The major determinant of plasma TGs is lipoprotein lipase (LpL). Many genetic studies implicate LpL in CVD, but it is not conclusive if LpL's function in maintenance of plasma lipid metabolism or its local effect in lipid uptake is more crucial in etiology of atherosclerosis. In this regard, several studies have shown that macrophage specific knockout of LpL reduces atherosclerosis. We investigated the effect of LpL deletion on atherosclerosis regression.

Methods and design

1. Animal models of atherosclerosis regression

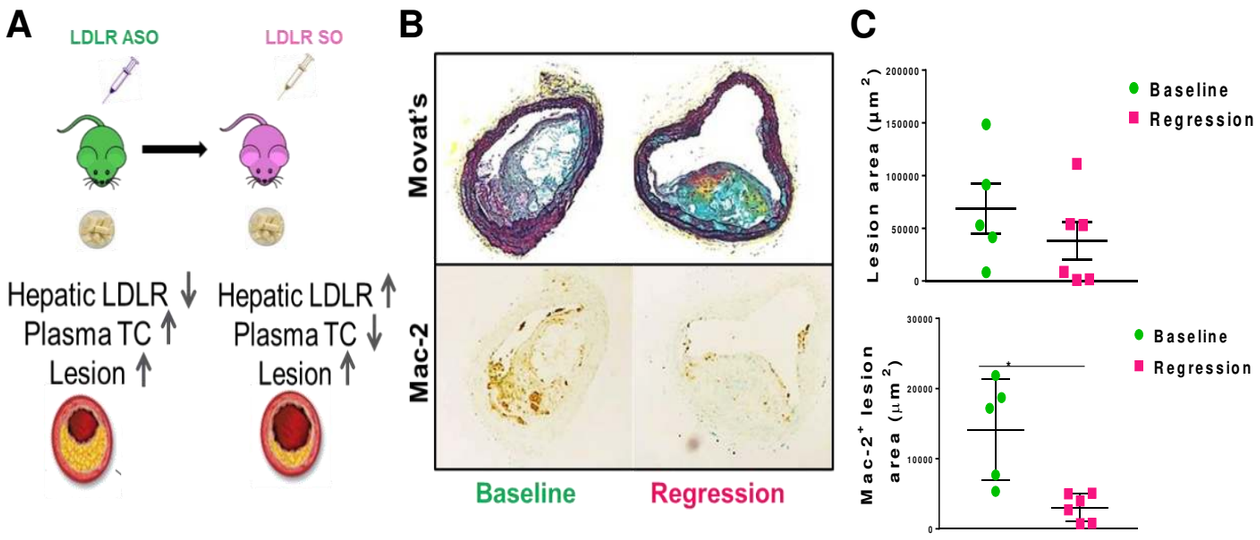

Figure 1. A novel anti-sense oligonucleotide (ASO) model to create atherosclerosis and regression: atherosclerosis was created in wild type mice with LDLR ASO and western diet feeding for 16 weeks, one set of mice were analyzed at this point as the baseline group and the rest of the mice were treated with sense oligonucleotides (SO) to induce regression and were analyzed after 3 weeks. (A) Experimental outline; (B) Lesions in the brachiocephalic artery (BCA) visualized by Movat's stain (top) and Mac-2 positive area showing lesion macrophages (bottom) and (C) quantification of total lesion area (top) and macrophage rich area (bottom). n=5-6/group, * $p < 0.05$ using one way ANOVA.

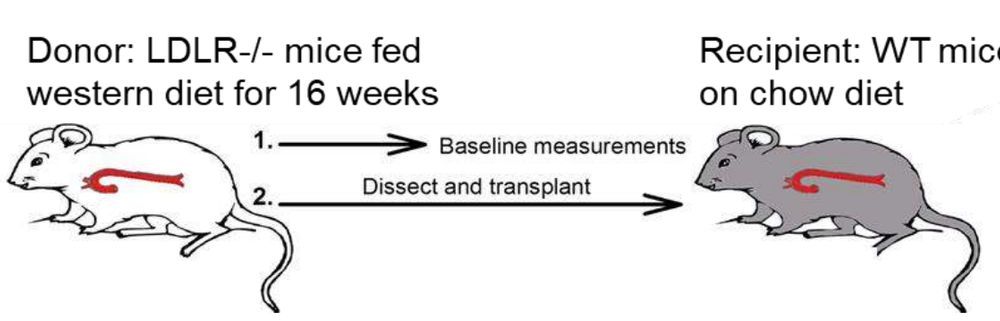

Figure 2. Aortic transplant model of regression: atherosclerosis was created in LDLR$^{-/-}$ mice by feeding a western diet for 16 weeks. Lesion containing aortic arch was transplanted into normolipidemic mice and lesions are analyzed after 2 weeks of regression and compared to baseline lesion of the LDLR$^{-/-}$ mice. .

2. Animal model of hypertriglyceridemia

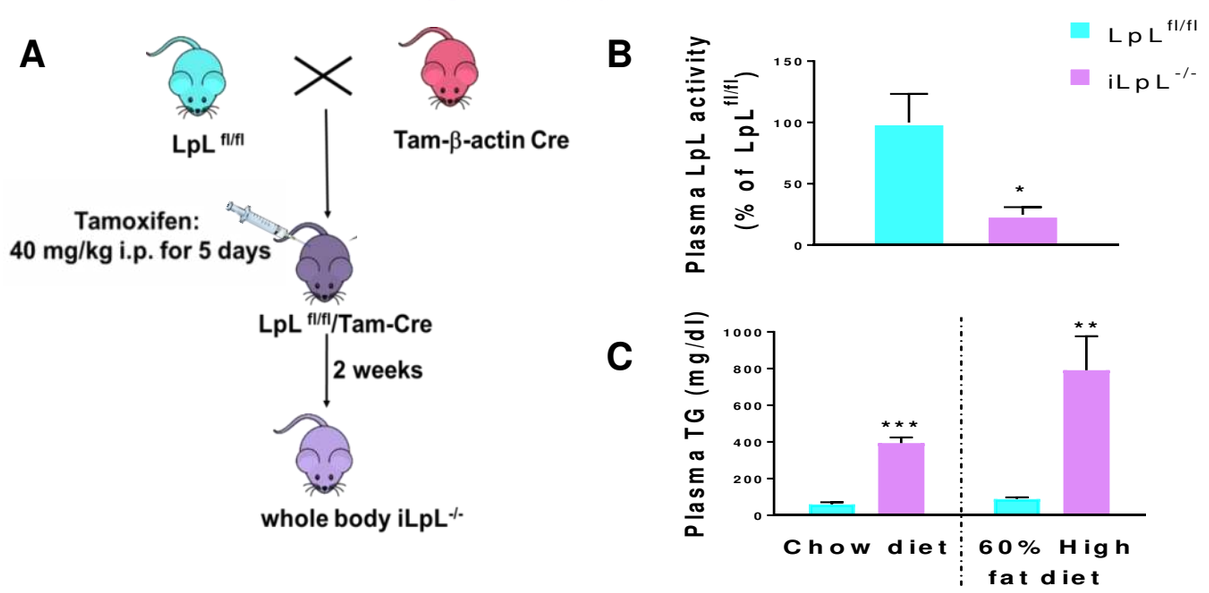

Figure 3. Induced total body LpL knockout mice. (A) Generation of iLpL$^{-/-}$ mice by crossing LpL$^{fl/fl}$ mice with Tam-B-actin cre mice and then treating with intraperitoneal injection of tamoxifen (40 mg/kg) daily for 5 days; (B) LpL activity in post heparin plasma obtained 5 min after intravenous heparin (5 U/mouse) injection and (C) Plasma TG in chow diet and 60% high fat diet fed mice. n=5-6/group, *p<0.05, ** p<0.01, *** p<0.001 using unpaired Student's t test.

Results

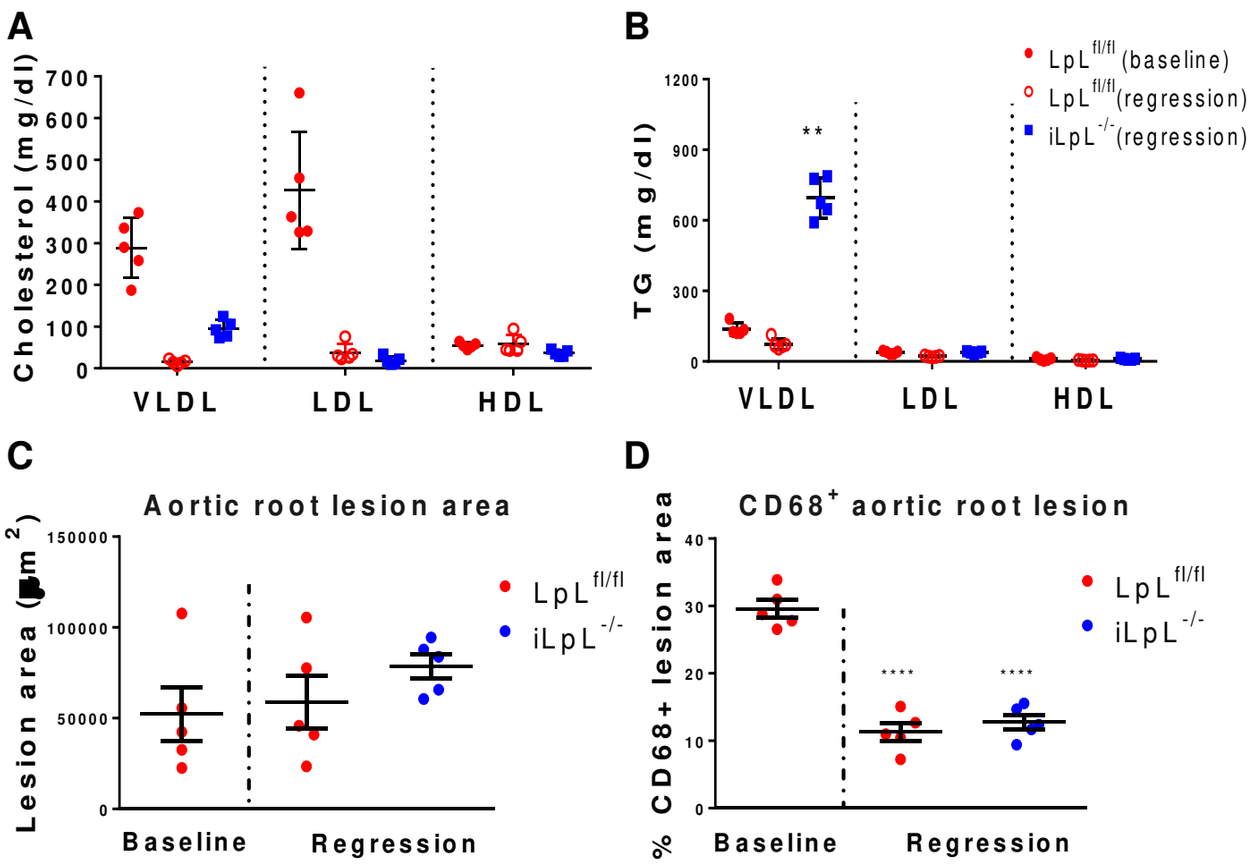

Figure 4. LpL deletion does not alter atherosclerosis regression. Atherosclerosis was created in LpL$^{fl/fl}$ and iLpL$^{-/-}$ mice with LDLR ASO and western diet feeding for 16 weeks, one set of mice were analyzed at 16 weeks as the baseline group and the rest of the mice were treated with SO to induce regression and were analyzed after 3 weeks. (A) TG measurements and (B) cholesterol measurements in plasma lipoprotein fractions at the end of the experiment; (C) total lesion area and (D) macrophage content in aortic root lesions; (E) total lesion area and (E) macrophage rich lesion area in the BCA in the baseline and regression groups. n=5-8/group, * $p < 0.05$ using one way ANOVA.

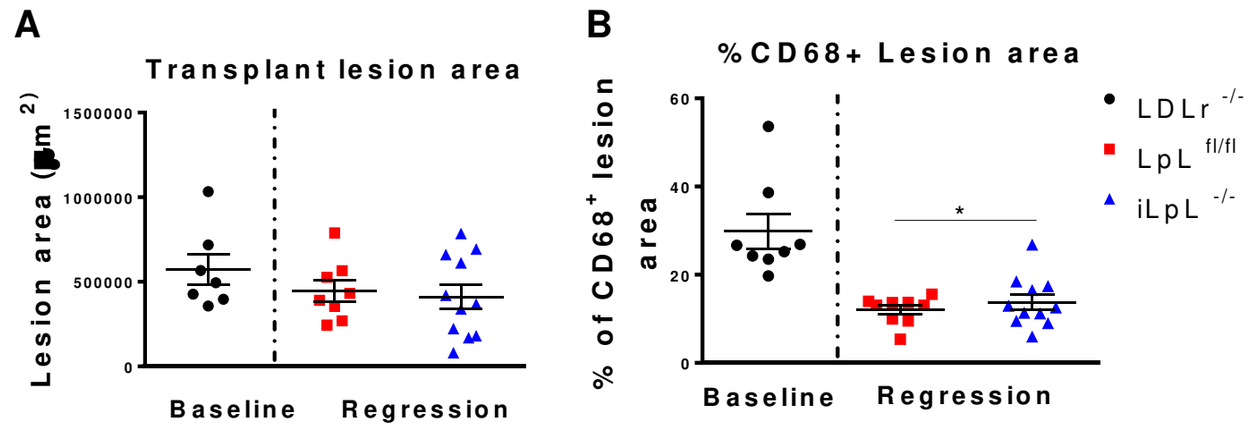

Figure 5. Transplantation of atherosclerotic aortas into LpL knockout mice does not retard regression. Atherosclerosis was induced in LDLR$^{-/-}$ mice by feeding a western diet for 16 weeks. Lesion containing vessels were transplanted into LpL$^{fl/fl}$ and iLpL$^{-/-}$ mice on chow diet and lesion size (A) and macrophage content (B) were analyzed after 2 weeks. N=7-11, * P<0.05 using one-way ANOVA.

Conclusion and future direction

- Hypertriglyceridemia due to whole body LpL deletion in mice did not affect atherosclerosis lesion regression in terms of macrophage lesions content
- We are characterizing the role of total deletion of LpL vs deletion in the non-hematopoietic compartment on atherosclerosis progression and regression in mice

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