Statins reduce hepatic Angptl3 expression and secretion, likely by interfering with LXR-mediated transcription

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Introduction

Loss of function mutations in *ANGPTL3* cause low plasma lipid concentrations.
Statins supposedly suppress hepatic *ANGPTL3* mRNA expression in healthy subjects¹, but the mechanism is unknown.
It is also not known whether statins reduce plasma Angptl3 concentrations in patients with elevated LDL-C, e.g., familial hypercholesterolemia (FH).

1. J. Intern. Med. 2011; 269: 333

Methods

Plasma Angptl3 concentrations were measured in 157 genetically confirmed FH patients and in 129 age and sex matched unaffected relatives.
The effect of simvastatin on *ANGPTL3* mRNA expression and Angptl3 secretion was assessed in the human hepatoma cell line Huh7.

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Results

1. Statins reduce plasma Angptl3

2. Simvastatin decreases *ANGPTL3* mRNA expression and Angptl3 secretion but not when LXR is activated

3. Lower LXR target gene expression upon simvastatin treatment

4. The LXR antagonist GSK2033 prevents reductions in Angptl3 by simvastatin

Conclusion

Statins reduce hepatic *ANGPTL3* mRNA expression and plasma Angptl3 concentrations by interfering with the effect of LXR on *ANGPTL3* transcription. This is likely due to a reduction of the endogenous LXR ligands, oxysterols.

Statin treatment → Reduced hepatic cholesterol synthesis → Lower intracellular cholesterol concentrations
→ Less oxysterols → Reduced LXR activation → Less *ANGPTL3* transcription → Reduced hepatic Angptl3 secretion