Functional interaction between apolipoproteins A2 and E in the regulation of plasma cholesterol and triglycerides levels

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Aim: Apolipoprotein A2 (APOA2) plays crucial role in HDL synthesis, function and plasma concentration. Accumulation of exchangeable apolipoproteins on HDL prevents their association with triglyceride rich lipoproteins (TRL) and the subsequent inhibition of lipoprotein lipase, resulting in physiological plasma triglyceride levels. Here, we investigated the role of APOA2-rich HDL in the regulation of plasma TRL metabolism.

Methods: We created a recombinant attenuated adenovirus expressing human APOA2 and the Green Fluorescent Protein (GFP) under the independent control of two CMV promoters (AdGFP-APOA2). Then, Apoa1-deficient (*Apoa1*$^{-/-}$) mice fed western-type diet for 2 weeks were infected with AdGFP-A2, or a control adenovirus expressing only GFP (AdGFP). Since APOE is a known modulator of plasma triglyceride metabolism, these mice were compared to mice with concomitant deficiency in APOE and APOA1 (*Apoe*$^{-/-}$ x *Apoa1*$^{-/-}$) infected with the same viruses. Biochemical analyses were then performed.

Results: Hepatic APOA2 production and subsequent APOA2-HDL formation leads to:

In *Apoa1*$^{-/-}$ mice

- Increased plasma total cholesterol and triglycerides levels,

In *Apoe*$^{-/-}$ x *Apoa1*$^{-/-}$ mice

- Reduced cholesterol and triglycerides levels found in VLDL and LDL
- Reduced TRLs
- Significantly reduced rate of VLDL triglyceride production only in AdGFP-APOA2 infected *Apoe*$^{-/-}$ x *Apoa1*$^{-/-}$ mice.

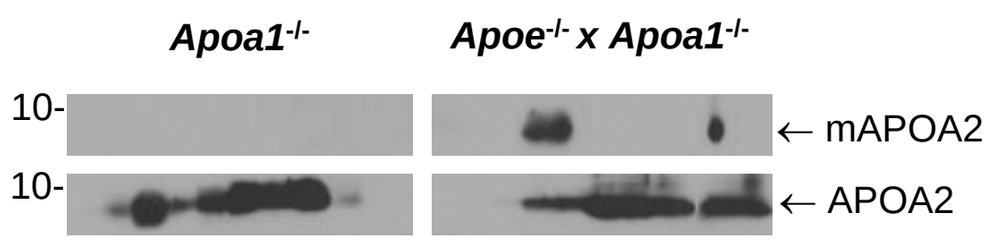

Fig. 1. Validation of human APOA2 expression in the lipoprotein fractions five days post infection. Representative western blot analysis

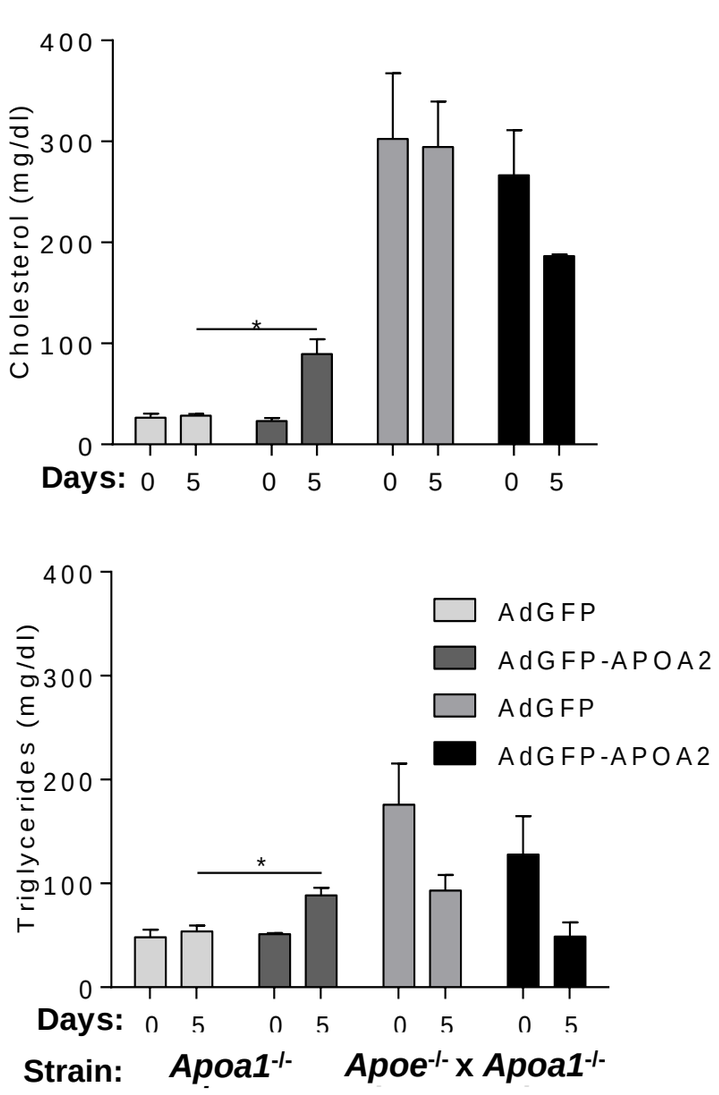

Fig. 2. Plasma total cholesterol and triglycerides levels five days post adenovirus infection.

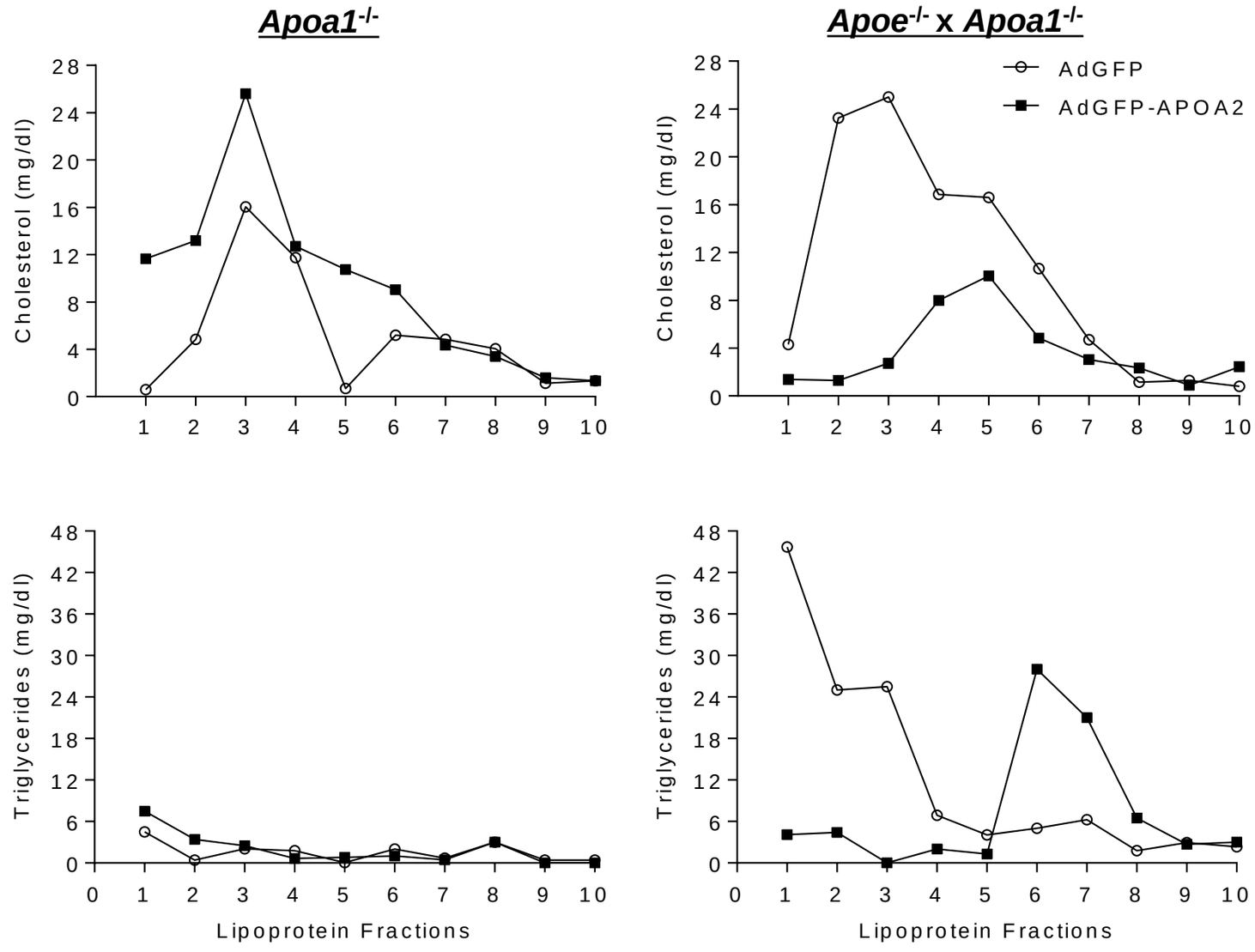

Fig. 3. Total cholesterol and triglycerides levels of lipoprotein fractions five days post adenovirus administration.

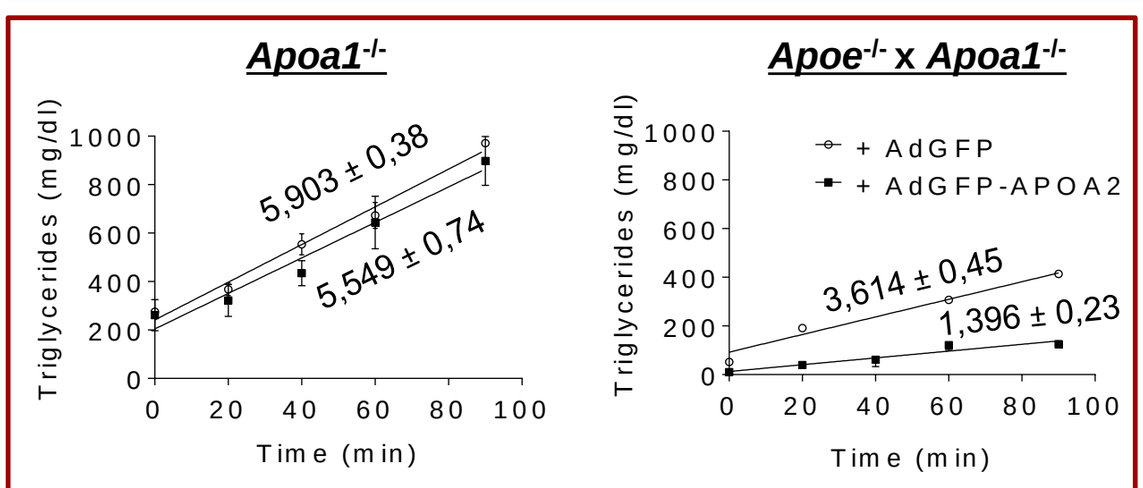

Fig. 4. Hepatic VLDL triglyceride production rate following i.v. administration of Triton WR1339, five days post adenovirus infection.

Conclusions: The effects of APOA2-HDL on plasma lipoprotein metabolism are significantly modified by endogenous functional APOE. Given the role of VLDL and LDL in atherosclerosis, the importance of this functional interaction in the pathogenesis of the disease is currently under further investigation.

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