Overexpression of Human ApoC3 Leads to Hypertriglyceridemia and Induces Key CVD-related Lipid Biomarkers

M1030-04-21

Ning Ren, Benjamin Xin, Valerie Young, Stephanie Liu, Amalia Esposito, Terri Knappenberger, Lorraine Gorelick, Thomas Murphy, Sharon Tong, Dawei Zhou and Joyce Hwa

DMPK, WuXi AppTec, Cranbury NJ 08512

CONTACT INFORMATION: ning.ren@wuxiapptec.com

PURPOSE

Elevated triglyceride (TG) is one of the key contributors of cardiovascular and metabolic diseases. ApoC3 increases plasma TG and causes hypertriglyceridemia. A strong correlation of apoC3 and plasma TG level was demonstrated using a mouse transgenic model, B6;CBA-Tg(APOC3)3707Bres/J, that overexpresses human apoC3 in liver and small intestine. To better understand this model, we investigated the link between apoC3, and the major cardiovascular diseases related metabolic risk biomarkers.

METHOD(S)

Twenty-nine female and 24 male B6;CBA-Tg(APOC3)3707Bres/J mice at age between 13 and 15 weeks were recruited in this study. The plasma concentrations of human apoC3 were measured by MSD, an electrochemiluminescence based immunoassay. The concentrations of total cholesterol (TC), TG, Low-density lipoprotein (LDL) and High-density lipoprotein (HDL) were analyzed by Cobas C311 analyzer from Roche.

RESULT(S)

A wide range of plasma human apoC3 protein concentration (from 5.1 to 41 mg/mL) was observed in this cohort (Figure 1). Compare with the background strain B6CBAF1/J and wild type C57BL/6, Tg(APOC3)3707Bres mice have remarkably higher levels of TG, TC, LDL and relatively lower level of HDL. The gap between TC elevation and the sum of HDL and LDL increasing was observed and suggests that although the increasing of LDL is noticeable, the major contribution of the TC elevation was likely from VLDL increasing. (Table 1 and Figure 2).

Compare with female mice, male Tg(APOC3)3707Bres exhibited significantly higher plasma human apoc3 concentration (10.0 +/- 0.005 vs. 27.5 +/- 0.013 mg/mL, female vs. male). In line with the protein level, male mice had much higher, but scattered plasma triglycerides, total cholesterol and LDL concentrations (Figure 1, 2).

To demonstrate the potential of using this model to evaluate apoC3 lowering agents, we calculated the correlations between the concentrations of human apoC3 and the lipid biomarkers of individual subject. Plasma human apoC3 protein level was positively correlated with the plasma TG (R^2=0.46, P<0.01) and TC (R^2=0.52, P<0.01) (Figure 3). However, when calculate the correlations of each gender group, the only strong correlation demonstrated was human apoC3 and TC in female group (R^2=0.86, P<0.01) (Figure 4). We have also revealed correlation between TC and TG and observed strong, positive correlation (R^2=0.70, P<0.01) (Figure 5).

Table 1. Summary of plasma lipid profile in humans and mice.

Species/strian	N	Plasma lipid concentrations (median+/- SE)			
		TG (mg/dL)	TC (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)
Dyslipidemias types V[2]	267	686 (580-792)	261 (209-314)	32 (24-40)	92 (43-142)
Dyslipidemic humans[1]	15	154 +/- 15	226 +/- 6	48 +/- 4	154 +/- 7
LDL$^{-/-}$ (Chol) mice[1]	10	404 +/- 35	1677 +/- 98	12 +/- 2	761 +/- 57
C57BL/6 mice	9	123+/-9.7	97.5 +/- 2.8	75.0 +/- 5.0	14.5 +/- 2.1
B6CBAF1/J (F)	3	192 +/- 3.6	75 +/- 3.5	61 +/- 5.0	10 +/- 1.2
B6CBAF1/J (M)	3	162 +/- 3.5	95 +/- 2.4	87 +/- 2.0	5.0 +/- 0.33
Tg(APOC3)3707Bres mice (F)	29	2288 +/- 1.1	315 +/- 0.1	35.0 +/- 0.02	34.0 +/- 0.02
Tg(APOC3)3707Bres mice (M)	24	8945 +/- 5.7	625 +/- 0.3	40.0 +/- 0.02	50.0 +/- 0.04

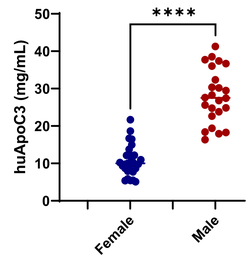

Figure 1. Comparison of plasma human ApoC3 level in male and female B6;CBA-Tg(APOC3)3707Bres/J mice.

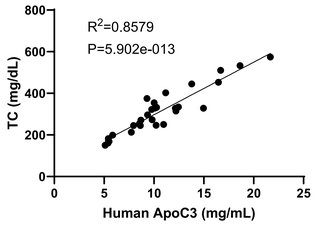

Figure 4. Stronger correlation of human apoC3 with total cholesterol in female B6;CBA-Tg(APOC3)3707Bres/J mice.

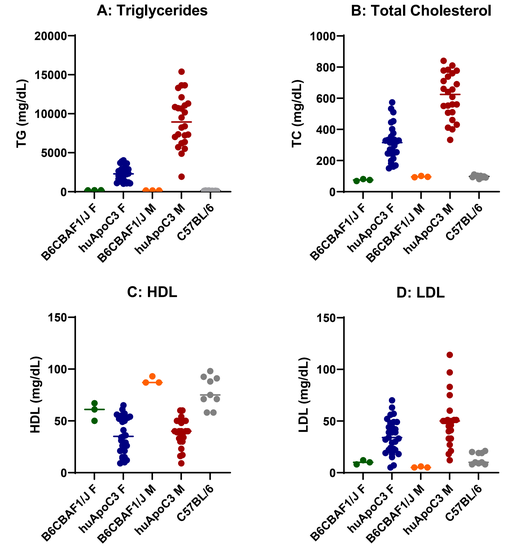

Figure 2. Comparison of the lipid profile in male, female B6;CBA-Tg(APOC3)3707Bres/J mice and B6CBAF1/J mice. Triglycerides (A), total cholesterol (B), HDL (C) and LDL (D).

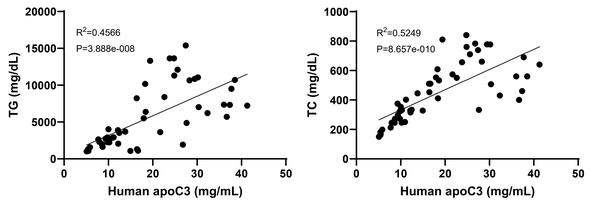

Figure 3. Correlations between plasma concentrations of human ApoC3 and TC, TG.

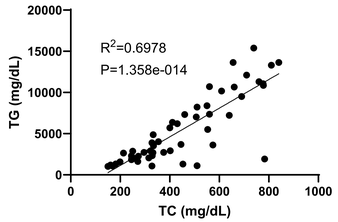

Figure 5. Correlation between total cholesterol and triglycerides in B6;CBA-Tg(APOC3)3707Bres/J mice.

CONCLUSION(S)

Over-expression of human apoC3 in B6;CBA-Tg(APOC3)3707Bres/J mice not only leads to hypertriglyceridemia, but also induced key CVD-related lipid biomarkers in hypercholesterolemia and elevated LDL-C. Compare with other mouse models, the unique lipid profile with high TG/TC, LDL-C/HDL ratio, would make B6;CBA-Tg(APOC3)3707Bres/J be a more suitable model for human hypertriglyceridemia / dyslipidemia research.

REFERENCE

[1] Yin W, Carballo-Jane E, McLaren DG, Tong X, et al. Plasma lipid profiling across species for the identification of optimal animal models of human dyslipidemia. Journal of Lipid Research. (2012) 53 (1), 51-65.

[2] Sampson M, Ballout RA, Soffer D, et al. A new phenotypic classification system for dyslipidemias based on the standard lipid panel. Lipids in Health and Disease (2021) 20, 170