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A distinct LDL profile to predict the risk of cardiovascular disease in familial hypercholesterolemia subjects: initial pre-clinical results

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Topic(s):
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Aim - Cardiovascular disease development is highly variable between patients with familial hypercholesterolemia (FH). Since current risk prediction methods fail to estimate the risk of individual patients, all patients are treated with high-intensity lipid-lowering medication like statins and PCSK9-inhibitors. To prevent overtreatment (with its associated costs and side effects) of patients with a low risk, reliable biomarkers are urgently needed. While studying atherosclerosis development in an FH porcine model, we discovered a specific LDL profile that was directly associated with the severity of atherosclerosis development.

Methods – 10 adult pigs with an LDLR mutation received a high-fat diet for 12 months. Atherosclerosis development in the three main coronary arteries was monitored with intravascular ultrasound (IVUS) and optical coherence tomography at three time points. After sacrifice, tissue was harvested for detailed histological analysis of the coronary plaque composition. Size-exclusion chromatography (SEC, n=10) and LC-MSMS (n=4) were used to assess the plasma lipoprotein profile, and the sphingolipid content of LDL, relative to cholesterol.

Results – Imaging and histology revealed a marked difference in pigs that developed large, lumen intruding plaques (IVUS-based plaque burden 13-77 %) within 9 months (n=5) and pigs (n=5) that only developed early lesions (IVUS-based plaque burden 8-34 %), even after 12 months of follow-up. The plaques seen in the fast responding pigs possessed distinct characteristics of advanced disease (i.e. heavy macrophage infiltration, large lipid-rich necrotic cores, neovascularisation, micro- and macrocalcifications and intraplaque haemorrhage, see figure). In these fast responders, fibrous cap atheroma occupied 34% of the total artery.

SEC revealed two distinct LDL subclasses: regular and 'larger' LDL particles. Fast responding pigs with advanced atherosclerosis displayed a significantly higher ratio in cholesterol concentration of regular/larger LDL than slow responding pigs (1.7 (1.3-1.9) vs. 0.8 (0.6-1.2); (p=0.004), see figure). Compared to regular LDL, 'larger' LDL contained relatively more sphingolipids in the fast responding than in the slow responding animals (regular LDL/larger LDL: S1P 0.5 (0.5-0.5) vs. 1.0 (0.8-1.2); Cer16:0 0.70 (0.67–0.73) vs. 1.04 (0.95–1.13); Cer18:0 0.60 (0.58–0.61) vs. 1.15 (1.13–1.16); Cer20:0 0.73 (0.73–0.74) vs. 0.94 (0.94–0.94)). 'Larger' LDL particles and comparable sphingolipid ratios were also observed in FH patients. Cardiovascular data from our FH patient cohort, coupled to the LDL subclass distribution, will provide more insight into the potential of this novel biomarker.

Conclusion – A distinct difference in LDL subclasses, including a new 'larger' LDL particle, was found in fast versus slow responding FH animals. This finding can potentially be used to identify FH patients at the highest risk of CVD to avoid overtreatment of low risk patients.
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