

Conclusions: Hepatic expression of CETP is confined to mature resident macrophages (i.e. F4/80+Clec4f+Vsieg4+Ly6c-) rather than immature activated macrophages (i.e. Ly6c+). LPS reduces hepatic CETP expression by activation of hepatic macrophages, consequently decreasing plasma CETP and raising HDL-C. This sequence of events may be relevant as the host defense mechanism against LPS-induced systemic inflammation.

CO1:5.

ELEVATED TRIGLYCERIDES PROMOTE THE EXTRAVASATION AND TISSUE RETENTION OF MONOCYTE SUBSETS

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Aim: Monocytes are heterogeneous effector cells involved in the maintenance of tissue integrity. However, their response to atherogenic hyperlipidemic environments remains poorly understood.

Methods: Using a combination of in-vitro and in-vivo assays, including intravital microscopy, we analysed the response of monocyte subsets to hypertriglyceridemia with or without hypercholesterolemia.

Results: In mice, we show that in the presence of elevated levels of triglyceride-rich lipoproteins (TRL), independent of hypercholesterolemia and systemic inflammation, numbers of non-classical (Ly6C/Gr1low) monocytes drop, whilst the number of bone marrow progenitors remained similar. We observed an increased crawling and retention of Ly6Clow monocytes at the endothelial interface and a marked accumulation of F4/80posCD68pos macrophages in several organs, including heart, liver and kidney. Hypertriglyceridemia was accompanied by an increased expression of tissue and plasma CCL4 and blood Ly6Clow monocyte depletion involved a pertussis toxin-sensitive receptor axis. In further studies, we find that increased TRL and kidney macrophage accumulation leads to aggravated kidney injury in an acute nephrotoxic nephritis model. Finally, we describe the functional impact of neutral lipid accumulation in human monocytes. Hyperlipidemia results in circulating monocytic foam cells in vitro and in vivo. These monocytic 'foam cells' lead to subset specific cytoskeletal modulation and marked changes in their extravascular migratory behaviour via RhoA.

Conclusions: Collectively, these findings demonstrate that a triglyceride-rich environment can alter blood monocyte distribution promoting the extravasation of non-classical monocytes via CCL4 and lipid vesicle accumulation can lead to tissue retention. Together these dyslipidemic phenotypes may aggravate atherosclerosis and highlights the impact of high levels of TRL on monocyte behaviour.

CO1:6.

ROLE OF IGE ANTIBODIES AND MAST CELLS IN ATHEROSCLEROSIS

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Aim: Epidemiologic studies and animal models suggest that IgE antibodies (Abs) could be pro-atherogenic. Furthermore, mast cell (MC) accumulation has been described in atherosclerotic aortas. Finally, we previously observed that ectopic germinal centers (GCs) rich in B cells develop in the adventitia next to the lesions. Our working hypothesis is that IgE Abs specific for antigens from atherosclerotic lesions locally activate MCs in atherosclerotic aortas. MC degranulation would weaken the plaques and guide the local adaptive immune response in ectopic GCs, especially the maturation of B cells toward plaque-specific IgE-producing plasma cells. This would lead to an amplification loop of atherosclerosis, and could lead to rupture of AAAs.

Methods: We analyzed by flow cytometry and immunofluorescence the phenotype and the proximity of B cells and MCs in the aorta of healthy controls, atherosclerotic patients, and patients with AAAs, and measured

the concentration of IgE Abs in conditioned medium from these aortas. We tested the capacity of these conditioned medium to stimulate MCs in an IgE-dependent manner.

Results: We observed an increase in MCs, plasma cells, GC B cells, and IgE concentration in AAA aortas compared to healthy aortas. MCs were present in the lesions as well as in proximity of B cell lymphoid aggregates in the adventitia. Interestingly, IgE-producing B cells could be observed in the diseased aortic wall, suggesting a local IgE production. Finally, conditioned medium from AAA patients induced MC degranulation.

Conclusions: Our data suggest that IgE and mast cells could be involved in the progression of atherosclerosis.

Late Breaking Session: Recent Clinical Trials And Hot Topics

LB1:1.

SAFETY AND EFFICACY OF EVINACUMAB, A MONOCLONAL ANTIBODY TO ANGPTL3, IN PATIENTS WITH HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA: A SINGLE-ARM, OPEN-LABEL, PROOF-OF-CONCEPT STUDY

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Aim: Carriers of homozygous inactivating mutations in the gene encoding Angiopoietin-like protein 3 (ANGPTL3) have >50% lower LDL-C, HDL-C and triglycerides compared to controls. Moreover, ANGPTL3 inhibition in a LDL-R -/- mouse lowers LDL-C levels. We therefore investigated the efficacy and safety of evinacumab, a human mAb inhibitor of ANGPTL3, in homozygous familial hypercholesterolemia (HoFH) patients on background lipid lowering therapy (LLT).

Methods: Nine molecular-defined HoFH patients (8 on background LLT) were enrolled. Evinacumab was dosed as 250 mg SC injection at baseline and at week-2 as 15 mg/kg IV. Two patients also received 450 mg SC at weeks-12, 13, 14, and 15. The primary endpoint was mean percent change in LDL-C levels from baseline to week-4.

Results: Mean baseline LDL-C was 376.0 mg/dL (SD=240.9 mg/dL). Evinacumab decreased LDL-C (mean=49.2%, SD=23.2%), apolipoprotein B (mean=45.9%, SD=18.2%) and total cholesterol (mean=47%, SD=19%) at week-4. Mean baseline triglycerides were 79.9 mg/dL (SD=41.1 mg/dL); mean reduction at week-4 was 46.5% (SD=17.1%). Mean baseline HDL-C was 38.8 mg/dL (SD=14.3 mg/dL); mean reduction at week-4 was 35.5% (SD=16%). Among the 3 null/null LDLR-mutation carriers (mean baseline 597.8 mg/dL, SD=248 mg/dL), mean LDL-C reduction at week-4 was 37.3% (SD=10%). One serious adverse event occurred (worsening coronary artery disease; not treatment related); there were no adverse events leading to discontinuations. Most common drug-related events were injection-site reaction and hot flush (mild; resolved without treatment).

Conclusions: These preliminary results show a pronounced effect of evinacumab added to LLT in lowering LDL-C in HoFH patients, regardless of genotype.

LB1:2.

SIRNA TO PCSK9 IN PATIENTS WITH HIGH CARDIOVASCULAR RISK AND ELEVATED LDL-C: THE ORION 1 TRIAL

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Aim: Background: ORION-1 is a Phase 2 double blind randomized controlled trial comparing 6 dosing regimens of a novel small interference RNA therapeutic compound to PCSK9 (inclisiran) vs placebo. An analysis of