P19 THE OMEGA 3 POLYUNSATURATED FATTY ACID, EICOSAPENTAENOIC ACID INHIBITS FOAM CELL FORMATION AND SECRETION OF PRO-INFLAMMATORY MEDIATORS

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Vascular endothelial dysfunction promotes intimal retention and oxidation of low density lipoproteins (oxLDL)). This incites a pro-inflammatory response. Monocytes are recruited and upon diapedesis, use scavenger receptor mediated pathways to internalise the oxLDL, thus forming arterial foam cells, a lineage widely assumed to be pro-inflammatory. Reversing this process may dampen the chronic pro-inflammatory state in atherosclerosis, propagated by foam cells. Here, we investigate the role of eicosapentaenoic acid (EPA) in targeting this process. Classical monocytes were separated from the blood of healthy donors and cultured in 10% autologous serum for 7 days under 3 conditions: 1) untreated or 2) treated with fluorescently labelled OxLDL (Di-OxLDL) or 3) treated with Di-OxLDL with EPA. Uptake of oxLDL was analysed using fluorescent confocal microscopy. Culture supernatants at day 7 from each condition were stored and the secretory profile for cytokines and chemokines was analysed using cytokine membrane arrays. Co-localisation analysis showed a significant reduction in Di-OxLDL uptake, and hence foam cell formation, with EPA treatment. Semi-quantitative analysis of cytokine arrays demonstrated an overall pro-inflammatory profile in foam cells compared to macrophages. Interestingly, EPA treatment was able to reverse this effect in foam cells. Thus, EPA has an inhibitory role in foam cell formation. In addition, EPA can affect the secretory profile of foam cells, promoting an anti-inflammatory environment. This study shows that further investigations into how EPA might be involved in the regression of atherosclerosis are warranted.

P20 ERYTHROCYTE-DERIVED INTERLEUKIN-33 INSTRUCTS THE SPECIFICATION OF IRON-RECYCLING MACROPHAGES

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Tissue-resident splenic red pulp macrophages (RPM) contribute to red blood cell blood homeostasis by phagocytosing damaged or senescent erythrocytes and releasing heme-associated iron for recycling during erythropoiesis. Hence, a metabolite of erythrocyte degradation, induces the SpiC transcription factor expression in monocyte-derived macrophages, and promotes their differentiation into a precursor pre-RPM phenotype (CD11bhi F4/80lo SpiClo). However, the requirements for differentiation into the mature RPM phenotype (CD11b+ F4/80hi SpiChi) remain unknown. Here, we demonstrate that IL-33, but not other IL-1 family or type 2 cytokines, co-operates with heme to induce high levels of SpiC in monocyte-derived macrophages, and promotes the generation of mature RPM. Mice deficient for the IL-33 receptor ST2 display a cell-autonomous defect in monocyte-derived RPM, with a profound phenotypic alteration of the remaining RPM. Mechanistically, we show that IL-33 is stored in erythrocytes and is required together with heme, to induce the differentiation of pre-RPM into tissue-resident RPM. Thus, reconstitution of RPM-deficient IL-33 mice with wild type, but not IL-33-deficient, erythrocytes substantially restores the generation of RPM. This IL-33-elicited promotion of RPM is dependent on the MyD88 and ERK1/2 pathways downstream of IL-33/IL1RL1 signalling. This work identifies an exquisite co-operation between two microenvironmental cues for the differentiation of a tissue-resident macrophage subset, and is (the first?) Try to distinguish from TGFβ, IL-34 example of a local cytokine-dependent functional specialisation of a tissue-resident macrophage subset. The work also provides new insights into the role of IL-33/ST2 pathway in iron homeostasis.

P21 ACCELERATED ATHEROSCLEROSIS AND MYOCARDIAL INJURY IN PEOPLE LIVING WITH HIV

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Background: Observational studies in the United States and Europe demonstrate the overall risk for developing coronary heart disease in people living with HIV (PLWH) is increased by 1.5 to 2.0 fold. Controversially in England this was not validated by Q-Risk 3

Methodology: This is a single centre retrospective analysis of our HIV cohort. We searched our pathology results system over a 3 year period looking for high sensitivity Troponin T (hsTropT) results. We used < 52ng/L as a negative result. We then analysed patient’s notes to confirm if they had a myocardial infarction, classify the type and attribute a cause.

Results: 490 results we reported, 16 samples were haemolysed, on 208 PLWH. 119 tests were positive (> 52ng/L) in 36 patients. The average age was 56.5 years, 24.3% women. 47% were Afro-Caribbean and 42% white British. Interestingly none of the PLWH who had a hsTropT < 100 had a coronary event. There were 10 acute coronary syndromes (ACS), but 29 PLWH had other causes for their raised hsTropT. All of the ACS were men with 50% being ST elevation Myocardial infarctions. 42% had end stage renal failure as a cause for their raised hsTropT, 14% heart failure, 11% arrhythmia and 8% pericardial disease.

Conclusions: From our UK data it does appear that PLWH are developing atherosclerosis and plaque rupture at a younger age than the general population. Of those patients who have a coronary event, it appears PLWH are at higher risk of having a STEMI than the normal population.

P22 PRO- AND ANTI-INFLAMMATORY MACROPHAGES DISPLAY DIVERGENT POLARISATION TOWARDS VASCULAR SMOOTH MUSCLE-LIKE AND ENDOTHELIAL-LIKE PHENOTYPES

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insulin was significantly decreased in hearts from overfed rats due to a decreased activation of the PI3K/Akt. On the contrary, in the vascular reactivity experiments insulin induced a higher vasodilation in aorta segments from L3 rats that was not mediated by the activation of the PI3K/Akt pathway.

Conclusion: Insulin reduced insulin sensitivity in heart and aorta segments from L3 rats via a PI3K/Akt independent mechanism.

References: