compounds such as endothelin-1 (ET-1) and NO are required to maintain vascular tine. An imbalance, resulting in increased ET-1 and reduced NO levels promotes vascular stiffening and consequently diseases such as diabetic retinopathy, nephropathy and atherosclerosis. Diseases caused by an increased atherosclerosis burden including coronary heart disease and stroke are major causes of death in obese and diabetic populations.

Aims Determine **(1)** whether enhanced Aβ levels are sufficient to induce vascular dysfunction and **(2)** if reducing Aβ production can reverse diet-induced vascular dysfunction.

Methods Measurements of vascular function was determined in vivo by the vascular response to Acetylcholine (endothelial dependent or Sodium Nitroprusside (endothelial independent) using laser Doppler imaging in two studies; (i) Wild-type (C57BL/6) mice fed a regular chow diet were infused with murine αβ42 or scrambled peptide (ScP; 3.36μg/kg) in aCSF for 6 weeks or (ii) a BACE1 inhibitor (M-3; 10mg/kg) or vehicle (DMSO/PBS) into diet-induced obese (DIO) C57BL/6 mice. Western blotting and ELISAs were used to measure vascular NO signalling and Aβ production.

Results Circulating levels of Aβ42, not the more prevalent Aβ40 isoform, are increased in both high fat fed mice and obese/diabetic human patients. Infusion of M-3 into DIO mice rescued endothelial dependent reactivity (M-3 27.1 ± 5.9, vehicle 1.3 ± 2.9; $P<0.01$). In contrast, infusion of Aβ42 promoted impaired vascular responses Aβ 14.1±3.7, ScP 38.3±3.2; $P<0.001$) on regular chow with no change in body weight. In line with our hypothesis infusion of Aβ42 increases the ET-1/NO ratio (ScP 1.12β± 0.05, Aβ42 5.35 ± 0.89; $P<0.001$), while DIO mice treated with a BACE1 inhibitor, thus with reduced plasma Aβ42 levels, have a low ET-1/NO ratio (M-3 1.29 ± 0.9, DIO 4.6 ± 1.3; $P<0.05$).

Conclusions We suggest that amyloid processing has a role in normal vascular function with aberrant processing leading to endothelial dysfunction and hypertension. Here we show that pharmacological inhibition of BACE1 can reverse diet-induced endothelial dysfunction, via modulation of plasma Aβ42 levels, as infusion of Aβ42 can promote the dysfunction independent of a high fat diet.

214 A HISTONE DEACETYLASE 7-DERIVED 7-AMINO ACID PEPTIDE ACTS AS A PHOSPHORYLATION CARRIER

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10.1136/heartjnl-2017-311726.212

Histone deacetylase 7 (HDAC7) belongs to the class II HDAC family and plays a pivotal role in the maintenance of endothelium integrity. There are 8 splicing variants in mouse HDAC7 mRNAs. Within the 5' terminal non-coding area of some variants, there exist some short open reading frames (sORFs). Whether these sORFs can be translated and whether the resulting peptides play roles in cellular physiology remain unclear. In this study, we demonstrated that one sORF encoding a 7-amino-acid (7-aa) peptide could be translated in vascular progenitor cells (VPCs). Importantly, this 7-aa peptide (7A) could transfer the phosphate group from the phosphorylated Ser393 site of MEKK1 to the Thr145 site of 14-3-3γ protein. The phosphorylated 7A (7Ap) could then directly phosphorylate 14-3-3γ protein in a cell-free, in-gel buffer system. The adjacent histidine and proline residues are essential for the phosphate group reception and transfer. In vitro functional analyses revealed that 7A and 7Ap increased VPC self-renewal and migration and enhanced vascular endothelial growth factor (VEGF)-induced VPC migration and differentiation toward the endothelial cell (EC) lineage, in which MEKK1 and 14-3-3γ served as the upstream kinase and downstream effector, respectively. Knockdown of either MEKK1 or 14-3-3γ attenuated VEGF-induced VPC migration and differentiation. Exogenous 7Ap could rescue the effect of VEGF on the MEKK1 siRNA-transfected VPCs but not on the 14-3-3γ siRNA-transfected VPCs. In vivo studies revealed that 7A, especially 7Ap, induced capillary vessel formation in Matrigel plug assays, increased re endothelialization and suppressed neointima formation in the femoral artery injury model, and promoted foot blood perfusion recovery in the hindlimb ischemia model by increasing Sca1+ cell niche formation. These results indicate that the sORFs within the non-coding area can be translated and that 7A may play an important role in cellular processes, such as proliferation, migration and differentiation, by acting as a phosphorylation carrier.

215 CARDIAC MACROPHAGE INFILTRATION DURING CHRONIC KIDNEY DISEASE ACCELERATES CARDIOVASCULAR DISEASE

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10.1136/heartjnl-2017-311726.213

The relationship between chronic kidney disease (CKD) and increasing rates of cardiovascular disease and mortality is complex, but is important due to the massive increased risk of cardiovascular events noted in CKD patients. Macrophages have critical roles in kidney and cardiovascular disease. However, since a deeper understanding of macrophage ontogeny and heterogeneity, we wanted to revisit the role of cardiovascular macrophages during CKD.

Using the folate induced nephropathy and 5/6 nephrectomy mouse models of CKD, we have new exciting data showing that during CKD, independent of atherosclerosis, inflammatory macrophages are infiltrating cardiac tissue. Using flow cytometry, RNA profiling, histology and ultrasound, we analysed the phenotype and function of the heart and immune cell infiltrate during CKD.

After 12 weeks of CKD, $CD11b^{pos}F480^{pos}CD169^{neg}$ monocyte derived macrophages infiltrate heart tissue in large numbers. This is only evident in cardiovascular tissue, with no systemic infiltrate in lungs, spleen, kidney or liver. Interestingly, we also noted an increase in cardiac $CD19^{pos}$ B-cell and $Gr1^{pos}$ neutrophil infiltrate over the course of CKD. The cellular infiltrate was associated with an increase in cardiac fibrosis markers and decrease in heart function, as shown by decreased ejection fraction. Measuring specific chemokine expression in heart and plasma identified a unique chemokine axis, which may be regulating macrophage and other immune cell recruitment to heart tissue during CKD. Moreover, we confirmed the ontogeny of these cardiac macrophages through $Ly6C^{high}$ monocyte lineages using CCR2 deficient mice, which improved cardiac function.

This work uncovers a unique pathway that mediates inflammatory monocyte derived macrophage infiltration in the heart during CKD. More work is now being performed to confirm mechanisms and cardiovascular phenotype in our CKD