Understanding the Germinal Centre B Cell Role of Neutrophil Elastase in Abdominal Heart Tamoxifen dosing via intra-peritoneal injection, AID-expressing fed chow or western diet (WD) for up to 8 weeks and upon timing of tamoxifen dosing was varied throughout the studies.

**Results**

Ldlr-/- mice develop an enlarged GC response within the spleen and lymph nodes, although not in gut-associated Peyer’s patches. Around 50% of Ldlr-/- mice on chow diet develop this response whereas >80% of WD-fed mice have an enhanced response. WT mice do not develop this response. The GC response consists of more class-switched (IgM-) GC B cells in Ldlr-/- mice compared to WT mice. This results in increased serum levels of the Th1-driven IgG isotype IgG2a, but no increase in Th2-driven IgG1 after 8 weeks western diet. Labelling GC cells during western diet (but not before) demonstrates that GC clones persist longer after western diet feeding than in chow-fed mice.

**Conclusion**

Atherosclerotic conditions increase not only numbers of GC B cells, but also change the type of response that occurs, providing an opportunity to target the atherosclerosis-specific responses therapeutically.

**Conflict of interest**

None

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UNDERSTANDING THE GERMINAL CENTRE B CELL RESPONSE TO ATHEROSCLEROSIS IN MICE USING LINEAGE TRACING

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Introduction

Elevated plasma low density lipoprotein (LDL) is a major risk factor for atherosclerosis and its immunogenic oxidation triggers an inflammatory response. The importance of B cells within cardiovascular disease is demonstrated by genome-wide association studies and transcriptomic studies that have identified genes involved in proliferation and activation of B cells. It has been shown that the germinal centre (GC) response, the process by which plasma and memory B cells are formed, is pathogenically dysregulated in atherosclerosis, and that class-switched plasma cells infiltrate into human diseased vascular tissue. We therefore sought to further characterise and understand the causes for this pathogenic response by using a lineage tracing mouse model.

Methods

Use of the tamoxifen-inducible AID-CreERT2-Rosa-EYFP-Ldlr-/- lineage tracing model mouse enables the tracking of atherosclerosis-specific B cell clones comprising GC, memory and plasma B cells. Ldlr-/- and Ldlr+/- (WT) mice were fed chow or western diet (WD) for up to 8 weeks and upon tamoxifen dosing via intra-peritoneal injection, AID-expressing cells (GC B cells) are fluorescently labelled with EYFP. The

Abdominal Aortic Aneurysm (AAA) affects 4–5% of men over 65, and Thoracic Aortic Dissection (TAD) is a life-threatening aortic pathology where 75% of patients die within 2-weeks post-onset. Relatively little is known about the underlying mechanisms, which warrants further investigation. Neutrophil Elastase (NE) is an enzyme with roles in priming of the immune system, clearance of large pathogens and remodelling of extra-cellular-matrix proteins, all influential in AAA and TAD. Our recent study suggests a causal role for NE in hyperlipidemia-induced atherosclerosis. However, little is known regarding implications of NE in AAA and TAD. This study aims to investigate the role of NE within both pathologies.

Gene-expression of NE and AAA-associated markers, MMP-2 and MMP-9, were significantly up-regulated by CaCl2-and AngII-treatment in the cultured vascular smooth muscle cells, endothelial cells and macrophages. In both AngII- and CaCl2-induced AAA mouse models, reduction of aortic expansion in NE-knockout mice was observed, compared with wild-type littermates. TAD experiments reaffirmed the functional importance of NE, with significant reduction in death within NE-knockout mice. Histological and Proteomics analysis was carried out in order to determine changes produced by loss of the NE gene within these models. Preliminary translational work is underway, with an Audit of Aneurysm patients’ blood profiles. Additionally, peripheral blood and aortic tissues were harvested from surgical repair patients with AAA for NE expression analysis. Initial results show an alteration in proportions of White Blood cell populations, namely macrophages.