

## **Aorta tertiary lymphoid organs: Powerhouses of B cell immunity in atherosclerosis**

Cardiovascular disease (CVD) is the leading cause of death worldwide. Yet, our understanding of how the immune system impacts CVD is very limited and immune system-based therapeutic approaches are not in sight. Lymphocytes are major cellular constituents of the immune system regulating both disease-protection and disease-promotion. B lymphocytes are a major pillar of the immune system: B cells are involved in antibody and cytokine (inflammatory and anti-inflammatory) production. We observed lymphocyte clusters in the diseased artery adventitia, i.e. the connective tissue coat that surrounds blood vessels in aged atherosclerosis-prone ApoE<sup>-/-</sup> mice. We termed these clusters artery tertiary lymphoid organs (ATLOs) (Fig. 1). TLOs have been observed in major clinically significant unresolvable inflammatory diseases, i.e. chronic infection, transplant rejection, autoimmune diseases, cancer, and atherosclerosis. TLOs are believed to organize disease-specific immune responses outside the systemic immune system such as spleen, lymph nodes, and the bone marrow. When we analyzed gene expression in the adventitia of aged ApoE<sup>-/-</sup> mice, genes related to B cell mediated immunity, B cell activation, proliferation, and differentiation were highly expressed.

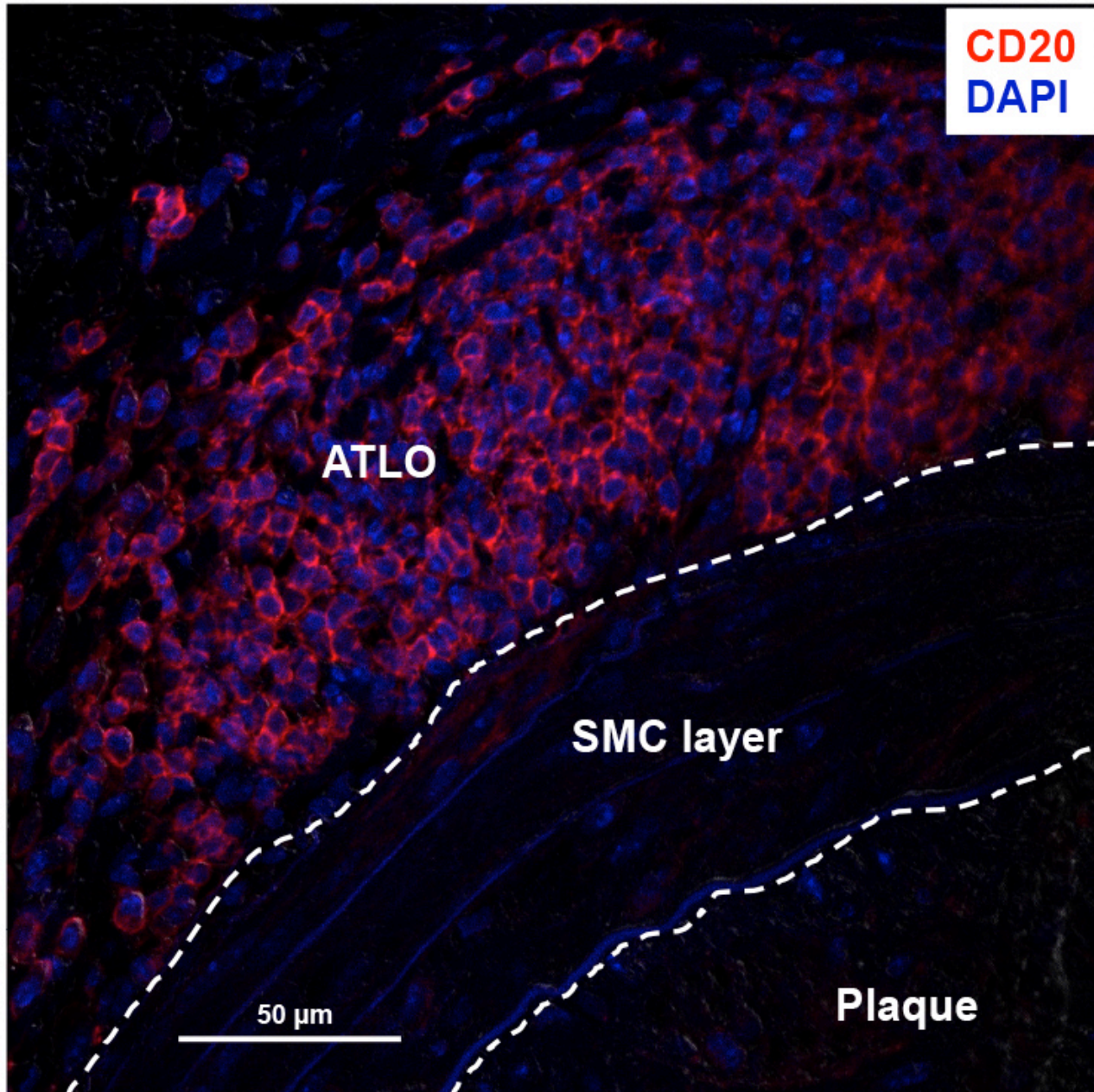


Fig. 1. B cells in adventitia of aged ApoE<sup>-/-</sup> mice: ATLOs develop in the aorta adventitia adjacent to atherosclerotic plaque. Immunofluorescence staining with an anti-CD20 antibody in the diseased aorta adventitia demonstrates B cells in the ATLO, but not in the SMC layer and plaque. DAPI used for nuclear staining.

Detailed analyses of ATLO B cells revealed major B cell subtypes within the aorta of diseased arteries but none in the aorta of healthy arteries. Importantly, ATLOs contain B cells with activities as varied as antibody production (also called plasma cells), B cells at various B cell maturation

steps, and activated germinal centers (the location where B cells undergo antigen-specific maturation and affinity maturation). This body of data together with our previous observation that B cells are major constituents of ATLO antigen-presenting cells reveals a yet unrecognized scenario of aorta atherosclerosis-specific B-cell immunity. These data are the first to suggest that (auto) antigen-dependent hypermutation, proliferation, affinity maturation, immunoglobulin class switching, memory B cell generation, and differentiation into plasma cells may be carried out within the arterial wall. These findings have major consequences for our understanding of immune system regulation of atherosclerosis: It is becoming evident that ATLOs provide a new paradigm of atherosclerosis-specific B-cell immunity and possibly autoimmunity: ATLO B-cell responses occur in aged animals. These data demonstrates that ATLOs are the principal lymphoid tissue that orchestrates atherosclerosis-specific B cell immunity. It is hoped that these data will lead not only to a better understanding of the pathogenesis of atherosclerosis but also to novel immune system therapeutic approaches.

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## **Publication**

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