Is Atherosclerosis a vascular or a systemic immune disease?

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The adaptive immune system plays a crucial role in atherosclerosis. Several immune cells reside in the vessel wall of normal arteries with accelerated recruitment observed in the pathology. However, little is known about the impact of vascular immune cell subsets on atherosclerosis development and progression. To support the importance of the local vascular adaptive immune response, I will discuss the capacity of antigen presenting cells (APCs) to present *in vivo* systemically administered antigens directly into the vessel wall and will detail the kinetic of local vs systemic antigen presentation in experimental atherosclerosis. I then will focus on the role of the plasmacytoid dendritic cells (pDCs) (Grassia et al., 2013), the main APC subset to expand in the mouse atherosclerotic aorta showing enhanced Ag presentation capacity. We first demonstrated that pDC depletion significantly reduced atherosclerosis formation in the aortic sinus leading to a more stable plaque phenotype (MacRitchie et al., 2012). Subsequently, we identified a critical role for MHCII-restricted antigen presentation by pDCs in driving proatherogenic T cell immunity (Sage et al., 2014). Finally, I will discuss the impact of artery tertiary lymphoid organs (ATLOs) on disease progression. We found in aged apolipoprotein-E $(apoe)^{-/-}$ mice that ATLOs control aorta T cell responses. ATLOs promote T cell recruitment, prime $CD4^+$ T cells, generate $CD4^+$, $CD8^+$, T regulatory (T_{reg}) effector and central memory cells. Vascular smooth muscle cell lymphotoxin β receptors (VSMC-LTβRs) maintain structure and size of ATLOs and protect against disease progression (Hu et al., 2015). In conclusion, vascular immune cells drive pro-atherogenic adaptive immunity in the early stages of the pathology; on the contrary, the immune system selectively employs ATLOs to organize vascular immunity and protect against plaque development during the advanced stages of the pathology.

Grassia et al. (2013). *Pharmacol Ther.* 137: 172-82.
McRitchie et al. (2012). *Arterioscler Thromb Vasc Biol.* 32: 2569-79.
Sage et al. (2014). *Circulation.* 130: 1364-73.
Hu et al. (2015). *Immunity.* 42: 1100-15.