Lymphatic Function Is Impaired Before Atherosclerosis Onset and can be rescued by VEGF-C treatment

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Introduction. Atherosclerosis is the pathological consequence of chronic inflammation of blood vessels. Macrophages and cholesterol are the two main constituents driving the inflammatory response that characterizes atherosclerosis. In a recent study, the lymphatic system has been identified as a novel prerequisite player in the removal of cholesterol out of the atherosclerotic lesion (Martel et al., JCI 2013). It has been shown that without a functional lymphatic network, cholesterol gets trapped in the artery wall and potentially aggravates the disease. Lymphatic development and regulation are dependent upon vascular endothelial growth factor - C (VEGF-C) and its receptor VEGFR3. The lymphatic vessels are composed of two main components, namely the absorptive capillaries, responsible for the uptake of the cells, molecules and fluid, and the collecting vessels, characterized by pumping units (lymphangions) that are propelling the lymphatic content toward the blood circulation in a unidirectional manner. The relative roles of the lymphatic capillaries and collectors in the context of atherosclerosis onset and progression are still unclear. However, gene therapy with VGEF-C) has been shown to reduce lymphedema by stimulating lymphangiogenesis, and recently, VEGF-C has been associated with lymphatic pump stimulation. As our unpublished preliminary data suggest that atherosclerosis-associated lymphatic dysfunction occurs before the onset buildup of the atherosclerotic lesion, we aim to determine whether and how early VEGF-C treatment can modulate lymphatic function to eventually prevent or abrogate the atherosclerosis process.

Methods. Cellular lymphatic transport and molecular lymphatic transport have been evaluated in pre- and atherosclerotic ($LDLR^{-/-}$; $hApoB100^{+/+}$, also called ATX, and wild-type (WT) mice, as well as the morphology and functionality of lymphatic capillaries. Lesion-free pre-atherosclerotic ATX mice (3 month-old) were injected i.p. with 25 ng of VEGF-C 152s, 3x/wk, for 4 weeks.

Results. Our preliminary data show that, despite the absence of atherosclerotic lesion, 1) pre-atherosclerotic ATX mice exhibit impaired lymphatic transport that deteriorates with age, 2) display morphologically and functionally normal lymphatic absorptive capillaries and that 3) systemic VEGF-C treatment rescues cell transport through the lymphatics.

Discussion. Our results suggest that, i) as lymphatic capillaries function are seemingly normal, collecting lymphatic vessels may be responsible for the impairment in lymphatic function of ATX mice, and ii) VEGF-C has a positive effect on lymphatic function, most likely by stimulating lymph flow through the lymphatic collecting vessels instead of promoting lymphangiogenesis. We now plan to investigate if VEGF-C treatment will limit atherosclerosis development in ATX mice, as well as its role in the pumping capacity of the collecting vessels. We are hopeful that, in the long run we will be able to identify new therapeutic targets to enhance lymphatic transport and ultimately limit atherosclerosis progression.

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