

13. Reverse cholesterol transport relies on a functional lymphatic network

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Abstract:

Although it is well established that HDL accepts free cholesterol from cells and transports it back to the liver for excretion and that nascent apoA-1 crosses the vascular endothelium to gain access to extravascular tissues, little is known about how HDL-C leaves such tissues to reach the bloodstream. HDL-C is a component of cannulated human lymph, but it remains unclear if lymphatic vessels play a major role in the mobilization of HDL-C out of tissues. Thus, we employed two models of disrupted lymphatic drainage—one a surgical resection of lymphatics in the mouse tail and the other genetic lack of skin lymphatics due to a mutation in the tyrosine kinase domain of VEGFR3—to quantitatively evaluate the importance of lymphatic vessels in the movement of HDL-C out of skin, following cholesterol efflux from macrophages. In these models and in control mice, we implanted congenic bone marrow macrophages loaded with [³H]-cholesterol and quantified the initial appearance of this cholesterol in plasma before its clearance in the liver and feces, in order to best capture the period corresponding to movement of HDL-C from tissues to plasma. During this initial phase (first 24 h), [³H]-cholesterol was reduced by approximately 80% in both models of disrupted lymphatics. To ensure that this reduction was not due to changes in macrophage efflux, but instead reflected events between efflux and appearance of cholesterol in the bloodstream, we implanted macrophages loaded with a modified cholesterol molecule containing bodipy in the cholesterol backbone that allowed us to monitor cholesterol efflux in individual macrophages by flow cytometry. Like native cholesterol, efflux of this modified cholesterol required macrophage expression of ABCA1/ABCG1. Retrieval of bodipy-cholesterol-loaded macrophages from sites of injection (tail skin, footpad) revealed a similar magnitude of macrophage cholesterol efflux in mice lacking functional lymphatics compared with controls. Thus, we conclude that mobilization of HDL-C from extravascular tissues like skin to the bloodstream depends upon an intact lymphatic vasculature. We are in the process of evaluating the role of lymphatics in RCT under conditions when the blood vasculature is leaky, a condition that may apply to advancing atherosclerotic plaques. Given that lymphatic vessels, like blood vessels, become compromised under conditions of hypercholesterolemia, it will be important in the future to determine whether hypercholesterolemia-induced impairments in lymphatic function influence the accumulation of cholesterol in extravascular tissues, including atherosclerotic plaques. Surprisingly little is known about lymphatics that drain the arterial supply. These data suggest that a better understanding of arterial lymphatic anatomy and function is warranted.

Aucun conflit d'intérêt.