Vascular Dendritic Cells as Gatekeepers of Lipid Accumulation Within Nascent Atherosclerotic Plaques

Gwendalyn J. Randolph, Stephane Potteaux

Recent studies, including a series of articles coauthored by Jongstra-Bilen and Cybulsky, have brought fresh and exciting insight to the earliest stages of atherosclerotic plaque formation in mouse models of the disease. Capturing outstanding images of the lesser curvature of the murine aorta, a site highly prone to atherosclerotic plaque development, the Cybulsky laboratory revealed in 2006 that cells bearing markers of dendritic cells (DCs), including CD11c (α, integrin), take up residence just beneath the endothelium in the lesser curvature of mice. Possible counterparts of these DCs have also been observed in lesion-prone arterial sites of rabbits and humans. The initial appearance of murine DCs in the lesser curvature depends on endothelium activated in response to disturbed blood flow and is independent of plasma cholesterol status, because it occurs in standard mouse strains that are not hypercholesterolemic (Figure). These DCs were recently visualized in the CD11c-YFP mouse and shown to possess capacity for potent antigen presentation to T cells. Although they sit primarily beneath the endothelial lining, vascular DCs occasionally extend projections into the bloodstream (Figure). Even in the absence of hypercholesterolemia, the density of DCs within the lesser curvature of mice varies according to strain and positively correlates with terolemia, the density of DCs within the lesser curvature of strains that are not hypercholesterolemic (Figure). These data argue that vascular DCs importantly regulate the accumulation of lipid in the earliest stages of plaque formation.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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held only by a subset of the DCs described? In their previous work, the authors reveal heterogeneity among vascular DCs, although this is scarcely discussed in the present study. Thus, 33D1 is a marker of many, but not all, vascular DCs. Another fraction of CD11c+ DCs in nascent plaques are CD11b+ cells that likely arise from Ly-6Chi monocytes. These monocyte-derived cells accumulate in nascent plaques simultaneously with the proliferation of 33D1+ vascular DCs. Apparently, DT treatment affected both of these populations in the CD11c-DTR mouse. In contrast to CD11c, neither the 33D1 nor CD11b marker was demonstrated to colocalize with lipid staining, so it remains unclear whether the possibly more DC-related 33D1+ cells accumulated lipid or whether it was in the CD11b+ cells, or both. The LysCre reporter mouse provides a useful approach for confirming which DC populations are not of monocyte origin and would be useful to apply here. Furthermore, application of CD11b-DTR mice would potentially allow for the removal of CD11b+ DCs, but not 33D1+ DCs, to determine whether these different DC populations have distinct roles with regard to the accumulation of cholesterol in the artery wall. In addition, use of other DTR models besides the CD11c-DTR mouse model, especially DTR models in which no changes in lipid deposition are found, would help to ensure that any spike in TGFβ1 released from DTR-induced apoptosis did not account for the changes in lipid deposition observed.

In summary, the appearance of vascular DCs in lesion-prone areas of arteries before the onset of hypercholesterolemia had already positioned these cells as suspect players in disease initiation. Now, the findings of the present study, together with images of vascular DCs extending projections into the lumen of the aorta, raise the tantalizing question of whether vascular DCs actually capture LDL that may interact...
with the activated endothelium as it flows past in the circulation, thereby collecting much of the first cholesterol that accumulates in the arterial intima. Because at least some DCs can retain intact protein for long periods after ingesting it,\textsuperscript{19–21} in contrast to macrophages,\textsuperscript{20} the idea that DCs are the earliest depot of cholesterol deposition in plaques may not be inconsistent with earlier studies that cholesterol accumulation in nascent plaques of rabbits involves selective retention of “intact” LDL within plaque-prone sites,\textsuperscript{22,23} even though those studies argued against the idea that the earliest plaque cholesterol was localized within phagocytes. To potentially reconcile the present study with the aforementioned earlier work in rabbits and add to our understanding of the sequence of early events in plaque formation, it will be interesting in future studies to determine whether vascular DCs indeed retain LDL-associated proteins in intact form for rather long periods. It will also be important to understand how this mechanism interfaces with lipoprotein retention mediated by proteoglycans in the artery wall\textsuperscript{24,25} and whether DC- versus proteoglycan-mediated retention operate cooperatively, possibly even through a positive feedback, to bring on rapid plaque growth or whether they represent independent mechanisms for cholesterol retention in the artery wall. In either case, vascular DCs, likely activated in response to lipid loading, would be in a position to produce a cascade of factors that orchestrate the recruitment of large numbers of monocytes and increased amounts of cholesterol that follow, thereby fueling plaque progression in a way that proteoglycan-mediated cholesterol retention alone may not. We eagerly wait for the next chapter in this series of studies to unfold.

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**Disclosures**

None.

**References**


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