Letters to the Editor

Natural Killer T Cells in Atherosclerosis

To the Editor:
Natural Killer T (NKT) cells comprise a heterogeneous subpopulation of T cells that coexpress T cell receptor (TCR) and Natural Killer (NK) surface antigen CD161 in humans and NK1.1 in mice.1,2 NKT cells are CD1d-restricted and express an evolutionary conserved TCR with invariant α-chain (Vα14-Jα18 in mouse and Vα24-Jα18 in human),1,2 NKT cells react to exogenous α-galactosylceramide (αGalCer), which is presented by monomorphic HLA class-I–like molecule CD1d.1,2 It has been shown also that, in humans, some conventional T cells might upregulate NK receptors on activation.2

A number of recent experimental studies using mouse models have indicated a proatherogenic role of CD1d-restricted NKT cells in atherogenesis.1,3 These works prompted us to examine whether T cells expressing perforin (CD161) are present in human atherosclerotic lesions.6 We found that, although small numbers of perforin-expressing T cells (CD161CD3+) were present in all types of human atherosclerotic lesions, perforin-expressing T cells were most frequent in rupture-prone regions of advanced atherosclerotic plaques where perforin-expressing T cells constituted up to 2% of the total T cell population.5 Direct contacts of CD1d+ dendritic cells with perforin-expressing T cells were observed in plaque rupture-prone regions,8 suggesting that dendritic cells might be involved locally in the regulation of perforin-expressing T cells.

In a very recent work, Aslanian et al7 examined the role of NKT cells in experimental atherosclerosis, comparing lesion size between CD1d+ and CD1d−/− mice after 4, 8, and 12 weeks of feeding on a Western diet. The study showed that lesions in CD1d+LDLR+/− mice were smaller at 4 weeks than in CD1d+/−LDLR+/− controls, but there were no differences in lesion size between CD1d+LDLR+/− and CD1d+/−LDLR+/− mice at 8 or 12 weeks.9 No differences in mRNA abundance for Th1 or Th2 cytokines were detected between CD1d+LDLR+/− and CD1d−/−LDLR+/− mice.9 Early atherosclerotic events in human atherosclerosis occur in the tunica intima, which is composed of several layers of intimal smooth muscle cells and which contains vascular-associated lymphoid tissue (VALT).10 VALT includes a small number of resident macrophages, T cells, and dendritic cells which may be responsive to the accumulation of atherogenic lipoproteins at the preatherosclerotic stage.10 In contrast to humans, the aortic tunica intima in mice consists of a monolayer of endothelial cells located along the acellular subendothelial matrix, which is separated from the tunica media by the internal elastic lamina. Thus, in mice, atherosclerosis depends on the invasion of medial smooth muscle cells and/or blood cells into the tunica intima.

At present there is no adequate model for investigating the rupture of atherosclerotic plaque. Although several studies have indicated that plaque rupture occurs in mice,11,12 mouse models may poorly mimic the plaque microenvironment typical of rupture-prone regions of unstable human plaques. Therefore, the conclusion by Aslanian et al7 that CD1d-restricted NKT cells “... do not influence the cytokine milieu or the degree of inflammation in the plaque during advanced atherosclerosis” might be restricted to the model used in that particular study.2 In spite of a limited number of studies on the CD1d–mediated NKT cell response triggered by atherogenic lipid antigens, the significance of NKT cells in atherosclerosis has yet to be clarified.

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In Response:
In the article by Aslanian et al,7 we examined the role of CD1d-restricted NKT cells in the development of atherosclerosis in LDL receptor–deficient (LDLR−/−) mice. In this model, lesion size was reduced in CD1d-deficient mice at a very early time point (4 weeks on a high-fat diet) but not after 8 or 12 weeks on the diet. Two other recent publications support the claim that NKT cells contribute to atherosclerosis. Tupin et al2 demonstrated that CD1d deficiency on the Apoe−/− background reduced lesion size by 25%, whereas administration of α-galactosylceramide, a synthetic lipid that activates CD1d, increased lesion size by 50%. Similarly, Nakai et al3 found that, on a high-fat diet, LDLR−/− mice with bone marrow transplants from CD1d+/+ mice had significantly smaller lesions than those with transplants from wild-type mice. Moreover, α-galactosylceramide exacerbated atherosclerotic lesions in wild-type mice; consistent with our findings, this effect was limited to early lesions.

We do not disagree with Dr Bobryshev that atherosclerotic lesions in mice fail to perfectly model lesions in humans, particularly with respect to advanced and complex lesions. It is thus reassuring that CD1d-restricted NKT cells play a functional role in two distinct murine models of atherosclerosis, and in both Nakai et al3 and Aslanian et al7 the contribution of NKT cells appears to be most important in the early phases of disease.

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