EDITORIAL COMMENT

Atherosclerosis: cell biology and lipoproteins

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Atherosclerosis is a complex disease associated with aberrant lipoprotein metabolism and leukocytic infiltration into arterial tissue [1]. Although it is widely appreciated that macrophages are a critical contributor in the crosstalk between disorders of lipoprotein metabolism and innate immunity responses, there are also complex roles of T lymphocytes evoking adaptive immune responses within lesions [2].

Apolipoprotein E (apoE) −/− and LDL receptor −/− mice are commonly used to define mechanisms of atherosclerosis. To understand the contribution of their divergent lipoprotein characteristics to atherosclerosis, Parks *et al.* [3••] studied G2A, a lysophospholipid-sensitive G protein-coupled receptor that is abundantly expressed by macrophages and endothelial cells [4,5]. Both proatherogenic and antiatherogenic effects have been ascribed to G2A [4,5]. To resolve this conundrum of contradictory effects, Parks *et al.* [3••] performed comprehensive atherosclerosis studies in mice with single or compound deficiency of apoE and LDL receptor. They found that G2A regulated HDL cholesterol concentrations only in the presence of apoE. Furthermore, deletion of G2A in mice with apoE deficiency or compound deficiency of apoE and LDL receptor had either no or augmented effects on atherosclerosis [3••]. In contrast, G2A deficiency reduced atherosclerosis in LDL receptor −/− mice [5]. However, chimeric LDL receptor −/− mice with G2A deficiency in bone marrow-derived cells had no effect on plasma HDL cholesterol concentrations and failed to ameliorate atherosclerosis. Although this finding indicates a critical role of G2A in resident tissues, cell-specific manipulation of G2A will be needed to define the mechanistic basis for the apoE-dependent modulation of HDL and atherosclerosis.

Cholesterol loading of macrophages stimulates a series of inflammatory mediators to promote atherosclerosis. Recent attention has focused on mannose-binding lectin (MBL). Studies [6,7] using humans provided conflicting findings with either proatherogenic or antiatherogenic effects of MBL. To unravel this dilemma, Matthijsen *et al.* [8•] studied the development of atherosclerosis in LDL receptor −/− mice. Interestingly, MBL was abundant in macrophage-rich atherosclerotic lesions from mice fed a fat-enriched diet for 10 weeks but was only expressed in necrotic cores of lesions in mice fed the same diet for 18 weeks. Bone marrow transplantation demonstrated that macrophage-expressed MBL was the dominant source influencing atherosclerosis. However, this was only studied in mice fed the fat-enriched diet for 10 weeks. It would also be interesting to determine whether MBL deficiency in macrophages changes atherosclerosis in these mice after an 18-week high-fat diet feeding because MBL was not present in macrophages in more advanced lesions.

As noted above, T lymphocytes are present in atherosclerotic lesions and have a complex role in lesion development [9]. Collective evidence shows that hypoxia-inducible factor-1α (HIF-1α), the oxygen-dependent transcriptional regulator, downregulates T helper 1 (Th1) programs while propagating T helper 2 (Th2) responses [10]. In spite of the potential role of HIF-1α, no atherosclerosis studies had been performed. To fill this void in knowledge, Ben-Shoshan *et al.* [11•] performed an atherosclerosis study in apoE −/− mice that were intravenously administered plasmids containing either no gene or HIF-1α. Robust expression of HIF-1α was evident in mouse spleen, accompanied by large increases in plasma concentrations of IL-10 and a corresponding decrease of IFNγ. A profound reduction of atherosclerosis was detected in mice injected with the HIF-1α plasmid. Interestingly, IFNγ was not only suppressed in $CD4^+$ spleen-derived lymphocytes, but also diminished in atherosclerotic lesions in these HIF-1α-expressing mice. IFNγ is expressed by both macrophages and T lymphocytes, but the main cell type expressing this cytokine was not defined in this study. This study is consistent with the literature demonstrating that an enhancement of Th2 responses has the beneficial effect of reducing atherosclerosis.

These recent animal studies further attempt to clarify some of the complexities in the literature regarding the interactions of lipoprotein metabolism and leukocytes in the development of atherosclerosis. This clarity will be required for the extrapolation of these data to the human disease. However, irrespective of the contradictions, it is clear that macrophages, lymphocytes and their consequent immune responses have important roles in atherosclerosis.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1 Rader DJ, Daugherty A. Translating molecular discoveries into new therapies for atherosclerosis. Nature 2008; 451:904–913.

2 Hansson GK, Libby P. The immune response in atherosclerosis: a double-edged sword. Nat Rev Immunol 2006; 6:508–519.

3 •• Parks BW, Srivastava R, Yu S, *et al.* ApoE-dependent modulation of HDL and atherosclerosis by G2A in LDL receptor-deficient mice independent of bone marrow-derived cells. Arterioscler Thromb Vasc Biol 2009; 29:539–547.

Previous studies have inferred that G2A has both proatherosclerotic and anti-atherosclerotic effects. This study is the first demonstration that G2A regulates HDL cholesterol concentrations only in the presence of apoE. G2A deficiency has either no or augmented effects on atherosclerosis in apoE −/− mice but reduces atherosclerosis in LDL receptor −/− mice.

4 Bolick DT, Whetzel AM, Skaflen M, *et al.* Absence of the G protein-coupled receptor G2A in mice promotes monocyte/endothelial interactions in aorta. Circ Res 2007; 100:572–580.

5 Parks BW, Lusis AJ, Kabarowski JH. Loss of the lysophosphatidylcholine effector, G2A, ameliorates aortic atherosclerosis in low-density lipoprotein receptor knockout mice. Arterioscler Thromb Vasc Biol 2006; 26:2703–2709.

6 Madsen HO, Videm V, Svejgaard A, *et al.* Association of mannose-binding-lectin deficiency with severe atherosclerosis. Lancet 1998; 352:959–960.

7 Rugonfalvi-Kiss S, Dosa E, Madsen HO, *et al.* High rate of early restenosis after carotid eversion endarterectomy in homozygous carriers of the normal mannose-binding lectin genotype. Stroke 2005; 36:944–948.

8 • Matthijsen RA, de Winther MP, Kuipers D, *et al.* Macrophage-specific expression of mannose-binding lectin controls atherosclerosis in low-density lipoprotein receptor-deficient mice. Circulation 2009; 119:2188–2195.

MBL is a complement component. This study demonstrated that MBL is abundant in macrophage-rich atherosclerotic lesions from mice fed a fat-enriched diet for 10 weeks. In addition, macrophage-expressed MBL was the dominant source influencing atherosclerosis.

9 Mallat Z, Taleb S, Ait-Oufella H, *et al.* The role of adaptive T cell immunity in atherosclerosis. J Lipid Res 2009; 50 (Suppl):S364–S369.

10 Sitkovsky M, Lukashev D. Regulation of immune cells by local-tissue oxygen tension: HIF1 alpha and adenosine receptors. Nat Rev Immunol 2005; 5:712–721.

11 • Ben-Shoshan J, Afek A, Maysel-Auslender S, *et al.* HIF-1α overexpression and experimental murine atherosclerosis. Arterioscler Thromb Vasc Biol 2009; 29:665–670.

HIF-1α is an oxygen-dependent transcriptional regulator that propagates Th2 responses. This is the first study to demonstrate that HIF-1α reduces atherosclerosis in mice.

Further recommended reading

• Teupser D, Wolfrum S, Tan M, *et al.* Novel strategy using F1-congenic mice for validation of QTLs: studies at the proximal chromosome 10 atherosclerosis susceptibility locus. Arterioscler Thromb Vasc Biol 2009; 29: 678–683.

Quantitative trait locus (QTL) mapping is a potentially powerful approach to identify new genes affecting atherosclerosis susceptibility. This study generated chromosome 10 (0–21 cM) interval-specific mice on the F1-congenic apoE −/− background. It demonstrated that these F1-congenic mice had strikingly increased atherosclerosis. In addition, this effect was not transferable by bone marrow-derived cells.

• Ortiz-Munoz G, Martin-Ventura JL, Hernandez-Vargas P, *et al.* Suppressors of cytokine signaling modulate JAK/STAT-mediated cell responses during atherosclerosis. Arterioscler Thromb Vasc Biol 2009; 29:525–531.

This study demonstrated the importance of suppressors of cytokine signaling 1 and 3 (SOCS1 and SOCS3) proteins in the development of atherosclerosis. Comprehensive approaches were used, including human sample immunostaining, in-vitro cell culture systems and in-vivo mouse models. Activation of endogenous SOCS pathway might be a potential treatment of atherosclerosis.

• van der Hoorn JW, Jukema JW, Havekes LM, *et al.* The dual PPARalpha/gamma agonist tesaglitazar blocks progression of preexisting atherosclerosis in APOE*3Leiden.CETP transgenic mice. Br J Pharmacol 2009; 156:1067–1075.

ApoE*3 Leiden cholesteryl ester transfer protein (E3L.CETP) transgenic mice have been used to determine the mechanism of atherosclerosis. In this study, E3L.CETP mice were fed a fat-enriched diet for 11 weeks to induce atherosclerosis. Subsequently, low-cholesterol diet containing the peroxisome proliferator-activated receptor (PPAR)α/γ agonist tesaglitazar was fed to these mice. It demonstrated that tesaglitazar reduced triglycerides and VLDL cholesterol but increased HDL cholesterol. As a consequence, atherosclerotic lesions were profoundly reduced.

• Collins AR, Lyon CJ, Xia X, *et al.* Age-accelerated atherosclerosis correlates with failure to upregulate antioxidant genes. Circ Res 2009; 104:e42–e54.

Obesity and diabetes are prevalent in the aging population. This study compared 12-month-old LDL receptor −/− mice with 3-month-old LDL receptor −/− mice that were fed a fat-enriched diet for 3 months. Using microarray analyses and subsequent treatment with either antioxidant apomycin or the insulin sensitizer rosiglitazone, they demonstrated that age-accelerated atherosclerosis was correlated with failure to upregulate antioxidant genes.

• Degirolamo C, Shelness GS, Rudel LL. LDL cholesteryl oleate as a predictor for atherosclerosis: evidence from human and animal studies on dietary fat. J Lipid Res 2009; 50 (Suppl):S434–S439.

This review focuses on the relationship among dietary fat type, plasma and liver lipid and lipoprotein metabolism with atherosclerosis. It extensively discussed the evidence from both human and animal studies and concluded that LDL cholesteryl oleate was a potential predictor for atherosclerosis.