CARDIOVASCULAR DISEASE

An emerging role for RAS?

Drugs that target components of the renin–angiotensin system (RAS), such as angiotensin-converting enzyme (ACE) inhibitors and AT1 receptor antagonists, are widely used to lower blood pressure. They have also been shown to decrease atherosclerosis but the mechanism of action is not well understood. Daugherty and colleagues now show that inhibiting renin — and therefore all downstream components of RAS — with the renin inhibitor aliskiren, approved in 2007 for the treatment of hypertension, reduces hypercholesterolaemia-induced atherosclerosis in mice.

To investigate the role of RAS in the development of atherosclerosis, the authors inhibited renin, the rate-limiting enzyme in the pathway, by giving three increasing doses of aliskiren (2.5, 25 and 50 mg per kg per day) to LDL receptor-deficient ($Ldlr^{-/-}$) mice (an established model of atherosclerosis). On increasing the dose they observed an increase in the plasma renin concentration and a decrease in the plasma concentrations of angiotensin peptides. There was also a sustained decrease in systolic blood pressure with the 25 and 50 mg per kg per day doses.

Measuring atherosclerotic lesion size in the aortic arch or root of $Ldlr^{-/-}$ mice showed that although 25 and 50 mg per kg per day doses of aliskiren were required for a sustained decrease in systolic blood pressure, profound reductions in atherosclerotic lesion size were observed at each aliskiren dose. This suggested that sustained decreases in blood pressure are not required to achieve reductions in atherosclerosis with aliskiren and the authors found no correlation between the two.

From previous observations the authors knew that all components of the RAS were identified in lesions associated with macrophages, which they confirmed by performing real-time PCR on cultured mouse macrophages. To further understand the contribution of macrophages to the production of atherosclerotic lesions, $Ldlr^{-/-}$ mice were irradiated and repopulated with bone marrow-derived cells from $renin^{+/+}$ or $renin^{-/-}$ mice, a procedure that predominantly repopulates macrophages in atherosclerotic lesions. The presence or absence of renin had no effect on systemic measurements such as plasma concentrations of cholesterol, renin or aldosterone, or systolic blood pressure. Despite this, mice repopulated with $renin^{-/-}$ cells had a large reduction in atherosclerotic lesion size, demonstrating that macrophage-derived renin has a pivotal role in the development of atherosclerosis. Overall, this study indicates a novel avenue for research into the therapeutic effects of targeting the RAS beyond lowering of blood pressure.

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ORIGINAL RESEARCH PAPER Lu, H. *et al.* Renin inhibition reduces hypercholesterolemia-induced atherosclerosis in mice. *J. Clin. Invest.* **118**, 984–993 (2008)