

G Protein–Coupled Receptor G2A
Friend or Foe of the Vasculature?

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Atherosclerosis is, in large part, an inflammatory process. White blood cells of different lineages are essential components of the atherosclerotic plaque. More important than their numbers, white blood cells influence the structure of an atherosclerotic plaque, and the function of the vessel in which the plaque is present, by secreting a host of agents that affect resident vascular cells.1

Macrophages, derived from circulating monocytes, are one class of white blood cells that, as part of the atherosclerotic plaque, play a critical part in the progression of the plaque, and in compromising its structural integrity.1 Long before an atherosclerotic plaque is clinically detectable, one of the earliest steps in its genesis is the adhesion of circulating monocytes to the endothelium, and subsequent transmigration into the vessel wall. Because it is well-recognized that these very early stages are critical to plaque development, a great deal of energy has been devoted to trying to understand the mechanisms underpinning them.

The work by Hedrick and colleagues in this issue of Circulation Research2 adds to this understanding. This work examines the part of a G protein–coupled receptor, G2A, in modulating the interaction between monocytes and the vascular endothelium. Using mice that are deficient for G2A, the authors convincingly demonstrate that endogenous G2A tonically inhibits accumulation of monocytes in the vascular wall. G2A is abundantly expressed in hematopoietic cells (including monocytes), and has been shown to inhibit proliferation of lymphoid cells.3 However, with transplants of bone marrows of G2A-deficient and wild-type mice into γ-irradiated wild-type and G2A-deficient hosts, the authors elegantly demonstrate that it is G2A expressed in cells other than those derived from the bone marrow, that is responsible for the greater numbers of monocytes observed in the aortas of G2A knockout mice. Furthermore, to refute the criticism that their observation may simply reflect a global increase in monocytes to the endothelium, and subsequent transmigration into the vessel wall. Because it is well-recognized that these very early stages are critical to plaque development, a great deal of energy has been devoted to trying to understand the mechanisms underpinning them.

These findings suggested to the authors that G2A expressed in monocytes is not part of the equation that leads to their greater numbers in aortas of G2A knockout mice.

Like any good piece of investigation, the report by Hedrick and colleagues goes on to explore the mechanistic basis of the observed phenomenon. Using vascular endothelial cells isolated from G2A-deficient mice, it shows that it is G2A expressed in the endothelium (or rather, its lack thereof), that is the culprit. Such endothelial cells display an “activated” phenotype, expressing monocyte adhesion molecules, and synthesizing monocyte proliferative and chemotactic factors. This novel observation is complemented with the finding that endothelial cells lacking G2A have activated nuclear factor-κB (NF-κB), a well-recognized mediator of inflammation, and that inhibition of NF-κB within these cells, mitigates the activated phenotype.

Based on the afore-mentioned findings by Hedrick and associates, one would predict that G2A knockout mice are more prone to the development of atherosclerosis. Quite the contrary. A very recent report shows that G2A deficiency in atherosclerosis-prone low density lipoprotein receptor-knockout (LDLR−/−) mice that are fed a high-cholesterol or Western diet, for a period of 20 or 26 weeks respectively, leads to a robust reduction in atherosclerotic burden (as measured by aortic lesion area).4 Furthermore, the G2A−/− LDLR−/− mice had reduced numbers of infiltrating macrophages in the aortic arch following 9 weeks of the high-fat diet.4 How then can atherosclerotic burden and macrophage accumulation be lower in these mice lacking G2A, whereas these same G2A-deficient mice have higher numbers of infiltrating macrophages, as observed by Hedrick and colleagues?

Part of the answer to this discrepancy may lie in the old cliché: timing is everything. Atherosclerosis is a slow, indolent process, even in mice lacking the LDL receptor, and to detect it, requires many weeks of a fatty diet. The experiments in mice reported by Hedrick and associates were done at a very early time point (96 hours), whereas those reported by Parks et al5 were, at a minimum, done 9 weeks after dietary intervention. However, the time of observation cannot alone explain the apparent paradox in these two findings. There must be a fundamental biological reason for this difference.

Which reminds one of another old adage: location, location, location. G2A expressed in leukocytes plays a role in the chemotactic response of macrophages and T cells to the oxidized lipid lysophosphatidylcholine (LPC),6 which can be derived from oxidation of the pro-atherogenic lipid particle low-density lipoprotein.6 Thus, G2A expressed in macrophages in atherosclerotic plaques may mediate a proatherogenic response of these cells to LPC. However, G2A ex-

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(Circ Res. 2007;100:450-451.)

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Circulation Research is available at http://circres.ahajournals.org
DOI: 10.1161/01.RES.0000260274.62236.8f
pressed in the endothelium may elicit or mediate a response that is quite distinct, and perhaps even anti-atherogenic, from the one it does in macrophages. Supporting this contention, it is important to recognize that Hedrick and colleagues examined the ligand-independent role of G2A in endothelial cells that were not exposed to LPC or other oxidized lipids, and in the aortas of mice that were not fed a high-lipid diet, whereas the pro-atherogenic role of G2A was observed in the context of a high-lipid diet.4

In conclusion, the work by Hedrick and colleagues shines new and important light on the true physiological function of G2A in the vasculature: maintaining vascular homeostasis by inhibiting activation of the endothelium, and subsequent adhesion and infiltration of the vascular wall by inflammatory cells. These inflammatory cells are programmed to respond to infection: a response that is mediated, at least partly, through LPC and G2A that they express.7 Therefore, when faced with circumstances that nature never intended, such as in high-lipid diet-induced atherosclerosis, in which there are elevated levels of LPC and other oxidized lipids,8 these inflammatory cells do respond in a natural manner, with unnatural consequences.

**Sources of Funding**
The author gratefully acknowledges the support of the NIH, and the AHA (Pennsylvania-Delaware Affiliate).

**Disclosures**
None.

**References**

**Key Words:** atherosclerosis | inflammation | endothelium
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Circ Res. 2007;100:450-451
doi: 10.1161/01.RES.0000260274.62236.8f

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