Translating GWAS Into the Flow-Regulated Modulation of Lipid Mediator Signaling

Ingrid Fleming

It is well accepted that the stimulation of endothelial cells by the blood flowing over them can alter the generation of endothelium-derived vasodilators, such as nitric oxide (NO), to fine tune vascular tone. The shear stress generated by the flowing blood can also affect endothelial cell signaling and while laminar shear stress, which has also been termed atheroprotective flow, generally activates anti-inflammatory signals, areas of the endothelium exposed to disturbed (turbulent or oscillatory) and low flow are characterized by an inflammatory footprint. The latter is typically associated with elevated nuclear factor κB activation and adhesion molecule expression accompanied by the concomitant attenuated expression and activation of major protective factors, notably the endothelial NO synthase and Kruppel-like factors, KLF2 and KLF4.1

In this issue of Circulation Research, Wu et al2 report that an integral membrane protein previously described as a p120-catenin–associated integrin ligand localized to the adherens junction of endothelial cells3 is implicated in endothelial cell responsiveness to flow. The protein in question is phosphatidic acid phosphatase type 2B (PPAP2B; also known as lipid phosphate phosphatase 3), and as the name suggests it is responsible for the dephosphorylation and inactivation of lipid substrates including lysophosphatidic acid (LPA), ceramide 1-phosphate, and sphingosine 1-phosphate.4 The proposed role of PPAP2B is not in mechanosensing per se but rather in the modulation of endothelial cell sensitivity to circulating LPA (Figure). The authors link PPAP2B with responsiveness to flow by (1) the fact that its expression was attenuated in areas of the pig aorta exposed to disturbed flow, as well as in areas downstream of atherosclerotic plaques in samples of human carotid arteries; (2) an in vitro model of disturbed flow also resulted in decreased PPAP2B expression in cultured endothelial cells and its downregulation decreased endothelial NO synthase expression and prevented the atheroprotective effects of laminar flow; (3) the endothelial cell elongation and alignment usually induced by laminar flow was prevented by the knockdown of PPAP2B; (4) micro-RNA-92a, which is known to be increased in response to endothelial cell exposure to disturbed flow,5,7 directly targeted the 3′ untranslated region of PPAP2B, and (5) the flow-sensitive transcription factor KLF2 was found to regulate the expression of PPAP2B.

Certainly, there are links between PPAP2B and vascular stability and homeostasis as mice lacking the Ppap2b gene demonstrate defects in vascular development.4 Also, the inducible postnatal deletion of Ppap2b resulted in the disruption of endothelial barrier function and impaired angiogenesis.5 Linking the loss of an LPA inactivating mechanism with endothelial cell activation or inflammation fits well with observations that decreasing LPA production or antagonizing its function are able to preserve barrier function. If an LPA-inactivating molecule is implicated in the endothelial cell response to flow, then its inhibition or downregulation should mimic the effects of disturbed or proatherogenic flow. Wu et al2 showed this to be the case as LPA-stimulated adhesion molecule expression in cultured endothelial cells previously exposed to disturbed flow but not to laminar flow. Furthermore, the authors made use of tandem mass spectrometry to demonstrate lower levels of LPA species in medium harvested from endothelial cells exposed to atheroprotective flow versus disturbed flow. LPA, like sphingosine 1-phosphate, signals via the endothelial differentiation gene family of receptors and are ligands for the P2Y10 receptor. Extracellular LPA can affect cellular responses via at least 6 G-protein coupled receptors (ie, LPA receptors 1–6) that are differentially expressed in various tissues. Wu et al2 found that an antagonist of LPA receptor 1β restored the anti-inflammatory phenotype of PPAP2B-deficient endothelial cells exposed to atheroprotective flow in vitro. Also given that LPA receptor 3 was not detectable in the cells studied, it seems that the proatherogenic signals associated with LPA are initiated by the LPA receptor 1, a supposition confirmed by decreased expression of inflammatory molecules in cells treated with small interfering RNAs directed against LPA receptor 1.

What makes PPAP2B perhaps even more interesting is that its gene Ppap2b has been implicated in cardiovascular diseases by genome-wide association studies, showing that single nucleotide polymorphism rs17114036 predicts coronary artery disease independent of traditional risk factors, such as cholesterol and diabetes mellitus.10 The major risk allele is located in the final intron of the 6 exon Ppap2b gene. Interestingly, in a comparative mouse study looking at genes identified in the genome-wide association studies and their differential expression in healthy mice, ApoE−/− mice and Ldlr−/− mice, PPAP2B was upregulated in murine aortic endothelial cells, foam cells, and atherosclerotic lesions and attributed a causative role in the susceptibility to atherosclerosis through a role in the vasculature.11 However, in the same study, the lower expression of PPAP2B was associated with higher risk in human aortic endothelial cells, an apparent contradiction that the authors interpreted as being consistent with the different functions

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attributed to PPAP2B in endothelial cells and smooth muscle cells. Also this aspect was addressed by Wu et al, who studied the genotypes of 147 donors and found that the risk allele was significantly associated with lower expression of PPAP2B. On top of that, the authors propose that the defect in PPAP2B expression is specific to endothelial cells as they determined that the single nucleotide polymorphisms in the risk locus were not associated with PPAP2B expression in other cell types, including whole blood, monocytes and macrophages, adipose tissue, or liver.

The article by Wu et al 2 is a veritable tour de force in the generation of a chain of evidence ranging from observations of altered protein expression to the identification of the molecular mechanisms, underlying it and the consequences of the decreased expression on endothelial cell signaling—all linked in with convincing human genome-wide association studies data. However, it also raises interesting questions. For example, assuming that LPA is a major proinflammatory signal to which the endothelial cells layer is constantly exposed—where does it come from? In the cultured cells, it seems that the medium used was a source of LPA. The bulk of LPA found in the circulation is generated by the action of autotaxin, a circulating lysophospholipase D enzyme secreted in large amounts by the liver and activated platelets, as well as from adipocytes. This in itself is interesting because it may strengthen the link between platelet activation and increased fat mass with the accelerated development of cardiovascular disease. Thus, the findings by Wu et al 2 add support to studies implicating the autotaxin-lipid phosphate phosphatase pathway as a risk factor for coronary artery disease.

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