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 \( \kappa B \) 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

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attributed to PPAP2B in endothelial cells and smooth muscle cells.\(^{11}\) Also this aspect was addressed by Wu et al.,\(^2\) 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.\(^{12}\) 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.\(^{13}\)

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**References**


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**Figure.** Role of blood flow in the regulation of phosphatic acid phosphatase type 2B (PPAP2B) and endothelial cell signaling. A, In the circulation autotaxin (ATX) is secreted from platelets or adipocytes and binds vascular cell integrins, it also generates lysophosphatic acid (LPA) from lysophospholipid choline (LPC). Under conditions of laminar or atheroprotective flow and an intact mechanosensor complex, Kruppel-like factor (KLF) 2 levels are high, which in turn ensures the expression of its target PPAP2B. The latter is responsible for the dephosphorylation of LPA, thus decreasing its local concentration in the vicinity of the LPA receptor 1 (LPAR1) and attenuating receptor signaling. B, Disturbed or atherosusceptible flow is associated with increased miR-92a levels, which directly attenuate KLF2 and subsequently PPAP2B levels. The consequence being that local levels of LPA increase to enhance proinflammatory signaling through LPAR1. In parallel, an increase in the generation of LPA by activated platelets and an expanded adipose tissue may contribute to the phenomenon by generating greater amounts of LPA.


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