Statin Islands and PPAR Ligands in Platelets

Richard P. Phipps, Neil Blumberg

Platelets are formed from megakaryocytes, where they are released into the blood stream via proplatelet extensions into the blood vessel lumen. Being the most numerous “white blood cell” and despite lacking a nucleus, they are highly complex cells containing a surface connected canalicular and tubular system, mitochondria, granules, and bioactive mediators. Platelets are well-known for their seminal role in hemostasis and thrombosis. Aside from these physiological functions, new roles for platelets are being identified in unwanted thrombosis that occurs in diabetes and cancer.

Platelets lack a nucleus, therefore why would they have need for transcription factors? Recently, our laboratory discovered that platelets do indeed contain transcription factors, in particular peroxisome proliferator activated receptor gamma (PPARγ) and its binding partner retinoic X receptor (RXR). There were existing clinical data showing that the use of PPARγ ligands, mainly in type-2 diabetics, lowered their blood levels of proinflammatory and prothrombotic mediators including CD40L and others. The discovery that human platelets expressed PPARγ and that PPARγ ligands attenuated platelet activation, showed that the platelet was a previously unknown target of the thiazolidinediones (such as rosiglitazone [Avandia] and pioglitazone [Actos]). Attenuating platelet activation would then blunt the release of CD40L and other mediators. Recently, platelets were also discovered to express PPARβ. The fact that human platelets express PPARs and that these factors are active (but not as traditional transcription factors), opens up the possibility that other small molecules could influence platelets through PPARs.

In this issue of ATVB, Ali et al uncover another facet of platelet regulation through PPARs. Statins are widely prescribed drugs owing to their ability to lower cholesterol levels. They also reduce the incidence of heart attack and stroke. Another class of drugs called fibrates reduces triglycerides and increases high-density lipoprotein cholesterol. Both of these classes of drugs, namely statins and fibrates, appear to have more biological effects than those originally targeted. In fact, both statins and fibrates have inhibitory activity on platelets. Ali and colleagues reveal that statins and fibrates activate the PPAR system in platelets, and this new finding helps reveal some of the pleiotropic effects of these drugs. The ability of statins, and in some cases fibrates, to lower blood levels of inflammatory mediators such as IL-6, IL-8, etc, is likely attributable to their influence on platelets. If, in low-level inflammatory states, platelet activation is reduced, they release less CD40L, one of the major cellular stimuli capable of activating many cell types to produce proinflammatory and prothrombotic mediators.

The Figure (see diagram) shows a summary of how statins, fibrates, and other molecules influence the platelet PPAR pathway and attenuate platelet activity.

The article by Ali and colleagues demonstrates that statins engage platelet PPARγ and PPARα, and that the dampening activity of statins appears to be PPAR-dependent. They also show that fibrates, through engagement of PPARα, attenuate platelet activation. Interestingly, fibrates increased the bleeding time in normal, but not PPARα−/− mice. In addition to the knockout mouse approach, they also performed a small-scale human study, where normal volunteers were treated with fluvastatin for 7 days and found that platelet PPARγ and PPARα were activated. Platelets from these statin-treated volunteers had a reduced ability to aggregate when provoked. Some of these effects were attributable to activated PPARγ ligands, mainly in type-2 diabetics, lowered their blood levels of proinflammatory and prothrombotic mediators including CD40L and others. The discovery of the mechanism by which statins and fibrates downregulate platelet function further reveals the complexity of the “simple” platelet. The study also raises many questions. For example, should one expect bleeding problems in patients taking low dose aspirin plus statins and other...
antithrombotic agents such as clopidogrel (Plavix)? What about those patients also taking PPARγ ligands such as rosiglitazone (Avandia) or pioglitazone (Actos)? What might be the consequences of statin or fibrate use and implications for blood transfusions, which may predispose to inflammation and thrombosis?120 Do these agents influence the ability of platelets to become subtly activated while being processed for transfusion?124,21 The number of drugs that attenuate platelet function is growing, which is useful, as it adds to the armamentarium of agents that can be used to treat patients.

In conclusion, the new data on statins and fibrates from the Warner laboratory are very exciting. It further reveals that traditional transcription factors such as the PPARs have complex nongenomic effects as evidenced by their function in platelets. The work also further supports the concept that the nontranscriptional roles of PPARs represent potential new therapeutic targets.

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**Disclosures**

None.

**References**

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