Unraveling Pleiotropic Effects Of Statins

Bit By Bit, a Slow Case With Perspective

Fatih Arslan, Gerard Pasterkamp, Dominique P. de Kleijn

For 2 decades, both physicians and scientists have been intrigued by the success of statin therapy in reducing morbidity and mortality among patients with cardiovascular disorders. Statins, or 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) inhibitors, are effective in primary as well as secondary prevention of cardiovascular disorders.1,2 However, several clinical studies have clearly demonstrated that the event-reducing effect is also independent of lipid-lowering,3–5 so-called pleiotropic effects. Much effort has been taken to clarify the mechanisms through which statins exert their pleiotropic effects. Increased understanding of responsible pathways may facilitate selective targeting for optimization and may blunt adverse side effects like myopathy6 and drug interactions via the cytochrome P-450 system.7,8 Clinical and experimental studies show that the pleiotropic effects involve reduced atherosclerotic plaque progression rate,9 plaque regression10,11 and stabilization,12 antiinflammatory effects,5,13 reduction of myocardial ischemia/reperfusion injury,14 and antiatherogenic12,15 and antithrombotic effects.16

Antithrombotic Effects of Statins

Statins influence both thrombogenic responses of the vessel wall and thrombotic factors in the blood. Studies have shown that statins decrease the susceptibility for coagulation and thrombosis by decreasing platelet aggregation, inhibiting tissue factor and plasminogen activator inhibitor (PAI)-1 expression17 and increasing tissue plasminogen activator (tPA).18 Furthermore, statins decrease the thrombogenicity of the vessel wall by increasing the expression of thrombomodulin (TM) via NO-dependent pathways.19 When thrombin binds to TM, it activates protein C and prevents thrombin-induced platelet and factor V activation and fibrinogen clotting.20 Statins increase endothelial NO synthase (eNOS) activity and concentration, thus increasing the bioavailability of NO.21 Experimental data indicate that statins induce heat shock factor (HSF)-1 translocation (via eNOS) and subsequently cause dissociation of HSF-1. Finally, the authors provide evidence for an intrinsic negative-feedback mechanism through which statin-induced TM and tPA upregulation is counteracted. They show, for the first time, that specific TM promoter sites are involved in statin-induced TM upregulation. Atorvastatin induces TM upregulation through the promoter regions heat shock element (HSE)-1 and -3. In addition, mutation of the TM promoter regions HSE-3 and SP1/KLF, to which Krüppel-like factor (KLF)-2 binds, appears to completely abolish atorvastatin- and pravastatin-induced TM upregulation. This suggests a synergism between the transcription factors KLF-2 (binds to SP1/KLF) and HSF-1 (binds to HSEs) in statin-induced TM upregulation. Using chromatin immunoprecipitation and electrophoretic mobility-shift assays with specific inhibitors for HSF-1, heat shock protein (HSP)-90 and mevalonate (statins inhibit the mevalonate pathway21), the authors confirm that TM and tPA upregulation is mediated by specifically binding of HSF-1 to HSE-1 and -3. Surprisingly, the statin-induced downregulation of PAI-1, tPA-1, and CTGF is not mediated by HSF-1.

As explained in the article, HSF-1 resides in the cytoplasm in an inactive state by forming a multichaperone complex with HSP-90. On stimulation, HSF-1 dissociates from HSP-90 and translocates to the nucleus to exert its action.24 The present study confirms that statin-induced TM upregulation is NO-dependent, subsequently causing dissociation of HSF-1. Finally, the authors provide evidence for an intrinsic negative-feedback mechanism through which statin-induced TM and tPA upregulation is counteracted. They show that the regulatory protein 14-3-3β increases in the cytosol and decreases in the nucleus of endothelial cells on atorvastatin treatment. Inhibition of 14-3-3β through small interfering RNA knockdown and MEK inhibition enhanced atorvastatin-induced TM and tPA upregulation. Again, the downregulation of PAI-1, TSP-1, and CTGF was not altered by 14-3-3β inhibition. This supports the notion that statin-induced downregulation of prothrombotic factors PAI-1, TSP-1, and CTGF is mediated via other pathways than HSF-1 and KLF-2.

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**Statin-Induced TM Upregulation Studies**

The present study corroborates previous observations of statin therapy, in which HSF-1 plays a central role in the upregulation of TM. Uchiyama et al. showed that simvastatin increased TM and eNOS expression and translocation of HSF-1 and decreased PAI-1 expression. These pleiotropic effects were mimicked by a constitutive active form of human HSF-1. However, there are a few inconsistencies. Fu et al. together with others, show that statin decrease HSP-70 and -90, whereas Uchiyama and colleagues show an increase of these HSPs. This discrepancy between the observations, however, does not alter the conclusion that statins (via either decreased or increased levels of HSPs) upregulate HSF-1-mediated TM expression. It would be interesting to elucidate further the above-mentioned difference, because HSP-90 plays a key role in statin-induced eNOS phosphorylation. Zhao et al. provide another intriguing difference between the previous studies. They show that increased HSF-1 expression results in increased PAI-1 expression in endothelial cells stimulated with glycated low-density lipoprotein or oxidized very-low-density lipoprotein. Although in both scenarios, HSF-1 increases, the regulation of PAI-1 seems to be stimulus-specific (statin versus lipoproteins). This partially supports the idea that statin-induced downregulation of PAI-1 is mediated via other pathways downstream of HSF-1 or via other unknown synergistic pathways.

**Conclusion**

The profound study by Fu et al. provides substantial evidence for and new insights on the antithrombotic effect of statin therapy. Statins induce HSF-1 dissociation from HSP-90 and activation of KLF-2, subsequently translocation of both transcription factors to the nucleus where they specifically bind to promoter regions (HSE-1 and -3 and SPI/KLF) of TM. Their findings offer novel therapeutic targets, to optimize pleiotropic effects of statins. On the other hand they have also fascinated us, for it seems that statin-induced downregulation of prothrombotic factors (eg, PAI-1) are mediated via other pathways still to be discovered. This shows that in terms of optimization of pleiotropic effect of statins, the right step is taken toward a solution, but much is yet to be discovered and to be gained.

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None.

**References**


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