Differential Modulation of Caveolin-1 Expression in Cells of the Vasculature by Statins

Pelat and coworkers\(^1\) demonstrated that rosuvastatin decreases caveolin-1 expression in the cardiovascularity of dyslipidemic mice. By decreasing the expression of caveolin-1, an inhibitor of endothelial NO synthase, rosuvastatin treatment promotes endothelial NO synthase function and concomitantly stabilizes heart rate and blood pressure variabilities. Thus, rosuvastatin exerts beneficial effects on vascular function beyond those attributed to its lipid-lowering capacity. The authors presume that caveolin-1 downregulation occurs at the endothelial cell level, although they also envisioned additional effects on other vascular cells involved in atherosogenesis.

We agree that effects of statins on other cells are indeed to be anticipated. In our studies on the molecular mechanisms underlying lipid trafficking via caveolae in human smooth muscle cells (SMC)\(^2\) and macrophages (MΦ), we evaluated caveolin-1 expression in response to the hydrophobic and hydrophilic statins lovastatin and pravastatin using the reverse transcription–polymerase chain reaction on total RNA (primers for human caveolin-1 were as follows: forward, GAGCTGAGCGAGAAGCAAG; reverse, ACAGCAAGCGGTAAAACCAG; GenBank accession No, NM-001753), with β-actin as an internal standard. Treatment with lovastatin stimulated caveolin-1 expression in SMC. The maximum induction level (8-fold) was reached after 2 days. Pravastatin showed no effect in SMC. In MΦ, however, both statins increased caveolin-1 mRNA expression markedly (lovastatin, 4-fold; pravastatin, 1.8-fold).

Thus, statins alter the expression of caveolin-1 differentially in vascular SMC and MΦ. Whether or not caveolin-1 expression is affected by a particular statin evidently depends on the nature of the statin used, because only the hydrophobic lovastatin elicited a response in SMC. Furthermore, the stronger stimulation elicited in MΦ by lovastatin indicates that the statins have different capabilities to trigger a cellular response. Taken together, these results imply that statin-mediated improvement of vascular function as observed by Pelat and coworkers\(^1\) is attributable to the summative effects of statin on caveolin-1 expression in several kinds of cells of the vessel wall, including at least endothelial cells, SMC, and MΦ. Further, the efficacy of statin treatment may depend on the type of statin used, yet this is not set in stone as already shown by other authors (see, eg, Huang et al\(^3\)). Future studies will be needed to elucidate the mechanisms underlying the effects of statins on specific cells of the vasculature.

**Response**

Plenz et al emphasize the potential cell specificity for the action of statins on caveolin-1 expression, as well as the difference among statins. Although one may envisage several hypotheses for the differential regulation in vitro, perhaps a more important issue is its impact on atherogenesis and vascular function in vivo.

The caveolin-1 gene contains several sterol regulatory elements (SREs) in its promoter, enabling its transcriptional regulation by cholesterol-responsive SRE binding proteins (SREBPs) among other factors. In human fibroblasts exposed to LDL particles (resulting in enrichment in intracellular free cholesterol), caveolin-1 mRNA increased.\(^4\) Similarly, we showed that exposure of endothelial cells to LDL cholesterol in vitro and in vivo resulted in an increase in caveolin-1 protein.\(^2,3\) This was paralleled with increased interaction between caveolin-1 and endothelial NO synthase (eNOS), resulting in functional inhibition of eNOS activity and NO production. Statins, on the other hand, decreased caveolin-1 protein abundance in endothelial cells in proportion to their inhibition of intracellular cholesterol synthesis and resultant decrease in free cholesterol concentration.\(^4\) Importantly, this resulted in improved eNOS function, both in vitro\(^4\) and in vivo.\(^3\) The fact that similar effects on caveolin-1 were obtained with at least two different statins (atorvastatin and rosuvastatin) suggests a common mechanism related to Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibition (this was also mevalonate-reversible in our hands). In other cell types, Plenz et al refer to the absence of effect of other statins in vitro, which is perhaps attributable to differences in physicochemical properties (eg, hydrophilicity), although this does not preclude well-established clinical benefits with the same drug(s) in clinical trials.

Improved eNOS activity with statins in the endothelium likely contributes to the improvements in NO-dependent cardiovascular function, such as blood pressure and heart rate variability.\(^3\) Provided it is confirmed at the protein level and in vivo, the differential regulation of caveolin-1 in other vascular cell types, as proposed by Plenz et al, may contribute as well. For example, increases in caveolin-1 may promote cholesterol export from these cells. However, important features still need verification. In vitro, the effect of LDL exposure on caveolae density (and cholesterol export) markedly differs according to the phenotype (ie, synthetic versus contractile) of vascular smooth muscle cells.\(^5\) Similar phenotypic differences in response to statins may be anticipated. The fate of caveolin-3, an important isoform in muscle cells, also remains undetermined. In peritoneal macrophages, increases in caveolin-1 are paralleled with increased apoptosis, although the two phenomena may not be causally related. If simvastatin produces similar events in macrophages, as proposed by Plenz et al, and if verified in vivo, a resultant decreased inflammatory infiltrate may hypothetically contribute to the benefits of statins on the vessel wall.

**References**


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**Authors**

Gabriele A.M. Plenz, MSc, PhD, FESC
Department Cardiology and Angiology
Department of Thoracic and Cardiovascular Surgery and Institute for Arteriosclerosis Research
University Hospital Münster, Germany
Oliver Hofnagel, MSc
Horst Robenek, MSc, PhD
Institute for Arteriosclerosis Research
University Hospital Münster, Germany

Michel Pelat, PhD
Chantal Dessy, PhD
Paul Massion, MD
Jean-Pierre Desager, PhD
Olivier Feron, PhD
Jean-Luc Balligand, MD, PhD
Department of Medicine
Unit of Pharmacology and Therapeutics
University of Louvain School of Medicine
Brussels, Belgium

balligand@mint.ucl.ac.be


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Gabriele A.M. Plenz, Oliver Hofnagel and Horst Robenek

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