Kruppel-Like Factor 2 as a Novel Mediator of Statin Effects in Endothelial Cells

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Background—Although 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are known to modulate endothelial function, the transcriptional mechanisms underlying these effects are incompletely understood. We hypothesized that Lung-Kruppel–like factor (LKLF/KLF2), a novel and potent regulator of endothelial gene expression, may mediate the downstream effects of statins. Here we report that statin-induced expression of endothelial NO synthase (eNOS) and thrombomodulin is KLF2 dependent.

Methods and Results—KLF2 mRNA was induced by treatment with multiple statins in a concentration-dependent manner. Multiple lines of evidence suggest that this induction is dependent on inhibition of the Rho pathway and requires de novo transcription. Furthermore, promoter deletion and mutational analyses suggest that mevastatin induced KLF2 promoter activity through a single myocyte enhancer factor binding site. Finally, small-interfering RNA–mediated knockdown of KLF2 strongly attenuated the ability of mevastatin to increase eNOS and thrombomodulin accumulation in endothelial cells.

Conclusions—Taken together, these observations indicate that statin-dependent induction of eNOS and thrombomodulin requires KLF2 and thereby provides a novel molecular target for modulating endothelial function in vascular disease. (Circulation. 2005;112:720-726.)

Key Words: endothelium | nitric oxide synthase | vessels | transcription

Cardiovascular disease remains the principal cause of morbidity and mortality in our society. Clinical studies over the past decade demonstrate that 3-hydroxy-3-methylglutaryl coenzyme A inhibitors (HMG-CoA reductase inhibitors, statins) can substantially reduce cardiovascular mortality. Although originally designed to reduce LDL levels, multiple lines of evidence suggest that the beneficial effects of statins exceed what may be anticipated by lipid lowering alone.1-3 These favorable lipid-independent effects are thought to occur, at least in part, through alterations in vascular cell gene expression.4 For example, in endothelial cells, statins increase the accumulation of factors such as endothelial NO synthase (eNOS) and thrombomodulin.5-9 The production of NO by eNOS not only is important for vasorelaxation but also has potent antiinflammatory and antithrombotic properties.10-12 Thrombomodulin is a key endothelial cell surface factor that increases the rate of thrombin-catalyzed protein C activation.13 Furthermore, accumulating evidence suggests that thrombomodulin not only affects coagulation but also imparts antiinflammatory, antithrombotic, and antiadhesive properties to the endothelium.2,14,15

The molecular basis for the manner in which statins differentially regulate gene expression remains incompletely understood. Studies to date implicate small GTP binding proteins (eg, Rho) and certain kinases (eg, Akt) as important in mediating statin effects.16-20 Much less is known about the nuclear mechanisms that may be involved. A recent study suggests that statins diminish the activity/function of nuclear factor-κB (NF-κB) and activator protein-1 (AP-1), 2 key pathways regulating the induction of many proinflammatory genes.21 However, the nuclear mechanisms responsible for the ability of statins to induce target gene expression are very poorly understood.

We recently identified a member of the Kruppel-like family of transcription factors termed Kruppel-like factor 2 (KLF2) as a novel regulator of endothelial gene expression.22,23 As such, we considered the possibility that KLF2 may mediate some of the favorable effects of statins. In the present study we provide evidence that statins can induce KLF2 expression. The induction of KLF2 by statins is dependent on the inhibition of cholesterol synthesis and the Rho pathway. Furthermore, this inductive effect requires de

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novel transcription involving the myocyte enhancer factor 2 (MEF2) proteins. Finally, small-interfering-RNA (siRNA)-mediated knockdown of KLF2 attenuates the ability of statins to induce eNOS and thrombomodulin. Our results identify a novel pathway by which statins regulate endothelial gene expression.

**Methods**

**Cell Culture and Reagents**

Human umbilical vein endothelial cells (HUVECs) were acquired from Cambrex Bioscience (Walkersville, Md) and cultured in EBM-2 media according to manufacturer’s instructions. All statins were purchased from Calbiochem and prepared according to manufacturer’s recommendations. The thrombomodulin and MEF2 antibodies were purchased from Santa Cruz Biotechnology (Santa Cruz, Calif); the eNOS antibody was from BD Biosciences (Palo Alto, Calif); the α-tubulin antibody was from Sigma (St Louis, Mo). The adenoviral constructs were generated by the Harvard Gene Therapy Initiative (Boston, Mass). The MEP2A and MEP2C plasmids were kindly provided by E.N. Olson (Dallas, Tex). The −1.7-kB KLF2-Luc promoter was a kind gift from J. Leiden (Abbott Laboratories). All deletion constructs of the KLF2 promoter were generated by polymerase chain reaction (PCR) and cloned into the PGL2 basic vector. Mutation of the MEF site was accomplished by using the QuickChange mutagenesis following the manufacture’s instruction (Stratagene). The RNA polymerase inhibitor 5,6-dichlorobenzimidazole riboside (DRB) was purchased from Sigma Chemical Co; the exoenzyme C3 from Clostridium botulinum was purchased from List Biological Laboratories, Inc. The Rho adenovirus was kindly provided by J. Galper, MD, PhD (Tufts–New England Medical Center) with permission from D. Kalman (Emory University) and used as previously described.24

**Northern and Western Blot Analysis**

Cellular protein was extracted in RIPA buffer, and Western blot analyses were performed with the use of the indicated antibodies as previously described.22 HUVECs were infected with Ad-GFP and Ad-GFP-KLF2 for 24 hours and then harvested for total protein analysis. Total RNA was obtained by using Trizol following the manufacturer’s instruction, and Northern blot studies were performed as previously described.22 The KLF2 and KLF6 cDNA fragments were generated by reverse transcriptase (RT)–PCR.

**mRNA Half-Life Studies**

Determination of KLF2 mRNA stability was performed as follows. HUVECs were treated with the RNA polymerase inhibitor DRB under basal conditions or after 24 hours of statin treatment (n=3). Total RNA was harvested at 0, 20, 40, 60, 80, and 100 minutes after addition of DRB. After hybridization with KLF2 cDNA, band intensities were analyzed by densitometry, normalized to 18S ribosomal RNA, and plotted semilogarithmically as a function of time. The eNOS and thrombomodulin intensities were analyzed by densitometry, normalized to 18S ribosomal RNA, and plotted semilogarithmically as a function of time.

**Transient Transfection Assays**

HUVEC cells were plated at a density of 5 × 10^4 per well in 12-well plates 1 day before transfection. A total of 0.3 µg of the indicated plasmid DNA were transiently transfected with the use of Fugene 6 reagent (Roche Molecular Biochemicals) according to instructions by the manufacturer. Cells were treated with mevastatin 24 hours after transfection, harvested 48 hours after transfection, and assayed for luciferase activity normalized with β-galactosidase activity in each sample. For all transfections, n=6 to 9.

**Gel-Shift Studies**

The MEF site within the KLF2 promoter was used for gel-shift studies. The wild-type sequence was 5'-CCAGGCTTATATACCGCCGCTAAATTTAGGCTGAGCCCGGA-3'. The mutant competitor sequence was 5'-CCAGGCTTATATACCGCCGCTATCGGT-

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**Figure 1.** Induction of eNOS and thrombomodulin (TM) by mevastatin and KLF2. A, Mevastatin induces eNOS and thrombomodulin. HUVECs were treated with mevastatin (10 µmol/L) for 24 hours, and expression of eNOS and thrombomodulin was assessed by Western blot analysis. Graph represents quantitative results from 3 independent experiments. *P<0.008 (statin vs vehicle). B, KLF2 induces eNOS and thrombomodulin. HUVECs were infected with control (Ad-GFP) and KLF2 adenovirus for 24 hours, and expression of eNOS and thrombomodulin was assessed by Western blot analysis. Graph represents quantitative results from 3 independent experiments. *P<0.004 (KLF2-infected cells vs control virus).

**Results**

**Effect of Mevastatin and KLF2 on Endothelial Gene Expression**

Previous studies indicate that statins can induce factors such as eNOS and thrombomodulin.5,7,8,9,26 Consistent with these observations, we found that treatment of human HUVECs with mevastatin (10 µmol/L) induced eNOS and thrombomodulin protein levels (Figure 1A).

We recently reported the observation that adenoviral overexpression of KLF2 in HUVECs alters the expression of endothelial products such as eNOS22 and thrombomodulin.23 As shown in Figure 1B, by comparison with uninfected (mock) and control infected cells (Ad-GFP), adenoviral
overexpression of KLF2 (Ad-GFP-K2) robustly induced both eNOS and thrombomodulin protein levels.

**Statin-Mediated Induction of KLF2 Expression Is Dependent on Cholesterol Synthesis**

The similar effect of statins and KLF2 on the expression of these target factors raised the possibility that KLF2 may mediate some of the statin effects. As a first step, we assessed the effect of several statins on KLF2 mRNA expression. As shown in Figure 2A, mevastatin, simvastatin, and lovastatin all induced KLF2 mRNA expression in HUVECs ≈3.5 to 4-fold (Figure 2A, graph). In contrast, no significant effect was seen with pravastatin. The specificity of this inductive effect was verified by the fact that expression of KLF6, another member of this family known to be expressed in the endothelium,27 was not significantly altered by statin treatment (Figure 2A). Furthermore, the induction of KLF2 by mevastatin, lovastatin, and simvastatin occurred in a concentration-dependent manner (Figure 2B).

As a consequence of their ability to inhibit HMG-CoA reductase, statins cause cells to be depleted in mevalonate. To test whether the statin-mediated induction of KLF2 expression was specific and dependent on mevalonate depletion, HUVECs were incubated with mevastatin in the presence or absence of GGPP, FPP, and mevalonate. The induction of KLF2 by mevastatin was dependent on cholesterol synthesis (Figure 2C). C3 exotoxin induces KLF2 levels. HUVECs were treated with C3 exotoxin (50 μmol/L) for 24 hours followed by harvesting for total RNA. Graph represents quantitative results from 3 independent experiments. \( P < 0.0001 \) (combination vs all other treatment groups).

**Figure 2.** Statins induce KLF2. A, Multiple statins induce KLF2 mRNA. HUVECs were treated with the indicated statin (10 μmol/L) for 24 hours, and total RNA was harvested for Northern blot analysis with the indicated cDNA. Graphs represent quantitative results from 3 independent experiments. \( P < 0.001 \) (statin treatment vs vehicle). B, Statins induce KLF2 in a concentration-dependent manner. HUVECs were treated with each statin at the indicated concentration for 24 hours, and total RNA was harvested for Northern blot analysis with the indicated cDNA. Graph represents quantitative results from 3 independent experiments. \( P < 0.01 \) (statin vs vehicle); \( **P < 0.009 \) (statin vs vehicle). C, Induction of KLF2 by statins is dependent on cholesterol synthesis. HUVECs were treated with mevastatin (10 μmol/L) for 24 hours. Treatment with GGPP, FPP, and mevalonate was performed simultaneously with mevastatin. Total RNA was harvested 24 hours later and assessed for KLF2 expression by Northern blot analysis. Graph represents quantitative results from 3 independent experiments. \( P < 0.0004 \) (treatment with GGPP or mevalonate vs mevastatin alone). D, C3 exotoxin induces KLF2 levels. HUVECs were treated with C3 exotoxin (50 μmol/L) for 24 hours followed by harvesting for total RNA. Graph represents quantitative results from 3 independent experiments. \( P < 0.03 \) (C3 exotoxin vs vehicle). E, RhoA overexpression inhibits KLF2 expression. HUVECs were infected with tetracycline activator-induced RhoA, tetracycline activator alone, or a combination. KLF2 mRNA expression was assessed by Northern blot analysis. Graph represents quantitative results from 3 independent experiments. \( P < 0.0001 \) (combination vs all other treatment groups).
absence of mevalonate. As shown in Figure 2C (lane 2 versus lane 5), supplementation with mevalonate completely blocked statin-dependent induction of KLF2.

Mevalonate is a precursor for cholesterol as well as isoprenoid intermediates such as farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP). The isoprenoids are important posttranslational lipid modifications of a variety of proteins such as Ras and Rho. Ras proteins are predominantly farnesylated, whereas the Rho proteins are mainly geranylgeranylated. To test whether Ras or Rho has a role in the statin-dependent induction of KLF2, HUVECs were incubated with mevastatin in the presence of the isoprenoid intermediates FPP and GGPP. As shown in Figure 2C, GGPP (lane 3) partially reversed the mevastatin-mediated induction of KLF2 mRNA. In contrast, no effect was seen with FPP (lane 4). Furthermore, treatment of HUVECs with the Rho inhibitor exotoxin C3 augmented KLF2 expression (Figure 2D). These data suggested that inhibition of Rho maybe important for KLF2 induction. To address this more directly, HUVECs were coinfected with an adenovirus expressing RhoA under the control of tetracycline transactivator and an adenovirus constitutively expressing the transactivator. Rho expression was seen only on coinfection with both adenoviruses. As a consequence, KLF2 expression was strongly reduced (Figure 2E). Taken together, these data strongly suggest that activation of RhoA reduces KLF2 expression.

**Statins Induce the KLF2 Promoter via MEF Binding Site**

To gain greater insight about the molecular basis for statin-mediated induction of KLF2, we first performed experiments in the presence or absence of the RNA polymerase inhibitor DRB. As shown in Figure 3A, the induction of KLF2 by mevastatin was completely abrogated by pretreatment with DRB (50 μmol/L). Furthermore, half-life studies revealed that KLF2 mRNA stability was not significantly affected by statin treatment. In the absence of mevastatin, KLF2 mRNA half-life was 56 minutes, whereas in the presence of mevastatin the half-life was 58 minutes (data not shown). These data suggest that the statin-mediated induction of KLF2 requires de novo transcription.

To understand the transcriptional basis for statin-mediated induction, promoter studies were undertaken. As shown in Figure 3B, mevastatin treatment induced the KLF2 promoter activity 3.5-fold. Using a series of deletion mutants, we found that the majority of the inductive effect was maintained using the 221-bp Luc promoter fragment but lost with further deletion to the 114-bp Luc construct.

**Figure 3.** Mevastatin induces the KLF2 promoter via a MEF site. A, Mevastatin-mediated increase in KLF2 mRNA requires de novo transcription. HUVECs were pretreated with DRB (50 μmol/L) at the indicated concentrations for 1 hour before mevastatin treatment. B, Mevastatin treatment induces KLF2 promoter activity. HUVECs were transfected with the indicated KLF2 promoter constructs, treated with mevastatin (10 μmol/L) for 24 hours, and assessed for luciferase and β-galactosidase activity. n=6 to 9 per group. *P<0.0004 (statin treatment vs vehicle). C, Mutation of the MEF site prevents mevastatin-mediated induction of the KLF2 promoter. Transfections were performed as described in B. n=6 to 9 per group. *P<0.0001 (statin treatment vs vehicle). D, MEF2A transactivates the KLF2 promoter. Transfections were performed as described in B. n=6 to 9 per group. *P<0.00001 (MEF2A vs pCDNA3). E, MEF2A and MEF2C bind to the KLF2 promoter. See Methods for oligonucleotide sequences. Gel-shift studies were performed with the use of in vitro transcribed and translated MEF2 cDNAs. Specificity was verified by competition and supershift studies.
Thus, treatment with statins induces the KLF2 promoter through a critical 107-bp region.

Through close inspection of this region of the KLF2 promoter, we identified a single consensus MEF binding site. This site is typically bound by members of the MADS-box family of transcriptional regulators that are key regulators of muscle development. Interestingly, 2 members of this family, MEF2A and MEF2C, have also been implicated as regulators of endothelial cell biology.28–30 To assess the importance of this site in statin-mediated induction of the KLF2 promoter, we mutated this region in the context of the −221-bp Luc construct. As shown in Figure 3C, mutation of the MEF site completely prevented the mevastatin-mediated induction of the KLF2 promoter.

To determine whether MEF factors were able to bind and transactivate via this site, we performed cotransfection and gel mobility shift assays. Indeed, as shown in Figure 3D, MEF2A can transactivate the KLF2 promoter, we identified a single consensus MEF binding site. This site is typically bound by members of the MADS-box family of transcriptional regulators that are key regulators of muscle development. Interestingly, 2 members of this family, MEF2A and MEF2C, have also been implicated as regulators of endothelial cell biology.28–30 To assess the importance of this site in statin-mediated induction of the KLF2 promoter, we mutated this region in the context of the −221-bp Luc construct. As shown in Figure 3C, mutation of the MEF site completely prevented the mevastatin-mediated induction of the KLF2 promoter.

Next, HUVECs were transfected with nonspecific or specific siRNA for 48 hours followed by treatment with mevastatin for 24 hours. As shown in Figure 4B and consistent with recent observations,23 the basal level of eNOS protein was reduced by ~40%. Furthermore, the ~2.7-fold induction of eNOS protein by mevastatin was completely abrogated after knockdown of KLF2. Similarly, an ~72% reduction in thrombomodulin levels was noted under basal conditions after knockdown of KLF2.23 In addition, although treatment with mevastatin induced thrombomodulin levels ~3.1-fold in the nonspecific siRNA-treated cells, only a 1.4-fold induction was noted after KLF2 knockdown. Taken together, these data support a critical role for KLF2 in mediating the ability of mevastatin to induce endothelial gene expression.

**Discussion**

The central findings of this study are that statins induce KLF2 expression and that a reduction in KLF2 expression attenuates statin-mediated accumulation of eNOS and thrombomodulin levels (Figure 4B). To our knowledge, KLF2 is the first transcription factor to be implicated as critical for the ability of statins to induce these key endothelial factors. Our data also implicate another family of transcription factors, the MEFs, as being involved in the induction of KLF2. Taken together, these observations provide a novel pathway by which statins may exert some of their favorable effects in endothelial cells.

Conditions that predispose to atherosclerosis such as diabetes, hypercholesterolemia, and hypertension are associated with endothelial dysfunction. As a consequence, the endothelial phenotype is altered to one that is proadhesive and prothrombotic. Basic and clinical observations strongly support the ability of statins to improve endothelial health through differential effects on the expression of certain factors.4,10,32 In this regard, one of the most important effects of statins is to increase eNOS and thrombomodulin levels in endothelial cells. This is thought to occur through both transcriptional and posttranscriptional means.6,7,26 Studies from our laboratory indicate that KLF2 can induce eNOS and thrombomodulin mRNA and promoter activity, suggesting that transcription events underlie, at least in part, the ability of this factor to induce these targets.22,23 However, this does not exclude the possibility that the KLF2 induction of eNOS and thrombomodulin accumulation in endothelial cells may also be, in part, through posttranscriptional effects as well as effects on protein synthesis and stability. Indeed, the requirement for KLF2 in the ability of mevastatin to induce eNOS and thrombomodulin strongly suggests that additional mechanisms are likely involved.

Another mechanism by which statins confer favorable effects is by preventing the cytokine-mediated induction of proadhesive molecules and procoagulant substances such as vascular cell adhesion molecule-1 (VCAM-1) and tissue factor.1,2 This is thought to occur by inhibiting the function of proinflammatory mediators such as NF-κB and AP-1.21 In light of our previous study demonstrating that KLF2 inhibits
NF-κB–mediated induction of VCAM-1/E-selectin, it is possible that some of the inhibitory effects on NF-κB function may be secondary to an increase in KLF2 levels.\(^2\)

Our results also demonstrate that multiple statins, namely, mevastatin, simvastatin, and lovastatin, can all induce KLF2 in a concentration-dependent manner (Figure 2A and 2B). In contrast, no effect was seen with pravastatin, probably because the uptake of this compound is poor in endothelial cells.\(^7\),\(^20\) Furthermore, the induction by mevastatin was dependent on inhibition of cholesterol synthesis (Figure 2C). Our data also support a potential relationship between Rho proteins and KLF2 expression. The Rho proteins are mainly geranylgeranylated, whereas Ras proteins are predominantly farnesylated.\(^18\),\(^20\) The fact that GGPP but not FPP was able to attenuate the ability of mevastatin to induce KLF2 suggests that activation of the Rho pathway negatively regulates KLF2 expression. Consistent with this possibility, treatment with a Rho inhibitor, C3 exotoxin, induced KLF2 expression (Figure 2D). Finally, adenoviral overexpression of Rho strongly reduced KLF2 expression. Interestingly, activation of Rho is thought to be an upstream event that mediates many of the deleterious effects of proinflammatory substances (eg, interleukin-1β, tumor necrosis factor-α, and thrombin) in endothelial cells.\(^33\) As we have shown previously, these stimuli also reduce KLF2 expression, raising the possibility that one of the mechanisms by which Rho activates the endothelium is through the inhibition of KLF2 expression.\(^22\)

An intriguing observation made in this study is that the inhibition of de novo transcriptional activity prevents the ability of mevastatin to induce KLF2 promoter activity (Figure 3A). These data support a link between the statin-mediated inhibition of cholesterol/Rho activation and a transcriptional event that culminates in the induction of KLF2 expression. Although the details of this link remain incompletely understood, our studies provide an important initial clue. Our promoter deletion studies suggest that the transcriptional mediator(s) inducing the KLF2 promoter likely bind within a specific 107-bp region (from \(-114\rightarrow-221\); Figure 3B). Our laboratory has recently assessed this critical region and identified a MEF site within the proximal promoter region as critical for activity (A. Kumar, PhD, unpublished data, 2004). The importance of this site, in the context of statin-mediated induction of the KLF2 promoter, was verified by mutational analyses (Figure 3C). These observations are particularly timely in light of a recent report that mutations in MEF2A are associated with severity of coronary atherosclerotic disease.\(^28\) Indeed, it will be interesting to determine whether MEF2A mutations affect KLF2 levels as well as patient response to statin therapy.

On the basis of its ability to differentially regulate endothelial genes, our previous observations implicate KLF2 as a key “molecular switch” governing endothelial function in health and disease.\(^22\),\(^23\) The observations presented here identify KLF2 as a downstream mediator of statin effects in the endothelium. The identification of this regulatory pathway may provide the foundation for novel strategies in the treatment of vascular disease.

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### References


CLINICAL PERSPECTIVE

Clinical studies over the past decade demonstrate that 3-hydroxy-3-methylglutaryl coenzyme A inhibitors (statins) can substantially reduce cardiovascular mortality. Although originally designed to treat elevated cholesterol levels, accumulating evidence suggests that the beneficial effects of statins exceed what may be anticipated by simply lipid lowering alone. Recent studies suggest that statins can impart favorable properties to vascular cells by alterations in gene expression. For example, treatment of endothelial cells with statins has been shown to result in the accumulation of key factors such as endothelial NO synthase (eNOS) and thrombomodulin that are known to confer antithrombotic, antiadhesive, and antiinflammatory properties to the vessel wall. However, the nuclear mechanism underlying the ability of statins to induce these factors has remained poorly understood. This study provides evidence that the transcription factor termed Kruppel-like factor 2 (KLF2) is a key mediator of statin effects. KLF2 is expressed in endothelial cells, and its levels are potently induced by multiple statins. Furthermore, it is shown that the statin-induced accumulation of eNOS and thrombomodulin in endothelial cells is KLF2 dependent. These observations identify a novel mechanism by which statins regulate endothelial gene expression and provide the foundation for the development of novel strategies in the treatment of vascular disease.
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