Sports or statins for atheroprotection?
New insight from Kruppel-like factor 2

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Editorial

See article by van Thienen et al. [6] (pages 231–240) in this issue.

Nitric oxide (NO) plays a central role in the control of vascular homeostasis. Adequate NO production stimulated by continuous laminar flow on the endothelial surface, so-called shear stress, prevents endothelial inflammation and development of endothelial dysfunction. Recently, a novel class of mechanosensitive transcription factors has been identified that in endothelial cells transfer shear stress to various downstream targets such as the endothelial NO synthase (eNOS) [1]. These Kruppel-like factors (KLFs) are zinc finger transcription factors that act as transcriptional activators or suppressors upon binding to a CACCC promoter/enhancer element. A total of 16 KLF family members have been identified thus far, but only some are expressed in vascular cells, including KLF2 (reviewed in [2]). In the past, KLF2 was identified as a regulator of T cell differentiation and activation [3]. Recently, shear stress was shown to affect endothelial KLF2 expression with up-regulation by laminar and repression by perturbed flow [4]. KLF2 induces eNOS expression, thereby contributing to the regulation of vascular tone [1]. Interestingly, the up-regulation of eNOS by 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) is also mediated by KLF2 [5].

In the current issue of Cardiovascular Research, van Thienen et al. [6] compared the stimulatory effects of moderate laminar flow and statin treatment on KLF2-dependent eNOS expression under inflammatory conditions. Although both laminar flow and statin treatment induced KLF2 transcription to a similar extent, endothelial cells exposed to shear stress displayed higher levels of the KLF2 downstream targets eNOS and thrombomodulin even in the presence of an inflammatory stimulus. The authors discovered laminar flow to result in mRNA stabilization of KLF2, which was at least in part dependent on phosphoinositide 3-kinase (PI3K) activity. Surprisingly, at first glance, inhibition rather than stimulation of PI3K enhanced shear stress-mediated KLF2 mRNA stabilization. In line with these findings, the authors found slightly reduced levels of phosphorylated Akt in endothelium exposed to prolonged laminar flow, whereas acute shear stress increases Akt phosphorylation (reviewed in [7]; see Fig. 1). As statins increase PI3K-mediated Akt phosphorylation and in turn activate eNOS [8], the effects of prolonged shear stress combined with statin treatment on KLF2 regulation and eNOS expression in endothelial cells should be investigated. Likely, the effects on eNOS expression will be synergistic, although statin-induced PI3K activity may limit the flow-mediated KLF2 mRNA stabilization. Further, the authors did not investigate whether shear stress may also affect proteases that degrade KLF2. Reduced consumption of KLF2 would be an additional explanation for the flow-mediated increase in KLF2 expression. Various alternative pathways of KLF2 regulation are already known, such as activation of KLF2 by the MEK5–ERK5–MEF2C pathway ([9] and Fig. 1). Also, one should keep in mind that KLF2 is not the single translator of mechanical signals in endothelial cells. For instance,
exercise training also increases eNOS, a response that is dependent on the tyrosine kinase cSrc [10]. However, whether this is independent of KLF2 remains to be investigated.

While laminar flow leads to stabilization of KLF2 and subsequent eNOS activation, perturbed flow or oscillatory shear stress increases endothelial production of reactive oxygen species (ROS), thereby limiting NO bioavailability [11]. Laminar flow increases expression of antioxidative enzyme systems, such as the cytosolic superoxide dismutase [12]. As the balance of NO and ROS influences atherosclerotic lesion development, it would be interesting to know whether KLF2 regulates oxidative and/or antioxidative enzyme systems. Dekker et al. performed genome-wide microarray expression profiling with and without overexpression of KLF2 in endothelial cells to detect potential direct or indirect KLF2 target genes [1]. Several genes coding for antioxidative enzymes, such as glutathione peroxidase 3, or thioredoxin were increased, whereas various inflammatory cytokines and cytokine receptors were repressed, e.g. the interleukin 8 receptor (see supplementary online Table 1 in Ref. [1]). Thus, overexpression of KLF2 during initiation/progression of atherosclerosis may be expected to protect the endothelium from NO depletion and endothelial dysfunction. Further KLF2 targets need to be identified to gain in-depth understanding of the vasculoprotective action of this transcription factor.

As shear stress also activates NFκB in endothelium [13], it would be important to investigate NFκB-mediated effects on KLF2 expression, mRNA stabilization and function. For instance, in human umbilical vein endothelial cells TNF-α increases NFκB and histone deacetylase 4, which in a cooperative manner inhibit the ability of MEF2 factors to induce the KLF2 promoter, thus leading to reduced KLF2 expression [14]. On the other hand KLF2 inhibits the protease-activated receptor-1 (PAR1) and as a consequence thrombin-mediated NFκB nuclear accumulation and DNA binding ([15]; see Fig. 1).

When confirmed on the in vivo level, the findings of van Thienen et al. have potential clinical implications: a physiological intervention with increased flow similar to that observed during physical exercise appeared to be superior regarding vasoprotection compared with statin treatment. Patients with metabolic syndrome or atherosclerosis regularly have increased levels of pro-inflammatory cytokines such as TNF-α (reviewed in [16]). Therefore, the finding that prolonged laminar flow increased KLF2-dependent eNOS expression even under inflammatory conditions is of paramount clinical importance. Indeed, increased flow through the vessel lumen induced by exercise training is the physiologically most relevant stimulus that augments endothelial, NO-dependent vasodilatation of blood vessels (reviewed in [17]). Exercise training improves endothelial function by activation of eNOS [18] as well as antioxidative enzyme systems and is associated with a reduction of cardiovascular events. The present study of van Thienen et al. adds further
evidence for a role of the mechanosensitive transcription factor KLF2 in translating exercise training into cardiovascular health.

References


