Proprotein convertase subtilisin/kexin type 9 links inflammation to vascular endothelial cell dysfunction

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Vascular endothelial cell (EC) dysfunction is a pathological mediator of the development, progression, and clinical manifestations of atherosclerotic disease. Inflammation is associated with EC dysfunction, but the responsible mechanisms are not well characterized. There is substantial evidence that serum proprotein convertase subtilisin/kexin type 9 (PCSK9) is increased in pro-inflammatory states and that elevated PCSK9 levels are associated with adverse cardiovascular outcomes after controlling for traditional risk factors, including low-density lipoprotein (LDL) cholesterol.

Here we investigate PCSK9 as a novel link between inflammation and vascular EC dysfunction, as assessed by nitric oxide (NO) bioavailability. Tumor necrosis factor alpha (TNF-α), a pro-inflammatory cytokine, increased PCSK9 mRNA expression (1.98 [0.7, 3.4]-fold increase, $p=0.02$ vs. control) and PCSK9 protein levels (1.52±0.1-fold increase, $p<0.01$ vs. control) in isolated human aortic ECs. This was accompanied by reduced phosphorylated endothelial nitric oxide synthase (eNOS) protein which was 56% ± 5.6% of that in the controls ($p<0.01$) and NO bioavailability, which was reduced by 29% ± 22.1% compared to that in the controls ($p<0.01$). Finally, genetic PCSK9 reduction utilizing a PCSK9 specific siRNA in human aortic ECs resulted in the rescue of eNOS phosphorylation and NO bioavailability. Our results demonstrate that PCSK9 is increased in human aortic ECs exposed to a pro-inflammatory stimulus and that this increase is associated with EC dysfunction. Silencing of TNFα-mediated augmentation of PCSK9 protein expression utilizing a small interfering RNA against PCSK9 rescued the inflammation-induced EC dysfunction. These results indicate that PCSK9 is a causal link between inflammation and EC dysfunction, a potent driver of atherosclerotic cardiovascular disease.