Letter by Wu et al Regarding Article, “Mechanical Activation of Hypoxia-Inducible Factor 1α Drives Endothelial Dysfunction at Atheroprone Sites”

To the Editor:

We read with interest the recent article “Mechanical Activation of Hypoxia-Inducible Factor 1α Drives Endothelial Dysfunction at Atheroprone Sites” in which Feng et al elegantly show that exposure of endothelial cells to mechanical low shear stress activates hypoxia-inducible factor 1α (HIF-1α). Because atherosclerosis develops near branches or bends of arteries where endothelial cells are exposed to low shear stress, these results suggest that HIF-1α activation in endothelial cells may play a causal role in the pathogenesis of atherosclerosis. Feng et al showed that upregulation of HIF-1α occurs via a dual mechanism involving transcriptional activation by nuclear factor-κB (NF-κB) and stabilization via the deubiquitinating enzyme Cezanne.

We were pleased to see that the study by Feng et al largely recapitulated our recently published findings. In our study, we took an unbiased approach and performed RNAseq in human arterial endothelial cells (ECs) exposed to either unidirectional flow (atheroprotective hemodynamics of high shear stress measured in human distal internal carotid artery) or disturbed flow (DF; atherosusceptible hemodynamics of low shear stress measured in human carotid sinus) to investigate the effects of shear stress on ECs. Analysis of our transcriptomic data showed that the dominant transcriptional events compared with static (no flow) conditions, significantly induces HIF-1α expression in vascular endothelium. These results suggest that cellular metabolism and related inflammation are distinct in vascular endothelium under flow and no flow conditions, and moreover, caution should be taken to interpret results collected from vascular endothelium under static conditions. In summary, targeting DF-induced HIF-1α stabilization or EC metabolic changes may potentially lead to new therapies for atherosclerosis.

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Disclosures

None.

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