GATA6

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Endothelial dysfunction results in chronic vascular inflammation, which is critical for the development of atherosclerotic diseases. Transcription factor Gata6 has been reported to regulate vascular endothelial cell activation and inflammation in vitro. Here, we aimed to explore the roles and mechanisms of endothelial Gata6 in atherogenesis. Endothelial cell (EC) specific Gata6 deletion was generated in the Apoe

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hyperlipidemic atherosclerosis mouse model. Atherosclerotic lesion formation, endothelial inflammatory signaling, and endothelial-macrophage interaction were examined in vivo and in vitro by using cellular and molecular biological approaches. EC-GATA6 deletion mice exhibited a significant decrease in monocyte infiltration and atherosclerotic lesion compared to littermate control mice. Cytosine monophosphate kinase 2 (Cmpk2) was identified as a direct target gene of GATA6 and EC-GATA6 deletion decreased monocyte adherence, migration and pro-inflammatory macrophage foam cell formation through regulation of the CMPK2-Nlrp3 pathway. Endothelial target delivery of Cmpk2-shRNA by intercellular adhesion molecule 2 (Icam-2) promoter-driven AAV9 carrying the shRNA reversed the Gata6 upregulation mediated elevated Cmpk2 expression and further Nlrp3 activation and thus attenuated atherosclerosis. In addition, C-C motif chemokine ligand 5 (Ccl5) was also identified as a direct target gene of Gata6 to regulate monocyte adherence and migration influencing atherogenesis. This study provides direct in vivo evidence of EC-GATA6 involvement in the regulation of Cmpk2-Nlrp3, as well as Ccl5, on monocyte adherence and migration in atherosclerosis development and advances our understanding of the in vivo mechanisms of atherosclerotic lesion development, and meanwhile provides opportunities for future therapeutic interventions.