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TET1 Alternative Isoform Regulates Oscillatory Shear Stress Induced Endothelial Dysfunction

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Abstract: Oscillatory shear stress (OSS) is one of the major risk factors related to endothelial (EC) dysfunction, which contributes to atherosclerosis. Our previous study indicated that inhibitor of DNA binding 1 (Id1) plays vital role in the regulation of OSS mediated EC function related to atherosclerosis. However, the initiation mechanism during this process remains to be elucidated. Ten-eleven Translocation protein 1 alternative isoform (Tet1s) is a newly reported protein that may have function in adult tissue. Here, we investigate the role of Tet1s in regulating OSS mediated endothelial dysfunction and its underlying mechanism. First, physical interaction between Tet1s and Id1 was found and proved by immunoprecipitation. By using carotid partial ligation mice model *in vivo* and OSS applied on human umbilical venous endothelial cell (HUVEC) *in vitro*, we found that EC proliferation rate and adhesion molecule expression were upregulated in the local area with OSS characteristics. Compared to the greater curvature (laminar shear stress), a lower Tet1s expression level in atheroprone lesser curvature (OSS) suggested Tet1s regulated the EC function under OSS. This notion is supported by the decline of Tet1s expression in cell culture model. In order to explore the mechanism regulated Tet1s expression, the potential binding sites in Tet1s promoter region for CEBPB was identified by *in silico* analysis. By using PKA/CEBPB inhibitor H89, we found that H89 inhibited Tet1s expression. HUVEC cell proliferation, proinflammation gene expression as well as monocytes adhesion were enhanced after knockdown of Tet1s by specific siRNA. And overexpression of Tet1s eliminated OSS induced HUVEC proliferation and inflammation. Further studies revealed Tet1s negatively regulated the expression of Id1. Meanwhile, knockdown of Tet1s induced nucleocytoplasmic shuttling of Id1. Our finding indicates a significant role of Tet1s in regulating OSS mediated endothelial dysfunction with respect to abnormal proliferation and inflammation through Id1-dependent pathway.

Keywords: Tet1s, oscillatory shear stress (OSS), endothelial dysfunction, Id1.

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