【Outstanding Academic Research Meeting II-1】

Flow Disturbance Induces Atherosclerosis and Venous Neointimal Hyperplasia of Hemodialysis Vascular Access

血液擾流誘導的動脈粥狀硬化和透析血管通路的靜脈內膜增生

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Arteriovenous fistula (AVF) is used for hemodialysis in patients with end-stage renal disease (ESRD), but its failure hinders long-term use. The most common cause of AVF failure is venous stenosis at the anastomosis. Clinical observations have shown the occurrence of flow disturbance in AVF anastomosis, which may induce neointimal hyperplasia. However, the detailed flow conditions in anastomosis and the mechanisms by which flow disturbance induces AVF neointimal hyperplasia remain unclear. The present study includes in vitro cell culture studies on the effects of disturbed flow on molecular signaling, in vivo investigations on the experimental rat AVF model, and measurements on clinical specimens from patients with ESRD undergoing hemodialysis to study the mechanisms underlying the effects of flow disturbance on neointimal hyperplasia of hemodialysis vascular access. Ultrasonography of conventional AVF in patients undergoing hemodialysis and experimental rat model demonstrated the occurrence of high and oscillatory shear stress (Hi-OS, 29.7±93.5 dynes/cm^2) in anastomosis, which is accompanied by up-regulation of histone deacetylase (HDAC)-1/2/3 and down-regulation of thrombomodulin in venous endothelia. Application of Hi-OS to venous endothelia up-regulates their HDAC3, which deacetylates krüppel-like factor-2 to inhibit its binding to the promoter of thrombomodulin and inhibits its expression. Administration of the HDAC inhibitor valproic acid or alteration of AVF configuration to increase flow rate and/or reduce disturbed flow inhibits AVF neointimal hyperplasia, with down-regulation of HDACs and up-regulation of thrombomodulin in venous endothelia. Our findings shed light on the mechanisms by which flow disturbance induces venous endothelial HDAC signaling to promote AVF neointimal hyperplasia, and suggest new strategies for chemical or mechanical treatment of AVF pathologies.

Keywords: Arteriovenous fistula; Disturbed flow; Endothelial cells; Shear stress