Shaping Tomorrow's Nephrology: Insight-Driven Kidney Care
KSN SEOUL, KOREA 2026
The 46th Annual Meeting of the Korean Society of Nephrology
THE KOREAN SOCIETY OF NEPHROLOGY
Jun 11 (Thu) – 14 (Sun), 2026
COEX, Seoul, Korea

Abstract Type : Poster exhibition
Abstract Submission No.: A-0648
Abstract Topic : Dialysis

Targeting Ligand-Independent MR Activation to Prevent Neointimal Hyperplasia in Hemodialysis Fistulas

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Objectives : Hemodialysis vascular access stenosis is a major clinical challenge driven by severe hemodynamic and uremic stresses. We hypothesize that these extreme conditions induce ligand-independent activation of the mineralocorticoid receptor (MR) in venous cells, serving as a critical trigger for pathogenic vascular remodeling.
Methods : To simulate the hemodialysis environment, we utilize a dynamic culture system applying cyclic stretch to human venous smooth muscle cells (HVSMCs) and shear stress to human umbilical vein endothelial cells (HUVECs). Cultured in an aldosterone-free environment, cells are exposed to mechanical stress and the uremic toxin indoxyl sulfate. We investigate MR activation by measuring its nuclear translocation via confocal microscopy and analyze the upstream Rac1-dependent signaling axis. Additionally, we evaluate HVSMC phenotypic switching from a contractile to a synthetic/osteogenic state by tracking markers like α-SMA, Osteopontin, and Runx2.
Results : Hemodynamic stress and uremic toxins synergistically triggered ligand-independent mineralocorticoid receptor (MR) nuclear translocation in vascular cells. This atypical MR activation was critically mediated by the upstream Rac1-ROS signaling axis, subsequently driving human venous smooth muscle cells to undergo a pathological phenotypic switch from a healthy contractile state to a disease-promoting synthetic and osteogenic state. Furthermore, administration of finerenone, a non-steroidal MR antagonist, successfully abrogated this Rac1-MR pathway.
Conclusions : Consequently, finerenone treatment significantly reduced mitochondrial reactive oxygen species (ROS) generation and restored cellular metabolic capacity, highlighting its therapeutic potential to prevent hemodialysis vascular access dysfunction.