

2nd World Congress on
MOLECULAR GENETICS AND GENE THERAPY
July 03-04, 2017 Bangkok, Thailand

The mechanism of VEGFR-2 cell migration and internalisation in endothelial cells

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The endogenous inhibitor Regulator of Calcineurin 1 (RCAN1) inhibits the cellular calcineurin pathway. RCAN1 is expressed in two isoforms, RCAN1.1 and RCAN1.4, within vertebrates. Expression of RCAN1.1 has been identified in most tissues whilst RCAN1.4 expression is activated by various stimuli that are also involved in activation of the calcineurin-NFAT pathway. RCAN1.4 is upregulated at greater levels than RCAN1.1 when in the presence of VEGF in human endothelial cells, and RCAN1.4 is also essential for migration of endothelial cells and morphogenesis of tubules. Here, we present evidence that RCAN1.4 has a function in regulating VEGFR-2 internalisation, which is agonist-stimulated, and determining the polarity of endothelial cells. siRNA-mediated gene silencing, revealed RCAN1 play a crucial role in regulation of VEGF-mediated cytoskeletal reorganisation, directed cell migration, and sprouting angiogenesis. Overexpression of RCAN1.4, mediated by Adenovirus, caused increased migration of endothelial cells. Anti-sense-mediated morpholino silencing of a Zebrafish RCAN1.4 orthologue indicated reorganised vascular development, this further signifies that the orthologue has a role in the regulation of the physiology of vascular endothelial cells. Our data has new implication for the investigation of RCAN1.4 with role in regulation of endothelial cell migration by determining polarity of endothelial cells as a response to VEGF.

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