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A histone deacetylase 7-derived 7-amino acid peptide acts as a phosphorylation carrier

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Histone deacetylase 7 (HDAC7) belongs to the class II HDAC family and plays a pivotal role in the maintenance of endothelium integrity. There are eight splicing variants in mouse HDAC7 mRNAs. Within the 5' terminal non-coding area of some variants, there exist some short open reading frames (sORFs). Whether these sORFs can be translated or resulting peptides play roles in cellular physiology remain unclear. In this study, we demonstrated that one sORF encoding a 7-amino-acid (7-aa) peptide could be translated in vascular progenitor cells (VPCs). Importantly, this 7-aa peptide (7A) could transfer the phosphate group from the phosphorylated Ser393 site of MEKK1 to the Thr145 site of 14-3-3γ protein. The phosphorylated 7A (7Ap) could then directly phosphorylate 14-3-3γ protein in a cell-free, in-gel buffer system. The adjacent histidine and proline residues are essential for the phosphate group reception and transfer. *In vitro* functional analyses revealed that 7A and 7Ap increased VPC self-renewal and migration and enhanced vascular endothelial growth factor (VEGF)-induced VPC migration and differentiation toward the endothelial cell (EC) lineage, in which MEKK1 and 14-3-3γ served as the upstream kinase and downstream effector, respectively. Knockdown of either MEKK1 or 14-3-3γ attenuated VEGF-induced VPC migration and differentiation. Exogenous 7Ap could rescue the effect of VEGF on the MEKK1 siRNA-transfected VPCs but not on the 14-3-3γ siRNA-transfected VPCs. *In vivo* studies revealed that 7A, especially 7Ap, induced capillary vessel formation in matrigel plug assays, increased re-endothelialization and suppressed neointima formation in the femoral artery injury model, and promoted foot blood perfusion recovery in the hind limb ischemia model by increasing Sca1+ cell niche formation. These results indicate that the sORFs within the non-coding area can be translated and that 7A may play an important role in cellular processes such as proliferation, migration and differentiation by acting as a phosphorylation carrier.

Biography

Lingfang Zeng has his expertise in Stem Cell Research in Vascular Biology field, specifically on Mechanotransduction, Epigenetic Modification and Alternative Splicing. He has done extensive investigation on HDAC3, HDAC7 and IRE1α/XBP1 signal pathway. His current research focuses on Alternative Translation. His group found that small open reading frame within so-called non-coding area or non-coding RNA could be translated to produce functional small peptides. In addition to ATG, they found that other codons could also initiate the translation to produce more small peptides.

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