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HDAC7-derived 7-amino acid peptide functions as a phosphate group transfer

Lingfang Zeng and **Junyao Yang**
King's College London, UK

Histone deacetylase 7 (HDAC7) belongs to the class II HDAC family and plays a pivotal role in the maintenance of endothelium integrity. There are 8 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 and whether the 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. *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 the 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 completed his PhD from Beijing Normal University, China. He is currently a Senior Lecturer in the Cardiovascular Division, Faculty of Life Science and Medicine, King's College London. He has published more than 40 papers in reputed journals and has been serving as an Editorial Board Member of repute.

lingfang.zeng@kcl.ac.uk

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