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# Functional Analysis of Clock Gene Products DEC1 and DEC2, as bHLH Transcription Factors

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## ABSTRACT

The circadian rhythms in mammals are regulated by a pacemaker located in the suprachiasmatic nucleus of the hypothalamus. The clock gene family, i.e., *Clock*, *Bmal*, *Per*, *Cry* and *Dec*, are involved in a transcription-translation feedback loop that generates the circadian rhythm at the intracellular level. Clock gene products DEC1 and DEC2 are basic-helix-loop-helix (bHLH) transcription factors, and are involved in cellular differentiation, responses to hypoxia and circadian rhythms. We recently showed that the expression of DEC1 and DEC2 was up-regulated by hypoxia; however, the functions of these two factors under hypoxic conditions have not been elucidated in detail. The present keynote talk demonstrates two projects: (1) Vascular Endothelial Growth Factor (VEGF); and (2) Epithelial-Mesenchymal Transition (EMT). (1) The expression of VEGF in response to hypoxia depends on transcriptional activation by a heterodimer comprising hypoxia-inducible factor 1α (HIF-1α) and Aryl Hydrocarbon Receptor Nuclear Translocator 1 (ARNT1). In the present study, we showed that DEC2, but not DEC1, suppressed VEGF gene expression under hypoxic conditions. DEC2 protein was co-immunoprecipitated with HIF-1α but not with ARNT1. The binding of HIF-1α to the Hypoxia Response Element (HRE) in the VEGF promoter was decreased by DEC2 overexpression and increased by DEC2 knockdown. We also showed that the circadian expression of VEGF showed a reciprocal pattern to that of DEC2 in cartilage. DEC2 had a circadian oscillation in implanted Sarcoma 180 cells. We conclude that DEC2 negatively regulates VEGF expression and plays an important role in the pathological conditions in which VEGF is involved. (2) Epithelial-Mesenchymal Transition (EMT) is an important step leading to invasion and migration of various tumor cells and TGF-β treatment has been shown to induce cancer cells to undergo EMT. We examined the role of DEC1 in EMT of PANC-1 cells, a human pancreatic cancer cell line. As a result, we found that DEC1 was upregulated by TGF-β in PANC-1 cells and regulated the expression and the levels of nuclear, cytoplasmic or membrane localization of EMT-related factors, including phosphorylated Smad3 (pSmad3), snail, claudin-4 and N-cadherin. In the presence of TGF-β, DEC1 knockdown by siRNA inhibited morphological changes during EMT processes; while TGF-β induced PANC-1 cells to taken on a spindle-shaped morphology. Furthermore, a combination treatment of DEC1 expression with TGF-β was closely linked to the migration and invasion of PANC-1 cells. These findings suggest that DEC1 plays an important role in the regulation of these EMT-related factors in pancreatic cancer.

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