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Poster Number

5 **Ubiquitination and proteosome-dependent degradation of the activated form of human liver-enriched transcription factor CREB-H regulated by protein kinase A**

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CREB-H is a membrane-bound bZIP transcription factor which is mainly expressed in liver and small intestine. CREB-H plays important roles in the regulation of lipid metabolism, iron metabolism, gluconeogenesis and acute phase response. CREB-H is proteolytically activated by regulated intramembrane proteolysis to generate a C-terminal truncated form known as CREB-HΔTC, which translocates to the nucleus to activate target gene expression. We have previously shown that CREB-HΔTC has a short half-life. In this study we report on ubiquitination and proteasome-mediated degradation of CREB-HΔTC. Proteasome inhibition led to the accumulation of CREB-HΔTC. The degradation of CREB-HΔTC was mediated by lysine 48-linked polyubiquitination of CREB-HΔTC. A DSGXS destruction box was identified in CREB-HΔTC and was also found to be conserved among orthologous proteins from different species. Disruption of this DSGXS destruction box resulted in stabilization of CREB-HΔTC. A potential E3 ubiquitin ligase implicated in CREB-HΔTC degradation was identified and characterized. In addition, CREB-HΔTC was also found to be phosphorylated by protein kinase A, leading to its stabilization. Taken together, our work revealed a new signaling pathway that controls ubiquitination and degradation of CREB-HΔTC. The rapid ubiquitination and degradation of CREB-HΔTC ensures transient and tightly regulated activation of its target genes in liver.

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6 **The Activation of Transient Receptor Potential Channel Vanilloid 3 (TRPV3) Suppresses Adipogenesis**

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Obesity is a major risk factor for metabolic diseases. Adipocytes in adipose tissues influence obesity, insulin resistance and diabetes mellitus. Therefore, discovery of anti-adipogenic pathways is crucial for the development of clinical therapies against obesity. We identified that the activation of $Ca2^{+}$ permeable channel Transient Receptor Potential Channel Vanilloid 3 (TRPV3) prevented differentiation of 3T3-L1 preadipocytes. The activation of TRPV3 by activators (-)-epicatachin and diphenylboronic anhydride (DPBA) was determined by fluorometric calcium imaging studies and patch clamp electrophysiology. The 3T3-L1 cells were induced to differentiate in the presence of the TRPV3 activators. Adipogenesis in stimulated 3T3-L1 preadipocytes was determined by oil red O-staining of intracellular lipid droplets and quantitative real-time RT-PCR. The activators attenuated adipogenesis at a dose-dependent manner and could be reversed by the TRPV3 inhibitor Diphenyltetrahydrofuran (DPTHF) and TRPV3 siRNA. Our immunoblotting results validated that the activation of TRPV3 attenuated insulin receptor and phosphoinositide 3-Kinase/Akt signaling, which downregulated the expression of CCAAT/enhancer binding protein alpha (C/EBPalpha) and peroxisome proliferator-activated receptor gamma (PPARgamma) in 3T3-L1 cells. TRPV3 also co-immunoprecipitated with insulin receptor substrate-1 (IRS-1), confirming association between TRPV3 and IRS-1 in 3T3-L1 preadipocytes. Compared with wild-type mice, we observed reduction in TRPV3 expression in ob/ob and db/db mice. We conclude that TRPV3 activation suppresses adipogenesis. The TRPV3 channel may regulate adipocyte metabolism.