Yap1 Hydroxylation Suppress Prostate Cancer Metastasis

Ming Zhu1, Ruiqing Peng1,2, Xin Liang1, Zhengdao Lan1, Ming Tang1, Pingping Hou1, Jian H Song1, Celia Sze Ling Mak1, Jiwon Park1, Shui-Er Zheng1, Ailing Huang1, Xingdi Ma1, Ruidong Chen1, Qing Chang1, Christopher J Logothetis1, Abhinav K Jain1, Sue-Hwa Lin4, 6, Hiroyuki Katayama5, Samir Hanash6, Guocan Wang1,*

1Department of Gastrointestinal Medical Oncology, and the David H. Koch Center for Applied Research in Gastrointestinal Cancers, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; 2Sun Yat-sen University Cancer Center, China; 3Department of Cell and Molecular Biology, the University of Texas MD Anderson Cancer Center, Houston, TX, USA; 4Department of Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; 5Department of Epigenetics and Molecular Carcinogenesis & Epigenomics Profiling Core Facility, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; 6Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; 7Department of Clinical Cancer Prevention, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; 8Department of Cancer Biology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.

Abstract

Yes-associated protein 1 (YAP1), a key transcriptional coactivator in the Hippo pathway, is an important driver in cancer development and progression (1). It plays an oncogenic role in various cancer types. However, multiple studies also support a tumor-suppressive function for YAP1 (2-8). Thus, the functions of YAP1 are likely context-dependent (9). On the cellular level, YAP1 promotes prostate cancer cell proliferation (10-13). Yet, the role of YAP1 in prostate cancer cell invasion, migration, and metastasis is not well defined. Through functional, transcriptomic, epigenomic, and proteomic analyses, we showed that prolyl hydroxylation of YAP1 plays a critical role in the suppression of cell migration, invasion, and metastasis in prostate cancer (14). Knockdown (KD) or knockout (KO) of YAP1 led to an increase in cell migration, invasion, and metastasis in prostate cancer cells. Microarray analysis showed that the EMT pathway was activated in Yap1-KD cells. ChIP-seq analysis showed that YAP1 target genes are enriched in pathways regulating cell migration. Mass spectrometry analysis identified Pro4HA2, a proline hydroxylase in the YAP complex, and YAP1 was hydroxylated at multiple residues. Proline-to-alanine mutations of YAP1 isoform 3 identified proline 174 as a critical residue, and its hydroxylation suppressed cell migration, invasion, and metastasis. KO of Pro4Ha2 led to an increase in cell migration and invasion, which was reversed upon Yap1 KD. Our study identified a novel regulatory mechanism of YAP1 by which Pro4HA2-dependent prolyl hydroxylation regulates its transcriptional activities and its function in prostate cancer metastasis.

Results

YAP1 Deletion/mutation is Associated with Poor Survival and Metastasis

YAP1 Suppresses Cell Migration/Invasion and Metastasis

YAP1 Interacts with P4HA2

YAP1 Suppresses Pathways Involved in Cell Mobility and Metastasis

YAP1 is Hydroxylated at Multiple Proline Residues

References