#2202

HMG box-containing protein 1 (HBP1) is a direct target of transcription factor FOXO1 in invasive oral cancer

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Constitutively activated PI3K/Akt signaling with deregulated activity of FOXO factors is often associated with tumorigenesis. Reduced HBP1 expression and/or loss-of-function HBP1 mutants have been observed in several types of cancer. FOXO1 and HBP1 seem to share common biological roles such as cell growth inhibition. We have previously demonstrated that, in oral cancer, reduced HBP1 expression expedited cell proliferation, growth, and migration, while the role of FOXO1 remains unclear. Hence, the objective of the current study is to investigate the reciprocal roles of FOXO1 and HBP1 in oral cancer. In a subset of oral tumor specimen, we found that both FOXO1 and HBP1 expression levels were significantly lower than those of the control tissues. In addition, FOXO1 expression was positively correlated with that of HBP1, and the status of low FOXO1 and HBP1 was associated with invasiveness of oral tumor, indicating a coordinated down-regulation of FOXO1 and HBP1 in invasive oral cancer. To further examine if HBP1 is a transcriptional target of FOXO1, we searched for putative binding sites within a 2-kb HBP1 promoter region, and identified two FOXO1 consensus sites, located -177 to -184 bp and -388 to -395 bp, from the transcription start site. As shown by reporter analysis and *in vivo* chromatin IP assay, these cis-acting elements and trans-acting FOXO1 factors, with functional DNA-binding domains, were necessary for complete activation. Furthermore, suppression of FOXO1 led to a reduction of HBP1 expression. In a reciprocal manner, FOXO1-mediated inhibition of colony formation, cell growth, and invasion was disrupted upon HBP1 knockdown in invasive oral cancer cells. Taken together, our data provide the significant findings that HBP1 is a novel downstream target of FOXO1 and that the FOXO1-HBP1 pathway might be a prospective means of intervention in invasive oral cancer.