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BMI1 activates WNT signaling in colon cancer by negatively regulating the WNT antagonist IDAX

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ABSTRACT

Absent activation of Wnt signaling plays a critical role in the development of colon cancer. BMI1, a component of the polycomb repressive complex (PRC1), is upregulated in various types of cancer and contributes to epigenetic silencing of tumor suppressors. In this study, we showed that BMI1 is upregulated in colon cancer tissues and cell lines. Overexpression of BMI1 in primary epithelial colon cells promotes cellular growth and activates WNT pathway, while BMI1 silencing in colon cancer cells represses these effects. We also found that BMI1 binds to the promoter of IDAX, a Wnt antagonist, and decreases its transcription. Expression of IDAX is downregulated in colon cancer tissues and cell lines and negatively correlated with BMI1 in colon cancer tissues. Furthermore, silencing of IDAX counteracts the effects of BMI1 suppression, while its overexpression reverses oncogenic effects of BMI1. Together, these findings indicate that BMI1-mediated IDAX epigenetic suppression is crucial for enhancement of colon carcinogenesis, suggesting that BMI1/IDAX axis as a potential novel diagnostic and therapeutic target of colon cancer.

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1. Introduction

Colon cancer is one of the most prevalent malignancies and the fourth leading cause of cancer mortality worldwide [1]. Although accumulating evidence suggests that colon carcinogenesis is associated with complex genetic and epigenetic changes [2], the precise molecular pathogenesis remains poorly understood. A detailed understanding of the molecular mechanisms and signaling pathways may provide insights for the treatment and prevention of colon cancer.

The WNT signaling pathway plays an important role in cell fate determination and tissue development and stem cell maintenance [3,4]. Aberrant activation of this pathway leads to tumorigenesis in several types of human cancers, including colon cancer [5–7]. According to recent reports from the Cancer Genome Atlas Network, the WNT pathway is hyper-activated in over 90% of colon cancer through genetic alterations to a number of genes that are implicated in the WNT signaling pathway, such as APC, β -catenin and Axin2 [8–10]. The high mutation rate of WNT pathway components in colon cancer suggests the promise of WNT signaling inhibition as a therapeutic approach. Activation of WNT signaling subsequently increases the transcription of WNT downstream genes, such as Cyclin D1, C-myc and Survivin, all of which play important roles in cell proliferation, apoptosis and cell cycle transition in the development and progression of colon cancer [11–13]. However, it is unknown which,

if any, genetic alterations cause WNT pathway hyperactivation in the 10–15% colon cancer that do not carry APC or downstream WNT pathway mutations.

Recently, accumulating evidence indicates that epigenetic changes play critical roles in the deregulation of WNT signaling in human cancers [14]. The BMI1 (B cell-specific Molony murine leukemia virus integration site 1) is a component of the polycomb repressive complex (PRC1) that maintain gene repression through chromatin modification, resulting in epigenetically silenced genes [15]. Overexpression of BMI1 has been identified in many malignancies including colon cancer, which is related with poor prognosis, contributing to cell proliferation, invasion, and metastasis [16,17]. In the present study, we found IDAX, a negative regulator of WNT signaling [18], as a novel target of BMI1 in colon cancer, and BMI1 enhances the activation of WNT signaling in colon cancer through repressing IDAX expression.

2. Materials and methods

2.1. Clinical samples, cell lines and transfection

Colon cancer tissues and corresponding adjacent normal tissues were obtained from 36 patients with colon cancer who received surgery at the Wuhan Tumor Hospital, Wuhan, China. Samples were obtained with informed consent, and the study had been approved by local institutional review boards on human subject research and in accordance with the Declaration of Helsinki. All the histological diagnoses for colon cancer and normal tissues were reviewed



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