VBIM technology identifies adenomatous polyposis coli like protein (ALP) as a novel negative regulator of NF-κB

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Colon cancer is the second leading cause of cancer related deaths in the United States. The nuclear factor κB (NF-κB) is an important family of transcription factors whose aberrant activation has been found in many types of cancer, including colon cancer. Therefore, understanding the regulation of NF-κB is of ultimate importance for cancer therapy. The purpose of this study is to use a novel validation-based insertional mutagenesis (VBIM) strategy to identify novel regulators of NF-κB, and further evaluate their roles in the regulation of NF-κB signaling in colon cancer cells. We infected Z cells (293 derived cells with hyper active NF-κB activity) with VBIM virus to cause the over expression of negative regulators of NF-κB, and then further selected the mutant cells with low NF-κB activity under ganciclovir (GCV) treatment. Targeted gene was then identified by using VBIM specific primers. In a preliminary screen, we identified the novel adenomatous polyposis coli like protein (ALP) gene as a negative regulator of NF-κB. Over expression of ALP led to decreased NF-κB activity by κB reporter assay, while knocking it down had the opposite effect. Furthermore, we found that over expression of ALP in HT29 colon cancer cells greatly reduced both the number and the size of colonies that were formed in a soft agar assay, while using shRNA resulted in an opposite effect, confirming that ALP is a tumor suppressor in HT29 cells. Future experiments aim to further assess the role of ALP in colon tumor formation in a mouse xenograft model. In summary, by using the novel VBIM technique, we identified ALP as a novel negative regulator of NF-κB. This discovery could lead to the establishment of ALP as a potential biomarker and therapeutic target in colon cancer.

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