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Fuse binding protein1 (FBP1) as antagonist of p53: A potential host target for drug development

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FUSE binding protein1 (FBP1) is a transactivator of transcription of human c-myc proto-oncogene and expressed mainly in undifferentiated cells. Immunohistochemistry of archived hepatocellular carcinoma (HCC) tumors revealed abundant FBP1 expression in HCC tumors with chronic hepatitis C (CHC) background but absent in other HCC tumors with alcoholic or cryptogenic background. Hepatitis C virus (HCV) is a leading cause of CHC, liver cirrhosis, HCC and liver failure. Oncomine data analysis of normal liver versus HCV-HCC tumors indicated a 4-fold increase in FBP1 expression with a concomitant 2.5-fold decrease in the expression of p53. It is our novel discovery that FBP1, which is abundantly expressed in HCV-HCC tumors, is involved in the suppression of transactivation activity of p53 by physically interacting with p53 and inhibiting its DNA binding activity. The p53 transcription activity is enhanced in FBP-kd cells resulting in increased sensitivity of the cells to radiation. Knockdown of FBP1 expression activates p53-mediated response to cellular stress while transient expression of FBP1 restores the control phenotype in which 53-mediated response to cellular stress is strongly suppressed. FBP1 also promotes HCV replication by inhibiting p53, and also by regulating BCCIP and TCTP, which, respectively, are positive and negative regulators of p53. The severe inhibition of HCV replication in FBP1-knockdown cells is restored to control level by downregulation of either p53 or BCCIP. Since normal differentiated cells are devoid of, or poorly express FBP1, our studies indicate that over-expression of FBP1 in HCV-HCC tumors may have a potential role in promoting liver cancer by suppressing p53 activity, and thus, could be a potential target for drug development.

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Drug development targeting cancer stem cells

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Conventional anti-cancer treatment excels at tumor size reduction leading to clinically evident responses. However, these effects are frequently transient and are not associated with increased patient survival. Treatments are often too toxic to normal cells and they fail to selectively kill cancer stem cells (CSCs), which can survive treatment and, like the queen bee of a beehive, give rise to new malignant cells. Therefore CSCs are an underlying cause of tumor recurrence and metastasis. For truly effective treatments that can create a durable clinical response drugs that can target CSCs must be developed. Here we present data showing how functional assays for drug screening may be used to unravel compounds that target cancer stem cells, with a case study on drugs that inhibit activation of HIF dependent pathways.

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