SMYD3 Promotes Tumorigenic Phenotypes and Progression of Bladder Cancer via Direct Activation of IGF-1R/AKT/mTOR Signaling Pathway

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Introduction

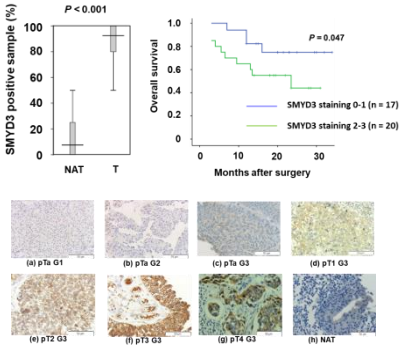
AKT/mTOR pathway is critical for bladder cancer (BC) and is aberrantly activated during BC progression. However, few studies have addressed the epigenetic regulation AKT/mTOR signaling in BC. SET and MYND domain-containing protein 3 (SMYD3) is a histone methyltransferase that targets histone H3-K4 for di/trimethylation. In the present study, we determine the role and the underlying mechanism of SMYD3 in the pathogenesis of BC.

Materials and methods

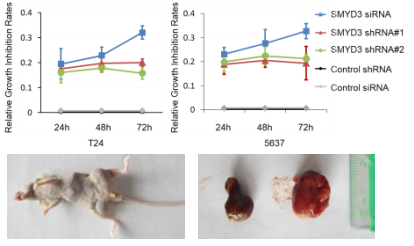
The expression of SMYD3 was examined via Western blot, real-time PCR and immunohistochemistry in a cohort of BC tissues. A series of *in vivo* and *in vitro* assays was performed to elucidate the contribution and underlying mechanism of the SMYD3/IGF-1R (insulin-like growth factor-1 receptor)/AKT axis in BC phenotypes and progression.

Results

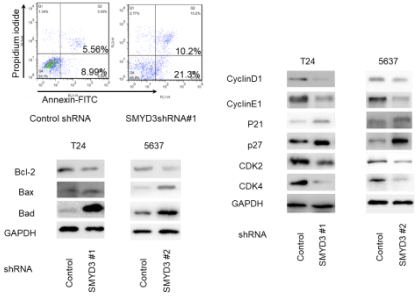
1. SMYD3 is upregulated in BC tissues and is a poor prognostic indicator of BC.



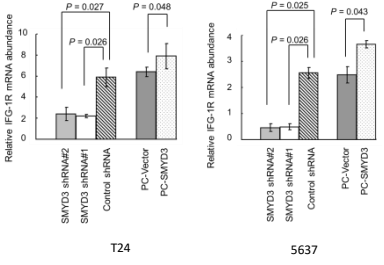
2. The SMYD3 requirement for tumorigenecity of T24 and 5637 cell lines.

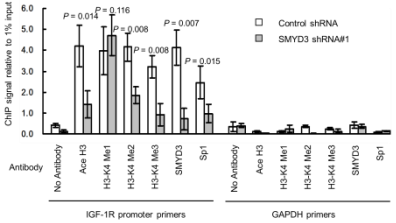


3.The induction of apoptosis and activation of the AKT/mTOR signaling pathway in BC cells.

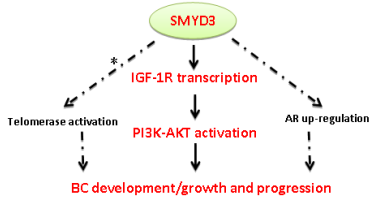


4. SMYD3-induced IGF-1R transcription through promoter chromatin remodeling.





5. The model for SMYD3-mediated BC development and progression.



The model for SMYD3-mediated BC development and progression

*Solid: The present finding and dash: the findings in other malignancies

Conclusions

Our findings suggest that IGF-1R is a new target gene of SMYD3, and by stimulating IGF-1R transcription, SMYD3 activates the AKT/mTOR pathway, thereby contributing to BC development and progression.