like IDH3A and PSAT1 were down regulated in cells treated with either disulfiram or sunitinib, and further down regulated in cells treated with a combination of both disulfiram and sunitinib.

CONCLUSIONS: This study showed that NPL4 suppression by disulfiram and si-RNA showed tumor suppressive effects in RCCs. In addition, the combination treatment of disulfiram and sunitinib showed additive effect in vitro as well as in vivo. Novel therapeutic implications targeting the ubiquitin-proteasome pathway in RCC were suggested.

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MTDH PROMOTES METASTASIS OF CLEAR CELL RENAL CELL CARCINOMA BY ACTIVATING SND1-MEDIATED ERK SIGNALING AND EPITHELIAL-MESENCHYMAL TRANSITION
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INTRODUCTION AND OBJECTIVE: Metastasis accounts for the principal reason for renal cell carcinoma-associated mortality. Metadherin (MTDH) was identified to be as a vital metastasis driver involved in the metastatic progression of various types of tumors, suggesting that MTDH could be a prognostic metastatic biomarker and potential therapeutic target. By now, the role and mechanism of MTDH in the metastatic progression of ccRCC still have not been adequately explored yet.

METHODS: The MTDH/SND1 mRNA expression of clear cell renal cell carcinoma (ccRCC) was comprehensively estimated in GEO-ccRCC and TCGA-KIRC datsets by R software and packages. The MTDH protein expression was assessed in a total of 111 ccRCC patients from Peking University First Hospital by Immunohistochemistry (IHC). In vitro migration, invasion assays and in vivo metastatic mouse model were conducted to investigate the biological functions of MTDH in ccRCC cells. Correlation analysis, immunoprecipitation, western blot and immunofluorescence were applied to explore the molecular mechanisms of MTDH in ccRCC.

RESULTS: Compared with normal kidney tissues, MTDH was remarkably elevated in ccRCC, especially in metastatic ccRCC and correlated with advanced clinicopathological features and poor prognosis. MTDH activated ERK signaling and EMT, thus promoting cell migration and invasion of ccRCC. The interaction between MTDH and SND1 at the protein level was confirmed using immunoprecipitation and immunofluorescence. Based on the analysis of GEO and TCGA data, SND1 was remarkably increased in ccRCC, especially in metastatic ccRCC and associated with advanced clinicopathological features and poor prognosis. Knockdown of SND1 mainly abolished cell migration and invasion of ccRCC by blocking MTDH mediated ERK and EMT signaling activation.

CONCLUSIONS: The results revealed MTDH could be a prognostic metastatic biomarker of ccRCC and promoted ccRCC metastasis by activating SND1-mediated EMT and ERK and EMT signaling pathways. MTDH may server as a potential anti-tumor therapeutic target that could be applied for the clinical treatment of metastatic ccRCC.
TOX HIGH MOBILITY GROUP BOX FAMILY MEMBER 3 SUPPRESSES EPITHELIAL-MESENCHYMAL TRANSITION IN CLEAR CELL RENAL CELL CARCINOMA BY TRANSCRIPTIONALLY REGULATING SNAI1 AND SNAI2

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INTRODUCTION AND OBJECTIVE: Although the survival of patients with clear cell renal cell carcinoma (ccRCC) was significantly extended, the poor prognosis of some patients with advanced tumors suggested the further studies on the mechanism of ccRCC progression are still needed. Here we identified TOX High Mobility Group Box Family Member 3 (TOX3) as a ccRCC suppressor gene and revealed how it affects the progression of renal cancer.

METHODS: In this study, TOX3 was screened from the Oncomine database and TCGA dataset and validated in clinical samples (n=22) by real-time PCR. Moreover, the clinical relevance of TOX3 in ccRCC specimens (n=151) was evaluated by immunohistochemistry analysis. Experiments in vitro and in vivo were conducted to detect changes in capacity to grow and metastasize by up-regulating or down-regulating TOX3 expression in RCC cells. Gene Set Enrichment Analysis (GSEA) was used to discover the