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Vactosertib combined treatment with T1-44, a PRMT5 activity inhibitor, improves the survival and inhibits tumor invasion of murine pancreatic cancer model

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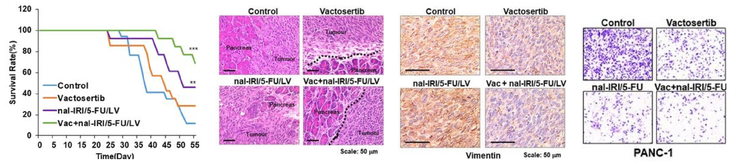
Abstract

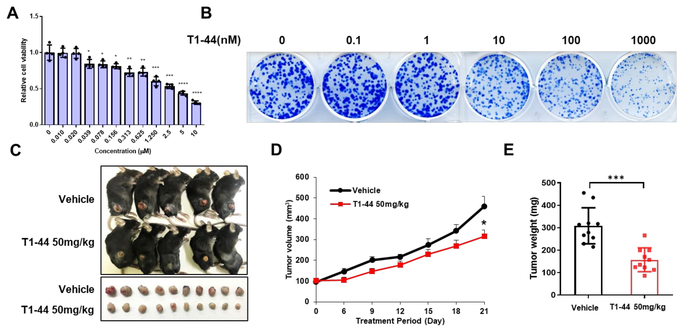
Pancreatic cancer is the deadliest cancer types, recording the third leading cause of cancer death with the lowest rate of 5-year survival. The heterogeneity, difficulty of diagnosis, and rapid metastatic progression are the reasons of high mortality in pancreatic cancer. PRMT5 (protein arginine methyltransferase 5) plays crucial role in tumor growth and metastasis through regulating lots of cancer-related pathways. In this study, we investigated that a selective inhibitor of PRMT5 activity, T1-44, reduces pancreatic tumor growth in vitro and in vivo. To synergize the effect of T1-44, we applied the combination with inhibitor of TGF-β signaling pathway associated with histone arginine methylation of PRMT5 to murine syngeneic orthotopic cancer model. The survival rate of combined group was significantly improved with markedly reduced tumor size and invasion. From the RNA-sequencing using mouse tumor, PRMT5 and TGF-β inhibitor combination altered the genes related to cancer progression such as cell migration, extracellular matrix, and apoptotic process. Particularly, Btg2, the tumor suppressor in various cancer, was upregulated by the co-treatment. Ectopic overexpression of Btg2 blocked cell migration with inhibition of EMT response, and induced cancer cell apoptosis. These data demonstrate that the combination of PRMT5 inhibitor and TGF-β inhibitor has synergetic effect on pancreatic cancer, suppressing cancer cell motility and enhancing apoptotic processes. This new combination regimen is valuable for therapeutic strategy of pancreatic cancer patients.

Introduction

1. TGFβ receptor kinase inhibitor, Vactosertib combined with other anti-cancer drugs improves survival rate through inhibiting tumor invasion and regulating tumor microenvironments.

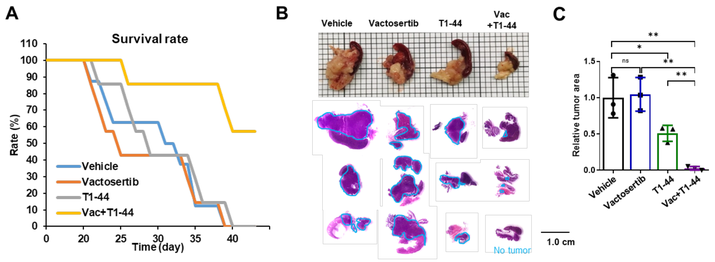


2. T1-44, a new PRMT5 activity inhibitor, reduces pancreatic tumor growth.

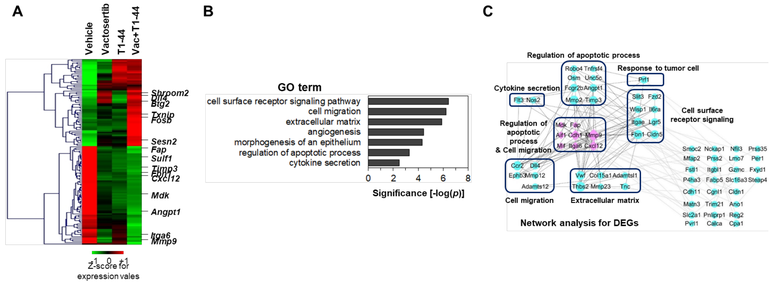


Results

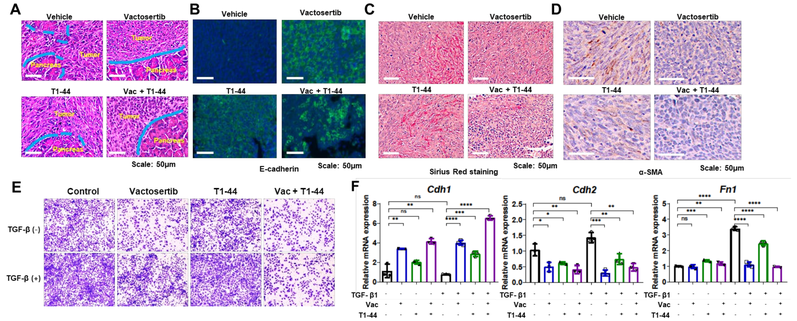
1. Combination therapy of Vactosertib and T1-44 prolonged the survival rate of pancreatic tumor mouse model.



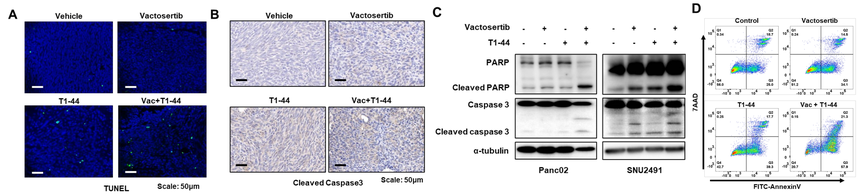
2. RNA-seq analysis with tumor RNA revealed Vactosertib and T1-44 combination regulates cell migration, ECM, and apoptotic process through altering cancer-related genes.



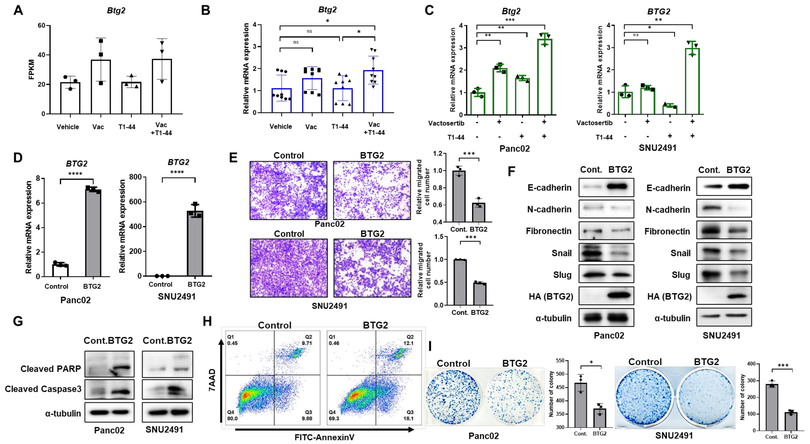
3. Vactosertib and T1-44 combination treatment reduced tumor invasion, EMT responses, and fibrosis in murine pancreatic cancer model.



4. Combination of Vactosertib and T1-44 induced apoptosis both *in vivo* and *in vitro.*



5. Tumor suppressor BTG2 was induced by combination treatment of Vactosertib and T1-44, and overexpression of BTG2 repressed pancreatic cancer progression.



Conclusion

1) Inhibition of PRMT5 activity by T1-44 reduces pancreatic cancer cell growth in vitro and in vivo.
2) Blockade of TGF-β signaling by vactosertib synergizes with T1-44, significantly improving the survival rate of mouse orthotopic model of pancreatic cancer.
3) Through RNA-sequencing analysis of tumor tissues, we have discovered that the combination of vactosertib and T1-44 regulates cancer cell migration and apoptotic pathways.
4) Combination treatment with vactosertib and T1-44 suppresses tumor growth and invasion to surrounding tissues in pancreatic cancer, via inhibiting EMT response and enhancing apoptotic processes.
5) Ectopic expression of BTG2, the unique target gene of the combined treatment, reduces cell migration and induced apoptotic responses in pancreatic cancer cells..

References

1. Hong, E., Park, S., Ooshima, A. et al. Inhibition of TGF-β signalling in combination with nal-IRI plus 5-Fluorouracil/Leucovorin suppresses invasion and prolongs survival in pancreatic tumour mouse models. Sci Rep 10, 2935 (2020).
2. Hong, E., Barczak, W., Park, S. et al. Combination treatment of T1-44, a PRMT5 inhibitor with Vactosertib, an inhibitor of TGF-β signaling, inhibits invasion and prolongs survival in a mouse model of pancreatic tumors. Cell Death Dis 14, 93 (2023).

Acknowledgements

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