Decitabine Reactivates Gene Expression of Silenced Genes in PDAC Preclinical Models

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BACKGROUND

Epigenetic deregulation is a critical factor in the development and progression of pancreatic ductal adenocarcinoma (PDAC). Understanding these alterations may pave the way for the development of new therapies aiming to improve patient outcomes.

This study evaluates the effectiveness of decitabine (DAC), a DNA methyltransferase (DNMT) inhibitor, in modulating the expression of key genes implicated in PDAC progression *in vitro* and *in vivo* (Fig.1).

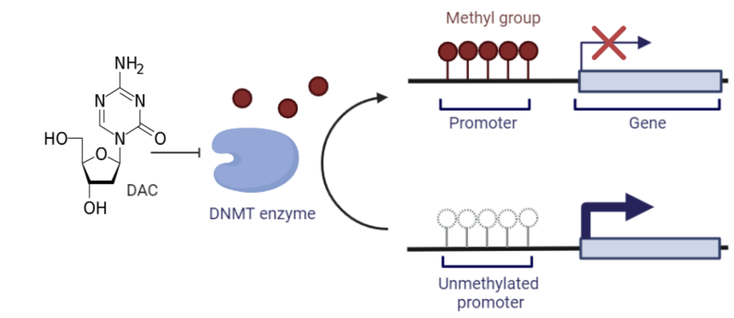

Figure 1. The effect of DAC on gene expression

METHODS

- Three PDAC cell lines were exposed to subcytotoxic concentrations of DAC every 24 h for a total of 72 h (Fig. 2A)
- The orthotopic xenograft model was derived from MIA PaCa-2 cells, DAC (0.125 mg/kg) was administered by intraperitoneal injection five days per week for a total of three weeks (Fig. 2B-D)
- The DNA methylation and gene expression changes were evaluated by pyrosequencing and quantitative RT-PCR

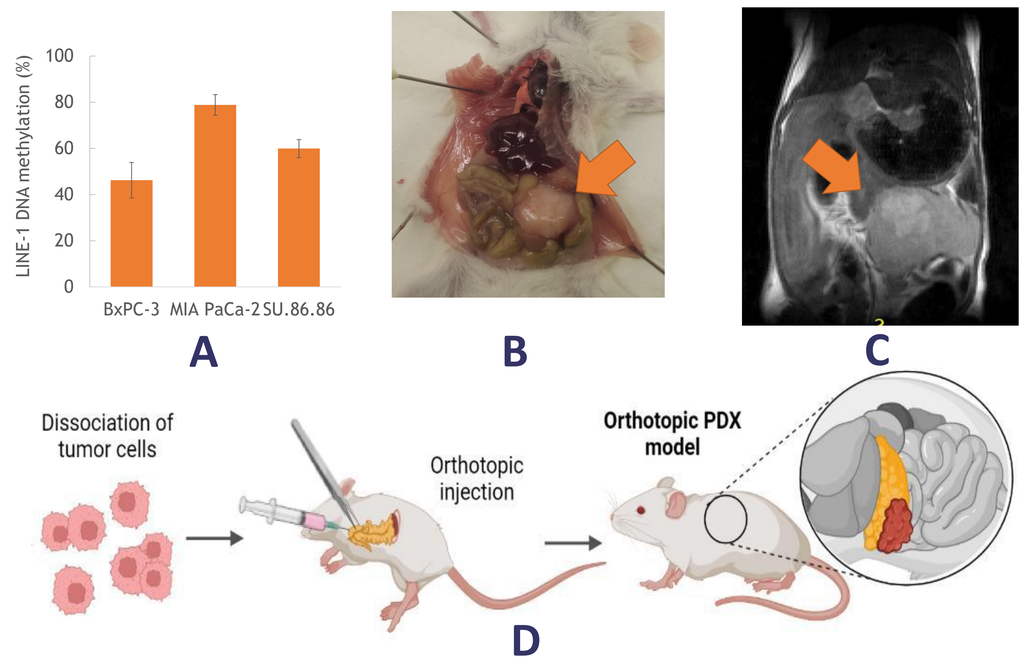

Figure 2. *In vitro* and *in vivo* PDAC models. (A) The global DNA methylation of studied PDAC cell lines evaluated by LINE-1 methylation level. (B) Orthotopic PDAC xenograft. (C) Monitoring the growth of the orthotopic xenografts by MRI. (D) Schematic diagram illustrating the development of orthotopic PDAC model.

RESULTS

- DAC efficiently decreased DNA methylation of highly methylated genes *in vitro*.
- Decrease of DNA methylation was accompanied by upregulation or reactivation of inhibited genes.
- The *in vivo* effect of DAC was lower. The DNA methylation decreased slightly, and significant upregulation of FN1 was observed in tumor xenografts.

MIA PaCa-2 xenografts

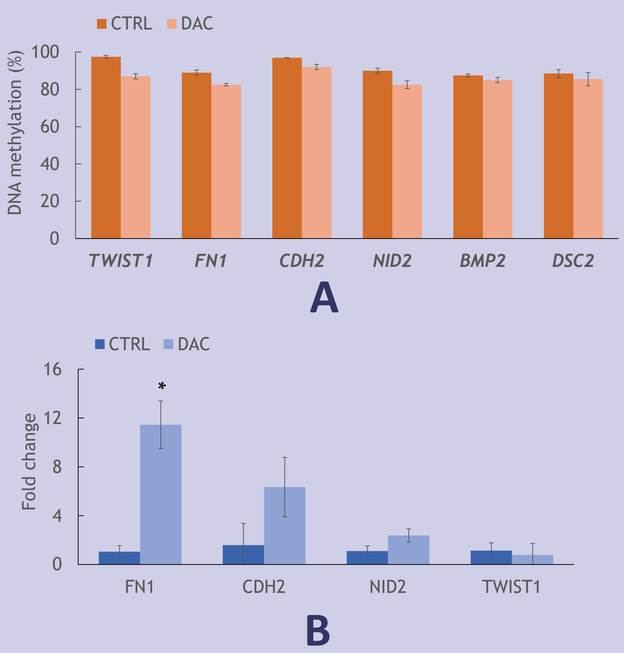

Figure 5. Effect of low-dose DAC on DNA methylation (A) and gene expression (B) in MIA PaCa-2-derived tumor xenografts. * p < 0.05.

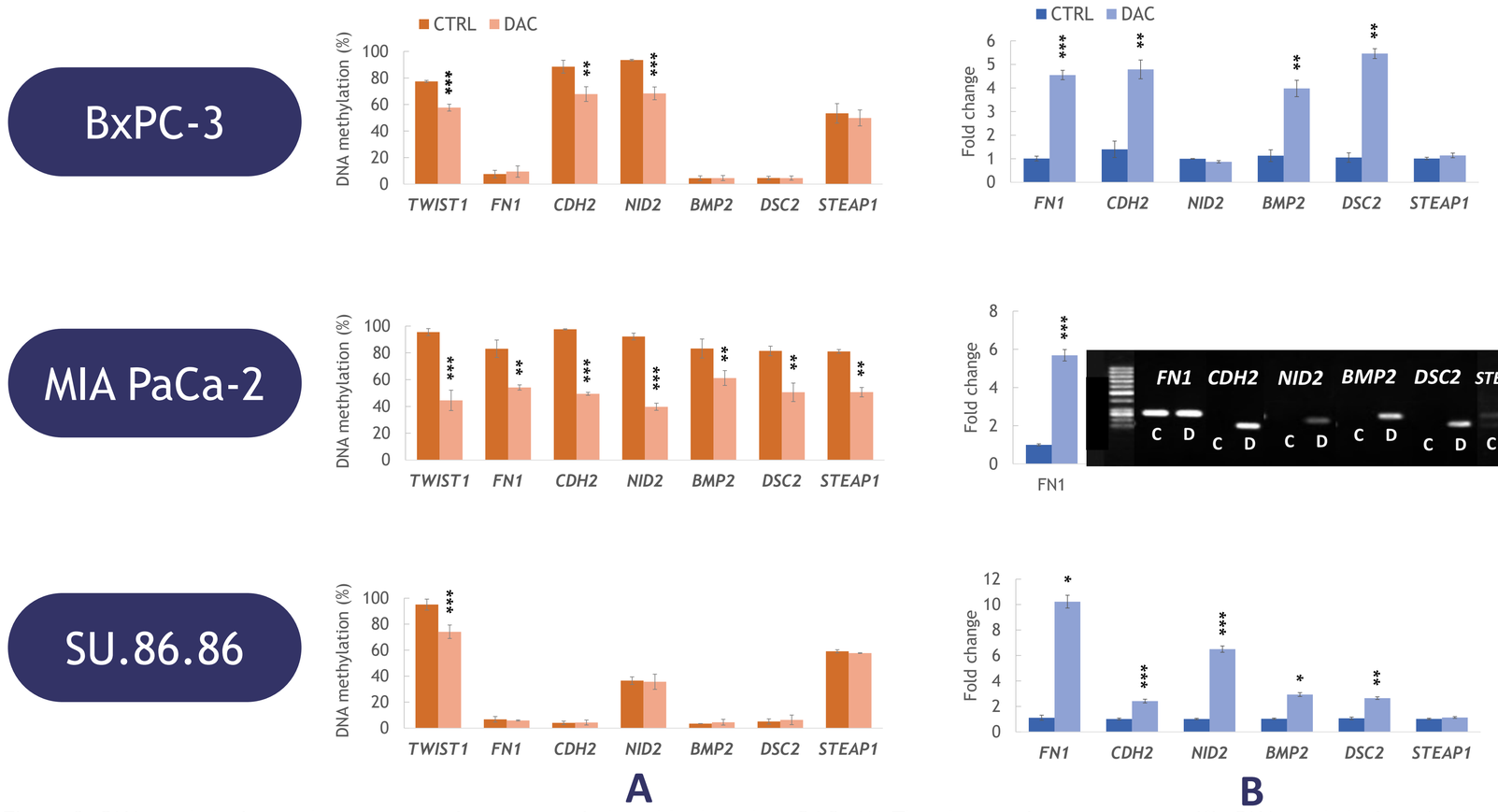

Figure 3. DNA methylation and gene expression changes induced by low-dose DAC. (A) The changes in the gene-specific DNA methylation of selected genes. (B) Expression of corresponding genes. In MIA PaCa-2 cell line, studied genes were not expressed at baseline except for *FN1*; * p < 0.05, ** p < 0.01, *** p < 0.001.

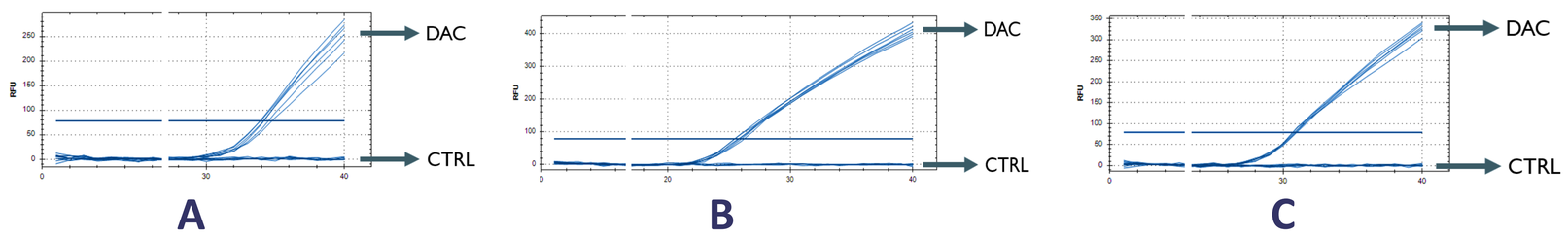

Figure 4. *TWIST1* reactivation by DAC. (A) BxPC-3; (B) MIA PaCa-2; (C) SU.86.86

CONCLUSIONS

This work shed light on the role of DNA methylation in the transcriptional regulation of genes involved in PDAC progression. DNA methylation-mediated reactivation of silenced genes has a critical translational impact. However, further studies are warranted to investigate epigenetic drug efficacy in synergy with other anticancer therapies and possible off-target effects.

ACKNOWLEDGEMENT

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