The glycogen synthase kinase-3 inhibitor, 9-ING-41, synergize with chemotherapy to inhibit pancreatic tumor growth *in vivo*

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Introduction

Glycogen synthase kinase-3 (GSK3) is a ubiquitously expressed serine-threonine protein kinase involved in multiple cellular functions ranging from the control of glycogen metabolism to transcriptional regulation. We have previously demonstrated that GSK-3β is overexpressed in human pancreatic ductal adenocarcinoma (PDAC) and aberrant nuclear accumulation of GSK-3β serves as a hallmark of poorly differentiated PDAC. Moreover, genetic ablation of GSK-3β or GSK-3 inhibition led to PDAC tumor cell killing, identifying GSK-3β as a therapeutic target in PDAC.

Recent studies have shown that 9-ING-41, a novel small molecule inhibitor of GSK-3 and clinical candidate currently approved by the FDA as an Investigational New Drug (IND), significantly enhances the antitumor activity of chemotherapy in patient-derived xenograft (PDX) models of neuroblastoma and breast cancer *in vivo*. Moreover, 9-ING-41 treatment in renal cancer cells results in G2-M phase arrest and autophagy.

Research Aim

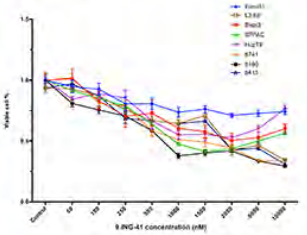
- Test the effect of GSK-3 inhibitor, 9-ING-41 on the growth and proliferation of pancreatic cancer cell lines.
- Investigate the cell cycle arrest following 9-ING-41 treatment in pancreatic cancer cell lines.
- Determine the underlying mechanism of the cell cycle progression defect induced by 9-ING-41 treatment in pancreatic cancer cell lines.

Methods

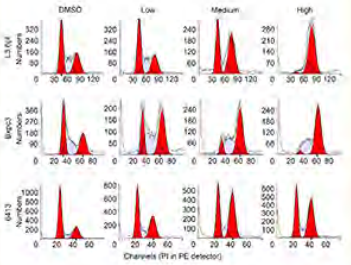
We use both established pancreatic ductal adenocarcinoma cancer (PDAC) cell lines and recently generated PDAC patient-derived Xenograft (PDX) cell lines for our study.

Results-1

1. 9-ING-41 reduces proliferation of PDAC and PDX cell lines.

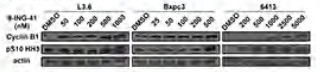


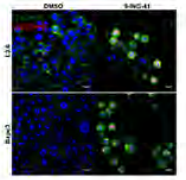
2. GSK-3 inhibition leads to a dose-dependent G2/M phase cell cycle arrest.

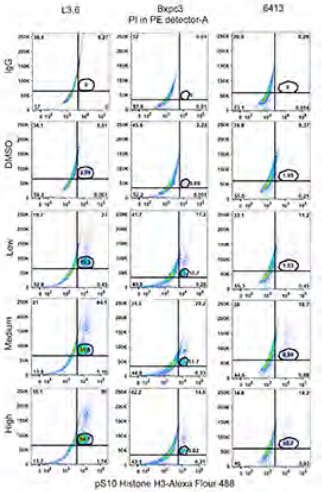


Results-2

3. GSK-3 inhibition leads to the accumulation of cyclin B1 and the M phase marker pS10 Histone H3.



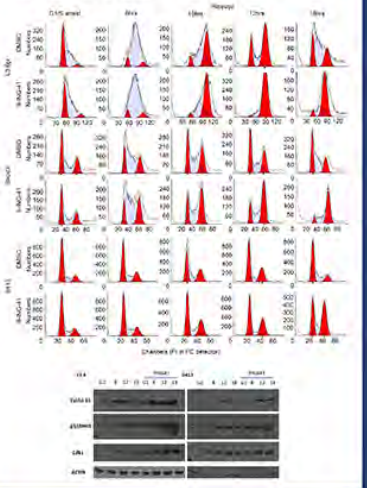




Work flow

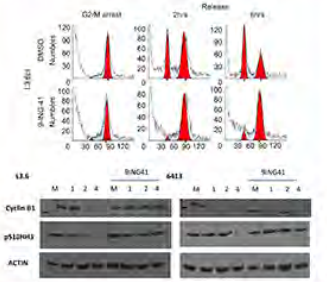
Results-3

4. GSK-3 inhibition impairs mitotic exit from G1/S arrest and release.



Results-4

5. GSK-3 inhibition impairs mitotic exit from G2/M arrest and release.



Conclusions

- 9-ING-41 reduces growth of PDAC cell lines.
- 9-ING-41 treatment leads to dose-dependent cell cycle arrest at Metaphase and impairs mitotic exit.
- Mechanistically, 9-ING-41 treatment stabilizes cyclin B1 and pS10 Histone H3.

References

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