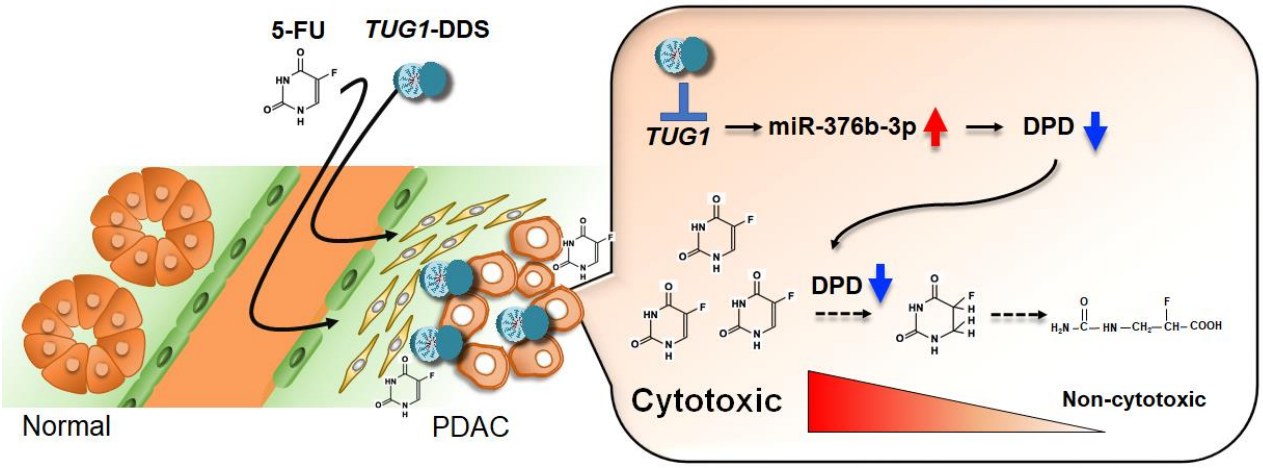
News Release

Title

Identification of a novel potent therapeutic strategy that the targeting of long non-coding RNA for the treatment of lethal pancreatic ductal adenocarcinoma.

Key Points

- Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive human malignancies. The poor prognosis is due to the lack of potent chemotherapy against PDAC.
- Many of the patients with PDAC suffer from resistance and toxicity to chemotherapy. Therefore, development of a cancer-specific therapeutic strategy to strengthen the effect of chemotherapy and overcome the resistance to chemotherapy is imperative.
- We demonstrated long non-coding RNA *TUG1* to be frequently upregulated in PDACs, causing acquisition of 5-FU resistance via enhancement of 5-FU catabolism.
- We made a new therapeutic drug that the targeting of *TUG1* by anti-*TUG1* coupled with our new cancer-specific drug delivery system (*TUG1*-DDS). Intravenous treatment with 5-FU plus *TUG1*-DDS efficiently repressed PDAC growth in PDAC xenograft mouse model.
- Our data provided a strong and novel rationale for targeting *TUG1* as a practical therapeutic approach to treat PDACs.



TUG1-DDS as an effective modulator to reduce or avoid the systemic adverse effects and meet appropriate 5-FU dosage requirements in targeted PDAC cells.

Summary

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive human malignancies, in which overall median survival is less than five months and the five-year survival rate is around 10%. The poor prognosis is due to lack of potent therapeutic strategies against PDAC. Particularly, in case of treatment failure, many of the patients with PDAC inevitably suffer from resistance to chemotherapy. Overcoming drug resistance is one of the biggest challenges in cancer

chemotherapy. In this study, we examine whether targeting the long non-coding RNA *TUG1* could be an effective therapeutic approach to overcome drug resistance in PDAC. We demonstrated *TUG1* to be frequently upregulated in PDACs, causing acquisition of 5-FU resistance via enhancement of 5-FU catabolism. We made a new therapeutic drug that the targeting of *TUG1* by anti-*TUG1* coupled with our new cancer-specific drug delivery system (*TUG1*-DDS). Intravenous treatment with *TUG1*-DDS and 5-FU significantly suppressed PDAC tumor growth compared to 5-FU treatment alone. This novel approach using *TUG1*-DDS in combination with 5-FU may serve as an effective therapeutic option to attenuate DPD activity and meet appropriate 5-FU dosage requirements in targeted PDAC cells, which can reduce the systemic adverse effects of chemotherapy.

Research Background

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive human malignancies. Although surgical resection is the only curative therapy for PDAC, only 20% of patients are considered to be a candidate for surgical resection. Almost of patients with PDAC have undergone 5-FU or Gemcitabine based chemotherapy. The overall survival of patients receiving that chemotherapy is still less than a year. Furthermore, many of the patients with PDAC suffer from resistance and toxicity to chemotherapy. In this study, we aim to elucidate the mechanism of resistance to chemotherapy and to identify a cancer-specific therapeutic strategy to strengthen the effect of chemotherapy.

Research Results

TUG1 was expressed at significantly higher levels across PDAC tissues compared to normal pancreatic tissues. Mechanistically, *TUG1* antagonized miR-376b-3p and upregulated DPD. Only a small fraction of 5-FU is converted into cytotoxic metabolites intracellularly, while 80% of 5-FU is catabolized to the non-cytotoxic metabolites by the enzymatic activity of DPD. There is a consistent relationship between the enzymatic activity of DPD and pharmacological activity of 5-FU. Therefore, aberrant upregulation of DPD might be the key determinants of resistance to 5-FU in PDACs. Our results showed that *TUG1* depletion induced

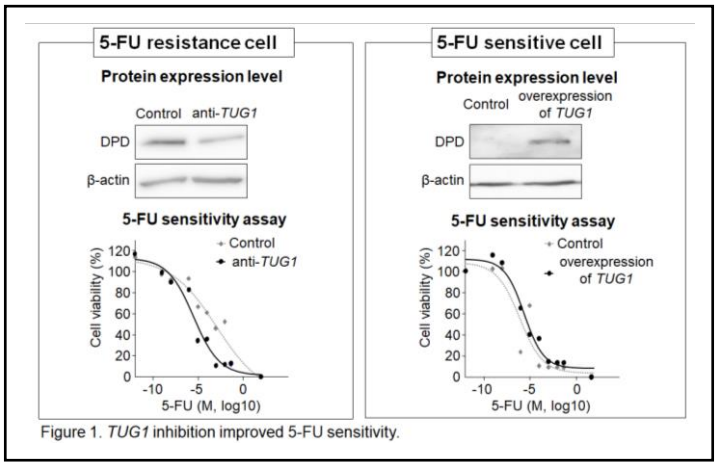


Figure 1. *TUG1* inhibition improved 5-FU sensitivity.

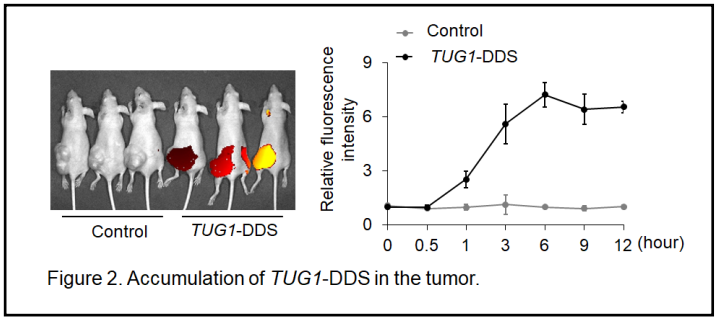


Figure 2. Accumulation of *TUG1*-DDS in the tumor.

susceptibility to 5-FU together with a decreased DPD expression in 5-FU resistant pancreatic cell, whereas overexpression of *TUG1* acquired resistance to 5-FU together with an increased DPD expression in 5-FU sensitive cell (Figure 1). We demonstrated *TUG1*-miR376b-3p-DPD axis to be frequently dysregulated in PDACs, causing acquisition of 5-FU resistance via enhancement of 5-FU catabolism. Next, we made a new therapeutic drug that the targeting of *TUG1* by anti-*TUG1* coupled with cancer-specific drug delivery system (*TUG1*-DDS). We found *TUG1*-DDS to accumulate in tumor cells (Figure 2). Finally, we examined the effect of combination therapy with 5-FU and *TUG1*-DDS in PDAC xenograft mouse model. Remarkably, combination therapy using 5-FU and *TUG1*-DDS further suppressed the tumor growth than 5-FU alone (Figure 3).

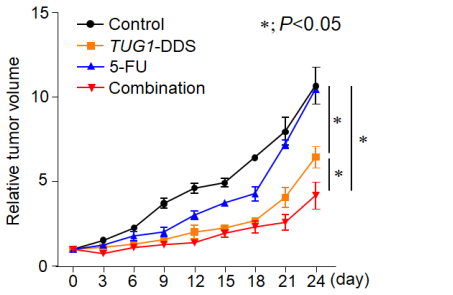


Figure 3. Combination therapy with 5-FU and *TUG1*-DDS suppressed tumor growth

Research Summary and Future Perspective

In the current study, we demonstrated *TUG1*-miR376b-3p-DPD axis to be frequently dysregulated in PDACs, causing acquisition of 5-FU resistance via enhancement of 5-FU catabolism. Treatment with *TUG1*-DDS, which can reduce or avoid the systemic adverse effects, combined with 5-FU-based chemotherapy, might be a promising therapeutic approach against PDACs, particularly those with resistance to 5-FU.

We aim to perform clinical trial of a *TUG1*-DDS for patients with PDAC in order to demonstrate that inhibition of *TUG1* is a practical therapeutic approach for PDAC with patients (Figure 4).

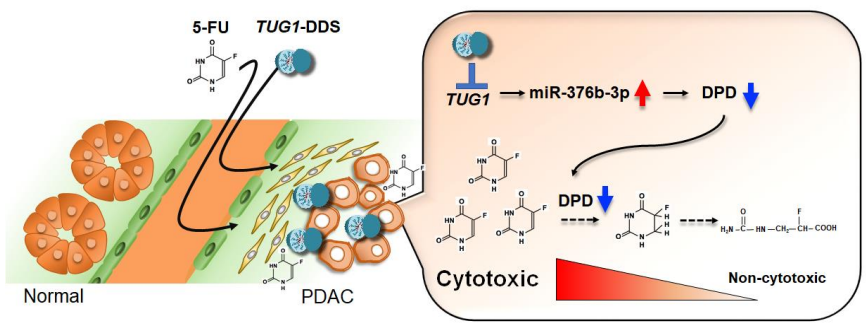


Figure 4. *TUG1*-DDS as an effective modulator to reduce or avoid the systemic adverse effects and meet appropriate 5-FU dosage requirements in targeted PDAC cells.

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Title: Cancer-specific targeting of taurine upregulated gene 1 enhances the effects of chemotherapy in pancreatic cancer

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