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MiR-198 sensitizes pancreatic cancer to gemcitabine treatment through downregulation of VCP-mediated autophagy maturation.

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Background: The mechanism of human pancreatic ductal adenocarcinoma (PDAC) resistance to nucleoside analog and first-line chemotherapy drug gemcitabine is not clearly understood, but some studies have associated it with increased autophagy. In cancer biology, autophagy plays dual roles as it can promote tumor suppression during early stages, but in established tumors, it plays a crucial role in tumor growth by enhancing survival under metabolic and therapeutic stress. We have previously found that miR-198 acts as a tumor suppressor in PDAC through the targeting of a network of tumorigenic factors, including the Valosin-containing protein (VCP), which has been reported to play an important role in autophagy. In this study, we investigate whether the repression of VCP through miR-198 replacement disrupts the autophagy process and sensitizes PDAC cells to gemcitabine treatment. **Methods:** MIAPaCa2 cells with forced overexpression of mesothelin (MSLN) and AsPC-1 cell lines and, CDX and PDX mouse models were used for gemcitabine sensitization studies. For miR-198 replacement, a miR-198 expression vector-loaded lactic co-glycolic-acid-modified polyethylenimine polyplex (LPNP-p198) was used. Autophagy disruption experiments were run over miR-198 and/or VCP overexpressing cell lines. Nude mice were used for subcutaneous and orthotopic CDX models and SCID/Beige were used for the subcutaneous PDX model. **Results:** Cell lines were treated with LPNP-p198 in combination with gemcitabine and cell growth was significantly inhibited when compared to gemcitabine alone. Additionally, it was determined that miR-198 disrupts the autophagy maturation process and, that it is then restored by overexpression of VCP. LPNP-p198 can effectively enter tumor cells and induce tumor sensitization *in vivo*, resulting in an 80-90% reduction of tumor burden and metastatic spread in the LPNP-p198 plus gemcitabine group when compared to controls, with the concomitant downregulation of VCP expression in the tumor tissue. In addition, this group had the fewest mice with jaundice, ascites, and metastases to the abdominal cavity, spleen, liver, and kidney. Finally, to address the potential of the observed effect in the context of the heterogenic nature of PDAC, we confirmed our findings in a PDX mouse model, where a marked reduction in tumor burden was observed in the LPNP-p198 plus gemcitabine group compared to controls. **Conclusions:** Our findings indicate that miR-198 replacement disrupts the autophagy maturation process and sensitizes PDAC cells to gemcitabine through VCP repression, indicating a potential therapeutic strategy for targeting gemcitabine-resistant PDAC and, establishing the use of LPNPs as a prototype for effective nucleic acid delivery *in vitro* and *in vivo*, with potential to be used from bench to clinic. Research Sponsor: U.S. National Institutes of Health, Speratum Biopharma, Inc.