A common genetic variation of melanoma inhibitory activity-2 labels a subtype of pancreatic adenocarcinoma with high endoplasmic reticulum stress levels.

HNF1 homeobox A (HNF1A)-mediated gene expression constitutes an essential component of the secretory pathway in the exocrine pancreas. Melanoma inhibitory activity 2 (MIA2), a protein facilitating protein secretion, is an HNF1A target. Protein secretion is precisely coordinated by the endoplasmic reticulum (ER) stress/unfolded protein response (UPR) system. Here, we demonstrate that HNFA and MIA2 are expressed in a subset of human PDAC tissues and that HNF1A induced MIA2 in vitro. We identified a common germline variant of MIA2 (c.A617G: p.I141M) associated with a secretory defect of the MIA2 protein in PDAC cells. Patients carrying MIA2(I141M) survived longer after tumor resection but the survival benefit was restricted to those patients who received adjuvant chemotherapy. The MIA2(I141M) variant was associated with high expression of ER stress/UPR genes--in particular those of the ERN1/XBP arm--in human PDAC samples. Accordingly, PDAC cell lines expressing the MIA2(I141M) variant expressed high levels of ERN1 and were more sensitive to gemcitabine. These findings define an interaction between the common MIA2(I141M) variant and the ER stress/UPR system and specify a subgroup of PDAC patients who are...
more likely to benefit from adjuvant chemotherapy.