CF-1.3 Haplotypes in melanoma inhibitory activity 2 determine chemotherapy response in pancreatic cancer through AKT/mTOR1 signaling

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**Background:** Response rates of pancreatic ductal adenocarcinoma (PDAC) to chemotherapy are low: identification of a subgroup of patients who are more likely to benefit from chemotherapy might constitute a rational approach to improve overall prognosis.

**Methods:** Expression of melanoma inhibitory activity 2 (MIA2) was examined in pancreatic tissues and pancreatic cancer cell lines. MIA2 polymorphisms were defined by conventional PCR sequencing and high-resolution melting curve analysis. To assess the functional relevance of MIA2, loss-of-function and gain-of-function studies were performed in pancreatic cancer cell lines.

**Results:** A moderate to strong MIA2 staining in cancer cells was found in 71% (43 out of 61) of the samples. Among the tested pancreatic cancer cell lines, ASPC-1, Capan-1 and Colo-357 expressed MIA2. Surprisingly, ELISA analysis demonstrated that MIA2 was secreted only by ASPC-1 and Capan-1. Sequencing of MIA2 exons in ASPC-1, Capan-1 and Colo-357 revealed a GG and CC genotype at the 617 and 1833 position in the mRNA sequence of Colo-357, while the other two cell lines maintained the 617AA and 1833GG polymorphisms, respectively. Analysis of these polymorphisms revealed that PDAC patients with 617 AA/1833 GG survived significantly longer than patients with 617 AG&GG/1833 GC&CC (median survival, 21 months vs. 15 months). Functional assays demonstrated that MIA2 polymorphisms influence the activity of the AKT/mTOR1 axis which further modulates sensitivity of cancer cells towards chemotherapy.

**Conclusion:** Haplotypes in MIA2 predict survival of patients with pancreatic cancer and are associated with AKT/mTOR1-mediated chemosensitivity.