CD147 silencing inhibits lactate transport and reduces malignant potential of pancreatic cancer cells in in vivo and in vitro models.

BACKGROUND: CD147 (basigin, EMMPRIN) is a multifunctional, highly conserved glycoprotein enriched in pancreatic ductal adenocarcinomas (PDACs) which is associated with poor prognosis in many malignancies. The role of CD147 in pancreatic cancer, however, remains elusive.

METHODS AND RESULTS: Silencing of CD147 by RNA interference (RNAi) reduced the proliferation rate of MiaPaCa2 and Panc1 cells. CD147 is required for the function and expression of the monocarboxylate transporters MCT1 and MCT4 that are expressed in human PDAC cells as demonstrated by real-time reverse transcription-PCR (RT-PCR) as well as immunohistology. MCT1 and MCT4 are the natural transporters of lactate, and MiaPaCa2 cells exhibited a high rate of lactate production, which is characteristic for the Warburg effect, an early hallmark of cancer that confers a significant growth advantage. Further induction of lactate production by sodium azide in MiaPaCa2 cells increased MCT1 as well as MCT4 expression. CD147 silencing inhibited the expression and function of MCT1 and MCT4 and resulted in an increased intracellular lactate concentration. Addition of exogenous lactate inhibited cancer cell growth in a dose-dependent fashion. In vivo, knock-down of CD147 in MiaPaCa2 cells by inducible short hairpin RNA (shRNA)-mediated
CD147 silencing reduced invasiveness through the chorioallantoic membrane of chick embryos (CAM assay) and inhibited tumourigenicity in a xenograft model in nude mice. CONCLUSION: The function of CD147 as an ancillary protein that is required to sustain the expression and function of MCT1 and MCT4 is involved in the association of CD147 expression with the malignant potential of pancreatic cancer cells exhibiting the Warburg effect.