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The expression and role of the new hypoxia-inducible gene matriptase in pancreatic cancer

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Pancreatic cancer is associated with low oxygen tissue levels. Since hypoxia induces genes that give pancreatic cancer a growth and invasion advantage, the aim of this study was to find and to characterize new hypoxia-inducible genes involved in PDAC pathogenesis. Current study identified a recently discovered member of the family of tissue type serine proteases – matriptase, as a new hypoxia-inducible gene in pancreatic cancer. Analysis of matriptase in pancreatic cancer tissues and cell lines revealed a significant overexpression of matriptase in malignant cells, especially in tubular complexes and ductal cancer cells close to the invasion front of tumors. Matriptase expression correlated with the degree of tumor cell differentiation: high expression was observed in well-differentiated G3 tumors cells and reduced levels in poorly-differentiated G1 tumor cells. Genomic overexpression of matriptase by stable transfection of Miapaca2 cells resulted in an altered morphology, delayed growth and reduced invasive tumor phenotype. Anti-invasive character of matriptase in pancreatic cancer cells was confirmed by applying specific inhibitors to the AsPc1 cells constitutively expressing high levels of matriptase. DNA microarray and QRT-PCR analyses of Miapaca2 cells, transfected or not with pEGF/N1 or PEGF/N1-full-length matriptase, elucidated complex transcriptional changes associated with matriptase overexpression. Whereas down-regulation of CD44, uPA, up-regulation of E-cadherin in the absence of N-cadherin expression and missing induction of MMP2 and MMP9 was in the line with reduced invasiveness of matriptase-positive cells, up-regulation of tPA, SPARC and MET remained without functional consequences. Apparently, activation of anti-invasive mechanisms was more effective that the pro-invasive ones. Transcriptional activation of other pathways indicated that matriptase may be a multifunctional protein involved in the regulation of angiogenesis (VEGF), de-differentiation (CK19, galectin 4, DIF 2), growth (erb2, CDC28 kinase2), oxidative stress (metallothionein, heat-shock protein 89a, HIF1α). To conclude, the results of the present study identified matriptase as a new member of genes induced by hypoxia in pancreatic cancer, established its overexpression and link to the differentiation status in human pancreatic cancer cells, and showed that contrary to the expected, matriptase may represent a protective anti-proliferative and anti-invasive factor. Owing to the complex matriptase-associated genomic changes, this protein's prognostic value, complete mechanism of action and the outcome of overexpression in the context of the tumor microenvironment should be further analyzed in appropriate (animal) models.