Hypoxia-induced endoplasmic reticulum stress characterizes a necrotic phenotype of pancreatic cancer.

Abstract:
Stromal fibrosis and tissue necrosis are major histological sequelae of hypoxia. The hypoxia-to-fibrosis sequence is well-documented in pancreatic ductal adenocarcinoma (PDAC). However, hypoxic and necrotic PDAC phenotypes are insufficiently characterized. Recently, reduction of tuberous sclerosis expression in mice together with oncogenic Kras demonstrated a rapidly metastasizing phenotype with histologically eccentric necrosis, transitional hypoxia and devascularisation. We established cell lines from these tumors and transplanted them orthotopically into wild-type mice to test their abilities to recapitulate the histological features of the primary lesions. Notably, the necrotic phenotype was reproduced by only a subset of cell lines while others gave rise to dedifferentiated tumors with significantly reduced necrosis. In vitro analysis of the necrotic tumor-inducing cell lines revealed that these cells released a significant amount of vascular endothelial growth factor A (Vegfa). However, its release was not further increased under hypoxic conditions. Defective hypoxia-induced Vegfa secretion was not due to impaired Vegfa transcription or hypoxia-inducible factor 1-alpha activation, but rather a result of hypoxia-induced endoplasmic
We thus identified hypoxia-induced ER stress as an important pathway in PDACs with tissue necrosis and rapid metastasis.