Levels of the Autophagy Related 5 Protein Affect Progression and Metastasis of Pancreatic Tumors in Mice.

Abstract:
Cells in pancreatic ductal adenocarcinoma (PDAC) undergo autophagy, but its effects vary with tumor stage and genetic factors. We investigated the consequences of varying levels of the autophagy related 5 (Atg5) protein on pancreatic tumor formation and progression. We generated mice that express oncogenic Kras in primary pancreatic cancer cells and have homozygous disruption of Atg5 (A5; Kras) or heterozygous disruption of Atg5 (A5+/--; Kras), and compared them with mice with only oncogenic Kras (controls). Pancreata were analyzed by histology and immunohistochemistry. Primary tumor cells were isolated and used to perform transcriptome, metabolome, intracellular calcium, extracellular cathepsin activity, and cell migration and invasion analyses. The cells were
injected into wildtype littermates, and orthotopic tumor growth and metastasis were monitored. Atg5 was knocked down in pancreatic cancer cell lines using small hairpin RNAs; cell migration and invasion were measured, and cells were injected into wildtypelittermates. PDAC samples were obtained from independent cohorts of patients and protein levels were measured on immunoblot and immunohistochemistry; we tested the correlation of protein levels with metastasis and patient survival times. A5+/-; Kras mice, with reduced Atg5 levels, developed more tumors and metastases, than control mice, whereas A5; Kras mice did not develop any tumors. Cultured A5+/-; Kras primary tumor cells were resistant to induction and inhibition of autophagy, had altered mitochondrial morphology, compromised mitochondrial function, changes in intracellular Ca2+ oscillations, and increased activity of extracellular cathepsin L and D. The tumors that formed in A5+/-; Kras mice contained greater numbers of type 2 macrophages than control mice, and primary A5+/-; Kras tumor cells had upregulated expression of cytokines that regulate macrophage chemotraction and differentiation into M2 macrophage. Knockdown of Atg5 in pancreatic cancer cell lines increased their migratory and invasive capabilities, and formation of metastases following injection into mice. In human PDAC samples, lower levels of ATG5 associated with tumor metastasis and shorter survival time. In mice that express oncogenic Kras in pancreatic cells, heterozygous disruption of Atg5 and reduced protein levels promotes tumor development, whereas homozygous disruption of Atg5 blocks tumorigenesis. Therapeutic strategies to alter autophagy in PDAC should consider the effects of ATG5 levels to avoid the expansion of resistant and highly aggressive cells.

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