The presence of stromal desmoplasia is a hallmark of spontaneous pancreatic ductal adenocarcinoma, forming a unique microenvironment that comprises many cell types. Only recently, the immune system has entered the pathophysiology of pancreatic ductal adenocarcinoma development. Tumor cells in the pancreas seem to dysbalance the immune system, thus facilitating spontaneous cancer development. This review will try to assemble all relevant data to demonstrate the implications of the immune network on spontaneous cancer development.