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G Protein-Coupled Receptor 55 in Pancreatic Cancer: An Immunomodulatory Role

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The G protein-coupled receptor 55 (GPR55) is a receptor that is considered to be part of an expanded endocannabinoid system (ES). It has been shown to have pro-tumorigenic effects in different cancer models, including models of pancreatic cancer. Most cells in the tumor microenvironment (TME) express cannabinoid receptors and thus can be influenced by the ES. However, the role of GPR55 in immune cells of the TME and its involvement in tumor growth is not well understood. Knowing that pancreatic cancer is characterized by low immune infiltration and poor treatment response, it is important to uncover the role of GPR55 in tumor immunity. KPCY cells (isolated from mouse pancreatic ductal adenocarcinoma with a high [T cell high; TCH] and low [T cell low; TCL] T cell response) were subcutaneously injected into GPR55 wild-type and knock-out mice. Flow cytometry and in situ hybridization were used to phenotype cells within the tumors, while cytokine array, ELISA, and qRT-PCR were used to determine the expression levels of proteins and cytokines. Functional in vitro assays were conducted on mouse and human neutrophils to elucidate their behavior in the TME. GPR55 knock-out mice injected with TCH KPCY cells had significantly smaller tumors than the wild-type mice. Additionally, they showed higher CD8+ T cell and dendritic cell infiltration with higher CCL21 expression, but lower infiltration of neutrophils when compared to wild-types. In the TCL model, tumor weight was significantly higher in the knock-out group compared to wild-types. The TCL GPR55 knock-outs also showed higher infiltration of neutrophils, suggesting that neutrophils could be important regulators of the TME in the KPCY tumor model. In summary, our data indicates that the knock-out of GPR55 in the TME of mouse pancreatic cancer models leads to differing immune cell infiltration, which could be important regarding future immuno-therapies of pancreatic cancer.