**Tumor Cell–Derived IL1β Promotes Desmoplasia and Immune Suppression in Pancreatic Cancer**

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**Presenter**: Yu-Hsuan Huang  **Date/Time**:2020/09/24, 16:00-17:00

**Commentator**: Kwang-Yu Chang, Ph.D. **Location**: Room 601, Med College Building

**Background**

Cell populations, collagen organization, and cytokines are profoundly different between normal pancreatic tissue and advanced pancreatic cancer. Pancreatic ductal adenocarcinoma (PDA) is mainly represented by desmoplastic stroma and weakly immunogenic tumor microenvironment. The desmoplastic tumor microenvironment consists of epithelial PDA cells and numerous stromal components, such as immunosuppressive cells, activated pancreatic stellate cells, collagens that promotes tumor evolution and contributes to therapeutic resistance. The cytokine IL1β is an inﬂammatory mediator that is frequently upregulated in a variety of cancers and its production is associated with poor prognosis. There is evidence that high intratumoral and serum IL1β levels in pancreatic cancer correlate with poor overall survival and increased chemoresistance. In addition, upregulation of IL1β expression in several cancers results in increased tumor inﬁltration of immunosuppressive macrophages and myeloid-derived suppressor cells (MDSC), thereby promoting immune evasion and tumor development.

**Objective/Hypothesis**

To investigate the mechanisms underlying the regulation and function of IL1β in PDA and assessing its potential as a therapeutic target.

**Results**

In this study, the author demonstrate that PDA tumor cell–derived IL1β is essential for the establishment of the protumorigenic PDA microenvironment. Tumor cell–derived IL1β promoted the activation of quiescent pancreatic stellate cells (PSCs). Activated PSCs play a crucial role in creating an immunosuppressive environment mediated by M2 macrophages, myeloid-derived suppressor cells, regulatory B cells, and Th17 cells. Loss of tumor cell–derived IL1β signaling in tumor stroma increased intratumoral inﬁltration and activation of CD8+ cytotoxic T cells, attenuated growth of pancreatic tumor, and also extended the PDA-bearing mice survival. In addition, the author identify that tumor cell expression of IL1β in vivo was driven by microbial-dependent activation of toll-like receptor 4 (TLR4) signaling and subsequent engagement of the NLRP3 inﬂammasome.

**Conclusion**

In this study, the authors identify a new modality for immune evasion in PDA that depends on IL1β production by tumor cells through TLR4-NLRP3 inﬂammasome activation.

**Reference**

1. Padoan A, Plebani M, Basso D. Inﬂammation and pancreatic cancer: focus on metabolism, cytokines, and immunity. Int J Mol Sci 2019;20.