**HMGA1 induces FGF19 to drive pancreatic carcinogenesis and stroma formation**

**Linda Resar et al. J Clin Invest. 2023 Mar 15; 133(6): e151601.**

**Presenter: Chin-Chun Lin                    Date and Time: 2023.9.14, 16:00-1700**

**Commentator: Chu-An Wang, PhD  Location: Room 601, Med**

**Background:**

Pancreatic ductal adenocarcinoma (PDAC) is becoming a significant public health concern, with its incidence on the rise in developed nations. Unlike many other solid tumors, PDACs are distinguished by a dense desmoplastic stroma that includes cancer-associated fibroblasts (CAFs) and fibrous scar tissue. However, the exact role of this stroma in tumor progression remains a subject of debate. The HMGA1 gene, typically active during embryonic development and in adult stem cells, is typically silenced after birth in most specialized cells. Nevertheless, overexpression of HMGA1, a chromatin regulator, is observed in many aggressive cancers, including PDAC. High levels of HMGA1 expression in PDAC often correlate with poor tumor differentiation and unfavorable clinical outcomes.

**Objective:**

The authors reveal how HMGA1 controls PDAC transcription and tumor-stroma interactions to promote tumor progression and BLU9931 inhibitory effect of BLU9931 on PDAC tumors.

**Results:**

HMGA1 plays a pivotal role in upregulating transcriptional networks associated with proliferation and tumor-stroma interactions in the progression of pancreatic ductal adenocarcinoma (PDAC). Specifically, HMGA1 directly binds to the promoter of fibroblast growth factor 19 (FGF19) and triggers active histone marks, leading to the expression and secretion of FGF19 from PDAC cells. This FGF19 secretion results in the phosphorylation of FGFR4 and downstream signaling molecules, ultimately enhancing cell proliferation in PDAC. Silencing either HMGA1 or FGF19 disrupts key traits required for tumor progression. In mouse models with human PDAC xenografts, the silencing of HMGA1 or FGF19 not only reduces tumor-initiating cells but also interferes with tumor growth and stroma formation. Intriguingly, even the loss of a single Hmga1 allele within the pancreatic ductal epithelium significantly extends the survival of KPC (Kras+/LSL-G12D; Trp53+LSL-R172H; Pdx1-Cre) mice compared to those with both Hmga1 alleles intact.

Furthermore, treatment with BLU9931, an inhibitor of FGF receptor 4 (FGFR4) to block FGF19 function, replicates the effects observed with HMGA1 or FGF19 silencing, resulting in reduced tumor growth and stroma formation in orthotopic models.

**Conclusion:**

High levels of both HMGA1 and FGF19 in human pancreatic ductal adenocarcinoma (PDAC) indicate a subgroup with notably poor prognosis. Treatment with BLU9931 in mice resulted in reduced tumor volumes, decreased expression of HMGA1, FGF19, Ki-67, and fibrosis, along with reduced cancer-associated fibroblast (CAF) subtypes. Targeting FGFR4 with BLU9931 appears promising for PDAC cases overexpressing HMGA1 and FGF19.