Targeting a Novel KRAS-Integrin-Linked Kinase Regulatory Circuitry in Pancreatic Cancer

Po-Chen Chu¹, Ming-Chen Yang², Samuel K. Kulp² and Ching-Shih Chen¹,²

¹Institute of Basic Medical Sciences, National Cheng Kung University, Tainan 70101, Taiwan and
²Division of Medicinal Chemistry, College of Pharmacy and Comprehensive Cancer Center, The Ohio State University, Columbus, OH 43221, USA

Activating KRAS mutations are the most frequent genetic abnormality in over 90% of pancreatic cancers. Evidence indicates that these mutations not only play a crucial role in initiating pancreas carcinogenesis, but also are required for pancreatic tumor maintenance. From a clinical perspective, oncogenic KRAS represents a therapeutically relevant target in pancreatic cancer, of which the proof-of-concept was demonstrated by the effectiveness of siRNA-mediated silencing of KRAS to suppress pancreatic tumor growth in vivo. Nonetheless, attempts to develop small-molecule agents to inhibit oncogenic KRAS activity have proven futile to date. Consequently, recent strategies have focused on targeting downstream effectors of KRAS signaling, including Raf, MEK, and PI3K kinase, each of which, however, shows limited clinical benefit as single agent. In this study, we have identified a novel KRAS-E2F1-ILK-hnRNP A1 regulatory circuitry that governs the expression of oncogenic KRAS. Integrin-linked kinase (ILK) is a serine/threonine kinase that mediates a diversity of cellular functions including cell survival, cell-matrix interactions, angiogenesis and also plays a role in epithelial to mesenchymal transition (EMT) in cancer cells. Dysregulation of ILK expression has been observed in several tumors including breast, ovary, melanoma, lung, prostate and pancreas and reported to be correlated with tumor progression, metastasis and chemoresistance to gemcitabine in pancreatic adenocarcinoma cells, but the mechanisms by which ILK is required for the tumorogenesis in pancreatic cancer are yet to be understood. In this circuitry, KRAS induces ILK expression via an E2F1-dependent mechanism, which, in turn, stimulates KRAS expression through hnRNP A1 upregulation. Mechanistically, hnRNP A1 binds and relaxes the G-quadruplex structure at the KRAS promoter, thereby enhancing the transcription initiation of the KRAS gene. As a result, disruption of this circuitry via siRNA-mediated knockdown of any of these intermediary effectors (E2F1, ILK, or hnRNP A1), or pharmacological inhibition of ILK by T315, a novel ILK inhibitor developed in our laboratory, led to suppression of KRAS expression and reversal of the mesenchymal phenotype of pancreatic cancer cells. The therapeutic relevance of ILK in regulating this regulatory circuitry is also evident in the suppressive effect of ILK knockdown on epidermal growth factor (EGF)-induced KRAS expression. Together, these findings provide a rationale for targeting ILK as a novel strategy to suppress oncogenic KRAS signaling.