PP2A complex disruptor SET prompts widespread hypertranscription of growth-essential genes in the pancreatic cancer cells

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Background: Pancreatic cancer, a malignancy with poor prognosis, relies on transcriptional hyperactivation of growth-essential genes for tumor progression. Transcription of growth-essential genes is mainly catalyzed by RNA polymerase II (Pol II), whose activity is determined by phosphorylation of its carboxy-terminal domain (CTD). Phosphorylation of Pol II CTD is catalyzed by Cyclin T/CDK9 complex and is attenuated by PP2A. Su(var)3-9, enhancer of zeste, Trithorax (SET), a nuclear oncoprotein, inactivates protein phosphatase 2A (PP2A) and was also reported to be a chromatin remodeling factor, which plays both a promoting and suppressing role in transcription. However, the drive factors for hypertranscription of pancreatic cancer, relationship between SET and hypertranscription of pancreatic cancer and clinical relevance of SET in pancreatic cancer remain unclear.

Objective: To explore the factors involved in promoting hypertranscription of pancreatic cancer and to characterize the molecular mechanism underlying the transcriptional hyperactivation in pancreatic cancer cells

Results: SET overexpression models showed increased phosphorylation of Pol II CTD , resulting in increased transcription of growth-essential genes like MET. Genome-wide binding site analysis revealed SET enrichment at transcription start sites (TSS) and enhanced Pol II recruitment and activity. SET knockout reduced nascent RNA synthesis and Pol II occupancy in TSS of widespread genes, directly linking SET to genome-wide hypertranscription. Mechanistically, SET caused PP2A-A subunit dissociation from PP2A-C subunit, thereby inhibiting PP2A activity, maintaining Pol II phosphorylation and enhancing transcription for sustaining oncogenic pathways. Transcriptomic analyses highlighted SET's role in oncogenic transcriptional regulation, with clinical data correlating high SET expression to poor survival outcomes.

Conclusion: SET functions as a PP2A complex disruptor in pancreatic cancer cells, enabling widespread transcription of growth-essential genes through persistent Pol II hyperactivation. These findings position SET as a critical driver of pancreatic cancer progression and a potential therapeutic target.