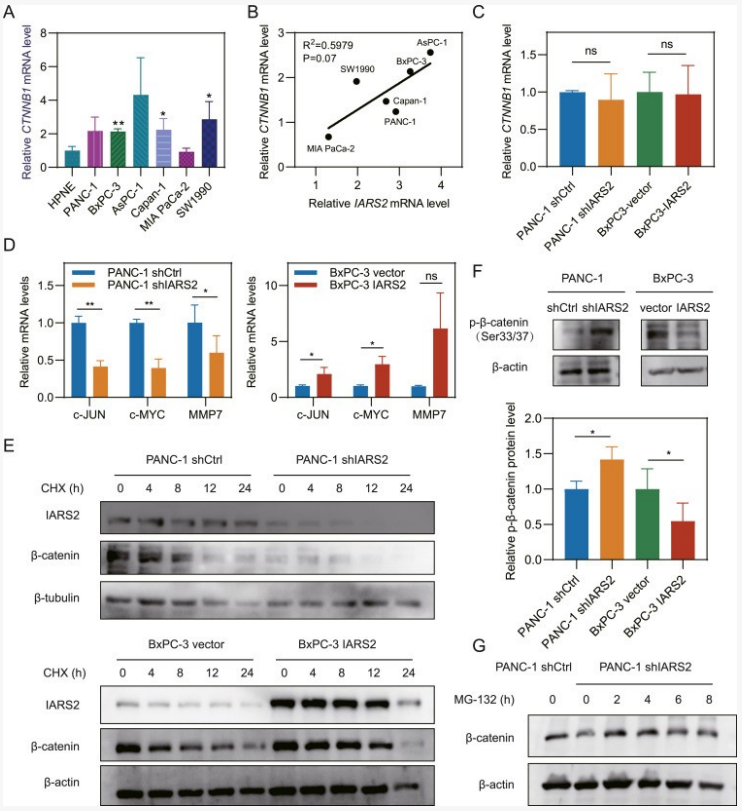
Isoleucyl-tRNA Synthetase 2 (IARS2) Promotes Pancreatic Ductal Adenocarcinoma (PDAC)

IARS2 facilitates PDAC proliferation and metastasis by stabilizing β-catenin and activating the WNT/β-catenin pathway.



(A) Relative CTNNB1 mRNA level in normal and pancreatic adenocarcinoma cell lines. (B) The correlation between relative IARS2 mRNA transcription level and CTNNB1 mRNA transcription level. (C) CTNNB1 mRNA level remained unchanged after IARS2 knockdown or o

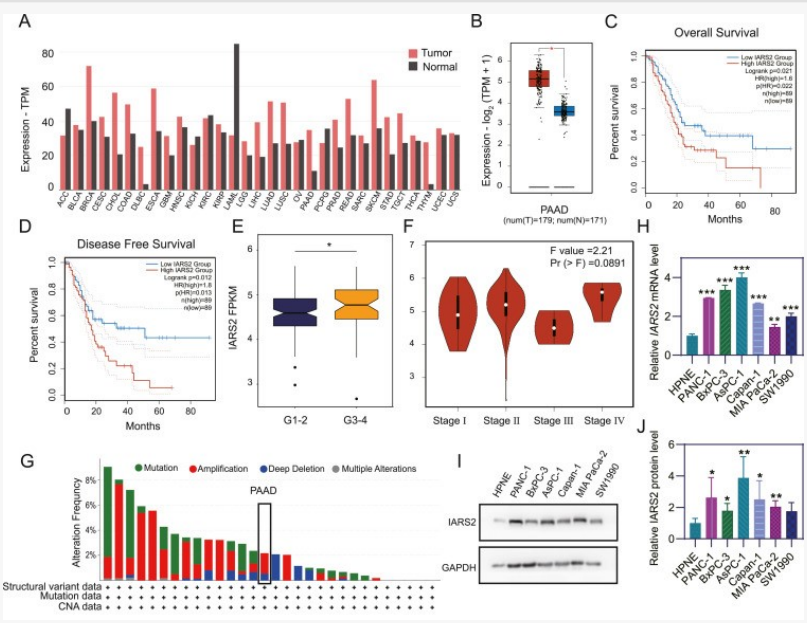
CHINA, March 18, 2025 /EINPresswire.com/ -- Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related mortality worldwide. Current treatment modalities are few or ineffective due to PDAC's heterogeneous molecular patterns, which cause it to respond variably to the same therapy. Understanding the molecular taxonomy of PDAC phenotypes may open avenues for therapeutic interventions.

A recent study published in the Genes & Diseases journal by researchers at Shanghai Jiao Tong University School of Medicine implicates isoleucyl-tRNA synthetase 2 (IARS2) in promoting the proliferation and metastasis of PDAC.

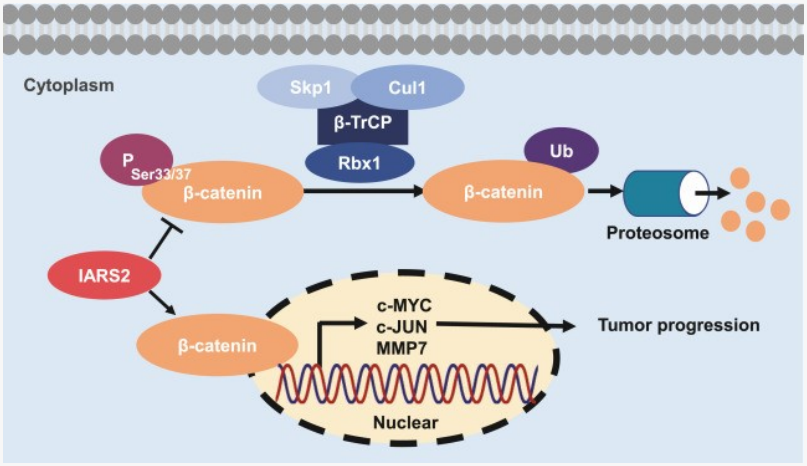
Isoleucyl-tRNA synthetase 2 (IARS2) has previously been shown to be dysregulated in various cancers. This study showed that IARS2 expression was higher in PDAC tissues and cell lines. Furthermore, high IARS2 expression was associated with a shorter overall survival and disease-free survival time and was significantly higher in grade 3–4 pancreatic cancer stages compared to grade 1–2. In vitro and in vivo experiments involving IARS2 knockdown and overexpression revealed that IARS2 promotes the proliferation, migration, and invasion of PDAC cells via upregulation of EMT transcription factors.

Transcriptomic analysis of the TCGA-PAAD cohort showed that IARS2 regulates biological

processes. Gene set enrichment analysis (GSEA) showed that WNT signaling, cell cycle, p53, and apoptotic pathways were enriched in the high-IARS2 expression group of TCGA-PAAD. The gene expression-based stemness index (mRNAsi) was higher in patients with high IARS2 expression. The expression of cancer stemness markers, like CD44, MET, CD133, FUT4, ACVR1, mTOR, and KLF4 correlated positively with IARS2 expression, suggesting that IARS2 promotes metastasis via regulation of cancer cell stemness. Additionally, high IARS2 expression was associated with lower infiltration of CD8+ T cells, indicating that IARS2 promotes an immunosuppressive microenvironment.



(A) Bar plot of IARS2 transcription level in different cancer types. (B) TCGA and GTEx databases showed IARS2 transcription level was higher in tumor tissue compared with normal pancreas tissue. (C) High IARS2 expression linked to shorter overall survival



IARS2 reduces β-catenin phosphorylation at Ser33/37 site, subsequently attenuating its ubiquitination and inhibiting degradation. Accumulated β-catenin translocates into nuclear and regulates the downstream targets genes, which leads to PDAC progression.

This study also showed that IARS2 protects β-catenin from phosphorylation-dependent proteasome degradation by β-TrCP (F-box protein beta-transducin repeat containing protein). Further results established that IARS2 promotes pancreatic tumorigenesis via activation of the Wnt/ β-catenin pathway by stabilizing β-catenin.

In conclusion, this study showed that up-regulated IARS2 in PDAC tissues correlates with poor prognosis and that IARS2 facilitates PDAC proliferation and metastasis by stabilizing β-catenin and activating the WNT/β-catenin pathway. These results indicate that IARS2 may serve as an underlying prognostic marker and a potential therapeutic target for PDAC. However, this study has limitations and need more experiments to explore how IARS2 impacts β-catenin degradation and the specific interaction between IARS2 and GSK3β.

Reference

Title of the original paper - Isoleucyl-tRNA synthetase 2 promotes pancreatic ductal adenocarcinoma proliferation and metastasis by stabilizing β-catenin

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