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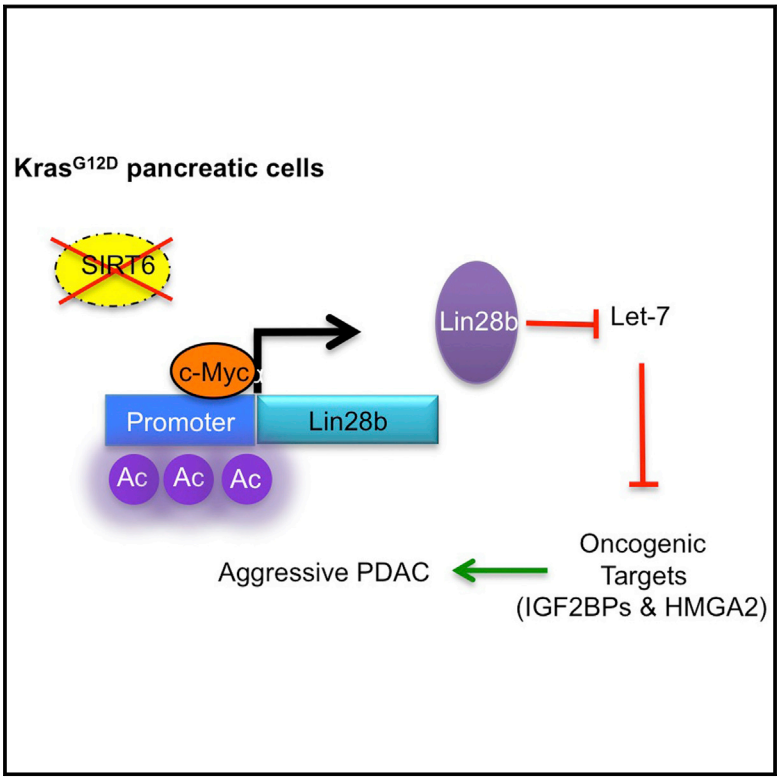
SIRT6 Suppresses Pancreatic Cancer through Control of Lin28b

Graphical Abstract



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In Brief

A subset of pancreatic carcinomas with mutant KRAS depend on expression of Lin28b and epigenetic control of its expression by SIRT6, suggesting avenues for stratifying patients with these malignancies.

Highlights

- Loss of SIRT6 cooperates with oncogenic Kras to drive pancreatic cancer
- SIRT6 regulates the oncofetal protein Lin28b through promoter histone deacetylation
- Lin28b drives the growth and survival of SIRT6-deficient pancreatic cancer
- SIRT6 and Lin28b expression define prognosis in specific pancreatic cancer subsets

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SIRT6 Suppresses Pancreatic Cancer through Control of Lin28b

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SUMMARY

Chromatin remodeling proteins are frequently dysregulated in human cancer, yet little is known about how they control tumorigenesis. Here, we uncover an epigenetic program mediated by the NAD$^+$-dependent histone deacetylase Sirtuin 6 (SIRT6) that is critical for suppression of pancreatic ductal adenocarcinoma (PDAC), one of the most lethal malignancies. SIRT6 inactivation accelerates PDAC progression and metastasis via upregulation of Lin28b, a negative regulator of the let-7 microRNA. SIRT6 loss results in histone hyperacetylation at the *Lin28b* promoter, Myc recruitment, and pronounced induction of Lin28b and downstream let-7 target genes, HMGA2, IGF2BP1, and IGF2BP3. This epigenetic program defines a distinct subset with a poor prognosis, representing 30%–40% of human PDAC, characterized by reduced SIRT6 expression and an exquisite dependence on Lin28b for tumor growth. Thus, we identify SIRT6 as an important PDAC tumor suppressor and uncover the Lin28b pathway as a potential therapeutic target in a molecularly defined PDAC subset.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal of all human malignancies and is responsible for hundreds of thousands of deaths each year. Thus, there is an urgent need to improve our understanding of the molecular underpinnings that drive PDAC initiation, progression, and metastasis and to leverage that understanding toward better therapeutic options. The current model proposes that a series of genetic alterations results in a stepwise progression through increasingly dysplastic precursor lesions, or pancreatic intraepithelial neoplasias (PanINs), toward invasive and finally metastatic PDAC. Initiating events identified in early PanIN lesions (PanIN I) include mutations and/or amplification of the *KRAS* oncogene and the loss of the *CDKN2A* (p16INK4A) tumor suppressor gene, present in >90% and >50% of PDAC/PanINs, respectively (Ryan et al., 2014). Higher grade lesions (PanIN III) and invasive PDAC may accumulate additional genetic lesions, including inactivation of *TP53* and TGFβ pathway components (*SMAD4, TGFβR1,* and *TGFβR2*) (Ryan et al., 2014). However, this fundamental model of PDAC pathogenesis, which is recapitulated in genetically engineered mice, has failed to identify either critical pathways that may be effectively targeted in the clinic or relevant molecular subsets for improved prognosis and stratification of patients toward a more effective therapy.

In addition to the above well-characterized genetic aberrations, it is becoming increasingly apparent that the dysregulation of epigenetic modifiers is central to the initiation and progression of human PDAC as well as many other tumors. Genomic deletions, mutations, and rearrangements recurrently targeting genes encoding many components of the switch/sucrose nonfermentable (SWI/SNF) chromatin remodeling complex have recently been identified in at least 10%–15% of PDAC cases. Additionally, mutations in the histone methyltransferase mixed-lineage leukemia protein 2 and 3 (*MLL2* and *MLL3*) and the histone demethylase KDM6A have been identified in 5%–10% of PDAC (Ryan et al., 2014). However, since these chromatin-modifying enzymes may simultaneously regulate the transcription of thousands of genes by altering chromatin structure throughout the genome or may be involved in other cellular functions such as DNA repair and replication, the mechanisms by which these proteins control tumorigenesis have been difficult to elucidate. Specifically, whether these enzymes regulate an individual target gene or set of genes to drive survival, proliferation, cellular transformation, metabolic adaptations, or invasive functions in PDAC is unknown; yet this understanding is critical to our ability to leverage data from the molecular profiling of human tumors to identify new therapeutic opportunities in molecularly defined subsets of disease.

Sirtuin 6 (SIRT6) is a nicotinamide adenine dinucleotide (NAD)$^+$-dependent histone deacetylase that removes acetyl groups from histone 3 lysine 9 (H3K9) and histone 3 lysine 56 (H3K56) motifs and has pleiotropic functions including glucose homeostasis, maintenance of genome stability, and suppression of cellular transformation (Mostoslavsky et al., 2006; Sebastián