Distinct roles of RBPJ and RBPJL in pancreatic development, inflammation and carcinogenesis (Review)

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Abstract. Recombination signal binding protein for immunoglobulin κ J region (RBPJ) and RBPJ-like protein (RBPJL) are members of the transcription factor family Suppressor of Hairless [Su(H)] and central components of Notch signaling. Aberrant Notch signaling is consistently involved in pancreatic inflammation and carcinogenesis. Importantly, RBPJ is the primary DNA-binding transcription factor in the canonical Notch signaling pathway. RBPJL is a pancreas-specific homolog that acts as a Notch signaling inhibitor and can promote terminal acinar cell differentiation. Functional differences set them apart from conventional Notch pathway components and underlie their involvement in diverse physiological and pathological processes. In a Notch-independent manner, RBPJ and RBPJL can both form a complex with pancreas transcription factor 1A (PTF1A). During pancreatic development, the progressive replacement of RBPJ by RBPJL in the PTF1A complex marks the transition from progenitor maintenance to mature acinar identity. In disease, RBPJL is frequently downregulated or silenced in pancreatitis and pancreatic ductal adenocarcinoma, while RBPJ persists or becomes dysregulated, contributing to inflammation, fibrosis and neoplastic progression. This review summarizes the structural and functional divergence of this antagonistic pair, their context-dependent roles in pancreatic development, inflammation and carcinogenesis and emerging therapeutic strategies targeting the RBPJ/RBPJL axis.

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1. Introduction

Recombination signal binding protein for immunoglobulin κ J region (RBPJ) is an evolutionarily conserved transcription factor in the Notch signaling pathway (1). It functions as a molecular switch that either represses or activates transcription depending on the absence or presence of Notch ligand stimulation (2-4). RBPJ-like protein (RBPJL), the homolog of RBPJ, is a pancreas-specific protein that possesses DNA-binding ability similar to that of RBPJ, but lacks the structural determinants required for Notch-mediated transcriptional activation (5-7). Therefore, RBPJL primarily functions as a constitutive transcriptional repressor (6).

During pancreatic development, RBPJ and RBPJL achieve temporal regulation by alternating composition of the pancreas transcription factor 1A (PTF1A) transcription complex (8). In early development, the PTF1A-RBPJ complex drives progenitor maintenance and initiates acinar differentiation (9). As development progresses, RBPJL gradually replaces RBPJ, forming the PTF1A-RBPJL complex to finalize acinar maturation and maintain high-level expression of digestive enzyme genes (10). This transition represents a molecular switch from a plastic progenitor state to a stable differentiated identity.

In pancreatitis, RBPJL is markedly downregulated (11,12), which relieves its anti-inflammatory function (13,14). In addition, RBPJ loss delays pancreatic refinement, which may become locked in a chronic state promoting fibrosis and neoplastic progression (15). In pancreatic ductal adenocarcinoma (PDAC), the most lethal malignancy worldwide,

RBPJL is frequently silenced. RBPJ loss cooperates with oncogenic Kirsten Rat Sarcoma viral oncogene homolog (KRAS) to accelerate precursor lesion formation, while RBPJ overexpression promotes chemoresistance through positive feedback loops (15,16). The RBPJL dominance shifts to RBPJ persistence, which creates a permissive environment for tumor initiation and stromal remodeling.

An increasing number of studies indicate that abnormal expression of RBPJ and RBPJL affects the normal physiological functions of the pancreas. This article reviews the existing evidence on their molecular characteristics, developmental roles and pathological functions, aiming to highlight the RBPJ/RBPJL axis as a key determinant of pancreatic acinar cell fate and a potential therapeutic target for pancreatic diseases.

2. Structural characteristics and functional divergence of RBPJ and RBPJL

Structural and functional characteristics of RBPJ. RBPJ is expressed across nearly all mammalian tissues. It comprises three structurally and functionally distinct domains: an N-terminal domain (NTD), a central b-trefoil domain (BTD) and a C-terminal transcriptional regulatory domain (CTD) (Fig. 1A; Table I) (17,18). The NTD and BTD cooperatively mediate DNA recognition and binding, specifically recognizing the CGTGGGAA motif (CSL binding site) within the promoter regions of target genes (Fig. 1B) (18-20). The BTD serves as the high-affinity binding site for the RAM domain of the Notch intracellular domain (NICD) to activate the signaling (21). The CTD mediates interactions with transcriptional cofactors, including the coactivator MAML and the corepressor SHARP/SPEN (17). Therefore, RBPJ integrates DNA binding and recruits transcriptional coactivators or corepressors to regulate downstream gene expression.

In a Notch-dependent manner, RBPJ functions as a dual transcriptional regulator capable of acting as either an activator or a repressor, thereby serving as the molecular switch that governs Notch signaling output (22). In the absence of the Notch signal, RBPJ functions as a sequence specific transcriptional repressor. Its C-terminal domain recruits SHARP/SPEN, which in turn bridges the NCoR/SMRT HDAC1/2 corepressor complex (22-24). Additionally, the CtBP-LSD1/CoREST histone demethylase complex can be recruited to establish a repressive chromatin environment at target gene promoters to maintain transcriptional silencing (25,26). When Notch signaling is activated, ligand binding to Notch receptors on adjacent cell surfaces triggers two successive proteolytic cleavages by a disintegrin and metalloproteinase domain-containing protein 10/17 (ADAM10/ADAM17) protease and γ-secretase, releasing the NICD to translocate into the nucleus (27). Its RAM domain, containing a conserved ΦWΦP motif, inserts into the hydrophobic pocket on the RBPJ BTD surface in an extended conformation, generating a high-affinity interaction. Subsequently the ankyrin repeat domain of NICD forms more extensive contacts with RBPJ and MAML, inducing substantial conformational changes in RBPJ that expose the MAML binding site (18,28). MAML1 simultaneously displaces the corepressor SHARP/SPEN and bridges histone acetyltransferases p300/CBP assembling a coactivator complex (29-31), thereby initiating the expression of canonical Notch target genes (such as *Hes1* and *Hey1)* (22). This functional conversion from repression to activation enables RBPJ to precisely respond to the dynamic changes of Notch signals.

As well as its classical function in the Notch signaling pathway, RBPJ can also directly regulate the expression of pancreas-specific genes by forming complexes with PTF1A (5,32,33). RBPJ interacts with residues W280 and W298 in the C1 and C2 regions of PTF1A (5). The PTF1A C2 motif competes with the NICD ΦWΦP hydrophobic motif for RBPJ binding, that determines cell fate specification during pancreatic development (5,17). PTF1A sequesters RBPJ away from canonical Notch signaling resulting in acinar lineage commitment redirection.

Structural and functional characteristics of RBPJL. RBPJL expression is predominantly restricted to pancreatic tissue, with minimal or undetectable expression in lung, spleen, brain and other tissues (5,6,9). Within the pancreas, RBPJL expression is highly enriched in the acinar cell population, exhibiting strong coexpression with classical acinar markers PTF1A, CPA1 and AMY2A (9,33). Detectable expression signals are also present in a subset of islet cells (34), whereas RBPJL is almost absent in ductal and mesenchymal cells (5,6,9).

The structure of RBPJL is predicted to be highly similar to that of RBPJ (Fig. 1C and D; Table I). The N-terminal region of RBPJL is identical to the respective region within RBPJ, whereas the C-terminal region exhibits ~60% identity with almost the same constitution of residues involved in DNA binding. Homology modeling based on the RBPJ crystal structure predicts that the C-terminal region of RBPJL lacks the hydrophobic pocket required for the NICD RAM domain and MAML interaction. Therefore, RBPJL cannot support Notch-mediated transcriptional activation (6,35). RBPJL maintains efficient interaction capability with the corepressor SHARP/SPEN and retains DNA-binding capacity. However, its binding affinity is lower than that of RBPJ (6,35).

Independent of Notch signaling pathway, RBPJL is also involved in PTF1A complex. PTF1A binds the E-box consensus sequence through its bHLH domain, while RBPJ and RBPJL both recognize the TC-box (TTTCCC) via their conserved BTD (Fig. 2B). This bipartite DNA recognition is required for PTF1A complex assembly and transcriptional activity. In mature acinar cells, RBPJ is progressively replaced by RBPJL at the TC-box, converting the complex from a signal-responsive to a lineage-committed regulatory state (10).

Regulation of RBPJ and RBPJL beyond canonical Notch signaling. RBPJ and RBPJL are regulated at several levels as well as canonical Notch signaling. At the transcriptional level, MYC drives RBPJ expression, whereas BET bromodomain inhibition reduces RBPJ levels in tumor-initiating cells (36). Hypoxia induces both RBPJ and MAML3 in PDAC cells, enabling RBPJ/MAML3-dependent activation of SMO transcription (37).

At the post-translational level, TRIM59 stabilizes RBPJ through K63-linked polyubiquitination, independent of Notch receptor activation (16). RBPJ binds SUMO2/3 and SUMO-modified PRC1.6 components facilitate its recruitment to Notch target genes (38). SUMOylation of the NICD RAM

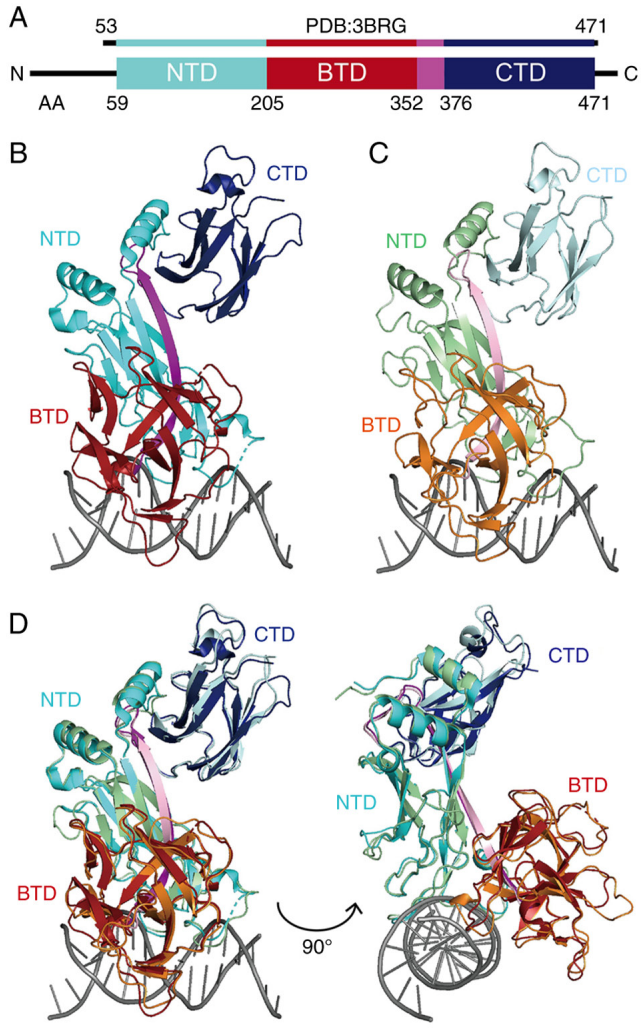


Figure 1. Structural comparison of mouse RBPJ and RBPJL. (A) Domain organization of RBPJ, comprising the NTD (cyan), BTD (red), linker region (magenta) and CTD (dark blue). (B) Crystal structure of RBPJ (aa 53-473; PDB: 3BRG) in complex with DNA (grey), visualized in PyMOL. (C) Predicted structural model of mouse RBPJL (aa 46-482; UniProt O08674), generated by the authors using SWISS-MODEL homology modeling and previously published in our earlier study (6). The crystal structure of mouse RBPJ/CSL bound to DNA (PDB: 3BRG) was used for structural alignment (template sequence identity, 55.5%; GMQE=0.69; QMEAN4 norm score=0.65, Z-score=−3.7). The model displays conserved domains: NTD (green), BTD (orange), linker (light pink) and CTD (light blue). (D) Structural alignment of RBPJ (cyan/red/pink/dark blue) and the predicted RBPJL (green/orange/light pink/light blue) in complex with DNA. The apparent absence of the ΦWΦP/RAM-binding pocket in RBPJL is a prediction derived from this homology model and awaits experimental validation. RBPJ, immunoglobulin κ J region; RBPJL, RBPJ-like protein; NTD, N-terminal domain; BTD, β-trefoil DNA-binding domain; CTD, C-terminal domain.

domain recruits HDAC4 under cellular stress and dampens Notch target gene expression (39). Conserved phosphorylation sites modulate Notch transcriptional activity (40). RBPJ also recruits CDK9-containing P-TEFb complexes to stimulate transcriptional elongation (36).

Epigenetic control differs between the two paralogs. The *Rbpjl* promoter carries H3K4me3 in differentiated acinar cells. In acinar-to-ductal metaplasia (ADM) and pancreatic cancer, it acquires H3K27me3 and H2AK119ub deposited by Polycomb complexes (41). Conversely, loss of RBPJ itself remodels the chromatin state of its target promoters, with enrichment of H4 acetylation and H3K4me3 and reduction of H3K9me3, which permits Notch-independent activation of former Notch target genes (42).

At the post-transcriptional level, the let-7a microRNA directly targets the RBPJ 3'UTR (43). SMAD3 forms a ternary complex with NICD and RBPJ that activates shared targets including *Hes1* (44). Stabilized β-catenin potentiates Notch/RBPJ-dependent *Hes1* transcription in neural precursor cells (45), illustrating functional cross-talk with the Wnt/β-catenin pathway. Most of these mechanisms were characterized in non-pancreatic systems. They define testable hypotheses for pancreatic development, inflammation and cancer.

3. Role of RBPJ and RBPJL in pancreatic development

The development of the pancreas is a highly ordered temporal process. It originates from the dorsal and ventral buds of the foregut endoderm, undergoing multiple stages of branching morphogenesis and cell fate determination, ultimately forming a mature organ with both endocrine and exocrine functions (9,46).

RBPJ and RBPJL are both DNA-binding subunits of the PTF1A transcription complex, but they govern distinct phases of pancreatic development (5). In the early stages of embryonic development (E9.5-E12.5), the mouse pancreas buds from the foregut endoderm. At this time, the PTF1A complex exists in the form of PTF1A-RBPJ (5,9,47). At E12.5, PTF1A-RBPJ binds to the PTF1A binding site on the *Rbpjl* promoter. With the accumulation of RBPJL, the proportion of PTF1A-RBPJL gradually increases to replace PTF1A-RBPJ. Once PTF1A-RBPJL becomes dominant, it drives acinar cells terminal differentiation and maintains acinar maturity (Fig. 2A) (5,9,10,47).

Disrupted regulation of RBPJ or RBPJL can directly lead to congenital developmental defects or dysfunctions of the pancreas. Thus, RBPJ provides the developmental foundation that is required for organ formation, whereas RBPJL drives terminal differentiation and functional specialization.

Dual regulatory mechanisms of RBPJ in early pancreatic development. At the Notch-dependent level, RBPJ precisely controls the timing and quantity of endocrine cell generation through lateral inhibition in multipotent progenitor cells (MPC; Fig. 2B) (48,49). Stochastic Neurog3 (Ngn3) initiation upregulates Notch ligands (Dll1, Jagged1), activating Notch receptors in neighboring cells (50-52). Upon ligand binding, Notch receptors undergo proteolytic cleavage, releasing the intracellular domain (NICD), which translocates into the nucleus and associates with RBPJ to form a transcriptional activation complex driving hairy and enhancer of split 1 (HES1) expression (48,53). HES1 directly suppresses *Ngn3* expression, thereby blocking endocrine differentiation in neighboring cells (49,54,55). Conversely, the initiating Ngn3-high cell preferentially completes endocrine commitment through positive feedback (50). RBPJ loss causes widespread *Ngn3* derepression and excessive endocrine cell generation (48). At the same time, the subsequent production of acinar cells is reduced due to the premature depletion of the progenitor cell pool (49,56). In

Table I. Comparison of structural, functional and expression characteristics of RBPJ and RBPJL.

Characteristics		RBPJ	RBPJL
Structural characteristics	Domain architecture	NTD, BTD and CTD (17,18)	NTD, BTD and CTD (6)
	Overall sequence homology	-	49% amino acid identity and 64% similarity to RBPJ (6)
	Crystal structures	Available[a]	No crystal structure determined (6); Homology model available (Fig. 1C)
	Critical functional residues	R218 (DNA binding); F261 and L388 (cofactor interaction) (17,18)	Corresponding residues R220, F262 and L393 are conserved (6,35)
	Linker sequence	Native	Sequence-divergent, length-conserved linker (6)
	ΦWΦP motif-binding surface	Intact; Binds RAM-domain proteins (17,18,21)	Non-conserved; Predicted to lack RAM-type binding (6,35)
Functional characteristics	Notch signaling	Core effector; Repressor and activator (1,22)	Notch-independent; Repressor only (6,35)
	Regulatory mode	Molecular switch: represses basal, activates upon Notch (2,22)	Constitutive repressor; no activation (6)
	NICD binding	High-affinity (18,21)	No NICD binding; no transactivation (6)
	Corepressor recruitment	Binds SHARP/SPEN; recruits NCoR/HDAC (22,35)	Retains SHARP binding; recruits repressive complexes (35)
	PTF1A complex	Pancreatic development (5,9)	Acinar-specific (5,10)
Expression characteristics	Tissue distribution	Ubiquitous (1)	Predominantly pancreas (5,6)
	Pancreatic cell types	Acinar, ductal, endocrine and mesenchymal cells (5,9)	Almost exclusively acinar cells (5,6,9)
	Developmental expression	Constitutive from embryonic stage through adulthood (9)	Low in embryonic stage; progressively upregulated postnatally (9,10)
	Adult expression level	Moderate and relatively stable (34)	Extremely high (9,10)
	Acute pancreatitis	Mildly upregulated or unchanged (15)	Markedly downregulated (13)
	Chronic pancreatitis	Relatively maintained or mildly altered (15,71)	Persistently low (12)
	PDAC tissue expression	Context-dependent; downregulated in ~40% of specimens; stabilized or upregulated by TRIM59 or hypoxia in others (15,16,37,42)	Downregulated or absent (6,12,70)
	PDAC cell line expression	Widely and highly expressed (16)	Nearly undetectable (6)

[a]RBPJ crystal structures are available at Protein Data Bank (PDB): 3BRG, 5EG6 and 2FO1. RBPJ, recombination signal binding protein for immunoglobulin κ J region; RBPJL, RBPJ-like protein; NTD, N-terminal domain; BTD, β-trefoil DNA-binding domain; CTD, C-terminal domain; RAM, RBPJ-associated molecule; ΦWΦP, hydrophobic-tryptophan-hydrophobic-proline motif; NICD, Notch intracellular domain; SHARP, SMRT/HDAC1-associated repressor protein; SPEN, split ends homolog; NCoR, nuclear receptor corepressor; HDAC, histone deacetylase; SMRT, silencing mediator for retinoid and thyroid hormone receptors; PTF1A, pancreas transcription factor 1a; PDAC, pancreatic ductal adenocarcinoma.

human embryos, RBPJ is co-expressed with PTF1A in ventral MPC, maintaining progenitor plasticity through canonical Notch signaling. As development progresses, mesenchymal DLK1-positive fibroblasts and JAG1-positive pericytes activate NOTCH1/2/3 receptors on trunk/duct lineage cells (57). Notch targets *HES1*, *HES4* and *HEY1* are markedly increased in the

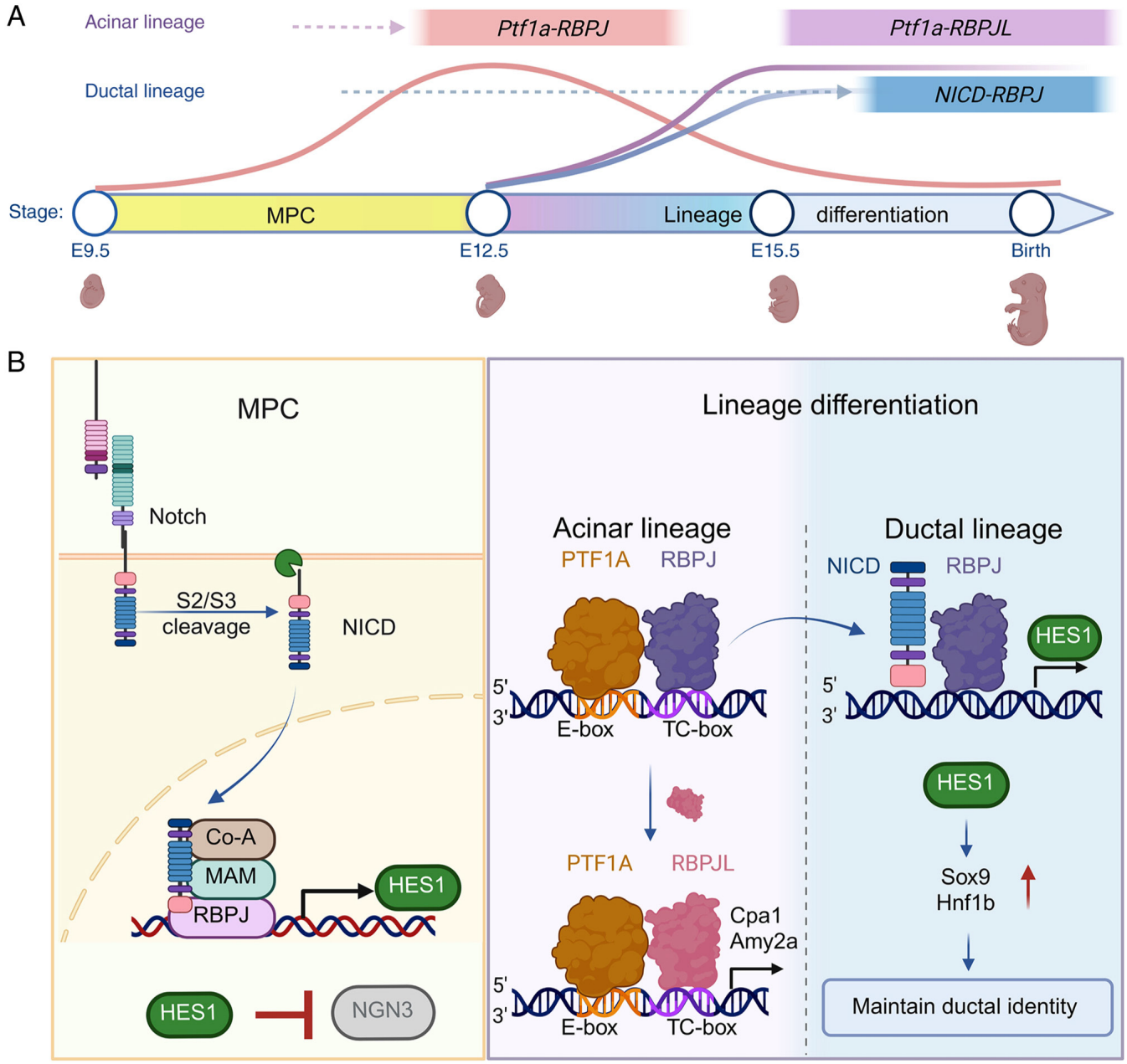


Figure 2. Divergent roles of RBPJ and RBPJL during pancreatic development. (A) During early pancreatic development (E9.5-E12.5), MPCs express the PTF1A-RBPJ complex, which initiates the acinar differentiation program by activating early target genes including *Cpa1* and *Amy2a*. Following the secondary transition (E12.5-E15.5), RBPJL progressively displaces RBPJ within the PTF1A complex. By birth, PTF1A-RBPJL dominates in the acinar lineage, where it drives terminal maturation and sustains high-level digestive enzyme expression. Concurrently, displaced RBPJ is redirected to canonical Notch signaling, where it partners with NICD to activate HES1 transcription and promote ductal lineage commitment. Thus, the RBPJ-to-RBPJL switch partitions the PTF1A complex into distinct lineage-specific configurations: PTF1A-RBPJL in acinar cells and NICD-RBPJ in ductal cells. (B) In MPCs, Notch receptor activation triggers sequential cleavage by ADAM protease and γ-secretase, releasing NICD. Nuclear NICD assembles a transcriptional activation complex with RBPJ and MAML1, driving *HES1* expression. HES1 directly suppresses *Ngn3* transcription, thereby restraining premature endocrine commitment and preserving the progenitor pool. During lineage differentiation, PTF1A-RBPJ binds bipartite DNA elements (PTF1A at the E-box; RBPJ at the TC-box) to specify acinar progenitors. As acinar maturation proceeds, RBPJL replaces RBPJ in the PTF1A complex to enforce terminal differentiation via *Cpa1* and *Amy2a* activation. The liberated RBPJ is instead recruited by NICD to sustain *HES1* expression, directing cells toward the ductal lineage. Created with BioRender.com. RBPJ, recombination signal binding protein for immunoglobulin κ J region; RBPJL, RBPJ-like protein; MPCs, multipotent progenitor cells; PTF1A, pancreas transcription factor 1a; NICD, Notch intracellular domain; ADAM, a disintegrin and metalloproteinase domain-containing protein; HES1, hairy and enhancer of split 1; MAML1, mastermind like transcriptional coactivator 1; Ngn3, neurogenin 3; Cpa1, carboxypeptidase A1; Amy2a, α-amylase 2A; Sox9, SRY-box transcription factor 9; Hnf1b, hepatocyte nuclear factor 1 homeobox B; Co-A, coactivator; MAM, mastermind.

ductal lineage, indicating the central role of RBPJ-mediated Notch signaling in maintaining ductal fate (57).

Independent of Notch signaling, RBPJ is the DNA-binding component of PTF1A to initiate the acinar differentiation program. PTF1A-RBPJ activates early acinar differentiation genes (such as *Cpa1*, *Amy2a*) while repressing non-pancreatic fate programs (such as hepatic gene programs) (5,8,9). RBPJ knockout results in early embryonic lethality (before E10.5), with death attributable to multi-systemic disorders including vascular developmental defects and neural tube closure

abnormalities (24,58). Pancreas-specific deletion of *Rbpj* (driven by *Pdx1-Cre* or *Ptf1a-Cre*) permits embryonic survival to birth but manifests severe pancreatic hypoplasia with reduced pancreatic volume and acinar cells. Endocrine cell numbers are also decreased but the relative proportion is increased. The ductal architecture is disorganized (8,56,59,60). Critically, the PTF1a W298A point mutation, which specifically disrupts the PTF1A-RBPJ interaction without affecting PTF1A-RBPJL binding, produces a phenotype highly similar to systematic *Rbpj* knockout (9,61). This proves that the physical interaction between RBPJ and PTF1A is indispensable for early pancreatic development that is independent of its role in canonical Notch signaling.

Progressive replacement of RBPJ by RBPJL in the PTF1A complex. During mouse E10.5-E12.5, the PTF1A complex is composed almost entirely of PTF1A-RBPJ. By E13.5-E15.5, as the *Rbpjl* gene is activated and RBPJL protein accumulates, the proportion of PTF1A-RBPJL gradually increases (62). At birth (P0), PTF1A-RBPJL has become the predominant form. In adulthood, PTF1A-RBPJL accounts for over 90%, while PTF1A-RBPJ resides only in rare cells or under specific physiological or pathological conditions (Fig. 2B) (10,61).

The molecular mechanism of this replacement has been elucidated. At the transcriptional initiation level, activation of the *Rbpjl* gene depends on binding of the early PTF1A-RBPJ complex. A small amount of RBPJL protein forms PTF1A-RBPJL, which binds the *Rbpjl* promoter more efficiently, thereby accelerating RBPJL accumulation. At the protein competition level, the affinity of RBPJL for PTF1A is slightly higher than that of RBPJ, allowing RBPJL to gradually outcompete RBPJ under dynamic equilibrium (5,10). These regulations ensure the precision and irreversibility of the replacement. Once PTF1A-RBPJL becomes dominant, acinar cells enter a stable terminally differentiated state (9,10,61).

Single-cell atlases have revealed the temporal switching mechanism of RBPJ/RBPJL in human embryos (57,63). During the early multipotent progenitor stage (post-conceptional week [PCW] 4-5), RBPJ is the sole expressed PTF1A complex component. As development progresses (PCW 7-11), RBPJL gradually upregulates in the tip/acinar lineage, while RBPJ persists in the trunk/duct lineage (57,64). This expression pattern switch closely matches lineage differentiation trajectories. RBPJL positive cells progressively acquire digestive enzyme gene expression (CPA2, CTRB2, CLPS), differentiating toward mature acinar cells. However, RBPJ positive cells maintain ductal characteristic gene expression such as *SOX9* and *HES1*/*HES4* (57). The study also found that human acinar cells still lack amylase gene expression at PCW 11, suggesting delayed acinar maturation in humans compared with mice and that RBPJL-driven terminal differentiation programs may be subject to species-specific regulation (57).

RBPJL as the terminal differentiation switch for acinar cell maturation. Once PTF1A-RBPJL complex dominance is established, the complex drives acinar cells into a terminally differentiated state and maintains their mature phenotype (10,61). RBPJL, as a digestive system-specific PTF1A complex component, has its expression timing strictly restricted to the late stage of acinar lineage differentiation (6).

In *Rbpjl* knockout mice, acinar differentiation is arrested accompanied by profound transcriptional repression of digestive enzyme genes, genes responsible for regulated exocytosis machinery as well as mitochondrial metabolism-related transcripts. Furthermore, *Rbpjl* deficiency leads to the ectopic expression of liver-specific mRNAs in the pancreas, suggesting that PTF1A-RBPJL actively suppresses a hepatocyte-like phenotype and thereby enforces strict maintenance of acinar cell identity (8,10,61).

In differentiated acinar cells, *Rbpjl* maintains high-level expression with active chromatin signatures (H3K4me3 enrichment), whereas in disease states such as ADM and pancreatic cancer, its promoter acquires repressive H3K27me3 and H2AK119ub marks mediated by Polycomb complexes (41).

During human pancreatic embryogenesis, transcriptional activation of RBPJL demarcates a critical functional shift of the PTF1A complex from the progenitor-preserving configuration (PTF1A-RBPJ) toward the differentiation-executing form (PTF1A-RBPJL). Single-cell data provide precise temporal coordinates for the transition along the tip to acinar differentiation trajectory (57,63). RBPJL expression progressively increases, co-expressing with digestive enzyme genes to form a stable acinar characteristic gene module. In the acinar lineage, the *RBPJL* locus has lineage-specific chromatin accessibility, suggesting that its expression is regulated by lineage-specific enhancers (57,63). This finding mirrors the established role of PTF1A-RBPJ in initiating *Rbpjl* transcription during early development, thereby establishing a coherent developmental regulatory chain that sequentially links RBPJ-dependent priming to RBPJL-driven terminal differentiation.

4. Role of RBPJ and RBPJL in pancreatitis

Pancreatitis is the most common pancreatic inflammatory disorder and is usually associated with edema, immune cell infiltration and even necrosis (65,66). Sustained inflammation could lead to chronic pancreatitis (CP) accompanied by acinar cell loss and fibrosis (67), which is considered as a risk factor for the development and acceleration of PDAC (68,69).

RBPJ in Pancreatitis. RBPJ is dispensable for acinar cell homeostasis under baseline conditions, but becomes a critical regulator upon injury (15). RBPJ deficiency lowers the threshold for ADM under inflammatory stress and delays the pancreatic regeneration process in acute pancreatitis (AP). However, in the context of $KRAS^{G12D}$ co-expression, pancreatic repair function is severely impaired, leading to persistent ADM and fibrosis, therefore increasing the risk of chronicity (15).

Notch signaling is robustly reactivated in CP with the upregulation of Notch receptors (Notch2, Notch3, Notch4) and ligands (Jagged-1, Jagged-2, Delta-1) (70). Pathological stimuli commonly associated with CP, including hyperglycemia, steroids and bile acids, can directly activate Notch signaling in resident pancreatic cells. Notably, high glucose levels are associated with increased collagen-I production in this context, whereas Jagged1 itself may exert a moderating effect on collagen induction (71). Within the fibrotic stroma, Notch3 is markedly enriched in activated pancreatic stellate cells (PSCs) and drives a-SMA expression and collagen

synthesis. Genetic inhibition of Notch3 by siRNA suppresses PSC activation, proliferation and migration and attenuates fibrogenic potential (72).

As the canonical transcriptional executor of Notch-RBPJ signaling, HES1 is positioned at the nexus of pancreatic injury responses. Sustained HES1 activation locks epithelial cells in a de-differentiated ADM state and promotes progressive fibrosis (15,73). It is therefore conceivable that transient HES1 induction may be necessary for efficient exocrine regeneration after acute damage, whereas its persistent activation drives chronicity. However, direct functional evidence for the transient beneficial role of HES1 in AP regeneration remains to be established.

In addition, the fibrogenic output of Notch-RBPJ signaling may be amplified through cross-talk with the TGF-b/Smad axis, as demonstrated by the formation of a pSmad3-NICD-RBPJ ternary complex that synergistically activates shared transcriptional targets including HES1 (44). However, this molecular integration has been characterized primarily in non-pancreatic cell systems. TGF-b-induced epithelial plasticity is functionally dependent on Notch activity in mammary and skin epidermal cell lines (74), but whether this Notch dependency operates in pancreatic epithelial cells has not been directly tested. TGF-b transcriptionally upregulates Jagged1 and, in specific epithelial contexts, Notch4 (74). Notch2 overexpression in CP tissue may reflect the integrated response to multiple profibrotic stimuli including TGF-b (71), although direct transcriptional induction of Notch2 by TGF-b in pancreatic cells remains to be demonstrated.

Anti-inflammatory function of RBPJL. RBPJL is markedly downregulated in AP. In experimental AP models, RBPJL mRNA and protein levels are markedly decreased in pancreatic tissues and LPS-stimulated acinar cells (13). RBPJL binds the *Arid5a* promoter and suppresses its transcription (13). ARID5A, in turn, stabilizes IL-6 mRNA by binding to its 3'UTR, promoting IL-6 protein overexpression and activating JAK/STAT3 pathway (75). Overexpression of RBPJL decreases the level of ARID5A and inhibits IL-6/STAT3 signaling. It reduces acinar cell inflammatory injury and oxidative stress and improves pancreatic histopathology in AP models (13). In addition, RBPJL has been known to maintain transcriptional repression of Notch target genes (*Hey1*, *Hey2*, *HeyL*, *Notch3*) through the SHARP corepressor (6). Therefore, RBPJL exerts its effects in acinar cells through at least two distinct mechanisms. On one hand, RBPJL directly suppresses the transcription of the pro-inflammatory Arid5a/IL-6/STAT3 axis. On the other hand, it inhibits Notch target genes in a SHARP-dependent manner. During acute pancreatitis, the downregulation of RBPJL may simultaneously weaken both aspects of inhibition, thereby potentially promoting the de-repression of *Hes1* and related genes. However, direct evidence linking the two is currently lacking.

5. Role of RBPJ and RBPJL in pancreatic ductal adenocarcinoma

PDAC arises in the exocrine compartment of the pancreas characterized by ductal differentiation, hypovascularity and strong desmoplasia (76). There are several precursor lesions, including pancreatic intraepithelial neoplasia (PanINs), intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs) (77-79). The most common precursor lesion is PanIN. PDAC development is a multi-stage process that is initiated by mutations in the *Kras* gene that are acquired in over 90% of PDAC patients (80). As a result, acinar cells de-differentiate into precursors through ADM, which then develop into pancreatic duct cells, expand and thereby trigger PanINs (81). With the accumulation of further mutations (such as in the genes for CDKN2A, TP53 or SMAD4) and re-activation of embryonic signaling pathways such as Notch signaling (52,73,82), PDAC ultimately emerges from these precursors (Fig. 3A).

RBPJ loss accelerates KRAS-driven tumorigenesis. RBPJ is frequently depleted in human tumors (42,83,84). Its loss derepresses target gene promoters through epigenetic remodeling (enrichment of H4ac and H3K4me3, reduction of H3K9me3), permitting NF-kB and MYC to activate Notch target genes (such as *HEY1* and *HEY2*) in a Notch-independent manner, thereby promoting tumor cell survival and growth (Fig. 3B) (42).

A clinical study showed that RBPJ is markedly downregulated in ~40% of human PDAC specimens (15). Conditional knockout of RBPJ in adult acinar cells (*Ptf1a-Cre^{ERT}*) does not perturb baseline pancreatic homeostasis, indicating that RBPJ is dispensable for acinar cell maintenance (15,68). However, upon oncogenic KRAS^{G12D} co-expression, RBPJ deficiency markedly accelerates PanIN formation and exhibits high-grade PanIN-2/3 lesions (15). This accelerated tumorigenesis is accompanied by massive desmoplastic stroma formation (15). At the molecular level, RBPJ loss derepresses Notch target genes including *Hes1* and *Hey1* (15). This persistent low-level Notch output synergizes with KRAS signaling to promote ADM and altered cell-microenvironment interactions.

TRIM59 stabilizes RBPJ to promote gemcitabine resistance. PDAC is often diagnosed at an advanced stage. Radiotherapy and resection show low efficacy at this stage and have little influence on survival. Gemcitabine remains a first-line chemotherapeutic agent for PDAC, yet acquired resistance limits clinical efficacy.

TRIM59 is an E3 ubiquitin ligase that is frequently overexpressed in PDAC and correlates with poor prognosis. TRIM59 directly interacts with RBPJ and promotes K63-linked polyubiquitination, thereby enhancing RBPJ protein stability and preventing proteasomal degradation (Fig. 3B) (16). The stabilized RBPJ protein subsequently binds to the TRIM59 gene promoter and activates its transcription, forming a self-sustaining positive feedback loop. Notch target genes including *Hes1*, *Hey1*, *Myc* and *Snai1* are upregulated, promoting tumor cell proliferation, survival and epithelial-mesenchymal transition. TRIM59 depletion reduces RBPJ protein levels and restores gemcitabine sensitivity, whereas RBPJ overexpression rescues the TRIM59-depletion phenotype (16). Catechin disrupts the TRIM59-RBPJ interaction, successfully reduces RBPJ protein levels and resensitizes PDAC cells to gemcitabine (16).

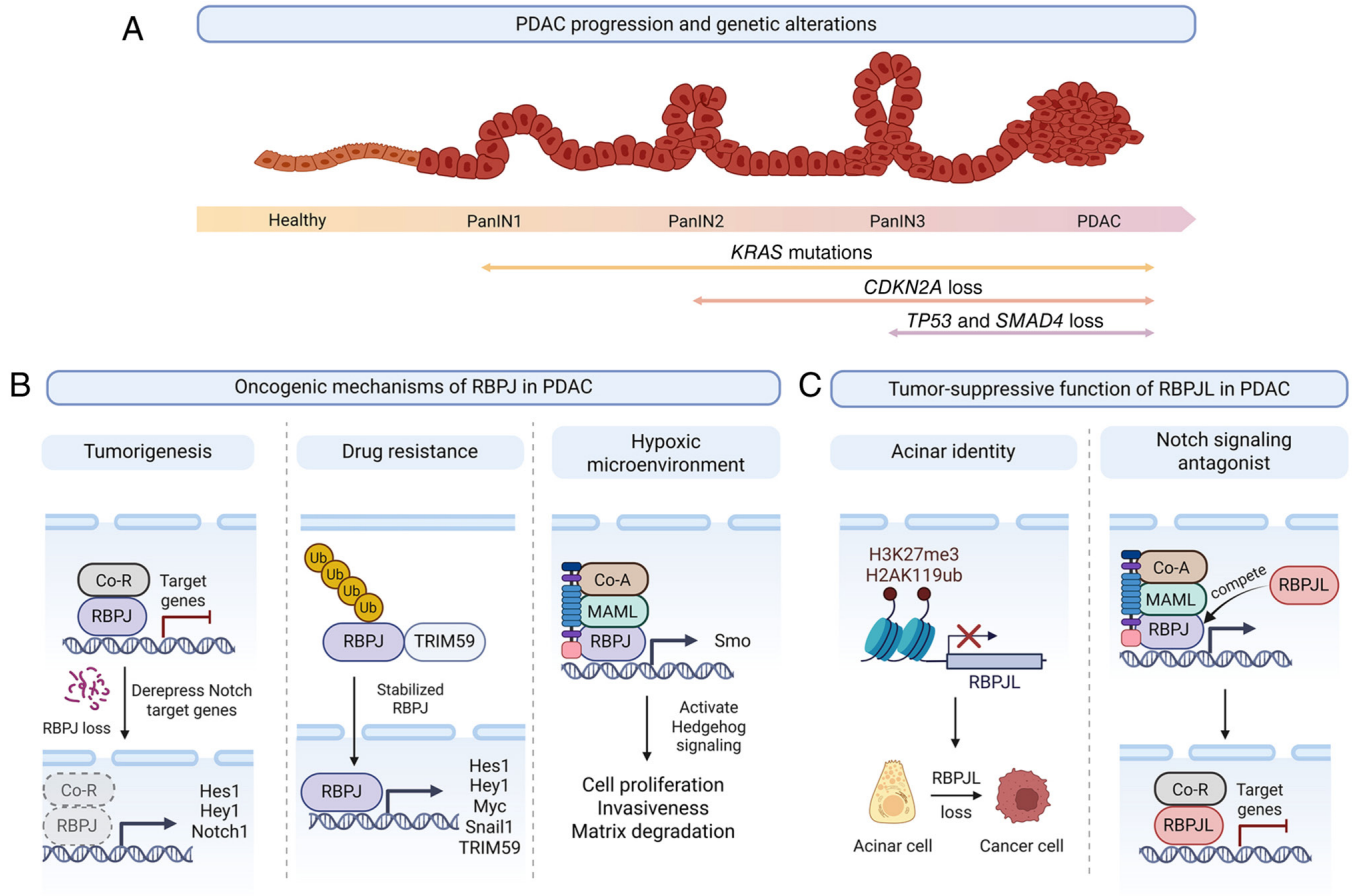


Figure 3. The role of RBPJ and RBPJL in PDAC. (A) Genetic progression model of PDAC. Upon sustained oncogenic KRAS expression, acinar cells (pink) can be reprogrammed into duct-like cells, subsequently initiating PanIN1 formation. With the accumulation of further genetic alterations (such as CDKN2A loss, TP53 mutations and SMAD4 deletion), PanINs progress further (PanIN2 and 3), ultimately developing into PDAC. (B) RBPJ exerts context-dependent oncogenic functions in PDAC. RBPJ deficiency derepresses Notch target genes (*Hes1*, *Hey1*) accelerating $KRAS^{G12D}$-driven PanIN formation. TRIM59-mediated K63-linked polyubiquitination stabilizes RBPJ, which in turn activates TRIM59 forming a positive feedback loop. Stabilized RBPJ also drives *Hes1*, *Hey1*, *Myc*, *Snail1* gene expression, promoting gemcitabine resistance. Under a hypoxic microenvironment, RBPJ/MAML3 complex activates SMO transcription to cross-activate Hedgehog signaling, enhancing proliferation, invasiveness and MMP-2-mediated matrix degradation. (C) Tumor-suppressive function of RBPJL in PDAC. RBPJL expression is markedly lost in PDAC. Epigenetic silencing by repressive histone modifications (H3K27me3, H2AK119ub) at the *Rbpjl* promoter contributes to its downregulation, resulting in acinar identity loss. RBPJL competes with RBPJ for canonical CSL binding sites on Notch target gene promoters, effectively blocking Notch signaling in cancer cells. Created with BioRender.com. RBPJ, recombination signal binding protein for immunoglobulin κ J region; RBPJL, RBPJ-like protein; PDAC, pancreatic ductal adenocarcinoma; KRAS, Kirsten Rat Sarcoma viral oncogene homolog; PanIN1, pancreatic intraepithelial neoplasia; CDKN2A, cyclin dependent kinase inhibitor 2A; TP53, tumor protein p53; SMAD4, SMAD family member 4; HES1/Hes1, hairy and enhancer of split 1; Hey1, hes related family bHLH transcription factor with YRPW motif 1; TRIM59, tripartite motif containing 59; Myc, myelocytomatosis proto-oncogene; Snai1, snail family transcriptional repressor 1; MAML3, mastermind like transcriptional coactivator 3; SMO, smoothened; MMP-2, matrix metalloproteinase-2; H3K27me3, histone H3 lysine 27 trimethylation; H2AK119ub, histone H2A lysine 119 monoubiquitination; CSL, CBF1/suppressor of hairless/Lag-1; Co-A, coactivator; MAML, mastermind-like; Co-R, corepressor; Ub, ubiquitin.

RBPJ upregulation in hypoxic microenvironment cross-activates Hedgehog signaling. As well as its loss-of-function effects, RBPJ upregulation in the hypoxic tumor microenvironment promotes PDAC progression through cross-activation of Hedgehog signaling. Hypoxia induces RBPJ and MAML3 expression in PDAC cells and the RBPJ/MAML3 complex directly activates transcription of Smoothened (SMO), the key transducer of Hedgehog signaling (Fig. 3B) (37). This Notch-Hedgehog cross-talk is specific to hypoxic conditions and enhances tumor cell proliferation, invasiveness and MMP-2-mediated matrix degradation. Xenograft experiments confirmed that RBPJ knockdown suppresses tumorigenicity under hypoxic conditions (37). This mechanism reveals that RBPJ functions as a hub integrating Notch and Hedgehog pathways in response to microenvironmental oxygen deprivation.

RBPJL expression loss in PDAC. In contrast to the oncogenic role of RBPJ, RBPJL demonstrates significant expression loss in PDAC (12,70). RBPJL is specifically expressed in the exocrine pancreas, whereas it is mostly undetectable in pancreatic tumor cell lines including PANC-1, MIA PaCa-2, BxPC-3, AsPC-1 and Capan-1 (6). This lack of expression reflects the loss of acinar differentiation identity that characterizes PDAC (Fig. 3B). The downregulation of RBPJL in PDAC likely results from the disruption of the PTF1A complex, as tumor cells typically lose PTF1A expression, leading to loss of the major transcriptional activator for the *Rbpjl* promoter (6). Additionally, epigenetic silencing through polycomb-mediated repressive histone modifications (H3K27me3, H2AK119ub) at the *Rbpjl* promoter has been documented in ADM and pancreatic cancer cells (41), suggesting a multi-layered suppression mechanism.

It is conceivable that forced restoration of RBPJL expression in PDAC cell lines would inhibit proliferation and tumor growth by reconstituting Notch target gene silencing. However, direct functional evidence from PDAC cell line overexpression experiments and xenograft models is currently lacking.

RBPJL as an endogenous Notch inhibitor. The tumor-suppressive function of RBPJL centers on its identity as an endogenous Notch signaling antagonist. RBPJL competes with RBPJ for binding to canonical CSL DNA elements on Notch target gene promoters (Fig. 3B). Importantly, RBPJL is unable to interact with NICD1-4 and does not support Notch-mediated transactivation. Instead, RBPJL interacts with the SHARP/SPEN corepressor, the central corepressor of the Notch pathway, to recruit HDAC-containing repressive complexes and maintain target gene silencing. In RBPJ-depleted HeLa cells, RBPJL can fully reconstitute transcriptional repression at endogenous Notch target genes including *HES1*, *HEY1*, *HEY2* and *HEYL*. By competing with RBPJ for promoter occupancy while being unable to mediate Notch activation, RBPJL effectively blocks the Notch signaling output in cells where it is expressed (6).

In human PDAC specimens, the Notch ligand Jagged1 is frequently overexpressed (85) and Notch target genes *HES1* and *HEY1* demonstrate sustained activation, correlating with tumor proliferation, survival and poor prognosis (86,87). RBPJL loss in PDAC therefore removes a constitutive brake on Notch signaling, contributing to the pathway dysregulation observed in this malignancy.

Functional antagonism between RBPJ and RBPJL. The opposing roles of RBPJ and RBPJL establish a functional balance that determines cellular fate in the pancreas. In normal acinar cells, PTF1A-RBPJL dominates and maintains terminal differentiation while suppressing Notch target genes. During PDAC development, the transition from PTF1A-RBPJL to PTF1A-RBPJ persistence correlates with de-differentiation and Notch pathway activation.

The reciprocal expression pattern positions the RBPJ/RBPJL balance as a potential molecular indicator of Notch signaling state. The functional significance of this antagonism lies in the competition between the two paralogues for shared binding sites and cofactors, with RBPJL serving as a differentiation safeguard whose loss sensitizes acinar cells to RBPJ-mediated oncogenic programs.

Collectively, the aforementioned evidence reconciles the two seemingly opposing roles of RBPJ in PDAC: its function is context-dependent and stage-specific. At tumor initiation, RBPJ acts as a tumor suppressor and its loss in acinar cells promotes ADM and $KRAS^{G12D}$-driven PanIN formation (as aforementioned). In established tumors, RBPJ acquires oncogenic properties through TRIM59-mediated post-translational stabilization and hypoxia-induced upregulation, promoting proliferation, invasion and gemcitabine resistance (16,37). Accordingly, the downregulation of RBPJ in a subset of PDAC specimens reflects its tumor-suppressive role at the initiation stage rather than contradicting its oncogenic functions in established tumors (Table I) (15).

6. Therapeutic and pharmacological targeting of the RBPJ/RBPJL axis

The distinct and often opposing roles of RBPJ and RBPJL suggest several strategies for therapeutic intervention. None of these strategies has entered routine clinical use.

The natural polyphenol catechin directly targets oncogenic RBPJ. It disrupts the TRIM59-RBPJ interaction, reduces RBPJ protein levels and resensitizes PDAC cells to gemcitabine in preclinical models (16). It indicates that RBPJ protein stability can be pharmacologically controlled independently of Notch receptor activity.

γ-Secretase inhibitors (GSIs) block RBPJ activation indirectly by preventing NICD release and abolishing NICD-RBPJ-mediated transactivation. In genetically engineered mouse models of PDAC, GSI treatment inhibited tumor progression, particularly in combination with gemcitabine (88). These preclinical findings prompted a phase I trial of the GSI MK-0752 combined with gemcitabine in patients with PDAC. The two agents could be combined safely at their full single-agent recommended phase II doses (89). Notch pathway activity was suppressed in hair follicles in most patients. However, Notch target gene modulation was not confirmed in paired tumor biopsies (89). The GSI RO4929097 was well tolerated in phase I studies of patients with advanced solid tumors, but showed limited activity in a phase II study of previously treated metastatic PDAC (90,91). The clinical utility of GSIs has been limited by on-target toxicities, including gastrointestinal toxicity and goblet cell metaplasia, which has motivated intermittent dosing schedules and the development of more selective Notch component inhibitors.

Notch receptor- and ligand-targeted antibodies offer more pathway-selective alternatives to GSIs. The anti-Notch2/3 antibody tarextumab inhibited tumor growth and reduced tumor-initiating cell frequency in preclinical PDAC models (92). However, a randomized phase II trial showed no benefit over gemcitabine plus nab-paclitaxel and progression-free survival was markedly worse in the tarextumab arm (93). This negative result underscores the need for biomarker-guided patient selection.

Restoring RBPJL expression offers a complementary approach that does not require RBPJ inhibition. Silencing of *Rbpjl* in ADM and PDAC is maintained by Polycomb-dependent repressive histone marks, including H3K27me3 deposited by the enhancer of zeste homolog 2 (EZH2)-containing PRC2 complex (41). Inhibition of EZH2 is therefore a rational strategy to de-repress *Rbpjl* and re-establish acinar differentiation. The EZH2 inhibitors GSK126 and tazemetostat reduce H3K27me3 levels and reactivate epigenetically silenced genes in PDAC models (94). However, direct restoration of RBPJL expression by EZH2 inhibition remains to be demonstrated.

Several challenges temper these opportunities. RBPJ restrains tumor initiation but promotes growth, invasion and chemoresistance in established tumors. Therapies directed at RBPJ or Notch signaling will therefore need to be stage-specific and biomarker-guided. Systemic Notch blockade must also be weighed against the homeostatic roles of Notch signaling in the pancreas and other organs. Forced restoration of RBPJL and catechin-based disruption of the TRIM59-RBPJ axis require rigorous *in vivo* validation before clinical translation.

To date, no Notch-pathway-directed agent has demonstrated clinical benefit in PDAC. Future progress will depend on stage-specific biomarkers and preclinical models.

7. Conclusion

RBPJ and RBPJL serve distinct and complementary roles in pancreatic biology across development, inflammation and malignancy. RBPJ functions as a dual Notch effector capable of transcriptional switching. RBPJL is a pancreas-specific, Notch-blind obligate repressor that competes for DNA occupancy without supporting signal transduction.

During pancreatic development, the sequential transition from PTF1A-RBPJ to PTF1A-RBPJL complexes drives terminal acinar differentiation. In pancreatitis, RBPJ deficiency lowers the threshold for ADM and cooperates with oncogenic stress to perpetuate fibrotic remodeling, whereas RBPJL downregulation relieves suppression of the ARID5A/IL-6/STAT3 pro-inflammatory axis. In PDAC, RBPJL is usually silenced potentially through Polycomb-mediated repressive modifications. RBPJ is downregulated in a subset of tumors. Its loss derepresses Notch target gene, synergizing with KRAS to accelerate PanIN formation. However, in established tumors, RBPJ acquires oncogenic functions through TRIM59-mediated stabilization and hypoxia-induced activation of Hedgehog signaling, promoting proliferation, invasion and gemcitabine resistance. Elucidating how RBPJ and RBPJL function in native pancreatic epithelium and how they compete for promoter occupancy *in vivo* remains an important frontier. Progress in this area will refine current models of how this axis governs acinar cell identity and disease progression.

Therapeutically, the RBPJ/RBPJL axis can be engaged at multiple levels. Catechin disrupts the TRIM59-RBPJ interaction and resensitizes PDAC cells to gemcitabine. GSIs and Notch-targeted antibodies block upstream pathway activation, although none has demonstrated clinical benefit to date. EZH2 inhibition offers a rationale for restoring RBPJL expression. The context-dependent, stage-specific functions of RBPJ demand biomarker-guided application of these strategies.

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Authors' contributions

Conceptualization was performed by LP, HZ, YL and TC. Writing and original draft preparation was performed by LP. Writing, reviewing and editing was conducted by TC. LP and TC acquired funding. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Conflict of interests

The authors declare that they have no competing interests.

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