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Loss of insulin receptor isoform B impairs proinsulin processing in pancreatic β cells

Eukaryotic pre-mRNA is a primary transcript synthesized from DNA, where exons are separated by introns ranging in length from hundreds to thousands of nucleotides long. For each expressed pre-mRNA, its exons must be joined together to maintain the reading frame—the continuous sequence that encodes proteins [1]. Alternative splicing (AS) is a prevalent post-transcriptional regulatory mechanism that allows a single gene to generate multiple mRNAs, resulting in functionally distinct protein isoforms. Transcriptome data from high-throughput sequencing indicate that 92–94 % of human genes undergo AS, highlighting its significant contribution to proteome diversity, as well as developmental and phenotypic plasticity [1,2]. Studies have found that AS events influence numerous important phenotypes, including neurodevelopment, muscle function, and pigmentation [3–5]. Dysregulation of AS contributes to cancer development, underscoring its clinical relevance. Consequently, therapeutic strategies targeting aberrant splicing isoforms in cancer have garnered significant interest in recent years [6,7]. Nevertheless, our understanding of the role of AS-generated protein isoforms in metabolism remains inadequate.

The insulin receptor (INSR, IR) undergoes alternative splicing to produce two isoforms, IRA and IRB. These isoforms differ solely in Exon 11, which is omitted in IRA but retained in IRB [8,9]. Clinically, IRA is more frequently found in embryonic and tumor tissues and mediates mitogenic effects, whereas IRB is predominantly expressed in insulin-target tissues and mediates metabolic effects [10–12]. The ratio of these two isoforms is dynamic yet strictly regulated across different organs and tissues. Given the pivotal role of IR in insulin signaling and the development of insulin resistance, the isoform-specific functions of IRA and IRB remain a fundamental question in the field of metabolism. Owing to the technical hurdles of editing Exon 11 of the IR gene, current research has been confined to cell line-based studies aimed at distinguishing the functions of these two isoforms. However, the pathophysiological roles of IR isoforms *in vivo* remain unclear.

In a recent study published in *iScience* [13], Wu et al. constructed the IRB Flox mouse model and specifically knocked out IRB in β-cells to investigate its impact on glucolipid metabolism and proinsulin processing. Their findings revealed that βIRBKO mice displayed worsened hyperproinsulinemia, insulin resistance, and glucose intolerance in diet-induced obesity. The secretion level of proinsulin was significantly elevated in βIRBKO mice under glucose challenge, and the P/I ratio in the primary islets of βIRBKO mice was notably increased. Moreover, transmission electron microscopy (TEM) analysis of isolated islets showed a significantly higher density and lower maturation rate of secretory granules (SGs), suggesting that the excessive accumulation of proinsulin in the β-cells of obese βIRBKO mice is attributable to a disruption in proinsulin processing.

Within secretory granules, prohormone convertases (PC1/3, PC2) and carboxypeptidase E (CPE) process proinsulin into mature insulin, which is stored in vesicles and released upon stimulation [14]. Tight regulation of PC1/3, PC2, and CPE is essential for insulin maturation. In this study, among the three key hydrolases, only a decrease in CPE protein levels was detected, potentially leading to impaired proinsulin processing. Despite the unaltered gene transcription, the reduced CPE protein levels implied a post-transcriptional regulation. The eukaryotic translation initiation factor (eIF4F) is a heterotrimer complex composing of eIF4G, eIF4E and eIF4A, which is required for cap-dependent translation initiation. Researchers discovered significant downregulation of eIF4G1, which may be responsible for the reduced CPE in IRB-deficient β cells. Transcriptomics revealed that the transcriptional repressor of eIF4G1, sterol-regulatory element-binding protein 1 (SREBP1), was significantly upregulated. A specific inhibitor of SREBP1 activation could alleviate the reduction of CPE and the accumulation of proinsulin in β cells. After IRB deletion in β cells, IRA responded to proinsulin signaling and activated extracellular signal-regulated kinase (ERK) through insulin receptor substrate 1 (IRS-1), augmenting the stability of SREBP1-N, which leads to aggravated β-cell lipotoxicity. Loss of IRB downregulated eIF4G1 expression by stabilizing SREBP1, thereby hindering the translation of CPE. Furthermore, excessive autocrine proinsulin in βIRBKO mice enhanced the activity of ERK through the remaining IRA to further stabilize nuclear SREBP1, thereby establishing a feedback loop.

These results highlight the crucial role of IRB in insulin processing and secretion efficiency, protecting β cells from lipotoxicity in obesity. This study provides novel insights into the isoform-specific function of IR *in vivo* (Fig. 1).

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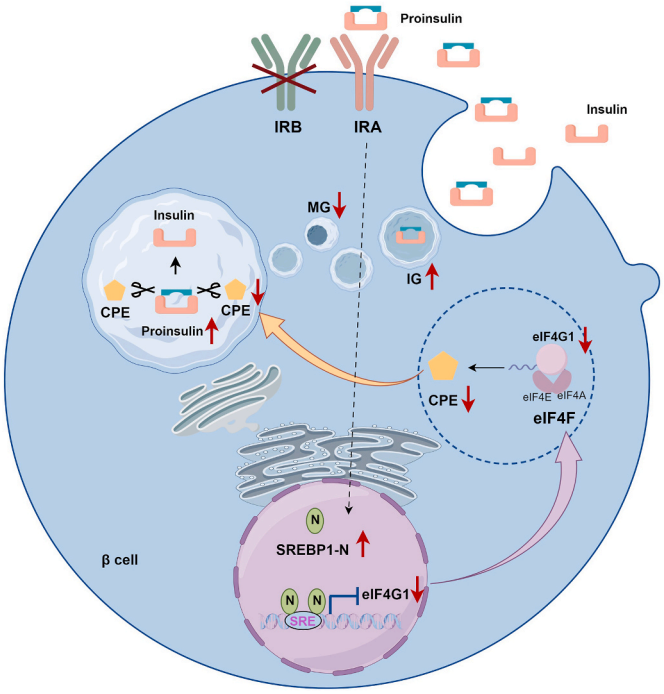

Fig. 1. Molecular mechanisms underlying impaired proinsulin processing in IRB-deficient β cells: In IRB-deficient β cells, proinsulin exhibits a stronger affinity towards IRA, towards in increased levels of SREBP1-N in the nucleus. SREBP1-N binds to the promoter of eIF4G1, repressing its expression. The decrease in eIF4G1 hinders the translation of CPE, reducing its levels and leading to impaired proinsulin processing. Consequently, proinsulin is secreted extracellularly in the form of immature granules (IGs). Proinsulin subsequently binds to IRA, forming a feedback loop.

CRediT authorship contribution statement

Hanrui Yin: Writing – original draft. **Suzhen Chen:** Writing – review & editing. **Junli Liu:** Writing – review & editing.

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