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**Targeting neuronal PAS domain protein 2 and KN motif/ankyrin repeat domains 1:
Advances in type 2 diabetes therapy**

NPAS2, KANK1 in T2D therapy

Chun-Han Cheng, Wen-Rui Hao, Tzu-Hurng Cheng

Abstract

This editorial summarizes the latest literature on the roles of neuronal PAS domain protein 2 and KN motif/ankyrin repeat domain 1 in type 2 diabetes. We highlight their involvement in β -cell dysfunction, explore their potential as therapeutic targets, and discuss the implications for new treatment strategies. We offer valuable insights into relevant gene regulation and cellular mechanisms relevant for the targeted management of type 2 diabetes.

Key Words: Type 2 diabetes; Neuronal PAS domain protein 2; KN motif and ankyrin repeat domain 1; β -cell dysfunction; Therapeutic target

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Core Tip: This editorial explores the pivotal roles of NPAS2 and KANK1 in type 2 diabetes. It elucidates their contribution to β -cell dysfunction, highlighting their

potential for targeted therapies. Insights from this editorial may guide the development of innovative treatment approaches against type 2 diabetes.

INTRODUCTION

The fight against type 2 diabetes (T2D) has gained momentum with new discoveries about the genetic and molecular foundations of this widespread disease. A study by Yin *et al.*, published in the *World Journal of Diabetes*, emphasized the importance of the transcription factor neuronal PAS domain protein 2 (NPAS2) and its downstream target KN motif/ankyrin repeat domain 1 (KANK1) in the dysfunction of pancreatic β -cells, a key event in the development of T2D[1]. Given that β -cell dysfunction is central to T2D pathogenesis, understanding these regulatory mechanisms is crucial for advancing therapeutic interventions. NPAS2, a component of the circadian clock system, regulates various physiological processes, including glucose metabolism[2]. Discovery of its role in β -cell function and insulin secretion has opened new avenues for diabetes research. Yin *et al.* demonstrated how NPAS2 modulates *KANK1* expression, thereby affecting the structural and functional integrity of β -cells. KANK1 is crucial for maintaining cell adhesion and cytoskeletal dynamics, both essential for β -cell function[3]. The interaction between KANK1 and focal adhesion proteins influences the stability and organization of microtubules and actin filaments, thereby affecting insulin secretion[4]. Changes in *KANK1* expression can disrupt these processes, causing β -cell malfunction and accelerating T2D development. This editorial contextualizes these findings within the broader scope of T2D research. By exploring the complex pathways involving NPAS2 and KANK1, we can better understand their implications for new T2D therapies. The study by Yin *et al.* underscores the need for probing these molecular pathways to preserve β -cell function and improve T2D outcomes.

ROLE OF NPAS2 IN β -CELL DYSFUNCTION

Yin *et al.* (2024) highlighted the vital role of NPAS2 in the dysfunction of β -cells in T2D[1]. The expression of *NPAS2* was upregulated in the islet β -cells of mice with T2D.

Upregulation of *NPAS2* regulated the expression of *KANK1*, a gene essential for cellular structure and function. Yin *et al.* (2024) demonstrated that *NPAS2* overexpression was correlated with elevated *KANK1* Levels, contributing to β -cell apoptosis and impaired insulin secretion. These findings suggest that *NPAS2* is a central regulator of β -cell health, and its dysregulation can drive the progression of T2D[1]. *KANK1* is involved in several cellular processes, including protein binding, mechanical force sensing, and phase separation, that are crucial for maintaining cellular integrity and function[3]. Specifically, *KANK1* shapes focal adhesions, which are essential for cell signaling and structural support[4]. In addition, these adhesions are integral to β -cell function because they form “secreting adhesions,” which are essential for insulin secretion[5]. The interactions between *KANK1* and other cellular components, such as cortical complexes regulating insulin secretion, underscore its importance in maintaining the functionality of β -cells[6]. Dysregulation of these interactions due to *NPAS2* overexpression disrupts the delicate balance needed for effective insulin secretion, thus promoting β -cell dysfunction in T2D. The findings of Yin *et al.* are supported by structural studies on *KANK1*, which revealed its role in coordinating the actin and microtubule cytoskeletons at focal adhesions; this coordination is crucial for maintaining cellular architecture and function[7]. Disruptions in these structures due to *NPAS2*-induced overexpression of *KANK1* lead to cellular dysfunction, facilitating the development of T2D. In summary, *NPAS2* serves as a major regulator of β -cell health by modulating *KANK1* expression. The upregulation of *NPAS2* expression in T2D upregulates the expression of *KANK1*, disrupting cellular architecture and function and thus causing β -cell apoptosis and impaired insulin secretion. These insights deepen our understanding of the molecular mechanisms underlying β -cell dysfunction in T2D and highlight the potential of *NPAS2* and *KANK1* as therapeutic targets against T2D progression.

KANK1 AS A DOWNSTREAM EFFECTOR

KANK1, a downstream target of *NPAS2*, contributes to β -cell dysfunction in T2D (Figure 1). Evidence suggests a significant correlation between *NPAS2* expression and

KANK1 expression in T2D, highlighting a potential pathway for therapeutic intervention[1]. Specifically, *KANK1* regulates cellular adhesion and structure, which are essential for maintaining β -cell function and insulin secretion[3]. Knocking down *NPAS2* and *KANK1* in cell models increased the proliferation of β -cells, implying that downregulating the expression of these genes can help preserve the function of β -cells in patients with T2D[4,5]. Therefore, the *NPAS2*-*KANK1* pathway may be targeted to treat T2D by enhancing β -cell survival and function. *KANK1* is essential for structural interactions occurring at focal adhesions; it coordinates the actin and microtubule cytoskeletons, which are vital for β -cell adhesion and insulin secretion[6,8]. These findings highlight the importance of *KANK1* in β -cell physiology and underscore its potential as a therapeutic target in T2D management. The ability of *KANK1* to influence cellular structures further emphasizes its role in the pathophysiology of T2D and its potential for use in T2D therapies aimed at modulating the expression or function of this protein[7,9].

IMPLICATIONS FOR T2D THERAPY

The discovery of the *NPAS2*-*KANK1* pathway mediating β -cell dysfunction has opened promising new avenues for therapeutic interventions against T2D. Novel T2D therapies can be developed by targeting the molecular mechanisms involving *NPAS2* and *KANK1* to preserve β -cell function and enhance insulin secretion—factors crucial for managing glycemic control. Yin *et al.* (2024) highlighted the feasibility of this approach by demonstrating that knocking down *NPAS2* and *KANK1* in cell models increased β -cell proliferation—a viable strategy for combating β -cell dysfunction[1]. *KANK1* plays a key structural role in coordinating the actin and microtubule cytoskeletons at focal adhesions; this role is essential for maintaining cell integrity and function[3,4]. The aforementioned coordination is crucial for β -cell function because it helps sustain the structural and mechanical properties necessary for insulin secretion. The interplay between cytoskeletal elements and focal adhesions, as described by Guo *et al.*[3], highlights the feasibility of targeting these interactions to improve the resilience and

functionality of β -cells. Notably, surgical interventions such as Roux-en-Y gastric bypass surgery have been demonstrated to downregulate the expression of *NPAS2* and *KANK1*; therefore, surgical approaches may be explored to manage T2D by modulating the NPAS2–KANK1 pathway[1]. Pharmacological and surgical interventions may be combined to preserve β -cell health and improve T2D outcomes. The role of the NPAS2–KANK1 pathway in mediating the function of β -cells emphasizes its significance in the pathophysiology of T2D. Targeting this pathway through pharmacological or surgical approaches can optimize therapeutic outcomes by improving β -cell viability and insulin secretion. Future treatments may harness these insights to optimize glycemic control and overall care for patients with T2D.

CONCLUSION

Yin *et al.* clarified the critical molecular pathways underlying T2D by highlighting the roles of NPAS2 and KANK1 in β -cell dysfunction[1]. The NPAS2–KANK1 pathway may serve as a promising therapeutic target for preserving β -cell function to optimize T2D management. Targeting this pathway can help maintain insulin secretion and glycemic control in patients with T2D. Understanding the structural and functional dynamics of KANK1 at focal adhesions can help researchers devise strategies for protecting β -cells from dysfunction[3,4]. The interaction between talin and KANK1 is essential for coordinating the actin and microtubule cytoskeletons at focal adhesions; this coordination is crucial for β -cell viability and insulin secretion[4,7]. These molecular connections should be leveraged to develop new therapeutic strategies aimed at enhancing the resilience of β -cells. Future studies should explore relevant genetic and molecular interactions, investigating how they can be modified to devise precise and effective therapies for T2D. Knowledge about the NPAS2–KANK1 pathway and its broader implications may ¹ guide the development of novel therapies for improving the quality of life of patients with T2D. Targeting this pathway can help preserve β -cell function and thus optimize T2D management[5, 6].

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