

## FOCUSED REVIEW

# The non-canonical NF- $\kappa$ B pathway and its contribution to $\beta$ -cell failure in diabetes

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## Abstract

The prevalence of diabetes has reached 8.8% in worldwide population and is predicted to increase up to 10.4% by 2040. Thus, there is an urgent need for the development of means to treat or prevent this major disease. Due to its role in inflammatory responses, several studies demonstrated the importance of the transcription factor nuclear factor- $\kappa$ B (NF- $\kappa$ B) in both type 1 diabetes (T1D) and type 2 diabetes (T2D). The two major NF- $\kappa$ B pathways are the canonical and the non-canonical. The later pathway is activated by the NF- $\kappa$ B-inducing kinase (NIK) that triggers p100 processing into p52, which forms with RelB its main dimer. Cytokines mediating the activation of this pathway are present in the serum of T1D and T2D patients. Conversely, limited information is available regarding the role of the alternative pathway on diabetes development and  $\beta$ -cell fate. In the present review, we will briefly describe the involvement of NF- $\kappa$ B on diabetes pathology and discuss new studies indicating an important role for the non-canonical NF- $\kappa$ B activation in  $\beta$ -cell function and survival. The non-canonical NF- $\kappa$ B pathway is emerging as a novel potential target for the development of therapeutic strategies to treat or prevent diabetes.

## Key Words

- ▶ pancreatic  $\beta$ -cells
- ▶ NF- $\kappa$ B
- ▶ diabetes (all)
- ▶ non-canonical
- ▶ dysfunction

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## Introduction

Nuclear factor- $\kappa$ B (NF- $\kappa$ B) is an important transcription factor controlling different biological processes, such as immune differentiation and activation, cell fate and response to stress (Zhang *et al.* 2017). Although controlled NF- $\kappa$ B activation is crucial for cell survival, deregulated NF- $\kappa$ B activation is associated with many diseases, including cancer, inflammatory and autoimmune diseases, such as diabetes (Zhang *et al.* 2017).

Diabetes is a metabolic disease characterized by high blood glucose levels due to insulin resistance and/or deficiency. The two main forms are type 1 diabetes (T1D) and type 2 diabetes (T2D). While T2D results from insulin resistance and consequent impaired  $\beta$ -cell function and survival (Chatterjee *et al.* 2017), T1D is mainly a result

of an autoimmune attack leading to  $\beta$ -cell destruction (Christofferson *et al.* 2016). Islet inflammation has been considered as a key feature of T1D, and it is now recognized that inflammation also contributes to insulin resistance and  $\beta$ -cell failure in T2D (Coope *et al.* 2016, Catrysse & van Loo 2017). Due to its major role in inflammatory responses, there are several studies demonstrating the importance of NF- $\kappa$ B in both T1D and T2D (Meyerovich *et al.* 2016b, Catrysse & van Loo 2017).

## NF- $\kappa$ B signaling

NF- $\kappa$ B signaling is mediated through homo- or heterodimers of the Rel homology domain-containing

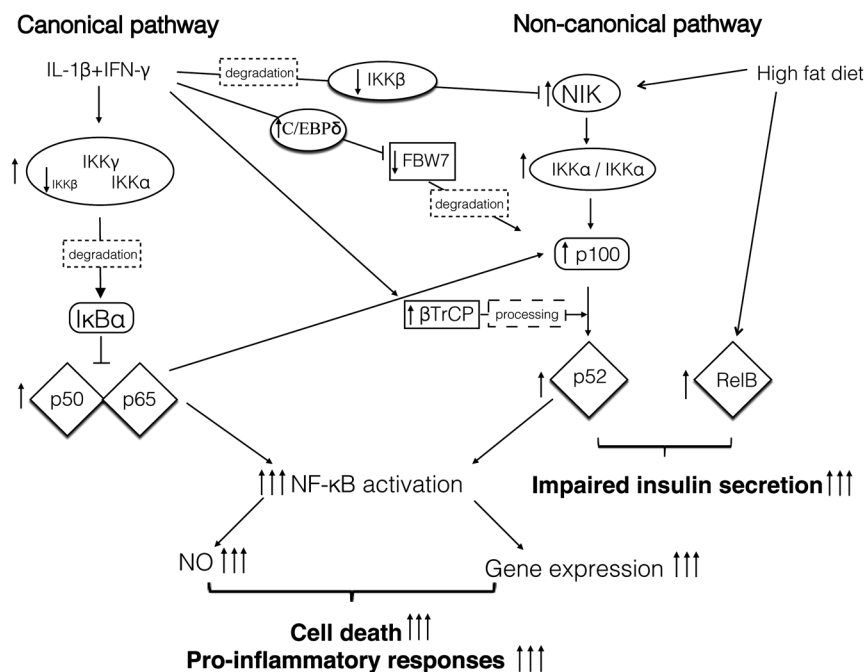
proteins such as RelA (also called p65), RelB, c-Rel, p50 and p52. p50 and p52 are active transcription factors that are generated and activated by cleavage of the inhibitory proteins p105 and p100, respectively (Zhang *et al.* 2017). NF- $\kappa$ B can be activated either via the canonical or the non-canonical (also named alternative) pathways.

Activation of the canonical NF- $\kappa$ B pathway is mediated by pro-inflammatory signals such as cytokines, pathogen-associated molecular patterns and danger-associated molecular patterns (Zhang *et al.* 2017). Binding of the respective ligands initiates activation of the inhibitory  $\kappa$ B proteins (I $\kappa$ B) kinase (IKK) complex containing IKK $\alpha$ , IKK $\beta$  and IKK $\gamma$  that in turn, phosphorylates I $\kappa$ B, leading to their degradation and allowing nuclear translocation of the NF- $\kappa$ B complexes, that is Rel-A/p50 and c-Rel/p50 (Fig. 1) (Zhang *et al.* 2017). The non-canonical NF- $\kappa$ B pathway is mostly associated with differentiation, maturation and survival of immune cells, including B cells and osteoclasts. The alternative pathway is activated by a number of ligands, such as lymphotoxin  $\beta$  (LT $\beta$ ), B cells-activating factor, receptor activator of nuclear factor kappa-B ligand (RANKL) and cluster of differentiation 40 ligand (CD40L) that bind to a subset of tumor necrosis factor (TNF) receptors (Sun 2017). Upon stimulation, TNF receptor-associated factor 2 recruits a complex containing

cellular inhibitor of apoptosis 1 and 2, leading to TRAF3 proteolysis and accumulation of the NF- $\kappa$ B-inducing kinase (NIK), which activates IKK $\alpha$  homodimers resulting in phosphorylation, ubiquitination and processing of p100 into the active subunit p52. Following its activation, p52 binds to RelB, leading to their nuclear translocation and induction of the target genes (Fig. 1) (Sun 2017). The canonical and alternative NF- $\kappa$ B pathways are believed to be independent and to have diverse physiological functions; however, crosstalk between these two signaling pathways are being unveiled (Sun 2012, Meyerovich *et al.* 2016a).

### NF- $\kappa$ B and diabetes

SNPs in the NF- $\kappa$ B gene and in the TNFAIP3 gene, encoding for the A20 protein (a negative regulator of NF- $\kappa$ B activation), are linked to T1D, indicating the involvement of NF- $\kappa$ B in T1D pathology (Hegazy *et al.* 2001, Fung *et al.* 2009). During T1D, NF- $\kappa$ B is activated in both immune cells and pancreatic  $\beta$ -cells. While NF- $\kappa$ B activation is crucial for maturation and activation of immune cells, in  $\beta$ -cells, it has mostly a deleterious effect (Meyerovich *et al.* 2016b). Pro-inflammatory cytokines such as interleukin-1 $\beta$  (IL-1 $\beta$ ) and TNF secreted by immune cells during insulinitis



**Figure 1**

Involvement of the canonical and non-canonical NF- $\kappa$ B pathways in pancreatic  $\beta$ -cell dysfunction and death. IL-1 $\beta$  initiates the canonical NF- $\kappa$ B signaling via activation of the IKK $\gamma$ /IKK $\alpha$ /IKK $\beta$  complex and degradation of I $\kappa$ B $\alpha$  allowing nuclear translocation of NF- $\kappa$ B subunits. This is followed by activation of the non-canonical NF- $\kappa$ B pathway characterized by NIK protein accumulation, activation of IKK $\alpha$ -only complexes, p100 cleavage and nuclear translocation of p52. IL-1 $\beta$ +IFN- $\gamma$  activate a crosstalk between the canonical and non-canonical NF- $\kappa$ B pathways via p100 upregulation. IL-1 $\beta$ +IFN- $\gamma$  also downregulate the expression of E3-ligase FBW7 (via C/EBP $\delta$ ) and induce the expression of the E3-ligase  $\beta$ TrCP leading to p100 accumulation and facilitating its cleavage to p52. IL-1 $\beta$ -mediated downregulation of IKK $\beta$  (Ortis *et al.* 2012) contributes to accumulation of NIK protein and IKK $\alpha$ -only complexes. This amplified NF- $\kappa$ B signaling initiated by cytokines induces pro-inflammatory and pro-apoptotic genes, contributing to  $\beta$ -cell death. HFD also induces activation of the non-canonical pathway in islets leading to p52 and RelB expression and impaired insulin secretion (adapted from Meyerovich *et al.* 2016a)).  $\beta$ TrCP, beta-transducin repeats-containing protein; IL-1 $\beta$ , interleukin-1 $\beta$ ; I $\kappa$ B, inhibitory  $\kappa$ B proteins; IKK, I $\kappa$ B kinase; NF- $\kappa$ B, nuclear factor- $\kappa$ B; NIK, NF- $\kappa$ B-inducing kinase.

in T1D, induce NF- $\kappa$ B activation in  $\beta$ -cells. Moreover, toll-like receptor activation and/or endoplasmic reticulum stress may also induce NF- $\kappa$ B activation in these cells (Meyerovich *et al.* 2016b). NF- $\kappa$ B inhibition renders human and rodent islets resistant to cytokine-induced  $\beta$ -cell apoptosis *in vitro* (Giannoukakis *et al.* 2000, Heimberg *et al.* 2001). Cytokine-mediated NF- $\kappa$ B activation induces an early and transitory expression of anti-apoptotic genes in  $\beta$ -cells but stimulates the expression of series of pro-apoptotic and pro-inflammatory genes (Cardozo *et al.* 2001, Meyerovich *et al.* 2016a). Inhibition of NF- $\kappa$ B signaling in mouse  $\beta$ -cells *in vivo* protects against multiple low doses of streptozotocin (MLDSTZ)-induced diabetes (Eldor *et al.* 2006), while mice with constitutive NF- $\kappa$ B activation in  $\beta$ -cells spontaneously develop insulinitis and immune-mediated diabetes (Salem *et al.* 2014). On the other hand, NF- $\kappa$ B inactivation in  $\beta$ -cells from non-obese diabetic (NOD) mice accelerates the disease development (Kim *et al.* 2007). This may be related to the prolonged inhibition of the expression of NF- $\kappa$ B-dependent anti-apoptotic proteins, such as XIAP and A20 (Kim *et al.* 2007, Fukaya *et al.* 2016). Additional potential anti-apoptotic role for NF- $\kappa$ B has been described. Thus, pharmacological inhibition of NF- $\kappa$ B using BAY, decreased the expression of the NF- $\kappa$ B target micro-RNA, miR-21, leading to increased cytokine-mediated expression of the pro-apoptotic protein Pcd4 and  $\beta$ -cell apoptosis (Ruan *et al.* 2011). Of note, although BAY has been shown to prevent IKK $\alpha$  phosphorylation (Pierce *et al.* 1997), the compound is not a selective inhibitor of the NF- $\kappa$ B signaling pathway since it can also inhibit a series of protein tyrosine phosphatases (Krishnan *et al.* 2013). Therefore, the involvement of NF- $\kappa$ B in this pathway should be re-evaluated using more specific approaches. Another micro-RNA regulated by NF- $\kappa$ B in  $\beta$ -cells is miR-146a (Roggli *et al.* 2010). This micro-RNA is induced by cytokines in isolated rodent and human pancreatic islets and in islets of NOD mice (Roggli *et al.* 2010) and has an anti-inflammatory function since it inhibits NF- $\kappa$ B activation (Li *et al.* 2010). Although inhibition of miR-146 was shown to be beneficial in MIN6 cell treated *in vitro* with IL-1 $\beta$  (Roggli *et al.* 2010), further *in vivo* studies are necessary to evaluate its role in  $\beta$ -cell demise during T1D.

Oxidative and endoplasmic reticulum (ER) stress, elevated levels of free fatty acids, glucotoxicity and a low-grade inflammation are associated with obesity and contribute to both, insulin resistance and  $\beta$ -cell failure/apoptosis in T2D (Coope *et al.* 2016). The inflammatory state is the result of cytokine production by infiltrating activated macrophages and insulin-responsive cells,

including adipocytes and hepatocytes and increased processing of fatty acids to pro-inflammatory lipid mediators (Coope *et al.* 2016, Imai *et al.* 2016). Production of IL-1 $\beta$  has been also described in pancreatic  $\beta$ -cells in conditions of glucolipotoxicity, but the literature is contradictory about these claims (Meyerovich *et al.* 2016b).

NF- $\kappa$ B activation under T2D/obesity is a consequence of a mild chronic inflammation, exposure to high glucose (advanced glycation end products (AGE)), free fatty acids (via TLR2 and/or TLR4) and/or ER stress (Catrysse & van Loo 2017). NF- $\kappa$ B signaling and production of pro-inflammatory mediators in liver contribute to insulin resistance in the early stages of T2D, whereas activation of NF- $\kappa$ B in adipose tissue macrophages is required to disseminate inflammation and promote systemic insulin resistance in muscle and other insulin-sensitive tissues; for a detailed review please refer to Catrysse & van Loo (2017). In line with these data, inhibition of IKK $\beta$ /NF- $\kappa$ B by salicylate improves glucose tolerance in T2D patients (Catrysse & van Loo 2017). Of note, salicylate was shown to facilitate metabolism in subjects with insulin resistance and T2D via activation of AMPK pathway, leading to a switch from fat synthesis to fat oxidation and an increased glucose uptake by muscle cells (Hardie 2013). Therefore, the beneficial effects of salicylate may not be related only to inhibition of NF- $\kappa$ B.

The role for NF- $\kappa$ B in T2D pathogenesis is principally focused on peripheral tissues (Catrysse & van Loo 2017), but a recent study has shed light on the role of the non-canonical NF- $\kappa$ B on  $\beta$ -cell dysfunction during T2D (see below).

### Non-canonical NF- $\kappa$ B pathway on glucose homeostasis and $\beta$ -cell dysfunction and death

Most of the studies analyzing the role of NF- $\kappa$ B on  $\beta$ -cell survival and function focused on the canonical NF- $\kappa$ B pathway, while almost no studies examined the role of the non-canonical NF- $\kappa$ B activation in  $\beta$ -cells.

Activation of the non-canonical NF- $\kappa$ B pathway has been described only by certain ligands, such as, RANKL, CD40L, lymphotoxin  $\beta$  and TNF ligand superfamily member 14 (also named LIGHT) (Sun 2017). However, it has been recently demonstrated that IL-1 $\beta$  and/or soluble TNF are capable of activating the non-canonical pathway in  $\beta$ -cells (Malle *et al.* 2015, Meyerovich *et al.* 2016a). Activation of the non-canonical NF- $\kappa$ B pathway by IL-1 $\beta$  and soluble TNF has not been previously described in other

cell types, and it may be a specific feature of pancreatic  $\beta$ -cells. The mechanisms by which these cytokines activate the non-canonical NF- $\kappa$ B pathway in  $\beta$ -cells have not yet been demonstrated, but they may be involved in crosstalk with the canonical NF- $\kappa$ B pathway (Fig. 1, see below) and/or cytokine-mediated induction of non-canonical ligands. In line with this,  $\beta$ -cells express both the CD40 and lymphotoxin  $\beta$  (LT $\beta$ R) receptors (Walter *et al.* 2000, Cardozo *et al.* 2001, Barbe-Tuana *et al.* 2006, Halvorsen *et al.* 2016) and inflammatory cytokines increase the release of LIGHT and upregulate the levels of its receptor (LT $\beta$ R) in human pancreatic islet cells (Halvorsen *et al.* 2016).

The regulation of the NF- $\kappa$ B pathway relies on ubiquitination of regulatory proteins (Zhang *et al.* 2017). Similar to what has been observed in other cell types (Sun 2017), in  $\beta$ -cells, the expression of the E3-ligase F-box and WD repeat domain-containing 7 (FBW7) is required for p100 degradation, while the E3 ligase beta-transducin repeats-containing protein (BTrCP) is probably responsible for p100 processing to p52 (Meyerovich *et al.* 2016a) (Fig. 1). However, while in tumoral cells, FBW7 silencing decreased expression of the canonical NF- $\kappa$ B targets, in  $\beta$ -cells, FBW7 exclusively regulates the non-canonical NF- $\kappa$ B pathway (Meyerovich *et al.* 2016a). Interestingly, in INS-1E cells exposed to IL-1 $\beta$ +IFN- $\gamma$ , FBW7 is downregulated (via increased expression of C/EBP $\delta$ ), while  $\beta$ TrCP is upregulated (Meyerovich *et al.* 2016a). These events result in an accumulation of p100 and its enhanced cleavage to the active form p52, favoring activation of the non-canonical NF- $\kappa$ B pathway in these cells (Fig. 1).  $\beta$ TrCP was also shown to ubiquitinate I $\kappa$ B $\alpha$  in other cell types targeting it for degradation and therefore being an important regulator of the canonical NF- $\kappa$ B pathway (Sun 2017). However, silencing  $\beta$ TrCP in INS-1E cells did not affect the regulation of the canonical NF- $\kappa$ B pathway (K Meyerovich & A K Cardozo, unpublished data). Thus, different from other cell types, FBW7 and  $\beta$ TrCP exclusively regulate the non-canonical NF- $\kappa$ B pathway in  $\beta$ -cells.

Activation of the non-canonical NF- $\kappa$ B pathway by IL-1 $\beta$ +IFN- $\gamma$  in  $\beta$ -cells induces a set of pro-apoptotic and inflammatory genes, while the expression of the anti-apoptotic NF- $\kappa$ B genes depends on the canonical pathway (Meyerovich *et al.* 2016a), indicating a pro-apoptotic effect for the non-canonical pathway in these cells. In line with that, inhibition of the non-canonical pathway (via knockdown of p100) decreases IL-1 $\beta$ +IFN- $\gamma$ -induced apoptosis in  $\beta$ -cells (Meyerovich *et al.* 2016a). Moreover, knocking down FBW7 increased the non-canonical NF- $\kappa$ B

signaling and apoptosis in both rat and human  $\beta$ -cells exposed to IL-1 $\beta$ +IFN- $\gamma$  (Meyerovich *et al.* 2016a). Finally, it was previously shown that exposure of human islets to LIGHT (a ligand for the LT $\beta$ R receptor) induced cell death (Halvorsen *et al.* 2016). These results suggest that activation of the non-canonical pathway is deleterious to  $\beta$ -cells. Ligands of the alternative pathway such as LT $\alpha_1\beta_2$ , CD40 and LIGHT, contribute to autoimmunity in NOD mice (Balasa *et al.* 1997, Ettinger *et al.* 2001, Wu *et al.* 2001, Wagner *et al.* 2002). Interestingly, LIGHT expression is induced in islets during insulinitis in NOD mice and specific overexpression of this ligand in  $\beta$ -cells leads to acceleration of the disease (Lee *et al.* 2006). These results suggest a role for the non-canonical NF- $\kappa$ B pathway on T1D development. However, it remains to be determined how activation of this pathway in  $\beta$ -cells can contribute to T1D development in *in vivo* rodent models and whether it is implicated in human diabetes. Interestingly, the levels of CD40L are significantly higher in plasma of T1D and T2D subjects as compared to non-diabetic controls (Cipollone *et al.* 2005, Neubauer *et al.* 2010). High serum concentration of soluble RANKL emerged as a significant and independent risk predictor of T2D (Kiechl *et al.* 2013). Moreover, the plasma levels of LIGHT and lymphotoxin are also elevated in serum of T2D patients (Mooradian *et al.* 1992, Halvorsen *et al.* 2016). These results indicate that during both T1D and T2D,  $\beta$ -cells are exposed to ligands of the non-canonical NF- $\kappa$ B pathway.

Few studies have now revealed a role for the non-canonical NF- $\kappa$ B pathway in metabolic syndrome. Thus, NIK is induced in muscle of obese individuals and contributes to insulin resistance (Choudhary *et al.* 2011). Moreover, NIK is overactivated in liver of obese mice, contributing to hyperglycemia and glucose intolerance (Sheng *et al.* 2012, Liu *et al.* 2017). The role for the non-canonical NF- $\kappa$ B pathway in  $\beta$ -cell failure during T2D has been recently revealed. Hence, in islets from mice fed with high-fat diet (HFD), increased levels of NIK, IKK $\alpha$  phosphorylation, p52 and RelB were observed (Malle *et al.* 2015) (Fig. 1). *In vitro*, NIK activation in human islets impaired glucose-stimulated insulin secretion (Malle *et al.* 2015). In line with that, mice with genetically induced NIK activation, specifically in islets, displayed glucose intolerance after diet-induced obesity (Malle *et al.* 2015). The observed decrease in  $\beta$ -cell function was not due to decreased  $\beta$ -cell mass or insulin content, but it was probably related to a defect in insulin secretion (Malle *et al.* 2015). Although the inhibition of the non-canonical NF- $\kappa$ B pathway partially prevented cytokine-mediated  $\beta$ -cell apoptosis and exposure to the non-canonical

ligand LIGHT induced human islet cell death (Halvorsen *et al.* 2016, Meyerovich *et al.* 2016a), activation of the non-canonical pathway using the chemical compound (MV1) did not lead to death of human islet cells (Malle *et al.* 2015). Moreover, in the *in vivo* models of HFD-induced diabetes, where only the non-canonical NF- $\kappa$ B pathway was activated, no  $\beta$ -cell death was observed (Malle *et al.* 2015). These results indicate that the effects of the activation of the non-canonical NF- $\kappa$ B pathway (dysfunction/cell death) on  $\beta$ -cells will depend on the cellular context. More studies are necessary to clarify this issue.

## Conclusion

Compared to the canonical NF- $\kappa$ B pathway, still little is known about the regulation of the non-canonical pathway in  $\beta$ -cells and its role in diabetes development. The studies described here show that activation of the non-canonical pathway occurs in diabetes and involves activation of NIK. While NIK activation contributes to  $\beta$ -cell dysfunction, activation of the non-canonical pathway may synergize with the canonical NF- $\kappa$ B pathway to induce  $\beta$ -cell apoptosis (Fig. 1). In IL-1 $\beta$ +IFN- $\gamma$ -treated  $\beta$ -cells, the non-canonical NF- $\kappa$ B pathway controls the expression of genes that regulate pro-apoptotic and inflammatory responses, which perhaps contribute to  $\beta$ -cell autoimmunity in T1D. In T2D, besides inhibiting  $\beta$ -cell function, NIK activation directly contributes to insulin resistance and glucose intolerance in diet-induced obesity. Therefore, we hypothesize that NIK and the non-canonical NF- $\kappa$ B are novel potential targets for developing therapeutic strategies to cure or prevent diabetes. Of note, chemical inhibitors of NIK are presently being developed (Castanedo *et al.* 2017) and have already been successfully utilized in some animal models (Ren *et al.* 2017). The availability of these molecules, together with development of specific mouse models, is essential to test this hypothesis.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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