Naunyn-Schmiedeberg's Arch Pharmacol (2017) 390:767–768
DOI 10.1007/s00210-017-1391-2

EDITORIAL

# The role of dual leucine zipper kinase (DLK) in β-cell apoptosis: a potential target for the prevention and treatment of type 2 diabetes?

## Commentary to: Börchers et al., TNF-α induced DLK activation contributes to apoptosis in the β-cell line HIT

**Hans-Georg Joost**[1]

Received: 21 May 2017 / Accepted: 24 May 2017 / Published online: 8 June 2017


Type 2 diabetes is a severe imbalance of glucose homeostasis caused by both insufficient insulin secretion and a reduced insulin sensitivity (insulin resistance). There is general agreement that the fatty liver associated with visceral obesity plays a major role in the pathogenesis of insulin resistance (Kahn and Flier 2000). The latter is compensated by enhanced insulin secretion during a latency period with only marginally increased glucose levels (pre-diabetes). In parallel with the reduction of insulin sensitivity, the function and number of insulin-producing β-cells deteriorate progressively in most, but not all, insulin-resistant individuals, and it is this deterioration of insulin secretion and the loss of β-cells that ultimately cause the decompensation of glucose homeostasis.

The molecular mechanisms that link obesity, insulin resistance and β-cell loss have been intensely investigated during the last decades. It was hoped that further insight into these mechanisms would lead to novel therapeutic strategies and targets. A key question is the mechanism of β-cell apoptosis. Three distinct scenarios have been proposed (Chadt et al. 2014):

(1) The "lipid overflow hypothesis" postulates that obesity results in increased ectopic lipid stores, and that harmful lipid metabolites ("lipotoxicity") in combination with elevated glucose levels ("glucotoxicity") exert cytotoxic effects in the liver and β-cells and play a major role in the impaired function, survival and regeneration of β-cells (Poitout and Robertson 2008; Kluth et al. 2011).
(2) The "adipokine hypothesis" is based on the finding that white adipose cells secrete cytokines with auto- and paracrine function such as leptin, adiponectin and others. The hypothesis postulates that expanding fat stores alter the secretion of these endocrine factors, which results in altered insulin sensitivity of target tissues (liver, muscle, adipose tissue) and impaired insulin secretion.
(3) The "inflammation hypothesis" postulates a major role of inflammatory cytokines secreted by macrophages that infiltrate adipose tissue in obesity. Consequently, adipose tissue is in a state of chronic inflammation and is a source of inflammatory cytokines such as TNF-α, IL-6, IL-1β and others which may produce pathological changes in insulin-sensitive tissues and β-cells.

With their paper published in the current issue of *Naunyn-Schmiedeberg's Archives of Pharmacology*, Börchers et al. 2017 support the inflammation hypothesis and provide important insight into the mechanism of cytokine-induced apoptosis of β-cells. Specifically, the study investigated the role of the dual leucine zipper kinase (DLK) in TNF-α-induced apoptosis of HIT cells. HIT cells synthesize and secrete insulin in response to a glucose stimulus and therefore represent the experimental model that comes closest to pancreatic β-cells. The group has previously shown that DLK is expressed in HIT cells as well as in the primary murine islets of Langerhans (Oetjen et al. 2006), and that its overexpression or activation induces apoptosis of HIT cells (Plaumann et al. 2008). Here, the authors show that TNF-α stimulates DLK activity and, as expected, apoptosis in HIT cells. Furthermore, TNF-α reduces CREB-directed gene expression which is considered essential for function and survival of β-cells (Oetjen

✉ Hans-Georg Joost
joost@dife.de

[1] Experimental Diabetology, German Institute for Human Nutrition, Arthur-Scheunert-Allee 114-116, D-14558 Potsdam-Rehbrücke, Germany

et al. 1994; Shin et al. 2014). Reduction of DLK expression by siRNA attenuated the effects, supporting the notion of a causal relationship between DLK activity and apoptosis. Of note, the JNK kinase inhibitor SP600125 also reduced the effects of TNF-α, suggesting that DLK activation by TNF-α was dependent on JNK kinase.

The second inflammatory cytokine tested in the study, IL-1β, failed to stimulate DLK and to induce apoptosis. This finding was unexpected, since IL-1β was believed to play a major role in β-cell loss in both type 1 and type 2 diabetes. The groups of Donath and Maedler proposed that IL-1β is released from β-cells in response to hyperglycemia (Maedler and Donath 2004). It should be noted that contradicting results have been obtained by others (Welsh et al. 2005; Elouil et al. 2005).

Based on their data, Börchers et al. 2017 suggest that inhibition of DLK could be a promising strategy for the prevention of type 2 diabetes. However, there are few limitations of the study which require further experiments, before a search for specific inhibitors of DLK is initiated: Firstly, the data were obtained solely by in vitro studies and need confirmation by in vivo experiments in mammals, preferably diabetic mouse models. Secondly, the experimental model employed by Börchers et al. 2017 is a tumor cell line. Consequently, it cannot fully be excluded that induction of apoptosis is regulated differently in primary β-cells and that DLK plays a minor role. Furthermore, it is debatable that TNF-α plays a major role in the pathogenesis of type 2 diabetes, since agents antagonizing TNF-α appear to lack antidiabetic efficacy (Dominguez et al. 2005; Martínez-Abundis et al. 2007).

In summary, the data by Börchers et al. 2017 demonstrate an important role of DLK in the pathogenesis of type 2 diabetes and elucidate a signaling pathway with the players DLK, JNK and CREB which appears to be critical for β-cell survival and apoptosis. The data represent an important contribution to our understanding of the pathogenesis of diabetes and have identified a potential target for the prevention of type 2 diabetes which should further be explored.

## References


Börchers S, Babaei R, Klimpel C, Duque Escobar J, Schröder S, Blume R, Malik MNH, Oetjen E (2017) TNF-α-induced DLK activation contributes to apoptosis in the β-cell line HIT. NS Arch Pharmacol. doi:10.1007/s00210-017-1385-0

Chadt A, Scherneck S, Joost HG, Al-Hasani H (2014) Molecular links between obesity and diabetes: "diabesity". In: De Groot LJ, Beck-Peccoz P, Chrousos G, Dungan K, Grossman A, Hershman JM, Koch C, McLachlan R, New M, Rebar R, Singer F, Vinik A, Weickert MO, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from http://www.ncbi.nlm.nih.gov/books/NBK279051/

Dominguez H, Storgaard H, Rask-Madsen C, Steffen Hermann T, Ihlemann N, Baunbjerg Nielsen D, Spohr C, Kober L, Vaag A, Torp-Pedersen C (2005) Metabolic and vascular effects of tumor necrosis factor-α blockade with etanercept in obese patients with type 2 diabetes. J Vasc Res 42:517–525

Elouil H, Cardozo AK, Eizirik DL, Henquin JC, Jonas JC (2005) High glucose and hydrogen peroxide increase c-Myc and haeme-oxygenase 1 mRNA levels in rat pancreatic islets without activating NFkappaB. Diabetologia 48:496–505

Kahn BB, Flier JS (2000) Obesity and insulin resistance. J Clin Invest 106:473–481

Kluth O, Mirhashemi F, Scherneck S, Kaiser D, Kluge R, Neschen S, Joost HG, Schürmann A (2011) Dissociation of lipotoxicity and glucotoxicity in a mouse model of obesity associated diabetes: role of forkhead box O1 (FOXO1) in glucose-induced β-cell failure. Diabetologia 54:605–616

Maedler K, Donath MY (2004) β-cells in type 2 diabetes: a loss of function and mass. Horm res 62(Suppl 3):67–73

Martínez-Abundis E, Reynoso-von Drateln C, Hernández-Salazar E, González-Ortiz M (2007) Effect of etanercept on insulin secretion and insulin sensitivity in a randomized trial with psoriatic patients at risk for developing type 2 diabetes mellitus. Arch Dermatol res 299: 461–465

Oetjen E, Diedrich T, Eggers A, Eckert B, Knepel W (1994) Distinct properties of the cAMP-responsive element of the rat insulin I gene. J Biol Chem 269:27036–27044

Oetjen E, Lechleiter A, Blume R, Nihalani D, Holzman L, Knepel W (2006) Inhibition of membrane depolarisation-induced transcriptional activity of cyclic AMP response element binding protein (CREB) by the dual-leucine-zipper-bearing kinase in a pancreatic islet β-cell line. Diabetologia 49:332–342

Plaumann S, Blume R, Börchers S, Steinfelder HJ, Knepel W, Oetjen E (2008) Activation of the dual-leucine-zipper-bearing kinase and induction of β-cell apoptosis by the immunosuppressive drug cyclosporin A. Mol Pharmacol 73:652–659

Poitout V, Robertson RP (2008) Glucolipotoxicity: fuel excess and β-cell dysfunction. Endocr rev 29:351–366

Shin S, Le Lay J, Everett LJ, Gupta R, Rafiq K, Kaestner KH (2014) CREB mediates the insulinotropic and anti-apoptotic effects of GLP-1 signaling in adult mouse β-cells. Mol Metab 3:803–812

Welsh N, Cnop M, Kharroubi I, Bugliani M, Lupi R, Marchetti P, Eizirik DL (2005) Is there a role for locally produced interleukin-1 in the deleterious effects of high glucose or the type 2 diabetes milieu to human pancreatic islets? Diabetes 54:3238–3244