

Defining the regulation of IL-1 β - and CHOP-mediated β -cell apoptosis

Nathan L. Vanderford

Markey Cancer Center; University of Kentucky; Lexington, Kentucky USA

Diabetes is a multifaceted metabolic disorder that can be caused by pancreatic β -cell destruction (type I diabetes) and/or heightened by β -cell failure (type II diabetes). The gross clinical and physiological characteristics of the disease are well characterized, and viable treatment options can drastically alter the course and effects of the disease. However, the molecular events occurring within the β -cell that cause or contribute to diabetes are not adequately understood, especially in terms of the interplay between the physiological signals that facilitate disease development. A recent report, focused on a mechanism by which IL-1 β induces β -cell apoptosis, underscores the complexity of the molecular events that may cause or affect the progression of diabetes. This commentary summarizes aspects of this report, discusses an example of the complexity of β -cell regulation and proposes more frequent use of complex in vitro systems that more closely mimic in vivo conditions so that greater advances can be made toward understanding the molecular mechanisms contributing to diabetes. Understanding the molecular etiology of β -cell dysfunction will likely enhance the possibility of developing novel therapeutic interventions for diabetes.

Chronic glucose, lipid and cytokine signaling play key roles in the etiology of diabetes both within peripheral tissues and within the β -cell.¹⁻⁶ Individually, chronic exposure to each of these stimuli has been shown to alter β -cell function, at least in part, by causing the dysregulation of key β -cell regulators such as the

transcription factor, MafA,^{3-5,7-12} and to induce β -cell apoptosis through transcription factors including NF κ B.¹³ However, the mechanism(s) by which β -cells are affected at the molecular level by chronic exposure to the combination of glucose, lipids and cytokines is not well understood.

The cytokine, IL-1 β , induces the expression of several genes in β -cells of which some are dependent upon NF κ B,¹⁴ and NF κ B is an important component of IL-1 β -induced apoptosis in β -cells.¹³ CHOP, a proapoptotic transcription factor that is involved in stress-mediated apoptosis and whose activation has been implicated in mediating several diseases including diabetes,¹⁵⁻¹⁷ is upregulated in β -cells that have been treated with IL-1 β and IFN γ .¹⁴ Blocking NF κ B activation in β -cells prevents cytokine-mediated induction of *CHOP* expression and apoptosis.^{14,18-20}

Shao C et al.¹² report on a mechanism that contributes to IL-1 β -induced pancreatic β -cell apoptosis and that is likely involved in contributing to β -cell dysfunction under diabetic conditions. As such, this mechanism may be relevant to the pathogenesis of diabetes as it occurs in vivo. Mostly within the confines of a cell culture system using the standard insulinoma cell lines, MIN6 and INS-1, IL-1 β is shown to suppress the expression of key β -cell transcription factors, including MafA and Pdx-1;¹² loss of these factors inhibits β -cell development and/or function.^{21,22} Additionally, IL-1 β is shown to stimulate NF κ B activation, and NF κ B subsequently and directly induces the expression of *CHOP*, thereby stimulating apoptotic processes. The MAPKs, JNK,

Key words: diabetes, β -cell, cytokine, glucolipotoxicity, NF κ B, MafA, CHOP, MAPK

Abbreviations: CHOP, CCAAT-enhancer-binding protein homologous protein; ERK, extracellular-signal-regulated kinase; IFN γ , interferon-gamma; IL-1 β , interleukin-1 β ; JNK, c-jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MafA, v-maf musculoaponeurotic fibrosarcoma oncogene homologue A; NF κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; Pdx-1, pancreatic and duodenal homeobox-1

Submitted: 06/17/10

Revised: 07/19/10

Accepted: 07/21/10

Previously published online:
www.landesbioscience.com/journals/islets/article/13095

DOI: 10.4161/isl.2.5.13095

Correspondence to: Nathan L. Vanderford;
Email: nathan.vanderford@uky.edu

p38 and ERK1/2, are activated by IL-1 β , and JNK or ERK1/2 inhibition slightly reduces IL-1 β -dependent CHOP induction without altering NF κ B activity, suggesting that JNK- or ERK1/2-dependent CHOP expression may be independent of NF κ B. The combined treatment of glucose and IL-1 β is used to show that the glucose-regulated action of ERK1/2 influences IL-1 β -dependent CHOP induction through an NF κ B-independent mechanism(s) speculated to be at the posttranscriptional level.¹² These data suggest that under IL-1 β insult, the action of NF κ B, CHOP and MAPKs coordinately halt β -cell function via downregulation of key proteins, such as MafA and Pdx-1, and induce β -cell destruction via CHOP-mediated apoptosis. Moreover, the MAPK experiments suggest that other currently undefined, intricate mechanisms likely contribute to CHOP-mediated β -cell failure and apoptosis under more complex conditions similar to those that occur in vivo as the result of diabetes. Activation of CHOP by multiple pathways highlights the importance of the protein in mediating β -cell apoptosis.

The MAPK studies conducted by Shao C et al.¹² are interesting and, as indicated by the authors, it will be important to extend these findings in order to understand the underlying mechanisms. MAPKs, especially ERK1/2,²³ are important complex regulators of β -cell function. Various stimuli likely influence MAPK downstream effectors through distinct mechanisms, thus leading to varying functional changes. An example of the complexity of MAPK signaling is found when comparing a result from Shao C et al.¹² to other recent reports regarding the regulation of *MafA* expression in β -cells by the JNK/c-Jun pathway. Shao C et al.¹² provide data suggesting that JNK does not impact the reduction in *MafA* expression caused by IL-1 β .¹² However, JNK inhibition has been shown to induce *MafA* and does so most drastically under low glucose conditions when its expression is significantly reduced; this data suggests that JNK activity may play a role in downregulating *MafA* under low glucose conditions.²⁴ The JNK downstream effector, c-Jun, has also been implicated in repressing *MafA* expression under the diabetic conditions

of the db/db mouse model, and in vitro studies have confirmed repression of *MafA* by c-Jun.²⁵ These three studies^{12,24,25} suggest that the JNK/c-Jun pathway may negatively regulate *MafA* expression under specific conditions. Similar complex regulatory scenarios are likely true for other MAPK downstream targets, especially in β -cells simultaneously activated by multiple stimuli.

Many laboratories are detailing the complexity of β -cell regulation. Investigators are finding that different exogenous stimuli and cellular conditions influence β -cell regulation through various mechanisms. The regulation of *MafA* expression by JNK is only one example illustrating the variable sensitivity of β -cells to different stimuli.^{12,24,25} Variable regulation of β -cell function has interesting functional implications. For example, MafA can both inhibit and stimulate *CHOP* expression in β -cells.²⁶ Considering the sensitivity of MafA to various β -cell stimulants, including glucose, lipids and cytokines,^{3,5,7-12,24,27-29} then this transcription factor may differentially regulate *CHOP* expression, and thus apoptosis, depending on the stimulant(s) and subsequent signaling pathway(s) initiated.

Combining β -cell stimulants, such as glucose, lipids and cytokines, that are relevant to the in vivo setting involved in diabetes development and progression within the context of in vitro systems is an approach not often used in the β -cell field. Moreover, analysis of multiple proteins and pathways, as conducted by Shao C et al.,¹² is not the norm as we too often single-out a particular protein and/or pathway in our studies. However, complex, integrated analyses are required to define the molecular details of β -cell failure as it occurs in vivo given that multiple molecular mechanisms and the interplay between glucolipotoxicity- and cytokine-mediated β -cell dysfunction/failure and destruction are likely critically important to the etiology of diabetes.¹⁻⁶ The data obtained by Shao et al.¹² demonstrate the type of hypothesis-generating findings that can result from studying the combined effect of β -cell stimulants and multiple proteins and pathways. More widespread use of complex in vitro experimental systems addressing the integration, crosstalk and

divergence of signaling events and the resulting functional changes in the β -cell should be embraced because such systems and analyses may accelerate targeted development of novel therapies for treating diabetes.

References

1. Bluestone JA, Herold K, Eisenbarth G. Genetics, pathogenesis and clinical interventions in type 1 diabetes. *Nature* 2010; 464:1293-300.
2. LeRoith D, Olefsky JM, Taylor SI. *Diabetes Mellitus: A Fundamental and Clinical Text*. Philadelphia, Baltimore, New York, London, Buenos Aires, Hong Kong, Sydney, Tokyo Lippincott Williams and Wilkins 2003.
3. Poitout V, Amyot J, Semache M, Zarrrouki B, Hagman D, Fontes G. Glucolipotoxicity of the pancreatic beta cell. *Biochim Biophys Acta* 2010; 1801:289-98.
4. Poitout V, Robertson RP. Glucolipotoxicity: fuel excess and beta-cell dysfunction. *Endocr Rev* 2008; 29:351-66.
5. Robertson RP, Harmon JS. Diabetes, glucose toxicity and oxidative stress: A case of double jeopardy for the pancreatic islet beta cell. *Free Radic Biol Med* 2006; 41:177-84.
6. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. *The Lancet* 2005; 365:1333-46.
7. Chin-Chance CV, Newman MV, Aronovitz A, Blomeier H, Kruger J, Lee EJ, et al. Role of the mitogen-activated protein kinases in cytokine-mediated inhibition of insulin gene expression. *J Investig Med* 2006; 54:132-42.
8. Hagman DK, Hays LB, Parazzoli SD, Poitout V. Palmitate inhibits insulin gene expression by altering PDX-1 nuclear localization and reducing MafA expression in isolated rat islets of Langerhans. *J Biol Chem* 2005; 280:32413-8.
9. Harmon JS, Stein R, Robertson RP. Oxidative stress-mediated, post-translational loss of MafA protein as a contributing mechanism to loss of insulin gene expression in glucotoxic beta cells. *J Biol Chem* 2005; 280:11107-13.
10. Kitamura YI, Kitamura T, Kruse JP, Raum JC, Stein R, Gu W, et al. FoxO1 protects against pancreatic beta cell failure through NeuroD and MafA induction. *Cell Metab* 2005; 2:153-63.
11. Oetjen E, Blume R, Cierny I, Schlag C, Kutschenko A, Kratzner R, et al. Inhibition of MafA transcriptional activity and human insulin gene transcription by interleukin-1beta and mitogen-activated protein kinase kinase kinase in pancreatic islet beta cells. *Diabetologia* 2007; 50:1678-87.
12. Shao C, Lawrence MC, Cobb MH. Regulation of CCAAT/enhancer-binding protein homologous protein (CHOP) expression by interleukin-1beta in pancreatic beta cells. *J Biol Chem* 2010; 285:19710-9.
13. Melloul D. Role of NF κ B in beta-cell death. *Biochem Soc Trans* 2008; 36:334-9.
14. Cardozo AK, Heimberg H, Heremans Y, Leeman R, Kutlu B, Kruhoffer M, et al. A comprehensive analysis of cytokine-induced and nuclear factor-kappaB-dependent genes in primary rat pancreatic beta-cells. *J Biol Chem* 2001; 276:48879-86.
15. Oyadomari S, Mori M. Roles of CHOP/GADD153 in endoplasmic reticulum stress. *Cell Death Differ* 2004; 11:381-9.
16. Song B, Scheuner D, Ron D, Pennathur S, Kaufman RJ. Chop deletion reduces oxidative stress, improves beta cell function and promotes cell survival in multiple mouse models of diabetes. *J Clin Invest* 2008; 118:3378-89.

17. Oyadomari S, Koizumi A, Takeda K, Gotoh T, Akira S, Araki E, et al. Targeted disruption of the Chop gene delays endoplasmic reticulum stress-mediated diabetes. *J Clin Invest* 2002; 109:525-32.
18. Baker MS, Chen X, Cao XC, Kaufman DB. Expression of a dominant negative inhibitor of NFkappaB protects MIN6 beta-cells from cytokine-induced apoptosis. *J Surg Res* 2001; 97:117-22.
19. Giannoukakis N, Rudert WA, Trucco M, Robbins PD. Protection of human islets from the effects of interleukin-1beta by adenoviral gene transfer of an IkappaB repressor. *J Biol Chem* 2000; 275: 36509-13.
20. Heimberg H, Heremans Y, Jobin C, Leemans R, Cardozo AK, Darville M, et al. Inhibition of cytokine-induced NFkappaB activation by adenovirus-mediated expression of a NFkappaB super-repressor prevents beta-cell apoptosis. *Diabetes* 2001; 50:2219-24.
21. Ahlgren U, Jonsson J, Jonsson L, Simu K, Edlund H. beta-cell-specific inactivation of the mouse Ipf1/Pdx1 gene results in loss of the beta-cell phenotype and maturity onset diabetes. *Genes Dev* 1998; 12:1763-8.
22. Zhang C, Moriguchi T, Kajihara M, Esaki R, Harada A, Shimohata H, et al. MafA is a key regulator of glucose-stimulated insulin secretion. *Mol Cell Biol* 2005; 25:4969-76.
23. Lawrence M, Shao C, Duan L, McGlynn K, Cobb MH. The protein kinases ERK1/2 and their roles in pancreatic beta cells. *Acta Physiol (Oxf)* 2008; 192:11-7.
24. Vanderford NL, Cantrell JE, Popa GJ, Ozcan S. Multiple kinases regulate mafA expression in the pancreatic beta cell line MIN6. *Arch Biochem Biophys* 2008; 480:138-42.
25. Matsuoka TA, Kaneto H, Miyatsuka T, Yamamoto T, Yamamoto K, Kato K, et al. Regulation of MafA Expression in Pancreatic beta-cells in db/db Mice with Diabetes. *Diabetes* 2010; 59:1709-20.
26. Lawrence MC, McGlynn K, Naziruddin B, Levy MF, Cobb MH. Differential regulation of CHOP-10/GADD153 gene expression by MAPK signaling in pancreatic beta-cells. *Proc Natl Acad Sci USA* 2007; 104:11518-25.
27. Kajihara M, Sone H, Amemiya M, Katoh Y, Isogai M, Shimano H, et al. Mouse MafA, homologue of zebrafish somite Maf 1, contributes to the specific transcriptional activity through the insulin promoter. *Biochem Biophys Res Commun* 2003; 312:831-42.
28. Kataoka K, Han SI, Shioda S, Hirai M, Nishizawa M, Handa H. MafA is a glucose-regulated and pancreatic beta-cell-specific transcriptional activator for the insulin gene. *J Biol Chem* 2002; 277:49903-10.
29. Vanderford NL, Andrali SS, Ozcan S. Glucose induces MafA expression in pancreatic beta cell lines via the hexosamine biosynthetic pathway. *J Biol Chem* 2007; 282:1577-84.

©2010 Landes Bioscience.
Do not distribute.