Comment on: Matsuoka et al. (2010) Regulation of MafA Expression in Pancreatic β-Cells in *db/db* Mice With Diabetes. Diabetes;59:1709–1720

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Matsuoka et al. (1) further define mechanisms regulating MafA levels in pancreatic islet β-cells under diabetic conditions using the *db/db* diabetic mouse model. MafA and insulin levels are shown to be reduced while c-Jun levels are increased in β-cells of *db/db* animals. Overexpression of c-Jun, but not c-Jun NH_2-terminal kinase (JNK), recapitulated this effect in MIN6 cells. c-Jun affects MafA expression at both the transcriptional and posttranslational level. This mechanism is concluded to be a probable cause of defective insulin production under diabetic conditions (1) given the role MafA plays in *insulin* expression (2,3).

Although not discussed by Matsuoka et al. (1), the JNK/c-Jun pathway has been implicated in regulating *MafA* expression (4). Inhibition of JNK, with SP600125, relieves the reduction in *MafA* and *insulin* expression that occurs under low glucose conditions in MIN6 cells (4), suggesting a similar model for reduced insulin production as described (1). The inability of JNK overexpression to reduce MafA mRNA or protein levels (1) versus the induction of *MafA* expression upon treatment with SP600125 (4) could be because of differences in substrate specificity of the isoform of JNK used (1) compared with the broad inhibition of JNK isoforms caused by SP600125. Matsuoka et al. (1) utilized a single human JNK isoform within mouse MIN6 cells; it is not clear whether this species difference affects JNK substrate specificity.

Among other significant points, Matsuoka et al. (1) further illustrate the complexity of MafA regulation in β-cells; an array of signaling events regulate the transcriptional activity and expression (both at the gene and protein level) of MafA (1,3,4,6,7,9). Understanding the regulation of MafA is critical given its role in regulating β-cell function (2,3,5) and in generating functional β-cells from non–β-cell sources (8).

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