LETTER

Reply to Gurgul-Convey and Lenzen: Cytokines, Nitric Oxide, and β-Cells

This is a response to a letter by Gurgul-Convey and Lenzen (1)

Drs. Gurgul-Convey and Lenzen (1) contend that IL-1 alone inhibits β-cell function but the addition of TNFα is required to cause β-cell death. This is a selective view of the literature. IL-1 alone kills rat islet cells, independent of TNFα, whereas human and mouse islets require a combination of IL-1 and IFNγ. TNFα is dispensable for β-cell death *in vitro* (2). Further, they propose that TNFα causes β-cell death in type 1 diabetes (T1D) because it is present in inflamed islets from rodents and humans with T1D (3). We argue that the presence of TNFα in insulitic lesions does not implicate this molecule as causative of β-cell death. Moreover, TNFR1 is not required for β-cell destruction in the nonobese diabetic (NOD) mouse (4).

It is suggested that the absence of peroxynitrite formation in cytokine-treated β-cells is due to the dismutation of superoxide by manganese superoxide dismutase (Mn-SOD), leaving H_2O_2 to react with NO-forming hydroxyl radical. Why would NO be necessary when iron and H_2O_2 generate hydroxyl radical by the Fenton reaction? Further, NO inhibits this reaction (5). A vast body of literature supports the idea that NO is freely diffusible and reacts at diffusion-controlled rates with superoxide to form peroxynitrite, allowing NO to effectively compete with Mn-SOD for mitochondrially generated superoxide. Consistent with many studies, peroxynitrite is formed when NO and superoxide are generated (6). We report that NO is the primary mediator of cytokine-induced damage, as β-cells fail to produce superoxide in response to cytokines. When chemically produced, superoxide scavenges nitric oxide (forming peroxynitrite) and protects against NO-mediated damage (6).

Katarzyna A. Broniowska[‡], Clayton E. Mathews[§], and John A. Corbett[‡1]

[‡]Department of Biochemistry, Medical College of Wisconsin, Milwaukee, Wisconsin and [§]Department of Pathology, Immunology, and Laboratory Medicine, University of Florida, Gainesville, Florida

1. Gurgul-Convey, E., and Lenzen, S. (2015) Is nitric oxide really the primary mediator of pancreatic β-cell death in type 1 diabetes? *J. Biol. Chem.* **290,** 10570
2. Mandrup-Poulsen, T. (1996) The role of interleukin-1 in the pathogenesis of IDDM. *Diabetologia* **39,** 1005–1029
3. Jörns, A., Arndt, T., Meyer zu Vilsendorf, A., Klempnauer, J., Wedekind, D., Hedrich, H. J., Marselli, L., Marchetti, P., Harada, N., Nakaya, Y., Wang, G. S., Scott, F. W., Gysemans, C., Mathieu, C., and Lenzen, S. (2014) Islet infiltration, cytokine expression and beta cell death in the NOD mouse, BB rat, Komeda rat, LEW.1AR1-iddm rat and humans with type 1 diabetes. *Diabetologia* **57,** 512–521
4. Chee, J., Angstetra, E., Mariana, L., Graham, K. L., Carrington, E. M., Bluethmann, H., Santamaria, P., Allison, J., Kay, T. W., Krishnamurthy, B., and Thomas, H. E. (2011) TNF receptor 1 deficiency increases regulatory T cell function in nonobese diabetic mice. *J. Immunol.* **187,** 1702–1712
5. Lu, C., and Koppenol, W. H. (2005) Inhibition of the Fenton reaction by nitrogen monoxide. *J. Biol. Inorg. Chem.* **10,** 732–738
6. Broniowska, K. A., Mathews, C. E., and Corbett, J. A. (2013) Do β-cells generate peroxynitrite in response to cytokine treatment? *J. Biol. Chem.* **288,** 36567–36578

DOI 10.1074/jbc.L115.648600

[1]E-mail: jcorbett@mcw.edu