Response to Comment on: Lin et al. (2010) Immune Cell–Derived C3 Is Required for Autoimmune Diabetes Induced by Multiple Low Doses of Streptozotocin. Diabetes;59:2247–2252

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The susceptibility and kinetics of diabetes induction following streptozotocin (STZ) administration is highly dependent on the specifics of the protocol (1). In our studies, we demonstrated that intraperitoneal administration of 40 mg/kg of STZ (Alexis Biochemicals, Farmingdale, NY) to male mice aged 6–10 weeks on 5 consecutive days induced autoimmune diabetes in wild-type (WT) C57BL/6 mice but not in congenic $C3^{-/-}$ mice. Autoimmunity was confirmed through showing T-cell reactivity to islet antigens and through demonstrating recurrent disease following syngeneic islet transplantation. We also showed a single high dose of STZ (180 mg/kg) induced diabetes in $C3^{-/-}$ mice and that the kinetics of developing hyperglycemia did not differ from WT controls. A single high dose of STZ did not induce an autoimmune disease because it caused diabetes in $RAG^{-/-}$ mice and was completely reversed following islet transplantation. We did not test the STZ protocol used by Østergaard et al. (2) in which the authors administered 45 mg/kg per mouse for 11–12 consecutive doses "until diabetes was achieved." Østergaard et al. do not state whether their STZ protocol induces autoimmunity nor did they state whether the protocol induces diabetes in $RAG^{-/-}$ recipients. The source of STZ, the sex and age of the animals, and the pathogen status of the animal facility could all influence disease susceptibility. As one of many examples, pathogen-free NOD mice lacking MyD88 protein did not develop autoimmune diabetes, an effect that was reversed by gut colonization (3). We thus believe that the differences noted between the two research groups are not contradictory but in fact reflect variances in model systems. Both sets of data provide useful insight. We agree with Østergaard et al. (4) that other components of the mannose-binding leptin pathway of the complement system need to be explored in the context of autoimmune diabetes.

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