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Abbreviations: EGP, endogenous glucose production; GNG, gluconeogenesis; NMR, nuclear magnetic resonance.

Comment

—to: Walter U, Toepfer T, Dittmar KE et al. (2003) Pancreatic NOD beta cells express MHC class II protein and the frequency of I-A(g7) mRNA-expressing beta cells strongly increases during progression to autoimmune diabetes. Diabetologia 46:1106–1114

To the Editor: Walter et al. [1] are to be congratulated for having done what may eventually be recognized as the definitive study on the controversial topic of MHC Class II expression by beta cells during the autoimmune attack of Type 1 diabetes. Since I consider this to be a carefully performed and important piece of work, I feel almost churlish in having to point out deficiencies in their presentation and interpretation. Walter et al. have studied the time course of MHC Class II (specifically A^{g7}) expression in the beta cells of NOD mice, examining mRNA production, protein expression within the cell and surface expression compared with histological appearance at 3, 6, 9 and 11 weeks of age, before onset of overt diabetes and after diabetes has developed. I believe their findings are of considerable interest, but I wish to make the following points. Firstly, the title given to this paper is very misleading. Unless one reads the full manuscript carefully it sounds as though Walters et al. have found extensive and increasing expression of Class II MHC in the beta cells of the NOD mouse as it develops diabetes. However, from the data they present it can be seen that although MHC Class II mRNA becomes increasingly detectable from 6 weeks onwards, there is still no detectable MHC Class II protein at this time, despite the fact that the immune destructive process was well under way and local production of cytokines promoting MHC expression would be expected. Intracellular MHC Class protein was subsequently found only in samples taken at 11 weeks or more, shortly before the onset of actual diabetes. Most importantly, at no timepoint were they able to detect surface expression of IA^{g7}. I can understand the authors' excitement at finding the mRNA at the earlier timepoints, but considering MHC molecules are purposely designed for membrane insertion, it is still the lack of surface expression in the face of what must be a considerable cytokine storm that is surely most remarkable. Bearing in mind that the NOD mouse also has the gene for the other mouse MHC class II molecule (IE) inactive, the deficiency in surface MHC Class II is striking. Perhaps Walter et al. would be more excited by their negative data if they were aware that it is in precise agreement with a mechanism for the underlying aetiology of Type 1 diabetes suggested to be due to a deficient inhibitory signal given by MHC Class II [2].

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