Letters to the Editor

Induction of class II MHC antigens on human and rodent islet parenchymal cells in vitro

Dear Sir,

Walker et al. [1] recently reported that islet parenchymal cells isolated from BB/E rats predisposed to diabetes (BB/E/H) can be induced to express class II MHC molecules by culture with rat recombinant interferon-gamma (rIFN- γ) for 4–5 days, but that islet cells from either BB/E rats resistant to diabetes or outbred Wistar rats could not. The authors state that IFN- γ will not induce class II expression on normal rodent or human pancreatic B cells, citing papers by Campbell et al. [2] and Pujol-Borrell et al. [3].

We have previously demonstrated that Ia antigen expression can be induced on normal murine islet parenchymal cells, including B cells, with either lymphokine supernatants containing IFN- γ or murine rIFN- γ [4]. Our results are not inconsistent with the results of Campbell et al. because they used lower doses of IFN- γ and a culture period of only 2 days; we were unable to demonstrate any Ia antigen expression with protocols of less than 5 days culture. However, there was clear positive and specific expression of Ia molecules when cultured with lymphokine supernatants for 5 or more days or with IFN- γ for 7 or more days.

More recently, we have examined whether HLA-DR antigen expression could be induced on dispersed human islet parenchymal cells after culture with human rIFN- γ . Islets were isolated from a 38 year-old male Caucasian (HLA type DR 4, 6) and immediately dispersed with Dispase. Cells were cultured in suspension either with or without rIFN- γ (100 ng/ml, specific activity 20 U/ng) in CMRL-1066 medium with 10% fetal calf serum and 1.0 mg/ml D-glucose for ten days, the period of time that we found to be optimal for demonstrating Ia antigens on dispersed murine islet cells [4]. DR expression was seen on 15–20% of islet parenchymal cells by immunofluorescent staining with a monoclonal antibody H-4/125 (One Lambda, Los Angeles, Calif, USA) diluted 1:10 and goat anti-mouse IgG-FITC diluted 1:16 (Fig. 1). Appropriate controls were negative.

As an explanation for their finding that class II molecules were induced only on islet cells from BB/E/H rats, Walker et al. suggest that the islets from this strain may be affected by other cytokines in vivo prior to culture with IFN- γ . This explanation would seem to be supported by the recent findings of another group from the same institution; Pujol-Borrell et al. [5] have demonstrated HLA class II antigen induction on human islet cells by culture with human rIFN- γ

plus tumor necrosis factor or lymphotoxin but not with rIFN- γ alone. We found that Ia expression induced by culture with lymphokine supernatants produced by activated mouse spleen cells was both qualitatively more intense and occurred more rapidly relative to that induced with murine rIFN- γ only [4]. Therefore, we concur that other cytokines may have a synergistic effect with IFN- γ on the expression of class II antigens, but do not agree that they are necessary for class II antigen expression on either rodent or human islet parenchymal cells.

Bottazzo has suggested that aberrant class II antigen expression on B cells may initiate the autoimmune cascade responsible for Type 1 (insulin-dependent) diabetes [6]. This is an interesting and provocative hypothesis which is based on the well-known requirements for expression of class II molecules in order to activate CD4 positive T cells. However, the finding that class II antigens are expressed on B cells in vivo after the onset of insulinitis in spontaneously diabetic BB rats [7] and the observations that class II antigen expression can be induced on both B and non-B islet parenchymal cells [4, 5] suggest that class II expression on islet parenchymal cells may be a non-specific sequela of insulinitis rather than the factor initiating insulinitis.

Yours Sincerely,

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References

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Fig. 1A and B. Photomicrographs showing a small clump of islet parenchymal cells. **A** Phase contrast microscopy showing parenchymal cell granulation. **B** The two cells marked by arrows correspond to the two cells with membrane-staining for HLA-DR antigens