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Response from the authors

Dear Sir,
We read with interest the comment by Drs. Odawara and Yamashita claiming a minor contribution of the mitochondrial DNA mutation at 3243 bp (A to G) (mtDNA 3243 mutation) to the aetiology of autoimmune insulin-dependent diabetes mellitus (IDDM). We would like to emphasize that a high proportion of diabetic patients with the mtDNA 3243 mutation have cytoplasmic islet cell antibodies (ICA) and an IDDM-related HLA-DQ allele [1]. Our diabetic patients with mtDNA 3243 mutation included subjects with various clinical phenotypes of diabetes ranging from non-insulin-dependent diabetes (NIDDM) to IDDM [1]. The prevalence of mtDNA 3243 mutation is not high in IDDM patients, ranging from 0 to 11 % [2–4]. Thus, one cannot simply extrapolate from our results to a general conclusion that the mtDNA 3243 mutation forms a background for beta-cell destruction in a majority of IDDM patients. However, fasting serum C-peptide levels were less than 0.17 nmol/l in 3 of 16 insulin-treated diabetic patients in our previous report [1], indicating that some of them actually had IDDM. A closer relationship between the mtDNA 3243 mutation and ICA was confirmed in Japanese and Caucasian populations [5, 6]. Oexle et al. [6] reported the presence of ICA in an extremely insulin-deficient diabetic mother (10 JDF units), and her son had impaired glucose tolerance (80 JDF units). They had at least one HLA-DQ allele associated with IDDM. Apparently, it is still premature to conclude that the presence of pancreatic autoantibodies in diabetic patients with the mtDNA 3243 mutation is a secondary consequence rather than a cause of beta-cell destruction. B lymphocyte mediated factor is essential in the development of autoimmune NOD mice [7]. It is generally assumed that IDDM is a heterogenous disease in which multiple loci and other factors influence the initiation and progression of beta-cell failure through immunological, viral and/or chemical mechanisms in an additive manner [8, 9]. In this context, mtDNA 3243 mutation constitutes one distinct genetic background for IDDM, even if a minor proportion of IDDM patients have this mutation.

The relationships among the mtDNA 3243 mutation, pancreatic autoimmunity and beta-cell destruction may be clarified by analysing the pancreas in diabetic patients with the mutation. We examined histological changes in the autopsied pancreases of 16 IDDM patients and 18 NIDDM patients [10]. One of 16 (6 %) IDDM pancreases had a high proportion of islet cells with mtDNA 3243 mutation, as well as some exocrine cells. We found beta-cells to be reduced along with decreased mitochondrial DNA-encoded enzyme related oxidative phosphorylation (OXPHOS): cytochrome c oxidase (COX), as well as enhanced nuclear-encoded enzyme related OXPHOS: succinate dehydrogenase (SDH) in the affected pancreas. Hyperexpressed SDH (complex II) activity in the islet cells may accelerate damage to beta-cells through increased toxic hydroxyl radicals generated from the accelerated electron transport system via the enhanced complex II pathway, which generates four times more mitochondrial superoxide than electrons channelled via the complex I pathway [11]. DNA damage in beta cells due to toxic hydroxyl radicals is assumed to be a possible cause of IDDM [12]. $CD8^+$ lymphocyte infiltration around the islets as well as pancreatic exocrine cells was also observed in the pancreas with the mutation.

In conclusion, pathological features in the pancreas of diabetic patients with the mitochondrial DNA mutation as well as humoral markers represented by ICA may provide new insights into the mechanisms of beta-cell destruction in at least one distinct clinical phenotype of IDDM.

Yours sincerely,
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