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CLINICAL PEARLS UPDATE#16

Type 1 Diabetes

January 13, 2004

Dear Colleague:

Our understanding of the fundamental roles of autoimmunity in **type 1 diabetes** continues to grow. Prof. Irun Cohen and colleagues have contributed some of our more profound insights. The following three studies point out that repair inducing 'heat shock proteins (HSP60 and HSP70)' and not others (HSP90) were significantly different in type1 diabetic children than non-diabetic control children and the role of T lymphocytes in diabetes. This is consistent with the view that overload of the immune defense system in early life increases the risk of developing diabetes, particularly in children lacking sufficient antioxidant repair enabling nutrients. **This is also consistent with the view that identifying and substituting for 'delayed allergens' can help reduce the complications of and improve the management of type 1 diabetes. This is what advanced LRA by ELISA/ACT® tests and treatment plans are designed to do in type 1 diabetics, particularly for the T cells (type IV DTH) that only a functional, *ex vivo* lymphocyte response assay like LRA by ELISA/ACT can measure.**

We encourage you to share this valuable clinical update newsletter with your colleagues and staff so they can learn more about how our comprehensive approach can be applied to their practice with beneficial results. Please also let us know if any of your colleagues or staff would like to be added to our email distribution list.

We are grateful for the opportunities to be of service to you and your patients.

Sincerely,

Russ Jaffe, MD, Ph.D., CCN, NACB
Lab Director

Abulafia-Lapid R, Gillis D, Yosef O, Atlan H, Cohen IR. **T Cells and autoantibodies to human HSP70 in Type 1 diabetes in children.** *J Autoimmun* 2003;20(4):313-321.

We studied T-cell proliferative responses (stimulation index: SI) and autoantibodies to human HSP60, HSP70 and HSP90 proteins in 25 children (mean age 10.1 ± 3.8 years) newly diagnosed with Type 1 diabetes. The control group for T cells included 25 adults and three pediatric donors without Type 1 diabetes. Controls for antibodies included 10 pediatric subjects. The T-cell responses to HSP70 of the test group (mean $SI=4.5 \pm 3.1$) were significantly greater than those of the control group (mean $SI=1.4 \pm 0.6$; $p < 0.0001$); the incidence of HSP70 responders was (85%) compared to 14% in the control group. All but three of the Type 1 children who responded to HSP70 also responded to HSP60 (85%). The T-cell responses of the Type 1 group to HSP90 (mean $SI=1.7 \pm 1.1$) were similar to those of the control group (mean $SI=1.5 \pm 0.7$). We mapped HSP70 epitopes recognized by T cells in seven subjects using overlapping peptides of the molecule. Among the Type 1 subjects, IgG seropositivity was 45% to HSP60, 30% to HSP70, and 15% to HSP90. Thus, we conclude that children with newly diagnosed Type 1 diabetes manifest heightened T-cell autoimmunity to HSP70 and HSP60, but not to HSP90.

Abulafia-Lapid R, Elias D, Raz I, Keren-Zur Y, Atlan H, Cohen IR. **T cell proliferative responses of type 1 diabetes patients and healthy individuals to human hsp60 and its peptides.** *J Autoimmun* 1999;12(2):121-129.

T cell responses to peptide epitopes of the 60 kDa heat shock protein (hsp60) have been shown to play a role in the pathogenesis of type 1 insulin-dependent diabetes mellitus (IDDM) in mice. To test whether hsp60 autoimmunity might be involved in human type 1 diabetes, we studied T cell proliferative responses (stimulation index; SI) to intact human hsp60, to hsp60 peptides and to a recall antigen (tetanus toxoid) in 25 newly diagnosed type 1 diabetes patients, in 22 type 2 (non-insulin-dependent diabetes mellitus, NIDDM) patients, and in 25 healthy blood donors. There were no significant differences between the T cell responses of the three groups to tetanus toxoid. However, the responses to hsp60 of the type 1 diabetes group (median $SI=5$) were significantly greater ($P < 0.01$) than those of the type 2 group (median $SI=1.67$) and of the blood donors (median $SI=1.7$). Epitope mapping revealed significant responses to at least seven different peptides, with prevalent responses to the p277 peptide previously mapped in NOD mice and to peptide p32. Thus, newly diagnosed type 1 diabetes patients, similar to prediabetic and newly diabetic NOD mice, show heightened autoimmunity to hsp60 and hsp60 peptides.

Birk OS, Cohen IR. **T-cell autoimmunity in type 1 diabetes mellitus.** *Curr Opin Immunol* 1993;5(6):903-909.

Insulin dependent diabetes mellitus is a T-cell mediated autoimmune disease. Several beta-cell antigens, mostly non-tissue-specific, have been implicated in the disease process. The antigens and the autoimmune T cells exist in healthy individuals, as do many of the genes required for the development of diabetes. The question, then, is why and how exposure to undefined environmental agents activates an existing autoimmune potential and directs it to damage the beta cells.

