

Functional Characterization of Patients With Autoimmunity and Defective Lymphocyte Apoptosis: Role of Caspases.

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Novel pathogenic mechanisms underlying the association of immune defects with autoimmunity are now emerging. However, in many cases the pathogenesis still remains to be clarified. Alterations of molecules involved in cell apoptosis lead to an abnormal lymphocyte accumulation, autoimmunity, characterized by intense polyreactive autoreactions, or lymphoid malignancies. Recent evidence indicates that caspase 8 alteration results in defective lymphocyte apoptosis and homeostasis, and defective activation of T, B and NK cells. Aim of this study was to identify, within a group of patients affected with Clustering of Autoimmune Diseases (CAD) and abnormal FAS-induced apoptosis, a subgroup of patients with defective cell activation. Patients were selected according to the presence of at least 2 distinct autoimmune disorders in the same individual. In all patients FAS induced apoptosis and the proliferative response to common mitogens (PHA, PWM, CD3 X-L) were evaluated by standard procedure. Caspase 8 molecular study consisted of direct sequencing of 7 out of 10 exons of the gene which were considered functionally relevant. Thirty four subjects with a CAD phenotype (19 women) were identified. Thirteen out of these 34 patients (38%) had reduced T-cell proliferation after stimulation. The presence of a IVS9nt53051 alteration in intron 9 of caspase 8 gene was found in 9 out the 13 patients. Seven subjects were heterozygous and 2 homozygous for the alteration. This change may potentially affect the site of alternative splicing between various isoforms of caspase 8. Our data indicate that the association between alterations of cell apoptosis and cell activation is more frequent than expected. Although, the role of the caspase 8 gene alteration still remains to be elucidated, it is conceivable that it may interfere as a cofactor in either inflammation or cell death.