Disturbed B-lymphocytes selection in autoimmune lymphoproliferative syndrome

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Meeting abstract

Autoimmune lymphoproliferative syndrome (ALPS) is characterized by lymphoproliferative disease, autoimmune cytopenias and increased susceptibility to lymphoid malignancies. Central to the pathophysiology of the disease are defects in the FAS signaling leading to impaired lymphocyte homeostasis. Most of the patients harbor heterozygous germline or somatic mutations in *FAS*. The hallmark of the disease is the impaired FAS-mediated apoptosis of activated T cells and presence of atypical "double-negative" T cells (CD3+TCRalpha/beta+CD4-CD8-). While FAS is essential for deletion of autoreactive B cells in the germinal center in murine models, the role of FAS in human B cell selection and development of autoimmunity in patients carrying *FAS* mutation is unclear.

We analyzed patients with somatic *FAS* mutation or germline *FAS* mutation plus somatic loss-of-heterozygosity allowing to compare the fate of B cells with impaired versus normal FAS signaling within the same individual. We found in the class-switched memory B cells: 1) accumulation of *FAS*- mutated B cells, 2) a failure to enrich single V genes and in single V-D, D-J gene combinations of the B cell receptor variable region, 3) increased frequency of variable regions with higher content of positively charged amino acids and longer CDR3 and 4) maintenance of polyreactive specificities. Importantly, *FAS*-deficient switched memory B cells showed increased rates of somatic hypermutation. Our data uncover a defect in B cell selection in ALPS patients and indicate a role for B cell dysregulation in the pathogenesis of autoimmunity and B-cell lymphoma in ALPS patients.