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Affective Lymphoproliferative Disorders and Immune Checkpoint Deficiency

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ALPS are a non-malignant and non-infectious lymphoproliferative condition caused by mutations in genes that alter the extrinsic apoptotic pathway [1]. The proliferation and build-up of auto reactive (double-negative) T cells caused by the FAS-mediated apoptosis deficiency leads to cytopenias, splenomegaly, lymphadenopathy, autoimmune diseases, and the risk of lymphoma. Other monogenetic disorders known as ALPS-like syndromes can be clinically similar to ALPS but are genetically and biologically distinct, such as those seen in patients with immune checkpoint deficiencies, particularly cytotoxic T-lymphocyte antigen 4 (CTLA-4) insufficiencies and lipopolysaccharide-responsive beige-like anchor protein LRBA deficiency. Heterozygous mutations in CTLA-4, an important negative immune regulator that is constitutively expressed on regulatory T (Treg) cells, induce CTLA-4 insufficiency [2]. Mutations in CTLA-4 affect CTLA-4 binding to CD80-CD86 costimulatory molecules, CTLA-4 homodimerization, or CTLA-4 intracellular vesicle trafficking upon cell activation. Abnormal CTLA-4 trafficking is also observed in patients with LRBA deficiency, a syndrome caused by biallelic mutations in LRBA that abolishes the LRBA protein expression.

Low amounts of CTLA-4 protein on the cell surface of Tregs define both immune checkpoint deficits, which accounts for the autoimmune symptoms seen in CTLA4-insufficient and LRBA-deficient individuals. Moreover, despite the differences in heredity and penetrance, both immune checkpoint defects present with an overlapping but varied clinical picture [3]. The most significant clinical aspects of ALPS, CTLA-4 insufficiency, and LRBA deficiency are described in this review, with emphasis on their related molecular causes. We also discuss several clinical and laboratory techniques for diagnosing these three uncommon immunological illnesses, as well as therapy options that have been shown to improve patient prognosis and quality of life [4].

The immune system can recognise and remember specific molecular structures from pathogens thanks to the enormous BCR (B cell receptor) and TCR (T cell receptor) repertoires that have been generated through a randomised gene rearrangement and somatic mutation process. This provides long-term protection against recurrent infections [5]. The development of lymphocytes reactive to self-antigens is, nevertheless, an unavoidable consequence of this receptor diversification process. Two primary strategies have been found to govern these auto-reactive cell clones: The first is called central tolerance, and it involves the thymus and bone marrow deleting self-reactive T and B cells, respectively.

- In patients with heterozygous CTLA4 mutations and individuals with biallelic LRBA mutations, immune checkpoint mechanisms are disrupted. Both illnesses have a decreased overall abundance of CTLA-4, resulting in Treg suppressive activity that is faulty

- Chronic lymph proliferation, organomegaly, and antibody-mediated autoimmune cytopenias are all symptoms of ALPS, CTLA-4 insufficiency, and LRBA deficiency. In contrast to ALPS, hypogammaglobulinemia, enteropathy, and recurrent respiratory tract infections can all be symptoms of CTLA-4 insufficiency and LRBA deficiency

- In ALPS with an autosomal dominant mode of inheritance and CTLA-4 deficiency, there is insufficient clinical penetrance as well as varying severity. To far, no gene or environmental modifier has been identified that accounts for the partial clinical penetrance, as well as the varying severity and expressivity.

- To identify ALPS patients, laboratory tests for differential diagnosis include: I high DNTs, ii) faulty in vitro lymphocyte apoptosis and iii) elevated soluble Fas ligand. Individuals with CTLA-4 deficiency have aberrant CTLA-4-dependent transendocytosis, whereas patients with LRBA deficiency have nil or reduced LRBA protein production when stimulated in vitro.

- Corticosteroids and immunosuppressive drugs, immunoglobulin replacement, and antibiotics are used to treat ALPS, LRBA deficiency, and CTLA-4 insufficiency. Sirolimus, in particular, has demonstrated effective management of illness symptoms. Patients with CTLA-4 deficiency and LRBA deficiency may be able to regulate their T cell activation with abatacept. HSCT, on the other hand, is the only potentially curative therapy.

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