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Scaling the tips of the ALPS

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ABSTRACT

This special issue contains four review articles that describe advances in analysis of mutations responsible for the autoimmune lymphoproliferative syndrome (ALPS). This disease is triggered by a family of mutations in genes involved in the extrinsic apoptotic pathway such as FAS, FASL and CASP10. Advances in sequencing technology have enabled extended genetic testing of patients with various defects in alternative biological pathways that can cause ALPS-like syndromes. Various gene mutations were identified which affect the CTLA-4 immune checkpoint, the STAT3 pathway and the RAS/MAPK pathway. Tips gleaned from analyses of the different gene mutations involved in ALPS and ALPS-like syndromes are contributing to a better understanding of their functional consequences. Genetic diagnoses of the disease should help us to identify specific therapeutic targets and design personalized treatment for each patient.

In 1995, heterozygous mutations in the FAS gene were found to be responsible for a rare pediatric disease referred as autoimmune-lymphoproliferative syndromes (ALPS) [1,2]. These mutations impair the apoptotic function of FAS, thereby preventing lymphocyte death and leading to a nonmalignant lymphoproliferative syndrome that manifests itself by lymphadenopathy, splenomegaly and sometimes hepatomegaly. This lymphoproliferation is associated with polyclonal hypergammaglobulinemia and is characterized by the accumulation of CD4⁺ CD8⁻ double-negative T lymphocytes. Autoimmune cytopenia are observed in two thirds of the patients.

Other rare gene mutations affecting the FAS apoptotic pathway were identified subsequently in ALPS, such as mutations in the FAS Ligand (FASLG), FADD and Caspase 10 genes. These findings identified the apoptotic function as a key checkpoint controlling lymphocyte homeostasis. However, several other ALPS-like disorders, with normal apoptotic activities, were also diagnosed. The development of Next Generation Sequencing (NGS) has enabled major progress in genetic analyses revealing defects in several biochemical pathways. These include CTLA-4 expression, a key immune checkpoint inhibitor, and JAK-STAT and RAS pathways, the latter two being major signaling pathways transducing signals

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from the antigen and cytokine receptors. Of note, lymphocytic tissue infiltration and solid organ autoimmunity is frequently observed in ALPS-like diseases, whereas the lymphoproliferative syndrome is restricted to the lymphoid tissue in ALPS-FAS patients. This highlights a specific and non-redundant role for these pathways in the regulation of immune homeostasis in lymphoid organs or tissues.

This special issue of the *Biomedical Journal* contains four review articles that describe: 1) mutations of the FAS/FAS-Ligand pathway, 2) deficiencies of CTLA-4 (Cytotoxic T Lymphocyte-associated Antigen-4) and LRBA (Lipopolysaccharide-Responsive Beige-like Anchor protein); 3) gain of function (GOF) mutations of STAT3 (Signal Transducer and Activator of Transcription 3); and 4) RASopathies, which consist of several disorders caused by mutations of constituents of the RAS/MAPK biochemical pathway.

In the first review article, Dr. Magerus and her colleagues analyze mutations affecting the FAS pathway associated with ALPS diagnosed in 130 patients of a French cohort, in addition to the mutations described in the literature [3]. In the first part of this review, the *Fas/Faslg* autosomal recessive mutations identified in mice are compared to the FAS/FASLG mutations in humans. The well-characterized mutations of the *Fas* (*lpr*, *lpr^{ce8}*) and *Faslg* (*gld*) murine genes are briefly described. Only animals homozygous for these mutations develop lymphoproliferation and autoimmunity. However, the severity of the pathology depends on the genetic background of the mouse strain in which the *Fas* and *Faslg* mutations are expressed. Thus, the homozygous *fas^{lpr}* mutation expressed on the MRL background induces a very strong lymphoproliferation associated with severe lupus, while in the C57BL/6 strain, both lymphoproliferation and autoimmunity are minimal. In contrast, in humans, the FAS mutations are more heterogeneous and different genetic mutations can lead to ALPS (1): germline heterozygous mutations (2), somatic dominant mutations (3), accumulation of germline and somatic FAS mutations (4), germinal homozygous or compound heterozygous mutations. The article provides interesting analyses of almost 100 different genetic mutations of FAS genes identified in 130 patients diagnosed with ALPS. Strikingly, while the causes of ALPS have been shown to involve mutations in various genes of the FAS/FASLG pathways such as FAS, FASLG, FADD, and *Caspase 10*, the majority (90%) of these ALPS patients had mutations in the FAS gene only.

Thus, the FAS mutations found in these patients can be schematically grouped in 3 categories: germline ALPS-FAS, somatic FAS, and FAS/Somatic FAS. The clinical penetrance of heterozygous mutations is variable, among mutations in the FAS intra-cellular domain 80% lead to ALPS, while only 30% of mutations in the FAS extra-cellular domain result in ALPS. Importantly, in several ALPS families bearing a FAS mutation with partial clinical penetrance, a lack of mutation on the second allele of FAS suggests that another unidentified mutated gene cooperates with the FAS mutation to abolish the FAS-mediated apoptotic pathway. In about 20–30% of ALPS-FAS patients, the additional mutated gene(s) have not been identified yet. This well documented and illustrated review (7 figures), should help readers understand how various FAS gene mutations (alone or combined) contribute to the development of ALPS.

The second article, by Drs. Gamez-Diaz and Grimbacher, analyzes the role of heterozygous mutations of CTLA-4 and of biallelic mutations of LRBA in patients with ALPS-like disorders [4]. Heterozygous mutations of CTLA-4 induce abnormal CTLA-4 binding to the co-stimulatory CD80/CD86 molecules, defective homodimerization of CTLA-4, a decrease in CD80/CD86-transendocytosis, and a default in CTLA-4 vesicle trafficking leading to decreased expression of CTLA-4 on T lymphocytes. Likewise, biallelic mutations of LRBA affect vesicle trafficking of CTLA-4. It had been demonstrated that LRBA is associated with CTLA4 in endosomal vesicles and that LRBA deficiency enhanced CTLA4 turnover, leading to decreased levels of CTLA-4 on FoxP3⁺ regulatory and activated conventional T lymphocytes. Thus, CTLA-4 deficiency generates a defective regulatory T cell compartment. CTLA-4 is constitutively expressed at the cell surface of regulatory T cells and plays a major role in maintaining immune tolerance. Thus, overlapping clinical features are associated with heterozygous mutations of CTLA-4 and biallelic mutations of LRBA, as both types of patients have reduced cell surface expression of CTLA-4 causing a decrease in regulatory functions of suppressive T lymphocytes. CTLA-4 deficient patients present several clinical symptoms such as autoimmune cytopenia, lymphocyte infiltrations of non-lymphoid organs, enteropathy, a loss of circulating B lymphocytes associated with a high frequency of infections, and rarely, EBV-associated Hodgkin lymphoma and gastric cancers. Importantly, heterozygous mutations of CTLA-4 lead to an incomplete clinical penetrance, with 30% of patients bearing the mutations affected by one or few clinical manifestations. This incomplete penetrance of CTLA-4 mutations is most probably due to additional genetic or environmental causes. In contrast, the heterozygous *Ctla4^{+/-}* mice are healthy and differ from human patients with heterozygous mutations of CTLA-4. However, *Ctla4^{-/-}* animals present a massive lymphoproliferation associated with fatal destruction of several organs.

An important paragraph is devoted to the topic of LRBA deficiency. It describes and discusses the differences between human disease and the murine model. In addition, it analyzes LRBA deficiency in different patients, some of whom present clinical symptoms even though their healthy siblings possess the same homozygous LRBA mutations. These observations suggest that other modifier genes are involved in the severity of clinical manifestations.

In the last part of the manuscript, the authors compare malignancy, differential diagnosis and treatment options in ALPS-FAS, CTLA-4 insufficiency and LRBA deficiency. Several laboratory tests can be performed to discriminate between the three diseases – which may begin with similar clinical pictures – before definitive genetic identification of the mutated genes. Fig. 1 presents the strategy used to discriminate CTLA-4 insufficiency from LRBA deficiency. Finally, a table in the article summarizes the principal characteristics of ALPS, CTLA-4 insufficiency and LRBA deficiency. These genetic diagnoses are critical for the patients as targeted therapies, such as mTOR inhibitors in ALPS-FAS or CTLA-Ig in CTLA-4 and LRBA deficiencies, have proven to be very specific and efficient depending on the underlying genetic defect.

In the third article, Dr. Faletti and colleagues summarize the cellular and clinical phenotypes of Germline STAT3 GOF

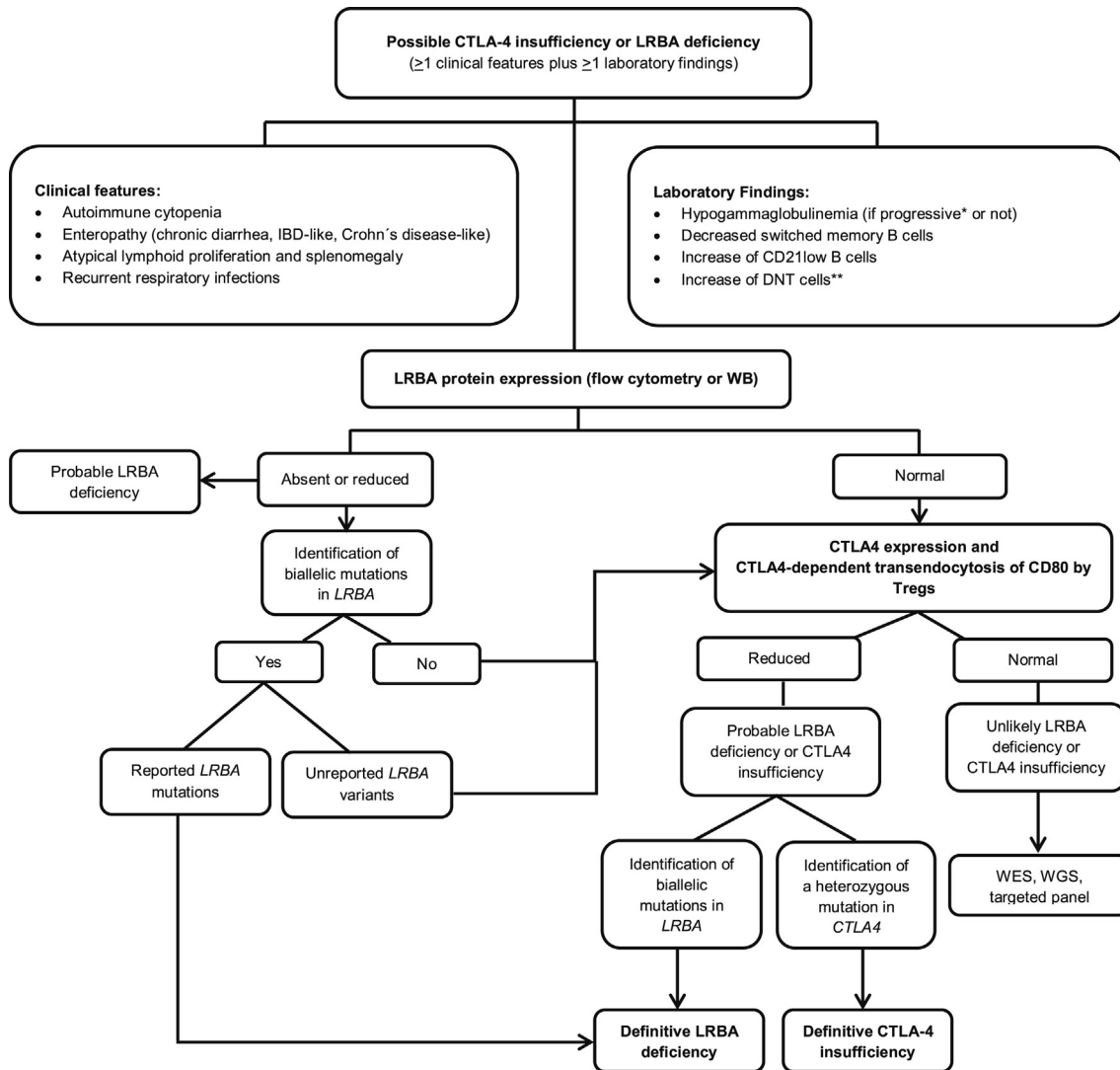


Fig. 1 Differential diagnosis for LRBA deficiency and CTLA4 insufficiency. (From reference 4.)

mutations in primary immunodeficiency [5]. STAT3 GOF diseases present a large phenotypic heterogeneity, with autoimmune cytopenia, lymphoproliferations, susceptibility to infections, hypogammaglobulinemia, enteropathy and growth deficiency being frequent clinical manifestations. As observed in ALPS and other ALPS-like diseases, an incomplete clinical penetrance for STAT3 GOF mutations is observed because not all mutation carriers become symptomatic, indicating that additional genetic or environmental factors are involved in the pathology. The authors summarize the STAT3 biochemical pathway and its post-translational modifications [Fig. 2]. Interestingly, most STAT3 GOF mutations in patients with autoimmunity and lymphoproliferation were localized to the 6 functional domains of the transcription factor. Thus, the different mutations should act at various stages of the signaling pathway and result in variable clinical and immunological manifestations. Analyses of the molecular mechanisms triggered by 17 distinct STAT3 mutations showed that STAT3 GOF mutations could be classified in one of three different groups which possess a characteristic molecular

pattern associated with different clinical manifestations. In this very stimulating review, the authors analyze and discuss the difficulties encountered in establishing the diagnosis of STAT3 GOF disease since presently we lack specific clinical or routine laboratory tests. The identification of STAT3 GOF mutations is also important for designing specific and efficient therapies. Indeed, JAK-inhibitors, a novel class of molecules currently used in cancer treatments, were found to be efficient for controlling the STAT3 GOF-mediated diseases. At first it could seem counter-intuitive to use the JAK-inhibitors in this context as the STAT3 GOF mutants lie downstream from the JAKs. The efficacy of the JAK-inhibitor treatment reveals a pathological molecular loop of activation that can be blocked by upstream inhibitors.

The last article, by Drs. Riller and Rieux-Laucat, analyzes several diseases called RASopathies which are due to various germline or somatic mutations in components or regulators of the RAS/MAPK biochemical pathway [6]. Importantly, these mutations are gain-of-function mutations that lead to the activation of the RAS/MAPK pathway by different mechanisms,

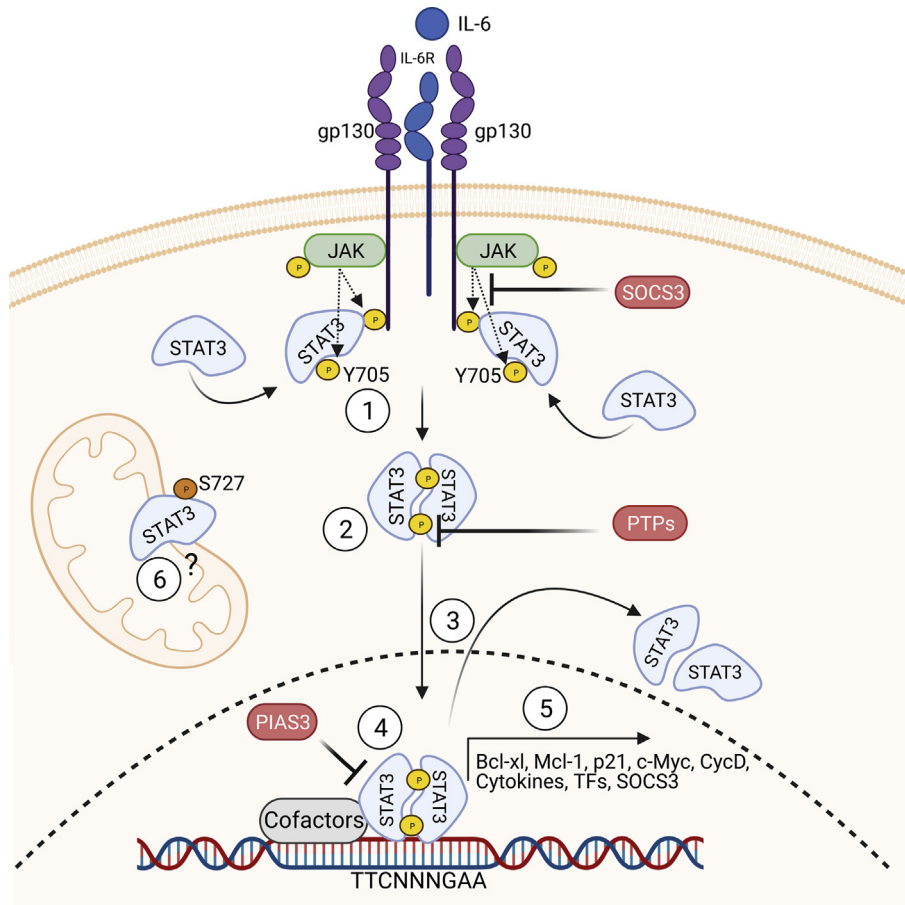


Fig. 2 Overview of the STAT3 signaling pathway. (From reference 5.)

which explains the heterogeneous clinical manifestations. The germline mutations are associated with a group of developmental syndromes, illustrating the central role of the RAS/MAPK pathway in many cell types. Interestingly, the same activating mutations, when somatic, are associated with an early-onset of hematological malignancies called Juvenile Myelo-Monocytic Leukemia (JMML). In particular, somatic KRAS or NRAS mutations can lead to three different pathological conditions. In most cases, they lead to an aggressive JMML requiring chemotherapy and allogeneic hematopoietic stem cell transplantation. Intriguingly, in some cases, the leukoproliferation resolves spontaneously, and the patients remain in remission all life-long, despite persistent hematological abnormalities. This condition is defined as JMML long survivors. Intriguingly, the third group of patients with somatic KRAS or NRAS mutations developed an ALPS-like phenotype with leukoproliferation, hypergammaglobulinemia and autoimmune cytopenia named RALD (Ras-Associated Leukoproliferative Disease). T cells from the RALD patients exhibit a defect of the so-called “intrinsic apoptosis pathway”. This Activated-Cell Autonomous Death (ACAD) is independent of the death receptors family, including FAS, and is mediated by the activation of BIM, a pro-apoptotic member of the BCL2-family. Although RALD is a benign disease – and is well controlled by

immunosuppressive treatments – these patients may develop acute leukemia later in life. The authors then discussed the mechanisms that, in the context of a KRAS or NRAS somatic activating mutations, could lead from autoimmunity to leukemia.

Taken together, these four complementary review articles provide a global view of the main genetic predispositions leading to uncontrolled lymphocyte expansion and autoimmunity in humans. They highlight the growing evidence of a key role for somatic mutations as predisposing factors to autoimmunity in these rare diseases. By extension, the somatic mutations could make a major contribution to more common diseases, as recently illustrated in an adult vasculitis called the VEXAS (vacuoles, E1 enzyme, X-linked, auto-inflammatory, somatic) syndrome [7]. Finally, these reviews stress the importance of genetic diagnosis to provide a better understanding of the pathophysiological mechanisms underlying autoimmunity and to identify specific therapeutic targets, paving the way to personalized medicine.

Conflicts of interest

The authors are editors with *Biomedical Journal*.

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