

Autoimmune lymphoproliferative syndrome

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Purpose of review

The autoimmune lymphoproliferative syndrome is a recently identified human disorder of lymphocyte apoptosis that has provided important information about Fas-mediated lymphocyte apoptosis. In this review we summarize current information regarding the diagnosis, management and underlying molecular basis of the syndrome.

Recent findings

The genetic basis of autoimmune lymphoproliferative syndrome has continued to expand with the recently identified defects in caspase-8 and caspase-10 along with the more frequent defect in Fas and unusual Fas ligand deficiency. Genotype–phenotype links and differences continue to be assessed while the variation in penetrance remains to be fully defined. An increased risk for lymphoreticular malignancy has clearly been established in those autoimmune lymphoproliferative syndrome patients with defects in the gene encoding for the death domain of Fas. Therapy remains directed at managing acute problems although a preliminary report suggests sulphadoxine–pyrimethamine treatment may be successful in patients with the syndrome or autoimmune lymphoproliferative syndrome-like disease and this approach is presently being studied in a controlled trial.

Summary

Defects in multiple molecules within the Fas apoptotic pathway may result in autoimmune lymphoproliferative syndrome and, despite recent advances, a number of patients remain with unidentified genetic defects. There is also clear need for improved understanding of mechanisms underlying the development of autoimmunity in this disorder and to provide early evidence for development of malignancy. This syndrome is the first human disorder linked to a germline defect in lymphocyte apoptosis and it continues to be an area of productive research and new information regarding this process of lymphocyte homeostasis and its role in human disease.

Keywords

apoptosis, autoimmunity, caspase, Fas, Fas ligand, lymphoma, lymphoproliferation, autoimmune lymphoproliferative syndrome

Abbreviations

ALPS	autoimmune lymphoproliferative syndrome
DNT	double-negative T
FADD	Fas-associated death domain
FasL	Fas ligand
NIH	National Institutes of Health
TCR	T-cell receptor
TNF	tumor necrosis factor
TNFRSF	tumor necrosis factor receptor superfamily

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Introduction

The autoimmune lymphoproliferative syndrome (ALPS) is caused by a defect in lymphocyte apoptosis resulting in the chronic accumulation of non-malignant lymphoid cells, increased circulating T cell receptor (TCR)- α/β^+ CD4 $^-$ and CD8 $^-$ T cells (double-negative T (DNT) cells) and autoimmune manifestations. The majority of cases result from a mutation in the tumor necrosis factor (TNF) receptor superfamily (TNFRSF)6 gene, *TNFRSF6*, encoding for Fas (CD95) with additional cases linked to defects in the genes encoding Fas ligand (FasL) (TNF superfamily 6 gene, *TNFSF6*) or molecules downstream in the Fas pathway (*CASP8* and *CASP10*) [1–4]. Canale and Smith [5] described a clinical syndrome compatible with ALPS originally in 1967. Sneller and colleagues [6,7] first made the link between ALPS and defective Fas-mediated apoptosis in 1992, when they described the similarities between this human disease and the autoimmune MRL/lpr mouse model that had been found to have a spontaneous Fas defect. Later, the first cases of human disease caused by Fas mutations were confirmed, including some of the original patients described by Canale and Smith [1,2,8]. This ‘experiment of nature’ highlights the importance of the Fas pathway in immune homeostasis. This review briefly discusses the clinical and laboratory findings, genetic basis and latest advances in the understanding of ALPS.

Lymphocyte apoptosis

Apoptosis is a genetically determined program of cell death responsible for the control of cell number and elimination of senescent, damaged or unwanted cells without provoking inflammation [9–11]. In mature T lymphocytes, apoptosis occurs by two major pathways: an extrinsic (active) mechanism mediated by membrane receptors of the TNFRSF and their ligands belonging to the TNF superfamily; and an intrinsic (passive) cell death following cytokine withdrawal after antigenic clearance, mediated by members of the Bcl-2 family of

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proteins [12]. Fas (also known as TNFRSF6, CD95 or APO-1) is a prototypical member of the TNF subfamily of receptors containing a death domain within the cytoplasmic region (death receptors) [13]. Other members of this family include TNF-R1 (TNRSF1A), DR3 (TNFRSF12), Trail-R1 and Trail-R2 (TNFRSF10A and B) and the death receptor DR6 [14]. Resting T cells express low levels of FasL (CD95L) and high levels of c-FLIP, a negative regulator of Fas signaling [12]. Following T cell receptor (TCR) encounter with cognate antigen, autocrine/paracrine stimulation with IL-2 and cell cycling, there is induction of the FasL gene and concomitant downregulation of c-FLIP levels, sensitizing the cells to apoptosis [15]. But cell death does not occur until TCR re-engagement occurs, promoting ligation of Fas by FasL present on the cell surface (through a clonotypical 'propriciidal' or 'fratricidal' mechanism) or by soluble FasL generated by cleavage of membrane-anchored FasL by metalloproteinases [12,16,17]. The finely tuned regulation of the lymphoid homeostasis allows the initial immune response to develop normally while providing a timely negative-feedback mechanism to avoid excessive and potentially dangerous over-expansion of the T lymphocyte pool after repeated stimulation as well as eliminating potentially autoreactive lymphocytes. Alternatively, if the activated T cells are not re-stimulated, the levels of IL-2 fall and the cells die by a mitochondria-mediated intrinsic apoptotic mechanism (cytokine withdrawal) [12].

The central role of Fas in lymphocyte biology was first recognized when the *MRL/lpr* and *gld* murine disease models were demonstrated to result from defects in Fas and FasL, respectively [6,18,19]. These mice present with lymphoid hyperplasia, hypergammaglobulinemia, autoantibody production, glomerulonephritis and accumulation of DNT cells [19]. The recognition of the similarities between the murine disease and the human syndrome paved the way to the identification of the first patients with Fas receptor defects in 1995 [1,2,7,8].

Fas receptor structure and signaling

The Fas receptor has three extracellular cysteine-rich domains, a transmembrane region and an 80 amino acid-long intracellular death domain (Fig. 1) [14]. It is present on the cell surface as a trimeric molecule, through pre-association via a preligand assembly domain formed by the first cysteine-rich domain and part of the protein N-terminus [20]. The intracellular death domain binds through homophilic interactions to an adaptor molecule called Fas-associated death domain (FADD) that also contains a death domain as well as a death effector domain that binds to a homologous death effector domain present in the procaspases 8 and 10 [12]. The complex formed by the Fas receptor, FADD and

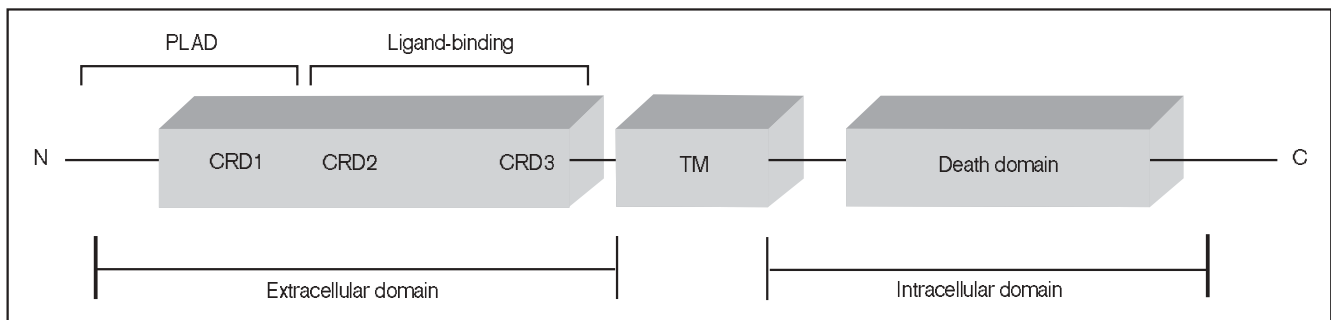
procaspases 8 and 10 is named the death-inducing signaling complex or DISC (Fig. 2) [21]. Although not absolutely proven, it appears that FasL binding to the Fas receptor causes oligomerization of these receptor trimers into super-clusters, bringing in close proximity the intracellular death domains and consequently the FADD and associated procaspase-8 or 10 molecules [22,23]. The forced proximity induces autoprocessing of the procaspases 8 and 10 into their active heterotetrameric forms that cleave several downstream targets including the procaspase-8 and procaspase-10 themselves, caspase-3 and Bid, initiating a cascade that culminates in apoptosis (Fig. 2) [12,24].

Autoimmune lymphoproliferative syndrome genetics and genotype/phenotype relationships

Most patients with ALPS bear heterozygous mutations in the *TNFRSF6* gene (encoding Fas) located on the chromosome 10q24.1 and consisting of nine exons [1,2,25]. Over 70 different mutations have been described so far, either in the coding regions or in the splice sites, with the majority (approximately two thirds) affecting the intracellular death domain (exon 9) (a complete description of all mutations can be accessed online in the ALPS database, ALPSbase, available at <http://research.nhgri.nih.gov/ALPS/>). In-vitro studies showed that co-transfection of the mutant Fas protein with wild-type Fas inhibited Fas function, acting as a dominant-negative mutation [1,2,8,26]. This effect is explained by the fact that pre-associated Fas trimers require three normal protein molecules to function normally (Fig. 2) [20]. In the case of a heterozygous mutation, seven of eight Fas trimers would contain at least one mutant protein rendering that trimer ineffective. Dominant interference has been demonstrated for most ALPS-associated mutations, particularly those affecting the death domain. In addition, a limited number of ALPS patients have been demonstrated to have homozygous and compound heterozygous *TNFRSF6* mutations with loss-of-function and generally more severe symptoms [27].

There is a complex relationship between genotype, phenotype and disease penetrance. In large kindreds studied by the US National Institutes of Health (NIH) and French groups, family members were identified with Fas mutations but no clinical or immunologic features of ALPS [2,28,29]. Despite the fact that all mutation-bearing relatives had defective in-vitro Fas-mediated apoptosis (thus full penetrance of the defect in Fas function), the penetrance of clinical disease varied. Detailed analysis revealed that penetrance was greatest with intracellular death domain mutations and least with extracellular mutations [30]. This data provides clear evidence that other factors, genetic and/or environmen-

Figure 1. Structure of the Fas receptor



The extracellular portion of the molecule is coded by exons 1 to 5; the TM region by exon 6; and the intracellular region by exons 7, 8 and 9. Most pathogenic mutations involve the intracellular death domain (exon 9). PLAD, preligand assembly domain.

tal, influence the clinical phenotype. This is consistent with the *lpr* and *gld* mice, in which the genetic background dictates the type and severity of disease. Recently Chiocchetti and colleagues [31] reported that polymorphisms in the osteopontin gene might increase the susceptibility for the development of an ALPS-like disease.

In a minority of ALPS cases the *TNFRSF6* gene is normal (Table 1) and among these one patient has been found with mutation in the FasL with a clinical presentation resembling systemic lupus erythematosus [32]. Mutations in the gene encoding caspase-10 (*CASP 10*) have been detected in two patients with ALPS, causing defective apoptosis in lymphocytes and dendritic cells and a clinical phenotype similar to patients with Fas defects [4]. Two siblings with mutations in the caspase-8 gene (*CASP 8*) have been recently reported by Lenardo's group [3]. Those patients presented with features of lymphoid accumulation and defective in-vitro Fas-mediated apoptosis but, unlike other ALPS patients, had clinical immunodeficiency characterized by recurrent sinopulmonary and herpes simplex virus infections and poor response to immunization [3]. Defective activation of T, B and natural killer cells also was observed in the caspase-8 deficient patients, implicating that caspase-8 is necessary for lymphocyte activation [3].

Based on the several different molecular abnormalities causing ALPS Sneller and colleagues [33] have proposed a classification scheme (Table 1). Patients with mutations in the *TNFRSF6* gene are classified as type Ia, *TNFSF6* as type Ib, *CASP 8* or *10* as type II and patients without known mutation are classified provisionally as type III. There is yet another category of patients that show signs of lymphoproliferation and autoimmunity but have normal Fas-mediated apoptosis and, thus, fail to fulfill the NIH diagnostic triad of the required features

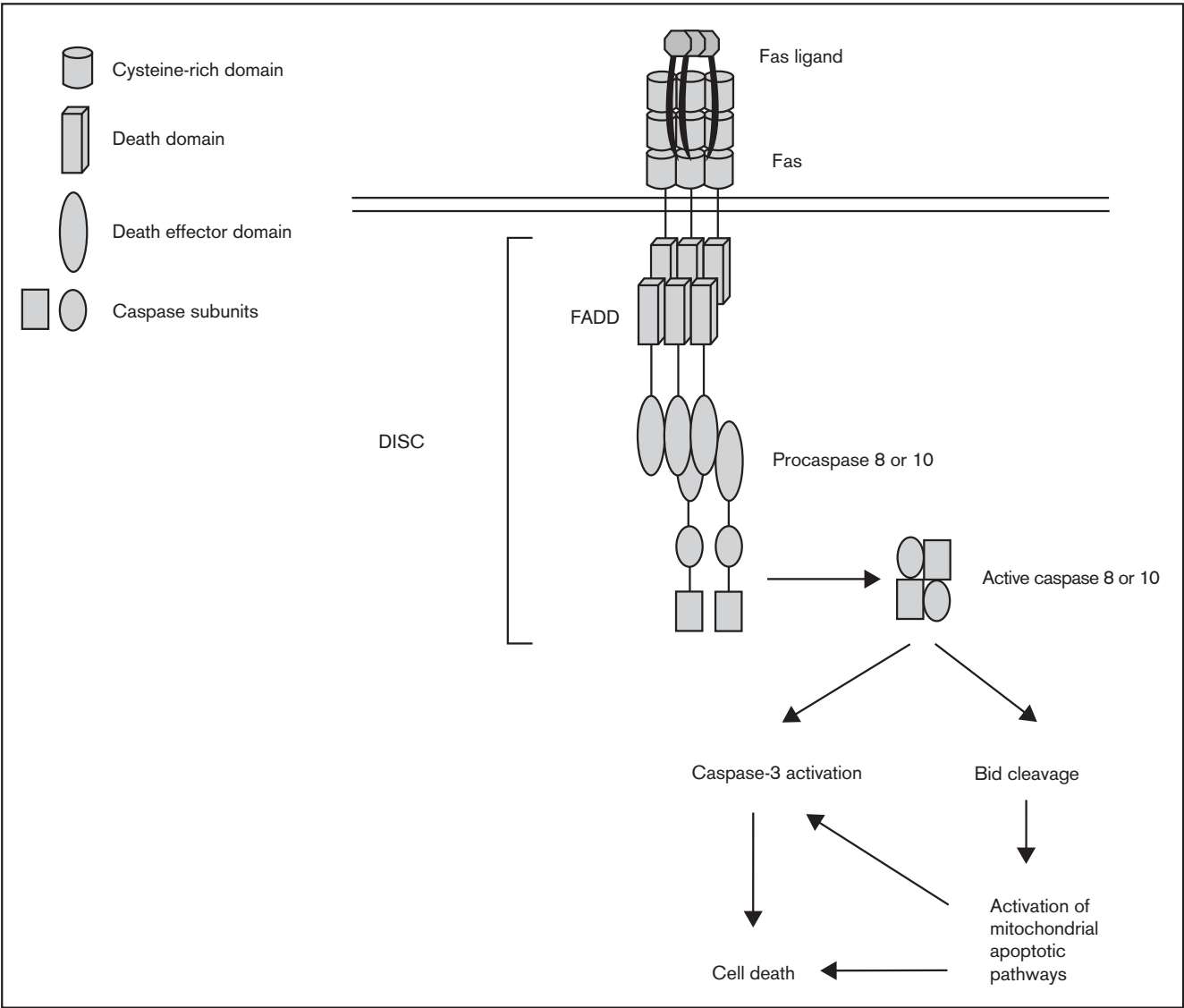
for ALPS: lymphoid expansion, increased α/β -TCR DNTcells ($>1\%$ or >20 cells/mm³) and defective in-vitro Fas-mediated lymphocyte apoptosis [12]. The patients in this last group are currently under intensive investigation. Additional supportive findings for the diagnosis of ALPS include a family history of autoimmune lymphoproliferative syndrome; typical findings on histopathologic analysis of lymph node or splenic tissue; autoimmune disease; and mutation of genes encoding Fas or related apoptosis signaling molecules.

Clinical and laboratory findings

The median age of presentation in the NIH cohort is 24 months, ranging from birth to 15 years old, with a slight skewing towards male sex [33]. By definition, all patients have splenomegaly, lymphadenopathy, or both to varying degrees of severity [34]. In the rare cases of homozygous Fas mutations, prenatal severe lymphoproliferation was observed [1,35,36]. There is usually gradual improvement of the lymphoid hyperplasia with aging, even without treatment [36,37].

Circulating autoantibodies or autoimmune manifestations are present in the majority (up to 80%) of ALPS patients. Coombs' positive autoimmune hemolytic anemia and immune thrombocytopenia are the most common autoimmune diseases associated with ALPS and tend to be severe but often with a variable course [37]. Neutropenia resulting from hypersplenism or of autoimmune origin is also a common finding, but rarely severe enough to cause infectious complications. Interestingly, the anti-platelet antibodies associated with ALPS bind to the same platelet glycoprotein complexes as those found in patients with idiopathic thrombocytopenic purpura [38]; and in one study the specificities of neutrophil-directed antibodies were similar to those in children with autoimmune neutropenia without ALPS [39]. There is a high incidence of anticardiolipin and anti-neutrophil antibodies, but there is no correlation

Figure 2. Simplified Fas pathway



Upon Fas/Fas ligand interaction, Fas-associated death domain (FADD) and procaspase-8 or 10 are recruited into a complex called the death-inducing signaling complex (DISC). The forced proximity induces proteolytic autoprocessing of the procaspases into active caspases, which trigger a cascade culminating in cell apoptosis.

Table 1. Genotype-based autoimmune lymphoproliferative syndrome classification adopted by the National Institutes of Health autoimmune lymphoproliferative syndrome group

Classification	Abnormality
Type Ia	Mutation on <i>TNFRSF6</i> gene
Type Ib	Mutation on <i>TNFSF6</i> gene
Type II	Mutation on caspase 8 or 10 genes
Type III	No known mutation

TNFRSF, tumor necrosis factor receptor superfamily; TNFSF, tumor necrosis factor superfamily.

between the presence of these antibodies and clinical manifestations of thrombosis and neutropenia, respec-

tively [39]. Infrequent manifestations include autoimmune hepatitis, uveitis, Guillain–Barre, anti-factor VIII antibodies and glomerulonephritis, in clear contrast with the mouse *lpr* model, which presents with prominent immune-complex-mediated glomerulopathy [37,40,41–43]. There is no clear explanation for the fact that patients with ALPS present almost exclusively with blood cell-directed autoimmune phenomena.

Demonstration of an in-vitro defect in Fas-mediated lymphocyte apoptosis is an absolute requirement for the diagnosis of ALPS (with the exception of ALPS type Ib, as discussed above). The assay used requires mitogen

activation of peripheral blood mononuclear cells followed by additional culturing in IL-2, to sensitize the cells to Fas killing. At the end of this culture period, the Fas receptor is cross-linked using an anti-Fas monoclonal antibody and the degree of cell death measured [37]. This assay is required for the diagnosis but there is no direct correlation between the magnitude of the in-vitro Fas-mediated apoptosis defect and disease severity.

The immunophenotypic finding required for the diagnosis of ALPS is increased levels of circulating α/β -DNT cells [44]. The α/β -DNT cells are polyclonal and in the murine models have been demonstrated to be derived from proliferating cytotoxic CD8⁺ T cells, although this has not been formally demonstrated in humans [44–46]. The DNT cells express the B220, CD57 and human leukocyte antigen-DR markers [44]. These cells are hypoproliferative and have a decreased capacity to secrete cytokines in response to in-vitro stimulation, but there is evidence they secrete large amounts of IL-10 *in vivo* [37,47]. Other abnormalities present in T cells from patients with ALPS include high expression of human leukocyte antigen-DR and low expression of CD25 [48]. The low expression of the marker CD25 appears to be caused by a selective reduction of the CD4⁺CD25⁺ population, and correlates with the severity of clinical ALPS [48]. The involvement of T regulatory cells in the modulation of ALPS severity is currently under investigation. In addition, increased numbers of CD8 cells expressing CD57 and B cells expressing CD5 are common findings, as well as low numbers of B cells expressing the memory marker CD27 [48].

Certain histopathologic features help to distinguish ALPS from other lymphoproliferative diseases. Lymph nodes show marked paracortical hyperplasia with infiltration of DNT cells and florid follicular hyperplasia with polyclonal plasmocytosis [45]. The spleens are enlarged, with both the white and red pulps expanded and infiltrated by DNT cells [45]. Despite these abnormalities the overall architecture of lymphoid tissues is well preserved and these findings together with the immunophenotypic data are specific enough to make a distinction between ALPS and lymphoid malignancies [45].

Treatment

The treatment of ALPS patients aims primarily at the control of autoimmune manifestations. Most patients receive corticosteroids or cytotoxic agents for the treatment of the immune cytopenias. As a general rule, the immune thrombocytopenia accompanying ALPS is more severe than primary immune thrombocytopenic purpura, and does not respond as well to intravenous immunoglobulin [49]. Many patients require the addition of cytotoxic agents such as azathioprine and

mycophenolate mofetil to maintain acceptable platelet counts [49]. Rituximab has also been anecdotally used with success, but no controlled prospective trials are available to support the widespread use of this drug in the setting of ALPS [50]. Many patients require splenectomy to control hypersplenism in the setting of immune hemolytic anemia, thrombocytopenia or granulocytopenia. Post-splenectomy sepsis has been seen in ALPS patients and appropriate immunization and antibiotic prophylaxis along with careful explanation to the patient and family regarding this risk are advisable.

A preliminary report suggested that sulphadoxine-pyrimethamine (Fansidar) treatment was successful in patients with ALPS or ALPS-like disease, with regression of the symptoms in six of the seven patients studied [51,52]. The suggested mechanism of action was an increased rate of lymphocyte apoptosis through a mitochondria-mediated mechanism [51]. Currently a pilot study to assess the efficacy of pyrimethamine in the treatment of ALPS is underway by the NIH ALPS group.

One case of a homozygous Fas mutation with complete absence of Fas and symptoms starting in the prenatal period has been successfully treated by allogeneic bone marrow transplantation, but homozygous mutations are exceedingly rare [53].

Complications

Patients with ALPS caused by mutations in the Fas death domain have a significantly higher risk of developing lymphoma than the general population (14 times greater for non-Hodgkin lymphoma and 51 times greater for Hodgkin lymphoma) [54]. This risk appears to be life long and at least one patient has developed two different lymphomas [54]. The response to therapy in ALPS-associated lymphoma is no different than in non-ALPS patients [54]. In addition, somatic mutations in the *Fas* and *CASP 10* genes have been reported in several different lymphoid malignancies, underscoring the importance of these genes as tumor suppressors [55]. Interestingly, the patients with lymphomas associated with somatic mutations in the *Fas* gene tended to have more frequent extranodal disease and features of autoimmunity [56].

Conclusion

The clinical and experimental findings in ALPS have helped to clarify the importance of Fas in lymphocyte homeostasis, the control of certain autoimmune processes and the protection against malignant transformation of B and T lymphocytes. Despite this significant advance in our understanding of the underlying defects in the majority of ALPS patients, there remain unanswered questions. What is the genetic defect or

defects underlying the patients with ALPS type III? What is the origin and biological significance of the DNT cells? What are the mechanisms that facilitate the development of autoimmunity in these patients and can these be manipulated to diminish this risk? What additional factors impact on the risk of lymphoma and do non-death domain defects carry an increased risk of lymphoma? The evolving story of ALPS is another example of the extraordinary information and scientific opportunities that are afforded by careful study of the 'experiments of nature'.

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