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Commentary

Idiopathic CD4$^+$ T cell lymphocytopenia (ICL) is a heterogeneous syndrome presenting with persistent CD4$^+$ T cell lymphopenia of unknown origin, and opportunistic infections in some patients. The underlying pathogenesis and appropriate management remain understudied. In this issue of the *JCI*, Perez-Diez and Wong et al. assessed the prevalence of autoantibodies from the sera of 51 adult ICL patients (out of a cohort of 72). Some patients showed high levels of IgG and IgM autoantibodies against numerous autoantigens, and some autoantibodies were specific for lymphocytes. The researchers implicate these autoantibodies as a possible pathogenic mechanism responsible for the reduction in circulating CD4$^+$ T cells. This study goes beyond defining a mechanism in a complex, poorly defined disease; it also brings a renewed focus on ICL that will likely result in improved diagnostic evaluation and treatment.

Expanding mechanistic insights into the pathogenesis of idiopathic CD4+ T cell lymphocytopenia

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Idiopathic CD4+ T cell lymphocytopenia (ICL) is a heterogeneous syndrome presenting with persistent CD4+ T cell lymphopenia of unknown origin, and opportunistic infections in some patients. The underlying pathogenesis and appropriate management remain understudied. In this issue of the *JCI*, Perez-Diez and Wong et al. assessed the prevalence of autoantibodies from the sera of 51 adult ICL patients (out of a cohort of 72). Some patients showed high levels of IgG and IgM autoantibodies against numerous autoantigens, and some autoantibodies were specific for lymphocytes. The researchers implicate these autoantibodies as a possible pathogenic mechanism responsible for the reduction in circulating CD4+ T cells. This study goes beyond defining a mechanism in a complex, poorly defined disease; it also brings a renewed focus on ICL that will likely result in improved diagnostic evaluation and treatment.

A heterogeneous syndrome

Idiopathic CD4+ T cell lymphocytopenia (ICL) is a heterogeneous syndrome initially identified in 1992 by the Centers for Disease Control in patients who presented with opportunistic infections, persistent CD4+ T cell lymphopenia (defined as fewer than 300 cells/μL or less than 20% of total T cells), and no evidence of human immunodeficiency virus (HIV) or inborn errors of immunity (1). Although this disorder always includes low CD4+ T cells, low CD8+ T cell counts have also been reported (2). The underlying etiology, pathogenesis and appropriate management of ICL remain poorly understood (1, 3).

Although pathogenic variants in *RAG1*/*RAG2*, *MAGT1*, *CD4*, and *ITK* genes associate with ICL, a monogenic cause for the disease has not been identified in most ICL patients. Further, there are many other monogenic immunodeficiencies, which are characterized by T cell lymphopenia in the context of other immunological anomalies (4–6). Previous work suggests that the observed T cell lymphopenia may result from (a) impaired proliferative responses to homeostatic cytokines, (b) sequestration (or lack thereof) of T cells within lymphoid tissues or the gut (7, 8), (c) defective surface expression of C-X-C chemokine receptor type 4 (CXCR4) and/or other chemokine receptors resulting in altered chemotaxis, (d) defects of the T cell receptor signal transduction pathway due to dysfunctional tyrosine kinase activity, or (e) excess apoptosis (peripheral destruction) due to increased CD95 (Fas) expression (4). Perez-Diez et al. in an earlier study (7) suggested that there are either T cell–intrinsic or T cell–extrinsic mechanisms at play. Interleukin 7 (IL-7) is a cytokine produced by epithelial, stromal, and endothelial cells in the bone marrow, thymus, and lymph nodes and is essential for thymopoiesis and T cell homeostasis and survival (9, 10). Previous studies have shown that the induction of phospho-STAT5 after IL-7 stimulation was decreased in memory CD4+ T cells of some ICL patients, which correlated with decreased expression of CD127 (IL-7 receptor α) and lower CD4+ T cell counts (11). This impaired signaling observed in some ICL patients could contribute to altered CD4+ T cell homeostasis.

Chronic lymphopenia has been associated with an increased incidence of autoimmunity, and previous human and murine studies have amply demonstrated this finding (12, 13). To date, there is no specific therapeutic approach other than the management of risk, including prophylactic antibiotics (especially for *Pneumocystis jirovecii* pneumonia when CD4+ T cells are < 200/μL), early and aggressive treatment of infections, and screening for malignancies.

Autoantibodies and pathogenesis

In this issue of the *JCI*, Perez-Diez and Wong et al. (14) implicate autoantibodies, some of which are specific for lymphocytes in a subset of adult ICL patients, as a possible pathogenic mechanism responsible for the reduction in circulating CD4+ T cells. The authors assessed the prevalence of autoantibodies in the sera from 51 adult ICL patients (out of a cohort of 72). Some patients had high levels of IgG and IgM autoantibodies against numerous autoantigens. The presence of autoantibodies did not correlate with the patients' clinical autoimmune status, and the level and class of immunoglobulins remained constant in longitudinal studies. The number and specificity of these autoantibodies were heterogeneous, and they were capable of targeting membrane molecules, transcription factors, and secreted proteins. One-third (30%) of the 72 patients were found to have IgG anti–CD4+ T cell antibodies

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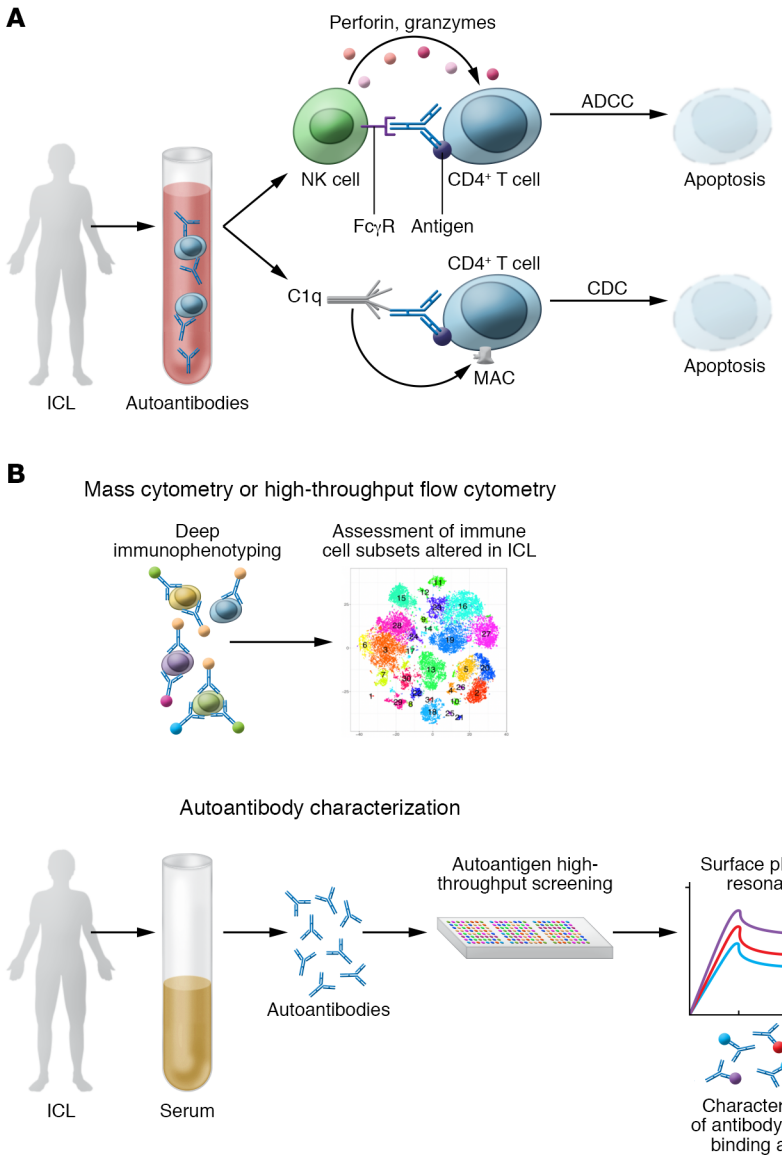

Figure 1. Pathophysiological mechanisms in idiopathic (CD4⁺) T cell lymphopenia. (**A**) Autoantibodies found in a subset of ICL patients induce peripheral CD4⁺ T cell destruction through antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) (14). (**B**) Future studies to elucidate additional mechanisms underlying ICL should focus on deep immune profiling of dysregulated immune cell subsets, (e.g., via mass cytometry [CyTOF] or other high-throughput flow cytometry methods) as well as high-throughput screening for target identification and characterization of autoantibody affinity.

and one-third (29%) had IgM anti–CD4⁺ T cell antibodies. There were also IgG and IgM antibodies binding CD8⁺ T, NK, and B cells. Mechanistic studies demonstrated that the anti-CD4 autoantibodies induced peripheral CD4⁺ T cell destruction through antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity (Figure 1A).

The clinical observations by Perez-Diez and Wong et al. provide evidence for a pathogenic mechanism in ICL — the potential contribution of autoantibodies against CD4⁺ T cells, which are capable of depleting these lymphocytes (14). Although ICL patients with opportunistic infections are likely to have more profound CD4⁺ T cell lymphopenia, those who have autoantibodies typically do not have opportunistic infections. However, whether the autoantibodies are causative or an outcome of a separate underlying process remains unclear. Prior data suggest that lymphopenia-induced proliferation of remaining T cells can lead to expansion of self-reactive clones that results in the generation of autoantibodies (15, 16).

A spectrum of pathologies

Overall, ICL is likely to represent a spectrum of pathologies, which may be interrelated and presenting at different ages. Diagnosis of adults with ICL often involves detection of lymphopenia by complete blood count (CBC) after patients also test negative for HIV and other proximate causes, such as medication or premature loss through the lymphatics or gut. Most of these adult patients do not undergo genetic testing (for evaluation of potential monogenic defects), except at specific research centers and generally when they have extreme T cell lymphopenia or in clinically symptomatic cases.

As only a subset of patients studied appear to possess autoantibodies, the question of alternate mechanisms of immune dysregulation remains to be fully unanswered. Deep immune profiling of T and B cell subsets (17, 18) in ICL patients with and without autoantibodies, with and without opportunistic infection may allow us to correlate dysregulated subsets to observed phenotype(s) (Figure 1B). Perez-Diez and Wong et al. have already made a start in this direction with their autoantibody profiling (14). It will be important to uncover further details about the effector mechanisms of the autoantibodies discovered, including the inciting factors and outcomes of these antibodies binding their target epitopes on T cells and either inducing or blocking specific signaling cascades. In addition, it will be necessary to consider the origin of these autoantibodies by studying the clonal diversity of T and B cells in these patients.

The cohort evaluated by Perez-Diez and Wong et al. (14) includes only adults. The inclusion of infant and older children cohorts with ICL in future studies will allow for a comparison of the similarities and differences in the pathophysiology of this syndrome (19) and how it changes with age, including whether these patients develop autoantibodies as infants or young children. Infants identified by newborn screening for SCID who are classified as idiopathic T cell lymphopenic (ICL or iTCL) are more likely to have genetic test-

ing and aggressive diagnostic work-up. Future studies will reveal what proportion of these children will eventually (a) have an inborn error of immunity identified (and therefore no longer classified as idiopathic), (b) remain as ICL, or (c) experience resolution of the T cell lymphopenia.

Identification of alterations in key pathways using transcriptomics and metabolomics, as well as epigenetic modifications in specific cell subsets may provide insights into pathogenesis and also therapy. Additionally, evaluation of soluble biomarkers, including serum cytokine levels, such as IL-7, and soluble BAFF may help facilitate diagnosis and even identify patients most likely to develop autoantibodies (20–22). Notably, serum levels of IL-7 have been found to be higher in patients with ICL compared with healthy donors and have been inversely correlated with $CD4^+$ T cell counts and decreased CD127 expression (23, 24).

Treatment strategies

There is no standard therapy for ICL, except management/screening for the associated conditions (e.g., cytopenias, warts, and malignancy), prophylactic antibiotics, and the prompt treatment of infections. Strategies to increase circulating $CD4^+$ T lymphocytes should be considered; such therapeutic options encompass administering exogenous cytokines to increase $CD4^+$ T cell numbers and/or improve function (25). Data suggest that IL-2 is relatively safe and a potentially effective treatment for ICL patients with opportunistic infections via increasing $CD4^+$ T cell counts (26). The role of IL-7 in thymopoiesis, T cell homeostasis, and survival provides a rationale for its potential use as an immunotherapeutic agent for ICL (9, 10). However, could treatment with a homeostatic cytokine such as IL-7 result in unregulated cell growth or the clonal expansion or further activation of self-reactive T cells? Could a patient develop neutralizing antibodies against the recombinant IL-7, thus ablating therapeutic benefit? In response to the data from Perez-Diez and Wong et al. (14), since the identified autoantibodies in ICL patients appear to play a pathogenic role, at least in some patients, therapies capable of suppressing the production of these autoantibodies also warrant evaluation. Belimumab, a BLyS/BAFF-specific inhibitor, has been approved by the United States Food and Drug Administration for patients with systemic lupus erythematosus (SLE) who have autoantibodies, and it has shown efficacy in reducing symptoms and leading to a modest decrease in autoantibodies (27). Currently, belimumab is being used in a trial in ICL, and the study results should prove informative. Although B cell–depleting therapies, like rituximab, have been used for the treatment of other autoimmune diseases, they have generally not been considered in ICL patients due to concerns of toxicity (28, 29). Finally, the role of high-dose intravenous immunoglobulin therapy, which has been used in other autoantibody-mediated autoimmune diseases, should be investigated further in this cohort, especially since it has the capacity to block autoantibodies binding to Fcγ receptors (30).

In this issue, Perez-Diez and Wong et al. (14) have provided thought-provoking insight into the pathogenesis of ICL. This study will likely spur new collaborations and investigations into the multifaceted pathology, facilitating completion of existing clinical trials, and development of new trials, ultimately resulting in improved diagnosis and treatment in patients of all ages who are presently placed into a seemingly nebulous clinical category.

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1. Ahmad DS, Esmadi M, Steinmann WC. Idiopathic CD4 lymphocytopenia: spectrum of opportunistic infections, malignancies, and autoimmune diseases. *Avicenna J Med*. 2013;3(2):37–47.
2. Yarmohammadi H, Cunningham-Rundles C. Idiopathic CD4 lymphocytopenia: Pathogenesis, etiologies, clinical presentations and treatment strategies. *Ann Allergy Asthma Immunol*. 2017;119(4):374–378.
3. Zonios DI, et al. Idiopathic $CD4^+$ lymphocytopenia: natural history and prognostic factors. *Blood*. 2008;112(2):287–294.
4. Vijayakumar S, Viswanathan S, Aghoram R. Idiopathic CD4 lymphocytopenia: current insights. *Immunotargets Ther*. 2020;9:79–93.
5. Tangye SG, et al. Human inborn errors of immunity: 2019 update on the classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol*. 2020;40(1):24–64.
6. Fernandes RA, et al. Complete multilineage CD4 expression defect associated with warts due to an inherited homozygous CD4 gene mutation. *Front Immunol*. 2019;10:2502.
7. Perez-Diez A, Liu X, Sheikh V, Roby G, Stroncek DF, Sereti I. Humanized mouse models reveal an immunologic classification of idiopathic CD4 lymphocytopenia subtypes. *JCI Insight*. 2019;4(14):127802.
8. Kovacs SB, et al. T-cell depletion in the colonic mucosa of patients with idiopathic $CD4^+$ lymphopenia. *J Infect Dis*. 2015;212(10):1579–1587.
9. Mackall CL, Fry TJ, Gress RE. Harnessing the biology of IL-7 for therapeutic application. *Nat Rev Immunol*. 2011;11(5):330–342.
10. Sheikh V, et al. Administration of interleukin-7 increases CD4 T cells in idiopathic CD4 lymphocytopenia. *Blood*. 2016;127(8):977–988.
11. Bugault F, et al. Altered responses to homeostatic cytokines in patients with idiopathic CD4 lymphocytopenia. *PLoS One*. 2013;8(1):e55570.
12. Lisco A, et al. Paradoxical CD4 lymphopenia in autoimmune lymphoproliferative syndrome (ALPS). *Front Immunol*. 2019;10:1193.
13. Chevalier N, et al. Inflammation and lymphopenia trigger autoimmunity by suppression of IL-2-controlled regulatory T cell and increase of IL-21-mediated effector T cell expansion. *J Immunol*. 2014;193(10):4845–4858.
14. Perez-Diez A, et al. Prevalence and pathogenicity of autoantibodies in patients with idiopathic CD4 lymphopenia. *J Clin Invest*. 2020;130(10):5326–5337.
15. King C, Ilic A, Koelsch K, Sarvetnick N. Homeostatic expansion of T cells during immune insufficiency generates autoimmunity. *Cell*. 2004;117(2):265–277.
16. Khoruts A, Fraser JM. A causal link between lymphopenia and autoimmunity. *Immunol Lett*. 2005;98(1):23–31.
17. Thorarinsdottir K, Camponeschi A, Gjertsson I, Mårtensson IL. $CD21^{-/low}$ B cells: a snapshot of a unique B cell subset in health and disease. *Scand J Immunol*. 2015;82(3):254–261.
18. Wehr C, et al. A new $CD21^{low}$ B cell population in the peripheral blood of patients with SLE. *Clin Immunol*. 2004;113(2):161–171.
19. Puck JM. Newborn screening for severe combined immunodeficiency and T-cell lymphopenia. *Immunol Rev*. 2019;287(1):241–252.
20. Steri M, et al. Overexpression of the cytokine BAFF and autoimmunity risk. *N Engl J Med*. 2017;376(17):1615–1626.
21. Kalled SL. Impact of the BAFF/BR3 axis on B cell survival, germinal center maintenance and antibody production. *Semin Immunol*. 2006;18(5):290–296.
22. Doreau A, et al. Interleukin 17 acts in synergy with B cell-activating factor to influence B cell biology and the pathophysiology of systemic lupus erythematosus. *Nat Immunol*. 2009;10(7):778–785.
23. Puronen CE, et al. Decreased interleukin 7 responsiveness of T lymphocytes in patients with idiopathic CD4 lymphopenia. *J Infect Dis*. 2012;205(9):1382–1390.
24. Malaspina A, et al. Idiopathic $CD4^+$ T lymphocytopenia is associated with increases in immature/transitional B cells and serum levels of IL-7. *Blood*. 2007;109(5):2086–2088.

25. Zonios D, Sheikh V, Sereti I. Idiopathic CD4 lymphocytopenia: a case of missing, wandering or ineffective T cells. *Arthritis Res Ther*. 2012;14(4):222.
26. Trojan T, Collins R, Khan DA. Safety and efficacy of treatment using interleukin-2 in a patient with idiopathic CD4(+) lymphopenia and Mycobacterium avium-intracellulare. *Clin Exp Immunol*. 2009;156(3):440–445.
27. Stohl W, et al. Belimumab reduces autoantibodies, normalizes low complement levels, and reduces select B cell populations in patients with systemic lupus erythematosus. *Arthritis Rheum*. 2012;64(7):2328–2337.
28. Pavlovic D, Patel MA, Patera AC, Peterson I, Progressive Multifocal Leukoencephalopathy Consortium. T cell deficiencies as a common risk factor for drug associated progressive multifocal leukoencephalopathy. *Immunobiology*. 2018;223(6–7):508–517.
29. Carson KR, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. *Blood*. 2009;113(20):4834–4840.
30. Shock A, Humphreys D, Nimmerjahn F. Dissecting the mechanism of action of intravenous immunoglobulin in human autoimmune disease: lessons from therapeutic modalities targeting Fcγ receptors [published online July 25, 2020]. *J Allergy Clin Immunol*. https://doi.org/10.1016/j.jaci.2020.06.036.