T(o) be, or (not) to B, or both? Somatically mutated clonal T cells in common variable immunodeficiency and related immunodeficiencies

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In common variable immunodeficiency (CVID), autoimmune diseases and lymphoproliferative disorders (LPD) often develop in addition to recurrent infections due to hypogammaglobulinemia and the decreased number of antigen-specific memory B cells.[1,2] While various T-cell abnormalities, such as $CD8^+$ T-cell expansion and suppressed regulatory T cells have been observed in CVID,[3] their pathophysiological backgrounds are unknown.

In this issue of *Haematologica*, Savola *et al.*[4] investigated the somatic mutations of T cells from patients with congenital immunodeficiency, including CVID, using deep amplicon sequencing with 2,355 gene panels and a T-cell receptor (TCR) β gene analysis to seek possible relationships between genetic alterations and T-cell abnormalities in these diseases. They found that 6 of 8 patients with CIVD harbored somatically mutated T cells and, in total, 59% of patients with congenital immunodeficiency were positive for somatic mutations in $CD4^+$ or $CD8^+$ T cells, which would be expected to have deleterious effects on the cellular functions of T cells (Figure 1). Clonal hematopoiesis-related gene mutations, including *DNMT3A*, were found in $CD3^+$ T cells from 24% of the patients. T-cell somatic mutations were also identified, albeit less frequently, in age-matched heathy controls. Patients with immunodeficiency had more convergent, namely restricted, TCR β chain CDR3 sequences, although these were not specific to previously known

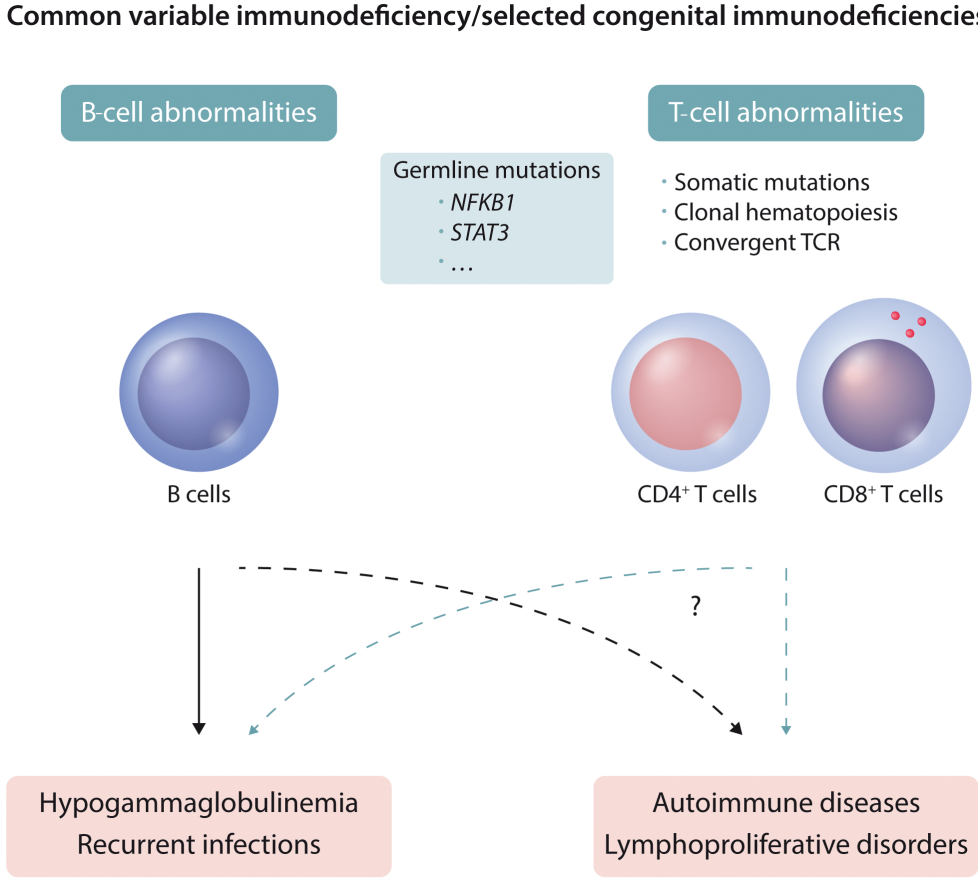

Figure 1. Germline mutations, abnormalities of B cells and somatically mutated clonal T cells identified in common variable immunodeficiency and other immunodeficiencies by Savola *et al.*[4] Savola *et al.*[4] demonstrated somatic mutation of selected genes in the T cells of patients with CVID and related immunodeficiencies. Somatically mutated clonal T cells would lead to T-cell abnormalities and might contribute to the recurrence of infection due to hypogammaglobulinemia and B-cell lymphoproliferative disorders in patients with these immunodeficiencies.

antigens. In $CD8^+$ T cells, the somatically mutated gene burden was correlated with the T-cell clone size.

The germline mutations of the genes associated with CVID are heterogenous, and only 30-50% of patients with CVID were positive for germline mutations, such as *NFKB1* in B-cell-signaling pathways,[5,6] while genetic abnormalities are still unknown in a significant proportion of CVID patients. In this study, Savola *et al.*[4] identified germline *TAC1* mutations in CVID patients, and *STAT3* and *ADA2* mutations in other immunodeficient patients. What role the somatically mutated T cells play in CVID and other immunodeficient states associated with these genetic backgrounds remains unclear. Furthermore, it is not known how or to what extent these identified mutations affect T-cell function. Further steps are needed to clarify the pathophysiology of a population of somatically mutated clonal T cells in whole T-cell networks in the settings of autoimmune diseases, LPD, and hypogammaglobulinemia in CVID or related immunodeficiency. The results presented in this paper provide new insights into the T-cell abnormalities of CVID and immunodeficiency, suggesting that clonal T cells with somatic mutations may contribute to the development of B-cell LPD, and that they may be attributed to B-cell abnormalities, such as decreased numbers of isotype-switched memory B cells, leading to hypogammaglobulinemia in CVID. To date, B-cell dysfunction and reduced concentrations of immunoglobulins have been considered fundamental characteristics of CVID.[1,7] Emerging evidence on T-cell abnormalities,[3,8,9] including clonal T cells with somatic mutations, in addition to frequent complication of autoimmune diseases and LPD, together with a variety of germline gene mutations, underlies the heterogeneity and complex nature of CVID and related immunodeficiencies.

Beyond this work, recent evidence shows that somatic mutations of non-neoplastic cells are indeed relevant in various diseases.[10-12] Clonal hematopoiesis of myeloid lineage cells in association with bone marrow failure, the development of hematologic neoplasms and arteriosclerosis is one of the issues in the field of hematology.[13-15] Now congenital immunodeficiency has been added to the list. Approaches such as a single cell analysis would provide further insight into the inherent genetic instability of T cells in association with the mechanism of TCR rearrangement, clonal hematopoiesis, or any other novel system pertinent to somatic mutations in T cells.

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References

1. Bonilla FA, Barlan I, Chapel H, et al. International consensus document (ICON): common variable immunodeficiency disorders. J Allergy Clin Immunol Pract. 2016;4(1):38-59.
2. Yakaboski E, Fuleihan RL, Sullivan KE, Cunningham-Rundles C, Feuille E. Lymphoproliferative disease in CVID: a report of types and frequencies from a US patient registry. J Clin Immunol. 2020;40(3):524-530.
3. Wong GK, Huissoon AP. T-cell abnormalities in common variable immunodeficiency: the hidden defect. J Clin Pathol. 2016;69(8):672-676.
4. Savola P, Martelius T, Kankainen M, et al. Somatic mutations and T-cell clonality in patients with immunodeficiency. Haematologica. 2020;105(12):2757-2768.
5. Abolhassani H, Hammarstrom L, Cunningham-Rundles C. Current genetic landscape in common variable immune deficiency. Blood. 2020;135(9):656-667.
6. Seidel MG, Kindle G, Gathmann B, et al. The European Society for Immunodeficiencies (ESID) registry working definitions for the clinical diagnosis of inborn errors of immunity. J Allergy Clin Immunol Pract. 2019;7(6):1763-1770.
7. Ameratunga R, Lehnert K, Woon ST, et al. Review: diagnosing common variable immunodeficiency disorder in the era of genome sequencing. Clin Rev Allergy Immunol. 2018;54(2):261-268.
8. Ramesh M, Hamm D, Simchoni N, Cunningham-Rundles C. Clonal and constricted T cell repertoire in common variable immune deficiency. Clin Immunol. 2017;178:1-9.
9. Le Saos-Patrinos C, Loizon S, Blanco P, Viallard JF, Duluc D. Functions of Tfh cells in common variable immunodeficiency. Front Immunol. 2020;11:6.
10. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med. 2014;371(26):2488-2498.
11. Vijg J, Dong X. Pathogenic mechanisms of somatic mutation and genome mosaicism in aging. Cell. 2020;182(1):12-23.
12. Savola P, Kelkka T, Rajala HL, et al. Somatic mutations in clonally expanded cytotoxic T lymphocytes in patients with newly diagnosed rheumatoid arthritis. Nat Commun. 2017;8:15869.
13. Jaiswal S, Natarajan P, Silver AJ, et al. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. N Engl J Med. 2017;377(2):111-121.
14. Yoshizato T, Dumitriu B, Hosokawa K, et al. Somatic mutations and clonal hematopoiesis in aplastic anemia. N Engl J Med. 2015;373(1):35-47.
15. Shen W, Clemente MJ, Hosono N, et al. Deep sequencing reveals stepwise mutation acquisition in paroxysmal nocturnal hemoglobinuria. J Clin Invest. 2014;124(10):4529-4538.