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

Fumihiro Ishida¹ and Hideyuki Nakazawa²

¹Academic Assembly School of Medicine and Health Sciences, Institute of Health Science and School of Medicine and Department of Biomedical Laboratory Sciences, Shinshu University and ²Division of Hematology, Department of Internal Medicine, Shinshu University School of Medicine, Matsumoto, Japan

E-mail: FUMIHIRO ISHIDA-fumish@s shinshu-u.ac.jp

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 While various T-cell abnormalities, such as CD8⁺ T-cell expansion and suppressed regulatory T cells have been observed in CVID,² their pathophysiological backgrounds are unknown.

In this issue of *Haematologica*, Savola et al.³ 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) b gene analysis to seek possible relationships between genetic alterations and T-cell abnormalities in these diseases. They found that 6 of 8 patients with CVID 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 CD8⁺ T cells from 24% of the patients. T-cell somatic mutations were also identified, albeit less frequently, in age-matched healthy controls. Patients with immunodeficiency had more convergent, namely restricted, TCR b 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.³ Savola et al.³ 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 50-50% of patients with CVID were positive for germline mutations, such as NFκB1 in B-cell-signaling pathways,1,2 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.1,2 Emerging evidence on T-cell abnormalities,3,4 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.13,14 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.

Acknowledgments
FL is supported by Kaken 20K08709 from Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References