# Immune cells with somatic mutations regulate tumor microenvironments

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***Abstract***

With aging, hematopoietic stem/progenitor cells acquire somatic mutations, leading to a phenomenon called "clonal hematopoiesis (CH)", wherein the hematopoietic system gradually transitions to cells with mutated blood cells. The discovery of CH has led to a significant paradigm shift in the understanding of hematopoietic system aging. Moreover, in elderly individuals harboring CH, "immune cells with somatic mutations" derived from CH have been increasingly implicated in inflammation in various tissues in the body, contributing to age-related diseases such as lifestyle diseases and cancers. Somatic mutations associated with CH are frequently observed in epigenetic regulators, such as *DNMT3A*, *TET2*, and *ASXL1*. Furthermore, in cancer patients exhibiting CH, "immune cells with somatic mutations derived from CH" may infiltrate cancerous tissues, potentially influencing cancer progression. However, the precise role of “immune cells derived from CH" in cancer progression remains unclear.

We have been dedicated to investigating the function of "immune cells with somatic mutations derived from CH" within various cancer microenvironments. As an example, angioimmunoblastic T-cell lymphoma (AITL) is a subtype of T-cell lymphoma and represents a prototypical blood cancer that arises from CH. In CH associated with AITL, *TET2* mutations are the most frequently observed, followed by *DNMT3A* mutations. Through analysis of patients’ samples and model mice, we have demonstrated that germinal center B (GCB) cells derived from CH serve as a niche to support tumor cells mimicking T follicular cells. Remarkably, inhibiting the interaction between tumor cells and the GCB- cell niche derived from CH resulted in the suppression of tumor progression.

These findings underscore the importance of targeting "immune cells with somatic mutations derived from CH" as a promising avenue for novel cancer treatment strategies in age-related cancers. By focusing on research concerning "CH and cancer," we anticipate the development of next-generation cancer medicine, which tailors treatment based on "genomic abnormalities in the cancer microenvironment”.

***Biography***

Dr. Sakata-Yanagimoto is a Professor in the Department of Hematology at the University of Tsukuba. She graduated from the University of Tokyo in 2000 and has since worked as a physician-scientist with a focus on blood cancers. Utilizing genomic approaches, she identified disease-specific p.Gly17Val RHOA mutations in a subtype of lymphomas (***Nature Genetics***, 2014), and subsequently engaged in translational research based on these findings (***Leukemi***a, 2018; ***Cancer Research***, 2020; ***Blood***, 2020). Furthermore, she integrated bioinformatics analyses of human samples and laboratory animal science to comprehensively elucidate the microenvironments of refractory blood cancers (***Blood***, 2022; ***Nature Cell Biology***, 2022; ***Leukemia***, 2024). These studies may provide novel treatment strategies for refractory blood cancers.