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# Targeting TACI Signaling Enhances Immune Function and Halts Chronic Lymphocytic Leukemia Progression

**Authors :** Yong H Sheng, Beatriz Garcillán, Eden Whitlock, Yukli Freedman, SiLing Yang, M Arifur Rahman, Nicholas Weber, Fabienne Mackay

**Abstract :** Chronic lymphocytic leukemia (CLL) is closely associated with immune dysfunction, yet the mechanisms underlying this immune deficiency remain poorly understood. Transmembrane Activator and CAML Interactor (TACI), a receptor known for its role in IL-10 regulation and autoimmunity, to the best of our knowledge has not been investigated in the context of anti-tumor immunity or its impact on CLL progression. This study addresses the gap by exploring the role of TACI in regulating CLL cells within the tumor microenvironment and its broader effects on disease progression and immune competence. We utilized the Eμ-TCL1 mouse model to generate CLL mice deficient in TACI and examined the consequences of TACI loss in adoptive transfer models over a five-week period. Comprehensive transcriptomic analysis, including RNA sequencing and microarray, was employed to determine TACI's influence on the CLL gene expression profile. Additionally, we studied TACI's direct role in CLL cell migration and immune modulation using patient-derived CLL cells in culture and Patient-Derived Xenograph (PDX) models. Our findings demonstrate that TACI signaling plays a pivotal role in promoting CLL progression and immune suppression. Loss of TACI signaling significantly inhibited CLL development and enhanced immune functionality. When TACI+/+ or TACI-/- TCL1 CLL cells were transferred into wild-type recipient mice, those receiving TACI-deficient cells showed reduced disease progression and lower incidence of CLL. Mice with TACI-/- CLL cells exhibited normalized serum levels of pro-inflammatory cytokines IL-6 and IL-10, restored proportions of T-cell subsets, and improved immune compartment function compared to counterparts with TACI+/+ CLL cells. Mechanistically, TACI-deficient CLL cells expressed significantly lower levels of IL-10, TNF, and inhibitory receptors such as PD-L1 and PD-L2. These cells also display restored circulating immunoglobulin levels and responses to T cell-dependent antigens, highlighting a recovery of immune competence. Further mechanistic studies revealed that TACI signaling drives CLL cell migration and homing to the spleen, where these cells actively establish an immunosuppressive microenvironment that supports immune evasion and tumor growth. Patient-derived CLL cells and PDX models confirmed TACI's direct role in enhancing CLL cell migration and fostering immune suppression, emphasizing its critical function in the tumor microenvironment. By disrupting TACI signaling, we observed a reduction in CLL-associated immune suppression and tumor progression, offering a promising therapeutic avenue. This study establishes, for the first time, that targeting TACI disrupts key mechanisms underlying CLL progression while preserving vital immune functions. Unlike existing treatments that often impair immunity and lead to infection-related complications, TACI inhibition offers the dual benefit of controlling disease and maintaining immune homeostasis. These findings provide a strong rationale for developing therapeutic strategies that inhibit TACI as a means to improve outcomes in CLL patients. Beyond its implications for CLL, this research underscores the broader importance of TACI in regulating immune-tumor interactions, paving the way for future studies into its role in other malignancies.

**Keywords :** chronic lymphocytic leukemia, TACI, IL-10, immune suppression
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