

CD25+, CD30+ Adult T-Cell Leukemia/Lymphoma cells, Virus-Infected Cells or Regulatory T-Cells?

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Short Communication

The levels of soluble cytokine receptors, especially of soluble forms of CD25 (sIL-2R) and CD30 (sCD30), are elevated in the sera of adult T-cell leukemia/lymphoma (ATLL) patients [1,2]. CD25 is an interleukin 2 (IL-2) receptor α -chain, which is one of the molecules of the IL-2 receptor complex (α -, β -, and γ -chain) [3]. IL-2 is a T-cell growth factor and activates T cells that express IL-2 receptor molecules on the cell surface [4]. Human T leukemia virus type 1 (HTLV-1), which is a cause of ATLL, induces the expression of IL-2 receptor molecules via transactivation of the Tax protein [5]. In addition to being activated by IL-2, the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathways are constitutively activated downstream of cytokine receptors in the absence of exogenous cytokines in ATLL [6]. Activated T cells produce sIL-2R following shedding of the IL-2R that is mediated by matrix metalloproteinase 9 (MMP-9) [7].

CD30, a member of the tumor necrosis factor receptor superfamily, is expressed on activated T cells, activated B cells, and virus-infected cells including HTLV-1 and Epstein-Barr virus-infected cells [8]. CD30 is a cytokine receptor and the CD30 ligand (CD153) is expressed on lymphocytes, granulocytes, eosinophils, and most white blood cells [9]. CD153 induces signaling downstream of CD30 and activates B cells, inducing antibody class switching, while it is thought to induce apoptosis in T cells [9]. The soluble form of CD30 (sCD30) is produced via shedding that is mediated by two types of MMPs, a disintegrin and metalloproteinase (ADAM)10 and ADAM17 [10].

It has been recently recognized that the T cell phenotype CD25+CD30+ T cells is a phenotype of regulatory T cells (Tregs). Constitutively expressed CD25 is an important molecule for the survival of Tregs [11]. IL-2 has mainly been described as playing an important role in STAT5 signaling that maintains the homeostasis and self-tolerance of CD4+CD25+ Tregs [12]. Regarding a role for the CD30 molecule in Tregs, the forkhead box P3 (FoxP3) transcription factor has a critical role in the development of naturally occurring CD4+CD25+ Tregs [13]. Although the expression of FoxP3 is a normal consequence of CD4+ T cell activation, CD30 expression can discriminate activation-induced FoxP3+CD4+CD25+ Tregs [14,15].

One critical question is whether ATLL cells can function as Tregs or not since ATLL cells contribute to the severe immune suppression of ATLL [10]. Satou and Matsuoka, et al. reported that the frequency of FoxP3+ cells in the CD4+ population in asymptomatic carriers with high proviral load and in patients with HTLV-1 associated myelopathy/tropical spastic paraparesis or ATLL was higher than that in uninfected individuals [16]. They concluded that HTLV-1 infection induces an abnormal frequency and phenotype of FoxP3+CD4+ T

cells. However, Toulza and Bnagham, et al. concluded that ATLL is not a tumor of FoxP3+ Tregs, and that a population of FoxP3+ cells distinct from ATLL cells has regulatory functions [17]. It remains to be determined whether CD25+CD30+ ATLL cells can be differentiated from virus-infected Tregs or be generated from activation-induced Tregs. Our recent multicenter study of ATLL minimal residual disease showed that there are two groups of ATLL patients with Tregs; one group has a high number of Tregs before initial therapy and another group has increased Tregs during chemotherapy (data not shown). Further study is required to figure out what type of cells they are derived from. In any case, the chronic infection status of HTLV-1 carriers and ATLL development of patients indicate that there is an imbalance in T cell subpopulations that can create a predominant Tregs compartment and that hampers efficient effector T cell responses [18]. If this hypothesis is true, then high-dose IL-2 therapy should help to reinstate the proper balance of T cell populations and thus high-dose IL-2 may lead to a potentially beneficial outcome in ATLL and HTLV-1 infection. IL-2 therapy against ATLL has not yet been considered. However, IL-2R monoclonal antibody therapy has been performed to block IL-2R signaling [19,20] even though ATLL cells show constitutive activation of the JAK/STAT pathway [6]. This constitutive activation of the JAK/STAT pathway may be the reason why ATLL has remained incurable to date.

References

1. Kamihira S, Atogami S, Sohda H, Momita S, Yamada Y, et al. (1994) Significance of soluble interleukin-2 receptor levels for evaluation of the progression of adult T-cell leukemia. *Cancer* 73: 2753-2758.
2. Nishioka C, Takemoto S, Kataoka S, Yamanaka S, Moriki T, et al. (2005) Serum level of soluble CD30 correlates with the aggressiveness of adult T-cell leukemia/lymphoma. *Cancer Sci* 96: 810-815.
3. Roessler E, Grant A, Ju G, Tsudo M, Sugamura K, et al. (1994) Cooperative interactions between the interleukin 2 receptor alpha and beta chains alter the interleukin 2-binding affinity of the receptor subunit. *Proc Natl Acad Sci U S A* 91: 3344-3347.
4. Mier JW, Gallo RC (1980) Purification and some characteristics of human T-cell growth factor from phytohemagglutinin-stimulated lymphocyte-conditioned media. *Proc Natl Acad Sci U S A* 77: 6134-6138.
5. Yoshida M (2001) Multiple viral strategies of HTLV-1 for dysregulation of cell growth control. *Annu Rev Immunol* 19: 475-496.
6. Takemoto S, Mulloy JC, Cereseto A, Migone TS, Patel BK, et al. (1997) Proliferation of adult T cell leukemia/lymphoma cells is associated with the constitutive activation of JAK/STAT proteins. *Proc Natl Acad Sci U S A* 94: 13897-13902.
7. Sakai A, Yoshida N (2014) The role of tumor-associated macrophages on serum soluble IL-2R levels in B-cell lymphomas. *J Clin Exp Hematop* 54: 49-57.

8. Horie R, Watanabe T (1998) CD30: expression and function in health and disease. *Semin Immunol* 10: 457-470.
9. Pornkuna R, Takemoto S (2014) A lack of cellular senescence, formation of microenvironment, and role of soluble CD30 in development of adult T-cell leukemia/lymphoma. *J Hematol Thrombo Dis* 2: 151.
10. Pornkuna R, Nishioka C, Takemoto S (2014) What is the role of soluble cytokine receptors in adult T-cell leukemia/lymphoma. *J Hematol Thrombo Dis* 2: 154.
11. de la Rosa M, Rutz S, Dorninger H, Scheffold A (2004) Interleukin-2 is essential for CD4+CD25+ regulatory T cell function. *Eur J Immunol* 34: 2480-2488.
12. Antov A, Yang L, Vig M, Baltimore D, Van Parijs L (2003) Essential role for STAT5 signaling in CD25+CD4+ regulatory T cell homeostasis and the maintenance of self-tolerance. *J Immunol* 171: 3435-3441.
13. Fontenot JD, Gavin MA, Rudensky AY (2003) Foxp3 programs the development and function of CD4+CD25+ regulatory T cells. *Nat Immunol* 4: 330-336.
14. Allan SE, Crome SQ, Crellin NK, Passerini L, Steiner TS, et al. (2007) Activation-induced FOXP3 in human T effector cells does not suppress proliferation or cytokine production. *Int Immunol* 19: 345-354.
15. de Kleer I, Vercoulen Y, Klein M, Meerding J, Albani S, et al. (2010) CD30 discriminates heat shock protein 60-induced FOXP3+ CD4+ T cells with a regulatory phenotype. *J Immunol* 185: 2071-2079.
16. Satou Y, Utsunomiya A, Tanabe J, Nakagawa M, Nosaka K, et al. (2012) HTLV-1 modulates the frequency and phenotype of FoxP3+CD4+ T cells in virus-infected individuals. *Retrovirology* 9: 46.
17. Toulza F, Nosaka K, Takiguchi M, Pagliuca T, Mitsuya H, et al. (2009) FoxP3+ regulatory T cells are distinct from leukemia cells in HTLV-1-associated adult T-cell leukemia. *Int J Cancer* 125: 2375-2382.
18. Bluestone JA (2011) The yin and yang of interleukin-2-mediated immunotherapy. *N Engl J Med* 365: 2129-2131.
19. Ishida T, Ueda R (2011) Antibody therapy for Adult T-cell leukemia-lymphoma. *Int J Hematol* 94: 443-452.
20. Zhang Z, Zhang M, Garmestani K, Talanov VS, Plascjak PS, et al. (2006) Effective treatment of a murine model of adult T-cell leukemia using 211At-7G7/B6 and its combination with unmodified anti-Tac (daclizumab) directed toward CD25. *Blood* 108: 1007-1012.