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Shedding by ADAM10 and ADAM17 is associated with progression of adult T-cell leukemia/lymphoma

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Abstract

Adult T-cell leukemia/lymphoma (ATL) is a retrovirus-associated mature T-cell leukemia/lymphoma. It is speculated that ATL is an age-related disease and some changes are involved in malignant transformation and monoclonal expansion of the HTLV-1-infected cells. We previously reported that HTLV-1-infected cells and ATL cells exhibit CD30 and soluble CD30 (sCD30) is elevated in the sera of patients with ATL. Recently, we also evaluated the levels of sCD30 in ATL patients underwent chemotherapy and allogeneic hematopoietic stem cell transplantation (HSCT) to predict prognosis of ATL patients under 2 different clinical settings; before initiation therapy and before HSCT. Our results suggest that sCD30 may be a useful biomarker in HSCT therapy, because a high sCD30 level before HSCT was implicated in early death after HSCT. In addition, we report that sCD30 elevation was followed by acute crisis from chronic type of ATL. Previously, high levels of soluble proteins including cytokine receptor and membrane-binding protein were observed in patients with ATL. A disintegrin and metalloproteinase (ADAM)10 and ADAM17 worked as sheddases of CD30 as well as the other proteins. ADAM10/17 also cleaved collagen and elastin which are structural proteins of tissues and may cause the tissue injury of important organs. It seems that ADAM10/17 plays a role as oncoproteins for tumorigensis in ATL.

Adult T-cell leukemia/lymphoma (ATL) is a retrovirus-associated mature T-cell leukemia/lymphoma [1-4]. A mean latency period of more than 50 years is required for only 2–5% of human T-cell leukemia virus type 1 (HTLV-1) carriers to develop ATL [5,6]. It is speculated that ATL is an age-related disease and some changes are involved in malignant transformation and monoclonal expansion of the HTLV-1-infected cells [7]. We previously reported that HTLV-1-infected cells and ATL cells exhibit CD30 and soluble CD30 (sCD30) is elevated in the sera of patients with ATL [8]. CD30 (also known as Ki-1, Ber-H2 and TNFRSF8) is a 120kDa type I cell surface glycoprotein and a member of the tumor necrosis factor receptor family. CD30 is physically expressed on activated T cells including CD45RO+ T cells, B cells, NK cells and monocytes. Pathologically, CD30 expression is observed on viral infected cells and tumor cells such as B cell lymphoma, T cell lymphoma, acute myeloid leukemia, and embryonal carcinoma [9,10]. CD30+ cells release soluble CD30 (sCD30) *in vitro* and *in vivo*, detected at low levels in the sera of healthy donors [11]. Levels of sCD30 have been proposed to be a prognostic factor for an unfavorable outcome in lymphoid malignancies such as Hodgkin's lymphoma, and T-cell lymphomas [12-14]. Recently, we also evaluated the levels of sCD30 in ATL patients underwent chemotherapy and allogeneic hematopoietic stem cell transplantation (HSCT) to predict prognosis of ATL patients under 2 different clinical settings; before initiation therapy and before HSCT [15]. Levels of sCD30 were significant predictors of Overall Survival (OS) both before the initial therapy and before HSCT. Especially, our results suggest that sCD30 may be a useful biomarker in HSCT therapy, because a high sCD30 level before HSCT was implicated in early death after HSCT. In most of them, patients died of diffuse pulmonary infiltrates and/or interstitial pneumonia within 76 days. This is reason why ATL patients with sCD30 level ≥170 U/ml may not be a suitable transplantation therapy. Hopefully, the use of this marker will help to reduce the early deaths and transplantation-related mortality of HSCT.

In addition, we reported that sCD30 elevation was followed by acute crisis from chronic type of ATL [16]. The lungs are the preferential site for HTLV-1–infected cells, and this peculiar tropism is responsible for the high incidence of pulmonary involvement [17-20]. A patient who progressed from indolent type to acute type of ATL showed lung invasion following elevation of the serum sCD30 levels. Furthermore, the level of sCD30 surged according to the formation of pulmonary lesions at relapse as well as at acute crisis of disease In the lung, Tax, trans-activator of HTLV-1 genome and cellular genes, is preferentially expressed in HTLV-1-infected cells [21] and the CD30 and CD30 ligand interaction plays an important role for inflammation [22,23]. Therefore, a sustained high level of sCD30 may be associated with Tax expression and pulmonary involvement of ATL.

Previously, high levels of soluble proteins including cytokine receptor and membrane-binding protein were observed in patients with ATL (Table 1). Soluble interleukin-6 receptor (sIL-6R) was shown

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Key words: *a disintegrin and metalloproteinase (ADAM)10, ADAM17, adult T-cell leukemia/lymphoma (ATL), human T-cell leukemia virus type 1 (HTLV-1), soluble CD30 (sCD30)*

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Table 1. High levels of soluble proteins cleaved by ADAM10/17 in ATL patients.

	ADAM10	ADAM17
Shedding proteins on ATL cells	CD30 [8,15]	CD30 [8,15]
	*Fas ligand (FasL) [28]	IL-6 receptor (IL-6R) [24]
	CD44 [27,32]	CD44 [27,32]

*This report was demonstrated in HTLV-1 carriers

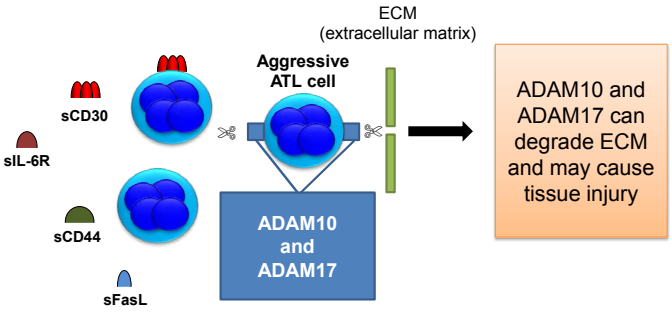

Figure 1. Aggressive phenotype of ATL cells.

ADAM10 and 17 cleave membrane-bound proteins, ligands and receptors, and fibrous proteins, which are involved in the tumorigenesis, development, and metastasis of tumors.

to circulate at elevated levels in HTLV-1-infected patients and to be associated activation of STAT3 signaling [24,25]. CD44 is a broadly distributed cell surface glycoprotein and has been identified as a tumor-promoting molecule that is implicated in cancer cell growth, invasion, and metastasis [26]. *In vivo*, plasma levels of soluble CD44 (sCD44) were significantly associated with the performance status, total number of involved lesions, and lactic dehydrogenase [27]. As mentioned above, HTLV-1 carriers are known to develop pulmonary complications characterized by T-lymphocytic alveolitis. Sakamoto N et al. measured soluble Fas (sFas) and sFas ligand (sFasL) in serum and bronchoalveolar lavage fluid of 16 seropositive asymptomatic HTLV-1 carriers and 32 healthy subjects, and the levels of sFasL were significantly higher in asymptomatic carriers than the control [28].

Accordingly, serum levels of sCD30 may be a marker of matalloproteinases activation on ATL cells (Figure 1). A Disintegrin and metalloproteinase (ADAM)10 and ADAM17 work as sheddases of CD30 as well as the other proteins (sFasL, sCD44, and sIL-6R) as shown in Table 1 [29-32]. ADAM10/17 also cleaves collagen and elastin which are structural proteins of tissues and may cause the tissue injury of important organs. It seems that ADAM10/17 play a role as oncoproteins for tumorigensis in ATL.

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