

## Serum Soluble CD30 Levels to Detect Activation and Aggression Status of Adult T-Cell Leukemia/Lymphoma Cells

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Rec date: Feb 14, 2015, Acc date: Apr 23, 2015, Pub date: Apr 30, 2015

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### Abstract

Adult T-cell leukemia/lymphoma (ATL) is one of aggressive mature T-cell malignancies. CD30 is a cell membrane protein expressed on activated T-cell. While a limited number of ATL cells show the CD30 expression, high levels of soluble CD30 (sCD30) are detected in serum of ATL patients. It is known that a disintegrin and metalloproteinase (ADAM)10 and ADAM17 are ubiquitously expressed in peripheral leukocytes including T cells. They are sheddases of CD30 and IL-6 receptor (IL-6R) from cell surface as well as cleaving enzymes of E-cadherin and extracellular matrix. High levels of sIL-6R/IL-6 complex induce CRP production in the liver of ATL patients. Therefore the elevation of sCD30 and CRP levels indirectly indicated the activation status of ATL cells and the risk of invasion and tissue injury of important organs such as lung via metalloproteinases activation on ATL cells *in vivo*. Activated ATL cells may play a role for clinical aggression in ATL.

**Keywords:** Soluble CD30 (sCD30); Adult T-cell leukemia/lymphoma (ATL); T-cell activation; A disintegrin and metalloproteinase

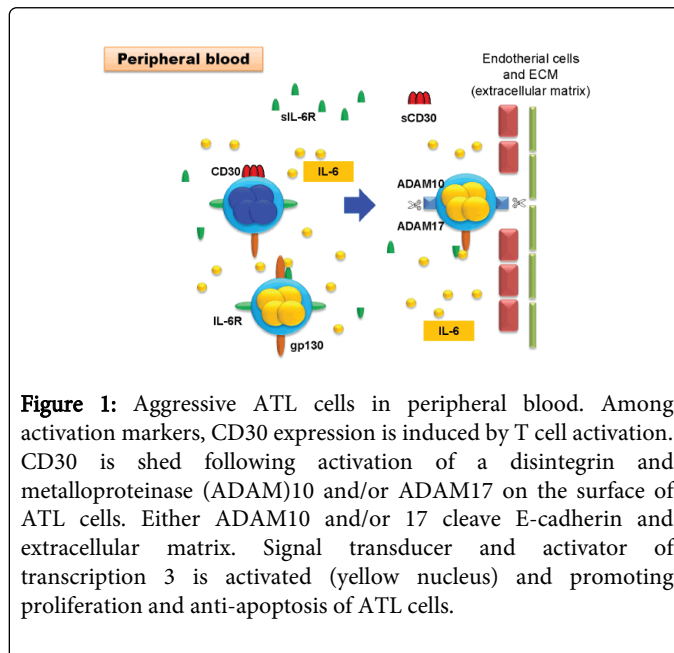
### Short Communication

Adult T-cell leukemia/lymphoma (ATL) is one of aggressive mature T-cell malignancies [1]. We recently reported that levels of soluble CD30 (sCD30) were significant predictors of overall survival both before the initial therapy and before allogeneic hematopoietic stem cell transplantation (HSCT) at National Hospital Organization Kumamoto Medical Center [2].

Regarding HSCT, we found that the combination of sCD30 levels and CRP levels may be a powerful tool to predict the early death of patients undergoing HSCT. It is conceivable that elevated sCD30 levels and C-reactive protein (CRP) values are associated with an active state of residual ATL cells before the immunosuppressant therapy (Figure 1).

Conditioning therapy probably activates tissue macrophages, leading to further activation of residual ATL cells following cytokine storm.

CD30 is a cell membrane protein of the tumor necrosis factor receptor superfamily and is expressed on activated T-cell and B-cell, as well as on some tumor virus-infected T cells and B cells [3]. CD30 is constitutively expressed in some pathological conditions such as Hodgkin/Reed-Sternberg cells or anaplastic large lymphoma cells [4], while a part of the ATL cells isolated from patients is positive for CD30 expression on the cell surface [5-7].



**Figure 1:** Aggressive ATL cells in peripheral blood. Among activation markers, CD30 expression is induced by T cell activation. CD30 is shed following activation of a disintegrin and metalloproteinase (ADAM)10 and/or ADAM17 on the surface of ATL cells. Either ADAM10 and/or 17 cleave E-cadherin and extracellular matrix. Signal transducer and activator of transcription 3 is activated (yellow nucleus) and promoting proliferation and anti-apoptosis of ATL cells.

Using 30% expression as a cut-off positive value, CD30 expression was predominantly seen in the acute type and lymphoma-type but not in the chronic type or smoldering type [6,7]. It is suggested that CD30 expression is induced on the surface of ATL cells as a progression of disease. In contrast, sCD30 levels were elevated in serum of ATL patients in spite of subtype of ATL but not in HTLV-1 carriers (Table 1).

Patient	Subtype (pg/ml)	IL-10 (pg/ml)	IL-4 (pg/ml)	IL-5 (pg/ml)	IL-6 (pg/ml)	IL-2 (pg/ml)	IFN-g (pg/ml)	sCD30 (U/ml)	IgG (mg/dl)	IgM (mg/dl)	IgA (mg/dl)
1	Acute	34.6	14.4	16.9	10.8	64.1	10.7	540	1557	71	151
2	Acute	43.4	16.5	16.9	111.1	3	11.8	480	913	227	170
3	Acute	37.7	21.6	17.6	4.5	2.5	13.7	542.8	928	37	144
4	Acute	205.3	16.5	128.8	20.8	4.4	11.8	568.4	1850	57	228
5	Acute	1.3	17.6	16.8	0	12.7	10.9	513.2	ND*	ND*	ND*
6	Acute (replapse)	33	14.8	25.9	16	4.9	11.8	626.8	ND*	ND*	ND*
7	Lymphoma	6.2	16.1	16.8	26	92.6	11.8	300.1	ND*	ND*	ND*
8	Lymphoma (relapse)	5.2	0	102.3	35.4	0	12.1	541.2	1210	77	385
9	Lymphoma	8.3	9.8	3.4	8.6	11.4	7.5	141.6	1430	64	264
10	Chronic	5.4	0	3.3	8.7	11	7.3	255.8	668	45	106
11	Carrier	6.2	1	3.3	26.1	11.9	12.2	39.9	ND*	ND*	ND*
	Healthy donor (n=5)	3.0 ± 2.4*	0.4 ± 0.6*	4.0 ± 0.6*	0.7 ± 1.5*	7.4 ± 4.7*	4.4 ± 3.6*	40.1 ± 9.0*	920 ± 1800●	60-285●	110 ± 450●

**Table 1:** Serum levels of Cytokines and Proteins, \*Average ± SD ●the normal changes \*no data.

The CRP level is controlled by circulating IL-6 levels, which are elevated in ATL patients [8,9]. Actually, IL-6 levels were elevated even in the serum of HTLV-1 carriers (Table 1). Furthermore, soluble IL-6 receptor (sIL-6R) is produced by ATL cells and sIL-6R/IL-6 complex works as the agonist of IL-6R signaling [10,11]. This may be the reason why signal transducer and activator of transcription 3 is constitutively activated in ATL cells *in vivo* [12].

It is known that a disintegrin and metalloproteinase (ADAM)10 and ADAM17 are ubiquitously expressed in peripheral leukocytes including T cells. They are sheddases of CD30 and IL-6R from cell surface as well as cleaving enzymes of E-cadherin and extracellular matrix [13-17]. It is speculated that the expression and shedding of CD30 is induced in only activated ATL cells [18]. High levels of sIL-6R/IL-6 complex induce CRP production in the liver of ATL patients. Therefore the elevation of sCD30 and CRP levels indirectly indicated the activation status of ATL cells and the risk of invasion and tissue injury of important organs such as lung via metalloproteinases activation on ATL cells *in vivo* (Figure 1) [2]. Activated ATL cells may play a role for clinical aggression in ATL.

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