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RESEARCH ARTICLE

CTLA4 Protein Abnormality And Its Role In The Progression Of Systemic Lupus Erythematosus.

M Divya[1]*, Sasirekha G[2], and Siva[3].

[1]Assistant Professor (Biochemistry), Madurai Medical College, Madurai, Tamil Nadu, India.
[2]Associate Professor (Biochemistry), Madurai Medical College, Madurai, Tamil Nadu, India.
[3]Associate Professor (Biochemistry), Trichy Medical College, Trichy, Tamil Nadu, India.

ABSTRACT

Systemic lupus erythematosus affects multiple organs by the antibodies produced against our own antigens. The inhibitory CTLA-4 molecule has a crucial role in regulation of this immune response. The normal T-cell activation requires a primary signal by way of T-cell receptors and supplementary signals received from co-receptor molecules CD28 and cytotoxic T-lymphocyte antigen-4 (CTLA-4). CD28 provides positive signals to promote T-cell response, while CTLA4 provides negative regulatory signal to down-regulate T-cells response. Any imbalance of these signals' paves way for autoimmune disorders like SLE. Here, we measured the level of soluble CTLA-4 (sCTLA-4) in plasma and thus assessed its role in the pathogenesis of systemic lupus erythematous. This is a case control study in which we estimated the level of sCTLA-4 protein in plasma of 50 SLE patients and compared them with 50 age and sex matched controls. SLE patients have significantly elevated levels of sCTLA4 protein in plasma of SLE patients compared to the healthy controls ($p<0.001$). We conclude that the CTLA-4 molecule abnormality appears to play a significant role in the development of SLE in the Indian population. Hence sCTLA-4 can prove a novel surrogate marker for the diagnosis of disease.

Keywords: CTLA-4 gene, polymorphism, Autoimmune disorder, Systemic Lupus Erythematosus, CD28

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Corresponding author

INTRODUCTION

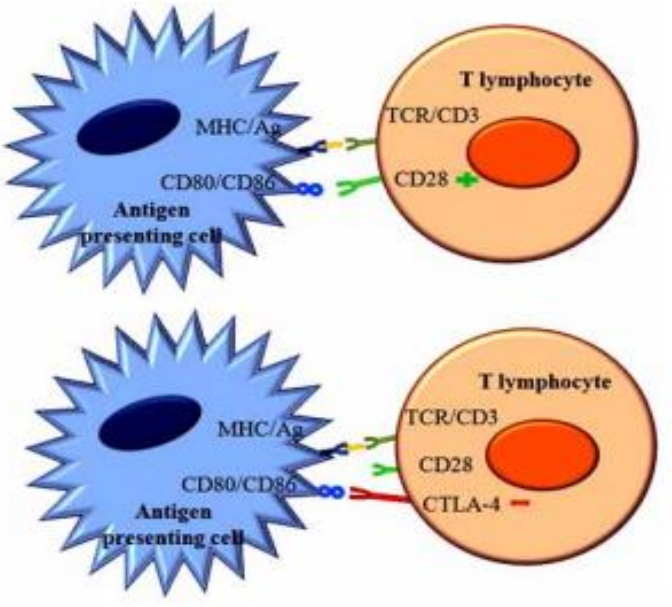
Systemic Lupus Erythematosus is an autoimmune disorder in which multiple organ systems are affected simultaneously. The interaction between genetic and environmental factors dys-regulate the immune response in the body. The disease exhibit itself most frequently among women of reproductive age group. Even if the recent improvements in therapeutic options were optimistic, many patients experience poor treatment outcomes [1]. One of the possible reasons is the ultimate mechanism that ends up in immune dys-regulation has not yet been clearly unraveled. A possible mechanism is the role of CTLA-4 molecule that acts as the suppressor molecule for T cells [2, 3].

Genetic studies clearly point the direct link between CTLA4 gene polymorphism at 2q33 and its subsequent susceptibility to SLE [4, 5]. The genetic abnormality results in elevated levels of soluble fraction of CTLA-4 protein (sCTLA-4). In the year of 2000, Oak and Hallet identified the alternate transcript from stable CTLA-4 gene, which lacks the trans-membrane region of the native CTLA-4 protein of membrane [6]. This protein present in plasma has been named soluble CTLA-4 protein (sCTLA-4). It was also identified low levels of sCTLA-4 have been detected in normal human serum, but the level of sCTLA-4 protein is elevated in the serum of patients with various autoimmune disorders including systemic lupus erythematosus [7].

The biological significance of such soluble fraction of CTLA-4 protein (sCTLA-4) elevation is that, the protein will block the interaction between membrane CTLA-4(mCTLA-4) with CD80/86 ligands. This results in reduced inhibitory signals to T cells and pathogenesis of autoimmune disorders [8].

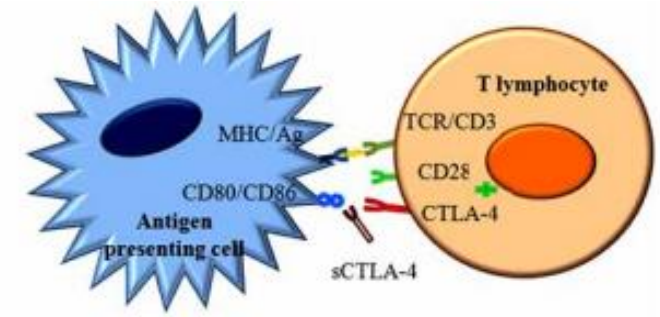
Normal T-cell activation requires dual signals. The initial signal is provided by antigen-T cell receptor engagement and the second signal described as co-stimulatory signal is provided by the interaction of the co-stimulatory molecules, CD28 or CTLA-4 with its ligands CD80/CD86 present on the surface of antigen-presenting cells. CD28 provides positive co-stimulatory signal and CTLA-4 provides negative co-stimulatory signal [9]. (FIGURE 1)

Figure 1



The increased levels of soluble CTLA-4(sCTLA-4) in plasma results in inability of membrane-bound CTLA-4(mCTLA-4) to engage with CD80/CD86 and consequently less negative signaling and subsequent autoimmunity [10]. (FIGURE 2)

Figure 2



MATERIALS AND METHODS

The Age, Sex, BMI, Serum urea/ creatinine/ uric acid level and plasma CTLA-4 protein levels 50 SLE patients and control population were compared. The concentration of soluble fragment of CTLA-4 protein in plasma was estimated by Enzyme linked Immunosorbent Assay. Plasma CTLA-4 protein level between cases and controls was compared by unpaired student t- test and P value <0.05 is statistically significant.

RESULTS

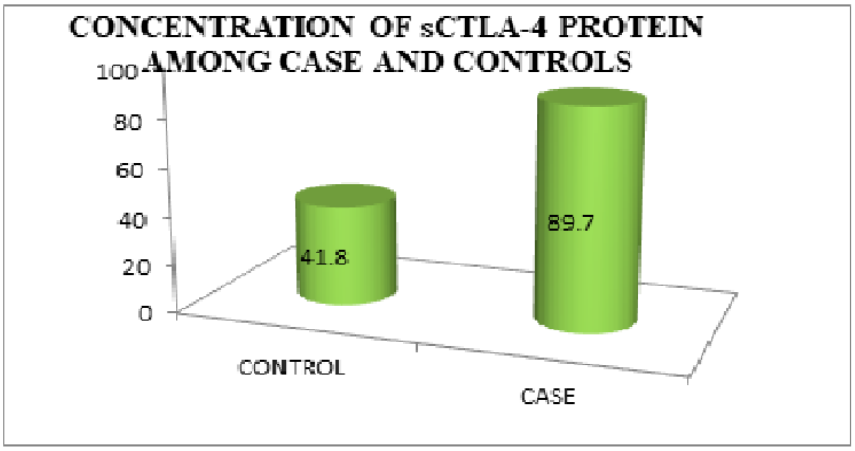
Among the 50 SLE patients chosen for the study the mean concentration of soluble fragment of CTLA-4 (sCTLA-4) protein is 89.7± 25.3 ng/ml. The control population has mean CTLA-4 concentration of about 41.8 ± 14.8 ng/ml. The values compared between cases and age/sex matched controls proves that SLE patients have significantly higher level of soluble fragment of CTLA-4 protein in plasma. The comparison of variables between cases and controls is given in Table 1. The bar chart comparing the concentration of soluble fragment of CTLA-4 protein (ng/ml) is shown in FIGURE 3.

Table 1: Comparison Of Variables Between Cases And Controls

VARIABLE	CASES (N=50)	CONTROLS (N=50)	p-VALUE
AGE	35.57 ± 7.47	34.83 ± 7.02	0.47- NS*
SEX (M/F)	9/41	11/39	
UREA (mg/dl)	44.7±13.6	26.4±7.12	<0.001-S*
CREATININE (mg/dl)	1.2±0.39	0.96±0.26	<0.001-S*
URIC ACID (mg/dl)	5.9±1.6	4.2±1.18	<0.001-S*
sCTLA-4 (ng/ml)	89.7±25.3	41.8±15.8	<0.001-S*

* NS – Non significant, S- Significant

Figure 3

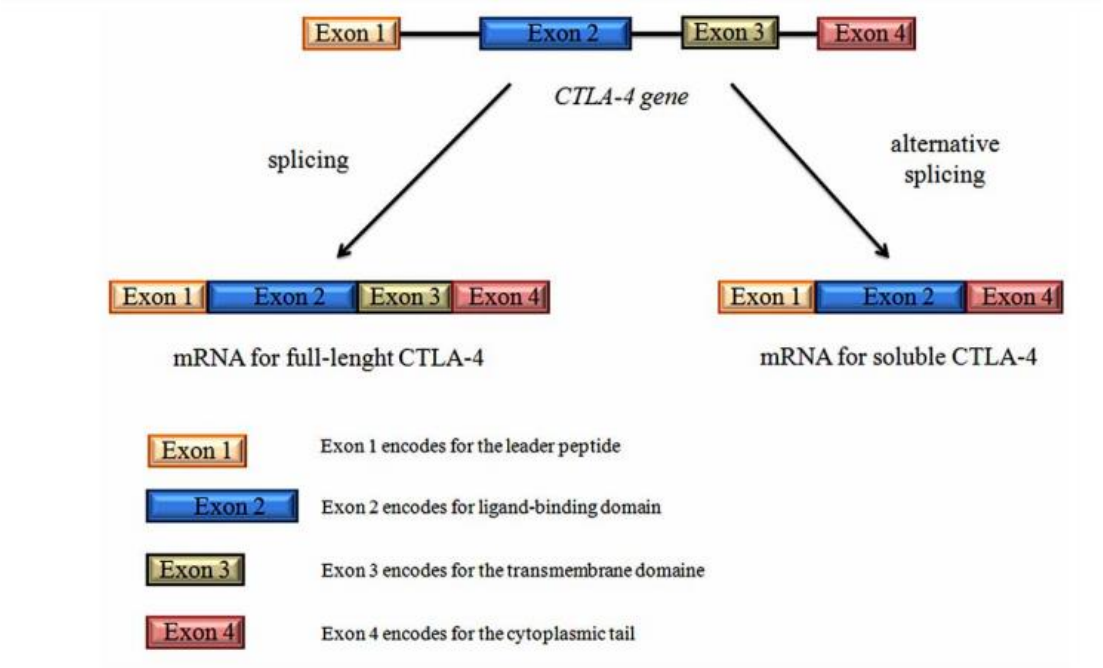


DISCUSSION

The generation the full-length CTLA-4 (membrane CTLA-4) and soluble fraction of CTLA-4 (sCTLA-4) depends on alternate splicing of mRNA. While the full-length membrane CTLA-4 has four exons, the alternative splicing result in loss of exon 3. The final outcome of this alternative splicing is 110-bp deletion corresponding to the entire trans-membrane domain of the CTLA-4 molecule [11, 12].

This specific genetic abnormality affects the intracellular trafficking of CTLA-4 protein. The alternatively spliced CTLA-4 protein could not attach to membrane and is released into general circulation. As a result of this surface expression of CTLA-4protein (mCTLA-4) gets reduced and soluble fraction of CTLA-4 protein(sCTLA-4) in the plasma gets elevated [13]. This ultimately reduces negative inhibitory signal to the T cells and thus paves the way for autoimmunity in SLE. (FIGURE 4)

Figure 4



There are many studies supporting the role of soluble fragment of CTLA-4 molecule in the development of immunological dysregulation. Toussirot et al proved that sCTLA-4 that results from an alternative splicing of CTLA-4 transcripts may influence immune activation in spondylarthritis [14]. Wang et al showed the elevated level of soluble fragment of CTLA-4 molecule in Myasthenia gravis [15]. Sato et al in 2004 proved serum soluble CTLA-4 levels are increased in diffuse cutaneous systemic sclerosis [16]. There are also many studies supporting the role of elevated soluble fragment of CTLA-4 protein in the development of Systemic Lupus erythematosus [8, 17]. The current study proves that there are significantly elevated levels of sCTLA4 protein in plasma of SLE patients compared to the healthy controls ($p<0.001$).

CONCLUSION

There is considerable elevation of sCTLA4 molecule in the plasma of SLE patients. This above result provides a new postulate for the potential pathogenesis of SLE, hence facilitating the development of a novel surrogate for the disease, sCTLA-4. There is recent advance in exploring therapeutic agents targeting T cells activation in SLE. It might be possible to use antibodies against the sCTLA-4 in the treatment of SLE.

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