lesional inflammatory cell infiltration, vascular adhesion molecules, or angiogenesis (Figure 2). When comparing C-Tg with C-NT mice, we found significantly more CD3+ cells, CD4+ cells, and CD8+ cells in the Tg strain's dermis (all with $P<0.001$). Similarly, the B-Tg dermis had significantly more CD3+ cells ($P<0.01$), CD4+ cells ($P<0.01$), and CD8+ cells ($P<0.05$) compared with its B-NT counterpart. Both C-Tg and B-Tg mice had significantly more PECAM+ vessels per high-power field compared with their NT littermates ($P<0.001$), further supporting a role of angiogenesis in AD (Chen *et al.*, 2008a). Similarly, C-Tg and B-Tg mice had more P-selectin+ and VCAM+ vessels than did their NT littermates ($P<0.001$); this was identical to the previous findings in AD patients and in an AD model (Sigurdsson *et al.*, 2000; Chen *et al.*, 2010). There was no difference in numbers of CD3+ and CD4+ lymphocytes, PECAM+, and P-selectin+ vessels between the dermis of the two Tg strains. The physiological implications of more CD8+ cells and VCAM+ vessels per high-power field in the dermis but with less skin inflammation in C-Tg mice, as compared with B-Tg mice, are unclear (Figure 2b and c).

The Th2 systemic immune milieu strongly enhances the rate and extent of cutaneous inflammation in our AD model by primarily increasing the expression of cutaneous Th2 cytokines and other proinflammatory cytokine.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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High Levels of Soluble ST2 and Low Levels of IL-33 in Sera of Patients with HIV Infection

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TO THE EDITOR

IL-33, a novel member of the IL-1 family, was recently identified as a ligand for the orphan receptor ST2 (Schmitz *et al.*, 2005). ST2 is selectively and stably expressed on the cell surface of T-helper 2 (Th2) cells, but not Th1 cells (Xu *et al.*, 1998). IL-33–ST2 interactions exacerbate Th2- and mast cell-mediated inflammatory diseases (Préfontaine *et al.*, 2009). The soluble form of ST2 functions as a decoy

Abbreviations: AD, atopic dermatitis; Th, T helper

receptor, which neutralizes IL-33 and acts as a negative regulator of Th2 cytokine production by IL-33 signaling (Hayakawa *et al.*, 2007). Although IL-33 was highly expressed in lesional skin of atopic dermatitis (AD), serum IL-33 levels in AD patients were not increased (Pushparaj *et al.*, 2009). On the other hand, serum soluble ST2 levels are elevated in patients with asthma (Oshikawa *et al.*, 2001). IL-33 is important in the lesion sites in Th2 type immune responses, while soluble ST2 seems to be a more sensitive serum marker for Th2 diseases. IL-33 also has important roles in host protection against infections (Humphreys *et al.*, 2008; Alves-Filho *et al.*, 2010; Jones *et al.*, 2010) and prevention of atherosclerosis (Sanada *et al.*, 2007). Patients with HIV infection exhibit a wide range of skin pathology, including bacterial, fungal, and viral infections, skin tumors, inflammatory and eczematous eruptions, and drug rashes (Spira *et al.*, 1998). HIV-infected adults commonly develop a condition that strongly resembles AD. Elevated IgE levels, eosinophilia, and increased Th2 activity are reported in patients with HIV infection (Rudikoff, 2002). In this study, we measured soluble ST2 and IL-33 levels in sera of patients with HIV infection or AD.

Twenty-six patients with HIV infection (mean ± SD age: 43.8 ± 11.3 years), 28 patients with AD and without HIV infection (28.5 ± 8.1 years), and 21 healthy control subjects (39.9 ± 19.1 years) were enrolled in this study. Eight of 26 patients with HIV infection had HIV-related eosinophilic folliculitis, four had pruritic papular eruptions, six had tinea pedis, and others had syphilis, herpes simplex, condyloma acuminate, or molluscum contagiosum. All the patients except one were receiving highly active antiretroviral therapy. The numbers of $CD4^+$ T cells were 32–757 per μl (median = 288). The HIV viral loads of six patients ranged from $10^{2.80}$ to $10^{5.81}$ copies per ml (median = $10^{5.04}$). The viral loads of the other 20 patients were <50 copies per ml. The 21 healthy controls had no history of allergy or any skin diseases. Serum samples were obtained with informed consent. The medical ethical committee of the University of Tokyo and the National Center for Global Health and Medicine approved all described studies, and the study was conducted according to the Declaration of Helsinki Principles. Immunoreactive soluble ST2 and IL-33 in sera were quantified by a human ST2/IL-1 R4 Quantikine ELISA Kit and a human IL-33 DuoSet (R&D systems, Minneapolis, MN), respectively. Both kits recognized the free form of soluble ST2 or IL-33 and IL-33/ST2 complex. Statistical analysis between two groups was performed using Mann–Whitney's *U*-test. Correlation coefficients were determined by using Spearman's rank correlation test. *P*-values <0.05 were considered statistically significant.

Serum soluble ST2 levels in patients with HIV infection were 18,637.8 ± 10,267.7 pg ml^{-1} (mean ± SD), which were significantly higher than those of healthy controls (11,650.1 ± 9,558.4 pg ml^{-1}; $P<0.01$; Figure 1). Serum soluble ST2 levels in patients with AD (18,850.5 ± 9,636.8 pg ml^{-1}) were also significantly higher than those of healthy controls ($P<0.01$; Figure 1). Serum IL-33 levels in patients with HIV infection were 53.1 ± 134.8 pg ml^{-1}. They were significantly lower than those of healthy controls (355.5 ± 439.1 pg ml^{-1}; $P<0.05$; Figure 2). Serum IL-33 levels in patients

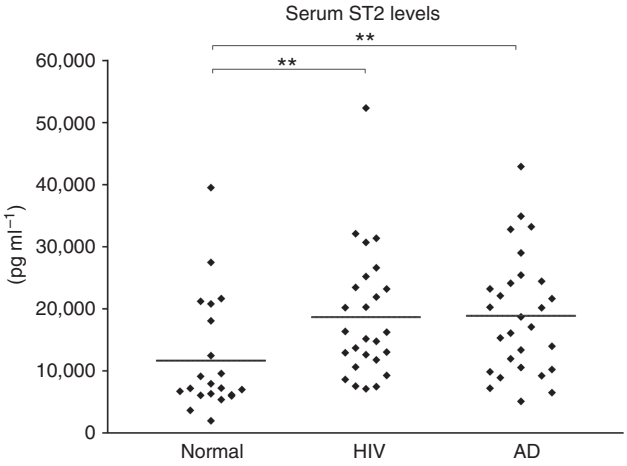

Figure 1. Serum levels of soluble ST2 in patients with HIV infection or atopic dermatitis (AD) and in healthy controls. The measured values from individual patients are plotted with dots. The horizontal lines represent the mean of each group. **$P<0.01$ by Mann–Whitney *U*-test.

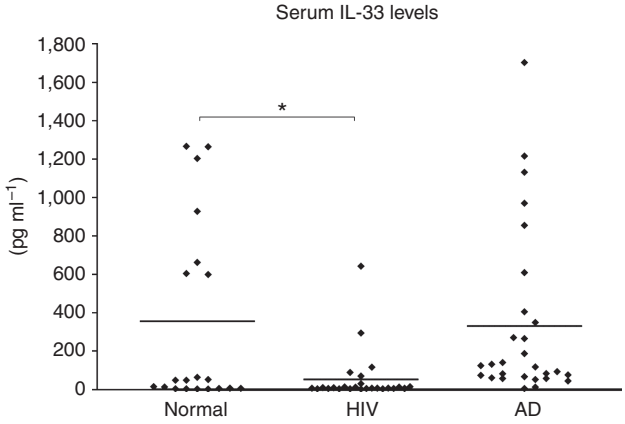

Figure 2. Serum IL-33 levels in patients with HIV infection or atopic dermatitis (AD) and in healthy controls. The measured values from individual patients are plotted with dots. The horizontal lines represent the mean of each group. *$P<0.05$ by Mann–Whitney *U*-test.

with AD were $330.6 \pm 440.3\,pg\,ml^{-1}$ (Figure 2), which were not significantly different from healthy controls. Serum soluble ST2 and IL-33 levels did not correlate with age, number of eosinophils, or other clinical and laboratory data. Serum IL-33 levels of HIV patients with <250 $CD4^+$ T cells counts were $31.9 \pm 82.6\,pg\,ml^{-1}$ and those with >250 $CD4^+$ T cells counts were $77.2 \pm 145.8\,pg\,ml^{-1}$. Serum IL-33 levels of patients with a viral load of >50 copies were $10.7 \pm 9.8\,pg\,ml^{-1}$ and those with a viral load of <50 copies were $68.7 \pm 152.1\,pg\,ml^{-1}$. Although the differences were not statistically significant, there was a tendency for serum IL-33 levels to decrease with the severity of HIV infection.

We have shown that serum soluble ST2 levels are elevated in patients with HIV infection as well as AD, which may reflect a Th2 dominant status, as seen in patients with asthma (Oshikawa *et al.*, 2001). Serum IL-33 levels in patients with AD are comparable with those in healthy controls, which is consistent with the previous report (Pushparaj *et al.*, 2009). Surprisingly, serum IL-33 levels in patients with HIV infection are significantly lower than those of healthy controls. There are emerging data suggesting that IL-33 has key roles in host immunity against various infections such as bacteria, *Toxoplasma gondii*, or intestinal nematodes (Humphreys *et al.*, 2008; Alves-Filho *et al.*, 2010; Jones *et al.*, 2010). Soluble ST2 plasma concentrations predicted mortality in severe sepsis (Hoogerwerf *et al.*, 2010). Besides a decrease in $CD4^+$ T cells, high levels of soluble ST2 and low levels of IL-33 in sera in patients with HIV may contribute to high risks of opportunistic infections. As IL-33 is reported to reduce the development of atherosclerosis (Miller *et al.*, 2008), low levels of IL-33 may also explain the high risk of atherosclerosis in patients with HIV (Currier *et al.*, 2008).

In summary, this is early evidence of high levels of soluble ST2 and low levels of IL-33 in sera of patients with HIV. Although more detailed study is necessary to know the regulations of serum levels of soluble ST2 and IL-33, our study has revealed a new aspect of immune impairment in HIV infection, which may contribute to high risks of opportunistic infections and atherosclerosis.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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