High circulating tumor necrosis factor levels correlate with increased levels of soluble CD14 in patients with non-Hodgkin's lymphoma

The levels of tumor necrosis factor (TNF) are increased in the plasma of patients with non–Hodgkin's lymphoma. We describe a correlation between plasma TNF and soluble CD14 (sCD14) levels emphasizing the immune system activation in this disease and the potential role of several mediators in lymphoid disorders.

The CD14 molecule, described as a receptor for lipopolysaccharide (LPS), is strongly expressed on monocytes. In normal human blood, a soluble form of CD14, sCD14, is detectable, and increased levels seem to be associated with a wide variety of infectious and inflammatory diseases.[1,2] The origin and mechanism of sCD14 production are still not clear. However, LPS and cytokines such as TNF appear to be able to stimulate the production of sCD14 *in vitro*.[3] Since patients with non-Hodgkin's lymphoma have high plasma levels of TNF[4] and the amount of this TNF is associated with an adverse outcome,[4] we were interested in the circulating amounts of sCD14 in this disease.

We report here plasma concentrations of sCD14, assessed by a specific immuno-enzymometric assay (Quantikine Human sCD14 Immunoassay, R&D Systems Europe, Abingdon, United Kingdom) in 21 newly diagnosed consecutive lymphoma patients and ten healthy subjects. The patients had not received any previous treatment and did not have active bacterial infection. From a clinical point of view, the patient group was subdivided into eight patients with indolent lymphoma (follicular lymphoma, seven patients; marginal zone B-cell lymphoma, one patient) and thirteen with aggressive lymphoma (diffuse large B-cell lymphoma, twelve patients; Burkitt's lymphoma, one patient).

Concentrations of plasma sCD14 were significantly higher in the lymphoma patients than in the control subjects (median 2.03 µg/mL, range [1.22-2.92] vs 1.72 µg/mL, range [1.13–1.96], respectively; $p = 0.01$ Mann Whitney U-test) (Figure 1). Nevertheless, these levels were moderately increased as compared with those in sepsis.[2] The patients with aggressive lymphoma showed a slightly higher median sCD14 (median = 2.13 µg/mL, range [1.22-2.92]) than patients with indolent lymphoma (median = 1.96 µg/mL, range [1.59–2.64]), but without significant difference (data not shown). Likewise, the sCD14 levels were not different according to the disease stage or lactate dehydrogenase (LDH) values (data not shown). Interestingly, in lymphoma patients, sCD14 levels were strongly correlated with plasma TNF amounts ($r = 0.55$, $p = 0.009$ Spearman's test) (Figure 2), suggesting that in these patients the elevated circulating TNF levels may be involved in sCD14 production, in agreement with previous data.[1,3] In addition, sCD14 levels were significantly correlated with C-reactive protein (CRP) ($r = 0.57$, $p = 0.017$ Spearman's test) and CRP with plasma TNF levels ($r = 0.70$, $p = 0.001$ Spearman's test), reflecting the cytokine-mediated inflammation.

Functionally, sCD14 has two opposite effects *in vitro*. If sCD14 mediates LPS stimulation of cells that do not express CD14, such as endothelial and epithelial cells,[5] it also prevents LPS-induced cytokine release by mononuclear cells, inhibiting the binding of the LPS–LPS binding protein complex to the CD14 receptor.[6] In B-CLL, the elevated sCD14 correlated with IgG serum values, supporting its eventual protective function.[7] However, the physiologic role of sCD14 remains unclear *in vivo*. Recently, sCD14 has been described as a novel soluble regulatory factor capable of modulating cellular and humoral immune responses by interacting directly with T- and B-cells.[8] Further investigations are necessary to understand the variations in plasma levels of sCD14

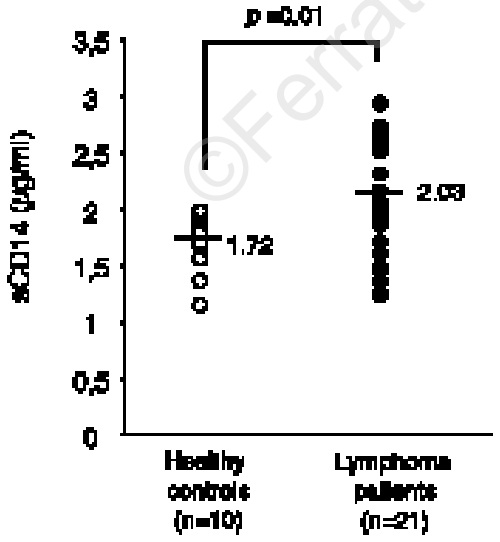

Figure 1. sCD14 plasma levels. Each point represents the sCD14 levels measured respectively for healthy subjects (open circle, n = 10) and for lymphoma patients (closed circle, n =21). The horizontal lines indicate the median.

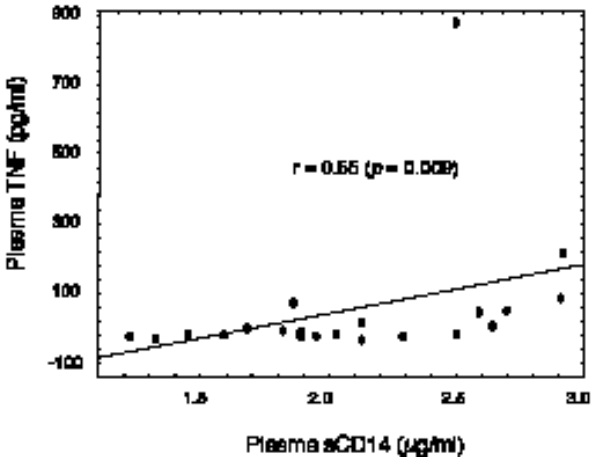

Figure 2. Correlation between sCD14 and TNF plasma levels. The TNF concentrations were quantified using an immuno-enzymometric assay (Medgenix TNF-α EASIA Kit, BioSource Europe SA, Fleurus, Belgium).

in pathologic conditions and to reveal other functions beside those in the LPS-target cell interaction.

In conclusion, although the clinical significance of circulating sCD14 has not yet been elucidated, the lymphoma patients show moderately increased levels of sCD14 in plasma correlated with circulating TNF concentrations. This correlation is in favor of a potential role of TNF in sCD14 production *in vivo*. In lymphoma patients, sCD14 levels may, therefore, represent a marker of activity of the monocyte/macrophage system and reflect immune system activation and inflammatory response.

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