

**INTERLEUKIN-18 (IL-18)**, a pro-inflammatory cytokine that plays an important role in the T-cell-helper type 1 response, is a new member of the family of cytokines produced in the brain. CD30 is a marker of T-cell-helper type 2 lymphocytes. We evaluated IL-18 and CD30 serum levels in 10 patients affected by moderate-severe depression (MSD). We demonstrated for the first time that serum IL-18 levels of MSD patients were significantly higher than those of healthy donors. On the contrary, no significant difference was found between serum CD30 levels of MSD patients compared with those of healthy donors. These data strengthen the hypothesis that MSD disease is associated with an inflammatory response, mainly T-cell-helper type 1, and suggest an important role for IL-18 in the pathophysiology of MSD.

**Key words:** Moderate-severe depression, IL-18, sCD30, Serum

## Interleukin-18 and CD30 serum levels in patients with moderate-severe depression

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It has been documented that there is a strong inter-relationship between the immune system, the central nervous system and psychological process.<sup>1</sup>

Cytokines are mostly glycoproteins that play a crucial role in cell-to-cell signalling. Furthermore, in providing communication between immune cells, specific cytokines play a role in signalling the brain to produce neuroimmune, neurochemical, neuroendocrine and behavioural changes.<sup>1</sup> The cytokines are actively transported into the central nervous system where activate glia cells produce other cytokines, and a cascade of cytokine effects may be initiated by this mechanism.<sup>1</sup>

The production of cytokines in the brain occurs following brain system irritation, infection, injury or ischaemia, or in response to various stresses such as anxiety or depression.<sup>1</sup> In particular, depression represents a major public health problem. There is now some evidence that depression may be accompanied by an immune response. The plasma concentration of pro-inflammatory cytokines has been reported as elevated in depressed patients, and in healthy persons on stress.<sup>1</sup>

Interleukin-18 (IL-18), also called interferon- $\gamma$ -inducing factor, is a pro-inflammatory cytokine that plays an important role in the T-cell-helper type 1

(Th1) response. IL-18 may contribute to inflammation because it is a potent inducer of gene expression and synthesis of tumour necrosis factor, IL-1, Fas ligand, and several chemokines.<sup>2</sup> Conti *et al.* demonstrate that microglia and astrocytes are sources of brain IL-18 and add a new member to the family of cytokines produced in the brain.<sup>3</sup>

IL-18 is also proposed to have a role in modulating immune function during immunological disturbances. In particular, an inappropriate production of this cytokine is known to be involved in schizophrenia. In fact, serum IL-18 levels are elevated in schizophrenic patients.<sup>3</sup>

CD30 is a member of the tumour necrosis factor-nerve growth receptor superfamily, existent as a membrane glycoprotein of 105 and 120 kDa, derived from a 90 kDa precursor and a 57 kDa intracellular form. CD30 is a marker of activated T-cell-helper type 2 (Th2) lymphocytes. There is also an 88 kDa soluble form of CD30 (sCD30), which originated from the proteolytic cleavage of the extracellular portion of sCD30, released by CD30<sup>+</sup> cells.<sup>4</sup>

In light of these findings, since at present there are no data about IL-18 and CD30 release on patients affected by depression disease, we investigated in this preliminary study a possible role for these molecules

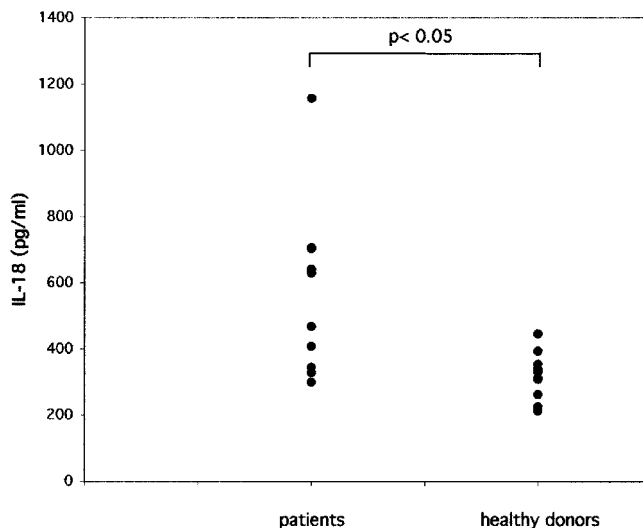


FIG. 1. IL-18 serum levels in patients affected by moderate-severe depression and in healthy donors.

in the pathophysiology of moderate-severe depression (MSD). In particular, we evaluated the presence of IL-18 and sCD30 in sera of patients affected by MSD before anti-depression drug administration.

To this end, we enrolled 10 patients (all females) affected by MSD in this study (mean age,  $38.60 \pm 14.68$  years; range, 21–60 years) who experienced a major depressive episode according to DSM-IV criteria recruited from the Outpatient Mental Health Service of the Department of Neurosciences, Psychiatry and Anesthesiology. Mood was assessed at baseline by using the Beck Depression Inventory (range, 0–63). The mean baseline score of the Beck Depression Inventory is 28.1 (standard deviation, 8.8), varying from 20 to 43. Ten healthy females (mean age,  $36.92 \pm 13.50$ ; range, 22–54 years) were also enrolled as the control group. Patients and healthy donors (HD) signed an informed consent form.

Sera were obtained from peripheral blood allowed to clot at room temperature for 2 h, separated by centrifugation at  $200 \times g$  for 15 min in a 4235 A (ALC Int. S.r.L., Milan, Italy) centrifuge, and stored at  $-80^\circ\text{C}$  until use.

Serum IL-18 was assayed by immunoenzymatic methods (Quantikine Human IL-18, R&D System; SPACE Import-Export, Milan, Italy). The detection limit for IL-18 was 12.5 pg/ml.

Serum sCD30 levels were determined by the commercial sandwich ELISA Dako CD30 (Ki-1 antigen; Dako, Milan, Italy). The limit of detection of the assay was 1 IU/ml.

Differences in serum levels were assessed by one-way analysis of variance and the Student–Newman–Keuls test. Data are expressed as the mean  $\pm$  standard deviation.  $p < 0.05$  was considered significant.

Serum IL-18 levels of MSD patients were significantly higher than those of HD ( $568.99 \pm 260.18$

versus  $319.00 \pm 72.31$ ,  $p < 0.05$ ) (Fig. 1). On the contrary, no significant difference was found between serum sCD30 levels of patients compared with those of HD; in fact, all subjects had sCD30 values  $< 1$  IU/ml.

There is clinical and experimental evidence that activation of the brain cytokine system is associated with depression, although the exact relationship between sickness behaviour and depression is still elusive.<sup>1</sup>

The results of the present preliminary study, which is the first to investigate circulating IL-18 levels in MSD disease, show higher levels of this cytokine in patients affected by this disease than HD. Our data support the demonstration, reported by many investigators, that the depression disease is characterized by increased activity immune response and that the systemic immune stimulation participates in the pathophysiology or pathogenesis of the depression disease.<sup>1</sup>

According to previous studies,<sup>1</sup> we may hypothesize that, as other pro-inflammatory cytokines, IL-18 may stimulate the hypothalamic–pituitary–adrenal axis and enhance sympathetic nerve system activity, suggesting a pivotal role in psychological process and psychiatric disorders. These results represent the first evidence in MSD disease of IL-18 involvement, a cytokine that promotes Th1 responses; supporting the hypothesis that this disease is associated with an activation of inflammatory response, mainly of Th1 type. This hypothesis is strengthened by our results: in fact, no significant difference was found between serum sCD30 levels of MSD patients compared with those of HD. CD30 is expressed only by activated Th2 cells.<sup>2</sup>

Moreover, it has been reported that IL-18 is highly involved in the pathogenesis of cardiovascular diseases.<sup>5</sup> In fact, circulating levels of IL-18 reflect

aetiologies of heart failure. A Th1/Th2 cytokine imbalance exaggerates the pathophysiology of advanced heart failure.<sup>5</sup> Then, the high IL-18 serum levels reported in this preliminary study, during MSD disease, may partially explain the increase of cardiovascular risks that occur frequently among patients with depression disease.

In conclusion, our preliminary findings suggest an important role for IL-18 in the pathophysiology of MSD disease and provide a direction for more specific immunomodulating therapy.

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## References

1. Maes M. Evidence for an immune response in major depression: a review and hypothesis. *Prog Neuro-Psychopharmacol Biol Psychiatry* 1995; **19**: 11-38.
2. D'Elia MM, Romagnani P, Scaletti C. In vivo CD30 expression in human disease with predominant activation of Th2-like T cells. *J Leukoc Biol* 1997; **61**: 539-544.
3. Conti B, Park LC, Calingasan NY, *et al*. Cultures of astrocytes and microglia express interleukin-18. *Brain Res Mol Brain Res* 1999; **67**: 46-52.
4. Tanaka KF, Shintani F, Fujii Y, *et al*. Serum interleukin-18 levels are elevated in schizophrenia. *Psychiatry Res* 2000; **96**: 75-80
5. Yamaoka-Tojo M, Tojo T, Inomata T, *et al*. Circulating levels of interleukin-18 reflect etiologies of heart failure: Th1/Th2 cytokine imbalance exaggerates the pathophysiology of advanced heart failure. *J Cardiac Fail* 2002; **8**: 21-27.

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