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## **Endogenous circulating granulocyte-macrophage colony-stimulating factor in multiple myeloma [letter; comment]**

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## ENDOGENOUS CIRCULATING GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR IN MULTIPLE MYELOMA

*To the Editor:*

Previously, Zhang et al<sup>1</sup> suggested that granulocyte-macrophage colony-stimulating factor (GM-CSF) might be implicated in the pathogenesis of human multiple myeloma (MM). In a technically excellent work, they showed that GM-CSF is able to augment myeloma cell proliferation. Although GM-CSF alone has no proliferative activity on purified myeloma cells or myeloma cell lines, this stimulating activity on tumor cells is at least partially mediated by interleukin-6 (IL-6). This pleiotropic cytokine, originally described as a B-cell growth and differentiation factor, has evolved as the major growth factor for multiple myeloma cells.<sup>2</sup> However, the mechanism by which IL-6 triggers myeloma cell growth still remains controversial. Paracrine as well as autocrine mechanisms are under discussion.<sup>3,4</sup> Recently, we demonstrated that in monoclonal gammopathies serum IL-6 levels correlate well with disease activity.<sup>5</sup> We also found a correlation with serum neopterin, which is secreted by monocytes/macrophages upon stimulation with interferon- $\gamma$  (IFN- $\gamma$ ).<sup>6</sup> These results implicate that circulating IL-6 might have its origin in an activated immune system rather than in the malignant cell clone.

In 35 patients with monoclonal gammopathies, serum samples were also screened for endogenous circulating GM-CSF using a commercially available enzyme-linked immunosorbent assay (ELISA; Medgenix, Brussels, Belgium). Twenty-six patients (pts) had an MM (14 pts with stage I disease, three with stage II, and nine with stage III) and nine presented with monoclonal gammopathy of unknown significance (MGUS). In contrast to the findings of Zhang et al,<sup>1</sup> significantly elevated levels of GM-CSF (>25 pg/mL) were detected in 18 of 26 pts (69.2%) with MM and in 6 of 9 pts (66.6%) with MGUS. Median levels were 36 pg/mL (range, 0 to 183) in MM and 34 pg/mL (range, 10 to 63) in MGUS. GM-CSF levels correlated neither with disease stage nor with any of the

other cytokines measured (IL-6, IL-1 $\beta$ , tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ],  $\beta$  2-microglobulin, neopterin) or with absolute granulocyte counts. Nevertheless, GM-CSF might be of a certain pathogenic significance in malignant plasma cell disorders, because in other hematologic malignancies such as chronic myeloproliferative diseases (n = 8) and low-grade non-Hodgkin's lymphomas of the B-cell type (n = 22), median values of GM-CSF were within the normal range (18 pg/mL, range, 0 to 80; and 19 pg/mL, range, 0 to 80, respectively). However, the source of circulating GM-CSF is still unknown. The findings of Zhang et al<sup>1</sup> suggest that GM-CSF is not produced by the malignant clone itself. It is more likely that GM-CSF is secreted by cells of the immune system (monocytes/macrophages or T lymphocytes) or accessory cells of the bone marrow upon stimulation by interleukins or IFNs, especially IFN- $\gamma$ . However, the lacking of correlation with neopterin, an established parameter for activation of the host's cellular immune system,<sup>7</sup> makes it questionable whether a simple positive feedback mechanism exists for all these cytokines. It would also be interesting to investigate the kinetics of these cytokines during the natural course of disease and, probably more importantly, under chemotherapy, especially with biologicals such as IFN- $\alpha$ . Finally, our findings of nearly identical GM-CSF median values in MM and MGUS do not support the hypothesis of Zhang et al<sup>1</sup> of a possible stimulation of myeloma cell proliferation after *in vivo* application of GM-CSF in leukopenic myeloma patients.

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## RESPONSE

Contrary to our findings, Dr Nachbaur reported detectable granulocyte-macrophage colony-stimulating factor (GM-CSF) levels in the sera of patients with multiple myeloma (MM) or benign monoclonal gammopathy (MGUS) using a commercially available enzyme-linked immunosorbent assay (ELISA). However, these levels were low (36 pg/mL) and we would like to point out the problems of nonspecificity frequently encountered when measuring cytokines in sera by ELISA, as recently reviewed by Grassi et al.<sup>1</sup> In our study, we failed to detect GM-CSF in the plasma of 25 patients with MM using an ELISA that detected 10 pg/mL GM-CSF. The differences between Dr Nachbaur's studies and our may be explained by a difference in the sensitivity or specificity of the ELISA used. In keeping with our results, we failed to detect GM-CSF messenger RNA in the bone marrow of 20 patients with MM (B. Klein, unpublished results). We therefore thought that an abnormal production of GM-CSF is not a key event in the development of MM *in vivo*, unlike what we found for interleukin-6.<sup>2</sup>

We disagree that the finding of identical levels of serum GM-CSF (if accurate) in patients with MGUS and MM does not support a possible stimulation of myeloma-cell proliferation after

*in vivo* application of GM-CSF in leukopenic myeloma patients. In the discussion part of our report, we were more careful and have only indicated that our *in vitro* study showing a stimulation of myeloma-cell proliferation by GM-CSF could not predict similar results *in vivo*. We think that this hypothesis should be specifically and carefully studied in several patients before generalizing the use of GM-CSF in MM.

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