CONCISE REPORT

Expression of the Macrophage-Specific Colony-Stimulating Factor in Human Monocytes Treated With Granulocyte-Macrophage Colony-Stimulating Factor

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The macrophage-specific colony-stimulating factor (CSF-1, M-CSF) regulates the survival, growth and differentiation of monocytes. We have recently demonstrated that phorbol ester induces expression of CSF-1 in human monocytes. These findings suggested that activated monocytes are capable of producing their own lineage-specific CSF. The present studies demonstrate that the granulocyte-macrophage colony-stimulating factor (GM-CSF) also induces CSF-1 transcripts in monocytes. Furthermore, we demonstrate that the detection of CSF-1 RNA in GM-CSF-treated monocytes is associated with synthesis of the CSF-1 gene product. The results thus suggest that GM-CSF may indirectly control specific monocyte functions through the regulation of CSF-1 production. These findings indicate another level of interaction between T cells and monocytes.

RESULTS

We have previously shown that TPA treatment of human peripheral blood monocytes induces CSF-1 expression. A maximum increase in CSF-1 RNA was achieved six hours after TPA induction and these transcripts declined thereafter. Treatment of resting human monocytes with GM-CSF similarly induced CSF-1 expression. The CSF-1 cDNA probe hybridized with a 4.6-kb transcript detectable at three hours of exposure to 500 CFU-C/mL GM-CSF (Fig 1). Similar findings have been obtained using poly A-selected monocyte RNA (data not shown). Furthermore, the level of CSF-1 RNA induced by GM-CSF remained detectable through 48 hours. In contrast, CSF-1 transcripts were undetectable following the same analysis of monocytes incubated in the absence of GM-CSF. The findings in GM-CSF-treated monocytes were also associated with a partial down-regulation of c-fms expression (Fig 1). Similar effects on CSF-1 and c-fms expression were obtained following treatment of monocytes with 20, 100, and 2,500 CFU-C/mL GM-CSF (data not shown).

We have also monitored production of the CSF-1 protein in GM-CSF-treated monocytes. CSF-1 levels in monocyte supernatants increased nearly tenfold at three hours of GM-CSF exposure (Fig 2). Furthermore, the CSF-1 levels remained elevated at 48 hours of treatment. In contrast, monocytes incubated in the absence of GM-CSF had no detectable supernatant CSF-1 at similar intervals and at 72 hours. Thus, CSF-1 expression at the RNA level corre-

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have demonstrated that CSF-1 also stimulates human monocytic production of interferon, tumor necrosis factor, and myeloid colony-stimulating activity.2 Taken together, these findings would suggest that GM-CSF, and therefore T lymphocytes, may indirectly control specific functions of monocytes through the regulation of CSF-1 expression.

Other cytokines appear capable of inducing CSF-1 in monocytes. Previous studies have demonstrated that T cell–derived gamma-interferon induces release of monocyte colony-stimulating activity from purified human monocytes.9,10 Thus, gamma-interferon and GM-CSF may both contribute to the interaction between T cells and monocytes.

DISCUSSION

The present results demonstrate that GM-CSF induces CSF-1 expression in human monocytes. This induction occurred during the continued expression of c-fms transcripts. Since c-fms encodes for the CSF-1 receptor, the findings would suggest that GM-CSF treated monocytes may regulate their own growth and differentiation through CSF-1 production. Thus, the in vitro effects of GM-CSF on macrophage colony formation1 may be mediated in part by induction of CSF-1 expression. Furthermore, recent studies have demonstrated that CSF-1 also stimulates human monocyte production of interferon, tumor necrosis factor, and myeloid colony-stimulating activity.11 Taken together, these findings would suggest that GM-CSF, and therefore T lymphocytes, may indirectly control specific functions of monocytes through the regulation of CSF-1 expression.

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REFERENCES


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