Decreased Macrophage Colony-Stimulating Factor mRNA Expression From Activated Cord Versus Adult Mononuclear Cells: Altered Posttranscriptional Stability

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We have previously shown that protein production and mRNA expression of granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), and interleukin-3 are decreased in stimulated mononuclear cells (MNCs) from human umbilical cord compared with adult peripheral blood. These deficiencies may contribute to the increased susceptibility of neonates to infection. Macrophage colony-stimulating factor (M-CSF) regulates the proliferation, differentiation, and functional activation of monocytes. In the present study, we compared the regulation of M-CSF gene expression and protein production from stimulated cord and adult MNCs. Upon adhesion to tissue culture flasks, both cord and adult MNCs constitutively expressed M-CSF mRNA. In response to both adhesion and recombinant human GM-CSF (rhGM-CSF) stimulation for 120 hours, radioimmunoassays and bioassays showed that cord MNCs produced twofold to threefold less M-CSF protein compared with adult MNCs. Northern blot analysis also showed a fourfold decrease in M-CSF mRNA expression in both unstimulated and GM-CSF-induced cord versus adult MNCs. M-CSF mRNA expression in both cord and adult MNCs peaked between 16 and 24 hours and decreased to normal levels by 48 hours. We next determined the relative rates of transcription of the M-CSF gene by nuclear run-on assays in both cord and adult MNCs. The basal level signal of the M-CSF gene was similar between cord and adult MNCs. The transcriptional rate after stimulation with rhGM-CSF appeared to increase to a similar extent in both cord and adult MNCs (130% ± 10% × 150% ± 15%, C v A, n = 3, mean ± SD). The comparative stability of M-CSF mRNA from cord versus adult MNCs was next determined by actinomycin D decay studies. The half-life of M-CSF mRNA from stimulated adult MNCs was 70 ± 7.0 minutes (n = 4) compared with 47 ± 2.8 minutes (n = 3) from stimulated cord MNCs (mean ± SD, P < .05). To further determine the involvement of labile protein factors in posttranscriptional regulation, cord and adult MNCs were incubated with cycloheximide (CHX; 10 μg/mL). There was a significant increase in the induction of M-CSF mRNA by CHX treatment in both cord and adult MNCs. The increase of M-CSF mRNA induction by CHX was 2.5 times higher in cord MNCs compared with that in adult MNCs. These results suggest that there are one or more labile proteins that regulate M-CSF transcript stability in both cord and adult MNCs. Taken together, these findings suggest that the reduced M-CSFs mRNA expression and protein production from stimulated cord versus adult MNCs may be secondary to posttranscriptional regulation involving the synthesis of labile proteins that affect the stability of M-CSF transcript. Reduced M-CSF mRNA stability may account in part for altered host defense in the neonate compared with the adult.

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MACROPHAGE colony-stimulating factor (M-CSF) is a hematopoietic growth factor that stimulates the growth, differentiation, and proliferation of cells of the monocyte-macrophage lineage.1 In vivo studies have shown that recombinant human M-CSF (rhM-CSF) induces peripheral monocytosis, neutrophilia, and lymphocytopenia in both rats2 and primates.3 rhM-CSF stimulates progenitor cells in vitro to differentiate into monoblasts and induce maturation into promonocytes and monocytes.4,5 A variety of immune effector functions of mature monocyes and tissue macrophages have been reported to be enhanced by M-CSF, including phagocytic activity and microbial killing,6 macrophage-mediated tumor cell cytolyis,7 and the ability to resist bacterial and fungal infection.8,9 M-CSF also induces monocyte production of granulocyte colony-stimulating factor (G-CSF),10 granulocyte-macrophage colony-stimulating factor (GM-CSF),11 γ interferon (γIFN), tumor necrosis factor (TNF),12 and interleukin-1 (IL-1).13 M-CSF is normally detected in human serum and may be an important in the regulation of the number and viability of circulating monocytes.14,15 Using enzyme immunoassays (EIAs), M-CSF levels have been measured to be in the range of 5.7 ± 0.7 ng/mL16 or 540 ± 100 Ul/mL.18 Using more specific radioimmunoassays (RIAs), endogenous M-CSF levels have been detected to be in the range of 118 ± 9 Ul/mL.15

During pregnancy, serum levels of M-CSF are increased above baseline.17-19,21 The M-CSF levels are also increased in cord blood and further increased in newborn infants (1 to 7 days), suggesting that fetuses and newborn infants are a source of M-CSF production.17,22 Human M-CSF levels in amniotic fluid at 30 to 40 weeks are higher than those in cord blood, suggesting that the uterus is an additional source of production of M-CSF.11,20 The elevated levels of M-CSF in newborns during pregnancy suggest that M-CSF may be an important regulator of mononuclear phagocytes production during the development of neonatal host defense.

Hematopoiesis in the preterm and term neonates is developmentally immature compared with adults.23,24 During overwhelming bacterial sepsis, neonates tend to develop neutro-
penia because of reduced mature effector neutrophil storage pools, reduced myeloid progenitor pools, and accelerated steady-state myeloid proliferative rates. Moreover, neonatal mature effector neutrophils also have qualitative deficiencies, eg, chemotaxis, phagocytosis, C3bi receptor expression, and bacterial killing, compared with adult neutrophils. Recently, our laboratory and others have shown differential regulation of cytokine expression in neonates versus adults. The expression of GM-CSF, G-CSF, IL-3, transforming growth factor-β1 (TGF-β1), IL-8, and macrophage inhibitory protein-1α (MIP-1α) genes are reduced in stimulated human peripheral blood mononuclear cells (MNCs) from umbilical cord compared with adult peripheral blood. However, the expression of IL-11 and SLF is higher in fibroblasts and endothelial cells in the neonate compared with the adult. Reduced mRNA expression and protein production of TNF-α and γIFN from stimulated human neonatal MNCs versus adult MNCs have also been described. The regulation of M-CSF gene expression from various types of cells from human adults has previously been examined. In contrast, the regulation of M-CSF gene expression in cord versus adult cells has not been extensively studied. In the present study, we compared the expression of M-CSF mRNA in human neonatal versus adult peripheral blood MNCs during basal and activated conditions. Additionally, we also compared transcriptional and posttranscriptional regulation of M-CSF expression between cord and adult MNCs to better delineate the underlying mechanisms associated with the disparate regulation of CSF expression and the immaturity in neonatal host defense.

MATERIALS AND METHODS

Isolation and stimulation of human MNCs. Heparinized venous blood was drawn from normal volunteers in accordance with the principles of the Declaration of Helsinki. Venous cord blood was drawn from umbilical vessels of placentas of normal, full-term, non-stressed infants immediately after vaginal delivery (10%) or scheduled delivery (86%) and 8.8% of the newborns immediately after the spontaneous delivery or for the duration of the stimulation. Total culture period DNA samples used in the hybridizations include M-CSF, 1,800-bp EcoRI/Xho I fragment from p3ACSFRI (kindly provided by Genetics Institute); β-actin, 1,000-bp BamHI fragment from pHβI/1 (L. Kedes); and glyceraldehyde-3-phosphate dehydrogenase (GAPDH), 775-bp Pst I/Xho I fragment from pHCGAP (ATCC, Rockville, MD). Filters were washed to a stringency of 0.3 × SSC at 65°C and exposed to Kodak XAR-5 film (Eastman Kodak, Rochester, NY). The hybridization signals were quantitated by densitometry of autoradiographs. The levels of mRNA were calculated by normalizing values with respect to the signals of internal standards.

Nuclear run-on transcription assay. A total of 10^6 MNCs from cord and adult blood were stimulated with rhGM-CSF (20 ng/mL) for 18 hours. Nuclear isolation and nuclear run-on assays were performed as previously described, which is a slight modification of the Weili et al and Grouinie et al. Target DNA samples used in the hybridizations include M-CSF, 1,800-bp EcoRI/Xho I fragment from p3ACSFRI (kindly provided by Genetics Institute); β-actin, 1,000-bp BamHI fragment from pHβI/1 (L. Kedes); and glyceraldehyde-3-phosphate dehydrogenase (GAPDH), 775-bp Pst I/Xho I fragment from pHCGAP (ATCC, Rockville, MD). Filters were washed to a stringency of 0.3 × SSC at 65°C and exposed to Kodak XAR-5 film (Eastman Kodak, Rochester, NY). The hybridization signals were quantitated by densitometry of autoradiographs. The levels of mRNA were calculated by normalizing values with respect to the signals of internal standards.

mRNA half-life. After stimulation of MNCs (2 × 10^6) with rhGM-CSF (20 ng/mL) for 18 hours, actinomycin D (Sigma) was added to a concentration of 5 μg/mL to block transcription. Cells were collected at the stated times and used thereafter for RNA preparation. Northern analysis was performed as described above. To assess the involvement of labile protein factors in the regulation of M-CSF expression, CHX (a protein synthesis inhibitor; Sigma) was added to cells at a concentration of 10 μg/mL. CHX was added to unstimulated cells for 18 hours and to rhGM-CSF-stimulated cells either 3 hours before harvesting or for the duration of the stimulation. Total culture period
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Fig 1. (A) Time course of induction of M-CSF protein accumulation in cord and adult MNCs by RIA. MNCs were cultured in RPMI without any stimulant (cord unstimulated [CUS] v adult unstimulated [AUS]) and after stimulation with GM-CSF (20 ng/mL; cord GM-CSF [CGM] v adult GM-CSF [AGM]) from 0 to 120 hours. Tissue culture supernatant samples were assayed by RIA for M-CSF protein (n = 3). *P = .0286 (AGM v CGM; 96 and 120 hours). **P = .0286 (AUS v CUS; 120 hours). (B) GM-CSF induction of M-CSF protein accumulation in cord and adult MNCs by bioassay. Cord and adult MNCs were cultured in RPMI without any stimulant (CUS and AUS) and stimulated with GM-CSF 20 ng/mL (CGM and AGM) for 120 hours. Tissue culture supernatant samples were assayed by bioassay for M-CSF bioactivity (n = 3). ***P = .0018 (AUS v CUS; 120 hours). ****P = .0286 (AGM v CGM; 120 hours).

was 18 hours. Total RNA from cells was extracted and analyzed by Northern blotting as described above.

Statistical analysis. Results are expressed as mean values ± SEM or mean ± SD of triplicate tests. The probability of significant differences when comparing two groups was determined with the use of the unpaired t-test, and the probability of significant differences when examining multiple groups was determined by using the analysis of variance followed by the Student-Newman-Keuls multiple range tests to define the unique subsets within the study. Statistical analyses were performed using Instat (Graph Pad Software, San Diego, CA).

RESULTS

Accumulation of M-CSF protein from cord and adult MNCs. Adherence has been reported to play an important role during development and maturation of monocytes into tissue macrophages.45,46 In contrast to GM-CSF, G-CSF, and IL-3,47,48 both adult and cord MNCs secreted M-CSF protein in vitro. Upon adhesion to a tissue culture flask for 120 hours, adult MNCs accumulated a 2.8-fold higher level of M-CSF protein than did cord MNCs (adult v cord, 4.7 ± 1.69 v 1.63 ± 0.41 ng/mL; n = 3; P = .0286; Fig 1; RIA). Bioassay showed a similar increased level of M-CSF protein from adult versus cord MNCs (adult v cord, 2.8 ± 1.18 v 1.13 ± 0.13 ng/mL; n = 3; P = .0018; Fig 1). Upon stimulation by GM-CSF for 120 hours, adult MNCs accumulated a twofold higher level of M-CSF than did cord MNCs (adult v cord, 22.3 ± 4.6 v 11.43 ± 2.86 ng/mL; n = 3; P = .0286; RIA). Bioassay also demonstrated a 2.4-fold increase of M-CSF from adult versus cord MNCs (adult v cord, 17.97 ± 4.07 v 7.43 ± 1.67 ng/mL; n = 3; P = .0286; Fig 1). M-CSF supernatant levels from freshly isolated adult and cord MNCs were less than the assay sensitivity level (<20 pg/mL; data not shown).

Upregulation of M-CSF mRNA expression from cord and adult MNCs. Upon adhesion to a tissue culture flask for 24 hours, adult MNCs expressed a fourfold higher level of M-CSF mRNA than did cord MNCs (adult v cord, 30.85 ± 5.9 v 8.04 ± 2.3 OD; n = 11; P = .007; Fig 2).
Next, a dose-response study with GM-CSF (0.2, 2.0, and 20 ng/mL) of M-CSF mRNA expression showed that, after 24 hours, 20 ng/mL of GM-CSF induced a 1.9-fold increase of M-CSF mRNA compared with unstimulated cord MNCs (unstimulated v GM-CSF–stimulated, 4.2 ± 0.8 v 7.85 ± 1.5 OD; $P = .016$). Additionally, after 24 hours, 20 ng/mL of GM-CSF induced a 3.1-fold increase in M-CSF mRNA expression compared with unstimulated adult MNCs (unstimulated v GM-CSF–stimulated, 9.6 ± 3.83 v 30.0 ± 11.75 OD; $P = .003$; Fig 3). Furthermore, a time course study showed that, after adhesion, both cord and adult MNCs expressed maximum levels of M-CSF mRNA between 16 and 24 hours and after stimulation by GM-CSF (20 ng/mL; Fig 4). Adult MNCs expressed a fourfold higher M-CSF mRNA expression compared with cord MNCs at 16 hours on GM-CSF stimulation (adult v cord, 49.5 ± 6.7 v 11.4 ± 2.9 OD; $P = .018$). PIXY321 alone or GM-CSF combined with IL-3 did not further increase M-CSF mRNA expression compared with GM-CSF alone (data not shown).

Transcriptional activity of M-CSF gene. To determine whether reduced M-CSF mRNA expression in stimulated cord MNCs was mediated at the transcriptional level, nuclear run-on assays for the M-CSF gene were performed. Nuclei from cord and adult MNCs were isolated. Nascent RNA was labeled with $\alpha$-32P UTP, purified, and hybridized to membrane-immobilized M-CSF cDNA and shorter-fragment DNAs. An equivalent amount of input radioactivity was used in the hybridization reaction. As shown in Fig 5, unstimulated MNCs from both cord and adult showed a detectable basal level signal of the M-CSF gene. The basal level signal of this gene was approximately the same between cord and adult MNCs. After stimulation with GM-CSF (18 hours), the transcriptional rate of the M-CSF gene was increased approximately 1.5-fold in both cord and adult MNCs. However, there was no appreciable difference between stimulated cord and adult MNCs in the degree of transcriptional activation (130% ± 10% v 150% ± 15%; C v A; n = 3; mean ± SD; Fig 5).

M-CSF mRNA half-life. Because the transcriptional activity of M-CSF gene was virtually the same for both cord and adult samples, studies on the stability of M-CSF mRNA were performed to confirm whether differential regulation was occurring at the posttranscriptional level. Cord and adult

![Fig 3. Dose-response of GM-CSF upregulation of M-CSF mRNA expression in (■) cord and (□) adult MNCs. Cord and adult MNCs were isolated (US-0), cultured in RPM1 without any agonist for 24 hours (US-24), and stimulated with GM-CSF at 0.2 ng/mL (GM-0.2), 2 ng/mL (GM-2), and 20 ng/mL (GM-20) for 24 hours. Cells were harvested and mRNA was analyzed by Northern analysis of M-CSF mRNA (4 kb) and β-actin mRNA (2 kb) expression (n = 4). *P = .02 (cord GM-20 v cord US; 24 hours). **P = .003 (adult GM-20 v adult US; 24 hours). (■) cord; (□) adult.](image)

![Fig 4. Time course of induction of M-CSF mRNA expression in cord and adult MNCs. MNCs were cultured in RPM1 without any agonist (US) and stimulated with GM-CSF (20 ng/mL) for a period up to 72 hours. Cells were harvested and RNA was analyzed by Northern blot analysis of M-CSF mRNA (4 kb) and β-actin mRNA (2 kb) expression (n = 4). *P = .001 (CGM v AGM; 6 hours). **P = .018 (CGM v AGM; 16 hours). ***P = .021 (CGM v AGM; 24 hours).](image)
REGULATION OF M-CSF mRNA EXPRESSION

MNCs were stimulated with rhGM-CSF 18 hours before actinomycin D (5 μg/mL) was added for various intervals (0 to 120 minutes). Total cytoplasmic RNA was collected and hybridized to 32P-labeled M-CSF cDNA. The levels of M-CSF mRNA progressively decreased during actinomycin D exposure in both cord and adult MNCs. Transcripts were quantitated by densitometric scanning of the autoradiographs. As shown in Fig 6, the estimated half-life (τ1/2) of M-CSF mRNA from stimulated adult MNCs was 70 ± 7 minutes (n = 4) compared with 47 ± 2.8 minutes (n = 3) from stimulated cord MNCs (mean ± SD, P < .05).

Effects of CHX on M-CSF mRNA. To examine whether the differential stability of M-CSF transcripts from cord versus adult MNCs is involved with the synthesis of labile proteins, MNCs from cord and adult were treated with CHX (10 μg/mL), an inhibitor of protein synthesis, during the last 3 hours of rhGM-CSF-stimulated cultures. The total culture period was 18 hours. As shown in Fig 7, M-CSF mRNA was not detected on treatment with CHX, whether alone or in the presence of the inducer. In contrast, delayed addition of CHX (3 hours before harvesting) led to a significant increase in the levels of M-CSF mRNA in both cord and adult MNCs. We compared the percent increase in densitometric values of M-CSF transcript by CHX treatment between stimulated cord and adult MNCs. The increase of M-CSF mRNA induction by CHX treatment was approximately 2.5 times higher in cord MNCs compared with that in adult MNCs (410% ± 120% v 186% ± 35%; C v A; mean ± SD; n = 3; P < .05; Fig 7).

DISCUSSION

During states of increased demand, mononuclear phagocytes and T lymphocytes contribute significantly to the production of M-CSF. M-CSF is an important mediator of the

![Fig 5](image_url) Nuclear run-on analysis of M-CSF transcription in cord and adult MNCs stimulated with rhGM-CSF. Equivalent amounts of radioactive labeled RNA were hybridized to filters containing the indicated DNA fragments (n = 3). Abbreviations: US, unstimulated; S, stimulated; PUC, control vector; F-I, 880-bp Xho I/BamHI fragment; F-II, 700-bp BamHI/BamHI fragment; cDNA, 1,800-bp EcoRI/Xho I fragment from p3ACSFRI (Genetics Institute).

![Fig 6](image_url) Northern blot analysis of the half-life of M-CSF mRNA in stimulated cord and adult MNCs. Actinomycin D (5 μg/mL) was added for the indicated times to cells stimulated with rhGM-CSF (20 ng/mL) for 18 hours. Total cellular RNA was isolated and analyzed for the presence of M-CSF (4 kb) transcript. T1/2: 47 ± 2.8 minutes (n = 3) v 70 ± 7 minutes (n = 4; P < .05; cord v adult).
inflammatory response and can regulate the release of proinflammatory cytokines and other inflammatory modulators.

M-CSF is constitutively produced by a variety of tissue and mesenchymal cells, including marrow stromal cells, fibroblasts, endothelial cells, and osteoblasts. Synthesis of M-CSF by mesenchymal cells probably accounts for the high levels of M-CSF present in the serum of normal individuals. Upon stimulation by IL-1, TNF-α, and epidermal growth factor, increased levels of M-CSF are expressed from human endothelial cells and murine stromal cells.

Synthesis of M-CSF can also be induced from peripheral blood MNCs in response to other cytokines and mitogens. Activated T cells express M-CSF mRNA in response to mitogens and T-cell adhesion molecules. Monocytes themselves also produce M-CSF in response to phorbol esters, γIFN, GM-CSF, IL-3, TNF, LPS, and IL-2 stimulation. Adherence is an additional important regulatory signal for M-CSF expression from both adult and newborn monocytes.

GM-CSF has been shown to induce M-CSF mRNA expression and bioactive protein secretion, whereas other inflammatory agonists (eg, TNF-α, γIFN, and LPS) only trigger M-CSF mRNA transcripts. In the present study, both RIA and bioassays showed a twofold to threefold decrease of M-CSF protein production induced by GM-CSF (120 hours) from cord compared with adult MNCs. Northern blot analysis also showed a fourfold decrease of M-CSF mRNA expression in cord MNCs in response to adhesion and rhGM-CSF stimulation (16 hours) when compared with adult MNCs (Fig 2 and 4). M-CSF mRNA expression peaked at 16 to 24 hours and decreased by 48 hours in both cord and adult MNCs. The fusion protein PIXY321 did not further induce M-CSF expression compared with the combination of GM-CSF and IL-3.

Our nuclear run-on studies suggested no difference in transcriptional activation of the M-CSF gene between cord and adult MNCs. However, transcriptional decay studies with actinomycin D suggested decreased stabilization of M-CSF mRNA from stimulated cord compared with adult MNCs. These results indicate that cord MNCs, during states of increased demand (stimulation), transcribe M-CSF gene expression at the same level as adult MNCs. These data also suggest that the reduced M-CSF expression from stimulated cord MNCs versus adult MNCs are not secondary to defects in transcriptional regulation. Alteration in posttranscriptional events appeared to account for the major difference of M-CSF expression between cord and adult MNCs.

Posttranscriptional mechanisms responsible for the regulation of gene expression can involve the modification of existing or de novo synthesized regulatory proteins. In the present study, we further determined the involvement of stable protein factors in M-CSF gene regulation by CHX inhibition studies. CHX treatment at the time of stimulation of cells with GM-CSF blocked mRNA induction of M-CSF in both cord and adult MNCs, suggesting that de novo protein synthesis is required for M-CSF mRNA induction by GM-CSF in both cord and adult MNCs. However, the addition of CHX at later time intervals resulted in a significant increase in the transcript level in both cord and adult MNCs. The induction of transcripts by protein synthesis inhibition suggests that there are one or more short-lived regulatory proteins that can regulate transcript stability. Interestingly, the fold increase of M-CSF mRNA induction by CHX was approximately 2.5 times higher in cord MNCs compared with that in adult MNCs. These findings suggest that a de novo synthesized protein(s) may be associated with the reduced M-CSF mRNA accumulation in stimulated cord compared with adult MNCs.

Control of mRNA stability is not completely understood, but the process is thought to involve various factors interacting with specific mRNA sequences. The AU-rich sequences in the 3' untranslated region of many short-living mRNA are shown to be the targets of a pathway for selective...
processing and mRNA degradation. Recently, an AU binding factor and a 32-kD protein have been shown to be involved in mRNA stability through binding to the AU-rich domain in the 3' untranslated regions of rapidly degraded mRNA. Evidence also suggests that rapidly turned over labile proteins are involved in the mRNA degradation. One potential target for such proteins might be the AU-rich sequence in the 3' untranslated region. Analyses of the published M-CSF sequence indicated the presence of several short AU-rich stretches in the 3' untranslated region which may, therefore, contribute to the instability of the M-CSF mRNA. It seems likely that various protein factors interacting with specific mRNA sequences exist in vivo and are involved in the regulation of AU-rich mRNA decay. Any alteration in the expression and/or in the biologic activities of one or a few of these factors in stimulated cord MNCs possibly contributes to the reduction of mRNA coding for M-CSF. Further studies are required to test these possibilities. Preclinical studies have shown that M-CSF can enhance phagocytic and cytotoxic activity of monocytes and substantially increase the ability of monocytes and macrophages to kill bacteria and fungi. Newborn infants are unusually susceptible to infection, especially with organisms such as Listeria monocytogenes and Candida albicans. The eradication of these organisms requires functionally active monocytes for adequate host defense. Kayashima et al. showed increased phagocytosis of Listeria monocytogenes by monocytes after treatment with M-CSF. Karbassi et al. showed enhancement of Candida albicans killing by murine macrophages after treatment with M-CSF. We hypothesize that altered M-CSF expression from activated cord versus adult MNCs may predispose the neonate to an alteration in host defense and increased susceptibility to infections with organisms such as Listeria and Candida.

In summary, the present study has shown that M-CSF mRNA and protein expression is decreased in stimulated cord compared with adult MNCs. This discrepancy in M-CSF production is secondary, at least in part, to the altered posttranscriptional regulation involving the synthesis of labile proteins that affect the stability of M-CSF transcripts. The present results, together with those of our previous studies, suggest that altered expression of hematopoietic regulators may be involved in the immaturity of host defense in human neonates and predispose them to overwhelming infection. Future studies are required to determine the clinical significance of the alteration of M-CSF regulation in the neonate.

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