Human Peritoneal Mesothelial Cells Produce Many Cytokines (Granulocyte Colony-Stimulating Factor [CSF], Granulocyte-Monocyte-CSF, Macrophage-CSF, Interleukin-1 [IL-1], and IL-6) and Are Activated and Stimulated to Grow by IL-1


To investigate the role of peritoneal mesothelial cells in regulating hematopoiesis, as well as inflammation, healing, and tissue regeneration processes, long-term cultures of peritoneal mesothelial cells from human endocavitarian fluids were established. The purity of the cell population was assessed by morphologic and immunocytochemical criteria. Five peritoneal mesothelial cell cultures were analyzed for cytokine expression. Macrophage colony-stimulating factor (M-CSF), granulocyte-CSF (G-CSF), interleukin-1α (IL-1α), IL-1β, and IL-6 transcripts were constantly but variably detected throughout the culture period, while granulocyte-monocyte-CSF (GM-CSF) expression started as the cell culture aged. No IL-2, IL-3, IL-4, IL-5, or IL-7 transcripts were detected in the same samples. Corresponding cytokine activities were detected in the supernatants of the cultures. Peritoneal mesothelial cells proliferated after the addition of exogenous IL-1β or IL-1α, whereas the addition of recombinant GM-CSF, G-CSF, M-CSF, or IL-6 failed to trigger proliferation. IL-1 receptor type 1 transcripts were detected in peritoneal mesothelial cells. Moreover, IL-1 was able to upregulate the expression of the genes that code for G-CSF, GM-CSF, IL-1α, and IL-1β in these cells. These data indicate that peritoneal mesothelial cells produce many cytokines and suggest that IL-1 is a regulatory molecule for peritoneal mesothelial cells.

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The mesothelium, a simple squamous epithelium, lines the pleural, pericardial, and peritoneal cavities. It is thought to function both as a slippery, nonadhesive surface for the internal organs and as a selective barrier that regulates the transport of molecules and cells between the circulation and the body cavities.1

It has recently been shown that human peritoneal mesothelial cells (HMC) are capable of producing hematopoietic growth factors, either constitutively (macrophage colony-stimulating factor [M-CSF] and interleukin-8 [IL-8]) or in response to a variety of stimuli, including epidermal growth factor (EGF), tumor necrosis factor (TNF), or lipopolysaccharide (LPS) (granulocyte-CSF [G-CSF], granulocyte-monocyte-CSF [GM-CSF], IL-1β, and IL-8).2,3 These findings suggest that HMC are involved in the regulation of hematopoiesis, as well as in inflammation, healing, and tissue regeneration processes. Some of these functions are pertinent to the anatomical position of HMC. Because they are the major cell population in the epithelium that lines serous cavities, peritoneal mesothelial cells would be expected to regulate cell traffic, to participate in the first-line barrier to infections, and, by consequence, to be equipped with several different cytokines.

To better define how HMC can respond and regulate cellular events in serous spaces, we undertook a systematic analysis of peritoneal mesothelial cytokine production and regulation. This report provides evidence that (1) a variety of cytokines (G-CSF, GM-CSF, M-CSF, IL-1α, IL-1β, and IL-6) are spontaneously released by peritoneal mesothelial cells; and (2) IL-1 regulates both growth and cytokine release by peritoneal mesothelial cells.

MATERIALS AND METHODS

Isolation and culture of peritoneal mesothelial cells. Peritoneal mesothelial cells were collected by centrifuging peritoneal fluids collected from 10 patients with hepatic cirrhosis. The cells were then resuspended in Iscove’s modification of Dulbecco’s medium supplemented with human transferrin, bovine serum albumin, and soybean lipids (IMDM; Flow Laboratories, Irvine, UK), and enriched with 10% fetal bovine serum (FBS; HyClone, Sterile Systems, Logan, UT) and 20% conditioned medium of human peripheral blood mononuclear cells stimulated for 3 to 4 days in the presence of purified phytohemagglutinin (PHA-P; Difco Laboratories, Detroit, MI). Cells were plated onto plastic Petri dishes at 10⁶/mL. Adherent cells were subsequently disaggregated for subculture by 5 minutes of incubation with 0.05% trypsin and 0.02% EDTA when they reached confluency.

Immunocytochemical staining. Confluent monolayers of HMC were grown on tissue culture chamber/slides (Labtek, Naperville, IL) at various time intervals during the culture period. Chamber slides were washed twice in phosphate-buffered solution (PBS), fixed in acetone, and stained by the immunoalkaline phosphatase (APAAP) technique as previously described.4 An alkaline phosphatase reaction was shown by the new Fuchsinsubstrate.5 At least 500 cells were scored for each slide. Monoclonal antibodies (MoAbs) directed against a number of human leukocyte antigens (CD3, CD4, CD5, CD7, CD8, CD19, CD22, CD11, CD45, and Ber-Mac3) were used, together with specific anticytokeratins (DAKO-MNF116 and DAKO-CK19; Dakopatts, Copenhagen, Denmark) and antivimentin (DAKO-vimentin; Dakopatts) MoAbs.

Northern blot analysis. Total cellular RNA was extracted according to the 4 mol/L guanidine isothiocyanate method.6 Five to 20 μg of RNA was electrophoresed in 1% agarose gels with 2.2 mol/L formaldehyde and transferred to nylon filters (Hybond-N; Amer sham, Amersham, UK). Approximately equal amounts of RNA were loaded per gel lane, as confirmed by hybridization to actin

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control probe (data not shown). Filters were hybridized with nick-translated complementary DNA inserts at 37°C in the presence of 50% formamide, 3× SSC, 0.5% sodium dodecyl sulfate (SDS), 10% dextran sulphate, and 100 μg/ml denatured salmon sperm DNA. Filters were washed at 60°C for 2 hours in 0.2× SSC (sodium chloride and sodium citrate), 0.5% SDS. Membranes were then exposed to Kodak Xomat XAR5 films (Eastman Kodak, Rochester, NY) for variable periods of time. The specific messenger RNA (mRNA) transcripts were detected with the human cDNA probes for different cytokines (G-CSF, GM-CSF, M-CSF, IL-1α, IL-1β, and IL-6).

Conditioned media preparation and biologic assay for cytokine production. Conditioned media from normal HMC (Mo-CM) were collected at different culture times, according to the presence of the mRNAs specific for the different cytokines. Eighty percent confluent 100 mm Petri dishes were washed twice with prewarmed PBS and the media replaced with IMDM plus 10% FBS for incubation periods ranging from 35 to 40 hours. For evaluation of the colony-stimulating activity of peritoneal mesothelial supernatants, normal human bone marrow was obtained by aspiration from adult volunteers. The nonadherent population was suspended in IMDM plus 20% FBS in the presence of scalars of Mo-CM in 0.3% soft agar (Difco). Colonies of differentiated BM cells (> 40 cells) were scored at days 7 and 14 of culture. The specific mRNAs were detected with the human cDNA probes for different cytokines (G-CSF, GM-CSF, M-CSF, IL-1α, IL-1β, and IL-6).

RESULTS

Long-term culture of normal HMC. Peritoneal mesothelial cells were obtained from the peritoneal fluid of 10 patients with either alcoholic or biliary cirrhosis of the liver. After a few passages in culture, adherent cells isolated by centrifugation from the endocavitarian fluids were morphologically homogeneous and had the typical spindly, fibroblast-like morphology of HMC by light microscopy (data not shown). Cells were grown in culture in the presence of FBS or PHA-CM or both. Twenty percent PHA-CM plus 10% FBS was found to provide the best culture environment for peritoneal mesothelial cells (see Fig 1 for the growth kinetics of a representative peritoneal mesothelial cell culture). In these conditions, only peritoneal mesothelial cells grew progressively from 100% of the ascites samples tested, regardless of the percentage of peritoneal mesothelial cells present in the initial samples (Table 1). The peritoneal mesothelial origin of the cultured cells was confirmed by intermediate filament typing. Keratin-type radioactivity was counted. All calculations and Scatchard analyses were performed according to Munson and Rodbard. Growth factor-dependent proliferation assays. Exponentially growing cells were made quiescent by serum and growth factor deprivation for 24 hours. For short-term proliferation assays, cells were plated in Cluster 96 plates at 5 x 10^5/well in IMDM plus 1% FBS and growth factors at the concentrations indicated in Fig 3. Twenty-four, 48, and 72 hours later, [3H]-Tdr at 0.5 μCi/well was added. After the 12-hour pulse, cells were harvested in trypsin-EDTA onto glass fiber filters and radioactivity determined with a liquid scintillation counter. Each assay point was the mean ± SD of triplicate cultures. Experiments were repeated at least three times. For long-term proliferation assays, cells were plated in Cluster 6 plates (Costar) at 5 x 10^4/well in IMDM plus 1% FBS and growth factors at three different concentrations. Culture medium was replaced every 3 days and cell growth followed by counts. Growing populations were subcultured, while medium was changed in nonproliferating wells until the cells died.

Fig 1. Effect of different culture conditions on the growth of HMC. Cells obtained from endocavitarian fluids were grown in culture in the presence of 20% PHA-CM (●), 10% FBS (▲), or both (■) and counted at weekly intervals by the Trypan blue dye exclusion test. Results are expressed as percent increase of the initial cell numbers. The percentage of cytokeratin-positive cells in this culture (Mo7) was 5% at the beginning of the culture and approximately 100% from day 15 on.
intermediate filaments were visible within the cytoplasm of HMC and not of the contaminating population of lymphocytes, macrophages, and neutrophils. Conversely, these cells were stained with antileukocyte antibodies (Table 1). Moreover, HMC were stained with MoAbs directed against a number of human leukocyte antigens (CD3, CD4, CD5, CD7, CD8, CD9, CD11, CD19, CD22, CD45, and Ber-Mac 3). Values are percentages.

Abbreviation: ND, not determined.

Peritoneal mesothelial cells were identified by positivity to an antivimentin (DAKO-vimentin) and anticytokeratin (DAKO-MNF116 and DAKO-CK19) antibodies and negativity to all the leukocyte markers (see below). Conversely, neutrophils, lymphocytes, and macrophages were identified by morphology after May-Grünwald-Giemsa staining and by positivity to MoAbs directed against a number of human leukocyte antigens (CD3, CD4, CD5, CD7, CD8, CD9, CD11, CD19, CD22, CD45, and Ber-Mac 3). Values are percentages.

Table 1. Phenotypic Characterization of Mesothelial Cultures

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Day 0</th>
<th>Day 22</th>
<th>Day 35</th>
<th>Day 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mo5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>50</td>
<td>0</td>
<td>ND</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>40</td>
<td>0</td>
<td>ND</td>
<td>0</td>
</tr>
<tr>
<td>Macrophages</td>
<td>10</td>
<td>0</td>
<td>ND</td>
<td>0</td>
</tr>
<tr>
<td>Mesothelium</td>
<td>0.5-1</td>
<td>100</td>
<td>ND</td>
<td>100</td>
</tr>
<tr>
<td>Mo6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>20</td>
<td>ND</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>50</td>
<td>ND</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Macrophages</td>
<td>20</td>
<td>ND</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mesothelium</td>
<td>10</td>
<td>ND</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Mo8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Macrophages</td>
<td>23</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Mesothelium</td>
<td>7</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Mo9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Macrophages</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mesothelium</td>
<td>20</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Confirmation of the cytokine mRNA expression data was sought at the protein level by testing the presence of cytokine activity in peritoneal mesothelial cell-conditioned media. Media conditioned by preconfluent cultures of peritoneal mesothelial cells were thus tested in proliferation bioassays using: (1) normal human bone marrow (BM) mononuclear cells as indicators of colony-stimulating activity (G-CSF and GM-CSF)\(^2\); (2) the MM5 cell line to detect M-CSF activity; (3) the 7TD1 cell line to detect IL-6 activity; and (4) the IL-1-dependent D10.G4.1 T-cell clone to detect biologically active IL-1α and IL-1β (see Materials and Methods for description of each bioassay). Consistent with the expression of cytokine transcripts, the corresponding cytokine activities were detected in the supernatants of HMC (Table 2). IL-1 bioactivity could be detected in the supernatant of most peritoneal mesothelial cell cultures. As shown in Table 3, supernatants contained a mixture of IL-1α and IL-1β. In fact, IL-1 activity could be partially blocked by polyclonal antibodies specific to either IL-1α or IL-1β and fully inhibited by the addition of both antibodies together. Different peritoneal mesothelial cell cultures released different amounts of bioactive IL-1 (from <5 to 400 U/mL), of which the majority was IL-1α (60% to 100%), except for Mo8 cells, which produced equal amounts of both IL-1α and IL-1β (Table 3).
IL-1α and IL-1β stimulate peritoneal mesothelial cell growth and are required for optimal peritoneal mesothelial long-term growth. We then asked whether mesothelial cell-derived growth factors stimulated growth of peritoneal mesothelial cells. Mesothelial cells were grown for 3 days in 1% FBS in the presence of various concentrations of the different cytokines. The addition of recombinant GM-CSF, G-CSF, M-CSF, or IL-6 failed to trigger proliferation at any of the concentrations tested (data not shown). In contrast, peritoneal mesothelial cells proliferated after the addition of exogenous IL-1β (Fig 3) or IL-1α (data not shown). Similar results were obtained when the potential of IL-1α or IL-1β to sustain growth was assessed in a long-term (20 days) culture test (data not shown).

The fact that peritoneal mesothelial cells release IL-1 and that IL-1 promotes mesothelial cell growth suggests that IL-1 is part of an autocrine pattern of growth. To test this possibility, we analyzed peritoneal mesothelial cell cultures for the presence of IL-1 receptors on the cell membrane.

Table 2. Cytokine Production by HMC Grown In Vitro

<table>
<thead>
<tr>
<th>Conditioned Media</th>
<th>G-CSF and GM-CSF (colonies/mL)</th>
<th>IL-6 (U/mL)</th>
<th>IL-1 (U/mL)</th>
<th>M-CSF (U/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium alone</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mo8 (30 d in culture)</td>
<td>25</td>
<td>&gt;1,250</td>
<td>112</td>
<td>682</td>
</tr>
<tr>
<td>Mo1 (40 d in culture)</td>
<td>31</td>
<td>&gt;1,250</td>
<td>57</td>
<td>547</td>
</tr>
</tbody>
</table>

Conditioned media from the indicated cell cultures were prepared as detailed in Materials and Methods. Recombinant cytokines (rGM-CSF, rG-CSF, rM-CSF, rIL-6, and rIL-1) were used in all assays as positive controls.
HMC SECRET CYTOKINES AND GROW WITH IL-1

Table 3. Production of Bioactive IL-1α and IL-1β by HMC Grown In Vitro

<table>
<thead>
<tr>
<th>Neutralizing Antibody</th>
<th>IL-1 Activity (U/mL) in the Supernatants of</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mo8 (30 d)</td>
</tr>
<tr>
<td>None</td>
<td>112</td>
</tr>
<tr>
<td>Anti-IL-1α</td>
<td>50</td>
</tr>
<tr>
<td>Anti-IL-1β</td>
<td>50</td>
</tr>
<tr>
<td>Both</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

Supernatants of peritoneal HMC cultures (grown for the indicated time as detailed in Materials and Methods) were titrated for bioactivity on D10.G4.1 cells in the presence of 10 μg/mL purified rabbit IgG to IL-1α, to IL-1β, or to the combination of the two.

The steady-state expression of M-CSF and IL-6 was not modified by the addition of exogenous IL-1β. Similar results were obtained with IL-1α.

DISCUSSION

Peritoneal mesothelial cells have recently been shown to produce some cytokines, either spontaneously (eg, M-CSF) or after stimulation with EGF, TNF, or LPS (eg, GM-CSF, G-CSF, IL-1β, and IL-8). The peritoneal mesothelial cell cultures described here displayed a different behavior in that they spontaneously expressed all these cytokines upon culture. This expression is unlikely to be the consequence of the presence of EGF, TNF, LPS, or other stimulation factors in culture media, because the expression/release of GM-CSF, G-CSF, and IL-1β could also be observed after peritoneal mesothelial cells were grown in the absence of conditioned media and even in serum-free conditions. Moreover, peritoneal mesothelial cells grown in the presence of EGF displayed a similar cytokine production pattern, even if the levels of cytokine mRNA were slightly higher. In our hands, peritoneal mesothelial cultures produce G-CSF, GM-CSF, M-CSF, and IL-1 spontaneously, but in different amounts and at different times during the culture period. Early passage cells did not express GM-CSF, whereas day 70 or even day 90 cells (data not shown) released all tested growth factors. In particular, G-CSF and GM-CSF expression increased with aging in culture. This can be related to the various functions of the peritoneal mesothelial cell, which is able to release different stimuli for the surrounding target cells depending on its differentiation stage.

We extended the analysis of cytokine production by peritoneal mesothelial cells to other cytokines and showed that they also produce IL-1β and IL-6, but no T-cell-derived interleukins, such as IL-2, IL-3, IL-4, IL-5, and IL-7. In their production of specific cytokines, peritoneal mesothelial cells resemble fibroblasts, macrophages, and endothelial and stromal cells, which, although of different histologic origin, are similarly distributed.

IL-6 is a multifunctional factor able to behave as a growth or differentiation factor and to induce the expression of other genes in different experimental systems. Originally described as a T-cell product that enhances Ig secretion in antigen-stimulated B cells, it also affects the growth of several hematopoietic and nonhematopoietic cell types. In particular, IL-6 mediates acute-phase responses, including fever; has lymphocyte-stimulating capacities; and has antiviral activity. The expression and production of IL-6 by normal HMC is indicative of cytokine-networking, whereby one cell population is dependent on mediators synthesized by a neighboring cell.

IL-1 appears to play a crucial role in the regulation of peritoneal mesothelial growth and activation. IL-1 is known to induce a wide range of biologic activities in numerous cell types. It participates in a variety of T- and B-lymphocyte responses, is an inflammatory cytokine, capable of conferring radioprotection and nonspecific resistance to infection, and is capable of augmenting responses of...
hematopoietic stem cells to other hematopoietic growth factors. IL-1 might be involved in an autocrine growth pattern in peritoneal mesothelial cells. Autocrine models in which cells are capable of producing their own growth factors and are independent of exogenous ones have been described in several tumor systems. Normal HMC cannot be considered autocrine in this sense because, although they secrete detectable amounts of IL-1 and express IL-1R, they need an addition of exogenous IL-1 for their long-term growth. To explain why peritoneal mesothelial cells are apparently unresponsive to endogenously produced IL-1, it can be hypothesized that their IL-1R are functionally blocked. This might be due to IL-1ra, an IL-1-like antagonist that binds to IL-1R with high affinity. If peritoneal mesothelial cells produce large amounts of IL-1ra, this would then block IL-1R and would not be displaced by the low amounts of endogenous IL-1. In contrast, high concentrations of exogenous IL-1 (50 ng/mL, corresponding to $5 \times 10^6$ U/mL) may effectively compete with IL-1ra for binding to IL-1R, thus becoming able to trigger cell activation. Alternatively, peritoneal mesothelial cells may release soluble IL-1R (sIL-1R) in amounts sufficient for complexing and blocking low amounts of IL-1. The natural production of sIL-1R has been reported for IL-1RII, but it may also occur for IL-1RI. In addition, peritoneal mesothelial cells may coexpress the IL-1RII together with IL-1RI.

Remarkably, we found that IL-1 regulates expression of G-CSF, GM-CSF, and IL-1 by peritoneal mesothelial cells. Previous work has shown that IL-1 can activate a variety of genes in different cells. IL-1 stimulates its own gene expression and synthesis in vitro in cultured smooth muscle cells, endothelial cells, and mononuclear cells. The massive production of G-CSF, GM-CSF, and IL-1 by peritoneal mesothelial cells in consequence to a strong IL-1 stimulus (such as that induced during inflammation) may enhance the local inflammatory response. G-CSF and GM-CSF induce mature polymorphonucleates to migrate to inflammatory foci, promote their retention in the region, increase their survival, and enhance their effector functions. IL-1-induced IL-1 may contribute to the outcome of immunologic and inflammatory responses.

In conclusion, peritoneal mesothelial cells spontaneously produce several cytokines. Because of the position peritoneal mesothelial cells occupy in the body, these cytokines may play important roles in both hematopoiesis and inflammation. They could contribute to maintaining a steady-state stimulation of hematopoiesis and, at the same time, trigger specific cellular functions of fully differentiated cells, such as macrophages and neutrophils. The upregulation of some of these cytokines by IL-1 suggests a role for peritoneal mesothelial cells in the development of the inflammatory defence reaction and emphasizes the importance and

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**Fig 4.** Northern blot analysis of cytokine mRNA regulation in HMC in the presence of exogenous IL-1. Twenty micrograms of total RNA was analyzed for M-CSF, GM-CSF, G-CSF, IL-1α, IL-1β, and IL-6 expression, as indicated. Peritoneal mesothelial cells were grown in IMDM plus 1% FBS (lane a) or IMDM plus 1% FBS plus 50 ng/mL IL-1β (lane b) for 48 hours.
complexity of paracrine molecular interactions involved in the inflammatory, immunologic, and hematopoietic responses.

Moreover, mesothelial cells are also important for the host's response to continuous ambulatory peritoneal dialysis (CAPD) and several attempts have been made to implant autologous mesothelial cells in animals and dialyzed patients. The long-term culture of mesothelial cells and the characterization of the cytokines that HMC produce and release and of those HMC respond to should add some information regarding their functional role in the peritoneum.

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Human peritoneal mesothelial cells produce many cytokines (granulocyte colony-stimulating factor [CSF], granulocyte-monocyte-CSF, macrophage-CSF, interleukin-1 [IL-1], and IL-6) and are activated and stimulated to grow by IL-1

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