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## CC-chemokine activation in acute pancreatitis: enhanced release of monocyte chemoattractant protein-1 in patients with local and systemic complications

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**Abstract** *Objective:* Systemic leukocyte activation is claimed to trigger inflammatory response and remote organ dysfunction in acute pancreatitis. Chemokines are inflammatory mediators with potent leukocyte-activating properties and have been shown to be involved in the pathophysiological process of experimental acute pancreatitis. However, as little is known about their role in human disease we investigated local and systemic concentrations of different CC-chemokine members in patients with acute pancreatitis.

*Patients and methods:* We included 68 patients with acute pancreatitis in the present study. Local complications in terms of necrosis were present in 37 (54%) patients of whom 21 (57%) developed pancreatic infections. Monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 $\alpha$  (MIP-1 $\alpha$ ) and macrophage inflammatory protein-1 $\beta$  (MIP-1 $\beta$ ) concentrations were measured daily over 2 weeks after study inclusion by ELISA in sera and lesser sac aspirates.

*Results:* MCP-1 serum concentrations showed a dramatic increase in patients who developed local complications and/or remote organ failure. Herein, a close correlation was found between the severity of remote organ failure and the degree of MCP-1 elevation. Multiple regression analysis identified pancreatic infections as well as renal and car-

diocirculatory failure as independent variables associated with enhanced systemic MCP-1 release. MIP-1 $\alpha$  levels remained unaffected by local complications and showed a significant increase only; if multiple organ dysfunction syndrome (MODS) developed or patients subsequently died. In contrast, MIP-1 $\beta$  concentrations correlated with neither the presence nor the severity of any complication. Compared with systemic concentrations, local lesser sac aspirates revealed significantly higher levels of MCP-1, whereas MIP-1 $\alpha$  and MIP-1 $\beta$  were not different.

*Conclusions:* Complicated acute pancreatitis is associated with significantly elevated local and systemic concentrations of the CC-chemokine MCP-1. Our results suggest that, among the CC-chemokine members investigated, MCP-1 might play a pivotal role in the pathological mechanism of complicated acute pancreatitis.

**Keywords** Acute pancreatitis · CC-chemokines · Monocyte chemoattractant protein-1 · Macrophage inflammatory protein-1 $\alpha$  · Macrophage inflammatory protein-1 $\beta$  · Necrosis · Pancreatic infection · Organ failure · Prognosis

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## Introduction

Acute pancreatitis is characterized by wide clinical variation ranging from a mild self-limiting to a severe life-threatening disease carrying high mortality rates. It is well established that the development of pancreatic necrosis is the main prognostic factor in acute pancreatitis. The presence of intra- and extra-pancreatic necrosis strongly influences the risk of infected necrosis [1, 2, 3] and remote organ failure [2, 3, 4], which is further associated with a significant increase in mortality rate [1, 3, 5]. A large number of experimental studies have shown that the subsequent infiltration of different leukocyte subsets into the damaged gland are the major source of the release of various toxic mediators such as proteolytic enzymes [6], oxygen free radicals [7, 8] and cytokines [9, 10], which enhance pancreatic tissue destruction and promote remote organ failure.

Chemokines are a family of small (8–10 kDa), inducible, secreted cytokines with chemotactic and activating effects on different leukocyte subsets; thus they provide a key stimulus for directing leukocytes to the areas of injury [11]. Chemokines can be subdivided on a structural basis into the CXC-subfamily in which the first two of four conserved cysteine residues are separated by another amino acid and the CC-subfamily, in which the first two cysteine residues are adjacent. The structural classification of the chemokines also determines their biological activity: while a subgroup of the CXC-chemokines, such as interleukin-8, are potent neutrophil chemoattractants and activators, the CC-chemokines, comprising monocyte chemoattractant protein (MCP)-1, -2, -3, macrophage inflammatory protein (MIP)-1 $\alpha$  and -1 $\beta$ , RANTES and eotaxin predominantly affect monocytes [10, 11]. Chemokines bind to specific receptors which can be broadly divided into those that bind a single chemokine or those that bind a number of chemokines of either CXC- or CC-type [12]. With respect to the CC-chemokines, the CC-CKR-2 receptor is exclusively located on monocytes and specific for MCP-1, whereas the CC-CKR-1, -3, -4, and -5 receptors are to be found on monocytes, eosinophil and basophil granulocytes as well as on T-cells, and variably bind to MCP-1, MIP-1 $\alpha$  or MIP-1 $\beta$  [12, 13].

Recent experimental data suggest that chemokines may be important inflammatory mediators within the early pathophysiological process of acute pancreatitis, promoting distant organ failure. In various experimental models an early upregulation of CXC-chemokines, such as mob-1/IP10 [14] or cytokine-induced neutrophil chemoattractant (CINC) [15], as well as CC-chemokines, such as MCP-1 [14, 15, 16] and RANTES, has been observed [16]. Moreover, pancreatitis-associated pulmonary damage is significantly attenuated following the application of neutralizing antibodies against CINC [17] or in mice deficient in the CC-CKR-1 gene [18].

With respect to the clinical setting, elevated plasma levels of the CXC-chemokines ENA-78 and GRO- $\alpha$  revealed a close correlation with disease severity in human acute pancreatitis [19], however, little is known about the course and dynamics of CC-chemokines in this context. To address this issue we assessed local and systemic concentrations of the CC-chemokines MCP-1, MIP-1 $\alpha$  and MIP-1 $\beta$  in a morphologically and clinically well-defined patient series with acute pancreatitis.

## Materials and methods

### Patients

Sixty-eight patients with acute pancreatitis entered the present study at the Department of General Surgery, University hospital at Ulm during the time from November, 1994, to June, 1999. Inclusion criteria were typical upper abdominal pain and at least three-fold elevated serum amylase and/or lipase levels. The median time interval between onset of symptoms and admission to hospital was 25 (range 0–141) h, patients were recruited in median on the 2nd day (range 1–7) of disease. Local complications comprised the development of intra-/extra-pancreatic necrosis and pancreatic infections, which were diagnosed on the basis of diagnostic imaging procedures and/or intraoperative findings as previously reported [20]. Thirty-one (46%) patients suffered from interstitial edematous (AIP) and 37 (54%) from necrotizing pancreatitis (NP), of which 21 (57%) developed pancreatic infections in terms of infected necrosis and pancreatic abscess. Pancreatic infections comprised primary pancreatic infections ( $n=13$ ) and secondary/postoperative pancreatic infections occurring after surgery for sterile necrosis ( $n=8$ ).

The biological data and etiology of pancreatitis in the morphological entities AIP and NP as well as in the total series of patients are summarized in Table 1. The extent of intra-pancreatic necrosis in the patient groups with sterile necrosis and pancreatic infections did not differ. Remote organ complications included pulmonary (arterial PO<sub>2</sub> <60 mmHg at room air or mechanical ventilation), renal (serum creatinine >200  $\mu$ mol/l or hemofiltration/dialysis) and cardiocirculatory insufficiency (need for inotropics); multiple organ dysfunction syndrome (MODS) was defined as failure of all three organ systems requiring mechanical ventilation, hemofiltration and inotropics. The overall severity of pancreatitis in terms of Ranson and APACHE II scores and the incidence of local and remote organ complications are presented in Table 2.

Initial treatment was conservative in all patients and included maximum intensive care support as well as the prophylactic administration of appropriate antibiotics in patients with pancreatic

**Table 1** Biological data and etiology in the morphological entities interstitial edematous pancreatitis (AIP) and necrotizing pancreatitis (NP) as well as the total series

	AIP ( $n=31$ )	NP ( $n=37$ )	Total ( $n=68$ )
Age (median, range)	56 (19–87)	54 (10–86)	55 (10–87)
Gender (M/F)	15/16	29/8	44/24
Etiology			
Alcohol	8 (26%)	16 (43%)	24 (35%)
Biliary	17 (55%)	16 (43%)	33 (49%)
Others	6 (19%)	5 (14%)	11 (16%)

**Table 2** Clinical severity and incidence of local and remote organ failure in patients with interstitial edematous pancreatitis (AIP), necrotizing pancreatitis (NP) and the total series

	AIP (n=31)	NP (n=37)	Total (n=68)
Ranson (median, range)	2 (0–7)	6 (2–10)	4 (0–10)
Apache II 24 h (median, range)	9 (1–20)	14 (4–25)	12 (1–25)
Apache II 48 h (median, range)	7 (1–17)	13 (7–29)	11 (1–29)
Apache II 72 h (median, range)	7 (0–17)	12 (3–19)	10 (0–19)
Local complications <sup>a</sup>			
Pancreatic infection	0	21 (57%)	21 (31%)
Systemic complications <sup>b</sup>			
Pulmonary failure	8 (26%)	32 (86%)	40 (59%)
Mechanical ventilation	0	26 (70%)	26 (38%)
Renal failure	0	18 (49%)	18 (26%)
Hemofiltration	0	18 (49%)	18 (26%)
Shock	0	25 (68%)	25 (37%)
Inotropics	0	25 (68%)	25 (37%)
MODS <sup>c</sup>	0	18 (49%)	18 (26%)
Death	0	14 (38%)	14 (21%)

<sup>a</sup> Primary and secondary/postoperative pancreatic infections after surgery of sterile necrosis defined as infected necrosis or pancreatic abscess

<sup>b</sup> During the sampling period of 14 days on at least 1 day:

Pulmonary failure: PaO<sub>2</sub><60 mmHg at room air or mechanical ventilation

Renal failure: serum creatinine >200 µmol/l or hemofiltration

Shock: catecholamine treatment

<sup>c</sup> Systemic multi-organ dysfunction syndrome (MODS): combined remote triple organ failure requiring mechanical ventilation, hemofiltration and administration of inotropics

necrosis. Indications for surgery were: (1) the presence of documented infection of necrosis with systemic signs of sepsis and (2) persisting organ failure or abdominal symptoms despite maximum intensive care support in the absence of positive FNA results. Twelve of 37 patients (32%) with NP were treated by conservative means, 25 (68%) patients underwent necrosectomy and postoperative continuous closed lavage of the lesser sac. Cholecystectomy was performed in two conservatively treated patients with biliary NP and in 18 patients with biliary AIP. One patient with AIP was subjected to laparotomy due to persisting ileus.

## Methods

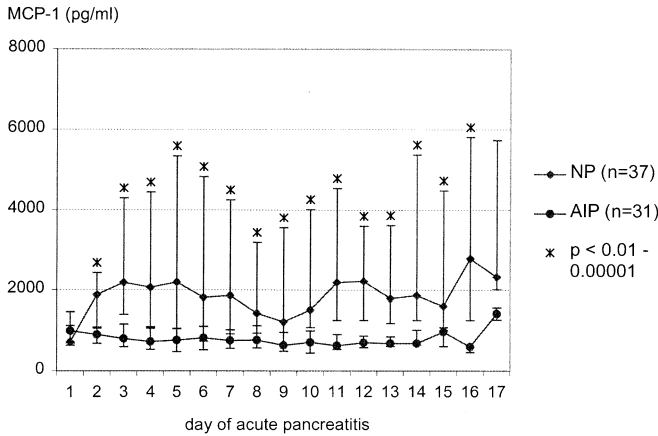
The study was approved by the local ethics committee of the University of Ulm, Germany, and informed consent was obtained from all patients before study inclusion. Blood samples were drawn from central venous lines in 24-h intervals over 14 days. Thereafter, blood was immediately spun at 3,500 g at 4°C for 10 min, divided up and stored at –70°C until later assay. Peri-pancreatic exsudate was obtained by guided fine needle aspiration in patients with suspected pancreatic infection or during surgery on day 6 (median, range 2–15) of acute pancreatitis and was available for analysis in 14 patients. All local measurements were compared with the corresponding systemic chemokine concentrations of the same day the local sample was taken. Concentrations of MCP-1 (reference range 133–1245 pg/ml in healthy subjects), MIP-1α (reference range 0–48 pg/ml in healthy subjects) and MIP-1β (reference range 42–264 pg/ml in healthy subjects) were measured by commercially available enzyme-linked immunosorbent assays (ELISA) (Endogen, Woburn, MA, USA) according to the manufacturer's protocol. Values of the respective parameters were related to the onset of symptoms starting with day 1 as the first day of acute pancreatitis.

## Statistics

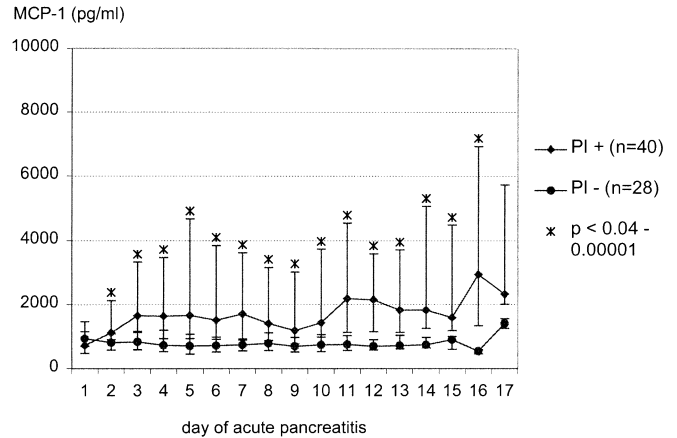
All variables are presented as medians + upper/lower quartiles or ranges. For comparison of independent samples we used the Wilcoxon's rank sum test and the Fisher's exact test for comparison of proportions. Probability values less than 0.05 at an  $\alpha$  less than 0.05 were considered significant. Receiver operating characteristic (ROC) curves and the respective areas under the curve (AUC) were calculated for the two highest values of each parameter reached during the whole observation period. Cut-off levels were determined as the value which optimized sensitivity (patients with local or systemic complications), specificity (patients without local or systemic complications) and likelihood ratio: LR = (probability of true positive + probability of true negative)/(probability of false positives + probability of false negatives). Multiple regression analysis was performed by using the two highest values of MCP-1, MIP-1α and MIP-1β reached within the whole observation period as dependent variables and the following complications as potential independent variables: necrosis, pancreatic infection, pulmonary, renal, cardiocirculatory failure, MODS and death. All statistical calculations were made with the MedCalc Software package [21].

## Results

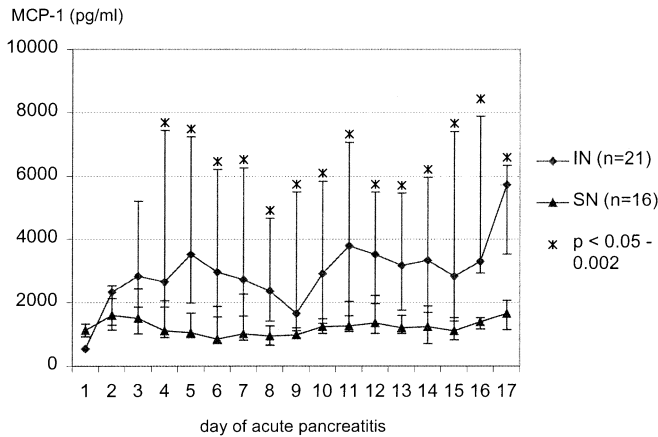
Monocyte chemoattractant protein-1 concentrations increased early in patients who developed local complications such as necrosis (Fig. 1,  $p<0.01$ – $0.00001$ ) or pancreatic infections (Fig. 2,  $p<0.05$ – $0.002$ ) during the course of the disease. In patients who did not develop necrosis or pancreatic infections MCP-1 levels remained within normal limits. In contrast, MIP-1α and MIP-1β concentrations did not show any significant elevation dependent on the presence of either of the local complications.



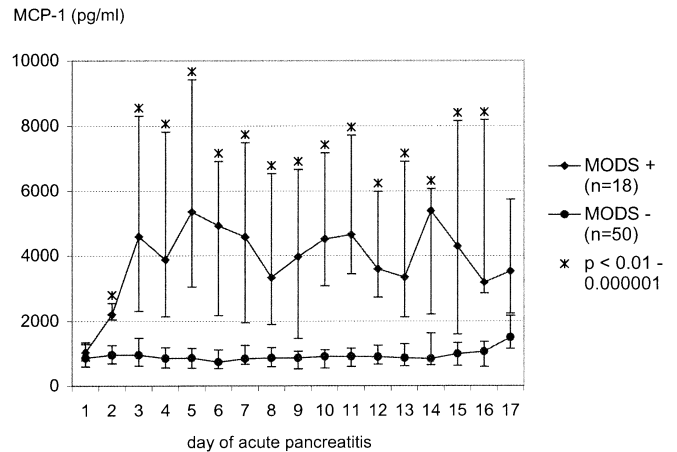
**Fig. 1** Course of monocyte chemoattractant protein-1 (*MCP-1*) (median ± upper/lower quartile) in patients with necrotizing (*NP*) and edematous (*AIP*) acute pancreatitis. *MCP-1* concentrations were significantly higher in *NP* from day 2 of acute pancreatitis. In patients with *AIP* *MCP-1* remained within the reference range



**Fig. 3** Course of monocyte chemoattractant protein-1 (*MCP-1*) in patients with (*PI+*) and without (*PI-*) pulmonary failure. If pulmonary failure was present, *MCP-1* levels significantly exceeded the upper normal reference range from day 2 of the disease



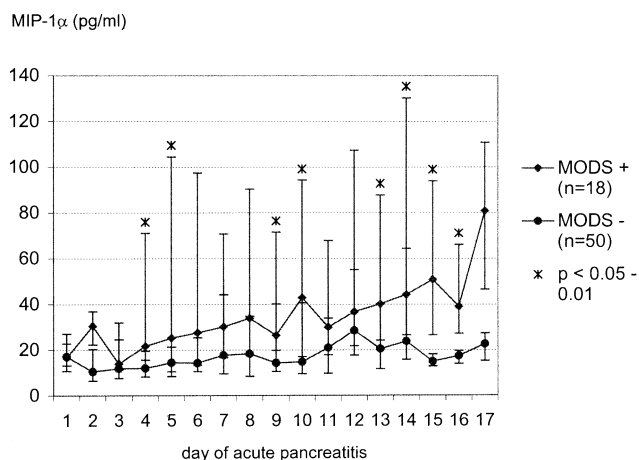
**Fig. 2** Course of monocyte chemoattractant protein-1 (*MCP-1*) (median ± upper/lower quartile) in patients with pancreatic infections (*PI*) and sterile necrosis (*SN*). In patients developing pancreatic infections *MCP-1* concentrations were significantly higher from day 4 of the disease, whereas in *SN* *MCP-1* did not exceed the upper reference range



**Fig. 4** Course of monocyte chemoattractant protein-1 (*MCP-1*) in patients with (*MODS+*) and without (*MODS-*) multiple organ dysfunction syndrome. A dramatic increase of *MCP-1* levels was observed in patients with *MODS* from the 2nd day of acute pancreatitis

The occurrence of single or combined remote organ failure strongly influenced systemic *MCP-1* release: patients with pulmonary failure revealed significantly higher *MCP-1* levels from day 2 after the onset of symptoms compared to patients without this complication (Fig. 3,  $p < 0.04 - 0.00001$ ). Similar observations were made for the presence of renal failure/hemofiltration ( $p < 0.01 - 0.00001$ ) and for cardiocirculatory failure/inotropic treatment ( $p < 0.02 - 0.00001$ ) with significantly elevated *MCP-1* levels from day 2 after the onset of symptoms. If *MODS* developed, *MCP-1* concentrations were dramatically increased and remained this level following the

first day of acute pancreatitis (Fig. 4,  $p < 0.01 - 0.00001$ ). *MIP-1β* levels remained unaffected by any single organ failure and *MODS* throughout the whole observation period (data not shown). *MIP-1α* levels significantly increased in patients with *MODS* during the second week of the disease only (Fig. 5,  $p < 0.05 - 0.01$ ), whereas single organ failure had no influence. However, even in patients with *MODS* the rise of *MIP-1α* was by far less marked than that of *MCP-1*. We did not observe a correlation between the patients' gender or the etiology of acute pancreatitis and the degree of *MCP-1* or *MIP-1α* elevation. Local *MCP-1* concentrations in ascites or peri-pancreatic



**Fig. 5** Course of macrophage inflammatory protein-1 $\alpha$  (*MIP-1 $\alpha$* ) in patients with (*MODS+*) and without (*MODS-*) multiple organ dysfunction syndrome. In patients developing MODS *MIP-1 $\alpha$*  concentrations were significantly higher during the 2nd week of the disease

exudate were at least twice as high as the corresponding systemic levels, whereas local and systemic *MIP-1 $\alpha$*  and *MIP-1 $\beta$*  levels did not differ (Table 3).

Receiver operating characteristics (ROC) analysis was based on the two highest *MCP-1*, *MIP-1 $\alpha$*  and *MIP-1 $\beta$*  values reached within the total observation period of 14 days. The results confirmed the high correlation of *MCP-1* levels with the development of pancreatic necrosis and infection, single or combined remote organ failure as well as the absence of any correlation of *MIP-1 $\beta$*  concentrations in this respect. Table 4 summarizes the results of ROC analysis including the optimum cut-off levels and areas under the curve (AUC) for the prediction of pancreatic necrosis, pancreatic infections, pulmonary, renal or cardiocirculatory failure, MODS and death, of *MCP-1*, *MIP-1 $\alpha$*  and *MIP-1 $\beta$* .

Multiple regression analysis revealed that only pancreatic infections (correlation coefficient:  $r=0.671$ ,  $p=0.008$ ) as well as renal (correlation coefficient:  $r=0.847$ ,  $p=0.001$ ) and cardiocirculatory failure (correlation coefficient:  $r=0.760$ ,  $p=0.01$ ) were independent variables associated with enhanced systemic *MCP-1* release, whereas

necrosis (correlation coefficient:  $r=0.564$ ,  $p=n.s.$ ), pulmonary insufficiency (correlation coefficient:  $r=0.683$ ,  $p=n.s.$ ), MODS (correlation coefficient:  $r=0.829$ ,  $p=n.s.$ ) and death (correlation coefficient:  $r=0.642$ ,  $p=n.s.$ ) were not.

## Discussion

Since our knowledge about the pathophysiology of acute pancreatitis has evolved considerably, it is well known that leukocytes and leukocyte-derived products contribute to pancreatic damage and trigger systemic inflammatory response as well as remote organ failure. A number of experimental studies have shown that activation of the monocyte/macrophage system is an important step in the severity progression of acute pancreatitis [22, 23, 24, 25, 26]. Because monocytes/macrophages represent a major source of proinflammatory cytokine release [9, 27], the beneficial effects of an inhibited activation of this cellular system is believed to be the consequence of decreased cytokine production [24, 25]. Currently, there is no more doubt that proinflammatory cytokine activation is detrimental in terms of the development of local and systemic complications in acute pancreatitis [9, 28].

Our results demonstrate that both local and systemic levels of the CC-chemokine member *MCP-1* are already dramatically increased early in the course of severe acute pancreatitis in humans. Herein, the degree of systemic *MCP-1* elevation showed the closest correlation with the development of pancreatic infections and with remote organ failure affecting the kidneys and the cardiocirculatory system. In fact, the results of this observational study do not allow any firm pathophysiological conclusions, however, they are well in line with previous experimental studies in this field [14, 15, 16]. In vitro experiments in isolated pancreatic acinar cells have shown that acinar cells themselves are an important source of chemokine production within the first hours after induction of acute pancreatitis [14, 15, 16]. As chemokines are typically induced and released at the site of injury [11, 12], the early *MCP-1* chemokine expression in both experimental and human acute pancreatitis supports the concept of a signal originating from the acinar cells to

**Table 3** Local (peri-pancreatic exudate)<sup>a</sup> and corresponding systemic CC-chemokine concentrations in patients with severe acute pancreatitis (*MCP-1* monocyte chemoattractant protein-1, *MIP-1 $\alpha$*

macrophage inflammatory protein-1 $\alpha$ , *MIP-1 $\beta$*  macrophage inflammatory protein-1 $\beta$ )

CC-chemokine	Local concentration (median, lower/upper quartile)	Systemic concentration (median, upper/lower quartile)	<i>p</i> value
<i>MCP-1</i> (pg/ml)	9,822 (1,2725/3,827)	4,173 (1,659/9,785)	<0.04
<i>MIP-1<math>\alpha</math></i> (pg/ml)	23 (16.9/79.4)	29 (15.7/71.7)	n.s.
<i>MIP-1<math>\beta</math></i> (pg/ml)	84 (21/209)	136 (89.6/155.0)	n.s.

<sup>a</sup> Aspirates were obtained by fine needle aspiration or intraoperatively on day 6 (median, range 2–15) of acute pancreatitis

**Table 4** Receiver operating characteristics (ROC) analysis of monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 $\alpha$  (MIP-1 $\alpha$ ) and macrophage inflammatory protein-1 $\beta$  (MIP-1 $\beta$ ) in predicting local and systemic complications in acute pancreatitis (AUC area under the curve, MODS multiple organ dysfunction syndrome)

	Chemokine	Cut-off (pg/ml)	AUC
Local complications			
Necrosis	MCP-1	>1650	0.879 $\pm$ 0.03
	MIP-1 $\alpha$	>25	0.731 $\pm$ 0.05
	MIP-1 $\beta$	>98	0.513 $\pm$ 0.05
Pancreatic infection	MCP-1	>4,250	0.887 $\pm$ 0.04
	MIP-1 $\alpha$	>67	0.736 $\pm$ 0.05
	MIP-1 $\beta$	>169	0.608 $\pm$ 0.05
Systemic complications			
Pulmonary failure	MCP-1	>1,550	0.819 $\pm$ 0.04
	MIP-1 $\alpha$	>27	0.683 $\pm$ 0.06
	MIP-1 $\beta$	>155	0.597 $\pm$ 0.05
Mechanical ventilation	MCP-1	>2,600	0.958 $\pm$ 0.02
	MIP-1 $\alpha$	>30	0.744 $\pm$ 0.06
	MIP-1 $\beta$	>220	0.594 $\pm$ 0.07
Renal failure/hemofiltration	MCP-1	>2,930	0.978 $\pm$ 0.02
	MIP-1 $\alpha$	>31	0.713 $\pm$ 0.06
	MIP-1 $\beta$	>187	0.613 $\pm$ 0.06
Shock/inotropics	MCP-1	>2,930	0.948 $\pm$ 0.02
	MIP-1 $\alpha$	>27	0.746 $\pm$ 0.05
	MIP-1 $\beta$	>155	0.614 $\pm$ 0.05
MODS	MCP-1	>2,930	0.978 $\pm$ 0.02
	MIP-1 $\alpha$	>31	0.713 $\pm$ 0.06
	MIP-1 $\beta$	>187	0.613 $\pm$ 0.06
Death	MCP-1	>5,500	0.910 $\pm$ 0.04
	MIP-1 $\alpha$	>72	0.746 $\pm$ 0.06
	MIP-1 $\beta$	>386	0.619 $\pm$ 0.06

For definitions of local and systemic complications see Table 3  
ROC analysis is based on the two highest levels reached during the observation period

attract inflammatory cells to the site of acinar cell injury. As a consequence, chemokine activation may be considered as a potential link between the process of local pancreatic injury, via induction of leukocyte infiltration, and the subsequent release of various inflammatory mediators to a systemic process involving distant organ systems [29, 30, 31].

Although local MCP-1 concentrations were significantly elevated in our clinical series as well, the correlation between systemic MCP-1 release and the development of remote organ failure was far stronger. This observation is probably biased by the fact that local chemokine measurements were only possible in 14 patients who, in addition, all suffered from severe disease. On the other hand, multiple regression analysis revealed the closest correlation between renal and cardiocirculatory failure and the degree of circulating MCP-1 concentrations. On the basis of these findings it could be hypothesized that MCP-1 is more important for mediating systemic rather than local severity in acute pancreatitis. This clinical observation is again supported by recent experimental studies in which a predominance of chemokine-mediated systemic effects have been described [17, 18].

In mice carrying a genetic deletion of the CC-CKR-1 receptor, supramaximal cerulein stimulation resulted in a significant reduction of pancreatitis-associated lung injury, pulmonary myeloperoxidase activity and both pulmonary and systemic TNF- $\alpha$  expression. In contrast, intra-

pancreatic edema formation and acinar cell damage remained completely unchanged [18]. A similar observation has been made for the neutrophil-inducing CXC-chemokine CINC: the application of a CINC-neutralizing antibody in rats with cerulein-induced pancreatitis was more effective in preventing pancreatitis-associated lung injury than ameliorating pancreatic necrosis [17].

Our data clearly demonstrate significantly different expression profiles of the CC-chemokine members MCP-1, MIP-1 $\alpha$  and -1 $\beta$  in acute pancreatitis. In terms of MIP-1 $\alpha$ , we found some correlation with the development of severe combined remote organ failure, however this was far less marked than this correlation observed for MCP-1. In terms of MIP-1 $\beta$ , no significant elevation was present, irrespective of whether any kind of local or systemic complication developed or not. In addition, local concentrations of both MIP-1 $\alpha$  and MIP-1 $\beta$  in peripancreatic exudates and ascites remained within the normal reference ranges.

From these observational data it is hard to draw any conclusions as to whether this may be of pathophysiological relevance. However, a similar predominance of MCP-1 over MIP-1 $\alpha$  and MIP-1 $\beta$  release has been described in other human inflammatory diseases. In chronic bronchitis bronchoalveolar concentrations of MCP-1 were significantly elevated but, in contrast to acute pancreatitis, an elevation of MIP-1 $\beta$  was also found and was associated with chronic obstructive disease, whereas

MIP-1 $\alpha$  levels were not detectable [32]. In alcoholic liver disease systemic concentrations of MCP-1 were markedly increased and correlated with the severity of hepatic inflammation; systemic MIP-1 $\alpha$  levels remained within normal limits [33], however, both MCP-1 and MIP-1 $\alpha$  secretion from peripheral blood mononuclear cells was increased in patients with severe alcoholic hepatitis. Enhanced expression of MCP-1, but not of MIP-1 $\alpha$ , was found in colonic biopsies in patients with ulcerative colitis [34]. In chronic pancreatitis various CC-chemokines, especially MCP-1, were found to be differentially expressed depending on the severity of the structural changes [35]. Interestingly, in accordance with *in vitro* findings in experimental acute pancreatitis, pancreatic acinar cells and not the inflammatory infiltrate were found to be the main source of chemokine synthesis in this study [35]. Taken together, although no proof, these data imply a dominant role for the CC-chemokine MCP-1 in inflammatory disorders and are well in accordance with our findings in acute pancreatitis in humans.

In the absence of experimental studies employing a direct approach to MCP-1 inhibition by either neutralizing antibodies or the use of MCP-1-deficient mice, the definite role of this CC-chemokine in acute pancreatitis remains to be defined. Recent studies in MCP-1 knockout mice have revealed a uniquely essential role of this chemokine in different inflammatory models such as aseptic peritonitis, contact hypersensitivity, tuberculin-

type hypersensitivity, pulmonary granulomatosis and tuberculosis [31]. Unfortunately, to date no studies are available which address the effects of CC-chemokine inhibition, especially of MCP-1 inhibition, on mortality in models of severe inflammation such as necrotizing pancreatitis or bacterial peritonitis/sepsis. This information will be of central importance as to whether anti-chemokine strategies in general could be of any therapeutic benefit in the clinical setting.

In summary, the CC-chemokine members MCP-1, MIP-1 $\alpha$  and MIP-1 $\beta$  reveal different expression profiles in clinically severe acute pancreatitis. Whereas MIP-1 $\beta$  concentrations remained within normal ranges in the course of the disease, MIP-1 $\alpha$  levels were increased in patients with multi-organ dysfunction only. In contrast, a marked and sustained elevation of MCP-1 concentrations was observed in patients with local complications as well as single and combined remote organ failure. Our results suggest that MCP-1 might play a dominant role in the pathological mechanism of complicated acute pancreatitis with specific regard to the development of systemic disease severity and distant organ failure. Based on the current experimental and clinical knowledge, further studies employing MCP-1-inhibiting strategies in inflammatory disorders, including acute pancreatitis, seem to be promising.

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