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Circulating Immune Signatures in Chronic Pancreatitis with and without Preceding Acute Pancreatitis: A Pilot Study

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Abstract

Objective: To investigate profiles of circulating immune signatures in healthy controls and chronic pancreatitis patients (CP) with and without a preceding history of acute pancreatitis (AP).

Methods: We performed a phase 1, cross-sectional analysis of prospectively collected serum samples from the PROspective Evaluation of Chronic Pancreatitis for EpidEmiologic and Translation StuDies (PROCEED) study. All samples were collected during a clinically quiescent phase. CP subjects were categorized into two subgroups based on preceding episode(s) of AP. Healthy controls were included for comparison. Blinded samples were analyzed using an 80-plex Luminex assay of cytokines, chemokines, and adhesion molecules. Group and pairwise comparisons of analytes were performed between the subgroups.

Results: In total, 133 patients with CP (111 with AP and 22 without AP) and 50 healthy controls were included. Among the 80 analytes studied, CP patients with a history of AP had significantly higher serum levels of pro-inflammatory cytokines (interleukin (IL)-6, IL-8, IL-1 receptor antagonist, IL-15) and chemokines (Cutaneous T-Cell Attracting Chemokine (CTACK), Monokine induced Gamma Interferon (MIG), Macrophage-derived Chemokine (MDC), Monocyte Chemoattractant Protein-1 (MCP-1)) compared to CP without preceding AP and controls. In contrast, CP patients without AP had immune profiles characterized by low systemic inflammation and downregulation of anti-inflammatory mediators, including IL-10.

Conclusion: CP patients with a preceding history of AP have signs of systemic inflammatory activity even during a clinically quiescent phase. In contrast, CP patients without a history of AP have low systemic inflammatory activity. These findings suggest the presence of two immunologically diverse subtypes of CP.

Keywords

Immune signatures; Chronic Pancreatitis

Introduction

Chronic Pancreatitis (CP) is a fibro-inflammatory disease characterized by progressive, irreversible fibrosis and destruction of the pancreatic tissue (1). The pathogenesis of CP is complex and involves a combination of genetic, environmental, and immune factors (2). The conceptual model of CP, based on the sentinel acute pancreatitis event hypothesis, suggests that CP is preceded by episode(s) of acute pancreatic inflammation, thus forming a disease continuum from acute pancreatitis (AP) via recurrent acute pancreatitis (RAP) to CP (3,4). However, a series of studies report that many patients with CP have no previous history of AP episode(s) (2,5–8). This challenges the notion of AP, RAP, and CP as a disease continuum, emphasizing the importance of gaining a deeper understanding of the mechanisms underlying this complex disease.

Animal and pilot studies have emphasized the critical role of immunological mechanisms in the development and progression of CP (9–13). In the context of pancreatic inflammation, when the pancreatic tissue is damaged, innate immune cells release pro-inflammatory cytokines in response to damage-associated molecular patterns (DAMPs). These pro-

inflammatory mediators then recruit and activate macrophages (1,10). Importantly, an imbalance in the communication between innate immune cells and macrophages can lead to alternative activation of macrophages (M2 polarization) (10). M2-polarized macrophages, in turn, stimulate pancreatic stellate cells (PSC), which play a central role in the fibrogenesis associated with CP (1,13). Activated PSCs not only promote fibrosis but also enhance the M2 polarization of macrophages, creating a self-perpetuating feedforward loop (13). These processes are mediated by complex immunological signaling. Unfortunately, pancreatic tissue is not readily available in human studies, and therefore, it is difficult to study the underlying disease mechanisms of inflammatory pancreatic diseases. However, recent studies have demonstrated that pancreatic inflammatory responses and immunological mechanisms can be characterized by analyzing immune signatures of cytokines, chemokines, and other inflammatory mediators in the systemic circulation (9,14).

Based on the improved understanding of CP epidemiology and the presence of two clinically distinct CP subtypes (with and without preceding acute pancreatic inflammation), it is prudent to gain a deeper understanding of putative differences in immunological mechanisms associated with these phenotypes (2,5–8). However, to our knowledge, no study has investigated circulating immune signatures in CP patients with and without preceding AP episode(s). We hypothesize that there are distinct profiles of circulating immune signatures. Our study aimed to explore serum levels of cytokines, chemokines, and adhesion molecules in CP patients with and without preceding AP episode(s) using healthy control subjects as a reference group.

Methods

We conducted a phase 1 biomarker discovery, cross-sectional pilot study according to the PROBE guidelines, investigating serum levels of cytokines, chemokines, and adhesion molecules in CP subjects with and without preceding episode(s) of AP (15). Human samples were obtained from the biorepository of the Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies (PROCEED), which is a longitudinal, observational study part of the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC) (16,17). PROCEED is approved by a single Institutional Review Board (MD Anderson Cancer Center), and the CPDPC Steering Committee approved this ancillary study.

Study population

The study population comprised 133 CP subjects from the PROCEED cohort randomly selected for another ancillary study focused on metabolic complications (18). Subjects with CP were selected amongst those with a definitive diagnosis of CP, defined as definitive findings of CP on cross-sectional imaging (Cambridge grade 3 or 4, and/or pancreatic calcifications) or pancreatic histology (16). CP subjects were categorized according to previous history of AP episodes(s) into the following subgroups: 1) CP with preceding AP episode(s) (referred to as CP with AP, n=111) and 2) CP without preceding AP episode(s) (referred to as CP without AP, n=22). Subsequently, CP patients with preceding AP episode(s) were subcategorized into two further subgroups: 1) CP with recent AP (last

AP episode within 1 year from enrollment, n=57) and 2) CP with remote AP (last AP episode more than 1 year from enrollment, n=41). Information on the timing of the last AP episode was missing for 13 patients. These subgroups were used for a sensitivity analysis investigating the impact of the timing of AP on serum immune signature expression.

Prior history of AP before baseline enrollment was based on a physician's retrospective ascertainment and assessment of the patient's medical history using a standardized case report form. The revised Atlanta criteria was used to define AP (two out of three of the following criteria: upper abdominal pain characteristic of AP, elevated serum amylase and/or lipase ≥3-fold above the upper limit of normal, or features of AP on cross-sectional imaging) (19). In addition, study coordinators interviewed patients and reviewed physician notes on prior AP episodes for additional verification. Discrepancy for prior AP was ultimately based on a physician's judgment. For the PROCEED study, patients with AP due to gallstones, medications, trauma, or autoimmune pancreatitis were not eligible for enrollment. Within the PROCEED study, RAP was defined as two or more attacks of AP separated by at least one month, with complete symptom resolution between the episodes.

A group of controls with no pancreatic disease (n=50) were included. This comprised of volunteers with no upper abdominal pain symptoms, no personal or family history of pancreatic disease, no history of cancer, inflammatory diseases requiring medical treatment, and organ transplant or human immunodeficiency virus / acquired immunodeficiency syndrome (16).

Demographics, anthropometrics, and clinical parameters

Clinical and demographic variables were derived from the PROCEED study database. Variables included sex, age, race, BMI, age at CP diagnosis, duration and etiology of CP, presence of intraductal calculus on computed tomography (CT), connective tissue disorders (Systemic Lupus Erythematosus, Rheumatoid Arthritis, Sjogren's Disease, Inflammatory Bowel Disease, Polyarteritis Nodosa, Mixed Connective Tissue Disorder, Undifferentiated Connective Tissue Disorder), and metabolic complications, including diabetes and exocrine pancreatic dysfunction (EPD). EPD diagnosis was defined as the presence of one of the following criteria: 1) clinical history of steatorrhea, 2) fecal elastase of < 100 μg/g stool, or 3) quantitative fecal fat of > 7 g/d on a 100-g fat diet. Diabetes diagnosis was defined according to the criteria by the American Diabetes Association, which include abnormal values on 2 of the following tests or two abnormal values of the same test: 1) fasting blood sugar ≥ 126mg/dL; 2) HbA1c ≥6.5 %; 3) random blood glucose ≥ 200 mg/dL, or 4) use of anti-diabetic medications (16). Further, variables of abdominal pain within the last year and abdominal pain patterns were included. Pain patterns were defined as 1) Usually pain-free, but episodes of mild to moderate pain, 2) Usually pain-free, but episodes with severe pain, 3) Constant mild to moderate pain, 4) Constant mild to moderate pain, with episodes of severe pain, and 5) Constant severe pain that does not change.

Blood samples and analysis of serum immune signatures

Serum samples were drawn during a clinically quiescent phase of CP at least one month after a preceding episode of AP (16). Samples were stored at −80 C° and were

only thawed once for this study. All analyses were done in one batch. The Stanford Human Immune Monitoring Centre carried out the Luminex Assay. The laboratory staff was blinded to group assignments. We used a Human 80-plex kit purchased from EMD-Millipore. The human 80-plex Luminex kits include 3 panels: Panel 1 includes the Milliplex HCYTA-60K-PX48, Panel 2 the Milliplex HCP2MAG-62K-PX23, and Panel 3 the Milliplex HSP1MAG-63K-06 and HADCYMAG-61K-03. A total of 150 μL of serum from each subject was processed. The detailed protocol description can be found at (https://iti.stanford.edu/himc/immunoassays.html). Briefly, 25 μL of each sample was incubated with antibody-linked polystyrene beads on 96-well filter-bottom plates for two hours at room temperature, followed by overnight incubation at four degrees Celsius. After re-warming to room temperature, the plates were washed thrice. Subsequently, samples were incubated with detection antibodies at room temperature on an orbital shaker for two hours at 500 rpm. After filtration and three washes, Streptavidin-PE was added to the plates and incubated at room temperature for 40 minutes on an orbital shaker at 500 rpm, followed by three washes. Lastly, the solution was incubated at room temperature for five minutes with a reading buffer and read on a Luminex 200 instrument. The analyte concentration was estimated using the average median fluorescence intensity (MFI). The Luminex Assay included 80 cytokines, chemokines, and adhesion molecules (Supplementary Table 1).

Statistical analysis

The primary analysis of this study was to identify differences in circulating immune signature levels in CP subjects with and without preceding episode(s) of AP before CP diagnosis. As this was a pilot study, the sample size was based on the sample and data availability (9,14).

Demographic and clinical data were presented as medians (interquartile range (IQR)) or frequencies (%) unless otherwise specified. Student's test, Wilcoxon rank sum tests, and Fisher's exact test were used to investigate differences in demographic and clinical characteristics between subgroups. Regression models were applied to examine differences in MFI between subgroups. Group comparisons were adjusted for sex, age, BMI, nonspecific binding, and plate effects (20,21). A robust variance estimator accounted for heteroskedasticity in the residual distribution. Volcano plots were used for the visual presentation of the data. Due to the exploratory nature of the study, P-values were not adjusted for multiple comparisons. The software packages R Studio, Version 1.3.1093 (RStudio PBC, Boston, Massachusetts, USA) and STATA, version 16.1 (StataCorp), were used for the statistical analyses.

Results

A total of 133 CP subjects and 50 controls were included in the analyses. Demographic and clinical characteristics are summarized in Table 1. The CP patients were older than controls (median age: 53 vs. 62. vs. 39 Years; P<0.01). A higher proportion of males was observed in CP with AP (60%) compared to those without AP (36%) and controls (40%) (P=0.02). CP subjects without AP were diagnosed with CP at an older median age (61 years) compared to those with AP (49 years) (P<0.01). Expectedly, a higher proportion of CP patients with

AP had abdominal pain within the last year from enrollment (87.4 % vs. 40.9 %, p<0.001). However, the severity of pain did not differ between CP patients with and without AP. Otherwise, groups were comparable regarding demographic and clinical characteristics.

Immune signature expression in the total CP population vs. controls

Among the 80 analytes studied, seven analytes showed significantly elevated MFI expression in the total CP population compared to controls (Figure 1 and Table 2): IL-6, IL-8, IL-1Ra, CTACK, MCP-1, MDC, and MIG (all P<0.05).

Immune signature expression in CP with AP vs. controls

Among the 80 analytes studied, eight analytes showed significant differences in MFI expression between CP with AP and controls (Figure 2 and Table 3). Specifically, the MFI of the following analytes was increased in CP with AP compared to controls: IL-6, IL-8, CTACK, MIG, MDC, IL-1Ra, IL-15, and MCP-1 (all P<0.05). Conversely, the MFI of TRAIL was reduced in CP with AP compared to controls (P=0.038).

Immune signature expression in CP without AP vs. controls

Among the 80 analytes studied, five analytes showed significant differences in MFI expression between CP without AP and controls (Figure 3 and Table 3). Specifically, the MFI of the following analytes was increased in CP without AP compared to controls: CTACK and IL-8 (both P<0.05). Conversely, the MFI of ENA-78, IL-10, and G-CSF was reduced in CP without AP compared to controls (all P<0.05).

Overlapping immune signature expression between CP with and without AP

Among the 12 analytes significantly differently expressed in CP with and without AP compared to controls, only two overlapped (IL-8 and CTACK) between the CP subgroups (Figure 4).

Immune signature expression in CP with AP vs. CP without AP

The MFI of six analytes was significantly elevated in CP with AP vs. CP without AP (Figure 5 and Table 3). Specifically, the MFI of GRO-alpha, ENA-78, GM-CSF, IL-27, IL-6, and FasL were significantly elevated in CP with AP compared to CP without AP (all p<0.05).

Immune signature expression in CP patients with recent AP vs. remote AP

The MFI of cytokine TRAIL and chemokine ENA-78 was significantly elevated in CP patients with recent AP compared to CP patients with remote AP (both p<0.05) (Table 4).

Discussion

We performed profiling of blood-based biomarkers of inflammation in healthy controls and CP with and without a history of AP before CP diagnosis. CP subjects with at least one episode of AP exhibited indications of systemic inflammatory activity even when sampled during a clinically quiescent phase. On the other hand, CP subjects without a history of AP episode(s) had low systemic inflammatory activity.

Immune signature expression in CP patients with preceding AP

While AP, RAP, and CP are considered a continuum of the same disease, a significant proportion of CP patients do not have episodes of (clinically overt) AP before CP diagnosis (1,3,5). In keeping with this, our study suggests the existence of two immunologically distinct subtypes of CP, indicating variations in disease pathogenesis and immunological characteristics.

CP patients with preceding AP expressed increased levels of IL-6, which mediates its action through the Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway. Through this pathway, IL-6 and other pro-inflammatory cytokines activate PSCs that are responsible for fibrosis generation during CP (22). The JAK/STAT signaling pathway cross-talks with the nuclear factor-kappa B (NF-kB), which is a transcription factor that amplifies the expression of inflammatory genes and releases MCP-1, MIG, and IL-8 (23,24). These analytes were increased in CP patients with preceding AP, thus emphasizing the involvement of the JAK/STAT and NF-kB pathways in these patients. IL-6, IL-8, and MCP-1 also recruit pro-inflammatory cells to the pancreas, and, in keeping with our findings, these inflammatory mediators have previously been reported to be increased in patients with CP (10,25–31). Further, elevated levels of IL-6, IL-8, IL-10, IL-1RA, and MCP-1 have been observed during AP (11,14,32). Interestingly, of these IL-6, IL-8, IL-1RA, and MCP-1 were elevated in CP patients with prior AP. This suggests that analytes may be mediators throughout the disease continuum from AP to CP (4).

In particular, IL-6 signaling has been associated with CP pathogenesis, and several previous studies reported elevated systemic and pancreatic levels of IL-6 in patients with AP and CP compared to healthy controls (29–31,33–36). Interestingly, therapeutic targeting of IL-6 signaling has demonstrated promising results in attenuating the severity of pancreatitis in AP patients and animal models of CP (10,37,38). Given the reproducibility of elevated pancreatic and systemic IL-6 levels in independent AP and CP populations, medications directed at IL-6 signaling (e.g., tocilizumab) warrant further investigations in this context (30,33,34).

CP patients with recent AP expressed increased levels of apoptosis-inducing cytokine TRAIL and pro-inflammatory chemokine ENA-78 (39,40). TRAIL was previously found to be increasingly expressed in the exocrine tissue in inflammatory infiltration and active fibrosis areas (39). ENA-78, a chemoattractant, and activator of neutrophil function, was found to be elevated in the exocrine tissue (40). This implies that recent or remote AP may not influence the immune profiles of CP based on AP history but rather reflect underlying differences in the pathophysiology of CP itself.

Immune signature expression in CP patients without preceding AP

In CP patients without preceding AP episode(s), the pro-inflammatory cytokine IL-8 was elevated (30). IL-8 was previously found to be released by PSCs and mediate autocrine activation of these cells (41). No other pro-inflammatory cytokines or chemokines were elevated in CP patients without AP. This indicates a low systemic inflammatory state in these patients and may suggest that the disease process is mainly driven by a

macrophage-independent activation of PSCs, possibly through Th17 and Th22 responses (23,42). However, we did not find any difference in IL-17 and IL-22 levels. Furthermore, we observed decreased systemic levels of the anti-fibrotic cytokine G-CSF and the anti-inflammatory cytokine IL-10 (23,37,43). This is in contrast to a previous observation of elevated levels of IL-10 in CP (34). However, the previous study did not differentiate between patients with and without preceding AP.

Another reason for the low inflammation noticed in the blood of individuals with CP without preceding AP could be due to unnoticed, minor episodes of AP. It is conceivable that the surge of certain immune system molecules responsible for triggering the scarring process through PSC activation in CP, without any clear signs of AP, may have lessened or stopped as time passed. To test this hypothesis, serial assessment of CP patients without clinically overt AP is required. Such studies will possibly use samples obtained in ongoing prospective cohort studies (16,44).

Clinical implications

Our study aligns with previous studies reporting that CP patients with previous episodes of AP are more symptomatic with more painful episodes and a potentially more aggressive course of disease compared to their counterparts without previous AP episodes. Our present findings suggest that this difference may be driven by sustained systemic (and possible pancreatic) inflammatory activity that likely mediates pain and may also accelerate disease progression (7,8,45,46).

The improved understanding of the immunological processes driving disease progression in CP subpopulations provides valuable insight into putative targets for disease-modifying therapies. For instance, administering anti-IL-6 antibodies could be considered for CP patients with preceding AP. In contrast, CP patients without AP may benefit from treatments like G-CSF or IL-10 to potentially ameliorate disease progression. Our data underscores the significance of considering clinical variables when designing future clinical trials.

Approved cytokine inhibition drugs, such as IL-6 inhibitors like Tocilizumab, JAK-inhibitors like Tofacitinib, and IL-17 inhibitors like Secukinumab, have demonstrated therapeutic effectiveness in various immune-mediated inflammatory diseases (47). Additionally, Pirfenidone and Nintedanib are approved anti-fibrotic therapeutic drugs used in treating pulmonary lung fibrosis (48), and they may have potential applications in halting fibrogenesis in CP. In animal studies of CP, IL-6 inhibitor TB-2–081 has been shown to reduce abdominal hypersensitivity (specifically pain evaluation in rats), JAK inhibitor Ruxolitinib has demonstrated reduced activation of PSCs, and the tyrosine kinase inhibitor Dasatinib has exhibited reduced pancreatic fibrosis and limited polarization of M1 and M2 macrophages (24,38,49). Clinical research is needed to elucidate the most effective therapeutic measures of CP.

Study strengths and limitations

The study’s key strength lies in its rigorous methodology employed across all sites for the prospective collection, processing, and storage of biospecimens. This is performed with respect to the PROBE guidelines to avoid biases (15). Hence, the PROCEED identified

the cohort and drew blood samples prospectively using standard operating procedures. Adjustments for potentially confounding variables were robust and carefully considered. We used MFI as the unit of measurement in this study to avoid potential bias in the statistical analysis caused by values below the limit of quantification when using concentration-based units. Research has demonstrated that MFI yields higher statistical power than concentration-based units (20).

The limitations of this study should be viewed in the context of its exploratory nature. The samples available for this study were derived from an analysis study focused on metabolic complications of CP (18). This resulted in unevenly distributed groups, potentially compromising statistical validity and the sample's representativeness. Future validation studies should strive for balanced group distributions to improve internal validity and generalizability. Also, previous literature highlights Transforming Growth Factor alfa and beta (TGF-α and β) as key mediators of fibrosis in CP. However, this study did not examine these mediators due to the limitations of the Luminex Assay (39–41). Also, this study did not investigate specific cell lines like Th-1, Th-2, Th-17, and Th-22, although specific cytokines in relation to the cell lines were evaluated, see supplementary table 1. Future studies exploring chemokines, cytokines, and adhesion molecules in CP should also consider investigating TGF-α/-β and cell line studies when possible. We adjusted regression models for important confounders, including age, which differed across CP subgroups. However, due to the limited sample size, we were not able to adjust for additional confounders, such as CP etiology, which may be associated with distinct immunological phenotypes (14). A final limitation of our study was the lack of formal case verification of all AP diagnoses, which was based on retrospective information available in case report forms and patient reports collected as part of the PROCEED documentation.

Conclusion

Our pilot study demonstrates distinct circulating immunological profiles in CP patients based on their history of AP before CP diagnosis. CP patients with preceding AP episode(s) were characterized by systemic inflammatory activity despite blood samples being drawn during a clinically quiescent phase. In contrast, CP patients without a preceding AP history were characterized by low systemic inflammatory activity. These findings suggest the presence of two immunologically diverse subtypes of CP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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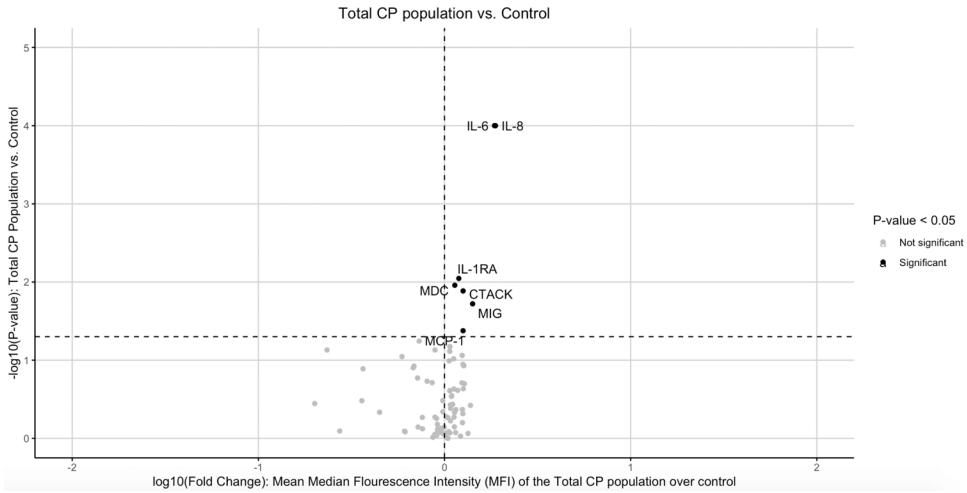

Figure 1:

Volcano plot of differential Median Fluorescence Intensity (MFI) expressions between the total chronic pancreatitis (CP) population and controls. The dashed line represents the delineation between p-values less than 0.05 (above the line) and those greater than 0.05 (below the line). The x-axis indicates fold change, and the y-axis the statistical significance level of group differences in immune signature expressions.

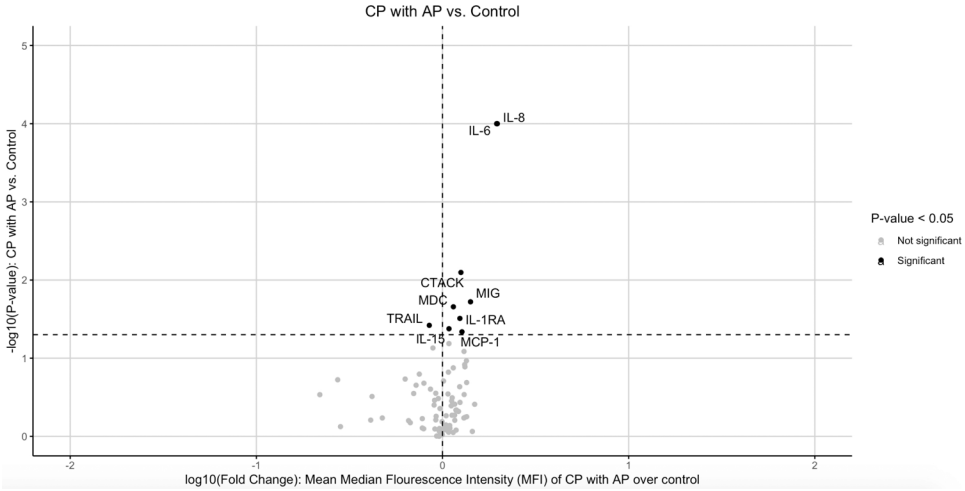

Figure 2:

Volcano plot of differential Median Fluorescence Intensity (MFI) expressions between chronic pancreatitis (CP) population with preceding acute pancreatitis (AP) episode(s) and controls. The dashed line represents the delineation between p-values less than 0.05 (above the line) and those greater than 0.05 (below the line). The x-axis indicates fold change, and the y-axis the statistical significance level of group differences in immune signature expressions.

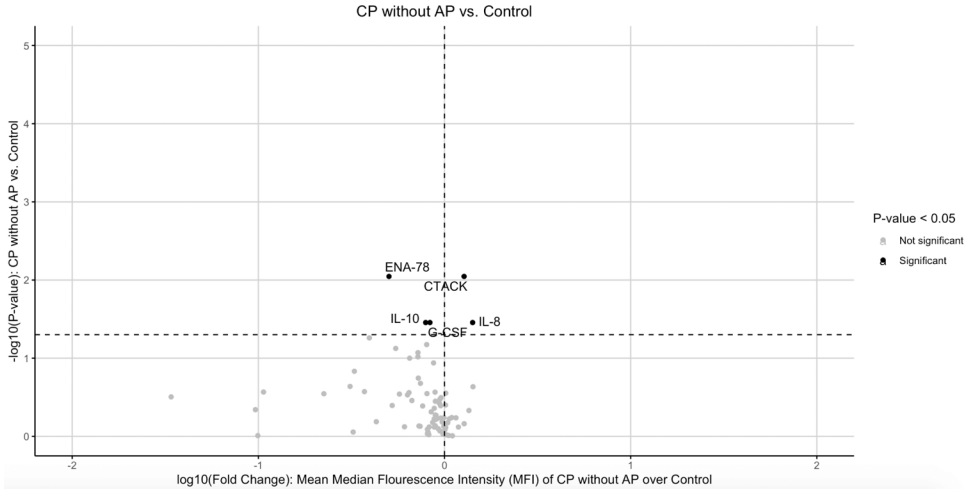

Figure 3:

Volcano Plot of differential Median Fluorescence Intensity (MFI) expressions between chronic pancreatitis (CP) population without preceding acute pancreatitis (AP) episode(s) and controls. The dashed line represents the delineation between p-values less than 0.05 (above the line) and those greater than 0.05 (below the line). The x-axis indicates fold change, and the y-axis the statistical significance level of group differences in immune signature expressions.

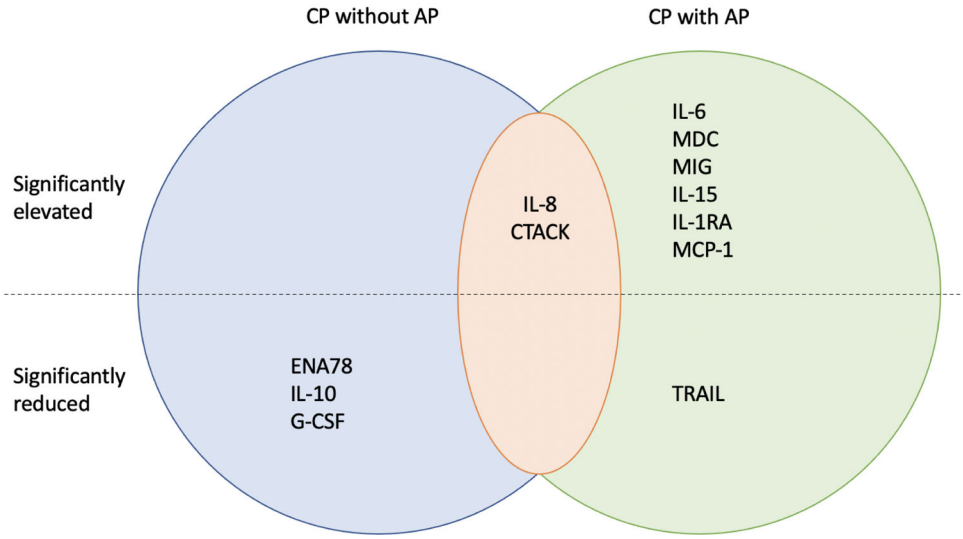

Figure 4:

Venn diagram of alterations in systemic immune markers in chronic pancreatitis (CP) with and without preceding acute pancreatitis (AP) episodes(s); healthy controls are used as the reference group.

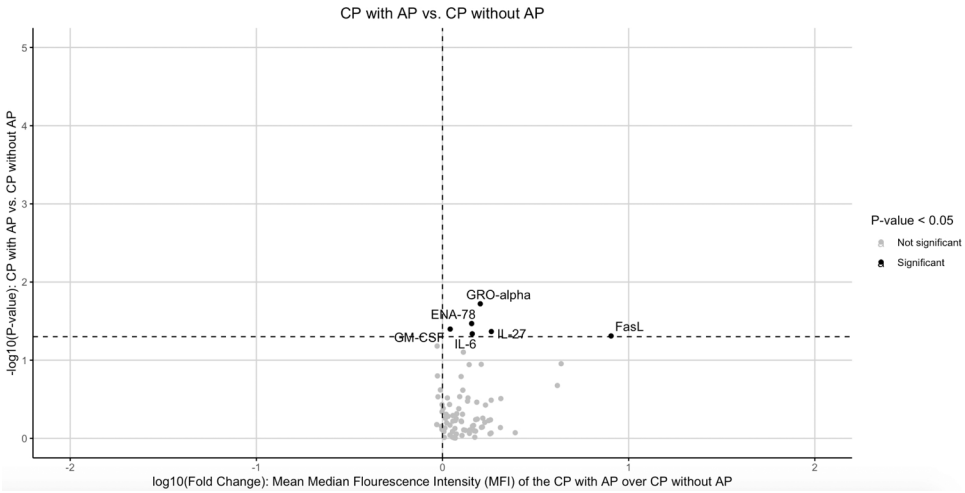

Figure 5:

Volcano Plot of differential Median Fluorescence Intensity (MFI) expressions between chronic pancreatitis (CP) patients with and without previous acute pancreatitis (AP) episode(s). The dashed line represents the delineation between p-values less than 0.05 (above the line) and those greater than 0.05 (below the line). The x-axis indicates fold change, and the y-axis the statistical significance of the observed immune signatures.

Table 1.

Clinical and demographic characteristics of controls and chronic pancreatitis patients (CP) with and without preceding acute pancreatitis (AP)

	Controls (n=50)	Total CP population (n=133)	CP without AP (n=22)	CP with AP (n=111)	P-value Controls vs Total CP population	P-values Controls vs CP without AP	P-values Controls vs CP with AP	P-value CP without vs. with AP
Gender, male, n (%)	20 (40.0)	75 (56.4)	8 (36.4)	67 (60.4)	0.017	0.799	0.018	0.058
Age at enrollment, years (IQR)	39.0 (24.0)	55.0 (24.0)	62.0 (14.0)	53.0 (16.0)	<0.001	<0.001	<0.001	0.004
Race, n (%)								
Black or African	12 (24.0)	11 (8.3)	2 (9.1)	9 (8.1)	0.071	0.301	0.047	0.248
White	34 (68.0)	109 (82.0)	17 (77.3)	92 (82.9)				
Asian	3 (6.0)	6 (4.5)	2 (9.1)	4 (3.6)				
Other	0	1 (0.8)	1 (4.6)	0				
More than one race	1 (2.0)	4 (3.0)	0	4 (3.6)				
Do not know	0	2 (1.5)	0	2 (1.8)				
Body mass index, kg/m^2 (IQR)	25.7 (8.7)	24.1 (8.7)	24.8 (6.1)	24.1 (6.4)	0.136	0.369	0.048	0.579
Age at CP diagnosis, years (IQR)		50.0 (17.0)	61.0 (15.0)	49.0 (18.0)				0.002
Duration of CP, years (IQR)		2.0 (4.0)	2.0 (4.0)	3.0 (4.0)				0.216
CP etiology, n (%)								
Alcoholic Pancreatitis		57 (42.9)	6 (27.3)	51 (45.9)				0.156
Idiopathic		52 (39.1)	15 (68.2)	37 (33.3)				
Genetic		17 (12.8)	1 (4.6)	16 (14.4)				
Obstructive		1 (0.8)	0	1 (0.9)				
Post-necrotic		2 (1.5)	0	2 (1.8)				
Hypertriglyceridemia		2 (1.5)	0	2 (1.8)				
Miscellaneous		2 (1.5)	0	2 (1.8)				
Abdominal pain within the last year, n (%)		106 (79.7)	9 (40.9)	97 (87.4)				<0.001
Abdominal pain pattern, n (%)[a]								
Usually pain-free, but episodes of mild to moderate pain		20 (18.9)	2 (22.2)	18 (18.6)				0.478
Usually pain-free, but episodes with severe pain		34 (32.1)	2 (22.2)	32 (33.0)				
Constant mild to moderate pain		8 (7.5)	2 (22.2)	6 (6.2)				

	Controls (n=50)	Total CP population (n=133)	CP without AP (n=22)	CP with AP (n=111)	P-value Controls vs Total CP population	P-values Controls vs CP without AP	P-values Controls vs CP with AP	P-value CP without vs. with AP
Constant mild to moderate pain, with episodes of severe pain		41 (38.7)	3 (33.3)	38 (39.2)				
Constant severe pain that does not change		3 (2.9)	0	3 (3.1)				
Intraductal calculus, n (%)								
Present		59 (44.4)	12 (54.5)	47 (42.3)				0.32
Not present		59 (44.4)	7 (31.8)	52 (46.8)				
Unknown		15 (11.3)	3 (13.7)	12 (10.8)				
Metabolic complications								
Diabetes, n (%)		63 (47.4)	11 (50.0)	52 (46.8)				0.819
EPD, n (%)		79 (59.4)	15 (68.2)	64 (57.7)				0.477
Connective tissue diseases, n (%)								
Systemic Lupus Erythematosus	0	0	0	0				
Rheumatoid Arthritis	0	4 (3.0)	1 (4.5)	3 (2.7)	0.036	0.365	0.031	0.096
Sjögren's Disease	0	0	0	0				
Inflammatory Bowel Disease	1 (2.0)	1 (0.8)	0	1 (0.9)	0.201	1.000	0.089	1.000
Polyarteritis Nodosa	0	0	0	0				
Mixed Connective Tissue Disorder	0	0	0	0				
Undifferentiated Connective Tissue Disorder	0	0	0	0				

EPD; exocrine pancreatic dysfunction

[a] Among patients with pain within the last year

Table 2.

Mean Median Fluorescence Intensity (MFI) values of analytes with significantly different expression between controls and patients with chronic pancreatitis (CP)

	Controls (n=50)	Total CP population (n=133)	P-value
IL-6	48.2 (19.8)	89.5 (112.9)	**<0.001**
IL-8	68.0 (22.0)	127.7 (206.4)	**<0.001**
IL-1Ra	53.3 (0.4)	63.6 (43.4)	**0.009**
CTACK	5447 (1387)	6856.9 (1754.9)	**0.013**
MCP-1	1827.3 (0.4)	2299.5 (1102.5)	**0.042**
MDC	8093.7 (0.3)	9191.0 (3569.4)	**0.011**
MIG	731.7 (0.8)	1035.5 (921.4)	**0.019**

Data are reported as mean MFI with standard deviations in brackets. Group comparisons were adjusted for sex, age, BMI, non-specific binding, and plate effects. Abbreviations: IL = interleukin, CTACK = cutaneous T-cell attracting chemokine, MCP-1 = monocyte chemoattractant protein-1, MDC = macrophage-derived chemokine, MIG = monokine induced gamma interferon

Table 3.

Mean Median Fluorescence Intensity (MFI) values of analytes with significantly different expression between controls and chronic pancreatitis (CP) with and without preceding acute pancreatitis (AP) episode (s)

	Controls (n=50)	CP without AP (n=22)	CP with AP (n=111)	P-value Controls vs. CP without AP	P-value Controls vs. CP with AP	P-value CP without vs. with AP
IL-6	48.2 (19.8)	65.3 (58.2)	94.3 (120.4)	0.467	**<0.001**	**0.046**
IL-8	68.0 (22.0)	96.3 (75.1)	133.9 (223.2)	**0.035**	**<0.001**	0.114
IL-10	46.3 (0.5)	36.8 (0.3)	67.2 (0.7)	**0.035**	0.866	0.325
IL-1Ra	53.3 (0.4)	51.0 (0.4)	66.1 (0.5)	0.320	**0.031**	0.079
IL-15	36.4 (10.7)	36.1 (8.1)	39.4 (14.4)	0.578	**0.042**	0.369
IL-27	378.0 (300.7)	273.5 (193.8)	500.5 (760.7)	0.096	0.573	**0.043**
CTACK	5447 (1387)	6940 (1793)	6839 (1753)	**0.009**	**0.008**	0.702
ENA-78	4038.1 (5639.3)	2031.9 (4822.3)	189.3 (4010.0)	**0.009**	0.222	**0.034**
FasL	1075.7 (4563.8)	36.6 (12.6)	294.2 (1527.4)	0.313	0.189	**0.049**
G-CSF	54.3 (0.4)	45.4 (0.3)	56.1 (0.5)	**0.035**	0.827	0.293
GM-CSF	102.4 (104.0)	90.2 (53.6)	99.2 (140.6)	0.438	0.441	**0.040**
GRO-alpha	308.6 (476.5)	121.8 (53.6)	194.3 (140.6)	0.055	0.185	**0.019**
MCP-1	1827.3 (0.4)	2170.4 (0.5)	2325.0 (0.5)	0.761	**0.046**	0.523
MDC	8093.7 (0.3)	8851.5 (0.4)	9258.3 (0.4)	0.575	**0.022**	0.493
MIG	731.7 (0.8)	1040.8 (0.6)	1034.5 (0.7)	0.232	**0.019**	0.457
TRAIL	334.7 (0.4)	302.5 (0.3)	284.2 (0.3)	0.598	**0.038**	0.159

Data are reported as mean MFI with standard deviations in brackets. Group comparisons were adjusted for sex, age, BMI, non-specific binding, and plate effects. Abbreviations: IL = interleukin, CTACK = cutaneous T-cell attracting chemokine, ENA = epithelial-neutrophil activating peptide, GCSF = granulocyte colony-stimulating factor, GM-CSF = granulocyte-macrophage colony-stimulating factor, GROα = chemokine growth-regulated protein α, MCP-1 = monocyte chemoattractant protein-1, MDC = macrophage-derived chemokine, MIG = monokine induced gamma interferon, and TRAIL = tumor necrosis factor-related apoptosis-inducing ligand.

Table 4.

Mean Median Fluorescence Intensity (MFI) values of chronic pancreatitis (CP) with recent and remote episode (s) of acute pancreatitis (AP)

	CP with recent AP (n=57)	CP with remote AP (n=41)	P-value
IL-6	83.4 (79.1)	105.0 (166.4)	0.994
IL-8	138.3 (276.0)	109.7 (67.0)	0.555
IL-10	43.8 (25.9)	103.2 (286.9)	0.079
IL-1Ra	67.6 (50.9)	66.1 (43.4)	0.602
IL-15	39.6 (15.5)	40.4 (14.5)	0.274
IL-27	482.6 (834.1)	583.6 (783.9)	0.435
CTACK	6669.9 (1855.5)	7004.5 (1631.3)	0.633
ENA-78	3779.9 (4434.3)	2153.3 (3726.6)	**0.023**
Fas-L	67.8 (210.0)	412.9 (1807.3)	0.081
G-CSF	55.9 (28.6)	60.3 (36.5)	0.720
GM-CSF	101.7 (160.7)	102.6 (131.0)	0.720
GRO-α	206.4 (150.9)	175.5 (195.6)	0.371
MCP-1	2438.9 (1399.8)	2156.3 (839.1)	0.746
MDC	9414.0 (3812.2)	9468.4 (3480.8)	0.712
MIG	964.9 (1083.6)	1075.5 (781.3)	0.558
TRAIL	303.5 (81.8)	261.8 (93.1)	**0.036**

Data are reported as mean MFI with standard deviations in brackets. Group comparisons were adjusted for sex, age, BMI, non-specific binding, and plate effects. Abbreviations: IL = interleukin, CTACK = cutaneous T-cell attracting chemokine, ENA = epithelial-neutrophil activating peptide, GCSF = granulocyte colony-stimulating factor, GM-CSF = granulocyte-macrophage colony-stimulating factor, GROα = chemokine growth-regulated protein α, MCP-1 = monocyte chemoattractant protein-1, MDC = macrophage-derived chemokine, MIG = monokine induced gamma interferon, and TRAIL = tumor necrosis factor-related apoptosis-inducing ligand.