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Local and Systemic Expression of Immunomodulatory Factors in Chronic Pancreatitis

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Abstract

Inflammatory and fibrotic events that drive chronic pancreatitis (CP) are likely orchestrated via signaling of soluble cytokines and chemokines systemically and within the pancreas. However, a comprehensive summary of the expression of such factors during CP has not been reported to date. This information is important given continued interest in targeting cytokines that influence CP pathogenesis. Reported data on the expression change of soluble immunomodulatory factors in human CP patients were identified via a literature search using a single search term. Thirty-one articles meeting the pre-specified inclusion criteria were identified to generate a compiled data summary. Compiled data demonstrated up-regulation of several factors in the blood or pancreas microenvironment of CP patients. Nine factors were elevated in both compartments, including fractalkine, interferon gamma (IFN- γ), interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), interleukin-8 (IL-8), macrophage inhibitory cytokine 1 (MIC-1), neutrophil gelatinase-associated lipocalin (NGAL/LCN2), transforming growth factor beta (TGF- β), and tumor necrosis factor alpha (TNF- α). Most up-regulated factors could be classified into one of several functional groups, including inflammation, chemotaxis, angiogenesis, bone remodeling, extracellular matrix

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remodeling, and pain. Following further validation, these factors may be used as biomarkers for disease diagnosis, identification of comorbidities, or as potential therapeutic targets.

Keywords

chronic pancreatitis; cytokines; chemokines; immunity; serum; pancreatic juice

Introduction

Chronic pancreatitis (CP) is a severe inflammatory condition with a prevalence of approximately 50 per 100,000 people^{1, 2}. Symptoms include abdominal pain, nausea, and maldigestion due to inflammation and fibrosis of the pancreas. As no curative or preventative therapies are available, parenchymal damage often progresses to irreversible endocrine and exocrine insufficiency³. Additionally, those with CP have an increased risk of developing pancreatic cancer compared to those without disease⁴⁻⁷. Thus, enhanced understanding and novel treatment strategies are desperately needed.

Factors which contribute to the development of CP are varied and multifactorial, including both lifestyle and genetic components^{8, 9}. Common among all etiologies is the damaging role of pro-inflammatory and pro-fibrotic factors in promoting disease progression. Accordingly, limiting the fibro-inflammatory response during CP could have a significant impact on the course of disease.

Though chronic inflammation is a hallmark of CP and contributes to much of the associated damage, our understanding of immune involvement remains limited. Analysis of human tissue reveals robust macrophage infiltration into the pancreata of CP patients in addition to the presence of CD4⁺ and CD8⁺ T cell populations^{10, 11}. Findings from animal models support these observations, demonstrating a role for both innate and adaptive immune cell populations in the pathogenesis of CP¹²⁻¹⁴. Accordingly, many features of the inflamed pancreas are influenced by the profile of cytokines and chemokines present, which control the infiltration, survival, and differentiation of immune cells¹⁵. Soluble factors arise from multiple compartments including innate and adaptive immune populations as well as parenchymal cells and local fibroblasts termed pancreatic stellate cells.

Though dysregulated expression of soluble immunomodulatory factors is reported consistently in patients and animal models of CP, surprisingly few studies have attempted to neutralize these soluble factors therapeutically; an observation that is true both clinically and pre-clinically¹⁵⁻¹⁹. In murine models, studies have demonstrated the pathologic role of IL-6 during acute pancreatitis and have shown therapeutic benefit of IL-6 blockade^{20, 21}. Additional animal studies suggest a role for TGF- β , TNF- α , and CXCL10 in promoting progression to CP²²⁻²⁴. Most efforts to confirm and target these and other soluble factors have been performed in animal models with diverse etiologies and are largely focused on acute pancreatitis. Data from human samples has also been derived primarily from patients with the acute condition, which displays marked differences in cytokine profiles compared to CP. As a result, data specific to human CP is lacking. With few *in vivo* studies and no

current clinical trials targeting soluble mediators in CP, there is little functional data to aid in the prioritization of cytokine targets.

Accordingly, the comprehensive changes in immunomodulatory factor expression during CP and the ability to target these factors remains poorly understood. To address this gap in knowledge, we performed a literature search to identify articles that characterize the expression of one or more soluble factors in human patients with CP as compared to control subjects. We have compiled and analyzed these data to enhance our understanding of changes in the expression of immunomodulatory factors during CP.

MATERIALS AND METHODS

We sought to compile data generated in CP patients that characterizes the expression of soluble factors compared to healthy control subjects. To accomplish this, we performed a literature search of PubMed for articles published between January 1, 1990 and July 1, 2016 using a focused search strategy (*cytokines[MeSH] AND chronic pancreatitis[MeSH]*) to reveal 126 results (Figure 1). From these articles we reviewed English and non-English articles that contained human data from CP subjects compared to healthy controls. Diagnostic criteria used to define CP varied by article; however, in general this relied on a combination of a consistent clinical syndrome, imaging (computerized tomography [CT], magnetic resonance imaging [MRI], and/or endoscopic ultrasound [EUS]), and occasionally, pancreatic function testing. Compiled data from these articles illustrate changes in expression of soluble factors systemically, in serum or plasma (Table 1), and locally, in pancreatic tissue and pancreatic fluid (Table 2). The expression levels of factors were analyzed using a variety of techniques, including ELISA, western blot, immunohistochemistry, and PCR.

RESULTS

Summary of Findings From Literature Search

Our literature search specifications and inclusion criteria resulted in a total of 36 articles included in this review. Within these articles, 90 unique soluble factors were assessed in blood, pancreatic juice, or pancreatic tissue of human subjects with CP compared to controls. Seventy-one of these 90 factors were mentioned by only a single article. For factors examined by more than one article, the direction of expression change was generally concordant between articles, except in the case of CXCL10 and CCL3, which were cited as both up- and down-regulated by two independent studies. Soluble factors concordantly identified as up-regulated by multiple references include TNF- α , IL-6, TGF- β , IL-1 β , fractalkine, MMP-9, IFN- γ , and IL-8 in systemic analyses and IL-6, fractalkine, IL-8, and the fractalkine receptor (CX3CR1) in the local environment. Overall, regardless of citation frequency, 24 factors were up-regulated in serum and 32 in local pancreatic tissue. Of these, 9 were up-regulated both systemically in blood and locally in pancreatic tissue (Figure 2).

Several factors were found to be down-regulated in CP compared to controls. In the blood these included IL-10, insulin, leptin, platelet factor 4, and vitamin D (25-hydroxyvitamin D/25OHD). Within the pancreatic microenvironment, a single article cited decreases in

CXCL10, EGF, eotaxin, IL-15, IL-1 α , IL-3, MIP-1 α , and PDGF levels in pancreatic juice obtained during endoscopic pancreatic function testing²⁵.

Patterns of immunomodulatory factor expression

Of the soluble factors up-regulated in CP samples, the majority could be organized into one of the following functional groups associated with CP pathogenesis: inflammation, chemotaxis, angiogenesis, bone remodeling, extracellular matrix remodeling, and pain (Table 3). In particular, factors involved in inflammation were prominently up-regulated in CP. In the local environment, a large number of chemokines were observed whereas in the blood the majority of soluble factors were pro-inflammatory cytokines.

These up-regulated factors were subsequently categorized by their ability to influence differentiation of T helper cell (Th) subsets (Figure 3). This analysis demonstrated that patients with CP display an up-regulated cytokine profile consistent with the differentiation of Th1, Th17, and Treg populations.

Discussion

To our knowledge, this review is the first study to systematically analyze available data concerning immunomodulatory factor expression in patients with chronic pancreatitis. Factors found to be up- or down-regulated by multiple independent studies offer increased confidence in the validity of these findings. These consistently up-regulated proteins, including TNF- α , IL-6, TGF- β , IL-1 β , fractalkine, MMP-9, IFN- γ , and IL-8, in the serum and IL-6, fractalkine, IL-8, and fractalkine-R in the local environment are likely to play an important role in disease progression or may serve as immunologic biomarkers in CP. Similarly, several factors that were down-regulated align with known clinical manifestations of disease. For example, decreased circulating insulin and leptin are likely the result of progressive pancreatic dysfunction during the course of disease. CP-associated exocrine insufficiency commonly results in fat malabsorption and fat-soluble vitamin deficiencies, notably 25OHD²⁶. Accordingly, our literature review noted a reduction in levels of circulating vitamin D in CP patients. Such findings increase confidence in the validity of the data and its relevance to CP disease progression.

Up-regulation of pro-inflammatory and chemotactic molecules was particularly evident in our analysis. The presence of elevated pro-angiogenic factors is also consistent with data that shows increased angiogenesis during CP and PDAC and its association with *KRAS* mutation status^{27–29}. Similarly, changes in factors associated with bone remodeling are anticipated based on clinical observations demonstrating high rates of bone remodeling, specifically bone loss, in the CP patient population, with approximately 65% experiencing either osteoporosis or osteopenia^{30–32}. Additionally, up-regulated factors involved in ECM remodeling mirror histological analysis demonstrating increased collagens and fibronectin with reduced fibril organization in fibrotic and normal tissue sections from human CP pancreatic tissue³³. PSC, which secrete matrix metalloproteinases (MMPs), tissue inhibitor of matrix metalloproteinases (TIMPs), and collagen in response to inflammatory cytokines, are known to contribute to pathogenic ECM alterations^{34–36}. Several soluble factors identified in this review are also involved in pain, which has a pronounced role in the clinical

course of CP^{37, 38}. Abdominal pain is present in up to 90% of CP cases and is the primary cause of hospitalization. Poulsen *et al.* have previously summarized the evidence for abnormal pain processing in CP, which includes nerve sensitization and altered pain control systems³⁹. Overall, the prevalence of factors involved in pain, ECM remodeling, bone turnover, angiogenesis, inflammation and chemotaxis is consistent with clinical manifestations of observed in CP patients.

Soluble factors up-regulated in CP were also organized based on their immune activity, revealing increased Th1 and Th17-associated signaling molecules. These data are in agreement with prior mechanistic studies, which suggest a role for these cells and cytokines in pancreatic inflammation as it relates to either CP or pancreatic cancer^{40–43}. Imbalances between Th17 and Treg populations and their cytokines have also been implicated in the development of inflammation, autoimmunity, tumorigenesis, and others^{44, 45}. The influence of these T-cell subsets and polarizing cytokines within the pancreatic microenvironment deserves further investigation to delineate the role of each in CP progression.

We are hopeful that enhanced understanding of pathogenic cytokine expression in CP, facilitated by this review, will catalyze future efforts to generate novel treatment strategies for this patient population. Despite increases in pro-inflammatory cytokines such as IL-6 and TNF- α , few pre-clinical *in vivo* studies and no clinical trials have been attempted to target these particular cytokines in CP. In theory, neutralization of these soluble factors or inhibition of downstream pathways, has the potential to block key signaling nodes in pathogenic inflammatory and fibrotic processes. In other inflammatory conditions, agents such as tocilizumab (anti-IL-6R) and daclizumab (anti-CD25) have shown efficacy in the treatment of rheumatoid arthritis and multiple sclerosis, respectively^{46, 47}. Data from this study may also be used to support development of advanced mathematical models that simulate cytokine interactions on cells within the pancreas microenvironment. Similar theoretical studies have been conducted by our group for pancreatic cancer and are currently underway as an extension into CP⁴⁸. Finally, these data may also aid efforts in implementing new diagnostic or prognostic strategies in CP. As early diagnosis of CP remains difficult, the addition of one or multiple soluble factors from analysis of blood or pancreatic fluid, in combination with current diagnostic methods has the potential to increase diagnostic accuracy. Earlier diagnosis will be critical as therapeutic options become available to facilitate timely intervention and prevent progressive organ dysfunction.

In theory, comorbidities of CP, including pancreatic cancer, diabetes, and metabolic bone disease⁴⁹, may be identified earlier via periodic screening with a panel of select soluble factors associated with each comorbidity. For instance, as almost two-thirds of CP patients develop metabolic bone disease, groups of validated cytokines associated with bone turnover, as shown in Table 3, may be used in future studies to monitor risk of bone disease in patients³². Such practices have the potential to greatly expedite diagnosis and intervention for the most common complications.

Despite the benefits of this comprehensive literature summary, there are challenges in interpreting such data that deserve mention. First, the specific soluble factors included in this review were not stochastically generated but were instead chosen to be analyzed in each of

the articles reviewed. Accordingly, soluble messengers which have already been implicated in CP progression or that are commonly involved in fibro-inflammatory conditions are more likely to be studied in the context of CP and may thus be overrepresented in a way not related to their importance or abundance during disease. However, congruent findings by independent sources serve to increase overall confidence in the direction of expression change for these factors. Additionally, our study was focused on expression of factors in chronic pancreatitis rather than acute pancreatitis, a condition that may have a distinct profile of inflammatory mediators¹⁷.

Second, it is also important to consider the diverse nature of CP etiologies when interpreting these data. The effect of etiology on immune profiles during CP is currently unclear. Accordingly, it is possible that each etiology (including toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, or obstructive) may require independent study to further understand the nuances of disease progression and to identify differences in potential therapeutic targets⁵⁰. Additionally, patient characteristics including age, gender, and stage of CP may affect the expression of soluble factors and should be considered in future studies.

This data summary will be useful for understanding the comprehensive changes associated with CP and identifying cytokines and chemokines of interest for continued investigation as diagnostic or therapeutic candidates.

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Figure 1.
Flow diagram of literature search strategy.

Figure 2.

Venn diagram displaying the number of proteins that exhibited increased expression in systemic (purple) and pancreatic (orange) analyses. Those that were shown to increase in both systemic and pancreatic compartments are listed in the center.

Figure 3. Th-cell differentiation and the Th-type cytokines involved. Cytokines that are up-regulated systemically, in the pancreas microenvironment, or both are highlighted in red.

TABLE 1
Changes in Soluble Factor Expression in Serum From CP Patients Compared to Healthy Controls

Factor	Expression Change in CP										Reference
TNF- α	+	+	+	+	+	+	+	+	+	+	51, 52, 53, 54, 55, 56, 57
IL-6	+	+	+	+	+	+	+	+	+	+	58, 52, 59, 55, 56
TGF- β	+	+	+	+	+	+	+	+	+	+	60, 51, 17, 61
IL-1 β	+	+	+	+	+	+	+	+	+	+	54, 55, 56
CX3CL1/Fractalkine	+	+	+	+	+	+	+	+	+	+	60, 61
MMP-9	+	+	+	+	+	+	+	+	+	+	51, 54
IFN- γ	+	+	+	+	+	+	+	+	+	+	55, 56, 62
IL-8	+	+	+	+	+	+	+	+	+	+	55, 56, 52
Chemerin	+	+	+	+	+	+	+	+	+	+	17
CRP	+	+	+	+	+	+	+	+	+	+	58
CTX-1	+	+	+	+	+	+	+	+	+	+	58
REG3 α /HIP/PAP	+	+	+	+	+	+	+	+	+	+	63
IL-4	+	+	+	+	+	+	+	+	+	+	55
IL-18	+	+	+	+	+	+	+	+	+	+	62
LCN2/NGAL	+	+	+	+	+	+	+	+	+	+	64
Osteocalcin	+	+	+	+	+	+	+	+	+	+	58
PINP	+	+	+	+	+	+	+	+	+	+	58
PDGF-BB	+	+	+	+	+	+	+	+	+	+	17
PTH	+	+	+	+	+	+	+	+	+	+	58
Resistin	+	+	+	+	+	+	+	+	+	+	65
TIMP-1	+	+	+	+	+	+	+	+	+	+	54
TNF- α RI	+	+	+	+	+	+	+	+	+	+	57
TNF- α RII	+	+	+	+	+	+	+	+	+	+	57
MIC-1	+	+	+	+	+	+	+	+	+	+	64
CA19-9	=	=	=	=	=	=	=	=	=	=	64, 63
CCL2/MCP-1	=	=	=	=	=	=	=	=	=	=	60, 61
Adiponectin	=	=	=	=	=	=	=	=	=	=	65
HMGB1	=	=	=	=	=	=	=	=	=	=	17

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Factor	Expression Change in CP	Reference
IL-12	=	62
MIP-3	=	52
Osteopontin	=	63
PACAP	=	66
Soluble CD14	=	62
TIMP-1	=	63
IL-10	-	67
Insulin	-	65
Leptin	-	65
Platelet Factor 4	-	68
25OHD	-	58

The plus symbol (+) represents an increase in expression, the equal symbol (=) represents no significant difference, and the minus symbol (-) indicates a decrease in expression in CP patients compared to controls. Each individual symbol represents results from a single article, with the corresponding reference number listed to the right.

TABLE 2

Local Changes in Soluble Factor Expression in Pancreatic Tissue or Pancreatic Juice From CP Patients Compared to Healthy Controls

Factor	Expression Change in CP	Reference	Source
IL-6	+	=	69, 70, 71, 25
CX3CL1/Fractalkine	+	=	72, 73, 25
CXCL8/IL-8	+	=	70, 71, 25
CX3CR1/Fractalkine-R	+	=	74, 72
CCL2/MCP-1	+	=	75, 25
TGF- β	+	=	76, 71
TNF- α	+	=	70, 25
IFN- γ	+	=	70, 25
IL-1 β	+	=	70, 25
CCL5/Rantes	+	=	77, 25
CCL4/MIP-1 β	+	=	77, 25
Annexin II	+		78
Artemin	+		79
CA19-9	+		80
CCR5	+		77
CXCL11	+		77
CXCL9	+		77
CXCR3	+		77
Decorin	+		75
GFRa3/Artemin-R	+		79
Glycoprotein Tenascin C	+		78
IL-12	+		70
IL-1RAcP	+		81
IL-24	+		82
IL-33	+		81
MFG-E8/lactadherin	+		73
MIC-1	+		80
LCN2/NGAL	+		80

Factor	Expression	Change in CP	Reference	Source
Osteopontin	+		83	tissue
ST2L/IL1RL1	+		81	tissue
CXCL10/IP10	+	-	77, 25	tissue, juice
CCL3/MIP-1 α	+	-	77, 25	tissue, juice
14-3-3- zeta	=		84	tissue
CCL20/LARC/MIP3A	=		84	tissue
CD44	=		85	tissue
bFGF/FGF2/FGF- β	=		25	juice
Flt-3L	=		25	juice
G-CSF	=		25	juice
GM-CSF	=		25	juice
GRO	=		25	juice
IAM1	=		25	juice
IFN- α 2	=		25	juice
IL-10	=		25	juice
IL-12p40	=		25	juice
IL-12p70	=		25	juice
IL-13	=		25	juice
IL-17	=		25	juice
IL-1R α	=		25	juice
IL-2	=		25	juice
IL-2R α	=		25	juice
IL-4	=		25	juice
IL-5	=		25	juice
IL-7	=		25	juice
IL-9	=		25	juice
CCL7/MCP-3	=		25	juice
CCL22/MDC	=		25	juice
sCD40L	=		25	juice
TGF- α	=		25	juice
TNF- β	=		25	juice

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Factor	Expression Change in CP	Reference	Source
VEGF	=	25	juice
EGF	-	25	juice
Eotaxin	-	25	juice
IL-15	-	25	juice
IL-1α	-	25	juice
IL-3	-	25	juice
PDGF	-	25	juice

The plus symbol (+) represents an increase in expression, the equal symbol (=) represents no significant difference, and the minus symbol (-) indicates a decrease in expression in CP patients compared to controls. Each individual symbol represents results from a single article, with the corresponding reference number listed to the right.

TABLE 3

Soluble Factors in Serum and Pancreas Microenvironment Organize By Function

Serum	Local
Chemokines	Chemokines
Fractalkine (CX3CL1)	CCL3
Pro-inflammatory factors	CCL4
Chemerin/RARRES2/TIG2	CCL5 (Rantes)
CRP	CCR5
Fractalkine (CX3CL1)	CX3CR1 (Fractalkine-R)
IL-18	CXCL10 (IP10)
IL-1 β	CXCL11
Interleukin-6 (IL-6)	CXCL9
MIC-1	CXCR3
NGAL/LCN2	Fractalkine (CX3CL1)
REG3a/HIP/PAP	IL-8/CXC18
Resistin/ADSF/XCP1	MCP-1 (CCL2)
TNF- α RI	Pro-inflammatory factors
TNF- α RII	CCL3
Transforming growth factor beta (TGF- β)	CCL4
Tumor necrosis factor alpha (TNF- α)	CCL5 (Rantes)
Angiogenesis	CCR5
PDGF-BB	CX3CR1 (Fractalkine-R)
Bone Remodeling	CXCL10 (IP10)
CTX-1	CXCL11
Osteocalcin/BGLAP	CXCL9
Matrix Remodeling	CXCR3
MMP-9	Fractalkine (CX3CL1)
TIMP-1	IFN- γ
	IL-12
	IL-1RAcP
	IL-1 β
	IL-24
	IL-33
	IL-6
	IL-8/CXC18
	MCP-1 (CCL2)
	MIC-1
	NGAL/LCN2
	ST2L/IL1RL1
	TGF- β
	TNF- α
	Angiogenesis

Serum	Local
	MFG-e8
	Bone Remodeling
	Annexin II
	osteopontin
	Matrix Remodeling
	Annexin II
	Decorin
	Glycoprotein Tenascin C (TNC)
	Pain
	Artemin
	GFRa3 (Artemin-R)

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