Circulating Biomarkers Involved in Chronic Pancreatitis

Subjects: Gastroenterology & Hepatology

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Chronic pancreatitis (CP) is the end-stage of continuous inflammation and fibrosis in the pancreas evolving from acute- to recurrent acute-, early, and, finally, end-stage CP. Currently, prevention is the only way to reduce disease burden. In this setting, early detection is of great importance. Due to the anatomy and risks associated with direct sampling from pancreatic tissue, most of the information on the human pancreas arises from circulating biomarkers thought to be involved in pancreatic pathophysiology or injury.

chronic pancreatitis fibrosis inflammation oxidative stress

1. Background

Acute pancreatitis (AP), chronic pancreatitis (CP), and pancreatic ductal adenocarcinoma (PDAC) place a significant burden on healthcare systems worldwide. AP is among the three most common benign gastrointestinal diseases, with a mortality rate of 0.9% and an estimated economic burden of USD2.6 billion per year in the US [1]. CP is characterized by gradual irreversible damage to the endocrine and exocrine parenchyma caused by inflammation and subsequent replacement of these tissues with fibrotic tissue and atrophy [2]. Over the last two decades, the incidence of CP has increased by 50%, and there are currently no treatments available to alter this disease's course, resulting in significantly reduced life expectancy and quality of life. Prevention is the only way to reduce the disease burden, as serious complications including exocrine pancreatic insufficiency, malabsorption, diabetes mellitus, and PDAC may evolve as this disease progresses [3].

Approximately 50% of patients with CP have a history of AP [3]. There is continual replacement of the pancreatic tissue with fibrosis. Individuals who experience first-time AP have a 22% chance of developing recurrent acute pancreatitis (RAP) [4], and patients who experience three episodes of RAP have a 16% chance of developing CP. In addition, patients with four or more episodes of RAP have a much higher risk, around 50%, of developing CP [5].

Thus, the continuum from the first episode of AP to the manifestation of CP provides a framework for epidemiologic studies and the time-dependent evolution of circulating biomarkers involved in the progression of this disease.

2. Inflammation

From 1994 to 2022, 55 articles examined 64 inflammatory biomarkers, of which 23 were examined multiple times. In addition, five of these studies included patients with AP [6][7][8][9][10]. Of the 23 biomarkers, 12 were either not elevated in CP or the findings were inconclusive. Several pro-inflammatory interleukins (IL-6, IL-8, and IL-12) were found to be elevated in patients with CP compared to healthy controls [11][12][13], along with vascular endothelial growth factor (VEGF), intercellular adhesion molecule (ICAM), chemerin, fractalkine, resistin, osteopontin, and neopterin [7][10][14][15][16][17][18]. In contrast, leptin was found to be reduced in patients with CP [16]. IL-1β, IL-6, IL-10, tumor necrosis factor α (TNF-α), adiponectin, and leptin were the most studied inflammatory biomarkers in CP. However, the findings were cohesive only for IL-6, TNF-α, and leptin. IL-10, IL-12, TNF-α, and INF-γ were elevated in patients with AP [6][8]. **Figure 1** demonstrates a schematic overview of the inflammatory biomarkers involved in the progression to CP.

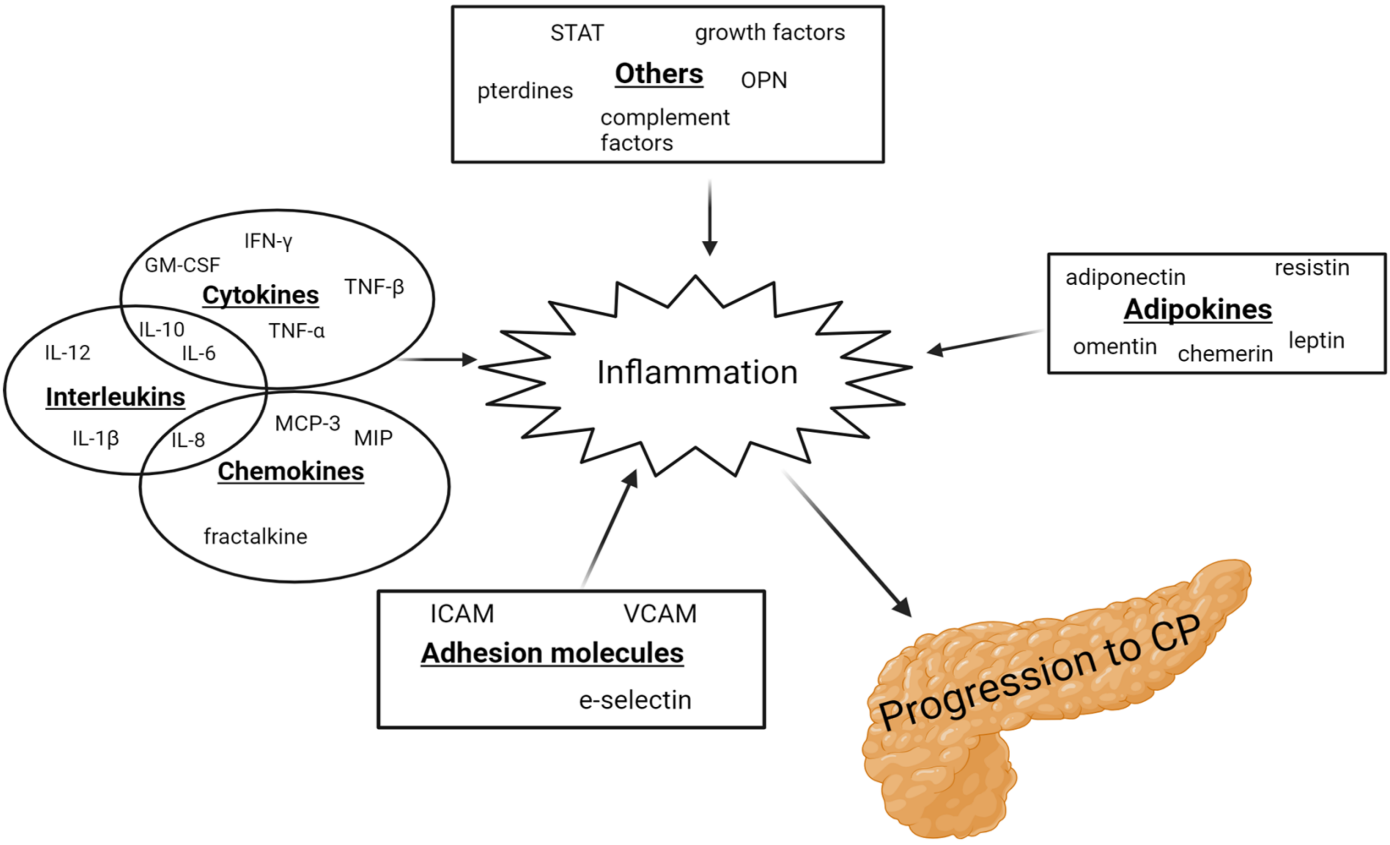

Figure 1. Schematic illustration of the inflammatory biomarkers involved in the progression to CP. GM-CSF: granulocyte-macrophage colony-stimulating factor; ICAM: intracellular adhesion molecule; IFN: interferon; IL: interleukins; MCP: monocyte chemotactic protein; MIP: macrophage inflammatory protein; OPN: osteopontin; STAT: signal transducer and activator of transcription; TNF: tumor necrosis factor; and VCAM: vascular cell adhesion molecule.

2.1. Interleukin 6

IL-6 induces the synthesis of acute-phase proteins and the production of other cytokines, including C-reactive protein (CRP) [19]. Sixteen studies measured IL-6, with twelve observing higher levels in patients with CP compared

to healthy controls [6][11][12][20][21][22][23][24][25][26][27][28], although the difference was not significant in three studies [20][25][28]. Four studies found no difference in the IL-6 levels [27][29][30][31]. In one study, a surge in IL-6 serum levels was observed in patients with alcoholic CP after the consumption of alcohol, with a decrease to the pre-stimulatory levels after 4–24 h, suggesting a correlation between alcohol consumption and IL-6 levels [24]. Elevated IL-6 levels were also evident in AP [6]. IL-6 rises 1–2 days before CRP, making it suitable for an early distinction between severe and mild AP [32][33]. Higher concentrations of IL-6 are linked to the increased risk of complications and death in severe AP [34][35][36][37]

2.2. Tumor Necrosis Factor α

TNF-α is a cytokine that facilitates both inflammation and fibrosis formation. It plays a key role in regulating other cytokines towards inflammation and activating pancreatic stellate cells (PSCs). TNF-α triggers the activation of PCSs, which, in turn, start producing extracellular matrix (ECM). This disorganization of the ECM leads to fibrosis formation and chronic inflammation of the pancreas [38][39]. The levels of TNF-α in patients with CP were investigated in 12 studies from 1999 to 2022. Elevated levels were found in six studies [9][11][22][31][39][40][41], one found lower levels [9], while the remaining five found no significant differences [8][20][25][29][42]. Kiyici et al. discovered significantly higher serum levels of TNF-α in AP compared to CP, indicating TNF-α's potential role in the progression of the disease. However, it is worth noting that this study included only 13 patients with AP, 36 patients with CP, and 14 controls [8].

2.3. Leptin

Leptin, an adipokine with a crucial role in metabolism, obesity, and cardiovascular diseases, has also been found to activate macrophages and T-lymphocytes, stimulating their cytokine secretion [43]. Moreover, it has been demonstrated to induce fibrosis in the liver by inhibiting hepatic stellate cell apoptosis [16][44][45]. Five studies found reduced levels of leptin in patients with CP [16][46][47][48][49], while one study found elevated leptin levels compared to healthy controls [41]. Because leptin is secreted by adipocytes, a higher fat percentage results in a higher amount of circulating leptin. Patients with CP had lower BMI across the involved studies, making it difficult to determine if the reduced levels were due to pancreatitis or to a lower fat mass. Additionally, patients with CP with diabetes mellitus (DM) were found to have higher levels of leptin than patients with CP without DM [41]. Lower levels of leptin may play a protective role in the development of CP by increasing apoptosis of the PSCs.

3. Fibrosis

A total of 46 studies spanning from 1995 to 2022 examined 28 potential biomarkers of fibrosis in patients with CP. Of these, 13 were studied multiple times. Three studies also included patients with AP [7][10][50]. The biomarkers mainly consist of PSCs activators, with the most extensively studied being TGF-β, PDGF, and MIC-1, and components of the ECM, with TIMP-1 and MMP-9 being studied the most. **Figure 2** demonstrates a schematic overview of the fibrotic biomarkers associated with the development of CP.

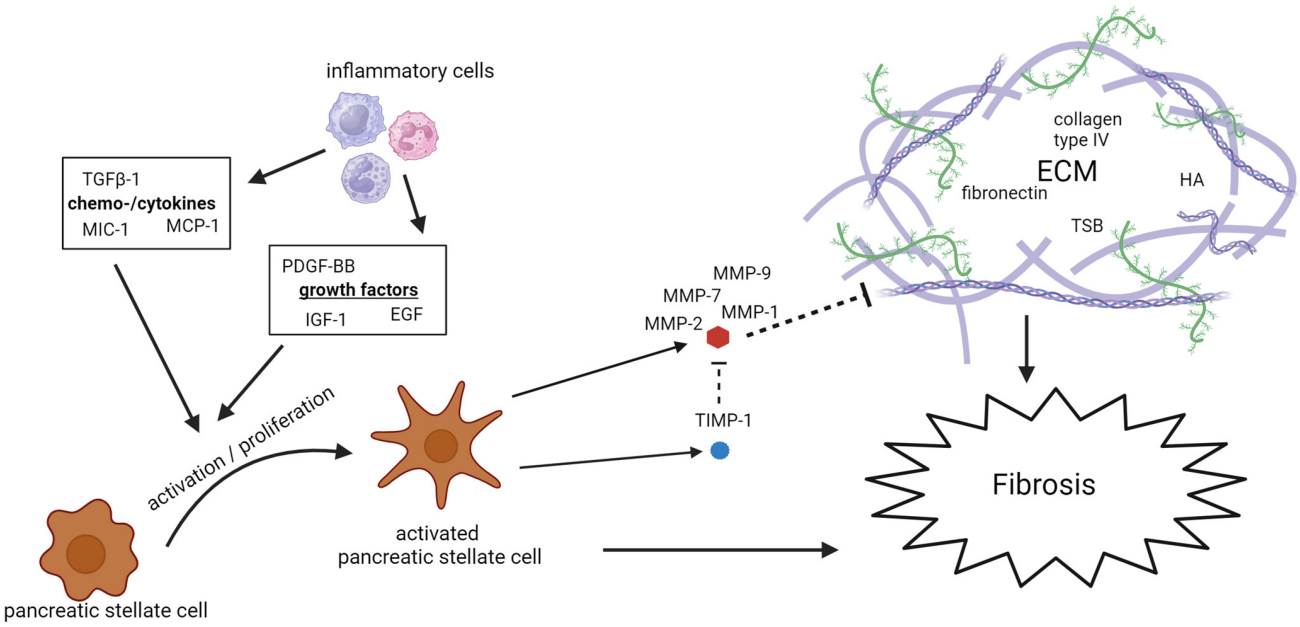

Figure 2. Schematic overview of the fibrotic biomarkers associated with the development of CP. ECM: extracellular matrix; EGF: epidermal growth factor; HA: hyaluronic acid; IGF: insulin-like growth factor; MCP: monocyte chemotactic protein; MIC: macrophage inhibitory cytokine; MMP: matrix metalloproteinase; PDGF: platelet-derived growth factor; TGF: tumor growth factor; TIMP: tissue inhibitors of metalloproteinases; and TSP: tissue polypeptide specific antigen.

3.1. Extracellular Matrix Remodeling

Continuous modulation of the ECM leads to fibrosis. Matrix metalloproteinases (MMPs) degrade the ECM, while tissue inhibitors of matrix metalloproteinases (TIMPs) inhibit MMPs. Numerous studies have measured the concentration of these biomarkers in patients with CP. MMPs are included in seven of the studies researchers reviewed [39][47][48][51][52][53][54]. Elevated levels of MMP-1, MMP-2, MMP-7, and MMP-9 were found in patients with CP compared to the control group, while MMP-3 was not seen to be elevated in patients with CP.

TIMP-1 concentrations in patients with CP were studied in nine of the studies researchers reviewed [15][48][51][53][55][56][57][58][59], all showing elevated concentrations in patients with CP, although three did not reach significance [48][55][56]. Hyaluronic acid (HA), laminin, and fibronectin are also important components of the ECM and are directly associated with the potential role of the ECM in the context of CP, see **Figure 2**. Elevated levels of all these components of the ECM were found in patients with CP. Four studies found elevated levels of HA [60][61][62][63], a fundamental component of the ECM in the pancreas. The Mac-2-binding protein (M2BP), a ligand which binds to ECM proteins and a novel biomarker of liver fibrosis, has also been found to be elevated in patients with CP.

3.2. Activation of PSCs

The activation and proliferation of PSCs influence the development of pancreatic fibrosis by the synthesis and remodeling of the ECM. The remodeling of the ECM is primarily mediated through the PCSs' secretion of MMP and

TIMP [64].

The cytokine transforming growth factor β1 (TGF-β1), the growth factor platelet-derived growth factor (PDGF), and the chemokine monocyte chemoattractant protein 1 (MCP-1) are among the most important mediators involved in the activation of PSCs. With few exceptions, these biomarkers are all found to be elevated in patients with CP compared to the controls. Elevated levels of TGF-β, PDGF, and MCP-1 were also found in patients with AP [7][10][50]. Macrophage inhibitory cytokine 1 (MIC-1), a cytokine part of the TGF-β family, has also been found to be elevated in patients with CP in five different studies. Its specific role in the pancreas is not extensively studied, but, as a part of the TGF-β family, it can be presumed that it has a role in the activation of PSCs.

4. Oxidative Stress

Twenty-three studies from 1981 to 2022 examined 34 biomarkers of oxidative stress, of which 23 were studied multiple times. Four articles also included patients with AP [65][66][67][68]. A potential relationship between oxidative stress and pancreatic inflammation has been extensively studied. Research indicates an early occurrence of pancreatic oxidative stress in AP. Free oxygen radicals play a crucial role in regulating the extent of necrosis in acinar cells, the development of pancreatic edema, the sequestration of inflammatory cells within the pancreas, and the release of inflammatory mediators [69]. Additionally, there is growing evidence connecting oxidative stress and CP. The use of antioxidant therapy has been shown to reduce the severity of CP, resulting in less fibrosis in murine models [70], as well as improve the well-being, decrease pain, and improve the overall functioning of patients with CP [71][72]. The biomarkers of oxidative stress are challenging to evaluate, primarily due to their complex metabolism and high turnover, making them difficult to measure in systemic circulation. The low blood antioxidant levels could be attributed to poor nutritional status due to malabsorption, maldigestion, and reduced food intake, often observed in patients with CP. **Figure 3** gives a schematic overview of oxidative stress biomarkers associated with CP development.

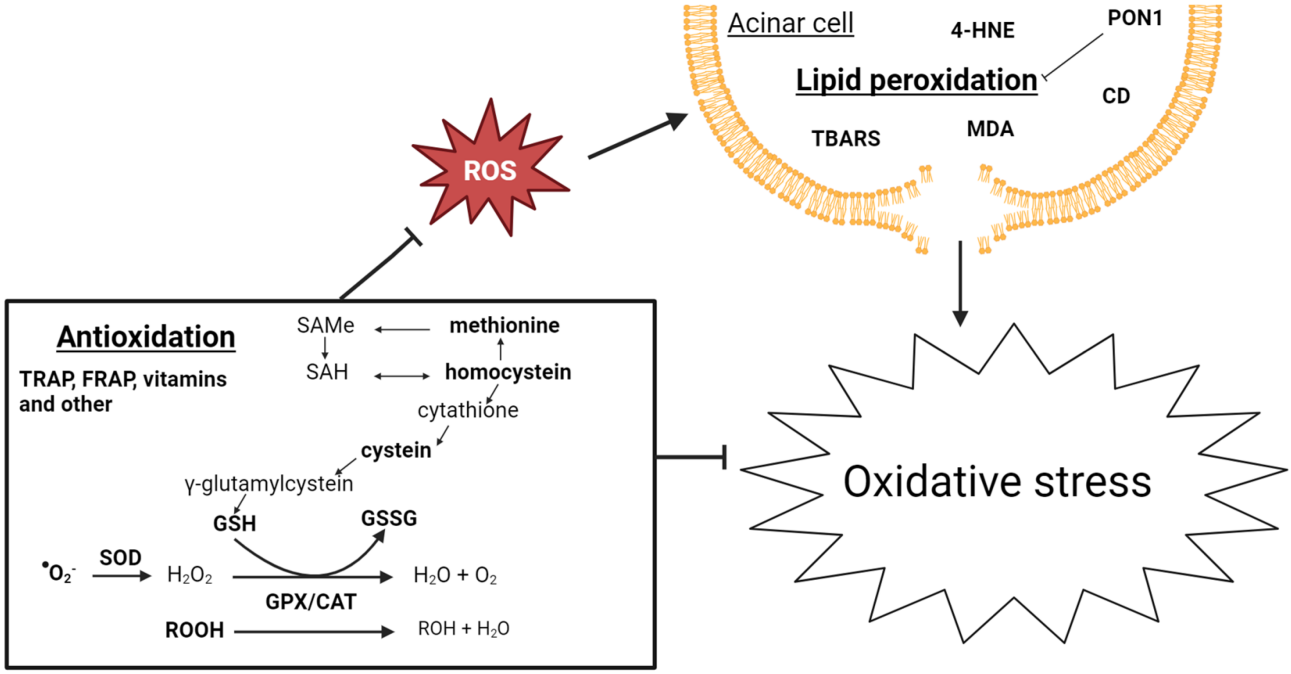

Figure 3. Schematic overview of biomarkers of oxidative stress associated with CP development. CAT: catalase; GPX: glutathione peroxidase; GSH: glutathione; GSSG: glutathione disulfide; ROOH: hydroperoxides; SAH: S-adenosyl homocysteine; SAMe: S-adenyl methionine; and SOD: superoxide dismutase.

4.1. Lipid Peroxidation

Prolonged exposure to oxygen radicals results in lipid peroxidation and the oxidation of fatty acids in cell membranes. Lipid peroxidation has been the focus of several studies investigating oxidative stress in CP [73]. Fourteen studies have included one of these biomarkers, and, apart from a few non-significant results, all these biomarkers are found to be elevated in patients with CP. Few studies include oxygen radicals in patients with CP. Superoxides, main reactive oxygen species (ROS) in cells, and ROS production in cells after phorbol myristate acetate (PMA) stimulation have all been investigated in patients with CP. These biomarkers are difficult to measure in the blood as they have a very short half-life. Elevated levels were found in all four studies; however, in two of them, the elevation was not significant. On the other hand, PON1 is a free radical-scavenging molecule contributing to the detoxification of free radicals involved in lipid peroxidation [74], and consistently reduced levels of PON1 were found in patients with CP in the studies researchers analyzed, indicating elevated lipid peroxidation in patients with CP. MDA, superoxide anion, and CAT were also found to be elevated in AP [65][66][67][68].

4.2. Antioxidation

The reactive superoxide is catalyzed to hydrogen peroxide by superoxide dismutase (SOD). The main ROS scavenger molecule is glutathione (GSH), which is used by glutathione peroxidase (GPX) and catalase (CAT) to reduce/neutralize ROS [75]; see **Figure 3**. GSH, GPX, CAT, and SOD have been measured in patients with CP in, respectively six, eight, four, and six studies. GSH, GPX, and SOD levels were reduced in patients with CP, while the results on CAT were contradictive, as two studies found no difference, one found lower levels, and one study

found elevated levels. The antioxidant capacity in the blood is measured by the ferrin-reducing ability of the plasma (FRAP) and the total peroxyl radical-trapping antioxidant parameter (TRAP). While FRAP is reduced in patients with CP, the TRAP concentrations are no different from the controls. Reduced levels of GSH and elevated levels of CAT and TRAP were found in patients with AP [65][66][67].

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