PANCREAPEDIA
Exocrine Pancreas Knowledge Base

APA AMERICAN PANCREATIC ASSOCIATION

The Role of Cytokines and Inflammation in the Genesis of Experimental Pancreatitis.

Peter Szatmary[1] and Ilya Gukovsky[2]*

[1] NIHR Liverpool Pancreas Biomedical Research Unit and Department of Cellular and Molecular Physiology, University of Liverpool, UK.

[2] David Geffen School of Medicine, University of California at Los Angeles and VA Greater Los Angeles, CA, USA.

e-mail: P.Szatmary@liverpool.ac.uk; igukovsk@ucla.edu

Version 1.0, October 10, 2016, 2016 [DOI: pending]

1. Introduction

Pancreatic acinar cell injury triggers the synthesis and release of pro-inflammatory cytokines and chemokines (32, 36, 39, 41, 82). Together with acinar cell death releasing damage-associated molecular patterns (DAMPs), such as histones, high-mobility group box1 protein (HMGB1) and ATP (60), this initiates an acute, sterile (43) inflammatory response, in a manner that shares similarities with the molecular/signaling events observed in sepsis (113). The resulting early cellular response, consisting of glandular infiltration with neutrophils and monocytes, appears to exacerbate pancreatic injury and is at least in part responsible for early onset organ failure seen in some cases of AP (85, 86). The clinical significance of these events is highlighted by the utility of cytokine measurements in predicting outcome in human acute pancreatitis (116). Inflammation is either self-limiting or self-perpetuating resulting in significant organ necrosis. Several days to weeks into the disease, development of immune anergy – or compensatory anti-inflammatory response syndrome – has been described in patients (74), associated with infection of pancreatic necrosis and multi-system organ failure. There are important differences in the immunological response to pancreatitis observed in humans and in experimental models (133); however, animal and cell models remain critical in furthering our understanding of molecular mechanisms, signaling pathways, and new drug targets. This review aims to describe the roles of key cytokines and chemokines in commonly used experimental models of pancreatitis and how the cytokine profile is affected by the choice of a specific model. Where relevant, we present and compare quantitative data reported in various models.

2. Tissue injury and inflammatory cell recruitment.

Tissue injury caused by pancreatitis toxins leads to the release of DAMPs – nuclear proteins (such as histones and HMGB1), nuclear and mitochondrial DNA, heat shock proteins, and ATP (60, 134). Nuclear proteins in particular can be measured as early as 4 h after induction of experimental acute pancreatitis (88, 111). These act via common immune sensors and mediators to initiate sterile inflammation (18). Another mechanism whereby injured pancreatic acinar cells trigger the inflammatory response is through synthesis and release of cytokines (36) and chemokines (11), and upregulation of adhesion molecules such as the intercellular adhesion molecule-1 (ICAM-1) (136), which together promote neutrophil and monocyte infiltration (27, 71) and exacerbate tissue injury (10, 27, 37).

3. Chemokines which recruit innate immune cells in pancreatitis

Chemokines (chemotactic cytokines) are positively charged polypeptides with highly conserved cysteine (C) residues within the N-terminal sequence, classifying them as 'C', 'CC', 'CXC' or 'CX3C' types (102, 143). The presence or absence of a glutamate-leucine-arginine sequence further divides chemokines into 'ELR' and 'non-ELR' chemokines, with ELR-chemokines exhibiting highest activity in chemotaxis assays (65, 130).

In the context of AP, the most extensively investigated chemokines are CC-ligand 2 (CCL2, also known as monocyte chemoattractant protein-1 or MCP-1), CXC-ligand 1 (CXCL1, also known as cytokine-induced neutrophil chemoattractant or CINC in rat and keratinocyte cytokine or KC in mouse), and CXC-ligand 2 (CXCL2, also known as macrophage inflammatory protein 2-alpha or MIP2a). CCL2 acts predominantly via the CC-receptor CCR2, although it also binds to CCR4 (138), whereas CXCL1 and CXCL2 both act via CXCR2 (125).

CXC-ligands

In response to cerulein (a CCK-8 ortholog widely used to elicit early pancreatitis responses in isolated acini an ex-vivo pancreatitis model), murine pancreatic acinar cells upregulate mRNA expression of both CXCL1 and CXCL2 within 90 min, with a supramaximally stimulating cerulein concentration of 0.1 μM producing 8 fold increase in CXCL1 and 10 fold increase in CXCL2 expression (87). In a mouse model of cerulein-induced acute pancreatitis (CER-AP), 10 hourly doses of 50 μg/kg cerulein result in an increase in CXCL2 concentration from <10 pg/ml to 110 pg/ml in serum, 190 pg/ml in pancreas, and 240 pg/ml in lung homogenates (91). A >40-fold increase in pancreatic CXCL2 mRNA expression was measured in rat CER-AP (38). Pre-treatment with an anti-CXCL2 antibody was shown to reduce pancreatic edema, inflammatory cell infiltration and necrosis, as well as reduce pancreatic and lung myeloperoxidase (91); antibodies against CXCL1 (8) elicit similar protection for pancreatic and lung injury in rats. Inhibition of CXCR2 with antileukinate (9), evasin-3 (77) or AZD8309 (73) improves the above parameters, as does CXCR2 knockout in the context of cerulein-induced acute and chronic pancreatitis (117). Glycyrrhizin, a licorice extract, reduces the ability of isolated pancreatic acinar cells to produce CCL2 and CXCL2 in response to cerulean (90), and treatment with glycyrrhizin was shown to attenuate pancreatic injury in response to cerulein in vivo (23). Taken together, these data convincingly demonstrate the crucial role of the CXCL2/CXCR2 axis in the genesis of experimental AP.

A chemokine that has gained recent prominence is CX3CL1, or fractalkine. CX3CL1 uniquely acts as both a chemoattractant and surface adhesion molecule; induced by other cytokines (in particular TNFα), it is expressed on the surface of vascular endothelium and enhances leukocyte adhesion by increasing binding avidity of integrins (121). In the rat bile-acid model of AP, serum CX3CL1 has been shown to rise from 150 pg/ml baseline levels to peak at 1400 pg/ml 16 h following intra-ductal taurocholate infusion (46). AR42J cells (rat cell line retaining some acinar cell characteristics) are able to synthesize and release CX3CL1 in response to cerulein, and express the CX3CR1 receptor, which on stimulation triggers the synthesis and release of TNFα (47). More recently, acinar cell CX3CR1 expression has been reported in normal rat pancreas; it is upregulated in models of acute and chronic pancreatitis in which it induces pancreatic stellate cell proliferation (120). To date, no specific inhibitors of CX3CL1 have been tested in AP; however, CX3CL1 siRNA has been shown to reduce pro-inflammatory cytokine release in the context of taurocholate-induced AP (TC-AP) (45).

CC-ligands

Expression of CCL2 was shown to increase in CER-AP by about 30% in lung, 60% in blood, and 140-fold in pancreas (26). Knockout of CCL2 (26) or inhibition with evasin-3 (77) reduced pancreatic leukocyte infiltration as well as necrosis, and decreased hyperamylasemia in

murine CER-AP, while evasin-4 treatment only ameliorated lung injury. Inhibition of CCL2 production with the relatively specific inhibitor bindarit reduced serum amylase as well as histopathologic scores in rat TC-AP (142). Antibody-mediated inhibition of CCL2 in this model had similar effects on the pancreas and also dramatically reduced other serum cytokines including TNFα, IL-6 and IL-10 (54). This effect, however, was only partially reproduced by genetic ablation of its known receptors, CCR2 or CCR4, suggesting alternatives and redundancies in CCL2 signaling pathways. Interestingly, CCR2 knockout exacerbated chronic pancreatitis in the repetitive cerulein model (80). Together, the findings highlight a key role of CCL2 in early inflammation.

4. Mediators of early cellular infiltration and systemic inflammatory response

Neutrophils are amongst the earliest innate immune cells to respond to tissue injury and the chemokines released in response to tissue injury in AP; with infiltration of the pancreas by neutrophils observed as early as 1 h after induction of experimental pancreatitis and infiltration of lung after 3 h (25). Severity of human acute pancreatitis correlates with circulating levels of interleikin-8 (IL-8), a major neutrophil-activating chemokine, as well as with neutrophil elastase (35). Antibody-mediated depletion of neutrophils ameliorates experimental AP (10, 53, 78, 108) (especially the lung injury), as does the genetic ablation of ICAM-1 (27) or neutrophil NADPH oxidase (37). Interestingly, the latter knockout (37) reduced the pathologic, intrapancreatic increase in trypsin activity in CER-AP, which was previously considered acinar cell autonomous. Inhibitors of neutrophil elastase have also shown promise in the treatment of pancreatitis-associated lung injury (52, 127).

Neutrophils and monocytes contribute to further cytokine release, which is amplified by activated peritoneal macrophages and hepatic Kupffer cells to enhance levels in the systemic circulation (29, 30, 70), manifesting clinically as systemic inflammatory response syndrome (SIRS). The amplification links pancreatic injury to organ dysfunction associated with severe AP. In this context, the most relevant cytokines for discussion are IL-6, IL-1β, and TNFα.

IL-6

IL-6 is a key cytokine involved in early inflammation in AP. It belongs to a family of nine IL-6 type cytokines and has unusual signaling properties. Although IL-6 is produced and secreted by many cell types, very few cells (predominately hepatocytes, neutrophils and macrophages) express IL-6 receptors, leading to the assumption of a very specific pro-inflammatory role for this cytokine (109). However, in complex with a soluble form of its receptor (sIL-6R) IL-6 can induce signals in cells not expressing the IL-6R – a phenomenon termed trans-signaling (28, 99, 106).

IL-6 expression is upregulated in AR42J cells (16, 56), rodent pancreatic acinar cells (59), and indeed murine salivary gland (97) following stimulation. In vivo models of experimental acute pancreatitis show the rise of serum levels of IL-6 correlating with the severity of the model used, from less than 10 pg/ml to 50-100 pg/ml (24 h) and 200 pg/ml (72 h) in mouse CER-AP (49, 135), to 400 pg/ml following intra-ductal infusion of taurolithocholate-sulfate (48). Intra-ductal infusion of taurocholate leads to the highest levels of serum IL-6, 2000 pg/ml 24-48 h following the induction of AP (110). Interestingly, the increase in pancreatic IL-6 mRNA expression in this model (as well as other parameters of injury) is much greater in the head than in the tail of the pancreas (124). A ~100-fold increase in pancreatic IL-6 mRNA expression has been reported in rat CER-AP (38).

Administering IL-6 together with cerulein produced total lethality in mice after 4 days, and IL-6 trans-signaling has been demonstrated to link experimental pancreatitis to acute lung injury(137). Furthermore, even though acinar cells are clearly able to secrete IL-6, pancreatic IL-6 in CER-AP appears to derive predominantly from invading myeloid cells(137). As may be

expected, inhibition of IL-6 signaling, either with neutralizing antibody(17, 19) or by genetic modification of an upstream signaling pathway(119), ameliorates cerulein and bile-acid induced AP. A very pronounced effect of IL-6 genetic ablation on CER-AP is in the context of diet-induced obesity; in this setting, IL-6 is responsible for delayed clearance of neutrophilic infiltrate and associated pancreatic necrosis(95).

TNFα

TNFα was initially identified as a serum factor able to induce necrosis in solid tumours(3). Since then, anti-TNF signaling strategies have been successfully employed in a number of inflammatory diseases resulting in a deeper understanding of its therapeutic manipulation(58). TNFα is synthesized in membrane-bound form in many tissues in experimental acute pancreatitis(83), and requires cleavage by TNFα converting enzyme (TACE, or ADAM17) to be released in soluble form(55). Activity of TNFα is dependent on its binding to one of two receptors, TNFR1 or TNFR2. TNFR1 is ubiquitously expressed and linked to TNFR1-associated death domain protein, with activation of this pathway resulting in the induction of programmed cell death(13). TNFR2 is predominantly expressed on immune and endothelial cells, lacks a death domain, and responds primarily to the membrane-bound form of TNFα(34) to promote cell survival, proliferation, and inflammation. Both receptors can be shed following inflammatory stimuli, rendering them soluble in order to bind and inactivate circulating TNFα(96).

Due to this complex binding pattern, measuring TNFα with commercial kits can be difficult, as some kits only measure free TNFα. In rat bile-acid induced AP, for example, free TNFα increased from 3 pg/ml to 7.5 pg/ml within an hour, only to return to baseline after 3 h(33). Total TNFα increased from 2.5 to 7.5 ng/ml in the same time period and remained at the higher level for 9 hours. Levels of soluble TNFR1 and 2 similarly increased within an hour and remained elevated for at least 9 hours. Plasma levels in rats with bile-acid induced AP rise from 20 pg/ml to a peak of 80 pg/ml within 24 h(100).

TNFα was one of the first cytokines whose mRNA expression was found to be induced in experimental AP(84). Pancreatic acinar cells can themselves synthesize TNFα(36), and gene expression is upregulated in response to cerulein and lipopolysaccharide as rapidly as within 30 min, with maximal expression after 6 h(122). Vascular endothelial cells are also able to synthesize and release TNFα in response to DAMPs such as double-stranded DNA(94), abundant in AP due to cellular necrosis and actively released from neutrophils in the form of neutrophil extracellular traps(76). While neutrophil recruitment can be sustained via TNFR1 alone, monocyte recruitment is dependent on TNFR2, and upregulation of this receptor on vascular endothelium contributes to selective recruitment of inflammatory monocytes(126). TNFα was the first cytokine (together with IL-1) implicated by genetic means in the pathogenic mechanism of pancreatitis(21). Genetic deletion of TNFα, or use of neutralizing antibodies prevents leukocyte-induced trypsin activation and necrosis in isolated acini(112). TNFα also regulates acinar cell apoptosis in AP(36). In rat TC-AP, infliximab (a monoclonal anti-TNFα antibody) attenuated pancreas and lung injury(72), an effect seemingly enhanced by concomitant octreotide therapy(50). Furthermore, the use of infliximab alone or in combination was proposed to limit intestinal dysfunction in this model(69).

The complex roles of TNFα in both pro- and anti-inflammatory processes, however, make it a difficult target for translation into clinical practice in AP.

IL-1

The IL-1 family of cytokines, which includes pro-inflammatory IL-1α/β, IL-18, IL-33 and IL-36, as well as anti-inflammatory IL-1ra, IL-36ra and IL-38, are another group of cytokines mediating sterile inflammation in AP. IL-1 (α and β) are

produced as pro-enzymes and require proteolytic cleavage by caspase-1 (also known as IL-1 converting enzyme, or ICE) or by neutrophil proteases to develop maximal biological activity(2). IL-1α/β both act via the same receptor and are inactivated by competitive binding to soluble IL-1 receptor antagonist (IL-1ra), a naturally occurring IL-1 inhibitor regulated through many of the same pathways as IL-1 itself(2). IL-1 blockade is proving particularly effective in rheumatological diseases, with a number of agents approved for clinical use(57).

IL-1β, ICE and IL-1ra mRNA are all expressed at low levels in mouse pancreas, but increase rapidly on cerulein stimulation or on a choline deficient, ethionine-supplemented (CDE) diet(24). Serum levels of IL-1β rise from a <10 pg/ml baseline to 150 pg/ml after 6 h in CER-AP, or to 200 pg/ml after 48 h in CDE-AP. Similar levels of IL-1ra could be detected in serum over the same time scales(24). Using glycodeoxycholic acid ductal infusion in rats, levels as high as 5000 pg/ml have been reported 12 h after induction of AP(111).

Targeted overexpression of IL-1β in murine pancreas produced inflammatory changes consistent with chronic pancreatitis in animals as young as 6 weeks(104), and co-administration of IL-1β exacerbated pancreatic and lung injury in rat CER-AP(81). Accordingly, recombinant IL-1ra effectively attenuated damage in mouse(114) and rat(131) chronic pancreatitis models. The synthetic IL-1ra Anakinra (a modification of recombinant IL-1ra licensed for the treatment of rheumatoid arthritis) also attenuated pancreatic injury in rat CER-AP(61). Reduction of biologically active IL-1β through inhibition of caspase-1 has also been shown to have some end-organ protective effects, for example by reducing renal injury(140), lung injury(141), and mortality(93) associated with rat TC-AP. It should be remembered, however, that IL-1β can be activated in other ways – for example, by neutrophil proteases. Another member of the IL-1 family, IL-33, links these signaling pathways by stimulating IL-6, CCL2 and CXCL2 release, demonstrated in isolated murine pancreatic acinar cells(63).

MIF

Activated T lymphocytes, inflammatory monocytes, and resident macrophages release macrophage migration inhibitory factor (MIF)(6), a pro-inflammatory cytokine which acts to further stimulate other macrophages(7) and T lymphocytes(4). In experimental AP in rats, MIF reaches peak concentrations of around 120 ng/ml (ascites and plasma) within 2-4 hours in CER-AP and 280 ng/ml (ascites) within 1 hour or 200 ng/ml (plasma) 10 hours following the induction of TC-AP. Pre-treatment with anti-MIF antibody decreased plasma levels of TNFα and reduced lethality of TCA-AP as well as CDE-AP(107).

5. Resolution of inflammation and delayed immune anergy

The interplay of inflammatory cells aims to control and clear the site of injury of cellular debris (and pathogens) quickly and effectively, and then repair and restore function to the surrounding tissue. Cessation of inflammation thus requires anti-inflammatory signals to overpower the pro-inflammatory ones. For example, monocyte/macrophage subsets encountering apoptotic cells including neutrophils respond by releasing anti-inflammatory cytokines and are critical to resolution of inflammation(22). Dysfunction of these regulatory systems together with ongoing injury can lead to non-resolving inflammation, progression to chronic pancreatitis or even pancreatic neoplasia(39). Many of these anti-inflammatory cytokines are released alongside their pro-inflammatory counterparts and have been discussed above (IL-1ra and soluble TNF receptors); the two other cytokines central to resolution of acute inflammation in AP are IL-10 and transforming growth factor beta (TGF-β).

IL-10

IL-10 is the foremost member of class-II cytokines, a family of anti-inflammatory cytokines that includes IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, and IL-29. It is produced by a wide range of leukocytes including B cells, T cells, monocyte/macrophages and dendritic cells, and

was initially described as a cytokine synthesis inhibitory factor, due to its ability to inhibit interferon gamma release by Th1 cells(115). In fact, IL-10 inhibits release of many pro-inflammatory cytokines on a transcriptional level via STAT3(51). IL-10 also directly inhibits T cell expansion through downregulation of class II major histocompatibility complex and costimulatory molecules such as CD80/CD86(89).

As with many other cytokines discussed in this review, pancreatic acinar cells also produce and secrete IL-10 and upregulate its production in response to pancreatitis toxins(101). Levels in systemic circulation, however, are likely to derive from infiltrating leukocytes as well as splenocytes(31) and hepatic Kupffer cells(5, 92). Knockout of B-cells, as another source of IL-10, exacerbates murine CER-AP in a manner that can be rescued by adoptive transfer of B cells(98).

In rat bile-acid infusion AP model, IL-10 rises from a baseline of 10 pg/ml to 5000 pg/ml after 6 h, earlier than the pro-inflammatory cytokines IL-1β and IL-6, and then drops to a new baseline of 2000 pg/ml for the next 6 h. Rats administered exogenous IL-10 either before or after induction of CER-AP had lower serum amylase and pro-inflammatory cytokine levels as well as less pancreatic damage on histology(105). Although there are currently no licensed IL-10 analogues in clinical use, agents shown to increase pancreatic IL-10, such as insulin-like growth factor 1 (IGF-1), have been tried in the context of experimental AP. Given during the course of rat CER-AP, IGF-1 ameliorated pancreatic damage and reduced pro-inflammatory cytokine levels (although other explanations are possible for such an effect)(128). Other strategies to enhance IL-10 secretion include administering IL-4 to cultured liver macrophages, which effectively reverses their polarization from a pro-inflammatory M1-type to an anti-inflammatory, IL-10 producing M2-type in vitro(132). Adenoviral transfer of IL-4 gene into pancreatic stellate cells similarly increased the endogenous IL-10 expression(14). Injection of such an IL-4 gene carrying vector into gastric artery of rats led to a transient increase in pancreatic IL-10 after 2 weeks(15). While these methods are clearly not ready for translation into clinical trials, they are important proof of principle studies and add to our understanding of this particular cytokine signaling axis. As could be expected, knockout of IL-10 greatly exacerbated pancreas injury in mouse repetitive-cerulein model of chronic pancreatitis(20).

TGF-β

TGF-β is a member of a family of about 40 related factors promoting growth and cellular differentiation. Of the three mammalian isoforms, TGF-β1, -β2 and -β3, TGF-β1 is the most extensively studied(62). Its overall effects are strongly cytostatic and anti-inflammatory (through inhibition of pro-inflammatory M1-type macrophages and Th1-type lymphocytes, as well as promotion of anti-inflammatory M2-type macrophages, Th2-type lymphocytes, and regulatory T cells)(1). TGF-β1 production is upregulated early in the course of mouse CER-AP; and expression of a non-functional, dominant negative TGF receptor type II ameliorated pancreatic injury in this model(129). Interestingly, acini isolated from these mice did not exhibit restricted stimulation at high cerulein concentrations(129). In rat CER-AP, increased TGF-β1 mRNA expression was detectable by the end of the first hour(68). As early as 5 h following ductal infusion with sodium deoxycholate, plasma levels of TGF-β in rats were reported as high as 10 ng/ml (twice as high as following macrophage depletion)(44). Hepatic injury in this model was reduced by both depletion of liver macrophages and by use of neutralizing antibody for TGF-β(44). Of note, TGF-β mRNA expression in rat L-arginine induced AP is upregulated much later (not until 2 days following the induction of AP(64)), in accord with slower development of pancreatitis in this model. In a comprehensive time-course analysis of TGF-β mRNA expression, increased TGF-β1 mRNA was detectable within 4 hours of cerulein injection in rats; however, there was a clear peak in expression between 2 and 3 days after AP induction(103). Peak TGF-β1

expression correlated well with collagen mRNA in that study, supporting a role in pancreatic repair for this cytokine. Administration of recombinant TGF-β1 was reported to have little effect on a single course of cerulein AP, whereas it led to increased collagen deposition and scarring after 6 courses of cerulein treatment(123). As such, this cytokine may be critical in the transition from recurrent acute to chronic pancreatitis(123). Inhibition of TGF-β activity via a viral vector expressing a soluble TGF-β receptor reduced fibrosis in a repetitive-cerulein model of chronic pancreaititis(79). Similarly, use of neutralizing TGF-β1 antibody reduced fibrosis and extracellular matrix deposition in rat CER-AP, demonstrating a key role of TGF-β in regulating pancreas repair/regeneration(75). In a recent study(139), TGF-β1 was identified as producing abdominal hyperalgesia in a rat model of bile-acid induced AP. TGF-receptors were upregulated in the dorsal root ganglion of rats in this model; administration of recombinant TGF-β1 enhanced while inhibition of TGF-β1 attenuated abdominal hyperalgesia, suggesting a major contribution of this cytokine to pain, a key response of human chronic pancreatitis(139).

6. Compensatory anti-inflammatory response syndrome

Prolonged disease activity is associated with immune anergy in acute pancreatitis. The concept of a compensatory anti-inflammatory response syndrome (CARS) was first raised in an attempt to understand the failure of anti-endotoxin strategies in sepsis(12). Mediators of CARS – predominantly TGF-β, IL-4, IL-10, and CCL2 – are released by neutrophils and monocytes(42, 118) and contribute to immunoparalysis by promoting a Th2-type adaptive immune response and predisposing to superinfection(66). The time scale of pro- and anti-inflammatory cytokine release is similar in patients(40), with peak cytokine concentration within 48 h of disease onset; thus the anti-inflammatory cytokines presumably limit the extent of systemic response. A significant subset of patients, however, develop considerable immune anergy, predisposing to superinfection(40). In CER-AP, myeloid-derived suppressor cells producing IL-10 acting via the MyD88 pathway(67) appear to contribute significantly to the development of immune anergy; targeting of this pathway and/or the cell type involved presents an untapped opportunity for novel therapy in the management of AP(67).

7. Summary

In AP, injured and dying acinar cells release DAMPs and cytokines to attract and recruit innate immune cells, rapidly initiating the inflammatory response (which can develop within an hour). Infiltrating cells augment cytokine signaling to encourage further immune cell recruitment and modulate inflammation. Cytokines and chemokines released in this way (**Table 1**) are responded to by resident hepatic macrophages, which further amplify the signals leading to cytokines being detectable in plasma and resulting in SIRS. Anti-inflammatory cytokines are produced and released in the same timescale as their pro-inflammatory counterparts; however, as long as there is ongoing tissue injury and DAMPs release the balance of cytokines promotes further inflammation. Excessive release of anti-inflammatory cytokines drives immune anergy, which contributes to late mortality by reducing immunity to opportunistic infections.

The overlap and redundancy of cytokine activities and signaling pathways, together with differences in responses depending on local factors, largely accounts for the limited success with which cytokine antagonists have been translated from bench to bedside. Any successful immune-therapy for pancreatitis will likely require detailed cytokine profiling and/or immune phenotyping to establish personalized responses to disease and therapy.

Table 1: Key cytokines and chemokines mediating the inflammatory response of pancreatitis

Signaling Molecule	Source in AP	Receptors and Targets	Function	References
Cytokines				
TNFα	Acinar cells, endothelium, monocytes, Kupffer cells	TNFR1 – widely expressed; TNFR2 – immune and endothelial cells	Pro-inflammatory; regulates apoptosis, mediates trypsin activation in acinar cells	1, 18, 71, 79-92, 140
IL-1β	Pancreas (beta cells, stellate cells), lung, liver, spleen, monocytes	Secreted as pro-enzyme, converted by ICE or neutrophil proteases to active form; acts on IL-1R (widely expressed)	Pro-inflammatory; increases vascular permeability. Soluble IL-1ra inhibits IL-1β activity.	79, 91, 96, 98-106
IL-6	Ubiquitous expression	IL-6R – hepatocytes, neutrophils, macrophages; soluble sIL-6R mediates trans-signaling	Pro-inflammatory; contributes to lung injury in AP; lethal if administered in the context of experimental AP	18, 32, 59, 63-65, 70-76
IL-10	Lymphocytes (B- and T-), monocytes/macrophages, dendritic cells, Kupffer cells	IL-10R – widely expressed	Anti-inflammatory; inhibits pro-inflammatory cytokine release from lymphocytes via STAT3; downregulates MHCII co-stimulatory molecules CD80/CD86, reducing clonal expansion of T-lymphocytes.	16, 113-121, 124-126, 140
Chemokines				
CCL2	Acinar cells; possibly, other cell types in the pancreas	CCR2, CCR4	Pro-inflammatory; monocyte chemoattractant; mediates pancreas and lung injury in experimental AP	2, 18, 35, 38, 45-48, 71, 139
CXCL1/2	Acinar cells, macrophages	CXCR2 – neutrophils and myeloid derived suppressor cells	Pro-inflammatory, strong neutrophil chemoattractants	18, 30-38, 71

8. References

Achyut BR and Yang L. Transforming growth factor-beta in the gastrointestinal and hepatic tumor microenvironment. *Gastroenterology* 141(4): 1167-1178,2011. PMID: 21839702.

Afonina IS, Muller C, Martin SJ and Beyaert R. Proteolytic processing of interleukin-1 family cytokines: variations on a common theme. *Immunity* 42(6): 991-1004,2015. PMID: 26084020.

Aggarwal BB, Gupta SC and Kim JH. Historical perspectives on tumor necrosis factor and its superfamily: 25 years later, a golden journey. *Blood* 119(3): 651-665,2012. PMID: 22053109.

Bacher M, Metz CN, Calandra T, Mayer K, Chesney J, Lohoff M, et al. An essential regulatory role for macrophage migration inhibitory factor in T-cell activation. *Proc Natl Acad Sci U S A* 93(15): 7849-7854,1996. PMID: 8755565.

Badger SA, Jones C, McCaigue M, Clements BW, Parks RW, Diamond T, et al. Cytokine response to portal endotoxaemia and neutrophil stimulation in obstructive jaundice. *Eur J Gastroenterol Hepatol* 24(1): 25-32,2012. PMID: 22027701.

Bernhagen J, Calandra T, Mitchell RA, Martin SB, Tracey KJ, Voelter W, et al. MIF is a pituitary-derived cytokine that potentiates lethal endotoxaemia. *Nature* 365(6448): 756-759,1993. PMID: 8413654.

Bernhagen J, Mitchell RA, Calandra T, Voelter W, Cerami A and Bucala R. Purification, bioactivity, and secondary structure analysis of mouse and human macrophage migration inhibitory factor (MIF). *Biochemistry* 33(47): 14144-14155,1994. PMID: 7947826.

Bhatia M, Brady M, Zagorski J, Christmas SE, Campbell F, Neoptolemos JP, et al. Treatment with neutralising antibody against cytokine induced neutrophil chemoattractant (CINC) protects rats against acute pancreatitis associated lung injury. *Gut* 47(6): 838-844,2000. PMID: 11076884.

Bhatia M and Hegde A. Treatment with antileukinate, a CXCR2 chemokine receptor antagonist, protects mice against acute pancreatitis and associated lung injury. *Regul Pept* 138(1): 40-48,2007. PMID: 17014919.

Bhatia M, Saluja AK, Hofbauer B, Lee HS, Frossard JL and Steer ML. The effects of neutrophil depletion on a completely noninvasive model of acute pancreatitis-associated lung injury. *Int J Pancreatol* 24(2): 77-83,1998. PMID: 9816540.

Blinman TA, Gukovsky I, Mouria M, Zaninovic V, Livingston E, Pandol SJ, et al. Activation of pancreatic acinar cells on isolation from tissue: cytokine upregulation via p38 MAP kinase. *Am J Physiol Cell Physiol* 279(6): C1993-2003,2000. PMID: 11078716.

Bone RC. Sir Isaac Newton, sepsis, SIRS, and CARS. *Crit Care Med* 24(7): 1125-1128,1996. PMID: 8674323.

Brenner D, Blaser H and Mak TW. Regulation of tumour necrosis factor signalling: live or let die. *Nat Rev Immunol* 15(6): 362-374,2015. PMID: 26008591.

Brock P, Sparmann G, Ritter T, Jaster R, Liebe S and Emmrich J. Adenovirus-mediated gene transfer of interleukin-4 into pancreatic stellate cells promotes interleukin-10 expression. *J Cell Mol Med* 10(4): 884-895,2006. PMID: 17125592.

Brock P, Sparmann G, Ritter T, Jaster R, Liebe S and Emmrich J. Interleukin-4 gene transfer into rat pancreas by recombinant adenovirus. *Scand J Gastroenterol* 40(9): 1109-1117,2005. PMID: 16165721.

Chan YC and Leung PS. Involvement of redox-sensitive extracellular-regulated kinases in angiotensin II-induced interleukin-6 expression in pancreatic acinar cells. *J Pharmacol Exp Ther* 329(2): 450-458,2009. PMID: 19211919.

Chao KC, Chao KF, Chuang CC and Liu SH. Blockade of interleukin 6 accelerates acinar cell apoptosis and attenuates experimental acute pancreatitis in vivo. *Br J Surg* 93(3): 332-338,2006. PMID: 16392107.

Chen GY and Nunez G. Sterile inflammation: sensing and reacting to damage. *Nat Rev Immunol* 10(12): 826-837,2010. PMID: 21088683.

Chen KL, Lv ZY, Yang HW, Liu Y, Long FW, Zhou B, et al. Effects of Tocilizumab on experimental severe acute pancreatitis and associated acute lung injury. *Crit Care Med* 44(8): e664-677,2016. PMID: 26963319.

Demols A, Van Laethem JL, Quertinmont E, Degraef C, Delhaye M, Geerts A, et al. Endogenous interleukin-10 modulates fibrosis and regeneration in experimental chronic pancreatitis. *Am J Physiol Gastrointest Liver Physiol* 282(6): G1105-1112,2002. PMID: 12016137.

Denham W, Yang J, Fink G, Denham D, Carter G, Ward K, et al. Gene targeting demonstrates additive detrimental effects of interleukin 1 and tumor necrosis factor during pancreatitis. *Gastroenterology* 113(5): 1741-1746,1997. PMID: 9352880.

Devitt A and Marshall LJ. The innate immune system and the clearance of apoptotic cells. *J Leukoc Biol* 90(3): 447-457,2011. PMID: 21562053.
Fakhari S, Abdolmohammadi K, Panahi Y, Nikkhoo B, Peirmohammadi H, Rahmani MR, et al. Glycyrrhizin attenuates tissue injury and reduces neutrophil accumulation in experimental acute pancreatitis. *Int J Clin Exp Pathol* 7(1): 101-109,2014. PMID: 24427330.
Fink GW and Norman JG. Specific changes in the pancreatic expression of the interleukin 1 family of genes during experimental acute pancreatitis. *Cytokine* 9(12): 1023-1027,1997. PMID: 9417814.
Folch E, Closa D, Prats N, Gelpi E and Rosello-Catafau J. Leukotriene generation and neutrophil infiltration after experimental acute pancreatitis. *Inflammation* 22(1): 83-93,1998. PMID: 9484652.
Frossard JL, Lenglet S, Montecucco F, Steffens S, Galan K, Pelli G, et al. Role of CCL-2, CCR-2 and CCR-4 in cerulein-induced acute pancreatitis and pancreatitis-associated lung injury. *J Clin Pathol* 64(5): 387-393,2011. PMID: 21345872.
Frossard JL, Saluja A, Bhagat L, Lee HS, Bhatia M, Hofbauer B, et al. The role of intercellular adhesion molecule 1 and neutrophils in acute pancreatitis and pancreatitis-associated lung injury. *Gastroenterology* 116(3): 694-701,1999. PMID: 10029629.
Garbers C and Scheller J. Interleukin-6 and interleukin-11: same same but different. *Biol Chem* 394(9): 1145-1161,2013. PMID: 23740659.
Gloor B, Blinman TA, Rigberg DA, Todd KE, Lane JS, Hines OJ, et al. Kupffer cell blockade reduces hepatic and systemic cytokine levels and lung injury in hemorrhagic pancreatitis in rats. *Pancreas* 21(4): 414-420,2000. PMID: 11075997.
Gloor B, Todd KE, Lane JS, Lewis MP and Reber HA. Hepatic Kupffer cell blockade reduces mortality of acute hemorrhagic pancreatitis in mice. *J Gastrointest Surg* 2(5): 430-435,1998. PMID: 9843602.
Gotoh K, Inoue M, Shiraishi K, Masaki T, Chiba S, Mitsutomi K, et al. Spleen-derived interleukin-10 downregulates the severity of high-fat diet-induced non-alcoholic fatty pancreas disease. *PLoS One* 7(12): e53154,2012. PMID: 23285260.
Grady T, Liang P, Ernst SA and Logsdon CD. Chemokine gene expression in rat pancreatic acinar cells is an early event associated with acute pancreatitis. *Gastroenterology* 113(6): 1966-1975,1997. PMID: 9394737.
Granell S, Pereda J, Gomez-Cambronero L, Cassinello N, Sabater L, Closa D, et al. Circulating TNF-alpha and its soluble receptors during experimental acute pancreatitis. *Cytokine* 25(4): 187-191,2004. PMID: 15164724.
Grell M, Douni E, Wajant H, Lohden M, Clauss M, Maxeiner B, et al. The transmembrane form of tumor necrosis factor is the prime activating ligand of the 80 kDa tumor necrosis factor receptor. *Cell* 83(5): 793-802,1995. PMID: 8521496.
Gross V, Andreesen R, Leser HG, Ceska M, Liehl E, Lausen M, et al. Interleukin-8 and neutrophil activation in acute pancreatitis. *Eur J Clin Invest* 22(3): 200-203,1992. PMID: 1582445.
Gukovskaya AS, Gukovsky I, Zaninovic V, Song M, Sandoval D, Gukovsky S, et al. Pancreatic acinar cells produce, release, and respond to tumor necrosis factor-alpha. Role in regulating cell death and pancreatitis. *J Clin Invest* 100(7): 1853-1862,1997. PMID: 9312187.
Gukovskaya AS, Vaquero E, Zaninovic V, Gorelick FS, Lusis AJ, Brennan ML, et al. Neutrophils and NADPH oxidase mediate intrapancreatic trypsin activation in murine experimental acute pancreatitis. *Gastroenterology* 122(4): 974-984,2002. PMID: 11910350.
Gukovsky I, Gukovskaya AS, Blinman TA, Zaninovic V and Pandol SJ. Early NF-kappaB activation is associated with hormone-induced pancreatitis. *Am J Physiol* 275(6 Pt 1): G1402-1414,1998. PMID: 9843778.
Gukovsky I, Li N, Todoric J, Gukovskaya A and Karin M. Inflammation, autophagy, and obesity: common features in the pathogenesis of pancreatitis and pancreatic cancer. *Gastroenterology* 144(6): 1199-1209 e1194,2013. PMID: 23622129.
Gunjaca I, Zunic J, Gunjaca M and Kovac Z. Circulating cytokine levels in acute pancreatitis-model of SIRS/CARS can help in the clinical assessment of disease severity. *Inflammation* 35(2): 758-763,2012. PMID: 21826480.
Habtezion A. Inflammation in acute and chronic pancreatitis. *Curr Opin Gastroenterol* 31(5): 395-399,2015. PMID: 26107390.
Ho YP, Chiu CT, Sheen IS, Tseng SC, Lai PC, Ho SY, et al. Tumor necrosis factor-alpha and interleukin-10 contribute to immunoparalysis in patients with acute pancreatitis. *Hum Immunol* 72(1): 18-23,2011. PMID: 20937337.

Hoque R, Malik AF, Gorelick F and Mehal WZ. Sterile inflammatory response in acute pancreatitis. *Pancreas* 41(3): 353-357,2012. PMID: 22415665.
Hori Y, Takeyama Y, Ueda T, Shinkai M, Takase K and Kuroda Y. Macrophage-derived transforming growth factor-beta1 induces hepatocellular injury via apoptosis in rat severe acute pancreatitis. *Surgery* 127(6): 641-649,2000. PMID: 10840359.
Huang L, Ma J, Tang Y, Chen P, Zhang S, Zhang Y, et al. siRNA-based targeting of fractalkine overexpression suppresses inflammation development in a severe acute pancreatitis rat model. *Int J Mol Med* 30(3): 514-520,2012. PMID: 22751862.
Huang LY, Chen P, Xu LX, Zhou YF, Li WG and Yuan YZ. Fractalkine as a marker for assessment of severe acute pancreatitis. *J Dig Dis* 13(4): 225-231,2012. PMID: 22435508.
Huang LY, Chen P, Xu LX, Zhou YF, Zhang YP and Yuan YZ. Fractalkine upregulates inflammation through CX3CR1 and the Jak-Stat pathway in severe acute pancreatitis rat model. *Inflammation* 35(3): 1023-1030,2012. PMID: 22213034.
Huang W, Cane MC, Mukherjee R, Szatmary P, Zhang X, Elliott V, et al. Caffeine protects against experimental acute pancreatitis by inhibition of inositol 1,4,5-trisphosphate receptor-mediated Ca2+ release. *Gut*,2015. PMID: 26642860.
Huang W, Cash N, Wen L, Szatmary P, Mukherjee R, Armstrong J, et al. Effects of the mitochondria-targeted antioxidant mitoquinone in murine acute pancreatitis. *Mediators Inflamm* 2015: 901780,2015. PMID: 25878403.
Huang YX, Li WD, Jia L, Qiu JH, Jiang SM, Ou Y, et al. Infliximab enhances the therapeutic effectiveness of octreotide on acute necrotizing pancreatitis in rat model. *Pancreas* 41(6): 849-854,2012. PMID: 22450369.
Hutchins AP, Diez D and Miranda-Saavedra D. The IL-10/STAT3-mediated anti-inflammatory response: recent developments and future challenges. *Brief Funct Genomics* 12(6): 489-498,2013. PMID: 23943603.
Imamura M, Mikami Y, Takahashi H and Yamauchi H. Effect of a specific synthetic inhibitor of neutrophil elastase (ONO-5046) on the course of acute hemorrhagic pancreatitis in dogs. *J Hepatobiliary Pancreat Surg* 5(4): 422-428,1998. PMID: 9931392.
Inoue S, Nakao A, Kishimoto W, Murakami H, Itoh K, Itoh T, et al. Anti-neutrophil antibody attenuates the severity of acute lung injury in rats with experimental acute pancreatitis. *Arch Surg* 130(1): 93-98,1995. PMID: 7802585.
Ishibashi T, Zhao H, Kawabe K, Oono T, Egashira K, Suzuki K, et al. Blocking of monocyte chemoattractant protein-1 (MCP-1) activity attenuates the severity of acute pancreatitis in rats. *J Gastroenterol* 43(1): 79-85,2008. PMID: 18297440.
Issuree PD, Maretzky T, McIlwain DR, Monette S, Qing X, Lang PA, et al. iRHOM2 is a critical pathogenic mediator of inflammatory arthritis. *J Clin Invest* 123(2): 928-932,2013. PMID: 23348744.
Jiang CY, Wang W, Tang JX and Yuan ZR. The adipocytokine resistin stimulates the production of proinflammatory cytokines TNF-alpha and IL-6 in pancreatic acinar cells via NF-kappaB activation. *J Endocrinol Invest* 36(11): 986-992,2013. PMID: 23765438.
Kahlenberg JM. Anti-inflammatory panacea? The expanding therapeutics of interleukin-1 blockade. *Curr Opin Rheumatol* 28(3): 197-203,2016. PMID: 26859478.
Kalliolias GD and Ivashkiv LB. TNF biology, pathogenic mechanisms and emerging therapeutic strategies. *Nat Rev Rheumatol* 12(1): 49-62,2016. PMID: 26656660.
Kang M, Park KS, Seo JY and Kim H. Lycopene inhibits IL-6 expression in cerulein-stimulated pancreatic acinar cells. *Genes Nutr* 6(2): 117-123,2011. PMID: 21484151.
Kang R, Lotze MT, Zeh HJ, Billiar TR and Tang D. Cell death and DAMPs in acute pancreatitis. *Mol Med* 20: 466-477,2014. PMID: 25105302.
Kaplan M, Yazgan Y, Tanoglu A, Berber U, Oncu K, Kara M, et al. Effectiveness of interleukin-1 receptor antagonist (Anakinra) on cerulein-induced experimental acute pancreatitis in rats. *Scand J Gastroenterol* 49(9): 1124-1130,2014. PMID: 24912987.
Katz LH, Likhter M, Jogunoori W, Belkin M, Ohshiro K and Mishra L. TGF-beta signaling in liver and gastrointestinal cancers. *Cancer Lett*,2016. PMID: 27039259.
Kempuraj D, Twait EC, Williard DE, Yuan Z, Meyerholz DK and Samuel I. The novel cytokine interleukin-33 activates acinar cell proinflammatory pathways and induces acute pancreatic inflammation in mice. *PLoS One* 8(2): e56866,2013. PMID: 23418608.

Kihara Y, Tashiro M, Nakamura H, Yamaguchi T, Yoshikawa H and Otsuki M. Role of TGF-beta1, extracellular matrix, and matrix metalloproteinase in the healing process of the pancreas after induction of acute necrotizing pancreatitis using arginine in rats. *Pancreas* 23(3): 288-295,2001. PMID: 11590325.
King AG, Johanson K, Frey CL, DeMarsh PL, White JR, McDevitt P, et al. Identification of unique truncated KC/GRO beta chemokines with potent hematopoietic and anti-infective activities. *J Immunol* 164(7): 3774-3782,2000. PMID: 10725737.
Kobayashi M, Kobayashi H, Herndon DN, Pollard RB and Suzuki F. Burn-associated Candida albicans infection caused by CD30+ type 2 T cells. *J Leukoc Biol* 63(6): 723-731,1998. PMID: 9620665.
Koike Y, Kanai T, Saeki K, Nakamura Y, Nakano M, Mikami Y, et al. MyD88-dependent interleukin-10 production from regulatory CD11b(+)Gr-1(high) cells suppresses development of acute cerulein pancreatitis in mice. *Immunol Lett* 148(2): 172-177,2012. PMID: 23022387.
Konturek PC, Dembinski A, Warzecha Z, Ceranowicz P, Konturek SJ, Stachura J, et al. Expression of transforming growth factor-beta 1 and epidermal growth factor in caerulein-induced pancreatitis in rat. *J Physiol Pharmacol* 48(1): 59-72,1997. PMID: 9098826.
Li WD, Jia L, Ou Y, Jiang SM, Qiu JH, Huang YX, et al. Infliximab: protective effect to intestinal barrier function of rat with acute necrosis pancreatitis at early stage. *Pancreas* 42(2): 366-367,2013. PMID: 23407490.
Lundberg AH, Eubanks JW, 3rd, Henry J, Sabek O, Kotb M, Gaber L, et al. Trypsin stimulates production of cytokines from peritoneal macrophages in vitro and in vivo. *Pancreas* 21(1): 41-51,2000. PMID: 10881931.
Lundberg AH, Granger N, Russell J, Callicutt S, Gaber LW, Kotb M, et al. Temporal correlation of tumor necrosis factor-alpha release, upregulation of pulmonary ICAM-1 and VCAM-1, neutrophil sequestration, and lung injury in diet-induced pancreatitis. *J Gastrointest Surg* 4(3): 248-257,2000. PMID: 10769087.
Luo S, Wang R, Jiang W, Lin X, Qiu P and Yan G. A novel recombinant snake venom metalloproteinase from Agkistrodon acutus protects against taurocholate-induced severe acute pancreatitis in rats. *Biochimie* 92(10): 1354-1361,2010. PMID: 20600562.
Malla SR, Karrman Mardh C, Gunther A, Mahajan UM, Sendler M, D'Haese J, et al. Effect of oral administration of AZD8309, a CXCR2 antagonist, on the severity of experimental pancreatitis. *Pancreatology*,2016. PMID: 27450968.
Mayerle J, Dummer A, Sendler M, Malla SR, van den Brandt C, Teller S, et al. Differential roles of inflammatory cells in pancreatitis. *J Gastroenterol Hepatol* 27 Suppl 2: 47-51,2012. PMID: 22320916.
Menke A, Yamaguchi H, Gress TM and Adler G. Extracellular matrix is reduced by inhibition of transforming growth factor beta1 in pancreatitis in the rat. *Gastroenterology* 113(1): 295-303,1997. PMID: 9207290.
Merza M, Hartman H, Rahman M, Hwaiz R, Zhang E, Renstrom E, et al. Neutrophil extracellular traps induce trypsin activation, inflammation, and tissue damage in mice with severe acute pancreatitis. *Gastroenterology* 149(7): 1920-1931 e1928,2015. PMID: 26302488.
Montecucco F, Mach F, Lenglet S, Vonlaufen A, Gomes Quindere AL, Pelli G, et al. Treatment with Evasin-3 abrogates neutrophil-mediated inflammation in mouse acute pancreatitis. *Eur J Clin Invest* 44(10): 940-950,2014. PMID: 25132144.
Murakami H, Nakao A, Kishimoto W, Nakano M and Takagi H. Detection of O2- generation and neutrophil accumulation in rat lungs after acute necrotizing pancreatitis. *Surgery* 118(3): 547-554,1995. PMID: 7652692.
Nagashio Y, Ueno H, Imamura M, Asaumi H, Watanabe S, Yamaguchi T, et al. Inhibition of transforming growth factor beta decreases pancreatic fibrosis and protects the pancreas against chronic injury in mice. *Lab Invest* 84(12): 1610-1618,2004. PMID: 15502860.
Nakamura Y, Kanai T, Saeki K, Takabe M, Irie J, Miyoshi J, et al. CCR2 knockout exacerbates cerulein-induced chronic pancreatitis with hyperglycemia via decreased GLP-1 receptor expression and insulin secretion. *Am J Physiol Gastrointest Liver Physiol* 304(8): G700-707,2013. PMID: 23449669.
Noel P, Patel K, Durgampudi C, Trivedi RN, de Oliveira C, Crowell MD, et al. Peripancreatic fat necrosis worsens acute pancreatitis independent of pancreatic necrosis via unsaturated fatty acids increased in human pancreatic necrosis collections. *Gut* 65(1): 100-111,2016. PMID: 25500204.
Norman J. The role of cytokines in the pathogenesis of acute pancreatitis. *Am J Surg* 175(1): 76-83,1998. PMID: 9445247.
Norman JG, Fink GW, Denham W, Yang J, Carter G, Sexton C, et al. Tissue-specific cytokine production during experimental acute pancreatitis. A probable mechanism for distant organ dysfunction. *Dig Dis Sci* 42(8): 1783-1788,1997. PMID: 9286248.

Norman JG, Fink GW and Franz MG. Acute pancreatitis induces intrapancreatic tumor necrosis factor gene expression. *Arch Surg* 130(9): 966-970,1995. PMID: 7661681.
Oiva J, Mustonen H, Kylanpaa ML, Kuuliala K, Siitonen S, Kemppainen E, et al. Patients with acute pancreatitis complicated by organ dysfunction show abnormal peripheral blood polymorphonuclear leukocyte signaling. *Pancreatology* 13(2): 118-124,2013. PMID: 23561969.
Oiva J, Mustonen H, Kylanpaa ML, Kyhala L, Alanara T, Aittomaki S, et al. Patients with acute pancreatitis complicated by organ failure show highly aberrant monocyte signaling profiles assessed by phospho-specific flow cytometry. *Crit Care Med* 38(8): 1702-1708,2010. PMID: 20512034.
Orlichenko LS, Behari J, Yeh TH, Liu S, Stolz DB, Saluja AK, et al. Transcriptional regulation of CXC-ELR chemokines KC and MIP-2 in mouse pancreatic acini. *Am J Physiol Gastrointest Liver Physiol* 299(4): G867-876,2010. PMID: 20671197.
Ou X, Cheng Z, Liu T, Tang Z, Huang W, Szatmary P, et al. Circulating histone levels reflect disease severity in animal models of acute pancreatitis. *Pancreas* 44(7): 1089-1095,2015. PMID: 26335015.
Palomares O, Martin-Fontecha M, Lauener R, Traidl-Hoffmann C, Cavkaytar O, Akdis M, et al. Regulatory T cells and immune regulation of allergic diseases: roles of IL-10 and TGF-beta. *Genes Immun* 15(8): 511-520,2014. PMID: 25056447.
Panahi Y, Fakhari S, Mohammadi M, Rahmani MR, Hakhamaneshi MS and Jalili A. Glycyrrhizin down-regulates CCL2 and CXCL2 expression in cerulein-stimulated pancreatic acinar cells. *Am J Clin Exp Immunol* 4(1): 1-6,2015. PMID: 26155433.
Pastor CM, Rubbia-Brandt L, Hadengue A, Jordan M, Morel P and Frossard JL. Role of macrophage inflammatory peptide-2 in cerulein-induced acute pancreatitis and pancreatitis-associated lung injury. *Laboratory Investigation* 83(4): 471-478,2003. PMID.
Pastor CM, Vonlaufen A, Georgi F, Hadengue A, Morel P and Frossard JL. Neutrophil depletion--but not prevention of Kupffer cell activation--decreases the severity of cerulein-induced acute pancreatitis. *World J Gastroenterol* 12(8): 1219-1224,2006. PMID: 16534874.
Paszkowski AS, Rau B, Mayer JM, Moller P and Beger HG. Therapeutic application of caspase 1/interleukin-1beta-converting enzyme inhibitor decreases the death rate in severe acute experimental pancreatitis. *Ann Surg* 235(1): 68-76,2002. PMID: 11753044.
Patel SJ, Jindal R, King KR, Tilles AW and Yarmush ML. The inflammatory response to double stranded DNA in endothelial cells is mediated by NFkappaB and TNFalpha. *PLoS One* 6(5): e19910,2011. PMID: 21611132.
Pini M, Rhodes DH, Castellanos KJ, Hall AR, Cabay RJ, Chennuri R, et al. Role of IL-6 in the resolution of pancreatitis in obese mice. *J Leukoc Biol* 91(6): 957-966,2012. PMID: 22427681.
Porteu F and Hieblot C. Tumor necrosis factor induces a selective shedding of its p75 receptor from human neutrophils. *J Biol Chem* 269(4): 2834-2840,1994. PMID: 8300617.
Purwanti N, Azlina A, Karabasil MR, Hasegawa T, Yao C, Akamatsu T, et al. Involvement of the IL-6/STAT3/Sca-1 system in proliferation of duct cells following duct ligation in the submandibular gland of mice. *J Med Invest* 56 Suppl: 253-254,2009. PMID: 20224192.
Qiu Z, Yu P, Bai B, Hao Y, Wang S, Zhao Z, et al. Regulatory B10 cells play a protective role in severe acute pancreatitis. *Inflamm Res*,2016. PMID: 27085321.
Rabe B, Chalaris A, May U, Waetzig GH, Seegert D, Williams AS, et al. Transgenic blockade of interleukin 6 transsignaling abrogates inflammation. *Blood* 111(3): 1021-1028,2008. PMID: 17989316.
Ramudo L, Manso MA, Sevillano S and de Dios I. Kinetic study of TNF-alpha production and its regulatory mechanisms in acinar cells during acute pancreatitis induced by bile-pancreatic duct obstruction. *J Pathol* 206(1): 9-16,2005. PMID: 15761843.
Ramudo L, Manso MA, Vicente S and De Dios I. Pro- and anti-inflammatory response of acinar cells during acute pancreatitis. Effect of N-acetyl cysteine. *Cytokine* 32(3-4): 125-131,2005. PMID: 16263306.
Repnik U, Starr AE, Overall CM and Turk B. Cysteine cathepsins activate ELR chemokines and inactivate non-ELR chemokines. *J Biol Chem* 290(22): 13800-13811,2015. PMID: 25833952.
Riesle E, Friess H, Zhao L, Wagner M, Uhl W, Baczako K, et al. Increased expression of transforming growth factor beta s after acute oedematous pancreatitis in rats suggests a role in pancreatic repair. *Gut* 40(1): 73-79,1997. PMID: 9155579.
Romac JM, Shahid RA, Choi SS, Karaca GF, Westphalen CB, Wang TC, et al. Pancreatic secretory trypsin inhibitor I reduces the severity of chronic pancreatitis in mice overexpressing interleukin-1beta in the pancreas. *Am J Physiol Gastrointest Liver Physiol* 302(5): G535-541,2012. PMID: 22173919.

Rongione AJ, Kusske AM, Kwan K, Ashley SW, Reber HA and McFadden DW. Interleukin 10 reduces the severity of acute pancreatitis in rats. *Gastroenterology* 112(3): 960-967,1997. PMID: 9041259.
Rose-John S and Heinrich PC. Soluble receptors for cytokines and growth factors: generation and biological function. *Biochem J* 300 (Pt 2): 281-290,1994. PMID: 8002928.
Sakai Y, Masamune A, Satoh A, Nishihira J, Yamagiwa T and Shimosegawa T. Macrophage migration inhibitory factor is a critical mediator of severe acute pancreatitis. *Gastroenterology* 124(3): 725-736,2003. PMID: 12612911.
Sandoval D, Gukovskaya A, Reavey P, Gukovsky S, Sisk A, Braquet P, et al. The role of neutrophils and platelet-activating factor in mediating experimental pancreatitis. *Gastroenterology* 111(4): 1081-1091,1996. PMID: 8831604.
Scheller J, Garbers C and Rose-John S. Interleukin-6: from basic biology to selective blockade of pro-inflammatory activities. *Semin Immunol* 26(1): 2-12,2014. PMID: 24325804.
Schmidt AI, Seifert GJ, Lauch R, Wolff-Vorbeck G, Chikhladze S, Hopt UT, et al. Organ-specific monocyte activation in necrotizing pancreatitis in mice. *J Surg Res* 197(2): 374-381,2015. PMID: 25982373.
Schneider L, Jabrailova B, Strobel O, Hackert T and Werner J. Inflammatory profiling of early experimental necrotizing pancreatitis. *Life Sci* 126: 76-80,2015. PMID: 25711429.
Sendler M, Dummer A, Weiss FU, Kruger B, Wartmann T, Scharffetter-Kochanek K, et al. Tumour necrosis factor alpha secretion induces protease activation and acinar cell necrosis in acute experimental pancreatitis in mice. *Gut* 62(3): 430-439,2013. PMID: 22490516.
Shanmugam MK and Bhatia M. The role of pro-inflammatory molecules and pharmacological agents in acute pancreatitis and sepsis. *Inflamm Allergy Drug Targets* 9(1): 20-31,2010. PMID: 19663805.
Shen J, Gao J, Zhang J, Xiang D, Wang X, Qian L, et al. Recombinant human interleukin-1 receptor antagonist (rhIL-1Ra) attenuates caerulein-induced chronic pancreatitis in mice. *Biomed Pharmacother* 66(2): 83-88,2012. PMID: 22281291.
Shouval DS, Ouahed J, Biswas A, Goettel JA, Horwitz BH, Klein C, et al. Interleukin 10 receptor signaling: master regulator of intestinal mucosal homeostasis in mice and humans. *Adv Immunol* 122: 177-210,2014. PMID: 24507158.
Staubli SM, Oertli D and Nebiker CA. Laboratory markers predicting severity of acute pancreatitis. *Crit Rev Clin Lab Sci* 52(6): 273-283,2015. PMID: 26173077.
Steele CW, Karim SA, Foth M, Rishi L, Leach JD, Porter RJ, et al. CXCR2 inhibition suppresses acute and chronic pancreatic inflammation. *J Pathol* 237(1): 85-97,2015. PMID: 25950520.
Takahashi H, Tsuda Y, Kobayashi M, Herndon DN and Suzuki F. CCL2 as a trigger of manifestations of compensatory anti-inflammatory response syndrome in mice with severe systemic inflammatory response syndrome. *J Leukoc Biol* 79(4): 789-796,2006. PMID: 16434696.
Tietz AB, Malo A, Diebold J, Kotlyarov A, Herbst A, Kolligs FT, et al. Gene deletion of MK2 inhibits TNF-alpha and IL-6 and protects against cerulein-induced pancreatitis. *Am J Physiol Gastrointest Liver Physiol* 290(6): G1298-1306,2006. PMID: 16423921.
Uchida M, Ito T, Nakamura T, Hijioka M, Igarashi H, Oono T, et al. Pancreatic stellate cells and CX3CR1: occurrence in normal pancreas and acute and chronic pancreatitis and effect of their activation by a CX3CR1 agonist. *Pancreas* 43(5): 708-719,2014. PMID: 24681877.
Umehara H, Bloom ET, Okazaki T, Nagano Y, Yoshie O and Imai T. Fractalkine in vascular biology: from basic research to clinical disease. *Arterioscler Thromb Vasc Biol* 24(1): 34-40,2004. PMID: 12969992.
Vaccaro MI, Ropolo A, Grasso D, Calvo EL, Ferreria M, Iovanna JL, et al. Pancreatic acinar cells submitted to stress activate TNF-alpha gene expression. *Biochem Biophys Res Commun* 268(2): 485-490,2000. PMID: 10679231.
Van Laethem JL, Robberecht P, Resibois A and Deviere J. Transforming growth factor beta promotes development of fibrosis after repeated courses of acute pancreatitis in mice. *Gastroenterology* 110(2): 576-582,1996. PMID: 8566606.
Vaquero E, Gukovsky I, Zaninovic V, Gukovskaya AS and Pandol SJ. Localized pancreatic NF-kappaB activation and inflammatory response in taurocholate-induced pancreatitis. *Am J Physiol Gastrointest Liver Physiol* 280(6): G1197-1208,2001. PMID: 11352813.
Veenstra M and Ransohoff RM. Chemokine receptor CXCR2: physiology regulator and neuroinflammation controller? *J Neuroimmunol* 246(1-2): 1-9,2012. PMID: 22445294.

Venkatesh D, Ernandez T, Rosetti F, Batal I, Cullere X, Luscinskas FW, et al. Endothelial TNF receptor 2 induces IRF1 transcription factor-dependent interferon-beta autocrine signaling to promote monocyte recruitment. *Immunity* 38(5): 1025-1037,2013. PMID: 23623383.
Wang HH, Tang AM, Chen L and Zhou MT. Potential of sivelestat in protection against severe acute pancreatitis-associated lung injury in rats. *Exp Lung Res* 38(9-10): 445-452,2012. PMID: 23005337.
Warzecha Z, Dembinski A, Ceranowicz P, Konturek SJ, Tomaszewska R, Stachura J, et al. IGF-1 stimulates production of interleukin-10 and inhibits development of caerulein-induced pancreatitis. *J Physiol Pharmacol* 54(4): 575-590,2003. PMID: 14726612.
Wildi S, Kleeff J, Mayerle J, Zimmermann A, Bottinger EP, Wakefield L, et al. Suppression of transforming growth factor beta signalling aborts caerulein induced pancreatitis and eliminates restricted stimulation at high caerulein concentrations. *Gut* 56(5): 685-692,2007. PMID: 17135311.
Wuyts A, Govaerts C, Struyf S, Lenaerts JP, Put W, Conings R, et al. Isolation of the CXC chemokines ENA-78, GRO alpha and GRO gamma from tumor cells and leukocytes reveals NH2-terminal heterogeneity. Functional comparison of different natural isoforms. *Eur J Biochem* 260(2): 421-429,1999. PMID: 10095777.
Xu C, Shen J, Zhang J, Jia Z, He Z, Zhuang X, et al. Recombinant interleukin-1 receptor antagonist attenuates the severity of chronic pancreatitis induced by TNBS in rats. *Biochem Pharmacol* 93(4): 449-460,2015. PMID: 25559498.
Xu L, Yang F, Lin R, Han C, Liu J and Ding Z. Induction of m2 polarization in primary culture liver macrophages from rats with acute pancreatitis. *PLoS One* 9(9): e108014,2014. PMID: 25259888.
Xue J, Sharma V and Habtezion A. Immune cells and immune-based therapy in pancreatitis. *Immunol Res* 58(2-3): 378-386,2014. PMID: 24710635.
Yu G, Wan R, Hu Y, Ni J, Yin G, Xing M, et al. Pancreatic acinar cells-derived cyclophilin A promotes pancreatic damage by activating NF-kappaB pathway in experimental pancreatitis. *Biochem Biophys Res Commun* 444(1): 75-80,2014. PMID: 24434144.
Yu JH, Kim KH and Kim H. SOCS 3 and PPAR-gamma ligands inhibit the expression of IL-6 and TGF-beta1 by regulating JAK2/STAT3 signaling in pancreas. *Int J Biochem Cell Biol* 40(4): 677-688,2008. PMID: 18035585.
Zaninovic V, Gukovskaya AS, Gukovsky I, Mouria M and Pandol SJ. Cerulein upregulates ICAM-1 in pancreatic acinar cells, which mediates neutrophil adhesion to these cells. *Am J Physiol Gastrointest Liver Physiol* 279(4): G666-676,2000. PMID: 11005752.
Zhang H, Neuhofer P, Song L, Rabe B, Lesina M, Kurkowski MU, et al. IL-6 trans-signaling promotes pancreatitis-associated lung injury and lethality. *J Clin Invest* 123(3): 1019-1031,2013. PMID: 23426178.
Zhang J, Patel L and Pienta KJ. Targeting chemokine (C-C motif) ligand 2 (CCL2) as an example of translation of cancer molecular biology to the clinic. *Prog Mol Biol Transl Sci* 95: 31-53,2010. PMID: 21075328.
Zhang X, Zheng H, Zhu HY, Hu S, Wang S, Jiang X, et al. Acute effects of transforming growth factor-beta1 on neuronal excitability and involvement in the pain of rats with chronic pancreatitis. *J Neurogastroenterol Motil* 22(2): 333-343,2016. PMID: 26645248.
Zhang XH, Li ML, Wang B, Guo MX and Zhu RM. Caspase-1 inhibition alleviates acute renal injury in rats with severe acute pancreatitis. *World J Gastroenterol* 20(30): 10457-10463,2014. PMID: 25132762.
Zhang XH, Zhu RM, Xu WA, Wan HJ and Lu H. Therapeutic effects of caspase-1 inhibitors on acute lung injury in experimental severe acute pancreatitis. *World J Gastroenterol* 13(4): 623-627,2007. PMID: 17278232.
Zhou GX, Zhu XJ, Ding XL, Zhang H, Chen JP, Qiang H, et al. Protective effects of MCP-1 inhibitor on a rat model of severe acute pancreatitis. *Hepatobiliary Pancreat Dis Int* 9(2): 201-207,2010. PMID: 20382594.
Zlotnik A and Yoshie O. The chemokine superfamily revisited. *Immunity* 36(5): 705-716,2012. PMID: 22633458.