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Cytokine storm in acute pancreatitis

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Abstract Efforts to unravel the events in the evolution of tissue damage in acute pancreatitis have shown a number of inflammatory mediators to be involved. The pathways of damage are similar, whatever the etiology of pancreatitis, with three phases of progression: local acinar injury, systemic response, and generalized sepsis. The proinflammatory response is countered by an anti-inflammatory response, and an imbalance between these two systems leads to localized tissue destruction and distant organ damage. Cytokines lie at the heart of the problem and are involved in all aspects of the cascade leading to systemic inflammatory response syndrome and multiple organ dysfunction syndrome. This review discusses the present knowledge about the role of various mediators in this process, their genetic control, and the effects of their modulation. The major proinflammatory mediators are tumor necrosis factor, interleukins 1, 6, and 8, platelet activation factor, and the chemokines. The major anti-inflammatory factors include interleukin 10, and interleukin 1 receptor antagonist. Emerging knowledge of new mediators as well as future strategy of damage control is discussed.

Key words Acute pancreatitis · Cytokine · Macrophage · Interleukin-l · Tumor necrosis factor

Introduction

Acute pancreatitis (AP) is a commonly encountered intra-abdominal catastrophe and is a world-wide problem. At the present time, no specific therapy has been shown to be uniformly effective in reducing the mortality, or indeed, the morbidity resulting from it. The current principles of treatment of AP remain the same as in the previous century, using supportive therapy. The constituents of supportive therapy have undergone a number of refinements; however, as yet, there is no treatment that can downregulate the powerful inflammatory processes.

The epidemiological data reveal the incidence of AP to vary from 48 to 238 cases per million population.[1] Of these cases, severe AP accounts for about 10%–25%[2,3] with the overall mortality from AP remaining at about 9%–20% over the past few decades.[1,4,5] Of the patients who die, 60% do so within the first 6 days following admission, and the major cause of death, among them, is pulmonary complications such as adult respiratory distress syndrome (ARDS).[1] The majority of deaths after the first week are from infectious causes such as infected pancreatic necrosis and septicemia.[5] The two common causes of AP are gallstones, accounting for 40%–50% of cases, and ethanol, which accounts for around 20%–30% of cases.[6] About 10% of cases have a diverse etiology, such as hyperlipidemia, viral infection, drugs, hypercalcemia, and ductal obstruction.[7]

After the initial injury to the pancreatic acinar cell, whatever the triggering factor, events take a similar path for all patients with AP. The disease progression can be viewed as a three-phase continuum: local inflammation of the pancreas, a generalized inflammatory response, and the final stage of sepsis, with multiple organ damage. The disease process can extend to any of the three phases, and is often resolved after the local inflammatory process, resulting in mild AP. After the initial pancreatic acinar cell injury, inflammatory cells adhere to the endothelium due to the expression of various adhesion molecules, such as vascular cellular adhesion molecule-1 (VCAM-1) and P- and E-selectins, etc. This propagates an exponentially increasing response which occasionally spirals out of control to give rise to severe AP and terminates in death.

Key cells involved in elaborating the inflammatory mediators are the pancreatic acinar cells, the endothelial cells, neutrophils, lymphocytes, and the macrophages/monocytes. A variety of inflammatory mediators of different chemical and functional classes

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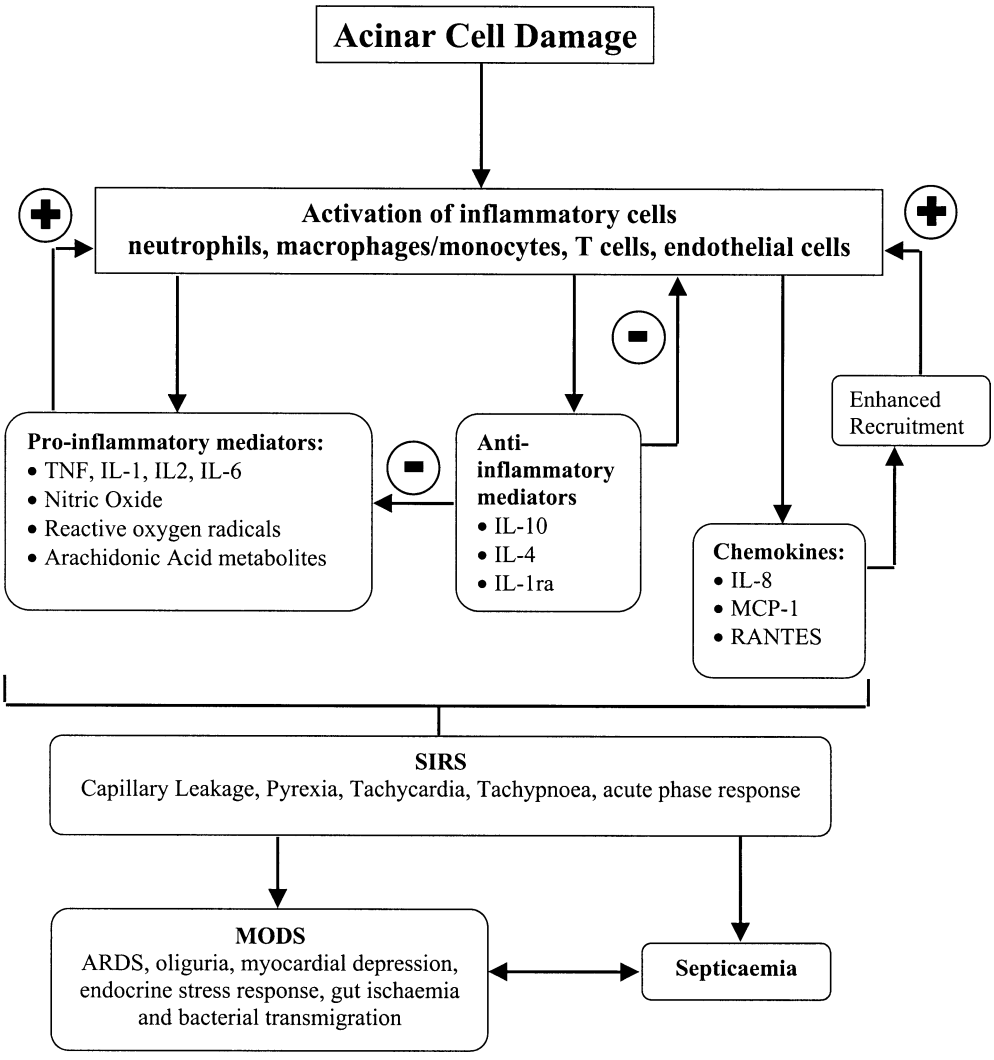

Fig. 1. An overview of the development of the inflammatory cascade after induction of acute pancreatitis. Activation of the various inflammatory cells leads to elaboration of various pro- and anti-inflammatory mediators and chemokines. An imbalance in this pathway leads to widespread tissue damage and mortality via multiple organ dysfunction syndrome (*MODS*) and septicaemia. *IL-1*, Interleukin-1; *TNF*, tumor necrosis factor; *IL-1ra*, interleukin-1 receptor antagonist; *MCP-1*, monocyte chemoattractant protein-1; *RANTES*, regulated on activation, normal T cell expressed and secreted; *SIRS*, systemic inflammatory response syndrome; *ARDS*, adult respiratory distress syndrome

are elaborated in the inflammatory process, such as arachidonic acid metabolites, nitric oxide, cytokines, and reactive oxygen species. These elicit responses resulting in increased vascular permeability, modulation of leukocyte trafficking, localized tissue destruction, and generalized inflammation, with damage to kidney, lung, and various other organs. The initial clinical response to pancreatitis is a systemic inflammatory response (SIRS), which, if abnormally persistent, develops into a worsening scenario of tissue damage and sepsis resulting in multiple organ dysfunction syndrome (MODS).[8] The spectrum of inflammatory responses of the body has been further studied in the past few years. These responses vary from SIRS that can progress on to MODS or take the more indolent form of a compensatory anti-inflammatory syndrome (CARS).[9] The current understanding is that SIRS is the proinflammatory response and CARS is the anti-inflammatory response that results in a prolonged period of depressed immune function and increased susceptibility to infections.[10] The initial SIRS cascade occurs over the first week of illness and its resolution is the crucial step in deciding the further course of events. The primary mediators of this process are the cytokines such as interleukin-1 (IL-1), tumor necrosis factor (TNF), and interleukin-8 (IL-8), among others (Fig. 1). The pro-inflammatory process is counterbalanced by the anti-inflammatory response that inhibits T-cell mitogenesis and decreases cytokine production.

Cytokines: in the eye of the storm

The cytokines are a family of low-molecular weight proteins (16–25 kDa) that are secreted by a multitude of cells. They are usually not found in normal tissue but are produced in response to stimuli via receptor-induced pathways. Cytokine secretion is a very closely

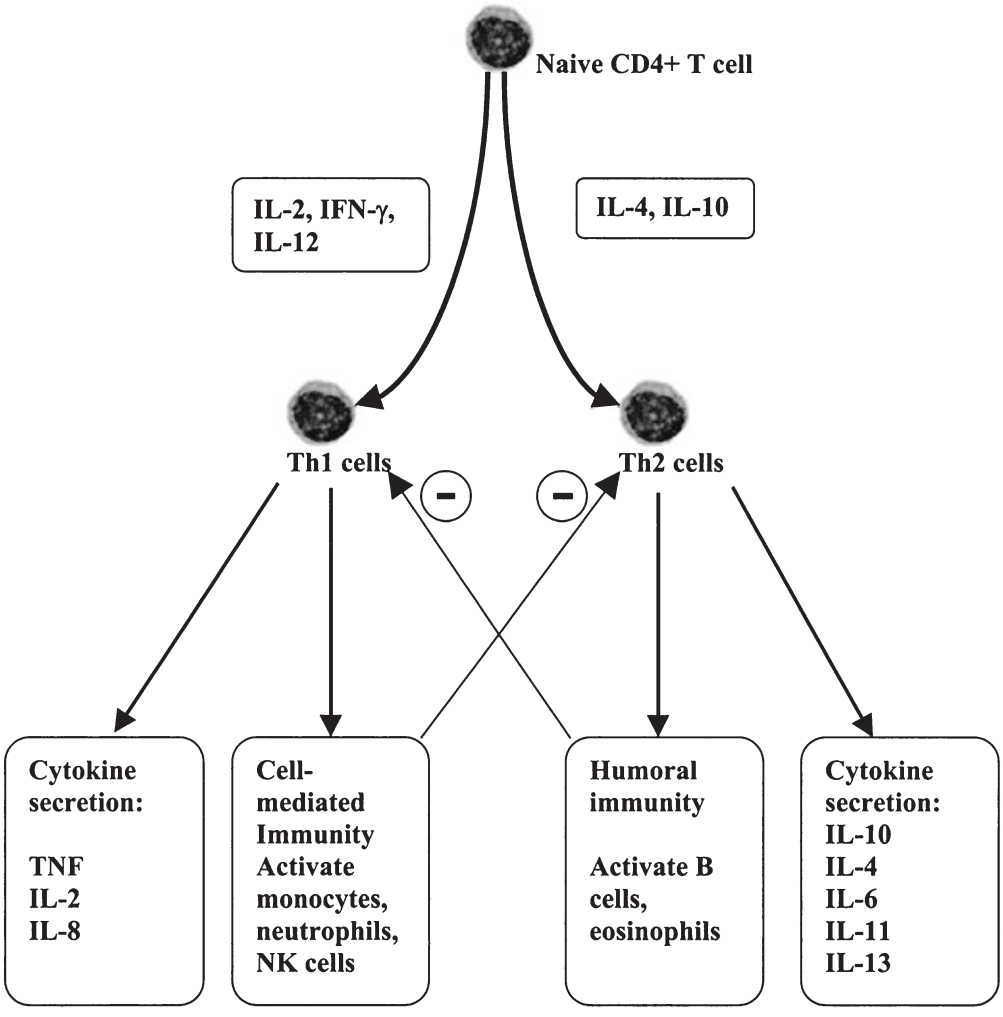

Fig. 2. Antigen-presenting cells elaborate cytokines that influence the differentiation of naïve CD4+ T cells into T-helper1 (*Th1*) and Th2 subsets. The cytokine products of these subsets reciprocally down regulate the differentiation of the opposite subset. *IL-2*, Interleukin-2; *IFN-γ*, interferon-γ; *TNF*, tumor necrosis factor; *NK*, natural killer

regulated process and the expression of most cytokines is modulated by transcription factors such as nuclear factor kappa B (NFkappaB). Few cytokines are constitutively expressed; for example, macrophage migration inhibitory factor (MIF). All cytokines cause their effects via highly specific cell-surface receptors. Most cytokines have pleiotropic activity and show multiple functional effects on a variety of target cells. There is immense redundancy within the system such that many cytokines can share similar biologic effects and in the absence of any one cytokine, others can fill the gap. This is of major consequence to the potential use of cytokine-antagonistic therapy, and single-cytokine antagonism has not proven to be of clinical benefit in trials.[11] T-helper (Th) cells are differentiated by the spectrum of cytokines they produce. Th1 cells are involved in cell-mediated defense mechanisms, including defense against intracellular pathogens, and they produce TNF-α, interleukin-2 (IL-2), and interferon-γ. Th2 cells secrete IL-4, IL6, IL-10, and IL-11 and modulate humoral immunity via B-cell responses[12] (Fig. 2). Various factors can influence the polarization of the Th cells, including the cytokine profile of the milieu in which Th cells undergo transdifferentiation. Th1 and Th2 cytokine products reciprocally downregulate each other.[13,14]

Tumor necrosis factor α (TNF-α)

TNF-α is a cytokine that is derived from a number of cells, but its main sources are the macrophages and monocytes. It interacts with a number of other cytokines such as IL-1, interleukin-6 (IL-6), and platelet activation factor (PAF) and has a pivotal role in the inflammatory response.[15] It has a short plasma half-life, of 14–18 min, due to rapid clearance by the liver, gastrointestinal tract, and kidney, making its presence difficult to assess by serum assays. Therefore absent or low levels of TNF in serum do not correlate well with actual events in the internal milieu. While it is difficult to measure TNF levels in peripheral blood, certain

studies have shown increased TNF levels in 30%–40% of patients with AP.[16,17]

TNF is secreted as a 26-kD transmembrane protein, and the extracellular domain is cleaved off enzymatically by TNF-α converting enzyme (TACE) to release the 17-kD active soluble form. TACE is a member of the ADAM (a disintegrin and metalloproteinase) family of proteins that have some homology with cell adhesion molecules.[18] Two receptors have been described for TNF, with molecular weights of 55 kDa and 75 kDa.[19] Both the p55 (TNFR-I) and the p75 (TNFR-II) receptor act to increase nuclear translocation of NFkappaB, which increases the expression of a variety of genes by binding to their promoter regions. The levels of these soluble receptors act as markers of TNF activity and these have been described to be elevated in AP, indicating a significant role for TNF,[20] especially in AP with MODS.[21] In addition, the p55 receptor is involved in the induction of programmed cell death via recruitment of MORT-1 protein and other cell-death factors.[22] Cell death is also promoted by the presence of TNFR associated death domains (TRADDS). It is possible that TNF-mediated apoptosis is the pathway by which other inflammatory mediators might act, such as intercellular adhesion molecule-1 (ICAM-1).[23] Pancreatic acinar cells have been shown to produce TNF and to respond to it.[24,25] In experimental conditions, AP induces TNF gene expression, beginning at 1 h and peaking at 6 h from the initial insult, and the infiltrating macrophages show increased reactivity to anti-TNF antibodies.[26] Cytokine secretion studies in primary mononuclear cell cultures from patients with AP have shown increased in-vitro production of TNF as compared with normal controls.[27]

Genetic studies into the role of polymorphisms within the *TNF* gene have so far not proven any increased susceptibility to AP;[28] however, some association has been found with the TNFa6 allele in chronic pancreatitis.[29]

Experimental studies have shown some promise with anti-TNF therapy. Recombinant soluble TNFR-I, acting as a competitive inhibitor, significantly reduced cytokine levels, pancreatic edema, and inflammatory markers as well as mortality in rats. Interestingly, this reduction in mortality was greatest if the treatment was given after pancreatitis had set in, as compared with at an earlier time.[30] Similar results were observed using polyclonal anti-TNF antibody in rats, with a significant reduction in mortality.[31,32] The future role of anti-TNF therapy in pancreatitis is unclear at present. More work needs to be done in TNF blockade in experimental pancreatitis in order to assess whether this fulfils its promise. Infliximab is an IgG1 anti-TNF monoclonal antibody that binds to TNF with high specificity and is currently being used for Crohn's disease (FDA licensed in the United States since 1998). This may be effective in pancreatitis and studies are awaited.

Interleukin-1

IL-1, a proinflammatory cytokine, is an important mediator of the inflammatory changes of pancreatitis. It initiates the inflammatory cascade and activates the endothelium, allowing migration of neutrophils into the post-venule space where they degranulate. IL-1 thereby results in neutrophil degranulation, expression of adhesion molecules, and chemokine activity. It has synergistic effects with TNF-α; however, it differs from TNF-α in that it does not cause apoptosis directly. IL-1 activity involves two receptors: IL-1R-I and IL-1R-II, as well as IL-1-related accessory protein (IL-1R-AcP).[33,34] Initiation of signal transduction requires IL-1β. IL-1R-I, and IL1R-AcP, as is revealed by studies involving their antibodies.[33] IL-1R-I and *Drosophila* Toll receptor have significant homology of structure. This is indicative of the fact that IL-1R-1 and toll-like receptors (TLRs) are derived from common ancestors with certain similarity of structure as well as function.[35] IL-1R-II serves as a "decoy" for IL-1 as it binds tightly to IL-1 and prevents signal transduction.[36] IL-1 receptor antagonist (IL-1ra) competitively inhibits receptor binding and prevents signal transduction. IL-1 receptor binding initiates several biochemical changes, for example, phosphorylation of mitogen-associated protein kinases (MAPK), activation of phosphatases and phospholipases, increased transcription of cyclooxygenase-2, and nuclear translocation of transcription factors such as NFkappaB and activator protein-1 (AP-1).[37,38] IL-1 is secreted in its precursor form, pro-ILβ-1, which is activated by IL-1β activating enzyme (ICE), which also activates IL-18.[39] ICE has now been renamed caspase-1 as over ten members of the caspase family have since been identified with different substrates.

There is ample evidence of IL-1 involvement in inflammatory cascades of pancreatitis. Its activities result in the clinical manifestations of SIRS.[40] Experimental studies show increased production and an important role of IL-1 in the early phases of pancreatitis.[41–43] Studies using IL-1 receptor gene knockout mice show that IL-1R-I is required for propagation of pancreatitis.[44] Intra-peritoneally administered IL-1ra decreases mortality and histologic destruction, as well as reducing inflammatory markers in pancreatitis induced by a choline-deficient, ethionine-supplemented diet. This effect was seen when treatment was started at the time of induction of diet, as well as when treatment was started 1.5 days later.[45] Experimental pancreatitis is significantly attenuated by pretreatment with ICE inactivator (VE-13045), resulting in decreased histologic grading of pancreatitis and mortality, while IL-1 mRNA levels

were increased 120-fold. This was also seen in ICE-knockout mice.[46] Similar results were noted by intraperitoneal application of ICE-inhibitor up to 12 h after the induction of pancreatitis.[47] Using acinar cell lines, it has been demonstrated that caspase-1/ICE is involved in acinar cell necrosis; however, it does not affect apoptosis, which is mediated by TNF-α.[48]

In human AP, IL-1 levels are difficult to measure and IL-1ra is thought to reflect in-vivo IL-1 activity. Several studies have shown increased IL-1Ra levels in AP, especially when organ failure is superimposed.[16,49] Functional genetic polymorphisms of *IL-1* have been explored as a possible determinant of severity of pancreatitis; however, no convincing association has been demonstrated so far,[28] although an association between *IL-1ra* gene polymorphisms and AP has been demonstrated.[50] Mononuclear cell cytokine production showed a significant decrease in the IL-1ra/IL-1β ratio in the patients with severe AP, as compared with mild AP.[28] The imbalance was primarily due to a differential production of IL-1ra rather than IL-1. This implies that those patients who produce higher levels of IL-1ra relative to IL-1 have milder pancreatitis. This may be the basis for further work in exploring the alteration of this ratio, rather than modulating IL-1 or IL-1ra in isolation.

A phase III trial of recombinant human IL-1Ra infused for 72 h showed no mortality benefit in a study involving 893 patients with sepsis.[51] This may have been due to the 100:10000 ratio of IL-1ra/IL-1 required in order to inhibit the biological effects of IL-1.

Promising areas of research include further delineation of the role of caspase-1 and IL-1R-II, which may be therapeutic targets of the future. Caspase-1 inhibitors, in particular, have been shown to be of benefit when given up to 12 h after the induction of pancreatitis, which mimics the clinical situation. Other areas of intervention include manipulation of gene transcription and intracellular processing.

Interleukin 10

IL-10 is a naturally occurring anti-inflammatory cytokine that modulates Th cell transdifferentiation into the Th2 subset and also forms a part of the Th2 response and is primarily synthesised by the Th2 cells, monocytes, and B cells. It decreases the release of the proinflammatory Th1 cytokines[52] and reduces DNA binding of NFkappaB after lipopolysaccharide (LPS) stimulation.[53] In primates injected with sublethal doses of endotoxin, IL-10 reduces cytokine levels, but does not affect the coagulation/fibrinolytic pathway.[54] In cultured monocytes, IL-10 increases IL-1ra and TNF P-75 receptor production and reduces IL-8 and monocyte chemoattractant protein-1 (MCP-1) levels.[55]

In experimental studies, IL-10 has been shown to decrease levels of inflammatory markers and reduce the severity of pancreatitis,[56,57] and this was also seen in studies using IL-10 knockout mice.[58] In experimentally induced pancreatitis, IL-10 levels parallel serum TNF levels and anti-IL-10 treatment reduces lung injury and pancreatic acinar necrosis, as well as reducing mortality from 42% to 0%.[59,60] Synthetic IL-10 agonist pretreatment reduced lung injury and mortality from experimental pancreatitis.[61]

In humans, IL-10 levels have shown variable association with tissue injury and severity of pancreatitis. Pezzilli et al.[62] showed that healthy subjects had undetectable IL-10 levels, while in AP patients, serum IL-10 levels were increased on the first day of the disease and then progressively decreased in the following days. On the first day of the AP, patients with the mild disease had serum levels of IL-10 significantly higher than those in patients with severe disease. This implies that an effective anti-inflammatory response early on in the course of the disease may help in reducing its severity. In other studies, plasma IL-10 levels were correlated with the severity of pancreatitis and could be used as a marker for severity prediction.[16,63,64] Two recent trials have shown contrasting results for IL-10 in post-endoscopic retrograde cholangio pancreatography (ERCP) pancreatitis. In both trials, patients received recombinant IL-10 or placebo before ERCP and had their course followed. One study reported no difference in clinical outcome between the two groups. However, they did not have any patients with severe pancreatitis.[65] In the other trial, patients having therapeutic ERCP received placebo or IL-10 in two different doses — 4 μg/kg or 20 μg/kg. Their study revealed no difference in inflammatory markers between the groups; however, a significant reduction in the severity of pancreatitis was seen with IL-10 at the higher dose. These results remain significant, despite a lower (not significant) use of therapeutic interventions and precut techniques in the placebo group.[66] While IL-10 seems to have potential as an anti-inflammatory agent, in some situations, such as meningococcemia and pneumococcemia, high IL-10 levels have been associated with increased mortality from infectious causes.[67,68]

Genetic control of IL-10 secretion may have a role to play in modifying the severity of pancreatitis, as polymorphic areas do exist within the *IL-10* gene. Unpublished work from our laboratory has failed to show any correlation between disease severity and the *IL-10* microsatellite locus or the promoter region polymorphisms.

Clearly, IL-10 holds the promise of a global diminution of the cytokine response, and further work is needed on its use in AP.

Interleukin 6

IL-6 is a cytokine that is produced in a spectrum of immunologically active cells, such as monocytes/macrophages, endothelial cells, and fibroblasts, in response to stimuli. It is also produced in the pancreatic tissue after experimentally induced pancreatitis,[42] as well as by periacinar myofibroblasts in response to TNF-α and IL-1β.[69] It is important in the generation of the acute-phase reactants by hepatocytes and appears to be the main driving impulse directing their secretion.[70,71] IL-6 levels are elevated in pancreatitis and serve as markers of severity of pancreatitis, in addition to paralleling the course of the disease.[1,72–74] IL-6 levels can also help to predict the possibility of pulmonary complications.[49] In this aspect, IL-6 is superior to C-reactive protein (CRP) or β-2 microglobulin and has been shown to rise 12–24 h before other inflammatory markers.[63,75,76] Mononuclear cell production of IL-6 is higher in patients with pancreatitis when compared with healthy volunteers.[77] When comparing patients with complicated versus uncomplicated pancreatitis, IL-6 production from mononuclear cells is much higher in the complicated group.[27] Post-ERCP pancreatitis serves as a good model for human pancreatitis and allows observation of the changes from time to initial injury. After ERCP, IL-6 has been shown to rise within 6 h, as well as to correlate with the incidence of abdominal pain.[78] In patients with proven post-ERCP pancreatitis, IL-6 levels are higher in severe compared with mild pancreatitis and rise within 12 h.[79]

The role of IL-6 is essentially a diagnostic one, in that it helps in early severity stratification of pancreatitis. This enables the patients at higher risk to undergo intensive monitoring and early identification of complication. As laboratory medicine develops further, this could eventually be the ideal test to select high-risk patients in whom various newer modalities of treatment for pancreatitis can be applied.

Platelet activating factor

Platelet activating factor (PAF) is a proinflammatory cytokine elaborated by inflammatory cells, such as endothelial cells, macrophages, and neutrophils. It increases vascular permeability, increases leukocyte trafficking, and causes tissue injury.[80] Administration of PAF causes pancreatitis,[81] and its antagonism ameliorates pancreatic damage and lung injury in pancreatitis, as well as decreasing mortality in experimental models of AP.[80,82–85] PAF-acetylhydrolase (PAF-AH) is the enzyme responsible for the inactivation of PAF. Studies using recombinant PAF-AH have shown improvements in pancreatitis as well as in lung injury.[86] Lexipafant (British Biotech, Oxford, UK), a powerful PAF antagonist, has undergone clinical trials recently. The initial trials showed a decrease in the incidence of organ failure, as well as improved clinical scoring and a reduction in inflammatory markers.[1,87] However, the phase III trial did not show any improvement in organ failure rate or mortality.[11] This may have been due to the presence of ongoing organ failure in many patients at the time of recruitment into the study (within 72 h) and therefore, there may be better results if Lexipafant is infused at the time of presentation, before organ failure has developed.

Chemokines

The chemokine family consists of small molecules that are involved in leukocyte activation and trafficking into areas of inflammation and infection. They can be structurally subdivided into two main subfamilies: CXC, in which the first two of four conserved cysteine residues have an intermediary amino acid (IL-8), and the CC subfamily (MCP-1), in which the first two cysteine residues are adjacent.[88] Many chemokines have been implicated in various aspects of the propagation of pancreatitis. MCP-1 and RANTES (regulated on activation, normal T cell expressed and secreted) have been shown to be released from pancreatic acinar cells by the effect of ethanol.[89] The role of chemokines extends beyond leukocyte attraction; they are increasingly being recognized as modulators of immune responses by the selective recruitment of Th1 and Th2 cells.[90,91]

Interleukin 8. IL-8 is synthesized by monocytes, endothelial cells, and neutrophils, among other cells. It is a chemokine that is responsible for neutrophil chemoattraction, degranulation, and release of elastase. Among patients with AP, IL-8 production closely parallels serum neutrophil elastase levels.[92] IL-8 levels are associated with the severity of pancreatitis and can be used as predictive markers.[1,63,93] Mononuclear cell production of IL-8 is increased in patients with AP versus controls[77] in complicated versus uncomplicated pancreatitis.[27] The ratio of IL-10 to IL-8 is decreased in patients with severe versus mild pancreatitis, showing that an imbalance in anti-inflammatory and proinflammatory cytokines influences severity.[94] The present position of IL-6 and IL-8 is that they are excellent predictive markers of outcome and used as such in research studies. Their clinical use is limited by the lack of an efficient, cheap, and easily accessible laboratory assay method at present.

Other cytokines

A number of other cytokines have been studied and are currently under investigation as possible mediators of inflammatory damage in AP.

IL-2 is known to be a Th1 subset product and an essential component of the normal immune response. In mice, induced AP is associated with lowered IL-2 production; this is further lowered by intraperitoneal endotoxin, and is accompanied by 90% mortality. This high mortality rate is attenuated by recombinant IL-2.[95] Soluble IL-2 receptor (sIL-2R) levels are elevated in AP and more so in severe AP,[96] and peak sIL-2R is predictive of lethal outcome in AP.[49] In patients with post-ERCP pancreatitis, soluble IL-2R levels peak at 6 days following ERCP.[97] This supports a role of IL-2 in the inflammatory processes of AP.

IL-4 is a powerful modulator of Th cell transdifferentiation into the Th2 subset and has an anti-inflammatory role in the body. Like IL-10, it downregulates proinflammatory cytokine production and, therefore, may have a role in ameliorating tissue damage in pancreatitis. Polymorphisms of this gene have been associated with colitis[98] and may be of importance in influencing the course of AP. A trial involving gene transfer therapy of IL-4 and IL-10 is currently underway for the treatment of colitis, and the results of this would be illustrative for other fields.[99]

IL-11 is a Th1 subset product that has anti-inflammatory effects. In mice, recombinant IL-11 ameliorated the histological severity of AP in the early stages and decreased TNF mRNA levels in pancreatic tissue.[100] In humans, IL-11 levels are elevated in severe AP more than in mild AP.[63]

IL-18 is a substrate for caspase-1, in addition to IL-1, and plays an important role in the pro-inflammatory Th1 response by co-stimulating interferon-γ production. A cohort study has recently demonstrated an association between IL-18 levels and complicated pancreatitis.[101] This serves to underline the importance of caspase-1 as a future target of study, as well as therapeutic modulation.

Future directions

From the work done so far a number of possible directions for future work have emerged.

There are a number of emerging mediators, receptors, and metabolizing enzymes that could have an important role in the inflammatory cascades which result in complicated AP. These would include macrophage migration inhibitory factor, IL-18, and caspase-1. Their roles need to be explored and defined.

As seen from the Lexipafant study, single-cytokine antagonism is less likely to be successful due to the overwhelming level of redundancy within the inflammatory cascade. A number of anti-inflammatory cytokines have emerged, and their roles are currently under study. Further research is needed into the areas that include IL-4, IL-11, and IL-1ra. The roles and biology of these cytokines are known in other disease conditions and they are candidates for study in pancreatitis. Trials of IL-10 in clinically predicted severe AP would be the next appropriate step after the encouraging results in preventing post-ERCP pancreatitis.

The genetic control and modulation of the cytokine network is an interesting field with many areas yet unexplored. A number of polymorphisms exist within the human genome, and many of these lead to functional alterations in the protein product which they encode for. Among these, PAF-AH has a missense mutation, which is found in 4% of the Japanese population. This has been associated with a number of diseases, among which is an increased incidence of aortic aneurysmal disease.[102] It would be interesting to see if this has any associations with AP. The results of gene transfer therapy trials of IL-4 and IL-10 in colitis may be relevant to AP.

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