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**Immune-modulating therapy in acute pancreatitis: Fact or fiction**

Akinosoglou K *et al*. Immune-modulation in pancreatitis

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**Abstract**

Acute pancreatitis (AP) is one of the most common diseases of the gastrointestinal tract, bearing significant morbidity and mortality worldwide. Current treatment of AP remains unspecific and supportive and is mainly targeted to aggressively prevent systemic complications and organ failure by intensive care. As acute pancreatitis shares an indistinguishable profile of inflammation with sepsis, therapeutic approaches have turned towards modulating the systemic inflammatory response. Targets, among others, have included pro- and anti-inflammatory modulators, cytokines, chemokines, immune cells, adhesive molecules and platelets. Even though, initial results in experimental models have been encouraging, clinical implementation of immune-regulating therapies in acute pancreatitis has had a slow progress. Main reasons include difficulty in clinical translation of experimental data, poor understanding of inflammatory response time-course, flaws in experimental designs, need for multimodal approaches and commercial drawbacks. Whether immune-modulation in acute pancreatitis remains a fact or just fiction remains to be seen in the future.

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**Key words:** Acute pancreatitis; Immune-modulation; Systemic inflammatory response syndrome; Multiple organ dysfunction syndrome; Endoscopic retrograde cholangiopancreatography

**Core tip**: Acute pancreatitis is a common entity with significant mortality worldwide. Treatment remains non-specific and mainly supportive, mostly focusing on intensive care. Presence of inflammatory response syndrome during AP has driven recent immune-modulating therapeutic attempts in experimental models, including cytokine, chemokine, immune cell and other inflammatory mediator blockade. Although initial data are promising, translation to clinical routine has been less encouraging. The authors attempt to elucidate whether and to what extent tampering with the immune burst triggered by acute pancreatitis could actually ensure better outcomes, or that remains a farfetched expectation.

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**INTRODUCTION**

Acute pancreatitis (AP) is a common disease, posing a tremendous burden in health care systems globally[1,2]. The incidence of AP varies between 4.9 and 73.4 cases per 100000 worldwide[3,4]. Progression to multiple organ dysfunction syndrome (MODS), as a consequence of the systemic inflammatory response syndrome (SIRS) represents a major contributor to high mortality in the early phase of the disease[5,6]. Consequent breakdown of intestinal integrity, bacterial translocation and increased infection risk can further complicate outcome in the late phases of AP[7-9].

Current treatment of AP remains non-specific and supportive and is mainly targeted to aggressively prevent systemic complications by intensive care. During the last decade, a number of new therapeutic modalities have changed the management of acute pancreatitis, including enteral feeding in severe AP, the use of early antibiotic treatment in necrotizing pancreatitis and therapeutic endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy in severe biliary pancreatitis[10,11]. However, although the case fatality rate for AP has decreased over time, the overall population mortality rate has remained unchanged[12].

Recent data has come to show that in the early phase of AP, excessive leukocyte activation and consequent inflammatory mediator release are critical for development of early organ failure[13-16]. As a result, current experimental and clinical research has been driven by the need to inhibit the systemic inflammatory reaction thus; prevent the development of MODS. This article attempts to critically review recent data on immune-modulating strategies in AP.

**LOCAL AND SYSTEMIC INFLAMMATION**

***Pancreatic self-digestion***

Acute pancreatitis represents an inflammatory disorder; hence, a complex cascade of immunologic events affects disease pathogenesis and progression. Alcohol and gallstones remain the major etiologic factors of AP. Irrespective of the cause, triggering events lead to premature activation of pancreatic proteases, as a result of intracellular co-localization with lysosomal enzymes[17,18]. An increase in intracellular calcium triggers activation of trypsinogen and induces local inflammation[19], further leading to auto-digestion, destruction of the parenchyma and finally necrosis of the pancreas[17,20-23](Figure 1).

The role of tumour necrosis factor alpha (TNF-α) in the potential activation of pancreas polypeptide and Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB)[24] has been recently investigated[25-29]. Whether there is a link between pancreatic NF-κB and trypsinogen activation remains controversial[27]. However, it seems that these processes may be unrelated and may both contribute to inflammation, possible through reactive O2 species (ROS) mediation and calcium (Ca2+) signalling[30,31] (Figure 1).

At this stage, it appears that the autophagy machinery interfaces with various cellular stress-response pathways including those involved in immune response and inflammation, entailing among others direct interactions between autophagy proteins and immune signalling molecules[32-34]. This complex interplay modulates both the induction and suppression of immune and inflammatory responses and vice versa, while it seems that the same genes that regulate autophagy are involved in xenophagy[35,36]. In this respect, a potential protective role for interleukin (IL)-22 against the autophagic pathway in pancreatitis is currently under investigation [37].

***Leukocyte activation and cascade reaction***

Endogenous molecules released as a result of tissue injury, referred to as damage-associated molecular patterns represent primary activators of the immune system[38-40]. Among those, high mobility group box 1 (HMGB1) protein, a nuclear DNA binding protein[41-43], has been recently suggested to act as a key mediator for inflammation and organ failure in AP[44-46]. Pancreatic-derived intracellular HMGB1 limits the severity of the disease by protecting cells from NF-κB activation, DNA damage, cell death, and release of nucleosomes from injured acinar cells[47]. On the other hand, extracellular HMGB1 released by necrotic cells, can, *via* members of the Toll-like receptor (TLR) family trigger acute lung injury[48,49] and a lethal systemic inflammatory process[50,51]. Extracellular HMGB1 can further stimulate the release of pro-inflammatory cytokines including TNF-α and IL-1β by inducing nuclear translocation of NF-κB and conversely, the pro-inflammatory cytokines can control further release of HMGB1 into the extracellular space (Figure 1)[52-54] .

Activated acinar cells also secrete pro-inflammatory factors including C-X-C motif chemokine (CXCL) 10, Chemokine (C-C motif) ligand 2 (CCL2) also referred to as monocyte chemotactic protein-1 (MCP-1), IL33[55,56], platelet activating factor (PAF), TNF-α and IL-1β leading to migration of monocytes and neutrophils into the pancreas[57,58]. Neutrophils are specifically activated by CXCL-1 and CXCL-2 (also called macrophage inflammatory protein 2-alpha, MIP2-α), while monocytes, eosinophils and T-cells are activated by CCL-2 (MCP-1) and CXCL-10[59] (Figure 1). However, monocyte and macrophage populations involved in AP are heterogeneous, with great phenotypic and functional plasticity[60]. Recently, a subtype of monocytes that derive from the bone marrow and express TNF-α has been identified, which appears to determine pancreatic oedema and acinar cell injury/necrosis[61]. T cells are also present in smaller numbers in the inflamed pancreas and appear to be necessary for progression of AP[62]. As AP progresses, changes in the number and ratio of CD4+ and CD8+ T cells has been noted, probably because CD4+ T cells contribute to activation of macrophage via antigen presentation and release of inflammatory cytokines[63]. In contrast to total depletion of CD4+ T cells, and consistent with functional heterogeneity of CD4+ T cells, recent data indicate that a subset of CD4+ IL22+ T cells likely protects against AP in mice, even though exact mechanisms remain elusive[64].

The magnitude of the inflammatory process is amplified following further secretion of inflammatory mediators by infiltrating immune-associated cells[65-67], and over-expression of adhesion molecules including intercellular adhesion molecule 1 (ICAM-1) and vascular adhesion molecule 1[68,69].The latter represent ligands for lymphocyte function-associated antigen 1[70] on leukocytes and lymphocytes, αLβ2 and CD11a-CD18 on monocytes and integrin macrophage 1 antigen (Mac-1) on neutrophils, while their secretion is promoted by ROS generation and TNF-α itself (Figure 1)[71-73]. Notably, ICAM-1 deficiency and systemic depletion of neutrophils were each shown to reduce the severity of AP and lung injury[71].

***Bacterial translocation***

Except for regulation of cellular apoptosis, TNF-α was shown to increase intestinal paracellular permeability, by affecting tight junctions[74] and facilitating bacterial translocation from the epithelium[75]. It has been suggested that, pathogen-associated molecular patterns (PAMPs) derived from the intestinal micro flora activate the host innate immune system via pattern recognition receptors, such as TLRs and nucleotide-binding domain and leucine-rich repeat-containing molecules[76] (Figure 1). Activation of TLRs and nucleotide-binding domain and leucine rich repeat-containing molecules likely mediates the mechanism by which bacterial translocation leads to severe AP. Consistent with this, mice that lack TLR4 develop less severe forms of AP[77], and polymorphisms in *TLR* genes have been associated with susceptibility to AP[78,79]. Interestingly, up-regulation of TLR4 has been associated with increased expression of TNF-α in peripheral blood mononuclear cells during early stages of AP[80].

***Pancreatic microcirculatory disturbance***

Various molecules and mechanisms appear to complete the full spectra of manifestations in AP, mainly attributed to microcirculatory disturbance including nitric oxide, endothelin, oxygen free radicals, bradykinin, prostaglandin I2 and endothelin[81]. Inflammatory mediators induce microcirculatory disturbance mainly through increasing capillary permeability and decreasing capillary blood flow velocity (such as ICAM-1), promoting the contraction of arteries and veins (such as endothelin), as well as, promoting platelet aggregation and inducing thrombosis (such as PAF and TXA2). In the latter case, PAF exerts its biological activity through binding to its specific receptors on the surface of leukocytes, endothelial cells and platelets leading to microcirculatory disturbance in AP[82-85](Figure 1). Furthermore, an increasing body of evidence reveals a pro-inflammatory role of platelets except for their established function in thrombosis and haemostasis[86-88]. During AP, data have come to show that platelets regulate neutrophil accumulation in the pancreatic tissue[89], even though exact mechanisms underlying platelet dependent leukocyte recruitment remain elusive. At the moment these mechanisms and various molecules[90], although important; surpass the purpose of this review and will not be discussed further. Figure 1 represents a schematic summary of innate and adaptive immune response mechanisms implicated in acute pancreatitis.

In mild AP, inflammation is regulated and confined by the host’s inflammatory response in the affected area. Although, most episodes of AP are mild, some patients proceed to SIRS, as a result of pro-inflammatory mediators’ release into the circulation[91,92], with local and extra-pancreatic complications[93], including respiratory, renal and hepatic dysfunction[94,95]. Systemic inflammation in AP is concomitantly associated with rapidly strengthening compensatory anti-inflammatory response syndrome (CARS)[96]. Even though, CARS may be sufficient to control SIRS and ensure favourable prognosis, excessive CARS may be overwhelming, leading to immune deficiency or suppression, which renders the host susceptible to secondary infections[97]. Increased serum concentrations of anti-inflammatory mediators including IL-10, IL-11, TNF-α receptors, and IL-1 receptors antagonist (IL-1ra) have been demonstrated in AP[98-102]. In immune-suppression monocytes are characterized by a significantly decreased human leukocyte antigen antigen-DR (HLA-DR) expression, process mostly attributed to IL-10 production[103]. Along with consequent impaired antigen presentation[104,105], monocytes show a profound reduction of their ability to produce pro-inflammatory cytokines *e.g.,* TNF-α[106,107], facts associated with development of secondary infections[97] and organ failure[108,109]. IL-1ra and IL-6 are also important anti-inflammatory cytokines. IL1-ra blocks IL-1 mediated responses[110] while IL-6 appears to prevent synthesis of IL-1β and TNF-a[111].

**THE STORY OF IMMUNE-MODULATING THERAPIES: FACT...**

Following understanding that, outcomes of our patients seem to be mostly dependent on pro- as well as, anti-inflammatory responses; in the last few years, a number of experimental and clinical studies have focused their interest in immune regulation during AP (Figure 2).

***TNF-α***

Recent data in animal models has come to show that, TNF-antagonism by either TNF-receptor blockade or anti TNF-antibodies protected from local intra-pancreatic damage, systemic complications and overall mortality in the vast majority of cases[29,112-117]. Administration of infliximab -a monoclonal TNF-antibody- appears to decrease serum amylase activity in both acute oedematous pancreatitis and severe necrotizing pancreatitis in a murine model[118]. In the latter case, a tendency to ameliorate both parenchymal and fatty tissue necrosis of the pancreas and alleviate acute respiratory distress syndrome-like pulmonary complications, was also noted. However, even though TNF-α has been clearly associated with failure of intestinal barrier, the latter study provided no information upon infliximab’s role on intestinal permeability since bacterial translocation was not considered a septic complication. However, previous reports that TNF-α blockage appears to correct intestinal permeability in people with Crohn’s disease[119], suggests that this effect may occur in other types of disorders and could represent a feasible therapeutic option. In a recent study, Aydin *et al*[120] showed that, infliximab administration 6 h after the induction of pancreatitis exerted beneficial effects on blood amylase levels and histopathologic changes in experimental necrotizing pancreatitis, while significant decrease in the degree of BT was noted. Even though, premature administration of anti-TNF 6 h post pancreatitis induction was beneficial, previous reports support that a prophylactic design starting the treatment before the induction could be superior, while the protective effect of TNF-antagonism on disease severity and mortality was still observed after the systemic effects had developed[116]. To date, no study has been conducted investigating TNF-a impact in clinical acute pancreatitis except for an isolated report in a patient with Crohn’s disease complicated with acute pancreatitis[121]. Interestingly, favourable outcome was observed following infliximab’s administration. However, data from two phase III sepsis trials [122,123] sharing an indistinguishable profile of inflammatory mediators with AP, have not been that optimistic. The use of an anti-TNF antibody in patients with sepsis failed to reduce 28-d mortality, suggesting that previous results from experimental studies or anecdotal reports should be interpreted with caution.

***Cytokines***

As previously described, pro-inflammatory cytokines such as IL-6, IL-1 and TNF are released in acute pancreatitis, while their plasma level correlates well with the severity of the disease and the occurrence of multi-organ failure[124-126]. By contrast, anti-inflammatory mediators such as IL-10, appear to mitigate the effects of inflammatory response and their level seems to be inversely proportional to the severity of pancreatitis[127,128].

**IL-1:** As observed for TNF, organ-specific expression of IL-1 is an early feature in experimental acute pancreatitis and is found in both the pancreas and distant organs[129,130]. Blockade of the IL-1 receptor by either targeted genetic disruption or pharmacological agents uniformly reduced the extent of intra-pancreatic damage, systemic complication, and mortality, similarly to TNF-α blockade[131-135]. Alternatively, the approach of inhibiting caspase-1, formerly termed interleukin 1β-converting enzyme (ICE) has been explored. Targeting ICE activity by a specific synthetic inhibitor dramatically attenuated both severity and mortality irrespective of the model used[136-139]. Interestingly, severity and mortality were still reduced even when a therapeutic window of 12 h following induction of severe acute pancreatitis was allowed[137]. Similarly to TNF-α, implementation of experimental findings to the clinical setting has been controversial. Even though, a post hoc analysis of a controlled trial of human recombinant IL-1ra in patients with sepsis showed a trend towards increased survival in patients with MODS[140], this observation could not be confirmed in a subsequent trial[141]. Technical reasons concerning the optimal dosage, duration and *in vivo* activity of the antibody could be responsible for these discrepancies [142].

**IL-10:** IL-10 - irrespectively of whether its activity has been blocked or augmented -has been shown to exert a protective effect in several models of acute pancreatitis in the past[143-149]. Cytokine manipulation appeared to significantly ameliorate organ specific damage in the pancreas and peripheral tissues, including the lung and the liver, while mortality was significantly reduced. Interestingly, IL-10 protective effect was still observed even when intervention occurred therapeutically after acute pancreatitis had already been induced [144,145,149]. However, this data has not been confirmed in the clinical setting. No significant differences were detected between IL-10 and placebo administration within 36 hours of onset of symptoms, in days of hospital stay, CT scan score, organ failure score and local complications[150]. Conflicting results have come to light from randomized double-blind studies regarding the ability of IL-10 to prevent ERCP–induced AP. In his study, Deviere *et al*[149] reported that, IL-10 decreased the incidence of post-ERCP pancreatitis, as well as, the length of hospital stay independently from other risk factors. This was not confirmed by a later American trial in which only a trend towards and not a significant decrease in the former parameters was noted[151].A recent meta-analysis including patients receiving recombinant IL-10 or placebo before ERCP could show that, IL-10 significantly reduces the risk of post-ERCP pancreatitis[152]. Whether IL-10 treatment can ultimately prevent post-ERCP still remains under investigation.

**IL-2:** In contrast to the late effects of IL-2 deficiency and immune-paralysis, the excessive IL-2 mediated T-cell response during the early course of the disease can be deleterious[62,153-157] Following transcriptional regulation by administration of the FK506 agent which inhibits IL-2 production, decreased early local and systemic disease severity was noted even when given in a therapeutic fashion[155]. Similarly, early data have come to show that, sirolimus, an immune-modulatory agent, acting through inhibition of response to IL-2, thereby blocking activation of T and B cells, reduces acute pancreatic damage in the first week and less chronic changes in the further course of disease[157]. However, opposite results were shown by other studies. FK506 administration significantly worsened survival in diet-induced murine pancreatitis[156]  while potentiation of IL-2 production through levamisole administration effectively decreased the incidence of pancreatic infections in a cat model of severe acute pancreatitis[153].

**IL-18:** IL-18 or interferon--inducing factor represents a novel key regulator of Th-1 response, through its ability to induce IFN-production in T and natural killer cells [158]. Scarce data on this interesting cytokine have shown that intra-pancreatic damage was decreased more effectively following neutralization of IL-18 activity by monoclonal antibodies than neutralizing IL-1 activityin cerulein-induced pancreatitis in mice [159]. Further research in IL-18 and its role during AP is currently in progress.

**IL-6:** Despite the numerous clinical studies investigating the role of IL-6 in the development of inflammatory syndrome, unfortunately only few reports have examined the role of this interleukin as potential target for modulating disease severity. Even though, IL-6 has been found to be a good predictor in predicting pancreatitis associated complications, including organ failure[160], limited experimental data have revealed that genetic deletion or prophylactic inhibition of IL- 6 rather worsened outcomes than exerted a protective effect on disease severity and mortality[161-163].

***PAF***

Following previous observations implicating PAF in classical morphologic and biochemical derangements induced during AP[164], a number of groups have pursued the potential therapeutic role of this novel cytokine[165-171]. Except for one case[172],pathophysiological changes of acute pancreatitis were reduced in all established experimental models following PAF antagonism[168-171]. When PAF antagonists were applied therapeutically, local intra-pancreatic damage and micro-circulatory derangement was significantly ameliorated while systemic complications and mortality was considerably decreased[168,170,171]. One of the most promising PAF antagonists Lexipafant has been recently tested in two phase II trials including patients with acute[173] or predicted severe pancreatitis[174]. Results were encouraging, showing significant improvement of organ failure or organ failure scores. Subsequently though, in a randomized, double blind trial encountering patients with severe AP, intravenous administration of lexipafant for 7 days did not show any benefit in reducing MODS or mortality[175]. Nonetheless, systemic levels of IL-8 and E-selectin, sepsis or pseudocysts development were significantly lower in the treated than in the non-treated group, especially in patients treated within 48 h from the onset of symptoms[175]. In view of the multiple prior experimental studies suggesting that lexipafant is highly effective in reducing SIRS associated with AP[176,177], discrepancies among results finally came to challenge the actual role of PAF antagonism in the clinical setting. Discordance among studies can be partly attributed to the timing of each intervention and/or commercial influence and are further discussed.

***Chemokines***

So far, only a limited number of experimental and clinical studies have examined the efficacy of chemokine blockade in AP, mostly due to their more distal position within the inflammatory mediator cascade in comparison to cytokines.

In view of IL-8 detrimental effect in experimental AP[178], Osman *et al*[179] investigated the impact of prophylactic blockade of IL-8 in a rabbit model. Interestingly, significant reduction in systemic severity including lung injury, and mortality was observed, whereas the degree of local intrapancreatic damage remained unchanged. Even though, this study could not assess for potential therapeutic effects, the above data strongly supported the role of chemokines in mediating distant organ failure in AP.

Besides IL-8, high concentrations of other chemokines such as MCP-1, growth-related oncogene alpha, and epithelial neutrophil-activating protein 78 could be also found during the early stages of clinical acute pancreatitis. Blockade of specific CXC chemokines via specific antibodies, synthetic inhibitors or genetic deletion appeared to reduce pancreatitis associated pulmonary damage in several experimental studies[59,180,181]. Nonetheless, similar to IL-8, a complete absence of effect on local intrapancreatic damage was also observed[59,180,181].So far, only MCP-1 seemed to exert a detrimental role on the degree of local intrapancreatic damage[182]. Even though, in most of these studies, protective effects of chemokine blockade were observed even in a therapeutic design[59,180,182], no systematic study of their impact upon mortality has ever been carried out.

***Adhesion molecules***

The expression of adhesion molecules is pivotal for the development of endothelial barrier dysfunction, transmigration of neutrophils and concomitant development of organ dysfunction. Treatment with antibodies against adhesion molecules like ICAM-1 and platelet endothelial cell adhesion molecule-1 (PECAM-1) has shown to be effective in the experimental setting[71,183-185]. Similarly, recent data demonstrate that platelets regulate leukocyte rolling in acute pancreatitis via induction of P-selectin, which was critical in supporting leukocyte rolling in inflamed venules of the pancreas[186]. It seems that inhibition of P-selectin protected against pancreatic tissue injury in experimental pancreatitis[187].

***Macrophages***

The roles of macrophages in the pathogenesis and progression of experimental AP make these cells interesting therapeutic targets since they exhibit both pro- and anti-inflammatory properties. Macrophages inhibitors (compounds such as gadolinium chloride, liposome-encapsulated dichloromethylene diphosphonate, and PAF antagonists) were shown to modulate the systemic inflammatory response[188]. However, most studies administered the inhibitors before AP was induced, which is clinically less relevant because most patients present after pancreatic injury. Other approaches to modify macrophages, either *in vivo* or *ex vivo*, into cells with anti-inflammatory properties have recently been tested. Currently, favourable effects of IL-4 and IL-13 have only been confirmed *in vitro*[189], while transfer of hemin-activated macrophages promoting production of anti-inflammatory agents seems promising[60,64,190,191]. In a study involving a xenogenic system, human bone marrow–derived clonal mesenchymal stem cells were administered to rats with mild or severe AP[192]. The human bone marrow–derived clonal mesenchymal stem cells induced Foxp3+T regulatory cells and suppressed pancreatic infiltration by T cells. Although more studies are needed in this area of research, stem cell–based immunosuppressive strategies could be developed as allogenic therapies for AP[193].

***Corticosteroids, NF-κB and HMBG1***

In rat models of AP, hydrocortisone has reduced mortality and blood cytokine levels[194-196]. At the moment, no human trials using steroids as treatment of AP have been published and attempts to show a beneficial effect of steroids as prophylaxis against post-ERCP pancreatitis in prospective placebo-controlled trials have been disappointing[197-199]. The use of glucocorticoids may, however, find a place as part of a combination therapy, as they suppress the inflammatory response, potentially through the inhibition NF-κB[200,201].

Increased levels of NFκB during acute inflammation correlate well with AP severity[24,25], indicating that potential inhibition could improve outcomes[202,203]. NFκB signalling seems to regulate autophagy during necrotising pancreatitis, while inhibition of NFκB pathway reduced serum amylase and autophagosome formation in experimental models[204]. Similarly, lung injury and pancreatic destruction was lower in rats with acute necrotising pancreatitis following administration of NF-kappaB-*N*-acetylcysteine inhibitor.[205]

The complex role of HMG1 in AP has not allowed the conduction of many studies. Previous results have shown that anti-HMGB1 antibody improves lipopolysaccharide (LPS)-induced acute lung injury in mice[51], and ventilator-induced lung injury in rabbits[207]. In AP blockade of HMGB1 has been reported to attenuate the development of severe disease, as well as, associated organ dysfunction[208]. However, even though, HMGB1 can increase the permeability in enterocytic monolayers and bacterial translocation in mice[209], blockade of HMGB1 eventually deteriorated gut barrier function in this study[208].

**THE STORY OF IMMUNE-MODULATING THERAPIES:...OR FICTION**

Inhibiting pro-inflammatory mediators (*e.g.,* PAF, IL-6, ICAM-1, TLR-4), enhancing anti- inflammatory mechanisms (*e.g.,* IL-10) or modulating cellular immune responses, have all been found to be beneficial in experimental pancreatitis models[71,149,210,211]. Unfortunately, at the moment, they have all failed to find their way from the laboratory bench to the patient’s bedside[211,212], with the possible exception of preventing post-ERCP pancreatitis[213,214]. In this respect, a number of issues must be considered and addressed.

First, we have to keep in mind that discouraging results coming from the few representative clinical studies available on single anti-inflammatory agents does not necessarily mean that this approach is flawed in principle. The inflammatory mediators identified so far, most likely represent only the “tip of the iceberg”[215]; a million other mediators, underlying, interacting and regulatory mechanisms awaiting elucidation. Therefore, the concept of blocking single pro-inflammatory mediators could be an over-simplistic strategy to deal with the complex problem of acute pancreatitis, if there is any “ultimate” target at all. Of note, disastrous effects have been noted when single proximal mediators of the inflammatory response were blocked including development of anti-DNA, antinuclear or antithyroid antibodies, leading to various muscoloskeletal, neurological and skin manifestations[216,217].

In the complex network of inflammatory response, a multimodal strategy to inhibit several pro-inflammatory agents instead of one may be more useful[218,219]. The combination of the broad-acting antioxidant *N*-acetylcysteine, monoclonal antibodies against the adhesion molecule PECAM-1 and lexipafant was effective in animals with organ failure associated with AP[220]. The acute phase response and organ dysfunction was decreased, while gut barrier failure and translocation was prevented[220]. However, even in the case of multimodal strategy the example of TNF and anti IL-1 that share similar characteristics in both their pathophysiological functions, as well as their regulation is worth noting[134,221]. As it was convincingly shown by Denham *et al*[131], no additive protective effects could be demonstrated by combined genetic disruption the IL-1 receptor and TNF in a murine model of AP, reflecting the huge challenges lying beyond the functional redundancy of the immune system[222].

However, even in such cases of multimodal management the timing of intervention remains critical. It is evident that the window for anti-inflammatory therapy to suppress excessive immune activation is very limited. Experimental and clinical evidence shows that the time limit for efficacious medical treatment is no more than 60 h from the onset of the symptoms of AP[223]. In fact, as stated by at least two controlled clinical trials including the European PAF-antagonist phase III trial[175, 224], beneficial effect was achieved when treatment was introduced no later than 48 hours after the onset of symptoms. Even though further trials are pivotal to clarify the proper timing for intervention, efforts are hampered by the fact that many patients present at a late stage of the disease, when organ failure may already be present and the patient may be already on his way to CARS or even immunosuppression[175].

This data challenges us to further explore and understand the tight balance and mechanisms underlying SIRS, CARS or even a mixed inflammatory response syndrome during the time-course of acute pancreatitis. In the last few years, an effort to monitor defects in monocyte function, as those reflected in reduced expression of HLA-DR during severe AP is under progress[107,225,226]. However, inflammatory stages may not be synchronous in the same patient, and even though immune-suppression may be evident in the peripheral blood, other end organs including the lungs may still be in the pro-inflammatory stage. Therefore, immune-stimulatory treatment must be used with caution and physicians should have the proper means to monitor the patients’ immune-inflammatory state, in order to most accurately identify patients who are at risk of organ failure. Signalling pathways and molecules of circulating leukocytes including HLA-DR, NF-κB, signal transducers and activators of transcription, and members of mitogen activated protein kinase family represent good candidates that could serve as future indices to identify the patients at risk for secondary infections and, thus, late organ failure[227-229].

Nonetheless, currently progress in AP research is slow, mainly due to the inaccessibility of the human pancreas to direct observation or biopsy, as well as, the self-destructive nature of the disease process itself which does not allow distinguishing initiating events from the concomitant or consequent inflammatory response. Flaws in study design, including small sample sizes, variable tools to stratify disease severity and non-comparable study endpoints further hinders understanding of this complex disease. Consequently, most of our knowledge comes either from circulating inflammatory mediators and cells or animal models that are inevitably unable to simulate the complexity and individuality of human condition[230-232]. As a result, the authors of this review note a relative gap in experimental but mostly clinical research pertaining to AP during the last decade. The latter is reflected in the year of publication of many of our references, in contrast to the flourishing field of animal model pancreatitis during the 90’s and the dawn of the new millennium.

The key to future advances lies in obtaining data upon actual patients, making use of correct scientific methods and better design of clinical trials[233]. Recording of other meaningful parameters besides mortality including time from the onset of symptoms to type of intervention, permanent target organ damage, quality of life, pain scores or hospital stay should also be recorded. Improvement of the communication of the results is also pivotal. Scientific and editorial community must share the responsibility of publishing well-designed and well-conducted clinical studies irrespective of commercial or financial influence. Examples of poor management of these issues could be partly mirrored by the controversial efficacy of protease inhibitors in human AP[234] as well as, the highly debated results following lexipafant administration[235].

**CONCLUSION**

Treatment of AP by immune modulation currently represents an attractive and highly promising concept. However, further meticulous work lies ahead in order to overcome the fundamental conceptual problems surrounding the complex pathophysiology of this challenging disease. Individualized and timely management calls for close monitoring so that best possible outcomes are ensured for our patients.

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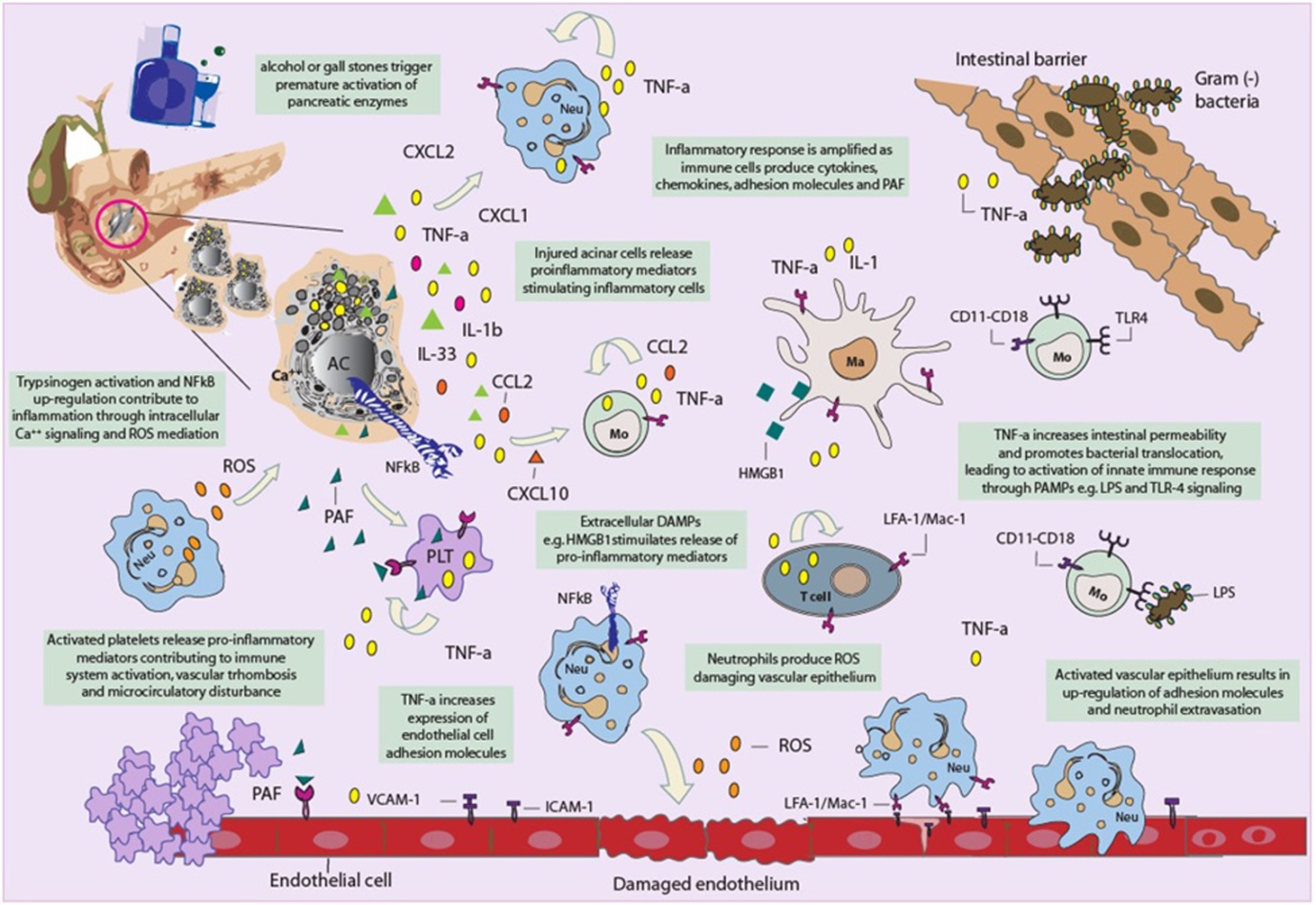
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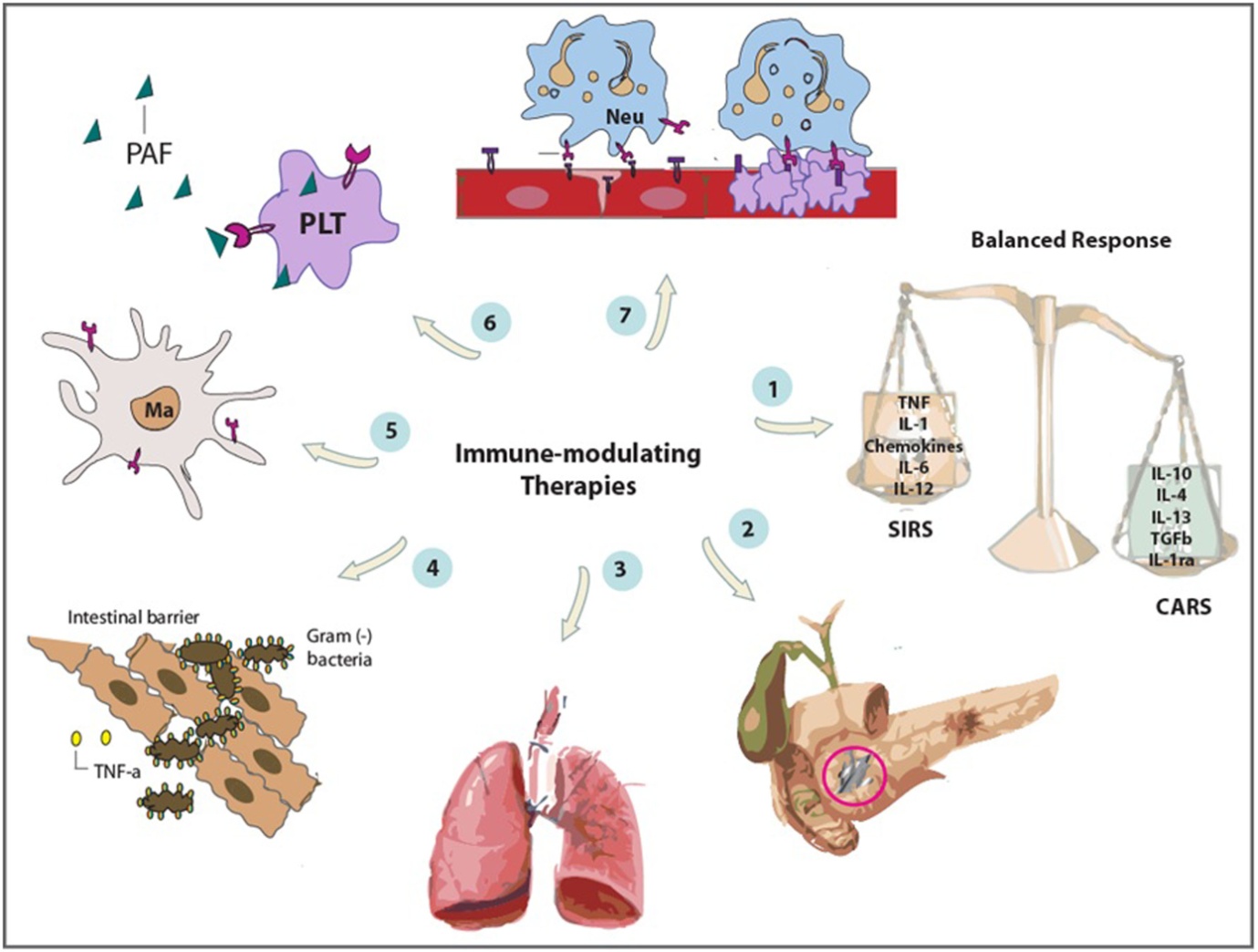
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**Figure 1** **Schematic representation of innate and adaptive immune response mechanisms implicated in acute pancreatitis.** Triggering factors initiate trypsinogen activation and pancreas autophagy. Damaged acinar cells release damage-associated molecular pattern molecules (DAMPs) and pro-inflammatory mediators attracting leukocytes at the site of inflammation. Leukocyte activation leads to increased leukocyte aggregation through increased expression of adhesion molecules and tissue infiltration within the microcirculation. There, these cells increase production of cytokines and other inflammatory mediators including prostaglandins, leukotrienes, thromboxanes, platelet activating factor (PAF), free radicals, nitric oxide and proteases. These substrates increase vascular permeability resulting in neutrophil extravasation and activation, oedema and microvascular disturbances which eventually lead to lack of oxygen and tissue injury. Pro-inflammatory mediators contribute to failure of intestinal barrier function and translocation of intestinal microflora or their products into the vascular bed. Neu: Neutrophil; AC: Acinar cell; Mo: Monocyte; Ma: Macrophage; ICAM-1: Intercelllular adhesion molecule 1; ROS: Reactive oxygen species; VCAM-1: Vascular adhesion molecule 1; TNF-α: Tumour necrosis factor alpha; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; IL: Interleukin; CXCL : C-X-C motif chemokine; CCL: Chemokine (C-C motif) ligand; PLT: Platelet; TLR: Toll like reseptor; LPS: Lipopolysaccharide; LFA: Lymphocyte function associated antigen; Mac-1: Macrophage-1 antigen.

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**Figure 2 Immune modulating therapies.** (1) Target inflammatory response promoting or attenuating anti and pro-inflammatory mediators respectively (recombinant cytokine/chemokine administration, cytokine/chemokine antagonists, receptor blockade); (2) ameliorate parenchymal and fatty tissue necrosis of the pancreas [*e.g.,* infliximab, blockade of interleukin (IL)-1 receptor, IL-10 blockade, IL-12 suppression, platelet activating factor (PAF)]; (3) alleviate alveolar oedema and development of acute respiratory distress syndrome (*e.g.,* infliximab, IL-10 blockade, IL-8 blockade); (4) correct intestinal barrier and prevent bacterial translocation (*e.g.,* anti-tumour necrosis factor, TNF); (5) modulate immune cell response (*e.g.,* stem cell immunosuppressive strategies); (6) impair platelet activation and further immune activation (*e.g.,* PAF); and (7) protect against endothelial barrier dysfunction, transmigration of neutrophils and concomitant microcirculatory derangements (*e.g.,* adhesion molecule blockade). Ma: Macrophage.