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New Frontiers in the Pharmacological Prevention of Post-ERCP Pancreatitis: The Cytokines

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Summary

Acute pancreatitis is a major complication of endoscopic retrograde cholangiopancreatography (ERCP), its incidence varying with the indications for the procedure (<5% for the management of common bile duct stones and up to 20% in the case of sphincter of Oddi dysfunction) and also with events occurring during the ERCP such as acinarization and pancreatic sphincterotomy.
If the triggering event of premature intra-acinar activation of trypsinogen is unknown, the acinar cell injury leads to oxidative stress, nuclear translocation of nuclear factor kappa B and subsequent transcription of chemo- and pro-inflammatory cytokines. These events are followed by chemoattraction and activation of monomacrophages, T lymphocytes and neutrophils which are responsible for acinar necrosis and amplification of the pro-inflammatory cascade. Finally, after amplification by Kupffer cells, systemic inflammatory response syndrome and multiple organ failure occur. All these events take place within a very short period of time, thus offering a very short therapeutic window during which it is theoretically possible to modulate the severity of human pancreatitis.
Prophylactic immunomodulation of this pro-inflammatory cascade is attractive, using anti-inflammatory cytokines, specific inhibitors of pro-inflammatory cytokines or inhibitors of the nuclear translocation of the nuclear factor kappa B. Good results have been obtained in experimental models, reducing the acute pancreatitis severity and its systemic complications.
The use of immunomodulators in the prevention of human post-ERCP pancreatitis is actually restricted to recombinant interleukin-10. Three of four randomized clinical trials, confirmed by a meta-analysis, have shown that prophylactic injection of recombinant interleukin-10 can significantly reduce the incidence of acute pancreatitis and may decrease the length of the hospital stay.
The use of recombinant interleukin-10 in this indication has to be established in a multicenter prospective trial and we need to investigate the safety and efficacy of other immunomodulatory drugs and develop new specific targets.

Cytokines and Acute Pancreatitis

Acute pancreatitis (AP) is a major complication of endoscopic retrograde cholangiopancreatography (ERCP), its incidence varying among indications for the procedure (<5% for the management of common bile duct stones and up to 20% in the case of sphincter of Oddi dysfunction [1, 2, 3]). If the triggering event of premature trypsinogen activation is still unknown in this particular case, all intra-cellular and intra-pancreatic pro-inflammatory cascades of events are the same as for other causes of AP.

Physiopathogeny of Acute Pancreatitis

Regardless of the etiology of acute pancreatitis, the first pancreatic events occur at the level of acinar cells. The primary injury of the acinar cell leads to intra-pancreatic

activation of trypsinogen and blockage of enzymes secretion. This is very quickly followed by the release of reactive oxygen intermediates (ROI) (within minutes) [4, 5] and oxidative stress responsible for the lesions of cells membranes and cytoskeleton, lipidic peroxidation, intra-cellular depletion of anti-oxidants such as reduced glutathione (GSH) and vitamins E, A, C and the translocation of the nuclear factor kappa B (NF-Kappa B) into the nucleus [6].

Nuclear translocation of NF-Kappa B has been well-demonstrated in several models of experimental AP induced by cerulein [7], taurocholate [8] or bile duct ligation [9] for example. Within the first 15 minutes following AP induction by cerulein injections, phosphorylation of inhibitory kappa B alpha (IKappa Bα) occurs, followed by that of IKappa Bβ, both leading to the detachment of NF-Kappa B units. These events induce the release and the nuclear translocation of NF-Kappa B1, followed by those of RelAp65 and finally NF-Kappa B2 [7, 10]. Within the nucleus, NF-Kappa B units will induce the transcription of several target genes. This results in intra-acinar transcription of chemokines - monocyte chemoattractant protein 1 (MCP-1), MOB-1, interleukin 8 (IL-8), interferon inducible protein 10 (IP-10), etc. [8, 11, 12] - which happens within the first 30 minutes. Transcription of pro-inflammatory cytokines such as IL-1, tumor necrosis factor alpha (TNF-α), IL-6 or those of adhesion molecules (i.e., intercellular adhesion molecule: ICAM-1) [13] occurs within the following hour. These expression and release of chemokines, adhesion molecules and pro-inflammatory cytokines is responsible for the pancreatic invasion by monomacrophages, T lymphocytes and polymorphonuclear neutrophils (PMN), but also for their activation and for their own release of pro-inflammatory mediators (including chemokines, cytokines, NO, elastase, etc.). This amplifies the intra-pancreatic pro-inflammatory cascade of events and finally activates hepatic Kupffer cells. These hepatic monomacrophages are the major systemic source of pro-inflammatory cytokines inducing systemic inflammatory response syndrome (SIRS) and multiple organ failure. In an experimental model of AP, hepatic Kupffer cell blockade reduces plasma levels of pro-inflammatory cytokines, the severity of acute respiratory distress syndrome (ARDS) lesions and related mortality [14, 15].

Physiopathology of Post-ERCP Pancreatitis

Currently, little is known about the physiopathogeny of post-ERCP pancreatitis. Several factors are mentioned such as chemical, mechanical or microbiological factors which can trigger the premature intra-acinar activation of trypsinogen into trypsin, and which have recently been reviewed by Pezzilli *et al*. [16]. But at this time, we have still not identified the cause of this activation.

As we know from human data, acinarization, due to high volume contrast (or air) injection and hyperpression in the pancreatic duct, is associated with an increased incidence of post-ERCP pancreatitis [16, 17, 18]. In their experimental study, Vaquero *et al*. [8] demonstrated that saline injection and secondary hyperpression within the rat pancreatic duct leads to nuclear translocation of NF-Kappa B and to the subsequent intra-acinar transcription of IL-6, MCP-1, KC, etc., but without any trypsinogen activation. We also know from other experimental studies that translocation of NF-Kappa B alone is not able to induce trypsinogen activation [19]. Therefore, the primary trigger of intra-acinar activation of trypsinogen is still not identified in post-ERCP pancreatitis. Nevertheless, intra-pancreatic transcription of pro-inflammatory cytokines is probably multifactorial in this case: activation of trypsinogen, intraductal hyperpression, oxidative stress, ischemia, etc..

Acinarization and intra-ductal hyperpression may probably increase the ischemia of the pancreatic tissue which occurs during AP. During tissue hypoperfusion, cells become ischemic and their reperfusion leads to oxidative stress, release of ROI, lipids peroxidation, transcription of pro-

Table 1. Experimental modulation of acute pancreatitis.

Authors	Modulator scavenger	Experimental model	Pancreatic lesions	Systemic complications
Guice [42]	SOD and catalase	Cerulein/Rat	Decrease	ND
Wisner [43]		Cerulein/Rat	Decrease	ND
Koichiro [44]		Ischemia-reperfusion/Rat	Decrease	ND
Schoenberg [45, 46]		Cerulein/Rat	Decrease	ND
Rutledge [47]		CDE/Mouse	No effect	No effect
Schoenberg [48]		Taurocholate/Rat	Decrease	ND
Lüthen [49]	OCT	Cerulein/Mouse	Decrease	ND
Neuschwander-Tétri [50]		Cerulein/Mouse	No effect	ND
Wisner [51]	Allopurinol	Cerulein/Rat	Decrease	ND
Niederau [52]		CDE/Mouse	Decrease	ND
Lankisch [53]		CDE/Mouse	No effect	ND
Norman [28]	mAb anti-TNF	CDE/Mouse	Decrease	Decrease
Hughes [29]		Bile duct infusion/Rat	Decrease	Decrease
Tanaka [31]	IL-1RA	Deoxycholate/Rat	Decrease	Decrease
Norman [30]		Cerulein/Mouse	Decrease	Decrease
Gukovsky [7]	PDTC	Cerulein/Rat	Decrease	ND
Fujimura [32]	Anti-PAF	Cerulein/Rat	Decrease	Decrease
Formela [33]		Microvascular ischemia/Rat	Decrease	Decrease
Rau [54]	mAb anti-ICAM	Taurocholate/Rat	Decrease	Decrease

CDE: cholin deficient ethionin supplemented diet
ICAM: intercellular adhesion molecule
IL-1 RA: interleukin-1 receptor antagonist
mAb: monoclonal antibody
ND: not determined
OCT: L-2-oxothiazolidine-4-carboxylate
PAF: platelet activating factor
PDTC: pyrrolidine dithiocarbamate
SOD: superoxide dismutase

inflammatory cytokines, and finally chemoattraction of monomacrophages and PMN which, in turn, increase the pro-inflammatory cascade and induce tissue necrosis.

Furthermore, as in every AP (whatever its etiology), nuclear translocation of NF-Kappa B and subsequent chemo- and pro-inflammatory cytokine transcription occur in post-ERCP pancreatitis [20, 21], therefore representing ideal targets for an immunomodulation.

Experimental Immunomodulation of Acute Pancreatitis

Immune mechanisms and their modulation have become a major topic of interest in acute pancreatitis; there are many experimental studies which have shown that early modulation of pancreatitis is feasible (Table 1). However, it has also become clear that all these modalities are effective when the drugs are given before or shortly after the appearance of the disease. This observation correlates in clinical practice with the fact that only a narrow therapeutic window exists during which it is still possible to modulate the severity of acute pancreatitis. Therefore, there are two potential clinical settings in which immunomodulation could be attempted: the early modulation of predicted severe cases and the modulation of the unique model of AP that exists in human, namely post-ERCP, acute pancreatitis. Indeed, we know that in high risk cases, we will induce pancreatitis, by endoscopic manipulation, in 5-20% of the cases [22, 23, 24].

Modulation of oxidative stress is a matter of study and different anti-oxidative compounds have been already tested, with varying success only when administered before AP induction. Even if this theory is interesting, it is not the purpose of this review.

Trying to reduce or to block the synthesis and the release of pro-inflammatory cytokines is a unique method for the immunomodulation of AP. Modulation of synthesis, release and bioactivity of pro-inflammatory cytokines can theorically be performed by:

- general inhibition of cytokine transcription using drugs or cytokines which block or reduce nuclear translocation of NF-Kappa B, and thus subsequent target gene transcription: IL-10, N-acetylcystein (NAC), catalase, corticoids, etc.;
- post-transcriptional specific inhibition: IL-10, IL-11;
- specific inhibition of bioactivity: monoclonal antibodies, receptor antagonists.

Experimentally, in mice and rats, pyrolidine dithiocarbamate (PDTC) [7], recombinant IL-10 [25, 26] , recombinant IL-11 [27], monoclonal antibodies and soluble receptors to TNF-α [28, 29] and interleukin-1 receptor antagonist (IL-1 RA) [30, 31], platelet activating factor (PAF) antagonist [32, 33] administration have already been tested and allow the reduction and control of the release of pro-inflammatory cytokines, and the severity of AP lesions and their systemic complications.

Up to now, in clinical practice, only IL-10 has been used for this indication.

Interleukin 10 and Acute Pancreatitis

IL-10

Briefly, IL-10 is a pleiotrophic cytokine expressed by almost all cells but principally by activated monomacrophages and Th2 CD4+ T lymphocytes [34].

This cytokine discloses major anti-inflammatory properties acting through 1) an inhibition of nuclear translocation of NF-Kappa B and subsequent transcription of target genes including pro-inflammatory cytokines such as IL-1, TNF-α or adhesion molecules such as ICAM-1 [35]; 2) the post-transcriptional control of cytokines by enhancing their mRNA instability (i.e. TNF-α) [36]; 3) the induction of natural agonists of

Table 2. Experimental modulation of acute pancreatitis severity using IL-10.

Authors	Design	Timing of drug administration	Experimental model	Pancreatic lesions	ARDS	Mortality
Kusske [25]	rIL-10	At induction then every 8 h	Mice	Decrease	ND	Decrease
		After 33 h then every 8 h	CDE	Decrease	ND	Decrease
Rongione [55]	rIL-10	1 h before then every 3 h	Rat	Decrease	ND	ND
		2 h after then every 3 h	Cerulein	Decrease	ND	ND
van Laethem [26]	rIL-10	30 min before, then every 4 h	Mice Cerulein	Decrease	ND	ND
Osman [56]	IT 9302 (IL-10 agonist)	30 min before	Rabbits Bile injection	Unchanged	Decrease	Decrease
Gloor [57]	IL-10 KO		Mice CDE	Increase	Increase	ND
van Laethem [58]	Anti IL-10 mAb	2 h before	Mice Cerulein	Increase	Increase	ND

CDE: cholin deficient ethionin supplemented diet
KO: knock out
mAb: monoclonal antibody
ND: not determined
rIL: recombinant interleukin

cytokines (IL-1 or TNF-α [37]); 4) the capability of deactivating macrophages [34] and decreasing macrophage antigen-presenting cell (APC) function through the inhibition of major histocompatibility complex (MCH) class II molecules, B7-1 and ICAM-1 expression [34, 38]; 5) by inducing Th2 phenotype of CD4+ T lymphocytes [39].
It must be noted however that, regardless of its anti-inflammatory properties, IL-10 induces recruitment, growth and differentiation of CD8+ T lymphocytes, natural killer and B lymphocytes. Its also enhances the cytotoxic properties of natural killer cells and CD8+ T lymphocytes [34]. Therefore, its clinical use by systemic administration seems to be better adapted to modulating an acute inflammatory condition.

IL-10 and Experimental Acute Pancreatitis

Prophylactic or early therapeutic injection of recombinant interleukin 10 (rIL-10) reduces AP severity and its systemic complications in various experimental models (Table 2). On the contrary, injection of specific antagonists (i.e., IT 9302) or genetic defects of IL-10 (IL-10 knock out (KO) animals) increase the severity of pancreatic and associated systemic lesions (Table 2).

IL-10 and Post-ERCP Acute Pancreatitis

Based on previously described anti-inflammatory properties of IL-10 and on experimental animal data, trials have been designed with the aim of reducing the incidence of post-ERCP pancreatitis by IL-10 prophylactic administration.
In 2001, our group reported on a single-center, double blind, placebo-controlled trial performed on 144 patients comparing a single injection of recombinant human IL-10 (at 2 different doses: 4 and 20 μg/kg, respectively) given 30 minutes before an ERCP procedure, to a placebo [18]. If primarily designed to evaluate the safety of rIL-10 treatment and its effects on hyper-hydrolasemia, this trial demonstrated that a single injection of rIL-10 given 30 minutes before ERCP was able to decrease the incidence of post-ERCP pancreatitis independently of other risk factors, with an odds ratio (OR) of 0.46. Two other independant risk factors were identified: pancreatic sphincterotomy (OR: 5.04) and acinarization (OR: 8.19) stressing the fact that IL-10 could also be effective in these very high risk cases. Moreover, rIL-10 treatment tended to decrease serum TNF release in patients presenting hyperhydrolasemia, and to decrease the length of the hospital stay.
Another important double-blind placebo-controlled study was published in 2001 but was not conclusive [40]. Two hundred patients were included: 101 of them received rIL-10 at a dose of 8 μg/kg and 99 received a placebo i.v. injection 15 minutes before ERCP. If rIL-10 treatment tended to decrease the incidence of pancreatitis and to reduce the length of hospitalization, it did not reach statistical significance, probably because it focused on lower risk patients, including those undergoing diagnostic ERCP.
To date, four randomized clinical trials have been performed and were the subject of a meta-analysis [Singh *et al.*, DDW2002, abstract T1726] concluding that IL-10 is effective in the prevention of post-ERCP acute pancreatitis. Pooling all patients, 294 patients received IL-10 before ERCP and 259 patients received a placebo. The incidence of post-ERCP pancreatitis was 7.1% in the IL-10 groups, and 13.9% in the placebo groups. Statistical analysis concluded that IL-10 significantly reduces the risk of AP (relative risk: 0.46, P=0.003; absolute risk reduction: 6.8%).
Even if the use of rIL-10 in the form of a prophylactic intravenous injection seems to be effective in preventing post-ERCP pancreatitis, this cytokine has advantages and disadvantages, and there are still questions about the standards of its administration. rIL-10 is easy to use and only needs one i.v. bolus injection before ERCP. Moreover, it remains active for 24 hours [41] and can be administered to patients treated on an ambulatory basis. Unfortunately, the cost is still unknown and could be a limiting factor for general administration. It is also necessary

to define the lowest effective dose. Moreover, if we can select patients at higher risk of AP (acinarization, sphincterotomy), we will be able to restrict rIL-10 administration to these cases only. As a parallel with animal studies (Table 2), effectiveness of a delayed injection (during or immediately after the ERCP procedure) might be preserved, but this needs to be confirmed by future studies. A multicenter study is now ongoing in the US and Europe.

Conclusions: Future of Immunomodulation

Acute pancreatitis is a frequent and major complication of ERCP. Its incidence varies greatly according to the indications and also with events occurring during the ERCP such as acinarization, pancreatic sphincterotomy and the need for precutting.
If the use of rIL-10 in the prevention of post-ERCP pancreatitis is relatively well-established, it needs to be refined and definitively proven and, to this end, there is currently a large ongoing multicenter study.
The use of other immunomodulatory drugs also deserves attention. Three specific targets should be investigated: decreasing or blocking the nuclear translocation of NF-Kappa B, development and use of other anti-inflammatory cytokines and specific neutralization of pro-inflammatory cytokines. In experimental animal models, all these targets have been studied. Even if such animal models are very important and helpful, clinical application is generally limited due to the toxicity of some compounds or to their secondary effects. Therefore, we need to test the efficacy and safety of existing molecules, but also to develop and discover new specific targets and drugs which are safe for human administration.

Keywords Acute Disease; Cytokines; Interleukin-10; NF-kappa B; Pancreatitis

Abbreviations AP: acute pancreatitis; APC: antigen-presenting cell; ARDS: acute respiratory distress syndrome; CDE: cholin deficient ethionin supplemented diet; ERCP: endoscopic retrograde cholangiopancreatography; GSH: reduced glutathione; ICAM: intercellular adhesion molecule; IKappa B: inhibitory kappa B; IL: interleukin; IL-1 RA: interleukin-1 receptor antagonist; IP-10: interferon inducible protein 10; KO: knock out; mAb: monoclonal antibody; MCH: major histocompatibility complex; MCP: monocyte chemoattractant protein; NAC: N-acetylcystein; ND: not determined; NF-Kappa B: nuclear factor kappa B; OCT: L-2-oxothiazolidine-4-carboxylate; OR: odds ratio; PAF: platelet activating factor; PDTC: pyrrolidine dithiocarbamate; PMN: polymorphonuclear neutrophils; rIL: recombinant interleukin; ROI: reactive oxygen intermediates; SIRS: systemic inflammatory response syndrome; SOD: superoxide dismutase; TNF: tumor necrosis factor

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References

1. Sherman S, Ruffolo TA, Hawes RH, Lehman GA. Complications of endoscopic sphincterotomy. A prospective series with emphasis on the increased risk associated with sphincter of Oddi dysfunction and nondilated bile ducts. Gastroenterology 1991; 101:1068-75. [AN 91365172]

2. Sherman S, Troiano FP, Hawes RH, Lehman GA. Sphincter of Oddi manometry: decreased risk of clinical pancreatitis with use of a modified aspirating catheter. Gastrointest Endosc 1990; 36:462-6. [AN 91032838]

3. Loperfido S, Angelini G, Benedetti G, Chilovi F, Costan F, De Berardinis F, et al. Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. Gastrointest Endosc 1998; 48:1-10. [AN 98347799]

4. Gough DB, Boyle B, Joyce WP, Delaney CP, McGeeney KF, Gorey TF, Fitzpatrick JM. Free radical inhibition and serial chemiluminescence in evolving experimental pancreatitis. Br J Surg 1990; 77:1256-9. [AN 91070205]

5. Nonaka A, Manabe T, Tamura K, Asano N, Imanishi K, Yamaki K, Tobe T. [Organ specific ESR features in mouse main organs and ESR application to the model of pancreatic disorders]. Nippon Geka Gakkai Zasshi 1990; 91:169-73. [AN 90220461]

6. Muller JM, Rupec RA, Baeuerle PA. Study of gene regulation by NF-kappa B and AP-1 in response to reactive oxygen intermediates. Methods 1997; 11:301-12. [AN 97237070]

7. Gukovsky I, Gukovskaya AS, Blinman TA, Zaninovic V, Pandol SJ. Early NF-kappaB activation is associated with hormone-induced pancreatitis. Am J Physiol 1998; 275:G1402-14. [AN 99061624]

8. Vaquero E, Gukovsky I, Zaninovic V, Gukovskaya AS, Pandol SJ. Localized pancreatic NF-kappaB activation and inflammatory response in taurocholate-induced pancreatitis. Am J Physiol Gastrointest Liver Physiol 2001; 280:G1197-208. [AN 21250583]

9. Dunn JA, Li C, Ha T, Kao RL, Browder W. Therapeutic modification of nuclear factor kappa B binding activity and tumor necrosis factor-alpha gene expression during acute biliary pancreatitis. Am Surg 1997; 63:1036-43. [AN 98054960]

10. Steinle AU, Weidenbach H, Wagner M, Adler G, Schmid RM. NF-kappaB/Rel activation in cerulein pancreatitis. Gastroenterology 1999; 116:420-30. [AN 99122967]

11. Han B, Logsdon CD. Cholecystokinin induction of mob-1 chemokine expression in pancreatic acinar cells requires NF-kappaB activation. Am J Physiol 1999; 277:C74-82. [AN 99345657]

12. Demols A, Le Moine O, Desalle F, Quertinmont E, Van Laethem JL, Deviere J. CD4(+)T cells play an important role in acute experimental pancreatitis in mice. Gastroenterology 2000; 118:582-90. [AN 20167112]

13. Zaninovic V, Gukovskaya AS, Gukovsky I, Mouria M, Pandol SJ. Cerulein upregulates ICAM-1 in pancreatic acinar cells, which mediates neutrophil adhesion to these cells. Am J Physiol Gastrointest Liver Physiol 2000; 279:G666-76. [AN 20461694]

14. Gloor B, Todd KE, Lane JS, Lewis MP, Reber HA. Hepatic Kupffer cell blockade reduces mortality of acute hemorrhagic pancreatitis in mice. J Gastrointest Surg 1998; 2:430-5. [AN 99059989]

15. Gloor B, Blinman TA, Rigberg DA, Todd KE, Lane JS, Hines OJ, Reber HA. Kupffer cell blockade reduces hepatic and systemic cytokine levels and lung injury in hemorrhagic pancreatitis in rats. Pancreas 2000; 21:414-20. [AN 20525256]

16. Pezzilli R, Romboli E, Campana D, Corinaldesi R. Mechanisms Involved in the Onset of Post-ERCP Pancreatitis. JOP. J Pancreas (Online) 2002; 3:162-8. [AN 22319326]

17. Kasugai T, Kuno N, Kizu M. Manometric endoscopic retrograde pancreatography: technique, significance and evaluation. Am J Dig Dis 1974; 19:485-502. [AN 74167051]

18. Deviere J, Le Moine O, van Laethem JL, Eisendrath P, Ghilain A, Severs N, Cohard M. Interleukin-10 reduces the incidence of pancreatitis after therapeutic endoscopic retrograde cholangiopancreatography. Gastroenterology 2001; 120:498-505. [AN 21100083]

19. Hietaranta AJ, Saluja AK, Bhagat L, Singh VP, Song AM, Steer ML. Relationship between NF-kappaB and trypsinogen activation in rat pancreas after supramaximal caerulein stimulation. Biochem Biophys Res Commun 2001; 280:388-95. [AN 21092616]

20. Kaw M, Singh S. Serum lipase, C-reactive protein, and interleukin-6 levels in ERCP-induced pancreatitis. Gastrointest Endosc 2001; 54:435-40. [AN 21460529]

21. Oezcueruemez-Porsch M, Kunz D, Hardt PD, Fadgyas T, Kress O, Schulz HU, et al. Diagnostic relevance of interleukin pattern, acute-phase proteins, and procalcitonin in early phase of post-ERCP pancreatitis. Dig Dis Sci 1998; 43:1763-9. [AN 98389559]

22. Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, et al. Complications of endoscopic biliary sphincterotomy. N Engl J Med 1996; 335:909-18. [AN 96365275]

23. Freeman ML, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, et al. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. Gastrointest Endosc 2001; 54:425-34. [AN 21460528]

24. Loperfido S, Angelini G, Benedetti G, Chilovi F, Costan F, De Berardinis F, et al. Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. Gastrointest Endosc 1998; 48:1-10. [AN 98347799]

25. Kusske AM, Rongione AJ, Ashley SW, McFadden DW, Reber HA. Interleukin-10 prevents death in lethal necrotizing pancreatitis in mice. Surgery 1996; 120:284-8. [AN 96350353]

26. van Laethem JL, Marchant A, Delvaux A, Goldman M, Robberecht P, Velu T, Deviere J. Interleukin 10 prevents necrosis in murine experimental acute pancreatitis. Gastroenterology 1995; 108:1917-22. [AN 95286011]

27. Shimizu T, Shiratori K, Sawada T, Kobayashi M, Hayashi N, Saotome H, Keith JC. Recombinant human

interleukin-11 decreases severity of acute necrotizing pancreatitis in mice. Pancreas 2000; 21:134-40. [AN 20427446]

28. Norman JG, Fink GW, Messina J, Carter G, Franz MG. Timing of tumor necrosis factor antagonism is critical in determining outcome in murine lethal acute pancreatitis. Surgery 1996; 120:515-21. [AN 96378843]

29. Hughes CB, Gaber LW, Mohey el-Din AB, Grewal HP, Kotb M, Mann L, Gaber AO. Inhibition of TNF alpha improves survival in an experimental model of acute pancreatitis. Am Surg 1996; 62:8-13. [AN 96127847]

30. Norman J, Franz M, Messina J, Riker A, Fabri PJ, Rosemurgy AS, Gower WR Jr. Interleukin-1 receptor antagonist decreases severity of experimental acute pancreatitis. Surgery 1995; 117:648-55. [AN 95296868]

31. Tanaka N, Murata A, Uda K, Toda H, Kato T, Hayashida H, et al. Interleukin-1 receptor antagonist modifies the changes in vital organs induced by acute necrotizing pancreatitis in a rat experimental model. Crit Care Med 1995; 23:901-8. [AN 95254836]

32. Fujimura K, Kubota Y, Ogura M, Yamaguchi T, Binnaka T, Tani K, et al. Role of endogenous platelet-activating factor in caerulein-induced acute pancreatitis in rats: protective effects of a PAF-antagonist. J Gastroenterol Hepatol 1992; 7:199-202. [AN 92239729]

33. Formela LJ, Wood LM, Whittaker M, Kingsnorth AN. Amelioration of experimental acute pancreatitis with a potent platelet-activating factor antagonist. Br J Surg 1994; 81:1783-5. [AN 95128746]

34. Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. Annu Rev Immunol 2001; 19:683-765. [AN 21139833]

35. Schottelius AJ, Mayo MW, Sartor RB, Baldwin AS Jr. Interleukin-10 signaling blocks inhibitor of kappaB kinase activity and nuclear factor kappaB DNA binding. J Biol Chem 1999; 274:31868-74. [AN 20011377]

36. Clarke CJ, Hales A, Hunt A, Foxwell BM. IL-10-mediated suppression of TNF-alpha production is independent of its ability to inhibit NF kappa B activity. Eur J Immunol 1998; 28:1719-26. [AN 98264642]

37. Seitz M, Loetscher P, Dewald B, Towbin H, Gallati H, Baggiolini M. Interleukin-10 differentially regulates cytokine inhibitor and chemokine release from blood mononuclear cells and fibroblasts. Eur J Immunol 1995; 25:1129-32. [AN 95255403]

38. Ding L, Linsley PS, Huang LY, Germain RN, Shevach EM. IL-10 inhibits macrophage costimulatory activity by selectively inhibiting the up-regulation of B7 expression. J Immunol 1993; 151:1224-34. [AN 93329101]

39. Mosmann TR, Sad S. The expanding universe of T-cell subsets: Th1, Th2 and more. Immunol Today 1996; 17:138-46. [AN 96417481]

40. Dumot JA, Conwell DL, Zuccaro G Jr, Vargo JJ, Shay SS, Easley KA, Ponsky JL. A randomized, double blind study of interleukin 10 for the prevention of ERCP-induced pancreatitis. Am J Gastroenterol 2001; 96:2098-102. [AN 21360265]

41. van Deventer SJ, Elson CO, Fedorak RN. Multiple doses of intravenous interleukin 10 in steroid-refractory Crohn's disease. Crohn's Disease Study Group. Gastroenterology 1997; 113:383-9. [AN 97390597]

42. Guice KS, Miller DE, Oldham KT, Townsend CM Jr, Thompson JC. Superoxide dismutase and catalase: a possible role in established pancreatitis. Am J Surg 1986; 151:163-9. [AN 86127952]

43. Wisner J, Green D, Ferrell L, Renner I. Evidence for a role of oxygen derived free radicals in the pathogenesis of caerulein induced acute pancreatitis in rats. Gut 1988; 29:1516-23. [AN 89092106]

44. Koichiro T, Manabe T, Tobe T. [Effect of short-term-ischemia and reperfusion on the rat pancreas]. Nippon Geka Hokan 1991; 60:335-41. [AN 92313195]

45. Schoenberg MH, Buchler M, Schadlich H, Younes M, Bultmann B, Beger HG. Involvement of oxygen radicals and phospholipase A2 in acute pancreatitis of the rat. Klin Wochenschr 1989; 67:166-70. [AN 89179733]

46. Schoenberg MH, Buchler M, Gaspar M, Stinner A, Younes M, Melzner I, et al. Oxygen free radicals in acute pancreatitis of the rat. Gut 1990; 31:1138-43. [AN 91192645]

47. Rutledge PL, Saluja AK, Powers RE, Steer ML. Role of oxygen-derived free radicals in diet-induced hemorrhagic pancreatitis in mice. Gastroenterology 1987; 93:41-7. [AN 87219735]

48. Schoenberg MH, Buchler M, Younes M, Kirchmayr R, Bruckner UB, Beger HG. Effect of antioxidant treatment in rats with acute hemorrhagic pancreatitis. Dig Dis Sci 1994; 39:1034-40. [AN 94228873]

49. Luthen R, Grendell JH, Haussinger D, Niederau C. Beneficial effects of L-2-oxothiazolidine-4-carboxylate on cerulein pancreatitis in mice. Gastroenterology 1997; 112:1681-91. [AN 97282539]

50. Neuschwander-Tetri BA, Barnidge M, Janney CG. Cerulein-induced pancreatic cysteine depletion: prevention does not diminish acute pancreatitis in the mouse. Gastroenterology 1994; 107:824-30. [AN 94357383]

51. Wisner JR, Renner IG. Allopurinol attenuates caerulein induced acute pancreatitis in the rat. Gut 1988; 29:926-9. [AN 88284505]

52. Niederau C, Niederau M, Borchard F, Ude K, Luthen R, Strohmeyer G, et al. Effects of antioxidants and free radical scavengers in three different models of acute pancreatitis. Pancreas 1992; 7:486-96. [AN 92350796]

53. Lankisch PG, Pohl U, Otto J, Wereszczynska-Siemiatkowska U, Grone HJ. Xanthine oxidase inhibitor in acute experimental pancreatitis in rats and mice. Pancreas 1989; 4:436-40. [AN 89345475]

54. Rau B, Bauer A, Wang A, Gansauge F, Weidenbach H, Nevalainen T, et al. Modulation of endogenous nitric oxide synthase in experimental acute pancreatitis: role of anti-ICAM-1 and oxygen free radical scavengers. Ann Surg 2001; 233:195-203. [AN 21091730]

55. Rongione AJ, Kusske AM, Kwan K, Ashley SW, Reber HA, McFadden DW. Interleukin 10 reduces the severity of acute pancreatitis in rats. Gastroenterology 1997; 112:960-7. [AN 97193674]

56. Osman MO, Jacobsen NO, Kristensen JU, Deleuran B, Gesser B, Larsen CG, Jensen SL. IT 9302, a synthetic interleukin-10 agonist, diminishes acute lung injury in rabbits with acute necrotizing pancreatitis. Surgery 1998; 124:584-92. [AN 98408120]

57. Gloor B, Todd KE, Lane JS, Rigberg DA, Reber HA. Mechanism of increased lung injury after acute pancreatitis in IL-10 knockout mice. J Surg Res 1998; 80:110-4. [AN 99009159]

58. van Laethem JL, Eskinazi R, Louis H, Rickaert F, Robberecht P, Deviere J. Multisystemic production of interleukin 10 limits the severity of acute pancreatitis in mice. Gut 1998; 43:408-13. [AN 99080856]