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REVIEW

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New insights into the etiology, risk factors, and pathogenesis of pancreatitis in dogs: Potential impacts on clinical practice

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[Correction added on 28 May 2022, after first online publication: The phrase "uncoupled protein response" has been replaced with "unfolded protein response" on pages 1 (abbreviations), 10, 11 (Figure 6), and 12 (Figure 8).]

Abstract

While most cases of pancreatitis in dogs are thought to be idiopathic, potential risk factors are identified. In this article we provide a state-of-the-art overview of suspected risk factors for pancreatitis in dogs, allowing for improved awareness and detection of potential dog-specific risk factors, which might guide the development of disease prevention strategies. Additionally, we review important advances in our understanding of the pathophysiology of pancreatitis and potential areas for therapeutic manipulation based thereof. The outcome of pathophysiologic mechanisms and the development of clinical disease is dependent on the balance between stressors and protective mechanisms, which can be evaluated using the critical threshold theory.

KEYWORDS
colocalization, critical threshold theory, ER stress, impaired autophagy, mitochondrial dysfunction, oxidative stress, pathologic calcium signaling

1 | INTRODUCTION

The etiology and pathogenesis of spontaneous pancreatitis are poorly understood in both humans and dogs and data is largely extrapolated from experimental models and observations in clinical disease. Experimental models provide mechanistic insights; however, spontaneous disease is likely far more complex and dependent on multiple genetic and environmental factors, some of which might be unknown. Additionally, animal models provide species-specific or etiology-specific data, which might not be directly relevant to spontaneous disease. Clinical observations are also not without limitations, and the complexity of spontaneous disease often limits determination of causation. Furthermore, discrepancies in diagnostic standards and evolution of these criteria over time likely further complicate interpretation of observational data in companion animal species. In this review we will utilize a combination of data types to review the latest understanding of the etiology, risk factors, and pathogenesis of pancreatitis in dogs and their relation to clinical disease.

Abbreviations: AP, acute pancreatitis; cPLI, canine pancreatic lipase immunoreactivity; cTLI, canine trypsin like immunoreactivity; DGGR, 1,2-O-dilauryl-rac-glycero glutaric acid-(6′-methylresorudin) ester; DM, diabetes mellitus; ER, endoplasmic reticulum; HAC, hyperadrenocorticism; ICAM-1, immunoglobulin-like cell adhesion molecule 1; IL, interleukin; KBr, potassium bromide; LAMP-1, lysosomal membrane protein 1; LAMP-2, lysosomal membrane protein 2; LFA-1, leukocyte function antigen-1; MPTP, mitochondrial permeability transition pores; NEFA's, nonesterified fatty acids; NF-κB, nuclear factor-kappa beta; OR, odds ratio; PB, phenobarbital; PSTI, pancreatic secretory trypsin inhibitor; ROS, reactive oxygen species; SPINK1, serine protease inhibitor Kazal type 1; STAT3, signal transducer and activator of transcription 3; TNF-α, tumor necrosis factor alpha; UPR, unfolded protein response.

2 | ETIOLOGY AND POTENTIAL RISK FACTORS FOR PANCREATITIS

The etiology of pancreatitis is much better understood in humans than in dogs. A systematic review and meta-analysis revealed that gallstones were the most frequent cause of acute pancreatitis in humans, followed by alcoholic pancreatitis (with geographical differences).[1]

TABLE 1 Suggested risk factors for pancreatitis in dogs

Category	Potential risk factor
Dietary factors	High fat diet[2–4]
	Ingestion of unusual food items[5,6]
	Ingestion of table scraps[5]
	Ingestion of trash[5]
Drugs/toxins	L-asparaginase[7,8]
	Phenobarbital and potassium bromide[9–11a]
	Azathioprine[12–14]
	Potentiated sulfonamides[15]
	Organophosphates[12,16]
	Corticosteroids,[12,17b]
	Furosemide[12]
	Atovaquone/proguanil (Malarone)[18]
	N-methyl-glucamine (Meglumine),[19b]
	Clomipramine[20]
	Zinc[21]
Endocrinopathies	Hyperadrenocorticism[12,22,23a]
	Hypothyroidism[12a]
	Diabetes mellitus,[12,24,25ac]
Hereditary/breed predispositions	SPINK 1 mutation,[26,27b]
	Acute: Terrier breeds, miniature poodles, dachshunds, cocker spaniel, Alaskan malamute, laika, miniature schnauzer[12,28–31]
	Chronic: Cavalier King Charles spaniel, collies, boxers[32]
Lipid disorders	Hypertriglyceridemia[28,29,33]
Miscellaneous	Babesiosis[34–36]
	Canine monocytic ehrlichiosis[37]
	Schistosomiasis (*Heterobilharzia americana*)[38–40]
	Honeybee envenomation[41]
	Organic acidemias[42]
	Immunoglobulin G4-related disease[43,44]
	Increasing age[12]
	Obesity/overweight status[5,12]
	Neutered status[5,12]
	Previous surgery[5]
	Hepatitis/cholangitis[45]

Note: Potential risk factors for AP in dogs. Many of these factors are implied by a temporal association alone and causation has not been established for many of these factors. Additionally, various definitions and indicators of AP were utilized in the referenced studies and clinical signs of AP were not always noted, thus some of these risk factors might represent risk factors for subclinical pancreatic injury rather than primary clinical AP. The relationship between the proposed risk factors and pancreatitis is often challenging to determine clinically and for some risk factors the direction of causation cannot be determined.

[aa]May be due to secondary lipid abnormalities.

[b]Contradictory evidence exists.

[c]Reverse direction of causation has been suggested.

The third most common cause is idiopathic acute pancreatitis (AP), which is suspected to be the most common cause in dogs.[1] It is important to note that research into the etiology of pancreatitis in dogs is limited. The term cryptogenic AP, might also, more accurately reflect the level of diagnostic investigation commonly performed into specific etiologies in dogs. In other words, pancreatitis in dogs might be classified as idiopathic, not because there is no underlying cause, but because the potential underlying causes have not been sufficiently studied.

Many factors have been identified as potential risks for AP in dogs. These factors are often established based on a temporal association with the onset of clinical signs, and it is important to consider that these risk factors might not represent a causative relationship. These risk factors can be broken down into: dietary factors, lipid disorders, drug and toxins, endocrinopathies, hereditary/breed predispositions, and miscellaneous causes (see Table 1).

2.1 | Dietary factors

High fat diets induce or worsen the severity of pancreatitis in dogs leading to the belief that high-fat diets are a predisposing factor to AP.[2,46] Unfortunately consensus criteria regarding what constitutes a high fat diet is lacking. However, a low-fat diet is considered to contain less than 20% fat on a metabolizable energy basis.[47] Animal models document associations with high protein and fat diets in the development of AP.[48–51] Further potential evidence for the role of high-fat diets in the development of AP comes from the results of a study evaluating ketogenic diets in the management of idiopathic epilepsy.[3] In that study 3/9 dogs fed a ketogenic diet (57% fat, 5.8% NFE, 25% crude protein; as dry matter) developed pancreatitis whereas only 2/31 dogs fed the control diet (16% crude fat, 54% NFE, 25% crude protein; as dry matter) developed pancreatitis.[3] This study is published in abstract form and information needed to calculate the fat content on an energy basis is unavailable. Additionally, the method of pancreatitis diagnosis is not reported. A more recent study prospectively evaluated the effect of dietary composition on serum concentrations of canine pancreatic lipase immunoreactivity (cPLI).[52] In that study there was no difference in serum cPLI concentration between a maintenance dog food (4.01 g of fat/100 kcal, 16% crude fat) and a low fat dog food (1.55 g of fat/100 kcal, 5% crude fat), but it is important to note that the dogs were all healthy dogs and that none of the diets are considered high in fat.[52] While the study investigated the effect of dietary fat content on serum cPLI concentration, this study cannot be extended to infer the effects of high fat diets on the development of pancreatitis. In another study 2/50 dogs receiving a struvite dissolution diet (5.7 g/100 kcal, 26.3% crude fat) were noted to develop pancreatitis.[4] A control group was not used as part of the study design and the basis for a diagnosis of pancreatitis is not reported. Given the current literature definitive conclusions on the significance of high levels of dietary fat in the development of pancreatitis cannot be made. Controlled clinical trials are required to evaluate this potential relationship. Further studies are also required to determine the influence of the type of fat on AP in dogs,

given differences in endoplasmic reticulum stress noted in in vitro studies.[53] The role that diet plays in the development of AP is also complicated by its association with other predisposing factors including obesity and hypertriglyceridemia. Two retrospective studies have identified potential relationships between being overweight and development of AP.[5,12] In a retrospective study 39/101 dogs diagnosed with AP were overweight and being overweight is associated with a 1.3× increased risk of AP.[5,12] Unusual food items (odds ratio [OR]: 4.3), table scraps (OR: 2.2) and access to the trash (OR: 13.2) increases the risk of pancreatitis in dogs.[5,6] It should be noted that this study is an association study and thus the level of evidence for a causative relationship should be considered weak. Additional factors other than dietary fat alone might modulate the disease risk toward pancreatitis and severe disease in a given dog. Potential factors might include the level of intrapancreatic and visceral fat present and its composition.[54,55] This phenomenon is observed in people with alcoholic pancreatitis.[56] While a certain daily consumption of alcohol is a significant risk factor for developing acute pancreatitis, certainly only the minority of human patients with such alcohol consumption develop pancreatitis.[56] Phosphate status (eg, hypophosphatemia) is a risk modifying factor in alcohol induced pancreatitis in people.[57] Unfortunately, these risk modifying factors are poorly understood in dogs fed a high fat diet.

2.2 | Lipid disorders

Hypertriglyceridemia is commonly investigated as a cause of AP given the results of ex vivo and in vivo studies. Triglycerides are hydrolyzed by pancreatic lipase, thus high levels of triglycerides might result in excessive production of free fatty acids which are toxic to pancreatic acinar cells.[58] Addition of triglycerides to a perfused canine pancreas results in structural changes including edema, hemorrhage, and weight gain suggestive of pancreatic injury.[59] Clinical studies evaluating the correlation between hypertriglyceridemia and AP have been focused on the miniature schnauzer. Miniature schnauzers with a history of pancreatitis are more likely to have hypertriglyceridemia than those without a history of pancreatitis (77% vs 33%) and there is an association between hypertriglyceridemia and elevated serum cPLI concentrations.[28,29] Additionally, severe hypertriglyceridemia (≥862 mg/dL) is associated with a 4.5× increased risk of an elevated cPLI concentration.[29] While the relationship between hypertriglyceridemia and AP has been described as bidirectional, there is a low prevalence of hypertriglyceridemia (18%) in dogs with AP.[33] This prevalence is lower than in earlier studies and likely reflects the study design, which controlled for causes of secondary pancreatitis in addition to medication and dietary factors that could affect serum triglyceride concentrations. Although the prevalence of hypertriglyceridemia was significantly different between the AP (18%) and the control (7.5%) group in that study, the magnitude of hypertriglyceridemia was low (median 67 mg/dL vs 54 mg/dL).[33] The results of these studies suggest that severe hypertriglyceridemia is unlikely to occur secondary to AP alone, and if severe hypertriglyceridemia is documented in a dog, it likely reflects a predisposing factor to AP and could be considered a therapeutic target. Of note, many dogs with hypertriglyceridemia do not develop pancreatitis, and risk modifying factors are unfortunately poorly understood.

2.3 | Drugs/toxins

Several drugs and toxins are implicated in the development of AP. In human patients several different classification systems have been developed for drug associated pancreatitis. Initial systems were based on 3-tiers with the relative weighting being determined by the number of cases and data from drug re-exposure (if performed).[60,61] More-recently, the Badlov classification system, utilizing a 4-class system, was introduced.[62] Class I drugs are classified as those with at least 1 case report documenting recurrence of AP with re-exposure to the drug.[62] Class II drugs are classified as those with a consistent latency (ie, time from initiation of treatment to development of disease) in 75% or more of reported cases.[62] Class III drugs are classified as drugs with 2 or more case reports, but no consistent latency period or rechallenge reports.[62] Class IV drugs are similar to Class III drugs. Except they have only 1 documented case report.[62] It is the authors' opinion that further detailed reports of cases of potential drug-associated pancreatitis are needed before the development of a veterinary classification scheme.

L-asparaginase is associated with pancreatitis in up to 16.2% of children being treated for acute lymphocytic leukemia or undifferentiated leukemia.[63] L-asparaginase depletes the body of L-asparagine, thus reducing protein synthesis, which also affects the pancreas and might predispose to AP.[64] Eleven of 52 dogs evaluated at various stages of a CHOP protocol for canine large-cell lymphoma developed clinical signs compatible with pancreatitis; however, the serum cPLI concentrations were not consistently increased, suggesting that the gastrointestinal signs that occurred were likely due to gastrointestinal toxicoses secondary to chemotherapy rather than drug-induced AP.[7] In the same study, 14% of dogs that received concurrent L-asparaginase and vincristine had serum cPLI concentrations ≥400 mg/dL; however no clinical signs of pancreatitis were noted.[7] There was no statistically significant difference in serum cPLI concentrations before and after vincristine therapy, suggesting that L-asparaginase was the cause of any subclinical increase of cPLI.[7] A further case study reported suspected L-asparaginase induced pancreatitis 2 days after therapy. In that case report the diagnosis of AP was made based on the presence of consistent clinical signs in conjunction with an increased serum cPLI concentration, although abdominal ultrasonography was normal.[8] Further studies are required to determine the incidence and clinical significance of AP in dogs treated with L-asparaginase.

Several studies suggest a relationship between anticonvulsant therapy and AP. Between 10.3% and 37.0% of dogs with idiopathic epilepsy being treated with potassium bromide (KBr) have biochemical variables and a clinical history consistent with pancreatitis.[9] This study was performed prior to the commercial development of cPLI assays. A group of researchers measured cPLI concentrations in 337 serum samples that had been submitted for measurement of serum phenobarbital (PB) levels, KBr levels, or a combination of both in dogs.[10] In

that study, there was an increased risk of an elevated cPLI concentration in dogs being treated with KBr, PB, or a combination of PB and KBr.[10] Given the study design, no information was available regarding clinical signs or diagnostic imaging findings, potentially limiting its application. An additional study documented that 6.8% of dogs receiving PB or KBr have an elevated cPLI concentration.[11] One potential confounding factor is that long term treatment of dogs with PB with or without KBr is associated with the development of hypertriglyceridemia in 33% of dogs, which might be an independent risk factor for pancreatitis.[65] The combined results of these studies suggest that a clinically relevant proportion of dogs receiving PB, KBr, or a combination of both might develop increases in serum cPLI concentrations.

Azathioprine is implicated in the development of AP based on data in humans in addition to ex vivo models and isolated reports in dogs. Exposure of an ex vivo perfused canine pancreas to azathioprine results in marked effects on pancreatic function, as determined by secretory volume, bicarbonate and trypsin output.[66] Acute pancreatitis has been documented in 2 case reports of dogs receiving azathioprine in conjunction with prednisone for various immune mediated disorders.[13,14] Acute pancreatitis was suspected to be related to the azathioprine and not the prednisone in both reports due to improvement in clinical signs after discontinuation of the drug; however, repeat exposure was not performed and as such causation is difficult to prove. These reports were published before the development of commercial cPLI assays. Azathioprine was also noted in the history of 2 dogs, but in conjunction with corticosteroids, in a retrospective study evaluating risk factors for AP in dogs.[12] While additional studies are needed to fully determine the risk profile of azathioprine with regard to AP, the authors suggest that dogs that develop gastrointestinal upset or abdominal discomfort while receiving azathioprine, should be evaluated for pancreatitis.

Knowledge regarding the role of exogenous steroids in the etiology of AP is perpetually evolving. Early studies documented an increase in serum lipase activity after steroid administration; however, postmortem examination rarely revealed evidence of pancreatitis, leading to the suggestion that serum lipase activity was an unreliable marker of AP in dogs receiving corticosteroids.[67,68] Histopathology might however miss focal areas of inflammation and this limitation should be considered. In another study 18/101 dogs received corticosteroids within 7 days of diagnosis of AP and in a study of dogs with "pancreatic abscesses" (peri-pancreatic fluid accumulations) 9/36 received corticosteroids prior to admission.[12,69] Given these seemingly contradictory results several additional studies have been performed utilizing cPLI assays. Six young female dogs with X-linked hereditary nephritis receiving 2.2 mg/kg/d prednisone PO for 4 weeks had no significant change in serum cPLI concentration.[70] Another study evaluated the effects of 4 mg/kg prednisolone daily for 2-3 weeks in 6 healthy beagle dogs. This study revealed an increase in cPLI concentration after prednisolone therapy; however, no ultrasonographic signs of pancreatitis were noted with the exception of 1 day when a single dog was assessed to have a hypoechoic pancreas.[71] Additionally, laparoscopic pancreatic biopsies noted no histologic evidence of pancreatitis.[71] The same caveat as above exists regarding the sensitivity of histopathology in the diagnosis of AP. The same research group evaluated the effects of 2.2 mg/kg prednisolone daily in dogs with various immune mediated diseases. In this study, 5/10 dogs showed serum cPLI concentrations ≥400 mg/dL; however, no clinical signs of pancreatitis were noted.[17] The potential contribution of the primary disease process to the cPLI concentration is unclear. A recent abstract also documented no effect of chronic administration of supraphysiologic doses of corticosteroids on cPLI concentration in 15 dogs.[72] Administration of corticosteroids prior to referral also had no effect on serum cPLI activities in a recent study of dogs with intervertebral disc disease.[73] The effect of exogenous corticosteroids on 1,2-O-dilauryl-rac-glycero glutaric acid-(6′-methylresorudin) ester (DGGR) lipase assays has also been evaluated.[74] In 17 dogs being treated with corticosteroids for several reasons DGGR lipase activity increased following initiation of treatment and reduced during drug tapering.[74] The magnitude of increase in DGGR lipase activity was however low, potentially reducing the clinical significance of this finding.[74] The combined results of the above studies suggest that exogenous corticosteroids are unlikely to result in clinically important AP in dogs, although markers of subclinical pancreatic injury/inflammation might be noted in some cases, and might be more importantly influenced by concurrent disease. Additionally, corticosteroids are being increasingly utilized at anti-inflammatory doses in the management of AP in dogs. In 1 study a 1 mg/kg dose of prednisolone was shown to reduce C-reactive protein concentrations, shorten time to clinical improvement, and decrease mortality in spontaneous AP in dogs.[75] A recent review, evaluating data from multiple species, suggested that corticosteroids might have a positive effect on outcome in the treatment of acute or acute on chronic pancreatitis in dogs.[76]

Several early studies documented a potential relationship between organophosphates and the development of AP. Sublethal doses of organophosphate anticholinesterase ex vivo results in AP in dogs as determined by histopathology.[16] Additionally in vitro acetylcholinesterase inhibitors result in marked increases in pancreatic amylase output.[77] Five dogs were also noted to have a recent exposure to organophosphate insecticides prior to the development of AP in a large retrospective study.[12] Organophosphates might therefore be a risk factor for the development of pancreatitis in dogs, but more studies are needed to confirm this suspicion.

Potentiated sulfonamides, furosemide, clomipramine, atovaquone/proguanil (Malarone), and n-methyl-glucamine (Meglumine) are associated with the development of AP in isolated dogs.[12,15,18–20] Another prospective study reported that none of 20 dogs treated with meglumine and allopurinol developed increased cPLI concentrations or clinical signs consistent with pancreatitis.[78] Isolated reports of toxins such as zinc causing AP have been reported.[21] Various antibiotics, chemotherapeutics, and endocrine therapies were also noted within 7 days of presentation, in a large retrospective study of AP; however, case details were sparse thus limiting the clinical utility of these data.[12] Given the infrequent nature of these reports many drug reactions are suspected to be idiosyncratic. Nonetheless a thorough drug and toxin history should be taken in cases of suspected AP.

2.4 | Endocrinopathies

Numerous endocrinopathies have been reported as risk factors for AP, including hyperadrenocorticism (HAC), hypothyroidism, and

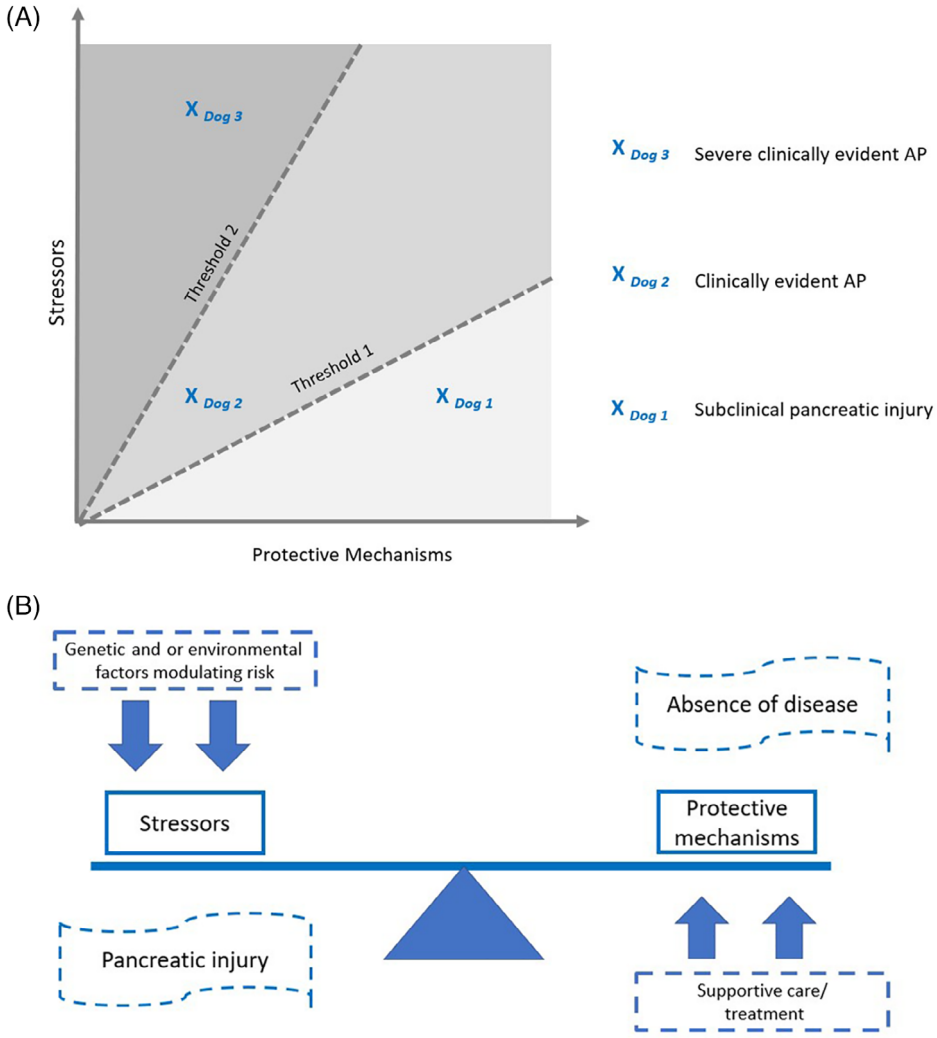

FIGURE 1 (A) Thresholds in the development of pancreatitis. A graphical representation of the critical threshold theory in which the balance between stressors and protective mechanisms determines whether clinical disease is present (threshold 1) and if so, its severity (threshold 2). Dog 1 and dog 2 have been exposed to the same stressor; however, dog 1 has greater protective mechanisms and as such, the disease burden falls below threshold 1 and the dog develops subclinical pancreatic injury. In contrast, dog 2's disease burden is above threshold 1 and the dog develops clinically evident AP. Similarly, dogs 2 and 3 have the same level of protective mechanisms, but the stressors are greater in dog 3. The disease burden for dog 3 is therefore above threshold 2 and the dog develops clinically severe AP. As depicted in (B) this balance is also likely influenced by factors such as supportive care, genetic and environmental factors, and amplification systems. While thresholds 1 and 2 are represented as dashed lines in the figure, we suspect that the thresholds are more fluid and vary between individuals. This figure was adapted with permission from Barreto et al. *Gut*. 2021;70:194-203. (B) A balance between protective mechanisms, stressors, and modulating factors determines the risk of pancreatitis in each individual dog. A schematic representation of the fine balance between stressors and protective mechanisms that determine whether pancreatic injury and inflammation occurs in an individual dog. Note that genetic and or environmental factors on one side and supportive care on the other can modulate the risk toward or away from pancreatic injury, respectively

diabetes mellitus (DM).[12,22–25,79,80] A retrospective study documented a preexisting or subsequent diagnosis of HAC in 12/101 dogs with AP.[12] It is important to note that this study did not include a control group. Although large prospective studies have not been performed to evaluate this relationship, recent studies suggest a potential relationship between HAC and higher cPLI concentrations and DGGR lipase activities in the absence of clinical pancreatitis.[22,23] Given that most studies evaluating exogenous steroids document only minor elevations in pancreatic lipase we suspect that increased pancreatic lipase concentrations in dogs with HAC reflect subclinical pancreatic injury/inflammation that has yet to reach a threshold, required to cause clinical pancreatitis (see Figure 1A). Additional studies are needed to evaluate whether there is a relationship between AP and HAC in dogs and the direction of the relationship. Hypothyroidism was documented in 4/101 dogs diagnosed with AP in a retrospective study, and it has been hypothesized that secondary hyperlipidemia might be responsible for this relationship.[12] A previous diagnosis of

hypothyroidism was also noted in a retrospective study of dogs with extrahepatic bile duct obstruction secondary to AP.[80]

Many studies have identified pancreatitis concurrently with DM in dogs and this might represent shared risk factors for disease or a causative relationship between the 2 diseases.[12,25,30,81] Pancreatitis has also been shown to increase the hazard risk of death in dogs with DM.[81] Proposed mechanisms by which pancreatitis could theoretically lead to DM include: islet cell damage, glucose toxicity, initiation of autoimmune injury, inflammation induced insulin resistance, and the action of cytokines and adipokines.[24] One study indicated that 5/18 dogs with diabetes mellitus had histopathologic features consistent with advanced chronic pancreatitis, which was the presumed cause of DM in those dogs.[82] Additionally, in a study utilizing glucagon stimulation tests in 6 dogs with presumed chronic pancreatitis, 5/6 had reduced ß cell response and glucose intolerance.[83] Proposed mechanisms in which DM could in theory lead to pancreatitis include the development of auto-antibodies or anti-insulin antibodies.[24] Although the relationship might be bidirectional, many clinicians suspect that the predominant direction of the relationship is pancreatitis leading to DM.[24] Further discussion on the relationship between pancreatitis and DM is available.[24]

2.5 | Breed associated risk and potential hereditary pancreatitis

Certain breeds are reported to be at greater risk for the development of AP. These predispositions likely reflect a combination of direct genetic predispositions, a predisposition to a secondary factor such as hypertriglyceridemia, or other disease modifying factors. The most consistently reported at-risk breeds for acute pancreatitis include the miniature schnauzer, miniature poodle, Yorkshire terrier, and other terrier breeds.[5,12,84] Other predisposed breeds include dachshunds, poodles, cocker spaniels, Alaskan malamutes, and laika.[30] Two potential explanations are suggested for the high incidence of AP in miniature schnauzers. One potential explanation is that AP occurs secondary to hypertriglyceridemia, which occurs commonly in this breed.[28,29] A second potential explanation is that AP might be heritable in the breed due to mutations in the serine protease inhibitor Kazal type 1 gene (SPINK1). The product of the SPINK1 gene, pancreatic secretory trypsin inhibitor (PSTI), is suspected to play a protective role in the prevention of premature zymogen activation.[85] A prospective study evaluated the presence of SPINK1 gene variants in 39 Miniature Schnauzers with pancreatitis, 25 healthy Miniature Schnauzers, and 23 healthy dogs of other breeds.[26] In that study 3 variants were identified, including 2 missense mutations in the second exon (N20K and N25T) in addition to a poly T insertion in the 3rd intron (IVS3 + 26-27ins[T]33-39,15_61dup11) and these variants were shown to correlate with the development of pancreatitis in this breed.[26] However, a subsequent study detected a high prevalence of SPINK1 variants in Miniature Schnauzers with and without pancreatitis and a relationship between the SPINK1 variant and clinical pancreatitis could not be established.[27] In this study however, diagnosis of pancreatitis was based solely on a semiquantitative point of care assay in approximately 30% of dogs, which might have affected the results of the study.[86] Additional potential explanations for the lack of an association between the SPINK1 variant and clinical disease is that the mutation might not be sufficient in isolation to cause pancreatitis and might require concurrent environmental or other genetic factors. Additional studies are therefore required to determine the potential role of SPINK1 variants and other gene mutations in AP in dogs.[87] Cavalier King Charles spaniels, collies and boxers are predisposed to chronic pancreatitis (CP).[32]

2.6 | Autoimmune pancreatitis IgG4-related disease

The English Cocker spaniel is suggested to have a distinct form of CP characterized by ductal destruction, interlobar fibrosis, and T lymphocyte infiltrations on histopathology.[88] Immunohistochemistry has also shown a predominance of IgG4 positive plasma cells in multiple tissues, including the pancreas, suggesting the presence of a multiorgan immune mediated disease similar to IgG4-related disease in human patients.[89] Many of these dogs have concurrent keratoconjunctivitis sicca, xerostomia, proteinuria, and other immune-mediated disorders.[90] The diagnostic criteria for IgG4-related disease(s) in dogs needs further clarification and consensus before a definitive diagnosis can be confirmed.[43,91] Also serum IgG4 concentrations have been noted to be high in other dogs with pancreatitis.[44] However, strict diagnostic criteria are required to prevent misclassification of other inflammatory or neoplastic diseases as IgG4-related disease.[43] It is hoped that ongoing study will further help to characterize this form of CP in dogs.

2.7 | Miscellaneous risk factors

Many miscellaneous risk factors have been proposed for AP in dogs, including weight/neuter status, infectious diseases (eg, *Babesia* spp., *Heterobilharzia americana*, *Leishmania infantum*), hepatitis, honeybee envenomation, snake envenomation, hypercalcemia and organic acidemias.[5,12,41,42,45] Although dogs of any age can be affected by AP, most dogs are middle-aged to older.[12,30,31,92] Overweight animals and those who are neutered are also reported to be predisposed to AP.[5,12,84,93] It is however, important to note that many of these factors are influenced by additional factors, such as diet, lifestyle, and exercise level.[94] A retrospective study revealed clinicopathologic evidence of AP in 16 dogs and histological evidence of AP in 4 dogs diagnosed with a *Babesia rossi* infection.[34] An additional study documented that 28% of dogs with a *B. rossi* infection had an increased serum cPLI concentration.[36] Other babesia species (eg, *B. gibsoni*) have been implicated in the development of AP, albeit at a lower prevalence.[35] Potential mechanisms include hypotension, secondary immune-mediated hemolytic anemia, hemoconcentration, and alterations in lipid metabolism.[34] Canine monocytic ehrlichiosis has

also been reported to be a predisposing factor to AP in dogs, with 20% of cases in a recent study having subclinical elevations in cPLI.[37] Necropsy studies of canine schistosomiasis (ie, *Heterobilharzia americana* infection) also document a high prevalence of parasitic infiltration of the pancreas.[38] Gross lesions consistent with pancreatitis were also noted during exploratory laparotomy in a dog subsequently diagnosed with schistosomiasis.[39] Several studies also noted elevated pancreatic lipase concentrations in systemically ill dogs such as those with cardiac disease, gastric-dilatation and volvulus, intervertebral disc disease, parvovirus, and foreign bodies.[73,95–99] In the authors' opinion elevations in pancreatic lipase concentrations in such dogs likely reflect a secondary pancreatic injury that might not be clinically relevant, although this can be difficult to definitively determine. But, in some diseases (eg, chronic enteropathies) increased serum cPLI concentrations have been associated with a worse outcome.[100]

Previous surgery, other than neutering, is associated with an increase in risk of AP (OR: 21.1), likely due to hypotension, tissue manipulation, or a combination of both.[5] A high prevalence of AP has also been noted in a recent retrospective study of dogs and cats with cholecystitis, although the direction of the relationship is unknown.[45] Therefore, many factors in a dogs history should be considered when evaluating a dog with suspected AP.

3 | PATHOGENESIS OF ACUTE PANCREATITIS

Over 100 years ago it was proposed that pancreatitis was caused by autodigestion of the pancreas from premature activation of digestive zymogens.[101] Since that time several experimental and clinical studies have documented a key role of intra-acinar trypsinogen activation.[102–108] Despite the long-standing concept of premature trypsinogen activation, the initiating cellular mechanisms and the potential role of alternate or complementary pathways have long been the source of ongoing research. While discussing these concepts we will relate the results of experimental data to implications for clinical practice by highlighting potential therapeutic targets. Development of such therapeutics will be critical in improving the outcome of this disease for which clinicians have traditionally been restricted to providing only supportive and symptomatic care.

In this section we will also review studies that suggest the presence of trypsinogen independent pathways of acinar cell injury and pancreatic and systemic inflammation. We will then discuss several proposed mechanisms that might initiate both trypsin-dependent and independent cellular damage. It is important to consider that the described pathogenic mechanisms do not always result in clinical disease and that the critical threshold theory (Figure 1A) is useful to help describe the relationship between pathologic stressors and clinical disease expression and severity (Figure 1B).

In 2011, a study utilizing trypsinogen isoform-7 gene knockout mice and wild type mice to determine the role of trypsinogen in experimentally-induced pancreatitis (cerulein model) was published.[109] Trypsinogen activation led to in vitro acinar cell death during early pancreatitis, which was responsible for ~50% of pancreatic injury.[109] Interestingly, however, the knockout mice demonstrated similar levels of local and systemic inflammation when compared to the wild-type cohort.[109] The results of this experimental study suggested that the inflammatory response and approximately 50% of acinar cell damage during pancreatitis was independent of premature trypsinogen activation.[109] This prompted reconsideration of the traditional trypsin-centric pathogenesis and allowed for consideration of potential alternate or complementary pathways. One potential caveat to this is that mice have various trypsinogen isoforms, and the clinical significance of each isoform might vary. A further study documented that intra-acinar activation of trypsinogen was able to induce AP but not CP, suggesting that different pathogenic mechanisms might exist between acute and chronic disease.[108] Although trypsin-independent mechanisms for pancreatitis have been suggested, they likely act in parallel with trypsin-dependent mechanisms, therefore therapeutic manipulation of trypsin and other proteases might still be of benefit. Reduced trypsinogen activation peptide concentrations, reduced pancreatic necrosis, and reduced mortality is seen in rats treated with the protease inhibitor nafamostat.[110] Multiple studies have also investigated protease inhibitors in humans, with varied, but most often disappointing, results.[111–113] Concern also exists regarding the vasoconstrictive properties of these drugs and the potential perpetuation of pancreatic necrosis.[114] Additionally, proteases other than trypsin, might play protective roles in the pathophysiology of pancreatitis. Chymotrypsin is a protease that regulates trypsin activity and is noted in early pancreatic injury.[109] Chymotrypsinogen knockout mice have been shown to have an increased severity of induced pancreatitis, when compared to a wild type cohort, thus protease inhibitors used in pancreatitis should ideally target trypsin, but spare chymotrypsin.[115] Somatostatin analogues have the potential of inhibiting exocrine secretions of the pancreas, including trypsinogen, thus these drugs have also been considered in disease management. Unfortunately, the somatostatin analogue, octreotide, is shown to have no benefit in an experimentally induced (bile injection model)pancreatitis in dogs.[116] Indeed, it is suspected that zymogen granule release is inhibited early during the pathogenesis of pancreatitis, a process that would be expected to be even further propagated by somatostatin or its therapeutic analogues.[117] Given the results of the above studies, and the presence of trypsin-independent mechanisms of pancreatic injury and inflammation, it is likely that detailed preclinical study would be needed before protease inhibitors or somatostatin analogues are considered for clinical use in dogs.

A major alternative or complementary pathway to the trypsinogen activation pathway of AP includes activation of nuclear factor-kappa beta (NF-κB), which has been documented in pancreatitis for over 20 years.[118] Intra-acinar NF-κB activation occurs alongside, and independent of, trypsinogen activation.[109,119,120] The critical role of NF-κB in the inflammatory response is evidenced by experimental studies in knockout mice, where absence of NF-κB activation results in reduced pancreatic inflammation relative to wild type mice.[121–123] The level of NF-κB activation correlates with the severity of pancreatitis in mice.[124] Nuclear factor-κB is also involved in the systemic

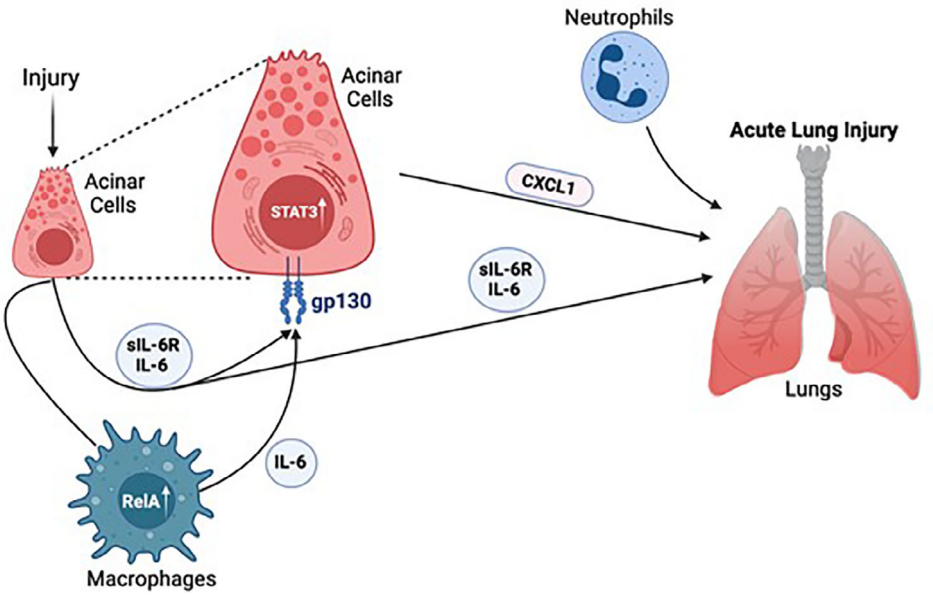

FIGURE 2 Systemic inflammatory response syndrome in AP. IL-6 transsignaling involves the interaction between IL-6 and a soluble IL-6 receptor which increases gp130-dependent STAT3 activation. Nuclear translocation of STAT3 results in release of cytokines such as CXCL1 which leads to acute lung injury. Cytokine secretion in macrophages depend on nuclear translocation of RelA

inflammatory response to pancreatitis.[125,126] While these studies lay strong evidence for a proinflammatory action of NF-κB in pancreatitis, some data suggests that NF-κB might play a multifaceted role in AP, and might be protective in some circumstances.[127–129] These discrepancies can also be explained with different approaches in the preclinical models (overactivation vs genetic deletion). Additionally, currently used inhibitors are not specific for the NF-κB pathway. Furthermore, inhibition of single subunits of the pathway might be compensated for by other components of the NF-κB family of proteins, such as *RelB* or *c-Rel*. Given the results of these studies targeted inhibition of the proinflammatory properties of NF-κB could be of therapeutic benefit but requires further study. Other key components of the inflammatory response include tumor necrosis factor alpha (TNF-α), interleukin (IL)-1, IL-1ß, IL-2, IL-6, IL-8, and IL-18.[93,130–134] Association studies correlating cytokines and chemokines with AP severity have been performed to identify surrogate biomarkers as predictors for severe AP. In humans serum levels of IL-6 and the IL-6 dependent acute phase protein C-reactive protein are the most reliable predictors of severe AP.[135,136]

Interleukin 6 has both anti-inflammatory and proinflammatory properties depending on the signaling type. Classic signaling requires the presence of an IL-6 receptor on a limited number of target cells and mediates its anti-inflammatory properties.[137] Transsignaling however involves the interaction of IL-6 with a soluble IL-6 receptor (sIL-6R) which then mediates gp130 activation, and IL-6's proinflammatory actions.[137] IL-6 transsignaling has effects on many cell types and can further increase the expression of signal transducer and activator of transcription 3 (STAT3) in pancreatic acinar cells.[138] Increased STAT3 expression further promotes the inflammatory cascade via release of cytokines and chemokines.[138] Cytokine secretion in macrophages is dependent on nuclear translocation of RelA.[138] Thus IL-6 has also been shown to have a direct impact on the course of disease (Figure 2). Cytokines and chemokines in the circulation induce further secretion of acute-phase proteins in the liver, activate complement factors, and activate bradykinin-kinin systems, thus increasing capillary permeability and in turn leading to hypovolemia and edema.

Neutrophils and macrophages also play a key role in both the local as well as systemic inflammatory response in acute pancreatitis.[139,140] Neutrophil invasion into the pancreas is suspected to occur due to the release of CXC ligand 2 (CXCL2) and other chemoattractants in early AP.[141,142] Experimental depletion of neutrophils results in reduced pancreatic injury and increased survival, highlighting the critical nature of neutrophils in disease pathogenesis.[143,144] Neutrophils also play a role in the development of systemic complications of AP including acute lung injury.[145,146] Neutrophil extravasation into the tissues is dependent on rolling, activation, adhesion, and migration of neutrophils from the capillaries. Leukocyte function antigen-1 (LFA-1), which binds to immunoglobulin-like cell adhesion molecule 1 (ICAM-1) during vascular adhesion, plays an important role in the recruitment of neutrophils to the pancreas and other tissues, CXCL2 formation, and subsequent tissue injury (Figure 3).[147] This pathway is amenable to therapeutic intervention and LFA-1 inhibitors such as fuzapladib sodium hydrate prevent extravasation of neutrophils into the tissue and have been approved for the treatment of pancreatitis in dogs in Japan. Data from a proof-of-concept study utilizing an experimental model of pancreatitis in dogs was recently presented at the ACVIM Forum.[148] This data suggests that fuzapladib improved survival rate in this experimental model, in a dose-dependent fashion. A subsequent clinical trial in Japan revealed improved clinical scores, and a faster resolution of serum C-reactive protein increases in dogs treated with fuzapladib.[148] A multicenter clinical trial in spontaneous pancreatitis in dogs is ongoing in the United States.

Multiple mechanisms have been proposed to explain trypsinogen and NF-κB activation during the early stages of pancreatitis. These mechanisms include deranged calcium signaling, colocalization of zymogens and lysosomes, impaired autophagy, endoplasmic reticulum stress and maladaptive unfolded protein response, mitochondrial dysfunction, and oxidative stress. For simplicity and given the focus of this review, we will

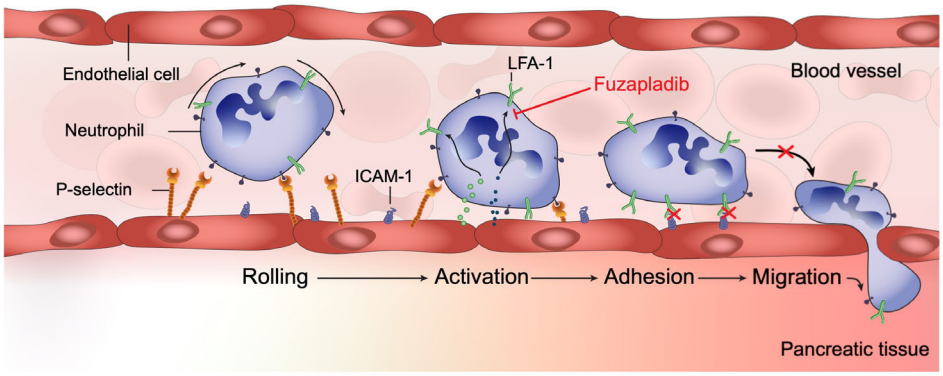

FIGURE 3 Neutrophil extravasation into the pancreas and therapeutic manipulation with fuzapladib sodium hydrate. Fuzadib sodium hydrate inhibits leukocyte function antigen-1, which prevents neutrophils from extravasating from capillaries into the surrounding tissue, which inhibits the systemic inflammatory response syndrome (SIRS). ICAM-1, immunoglobulin-like cell adhesion molecule 1; LFA-1, leukocyte function antigen-1

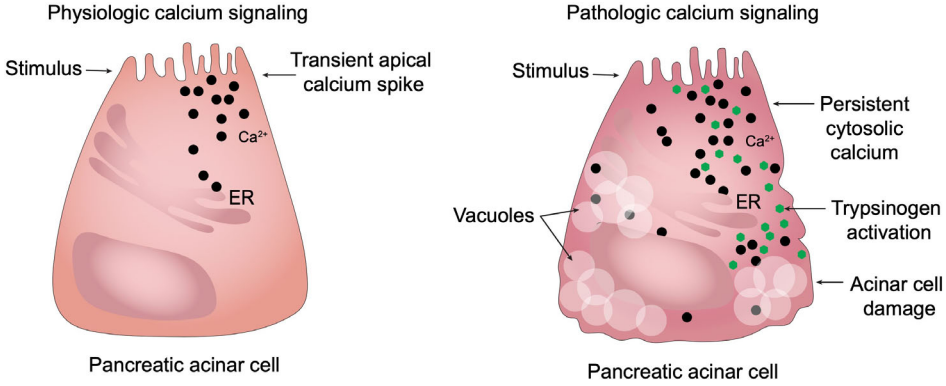

FIGURE 4 Persistent cytosolic calcium accumulation in AP. Under physiologic conditions there is a transient spike in apical calcium concentration, which results in release of digestive zymogens from the apical border of the pancreatic acinar cell. During AP there is a global and persistent increase in cytosolic calcium concentration, which causes calcium overload, premature trypsinogen activation and subsequent acinar cell damage. Deranged calcium signaling is associated with mitochondrial dysfunction

discuss each of these mechanisms sequentially; however, there is likely a complex interaction between these mechanisms in spontaneous disease.

Deranged calcium signaling is suspected to play a role in the pathogenesis of AP. Under physiologic conditions a stimulus results in a transient spike in calcium in the apical region of the acinar cell.[149] However, during pancreatitis there is a global and persistent increase in cytosolic calcium.[150,151] Calcium overload then causes the premature activation of trypsinogen, in addition to the development of vacuoles, and acinar cell damage (Figure 4).[152,153] Pathological calcium overload is associated with release of calcium from the endoplasmic reticulum (ER) and acidic calcium stores, which acts as a positive feedback mechanism.[154,155] A variety of receptors are involved in pathologic calcium signaling.[155–157] Calcium overload causes mitochondrial permeability transition pores (MPTP) to open, leading to a loss of mitochondrial membrane potential and mitochondrial dysfunction.[158,159] Mitochondrial dysfunction is a key acinar event in early pancreatitis.[160,161] Loss of mitochondrial function leads to ATP depletion. Removal of cytosolic calcium is ATP-dependent, therefore mitochondrial dysfunction might further the global and persistent increase in cytosolic calcium, thus forming a self-perpetuating increase in cytosolic calcium, which is characteristic of pathological calcium signaling during pancreatitis.[151,160–162] Pathologic calcium signaling ultimately results in downstream activation of calcineurin, trypsinogen, and NF-κB.[163,164] Calcineurin knockout mice have been shown to have reduced zymogen activation and acinar cell injury in response to an experimental model of pancreatitis.[165] Additionally, genetic mutations in calcium channels such as transient receptor potential vanilloid subfamily member 6 (TRPV6) have been shown to be associated with nonalcoholic chronic pancreatitis (CP) in human patients.[166] Given these findings, manipulation of calcineurin has garnered considerable attention as a potential therapeutic target for the treatment of pancreatitis in humans. Pharmacologic inhibition of calcineurin via cyclosporine A and tacrolimus has protective effects in a rodent model of pancreatitis.[163,165] The protective effects of calcineurin inhibition appear to be dependent on the source of its expression.[167] Studies are ongoing to investigate cyclosporine therapy in both canine and feline CP (personal communication JMS). Given the immunosuppressive properties of cyclosporine it might have multiple beneficial effects in pancreatitis, particularly in those with suspected immune-mediated etiology.[168] Research into drugs manipulating calcium signaling and mitochondrial dysfunction are ongoing in experimental models and might offer future promise in the management of pancreatitis.[169–171]

Under physiologic conditions, digestive enzymes are packaged as inactive enzymes, called zymogens, and are stored in granules. Lysosomal enzymes are packaged into lysosomes, thus preventing the

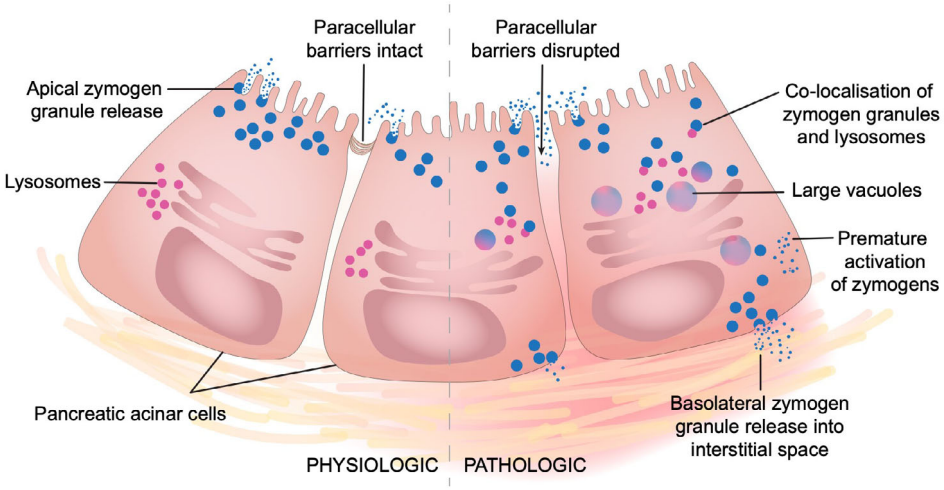

FIGURE 5 Colocalization theory. Under physiologic conditions, digestive zymogens and lysosomes do not interact with each other within pancreatic acinar cells. During AP an apical block results in redistribution of lysosomes, which then colocalize with digestive zymogens. Colocalization allows the lysosomal enzyme cathepsin-B to activate the digestive zymogens within the pancreatic acinar cell, resulting in cell damage. Basolateral release of granules might occur leading to damage to the interstitial space

interaction of zymogens and lysosomal enzymes until zymogens enter the duodenum. During pancreatitis, lysosomes redistribute and colocalizes with zymogen granules in the subcellular compartment, resulting in the formation of large vacuoles.[172,173] This colocalization allows the lysosomal enzyme cathepsin B to prematurely activate trypsinogen (Figure 5).[174] Maximal activation of trypsinogen by cathepsin B is reported to occur at an acidic pH, but might also occur at a higher pH.[174,175] This hypothesis was further evaluated in a cathepsin B gene knockout mouse cohort.[176] In these mice, trypsin activity and pancreatic necrosis in response to cerulein stimulation is markedly reduced relative to the wild-type cohort, suggesting that cathepsin B plays a key role in the induction of pancreatitis.[176] Absence of the cathepsin B gene did not however completely prevent the onset of pancreatitis.[176] Similar results have been noted in several studies using cathepsin B inhibitors.[177,178] While colocalization is a popular theory and is well supported by the literature, there are some studies that suggest that we do not fully understand this process. For example, colocalization of cathepsin B with secretory vesicles is seen in regulated secretion from the exocrine pancreas and redistribution of lysosomal enzymes into the zymogen-rich subcellular compartment fails to result in pancreatitis in some studies.[175,179] Thus, it is suspected that cathepsin B redistribution is involved in pancreatitis, but alone, it might not be sufficient to induce disease and might be influenced by other factors, such as cathepsin D.[180] Cathepsin B gene mutations have also been associated with some forms of pancreatitis in humans, but the role of cathepsin B has yet to be studied in dogs.[181,182] Further studies are needed to understand apparent discrepancies in the results of prior studies, and to determine whether these pathways could act as therapeutic targets.

Autophagy is cytoprotective and involves the catabolic removal of various obsolete cellular components preventing cell damage and promoting survival in response to insults.[183] Basal autophagy has been shown to play an important role in the homeostasis of pancreatic acinar cells.[184] Genetic disruption of Atg5 induced pancreatic degradation also supports the role of autophagy in exocrine pancreatic homeostasis.[185] During pancreatitis impaired autophagy occurs as a result of lysosomal dysfunction.[162] Colocalization of organelles is autophagic in nature.[186] Lysosomal dysfunction results in degradation of lysosomal membrane proteins 1 (LAMP-1) and 2 (LAMP-2). Lysosomal membrane proteins play an important role in lysosomal stability. The role of LAMP-2 in pancreatitis is demonstrated in knockout mice, which were shown to have impaired autophagy and developed pancreatitis.[187] Ultimately these processes result in acinar cell vacuolation, trypsinogen activation, inflammation and necrosis.[162] Pharmacological manipulation of impaired autophagy was studied in mice.[188] Inhibition of a transcriptional regulator of autophagy alleviated pancreatic acinar cell injury in experimental pancreatitis.[188,189] Further studies are needed to determine whether pharmacological manipulation of autophagy offers promise in the management of AP. Impaired autophagy might also be interrelated with other pathomechanisms of AP including mitochondrial dysfunction and endoplasmic reticulum (ER) stress.[190]

The exocrine pancreas is rich in ER, which plays a key role in protein synthesis. Endoplasmic reticulum stress is a key acinar event during early pancreatitis and is associated with accumulation of unfolded proteins in the ER.[191–193] Under physiologic conditions, ER stress is countered by an unfolded protein response (UPR), thus preventing cell injury.[194] This physiologic response involves autophagic processes.[194] During excess and prolonged ER stress, the UPR becomes maladaptive and upregulated NF-κB triggers proinflammatory genes (Figure 6).[122,124,194] Thus, dysregulated UPR results in the initiation of acinar cell injury and apoptosis.[194] Interestingly, drugs such as HMG-coA reductase inhibitors, have been shown to act on the UPR and reduce ER stress.[195] Observational studies also document a lower incidence of pancreatitis in humans treated with HMG-coA reductase inhibitors (OR: 0.29).[196] Furthermore preexisting statin therapy is associated with a reduced severity of pancreatitis in humans.[197] To the authors' knowledge no studies have been performed investigating the use of HMG-coA reductase inhibitors in dogs with pancreatitis.

Oxidative stress has long been implicated in the pathogenesis of pancreatitis and free-radical concentrations have been correlated with the degree of inflammatory response and disease severity.[198–201] Antioxidants have been shown to reduce pancreatic damage in experimental models; but this contrasts with the results of clinical trials in

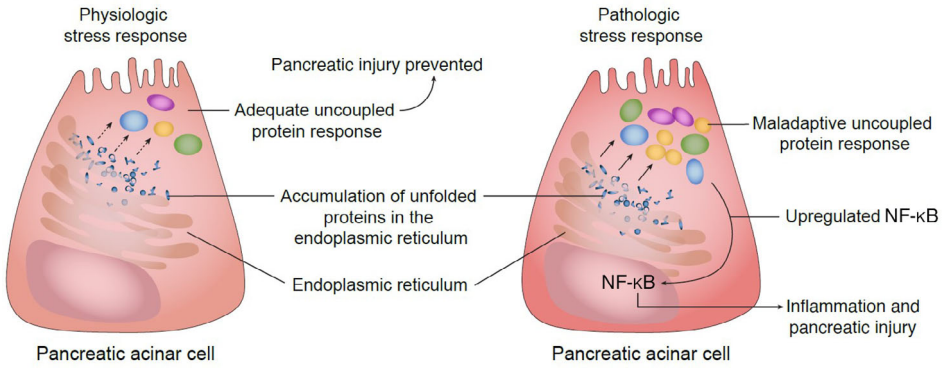

FIGURE 6 Endoplasmic reticulum stress and the unfolded protein response. Under physiologic conditions endoplasmic reticulum stress is countered by the unfolded protein response, which prevents cellular injury. However, in AP excessive and prolonged ER stress results in a maladaptive UPR and subsequent upregulation of NF-κB, resulting in acinar cell injury

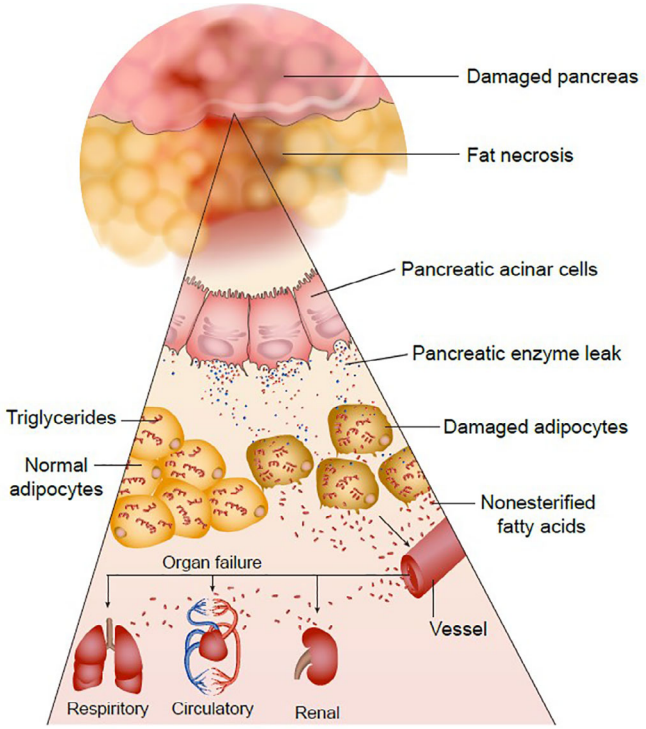

FIGURE 7 Pancreatic enzyme leakage and the role of fatty acids in the pathogenesis of AP. Leakage of pancreatic enzymes, particularly classical pancreatic lipase, into the intrapancreatic and peri-pancreatic fat results in the generation of nonesterified fatty acids. These nonesterified fatty acids lead to systemic inflammation and organ failure; thus, the level of visceral adipose tissue might influence the clinical course of AP
Source: This figure was adapted with permission from de Oliveira et al. *J Clin Invest*. 2020;130(4):1931-1947

spontaneous disease.[202–204] A decisive study might help to explain the lack of efficacy of antioxidants in some clinical trials.[205] Booth et al. showed that reactive oxygen species (ROS) promoted apoptosis of pancreatic acinar cells, and inhibition of ROS resulted in pathologic necrosis, suggesting an unexpected protective role of ROS within the pancreatic acinar cells during pancreatitis.[205] Contrasting findings were noted regarding oxidative stress in neutrophils, suggesting a dual role of ROS in pancreatic injury.[205,206] This dual role likely complicates manipulation of oxidative stress pathways. Given these results, further studies are needed to investigate the role of oxidative stress in dogs with pancreatitis before therapeutic manipulation is considered. Studies are being performed at the primary author's institution to evaluate reactive metabolite concentrations, plasma antioxidant potential, and urinary F2-isoprostane concentrations in dogs with spontaneous AP.

An additional factor implicated in determining the clinical course of AP is the role of nonesterified fatty acids (NEFA's).[54,55] Lipolysis of visceral fat by pancreatic lipase results in the formation of NEFA's, which results in systemic inflammation and organ failure (Figure 7).[54] Nonesterified fatty acids have been shown to alter the severity of AP, independent of the necroinflammatory response.[207] Free fatty acids have also been shown to induce hypocalcemia.[208] The mechanism of NEFA-induced organ failure is suspected to involve inhibition of mitochondrial complex I and V and release of intracellular calcium.[209] The systemic effects of NEFAs have been evidenced by induction of mitochondrial damage in the kidney.[209,210] Therapeutic manipulation of these pathways has been considered in the management of AP. Calcium supplementation and Ringer's lactate to counter the hypocalcemia induced by NEFA's reduces C-reactive protein concentrations and the systemic inflammatory response during early pancreatitis.[211] Additionally, inhibition of lipases is considered a therapeutic target, with the aim of reducing the generation of NEFA's. Orlistat, a lipase inhibitor, reduces organ failure and mortality in experimental AP.[207] Other case reports have suggested that orlistat might induce pancreatitis in some people and thus more studies are needed to investigate the effects of lipase inhibitors on disease outcome before they can be considered for clinical use.[212]

Having discussed potential initiating mechanisms of pancreatitis, it is important to note that, the development of pancreatitis and the disease severity is dependent on a balance between stressors and protective mechanisms, with several genetic and environmental factors modifying the individuals risk profile (Figure 1B).[139] Protective mechanisms of the pancreas include: synthesis and storage of digestive enzymes as inactive zymogens, physical separation of lysosomal enzymes from zymogens, pancreatic secretory trypsin inhibitor, suboptimal pH for autoactivation in zymogen granules, unidirectional flow in pancreatic ducts, and circulating antiproteases in the vascular space.[93] Acinar cell injury results in the release of inflammatory mediators, which are then amplified by pancreatic stellate cells resulting in a necroinflammatory amplification loop that furthers acinar cell injury as well as a systemic inflammatory response.[139] A critical threshold of

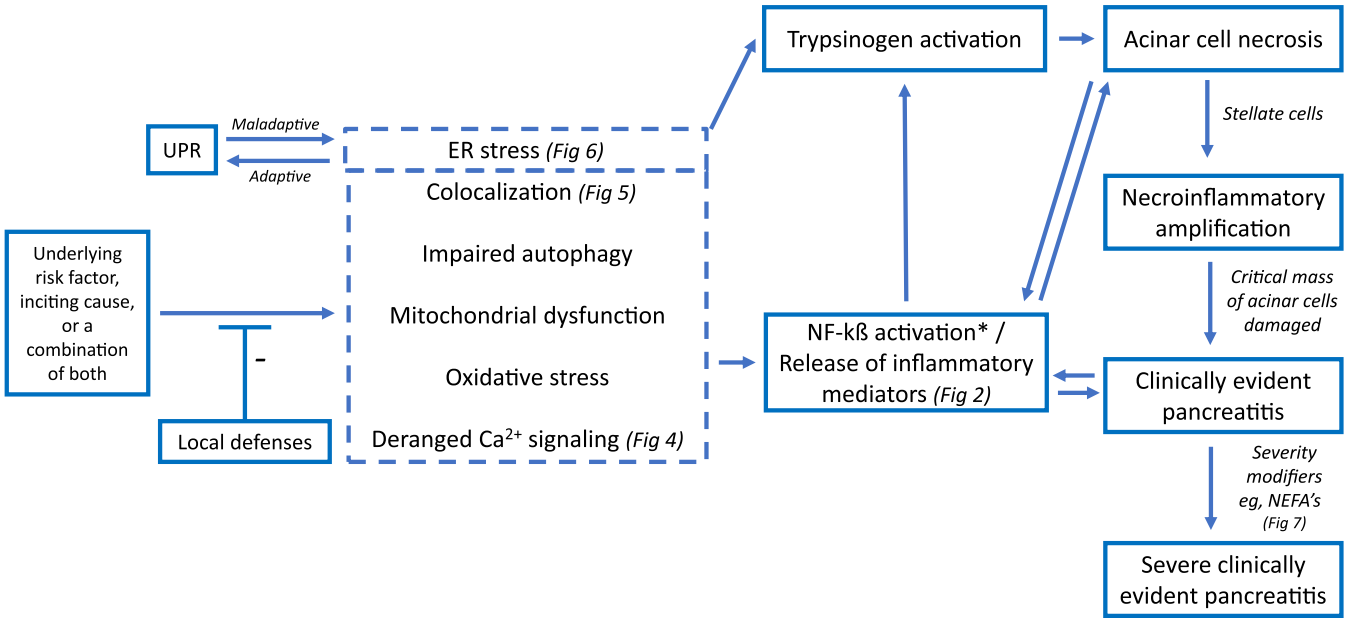

FIGURE 8 Proposed pathogenesis of pancreatitis. This figure outlines the key pathophysiologic mechanisms proposed in the development of clinically evident acute pancreatitis. UPR, unfolded protein response; *, context specific proinflammatory role
Source: This figure was adapted with permission from Barreto et al. *Gut*. 2021;70:194-203

acinar cell injury is likely required prior to the development of clinical disease (Figures 1A,B and 8).[139] This critical threshold theory is important when interpreting abnormalities in pancreatic lipase or imaging findings suggestive of pancreatitis, in the absence of clinical disease. This theory would suggest that while various pathophysiologic mechanisms might be at play in each dog, clinical disease only develops if a certain clinical threshold is reached, and severe pancreatitis occurs only when another threshold is reached. This theory might provide a useful model for pancreatitis in dogs. It is important to note that these thresholds are likely not true thresholds, but rather theoretical ones and that the actual thresholds might vary widely between dogs.

4 | CONCLUSIONS

While most cases of pancreatitis are thought to be idiopathic, our knowledge regarding the etiology of pancreatitis in dogs is more limited than it is for humans and a thorough diagnostic work-up evaluating potential risk factors is not always performed. Thus, the term cryptogenic AP might be more appropriate in most cases. A thorough medical, surgical, drug, and dietary history is indicated in all dogs with suspected pancreatitis, and the results of which might be of particular importance in dogs with recurrent episodes of pancreatitis. If a temporal association is noted between a drug and pancreatitis the relationship might be causative or associative. Where it is deemed likely that a drug or other risk factor is associated with pancreatitis, objective markers such as cPLI might be useful to identify reduction in pancreatic inflammation with risk factor elimination. However, repeat exposure would be required to prove causation. Many systemic disorders have been identified as potential risk factors for pancreatitis in dogs, and where biochemical markers or imaging are suggestive of pancreatic inflammation in the absence of clinical signs, this might reflect secondary acinar cell damage below the critical threshold required for clinical disease.

In recent years, important insights have been gained into the pathophysiologic mechanisms of pancreatitis, many of which appear to have complex interactions and situation specific expressions. The use of animal models, and more specifically knockout mice, has been critical to determine these interactions and elucidate potential explanations for apparently contradictory studies. The mechanistic insights from these studies offer promise in the identification of therapeutic targets, but species specific or etiology specific mechanisms might mean that the results of experimental studies might not be directly relevant to dogs with spontaneous disease.

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CONFLICT OF INTEREST DECLARATION

Dr Steiner and Dr Lim are associated with the Gastrointestinal laboratory at Texas A&M University, which offers Spec cPL testing on a fee-for-service basis. Dr Steiner acts as a paid consultant and Speaker for Idexx Laboratories, which offers Spec cPL testing on a fee-for-service basis. Dr Steiner is also a paid consultant of ISK, who manufactures fuzapladib. No other authors have a conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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