Summary

Chronic pancreatitis (CP) is a progressive inflammatory disease characterized by pancreatic parenchymal remodeling, impaired exocrine function, and numerous extrapancreatic consequences. Increasing evidence suggests that the small intestine is one of the secondary organs affected during the course of CP; however, the mechanisms underlying intestinal wall alterations remain poorly understood, particularly in large-animal models. The aim of this study was to determine the effects of cerulein-induced chronic pancreatitis on the morphometry of the jejunal wall, enteroendocrine cell populations, and the organization of the enteric nervous system (ENS) in pigs.

The study was conducted on tissues collected from young, 10-week-old intact male pigs (*Sus scrofa domestica*) assigned either to a control group or to a chronic pancreatitis group induced by repeated administration of cerulein (n = 5 per group). The expression of selected genes was analyzed using RT-qPCR. Immunohistochemical evaluation of GIP- and GLP-1-immunoreactive cells was performed, together with histological and histomorphometric analyses of the jejunal wall and assessment of enteric nervous system structures.

Chronic pancreatitis resulted in a significant reduction in body weight. Histomorphometric analysis revealed selective remodeling of the deeper layers of the jejunal wall, including reduced thickness of the circular and longitudinal muscle layers as well as the submucosa, while the overall mucosal thickness remained unchanged. In addition, intestinal crypts were shortened, villi tended to be longer, and goblet cell numbers were increased, indicating epithelial remodeling and activation of protective mucosal barrier mechanisms.

Molecular analysis demonstrated a significant decrease in *GIP* expression and increased expression of *GCG*, *NPY*, and *FABP2*, together with a tendency toward increased *IL10* expression. Immunohistochemical analysis showed no changes in the number of GIP-immunoreactive cells, whereas the number of GLP-1-immunoreactive cells more than doubled in both villi and intestinal crypts. No differences were observed in the expression of incretin receptors. These findings indicate a reprogramming of the local enteroendocrine axis, characterized by a shift from GIP-related signaling toward activation of the proglucagon axis.

Within the ENS, the area of myenteric plexuses was significantly increased, whereas neuronal numbers and the parameters of submucosal plexuses remained unchanged. These findings

suggest selective remodeling of the neuromuscular component of the intestine, likely associated with neuroplastic adaptations to chronic inflammation.

In conclusion, cerulein-induced chronic pancreatitis triggered complex remodeling of the porcine jejunum involving structural, enteroendocrine, barrier-related, and neurogenic components. The observed phenotype exhibited both degenerative features, mainly associated with muscular atrophy and body weight loss, and adaptive responses, including activation of the proglucagon axis, increased goblet cell abundance, and ENS remodeling. These findings indicate that the jejunum is an active component of the pancreas-gut axis and participates in the multifaceted systemic response to chronic pancreatitis.