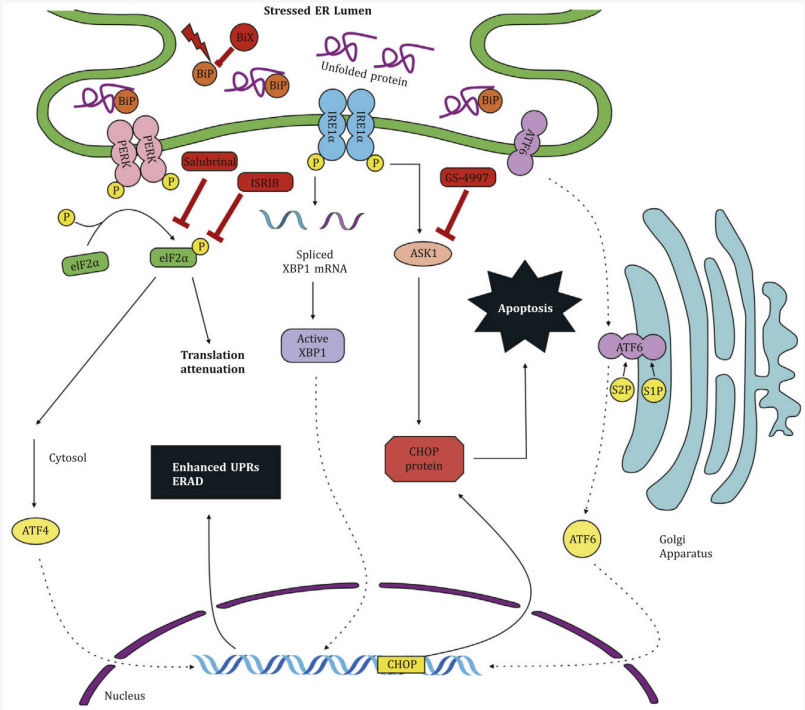
New drug targets identified for acute pancreatitis treatment

GA, UNITED STATES, November 17, 2025 /EINPresswire.com/ -- Acute pancreatitis (AP) remains a major medical challenge, with high morbidity and no approved drug that directly alters its course. Recent advances reveal that the earliest and most critical trigger of AP is intracellular calcium overload in pancreatic cells, which drives mitochondrial dysfunction, impaired autophagy, and endoplasmic reticulum stress. By focusing on these mechanisms, researchers have identified promising molecular targets that could prevent pancreatic injury and reduce systemic inflammation. Experimental and early clinical studies show that blocking calcium influx channels, enhancing calcium extrusion, protecting mitochondria, and modulating autophagy or ER stress responses may transform AP therapy, offering a window for effective early intervention.



Modulating unfolds protein responses.

Acute pancreatitis (AP) affects tens of thousands worldwide each year and carries significant risks of organ failure and death. The disease is usually triggered by gallstones or alcohol, but can also result from drugs, trauma, or metabolic disorders. One in five patients develops severe complications, leading to prolonged hospitalization and high costs for health systems. Despite extensive research, no pharmacological treatment has proven effective, leaving supportive care as the only option. Key cellular events—calcium toxicity, mitochondrial collapse, and inflammatory cascades—are now recognized as central drivers of the disease. Due to these problems, there is a pressing need to conduct in-depth research into novel molecular targets for therapy.

Researchers from Professor Li Wen, Peking Union Medical College Hospital and Professor Robert Sutton University of Liverpool published (DOI: 10.1016/j.hbpd.2025.06.001) a comprehensive

review on June 6, 2025, in Hepatobiliary & Pancreatic Diseases International. The study highlights calcium signaling as the earliest trigger of acute pancreatitis and explores drug targets that could prevent disease progression. By focusing on intracellular mechanisms—such as ORAI calcium channels, mitochondrial protection, and autophagy regulation—the authors emphasize opportunities for translating laboratory findings into clinical treatments, marking important progress in the search for the first effective therapy against this devastating disease.

The review pinpoints calcium overload as the central switch that initiates acute pancreatitis. Pancreatic acinar cells, when exposed to toxins such as bile acids or alcohol metabolites, release calcium from internal stores, activating store-operated calcium entry (SOCE). This sustained influx triggers mitochondrial calcium overload, ATP depletion, premature digestive enzyme activation, and necrotic cell death. The ORAI1 channel was identified as the primary SOCE pathway; inhibitors such as CM4620 (Auxora) significantly reduced pancreatic injury in animal models and showed encouraging results in phase II clinical trials. Other strategies include enhancing calcium extrusion through plasma membrane calcium ATPases, supported by protective effects of insulin and renalase. Preventing mitochondrial membrane permeabilization, either by inhibiting cyclophilin D or targeting the translocator protein (TSPO), also reduced injury in preclinical studies. Impaired autophagy, particularly defective lysosome–autophagosome fusion, was recognized as a major driver of disease, while restoring autophagic flux alleviated pancreatitis in models. Endoplasmic reticulum stress and unfolded protein response pathways were also highlighted as therapeutic nodes. Together, these findings establish a roadmap of potential targets that intervene early in the disease cascade and may be translated into clinical therapies.

“Acute pancreatitis is one of the last common emergencies without a disease-modifying drug,” said Professor Robert Sutton of the University of Liverpool, a co-author of the review. “Our analysis underscores that targeting the earliest molecular events—particularly calcium overload and mitochondrial dysfunction—offers the greatest chance to change outcomes for patients. The progress of Auxora in clinical trials validates this approach, and with continued research, we may finally bring a targeted therapy into practice. This would be a transformative step for both patients and healthcare systems worldwide.”

The identification of calcium signaling pathways, mitochondrial stabilizers, and autophagy regulators as drug targets creates new possibilities for treating acute pancreatitis. These strategies could reduce early pancreatic cell death, dampen inflammatory responses, and prevent life-threatening organ failure. Auxora's clinical progress demonstrates that translation from bench to bedside is feasible, with potential regulatory approval in sight. Beyond pancreatitis, these insights may apply to other conditions involving calcium-mediated injury, such as ischemic stroke or myocardial infarction. Developing the first effective therapy for acute pancreatitis would not only save lives but also alleviate the global economic and healthcare burden associated with this disease.

DOI

10.1016/j.hbpd.2025.06.001

Original Source URL
https://doi.org/10.1016/j.hbpd.2025.06.001

Funding information
This study was supported by grants from the National Natural Science Foundation of China (82122010 and 82070659), the National High Level Hospital Clinical Research Funding (2022-PUMCH-E-003), the CAMS Innovation Fund for Medical Science (2022-I2M-1-004) and an NIHR Senior Investigator Award.

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