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Mini Review
Published: 26 Jan, 2018

Journal of Gastroenterology Forecast

Inflammasomes in Pathophysiology of Acute Pancreatitis: "Et Facta Est Lux"

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Abstract

When Hans Chiari invented the term auto digestion little was known about pancreatic pathophysiology. However, that concept posed more questions than it explained up until recently. In 2000 a major medical breakthrough, the discovery of the inflammasome took place and in the last decade its role in inflammation was researched in great detail. This discovery could be the hidden link in the defussyfication of pancreatic pathophysiology. This paper focuses on that probability and in the latest advances in the field.

Keywords: Inflammasomes; Acute pancreatitis; Pancreas inflammation

Introduction

Although pancreas has been described by ancient anatomists, up until at least the 17th century little was known about its physiology. Galen and the school of Alexandria seem to have been aware of the organ but failed to connect it with a certain illness and it was not until mid 1600 that anatomist Nicholaes Tulp managed to indentify pancreatic pathology during an autopsy (Pannala R. et. al. 2009). In the early 20th century Hans Chiari studied the organ thoroughly and purposed the mechanism of auto digestion in pancreatitis. Located deep in the abdomen and with no apparent function this mysterious organ remained an unknown land for scientists for circa two thousand years. This editorial discuses previous knowledge on pancreatic pathophysiology and focuses on the role of the inflammasome and it possible part in future discoveries on the field.

From Chiari to the 20th century

Based on Hans Chiari's work it seemed that the main mechanism of acute pancreatitis was auto digestion of the pancreas as a direct result of intracellular activation of certain enzymes –pancreatic zymogens. In 1946 John Howard Northrop won the Nobel Prize in Chemistry for crystalling the pancreatic enzymes. Up until late 1990 the role of trypsinogen activation via cathepsin B, auto activation and Ca concentration were meticulously studied in numerous papers as reviewed by FS Gorelick and T. Ortani in 1999 (1). Soon after M. Bahtia, M. Brady et. al. (2000) reviewed the inflammatory cascade in acute pancreatitis and confirmed the role of several mediators such as TNF-a, IL-1b, IL-6, IL-8, PAF, IL-10, C5a, ICAM-1, and substance P. Their paper partly focused on the role of leukocyte in acute pancreatitis, MODS and SIRS suggesting this cell type as a possible new therapeutic target.

The 21th century

In early 2000s' a great discovery took place by Professor Jurg Tscopp and his collegues: the inflammasome. The (canonical) inflammasome was identified as part of the innate immunity response and it is believed to be a complex of proteins that mediates the activation of caspase 1. Caspases (cysteine aspartic proteases) are known to regulate pyroptosis or inflammatory programmed cell death. In the meantime another study (Dawra et. al. 2011) revealed that in mice, trypsin-mediated pancreatic injury was well compensated. Thus the inflammasome and its possible role in pancreatic injury is a current trend for gastrointestinal research in hopes for better understanding of tissue damage in pancreatitis. Recent studies (Kang R. 2014 and R. Hoque and W.Z. Mehal 2015) shed light to this new concept. The first one suggested certain damage associated molecular patterns (DAMPs) in acute pancreatitis such as high mobility group box 1 [HMGB1], DNA, histones and ATP. The latter, suggested that DAMPS and pathogen-associated molecular patterns (PAMPs) –such as ethanol or fatty acids- necrotic cells promotes NLRP3 inflammasome activation which promotes pyroptosis which has a pro-inflammation effect. Moreover, authors discussed the regulation of the inflammasome and novel models for pancreatitis pathophysiology in mice.

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Received Date: *30 Dec 2017*
Accepted Date: *15 Jan 2018*
Published Date: *26 Jan 2018*

Citation: *Filippou D, Kripouri P. Inflammasomes in Pathophysiology of Acute Pancreatitis: "Et Facta Est Lux". J Gastroenterol Forecast. 2018; 1(1): 1003.*

Future

Interleukins have already been targeted it treatment of auto-inflammatory disease and cancer. Inflammasome is a more recent concept and thus it is not yet certain if it will bring therapeutic results. However, scientists are now studing its role in various diseases apart from acute pancreatitis such as in multiple sclerosis (Barcley et. al. 2017), in acute glaucoma (Chi W. et. al. 2015), in atherosclerosis (Hoseini et. al. 2018), in COPD (Eapen M.S. et. al. 2017). Thi THT and Hong S. (2017) researched the possibility of inflammasome targeting in cancer treatment, Tsai YL et. al. in IgA nephropathy (2017), Felini G. et. al. in skin diseases. Ren JD et. al. published their research in targeting the inflammasome in acute pancreatitis in mice in 2014 and Wang G. et. al. (2016) showed a rather different target: the necrosome. The field of immunopharmacology is new and authors of this editorial are moderaly optimistic that it is promising, as well.

Conclusion

The pancreas kept its secrets for hundreds of years. Scientists have walked a great distance from Galen to modern understanding of this organ. Its complex physiology is partially revealed and today it is both surgically and pharmacologically treated for various diseases. However, acute pancreatitis remains a public health issue with serious complications and a high death toll. As biomedical science evolves novel discoveries give promising results for the future. Could the discovery of the inflammasome be the answer to pancreatitis pathophysiology? Will it lead to new therapeutic approaches? Authors of this paper conclude that even more research is needed; inflammasomes do raise some charming questions for the researchers of our time.

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