New therapeutical approach in acute pancreatitis

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CLOSING REPORT

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Acute pancreatitis (AP) is an inflammatory disorder of the pancreas with an unacceptable high mortality (5-10%) and with no specific pharmacological treatment. Therefore, pathophysiological studies aiming to understand the development of the disease are crucially important. In this project **we proposed** to employ both in vitro and in vivo cutting-edge cell **physiological and biochemical techniques to find new therapeutic targets and develop novel treatment possibilities in acute pancreatitis.**

In our research period we performed several genetic, biochemical and physiological techniques to understand the pathophysiology of the acute inflammation. **Our results were published in leading prestigious journals** (detailed results can be found in the articles listed at the end of the report).

DETAILS OF THE MOST IMPORTANT DISCOVERY OF THIS PROJECT:

We are very proud that by the end of the research period we could demonstrate that CFTR inhibition plays a crucial role in acute pancreatitis. Because genetic alterations of the CFTR Cl^- channel can cause pancreatic damage and increase the risk of acute pancreatitis, we hypothesized that alcohol (which is one of the most common causes of acute pancreatitis) may exert its detrimental effect through affecting CFTR function. To prove our hypothesis we used several different experimental approaches, including human studies, *in vivo* and *in vitro* animal models and genetically modified animals and cell lines such as CFTR -/- mice and CFTR overexpressing MDCK cells.

Using patch clamping, confocal and fluorescence microscopy we detected a strong inhibitory effect of alcohol and fatty acids on the activity of CFTR and we also found impaired bicarbonate secretion. The inhibitory effect was mediated via sustained calcium overload, impaired cellular cAMP levels, ATP depletion and mitochondrial membrane depolarization. We also successfully reproduced the alcohol-induced decreased CFTR expression *in vitro* in cultured pancreatic epithelial cells and *in vivo* in guinea pigs, which was caused most likely by decreased cell surface stability and ER folding defect of CFTR as demonstrated in cultured CFTR overexpressing MDCK cells. Finally, we demonstrated using CFTR knock-out mice that deletion of CFTR leads to more severe pancreatitis induced by ethanol and fatty acids.

These data indicate that inhibition of CFTR function is critical in the development of alcoholic pancreatitis, therefore, correcting CFTR function could be the first specific therapy in acute pancreatitis.

Our discovery was published in Gastroenterology (IF:13,928) which is the leading GI journal of the field. Importantly, this publication was quickly recognized and highlighted by the prestigous Nature Reviews HG.
http://www.nature.com/nrgastro/journal/vaop/ncurrent/full/nrgastro.2014.204.html

LIST OF PUBLICATIONS:

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