Az akut és krónikus pancreatitis kezdeti szakaszának vizsgálata:

a betegágytól a laboratóriumi vizsgálatokig

OTKA 116634

Closing report

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Details of the most important findings

At the first part of our project we demonstrated an increased epithelial mucus production in the small pancreatic ducts in the early phase of Chronic pancreatitis (CP), which is paralleled by an impairment of pancreatic ductal fluid secretion (25). The evidence that we have found during our project supports that mucus dehydration is an important aspect of the early-pathogenesis and argues the rationale for therapeutic targeting of defective mucus in CP. In human pancreas samples have found that mucus content is increased in small ducts in CP. Mucus was found to be localized to the epithelial surfaces and to the luminal area of pancreatic ducts. In control samples, we found reduced amount of mucus in intralobular ducts, while in CP tissue small ducts exhibited substantial amounts of mucus that often completely plugged the lumen. Analysis of pancreatic morphology revealed a significant increase of epithelial mucus content in small ducts, while no difference was observed in large interlobular ducts. Experiments revealed an increased intraluminal mucus in the smallest ducts in CP, while proteinaceous material was less extensive, which could reflect decreased acinar secretion, i.e., exocrine dysfunction in CP. Furhermore, we examined the mucus changes in experimental CP which was induced by 4 weeks of cerulein injections in mice. In contrast to what we have found in the the human samples, alcian-blue positive staining was virtually absent in the ducts of control mice. In cerulein-induced CP tissue formation of novel ductal structures due to acinar-to-ductal metaplasia (ADM) was apparent. Similarly to human CP, we found alcian-blue positive mucus on the surface of the ductal epithelium and intraluminally in small ducts of mice. Morphometric analysis revealed that the density of mucus volume was significantly higher in small ducts in cerulein-treated mice . Experiments revealed that secreted

mucins *MUC5B* and *MUC6* were significantly upregulated in CP suggesting epithelial mucus hypersecretion. Another secreted mucin *MUC5AC* was not detectable in most of the samples. *MUC1* and *MUC4* (membrane bound mucins) were not significantly altered.. In cerulein-induced experimental CP we found that *Muc6*, but not *Muc5b* was upregulated by three orders of magnitude, indicating that *Muc6* glycoprotein is the dominant secreted mucin in the mouse pancreatic duct. Membrane-bound mucin *Muc1* was downregulated that could be attributed to lower number of acinar cells, that also express *Muc1*. All in all, we found that secretory mucins are differentially expressed in human and experimental chronic pancreatitis. Defective mucus hydration may develop if increased mucus secretion is accompanied by an epithelial ion and fluid transport defect. To assess the pancreatic ductal function in CP first, we used magnetic resonance imaging cholangiopancreatography (MRCP) to measure total excreted volume in control and 4-week cerulein-treated mice *in vivo.* We found that the total excreted volume was significantly decreased in CP mice compared to the controls. In order to study the time-changes of ion and fluid transport, we examined pancreatic ductal secretory function *in vitro* using different cerulein treatment time-series. We isolated pancreatic duct fragments from control and 1–2–3–4-week cerulein-treated mouse pancreata, and measured fluid secretion by the swelling assay. Basal ductal secretion in HCO_3^- containing buffer in 4-week cerulein-treated mice was significantly lower, than in controls. Upon administration of IBMX and forskolin, stimulated fluid secretion was markedly reduced in 3- and 4-week cerulein-treated mice.

Next, we identified novel variants in human cationic trypsinogen gene ; p.P17T and p.L104P (14). Trypsinogen is a major digestive enzyme produced and secreted by the pancreas, therefore the enzyme is a significant component of the pancreatic fluid. Intraductal trypsinogen activation leads to the development of pancreatitis. Our experiments revealed that the novel mutation p.P17T causes accelerated trypsinogen activation, while mutation p.L104P encodes genetically determined endoplasmatic reticulum stress which is a trypsin-independent pathway of pancreatitis. We were the first who described that the endoplasmatic reticulum stress inducing p.L104P mutation cause hereditary pancreatitis. We provide evidence of the crucial role of trypsinogen activation in the pathophyisiology of pancreatitis (11,14,15,22,27). Henceforth, we have shown data regarding the expression and role of AQP1(aquaporin) in the physiology and pathophysiology of the pancreas. Our data indicate that AQP1 interacts

with the CFTR (cystic fibrosis transmembrane conductance regulator) Cl^- channel and takes part in the formation of pancreatic fluid (22, 35). We also found that AQP1 plays role in the pathology of pancreatitis. We hypothesize that absence of the channel makes the pancreas more sensitive to pancreatitis, probably due to the decreased pancreatic fluid and HCO_3^- secretion.

Our results show a link between CFTR dysfunction and mucus dehydration, howewer further confirmation are needed to evaluate the direct role of CFTR-mediated bicarbonate transport on the regulation of mucus secretion and the development of ductal obstruction in the pancreas (22). Our novel findings not only help to understand the pathomechanism of pancreatitis better, but open up new therapeutic opportunities in the treatment of the disease.

Besides the experimental work we also made a large effort to build up a clinical database to monitor the patients after acute and chronic pancreatitis. We have published several papers on this topic as well (1-10, 12, 13, 16-21).

All together 36 First or Last author publications came out from the project.

List of publications (36) as FIRST or LAST author during the project:

1: Szentesi A, Párniczky A, Vincze Á, Bajor J, Gódi S, Sarlós P, Gede N, Izbéki F, Halász A, Márta K, Dobszai D, Török I, Farkas H, Papp M, Varga M, Hamvas J, Novák J, Mickevicius A, Maldonado ER, Sallinen V, Illés D, Kui B, Erőss B, Czakó L, Takács T, Hegyi P. Multiple Hits in Acute Pancreatitis: Components of Metabolic Syndrome Synergize Each Other's Deteriorating Effects. Front Physiol. 2019 Sep 20;10:1202. doi: 10.3389/fphys.2019.01202. eCollection 2019. PubMed PMID: 31620021; PubMed Central PMCID: PMC6763590.

2: Farkas N, Hanák L, Mikó A, Bajor J, Sarlós P, Czimmer J, Vincze Á, Gódi S, Pécsi D, Varjú P, Márta K, Hegyi PJ, Erőss B, Szakács Z, Takács T, Czakó L, Németh B, Illés D, Kui B, Darvasi E, Izbéki F, Halász A, Dunás-Varga V, Gajdán L, Hamvas J, Papp M, Földi I, Fehér KE, Varga M, Csefkó K, Török I, Hunor-Pál F, Mickevicius A, Maldonado ER, Sallinen V, Novák J, Ince AT, Galeev S, Bod B, Sümegi J, Pencik P, Szepes A, Szentesi A, Párniczky A, Hegyi P. A Multicenter, International Cohort Analysis of 1435 Cases to Support Clinical Trial Design in Acute Pancreatitis. Front Physiol. 2019 Sep 4;10:1092. doi: 10.3389/fphys.2019.01092. eCollection 2019. PubMed PMID: 31551798; PubMed Central
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Moore D, Sutton R, Gougol A, Papachristou GI, Susak YM, Tiuliukin IO, Gomes AP, Oliveira MJ, Aparício DJ, Tantau M, Kurti F, Kovacheva-Slavova M, Stecher SS, Mayerle J, Poropat G, Das K, Marino MV, Capurso G, Małecka-Panas E, Zatorski H, Gasiorowska A, Fabisiak N, Ceranowicz P, Kuśnierz-Cabala B, Carvalho JR, Fernandes SR, Chang JH, Choi EK, Han J, Bertilsson S, Jumaa H, Sandblom G, Kacar S, Baltatzis M, Varabei AV, Yeshy V, Chooklin S, Kozachenko A, Veligotsky N, Hegyi P; Hungarian Pancreatic Study Group. Antibiotic therapy in acute pancreatitis: From global overuse to evidence based recommendations. Pancreatology. 2019 Jun;19(4):488-499. doi: 10.1016/j.pan.2019.04.003. Epub 2019 Apr 19. PubMed PMID: 31068256.

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