SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

The role of OGG1 enzyme in acute pancreatitis

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UNIVERSITY OF DEBRECEN
DOCTORAL SCHOOL OF MOLECULAR MEDICINE
DEBRECEN, 2023

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The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, at 1 PM, 27th of October, 2023.

Introduction

Incidence and etiology of AP

Acute pancreatitis (AP) is an acute inflammatory disease of the pancreas characterised by significant mortality. The disease is associated with radiating abdominal pain, nausea, vomiting, and in severe cases fever, tachycardia, and multi-organ failure can also occur. The modified Atlanta classification distinguishes between mild, moderate and severe forms. The course of the disease is mild in 80% of the cases, resolving within a week with fasting and hydration; however, in 20% of the cases a severe necrotizing form of inflammation develops, which can lead to a life-threatening condition.

The annual incidence of AP varies from country to country. A recent meta-analysis of 44 studies shows an increasing tendency in most countries in the western world. In Hungary there are approximately 20-50 cases per 100,000 inhabitants per year.

Gallstones and chronic alcohol consumption are largely responsible for its development, but many other etiological factors (viral infection, drugs, hypertriglyceridemia, tumour, trauma) can be also present. In 10-30% of the cases, the underlying cause cannot be identified (idiopathic AP). In biliary pancreatitis, gallstones are formed and get stuck in the Vater's papilla at the junction of the bile duct and the pancreatic duct. The obstruction leads to reflux of bile into the pancreas and increase intraductal pressure. The consequence is disruption of calcium homeostasis and activation of digestive enzymes within the gland. In Hungary, alcohol consumption is responsible for 50% of acute pancreatitis cases, in Europe only Latvia, Finland, Romania and Russia are ahead of our country. Alcohol increases exocrine pancreatic function, leading to the thickening of protein-rich pancreatic fluid and obstruction of the duct. It also has a toxic effect on acinar cells, as oxidative metabolism generates reactive oxygen species that damage the cell membrane, proteins and DNA.

Pathomechanism of acute pancreatitis

There are several factors playing important roles in the pathomechanism of AP: NF-κB which is responsible for the synthesis of proinflammatory cytokines; early activation of trypsinogen; mitochondrial damage and oxidative stress. However, the interrelationship and the chronological order of these processes are still not fully understood. I will briefly discuss these mechanisms below and describe them in detail in Chapter IV.5 of my dissertation.

Intra-acinar activation of proenzymes

According to our current understanding, one of the early events in AP is the disruption of the transport of proenzymes within the acinar cell. Under physiological conditions, digestive enzymes are transported to zymogen granules after their synthesis in the endoplasmic reticulum and are activated only after secretion into the lumen of the small intestine. In pathological cases, however, proenzymes may get into a common organelle with lysosomal hydrolases. During colocalisation, the lysosomal cysteine protease cathepsin B activates trypsinogen-trypsin conversion which triggers a cascade of further proenzyme activation. This leads to acinar cell damage and self-digestion of the gland.

The role of cytokines in AP

The role of NF-κB in pancreatitis has been highlighted since the 1990s. Researchers have shown that the transcription factor is activated in the early stage of pancreatitis and induces the transcription of several mediators involved in inflammation such as cytokines (tumour necrosis factor, interleukins, chemokines) and adhesion molecules. Cytokines are small molecular weight proteins whose source are activated leukocytes and also the acinar cells. Damage of acinar cells and production of cytokines lead to a local inflammatory response accompanied by leukocyte infiltration. Immune cell migration through the endothelium of capillaries is facilitated by adhesion molecules (e.g. ICAM-1) whose expression are increased in AP. Among the cytokines, one of the most widely studied proteins is tumour necrosis factor-α (TNF-α) which is mainly produced by macrophages but can also be synthesised by acinar cells. The cytokine is involved in the initiation of inflammatory processes through activation of NF-κB. Other important factors in the inflammatory cascade are IL-1β and IL-6 whose levels in the pancreas correlate with the severity of pancreatitis. The former activates neutrophils and induces the upregulation of adhesion molecules, while the latter is involved in the induction of proinflammatory processes by binding to the sIL-6 receptor (trans-signaling pathway). In my dissertation, in chapter IV.5.6 I also discuss the role of several chemokines whose level is significantly elevated in AP.

The role of cholecystokinin in AP

Cholecystokinin (CCK) is a peptide hormone. It is produced primarily by enteroendocrine cells in the small intestine which are stimulated by the initiation of the digestive process. The peptide hormone is released into the bloodstream and triggers gallbladder contraction and secretion of pancreatic enzymes via CCKR. Basal CCK level is low in the blood

(0.5-1 pmol/L); upon stimulation, it increases to 5-15 pmol/L. There are several molecular variants of CCK, with CCK33 being the most abundant type in humans. The secretion of CCK is induced by fatty acids and proteins in the chyme, and as their levels decrease, CCK levels return to baseline.

High plasma CCK levels have been reported in patients with biliary pancreatitis. It is believed that elevated hormone concentrations may further exacerbate inflammation and worsen the prognosis of AP by stimulating the damaged pancreas. The mechanism of CCK has also been studied in animal studies, which showed that CCK applied at supramaximal concentrations (above the maximum dose that induces amylase secretion) inhibited enzyme secretion, leading to accumulation and activation of zymogens within the cell. The cerulein-induced AP model used in our experiments is based on this mechanism of action. Cerulein is a CCK analogue that induces exocytosis of zymogens by binding to CCK1R (high affinity CCKR) in physiological amounts. At supramaximal concentrations, CCK1 receptors are saturated and cerulein then binds to CCK2R (low affinity CCKR) which has a secretion blocking effect. The advantage of this model is that the phenomenon described in human AP (hyperamylasemia, inflammatory cell infiltration, edema) can be well reproduced in animal studies.

The role of oxidative stress in AP

Over the past decades, the contribution of reactive oxygen species (ROS) to AP has been in the centre of several studies. It has been shown that while the source of ROS in the milder form of pancreatitis is infiltrated leukocytes, in necrotizing AP it is xanthine oxidase. Proteolytic enzymes released during acinar cell injury catalyse the xanthine dehydrogenase → xanthine oxidase conversion. Xanthine oxidase produces superoxide during the oxidation of hypoxanthine and xanthine. Another source of oxygen radicals is NADPH oxidase in granulocytes, but researchers have also described the expression of this enzyme in acinar cells.

Reactive species are released early in AP, accompanied by a decrease in endogenous antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase). This leads to an imbalance between pro- and antioxidant processes and oxidative stress. Excess amount of ROS act on acinar cells through multiple pathways. Firstly, they damage the cell membrane by reacting with fatty acids to cause peroxidation of membrane lipids and cell disintegration. Damage also extends to the endothelial layer of capillaries and veins, resulting in increased permeabilisation of blood vessels, causing edema. On the other hand, ROS are also involved in

the activation of NF-κB. For example, it has been shown that H_2O_2 induces NF-κB activation in pancreatic lobules via an IKK-independent pathway.

The pathological processes induced by reactive oxygen species include the disruption of calcium homeostasis. This phenomenon is explained by alterations in the channels involved in the regulation of calcium ion trafficking in acinar cells. Oxidation of ryanodine receptors (RyR) leads to activation of the channel, while ROS increases the sensitivity of inositol trisphosphate receptor (IP_3R) to IP_3. Ca^{2+}-ATPase pumps are also sensitive to changes in the redox environment. PMCA is inhibited in acinar cells treated with H_2O_2. Furthermore, SERCA pumps contain 6 redox-sensitive cysteine residues of which the sulphonylation of Cys674 takes place under prolonged oxidative stress leading to the inhibition of SERCA. These processes result in a sustained increase in cytosolic Ca^{2+} levels, causing intracellular activation of digestive enzymes. A further consequence of intracellular Ca^{2+} oversaturation is mitochondrial damage. Elevated cytosolic Ca^{2+} causes calcium ions to flow into the mitochondria. If sustained mitochondrial Ca^{2+} levels develop, the mitochondrial permeability transition pore (MPTP) opens, leading to a decrease in mitochondrial membrane potential, impaired ATP synthesis and cell death.

Role of PARP-1 in AP

ROS generated during inflammation damage not only proteins and lipids, but also nucleic acids. The repair of DNA damage is essential to maintain genome integrity in which the poly-ADP-ribose-polymerase 1 (PARP-1) enzyme has an important role. It binds to DNA through its two zinc-finger domains in response to DNA breakage, then produces nicotinamide and ADP-ribose (ADPR) by cleavage of NAD^+ and covalently links ADPR to the side chain of acceptor proteins. The branched-chain PAR polymers serve as signal molecules for enzymes involved in DNA repair.

The role of the PARP-1 enzyme in AP can be linked to the use of NAD^+. Oxidative stress during inflammation induces a large amount of DNA damage, leading to hyperactivation of PARP-1, resulting in depletion of the NAD^+ and ATP. The energy imbalance eventually causes necrotic death of the cell. It is also important to mention the another form of PARP-1-mediated cell death, whereby translocation of the PAR polymer from the nucleus to the mitochondria triggers a characteristic AIF-dependent necrotic cell death, parthanatos.

PARP-1 also contributes to the development of pancreatitis through the regulation of transcriptional processes. PARylation of histones transfers a large negative charge onto the protein. This results in electrostatic repulsion between DNA and histones, which facilitates the

access of transcription factors to DNA. Furthermore, PARP-1 synergistically co-activates NF-κB by forming a complex with p300.

The role of the enzyme in the disease is confirmed by the fact that PAR accumulation was observed in pancreas immunohistochemistry in patients died in AP, whereas no PARylation was detected in healthy individuals. These observations drew the attention of researchers to the use of PARP inhibitors. The use of PARP inhibitors (PJ34, 3-AB, olaparib) reduced the levels of amylase, lipase and cytokines (TNF-α, IL-1β, IL-6, MCP-1) in serum, and also reduced the rate of lipid peroxidation and myeloperoxidase activity in pancreas. Furthermore, the inhibitors also decreased the levels of PAR and ICAM-1 in pancreas.

The role of 8-oxoG and OGG1 in inflammation

One of the latest developments in redox pathobiochemistry is related to the most common oxidative DNA lesion (8-oxo-7,8-dihydroguanine) caused by ROS. István Boldogh and his research team observed that the promoters of proinflammatory genes are high in GC content and the amount of 8-oxoG lesions generated during inflammation correlates with transcriptional activity in these regulatory regions. The enzyme responsible for repairing 8-oxoG is 8-oxoguanine DNA glycosylase-1 (OGG1), which induces a 70º bending of DNA in the plane of 8-oxoG:C base pair in order to access the lesion. After removal of the oxidized base, the base excision repair proteins complete the DNA repair. However, under intense oxidative stress, the cysteine residues of OGG1 are oxidized, leading to inactivation of the enzyme. Although under these circumstances, OGG1 does not have catalytic activity, it is still capable of the following: (1) extraction of 8-oxoG from the DNA, (2) insertion of the damaged base into OGG1 active-site pocket, (3) unstacking the cytosine opposite to 8-oxoG from the DNA helix. These events result in a sharp bending of DNA, promoting NF-κB binding and transcription of proinflammatory genes until redox balance is restored. In this case OGG1 regains its enzymatic activity, leading to excision of the damaged base and disassembly of the transcriptional machinery.

The role of OGG1 in the inflammation has been proved by a number of experimental studies. OGG1 knockout mice are resistant to inflammation induced by LPS, oxazolone or ovalbumin. Furthermore, small interfering RNA depletion of OGG1 in mice reduced airway inflammation.

Aims

The incidence of acute pancreatitis has been increasing over the last decades due to the rising prevalence of lifestyle-related risk factors (gallstones caused by high-fat foods, chronic alcohol consumption). The mortality rate is unacceptably high, despite rapid medical intervention, due to the underlying cause of the disease is often undetectable. In the absence of the etiological factors, therapeutic efforts are focused on controlling the initial phase of inflammation.

Our aim was to investigate molecules that may be involved in inflammatory processes in the pancreas. Uncovering the pathomechanism may open up the possibility to develop additional therapies and reduce mortality rates.

Over the past decades, several studies have reported that reactive oxygen species are released in the early course of AP and play an important role in the development of the disease. One of the latest developments in redox biology research is that 8-oxoG lesions in DNA also contribute directly to inflammatory processes. The importance of the repair enzyme OGG1 in the pathomechanism of AP remains an unexplored area.

At the Department of Medical Chemistry, the Oxidative Stress and PARylation group has been investigating the role of ROS mediated DNA damage – PARP activation pathway in cell death and in the pathomechanisms of various diseases for a long time. Since PARP-1 is a major determinant of cellular NAD^+ levels, we hypothesize that the enzyme may be a promising target for the prevention of necrotizing pancreatitis.

We set the following goals for our project:

- to set up the AP model in C57BL/6 mice
- to optimise the isolation and treatment protocol for primary acinar cells
- to investigate the role of OGG1 in AP using a selective inhibitor of OGG1 (TH5487) *in vitro* and *in vivo* experiments
- to investigate the effect of OGG1 inhibition on PARylation and PARP-1
- to explore the role of PARP-1 using PARP-1 knockout mice and primary acinar cells isolated from these mice

Methods

Animal experiments provide an excellent opportunity to model pancreatitis, study the pathomechanism and test different pharmacological agents. For our experiments, we have chosen the cerulein-induced AP model. It is a highly reproducible, non-invasive model that adequately represents the characteristics and histological alteration of human inflammation.

In our experiments, we separated three treatment groups: control, cerulein and cerulein + TH5487. In the latter group, mice were pretreated with 30 mg/kg TH5487, while in the first two groups, mice were pretreated with the vehicle of TH5487. Afterwards inflammation was induced with 8 intraperitoneal injections of cerulein at 50 μg/kg, while control mice received physiological saline only. Blood and tissue samples were collected 10 hours after the first cerulein injection.

The effect of TH5487 was also tested on primary acinar cells, which provide a good opportunity to study cerulein-induced cell death of exocrine pancreas *in vitro*.

For reasons of space, the materials and methods used in our work are not described in thesis, but can be found in Chapter VI. of the dissertation.

Results

OGG1 inhibition reduces acinar cell damage and inflammatory cell extravasation

In order to determine the efficacy of OGG1 inhibition in the AP model, we first measured the levels of serum α-amylase, lipase and tissue levels of MPO. The increase in serum enzyme levels indicates acinar cell damage, while the latter parameter indicates granulocyte infiltration of the pancreas. Cerulein treatment increased serum α-amylase levels by 4-fold and serum lipase levels by 14-fold. MPO levels increased by almost 7-fold. OGG1 inhibitor pretreatment reduced the increase in serum enzyme levels and the amount of neutrophils in the tissue induced by cerulein injections.

Inhibition of OGG1 reduces pancreatic tissue damage

Histological lesions of AP were examined on paraffin sections of the pancreas stained with hematoxylin and eosin. The morphological changes were evaluated by collaborators from the Department of Pathology of the University of Debrecen and scored on a scale from 0 (no pathological alteration) to 3 (severe pathological alterations). Inhibition of OGG1 significantly reduced interstitial edema, the number of infiltrated immune cells and the degree of necrosis.

Inhibition of OGG1 reduces nuclear PARylation but has no effect on PARP-1 enzyme expression

The effect of OGG1 inhibition on PARylation was investigated by immunofluorescence assay. The amount of PAR polymers was significantly increased in cerulein-induced inflammation, which was reduced by TH5487 treatment. PARP-1 immunostaining was performed to determine whether reduced PARylation was related to changes in PARP-1 enzyme levels in the pancreas. In cerulein-treated mice, PARP-1 enzyme levels increased 2-fold compared to the control group, but TH5487 treatment had no effect on enzyme expression. Based on these results we came to the conclusion that inhibition of OGG1 affected PARP-1 activity in the AP model.

OGG1 inhibition shifts acinar cell death from necrosis to apoptosis, while cell viability increases

We have examined the extension of apoptosis in the pancreas by cleaved PARP-1 immunostaining. The amount of cleaved PARP-1 was significantly increased in both cerulein-treated group compared to the control mice, whereas mice pretreated with TH5487 had the highest apoptosis rate. The effect of the OGG1 inhibitor on cell death was also studied in *in vitro* experiments, in which primary cells isolated from C57BL/6 mice were used. The cells were pretreated with different concentrations of TH5487 and cell death was induced by cerulein treatment for 24 hours. Cell viability was determined by calcein assay, while necrosis by Sytox Green staining and measurement of LDH levels in the supernatant. TH5487 treatment significantly reduced necrosis and increased cell viability. Apoptotic cell death was assessed by caspase 3/7 activation assay: measurements were performed for 24 hours under environmental control (5% CO_2, 37 °C), detecting the change in fluorescence signal at 502/530 nm in every 3 h. TH5487 significantly increased the apoptosis in cells.

OGG1 inhibition reduces the expression of inflammatory cytokines in acute pancreatitis

The effect of OGG1 inhibition in AP was examined by measuring the levels of cytokines in the pancreas. Of the 40 cytokines investigated, the levels of ten cytokines increased more than 3-fold in cerulein-treated mice compared to the control group. The TH5487 treatment decreased the levels of several cytokines. To confirm the results obtained in the cytokine array, the expression of cytokines was also examined by qPCR. The expression of 10 cytokines out of 12 involved in the development of inflammation was significantly reduced by the OGG1 inhibitor.

OGG1 inhibition reduces the DNA-binding activity of NF-κB

Since the levels of inflammatory cytokines and chemokines were reduced in TH5487-treated mice, we hypothesized that OGG1 inhibition targets the NF-κB inflammatory signaling pathway. Under intensive oxidative stress, OGG1 increases the binding affinity of NF-κB to DNA through allosteric modification of DNA, and thereby increases transcription of inflammatory genes. We hypothesized that this process can be inhibited by the selective inhibitor of OGG1. The effect of the OGG1 inhibitor on NF-κB DNA binding was confirmed in EMSA experiments. In cerulein-treated mice, NF-κB was detected in the nucleus 30 minutes after the cerulein injection. The 8-oxoG modification enhanced the DNA-binding activity of the transcription factor compared to the double-stranded probe without 8-oxoG (native). In the second part of the experiment the effect of the OGG1 inhibitor on NF-κB DNA binding was tested. TH5487 reduced binding of NF-κB to 8-oxoG containing double stranded DNA in a concentration dependent manner, but had no effect on binding of transcription factor to the native probe.

Inhibition of OGG1 increases the accumulation of 8-oxoG in the pancreas but decreases single-strand DNA breaks

The effects of TH5487 on cell death and inflammation were examined in animal and primary acinar cell experiments, but we were also interested in whether OGG1 inhibition have an effect on the level of oxidative DNA damage in the pancreas. For this purpose, we performed 8-oxoG immunofluorescence staining. Nuclear 8-oxoG levels were increased in cerulein-treated mice, which were further increased by TH5487 treatment. In comet assays, we found that amount of single-strand DNA breaks induced by cerulein treatment was reduced by TH5487 treatment.

Knockout of PARP-1 reduces inflammation and acinar cell damage

The role of PARP-1 enzyme was investigated in cerulein-induced AP model with C57BL/6 male wild-type (WT) and PARP-1 KO (KO) mice of the same genetic background. Four groups were set up: WT control group, WT cerulein-treated group, KO control group, and KO cerulein-treated group. Inflammation was induced in mice by hourly intraperitoneal injections of cerulein (50 μg/kg), for a total of 8 injections. Control mice received physiological saline. Blood and tissue samples were collected 10 hours after the first cerulein injection. PARP-1 inactivation decreased serum α-amylase and lipase levels, as well as MPO level in pancreas. Primary acinar cells were treated with cerulein for 24 h, followed by MTT assay and PI staining. The viability of KO cells increased and the necrosis rate decreased compared to wild-type mice in the cerulein-treated groups.

Conclusions

To elucidate the role of OGG1 and PARP-1 in the pathogenesis of acute pancreatitis, experiments with animals and primary acinar cells were performed. Based on our experiments the following conclusions can be drawn:

1. The 8-oxoG level is increased in the pancreas during AP.
2. Binding of OGG1 to oxidized guanine increases the DNA-binding activity of NF-κB, which leads to increased expression of several inflammatory cytokines and chemokines.
3. OGG1 increases immune cell infiltration and edema in the pancreas through the progression of inflammatory processes.
4. OGG1 affects PARP-1 activity causing increased PARylation in the pancreas.
5. Increased PARP-1 activity induces energy depletion leading to necrosis of acinar cells in the gland.
6. Tissue injury to the pancreas leads to elevated serum levels of digestive enzymes and infiltration of granulocytes in the gland.

Hopefully our research will contribute to the development of new therapeutic approaches in the future, beyond palliative methods of treating acute pancreatitis, which only temporarily relieve symptoms.

Summary

Acute pancreatitis is one of the most common gastrointestinal disorders. Its pathogenesis is often unknown and its pathomechanism is still not entirely clarified. During the course of the disease, pro- and antioxidant processes become unbalanced relatively early on, leading to the accumulation of ROS-induced tissue damage.

We investigated the role of OGG1 and PARP-1 proteins as both enzymes are involved in the repair of oxidative stress-induced DNA damage. Under physiological conditions, the enzymes promote cell survival by maintaining DNA integrity but under intense oxidative stress they contribute to the progression of inflammation.

We found that inhibition of OGG1 with TH5487 reduced acinar cell necrosis, proinflammatory cytokine formation, PAR accumulation, leukocyte infiltration and edema in the pancreas. We have confirmed the anti-inflammatory effect of TH5487 by examining two possible mechanisms. One explanation is that the OGG1 inhibition decreases DNA-binding activity of NF-κB, thereby reducing the expression of inflammatory genes. The other phenomenon is related to cell death. TH5487 diverts necrosis to apoptosis in cells which decreases tissue damage. Furthermore, since 8-oxoG deletion and DNA cleavage caused by apurinic/apyrimidinic endonuclease 1 (APE1) are prevented, PARP-1 activation and PARP-1-mediated necrosis are both reduced. The latter phenomenon and the role of PARP-1 in transcriptional regulation may explain the decreased serum amylase and lipase levels, decreased granulocyte infiltration and necrosis of acinar cells in PARP-$1^{-/-}$ mice.

The results obtained in our experiments highlight the importance of OGG1 which may be a promising therapeutic target for the treatment of acute pancreatitis. However, before TH5487 could be therapeutically used, further experiments are needed to elucidate the long-term mutagenic effects of OGG1 inhibition. Studies discussing the role of PARP-1 in acute pancreatitis have drawn attention to the potential therapeutic use of PARP inhibitors. PARP inhibitors are already used in human therapy to treat *BRCA* mutant ovarian and breast cancers, but concerns related to compromised DNA repair and increased mutagenesis so far prevented the use of PARP inhibitors in non-oncological diseases.

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Registry number: DEENK/12/2023.PL
Subject: PhD Publication List

Candidate: Zoltán Hajnády
Doctoral School: Doctoral School of Molecular Medicine

List of publications related to the dissertation

1. **Hajnády, Z.**, Nagy-Pénzes, M., Demény, M. Á., Kovács, K., El-Hamoly, T., Maléth, J., Hegyi, P. J., Polgár, Z., Hegedűs, C., Virág, L.: OGG1 Inhibition Reduces Acinar Cell Injury in a Mouse Model of Acute Pancreatitis.
   Biomedicines. 10 (10), 1-17, 2022.
   DOI: http://dx.doi.org/10.3390/biomedicines10102543
   IF: 4.757 (2021)

2. El-Hamoly, T.*, **Hajnády, Z.***, Nagy-Pénzes, M., Bakondi, E., Regdon, Z., Demény, M. Á., Kovács, K., Hegedűs, C., Abd El-Rahman, S. S., Szabó, É., Maléth, J., Hegyi, P. J., Virág, L.: Poly(ADP-Ribose) Polymerase 1 Promotes Inflammation and Fibrosis in a Mouse Model of Chronic Pancreatitis.
   Int. J. Mol. Sci. 22 (7), 1-15, 2021.
   DOI: http://dx.doi.org/10.3390/ijms22073593
   * These authors contributed equally this work.
   IF: 6.208

List of other publications

3. Nagy-Pénzes, M., **Hajnády, Z.**, Regdon, Z., Demény, M. Á., Kovács, K., El-Hamoly, T., Maléth, J., Hegyi, P., Hegedűs, C., Virág, L.: Tricetin Reduces Inflammation and Acinar Cell Injury in Cerulein-Induced Acute Pancreatitis: the Role of Oxidative Stress-Induced DNA Damage Signaling.
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   IF: 4.757 (2021)

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DOI: http://dx.doi.org/10.1038/s41467-017-02651-5
IF: 11.878

Total IF of journals (all publications): 41,629
Total IF of journals (publications related to the dissertation): 10,965

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

16 January, 2023

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