Journal of Pathology
J Pathol 2020; **251:** 1–3
Published online 25 February 2020 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/path.5391

INVITED COMMENTARY

A critical role for Akt1 signaling in acute pancreatitis progression†

Rim SJ Sarker and Katja Steiger*

Comparative Experimental Pathology, Institute of Pathology, School of Medicine, Technical University of Munich, Munich, Germany

**Correspondence to: K Steiger, Comparative Experimental Pathology, Institute of Pathology, School of Medicine, Technical University of Munich, Trogerstr. 18, 81675 Munich, Germany. E-mail: katja.steiger@tum.de*

†Invited commentary for Chen, Malagola *et al*. Akt1 signalling supports acinar proliferation and limits acinar-to-ductal metaplasia formation upon induction of acute pancreatitis. *J Pathol* 2020; **250:** 42–54.

Abstract

Acute pancreatitis (AP) is an inflammatory disease of the pancreas that causes significant morbidity and mortality worldwide. Unfortunately, there is no specific treatment available to date. Several studies have previously shown that inhibitors of the PI3K/Akt axis downregulate the degree of inflammation in animal models of AP. However, studies on *in vivo* side-effects of such inhibitors are still lacking. In a recent issue of *The Journal of Pathology*, Chen, Malagola *et al* investigated if inhibition of Akt signaling plays a negative role in the regenerative phase of AP. They showed that treating AP mice with an Akt inhibitor (MK2206) impaired acinar regeneration and increased the development of acinar-to-ductal metaplasia. This is the first study to highlight the negative impact of an Akt inhibitor on cellular regeneration while simultaneously inhibiting inflammation in AP. The authors also suggested combining Akt activators to recover pancreatic regeneration.

Keywords: acute pancreatitis; pancreatic acini; acinar-to-ductal metaplasia; PI3K–Akt1 axis; disease model; targeted therapy

Received 21 November 2019; Revised 24 January 2020; Accepted 29 January 2020

No conflicts of interest were declared.

In the January 2020 issue of *The Journal of Pathology*, the study by Chen, Malagola *et al* [1] eloquently describes a potential mechanism of a therapeutic strategy to treat acute pancreatitis (AP) using a caerulein-induced injury model. Their critical findings provide new insights into damage-associated inflammation, cellular reprogramming called acinar-to-ductal metaplasia (ADM) and organ regeneration (Figure 1). Their data reveal the potential risk of using small molecular inhibitors of the PI3K–Akt axis to treat AP. On the one hand, Akt inhibitors effectively suppress acute inflammation; on the other hand, they impede pancreatic regeneration. Future studies should consider the side-effects while designing and testing new therapies.

The incidence of AP is increasing and generates an increasing share of health costs worldwide. AP is one of the most frequent gastroenterological reasons for emergency admissions to hospital [2]. In critical cases, the mortality rate can range from 5 to 10%, up to even 30%, depending on the degree of disease severity [3]. Briefly, AP arises when the pancreas encounters a sudden and severe form of inflammation, which injures the organ. This condition leads to an inappropriate activation of digestive enzymes derived from pancreatic acinar cells. The auto-digestion triggers a domino effect that further damages the acinar and organ architecture.

Animal models of AP

In human patients, gallstones/biliary sludge and alcohol consumption are the most frequent causes of AP, whereas in animal (mostly rodent) models, AP is induced by various chemical or surgical strategies [4]. The most widely used mechanism is secretagogue hyper-stimulation induced by intraperitoneal injection of caerulein, as used in the study by Chen, Malagola *et al* [1]. This model does not require surgery or sophisticated manipulations, making it highly suitable for the investigation of intracellular signaling pathways. Other possible rodent models of AP use duct obstruction and bile acid infusion to mimic gallstone etiology (often lacking disease severity), application of L-arginine (difficult to standardize in mice), special diet (choline-deficient ethionine-supplemented) or injection of specific cytokines or infectious pancreatitis induction (reviewed in [4]).

Regulatory role of the PI3K–Akt axis in AP

Although there is currently no definitive cure for AP, there are increasing reports in animal models that genetic ablation or pharmacological intervention of the PI3K–Akt

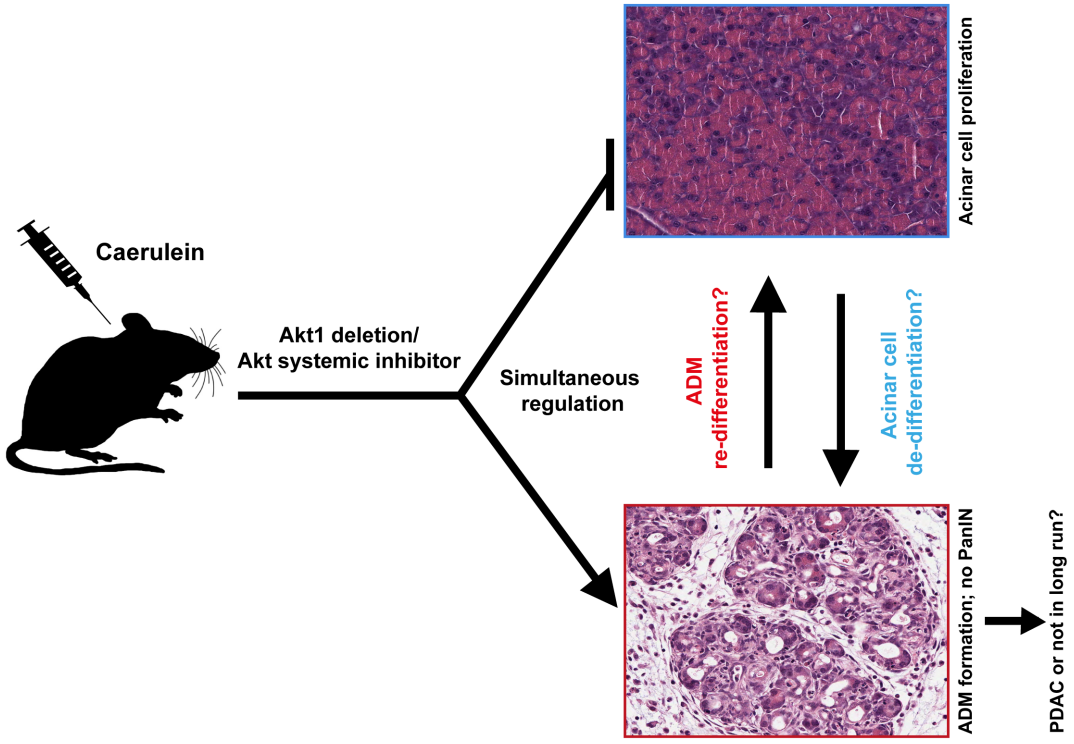

Figure 1. Overview of cellular reprogramming upon blocking Akt1 signaling in a caerulein-induced mouse model.

axis might protect against inflammatory tissue damage. Mechanistically, this is due to the PI3K-dependent activation of trypsinogen modulating the severity of AP [5] as the triggering point in the early course of disease progression in experimental models. Thus, pharmacological reduction of the preliminary pancreatic enzyme activation via inhibiting the PI3K–Akt signaling axis might diminish or interrupt the severe and self-sustaining tissue damage.

The extent of the systemic inflammatory response (which can also lead to multiorgan failure, including acute lung injury) to AP depends on mediators produced by the damaged acinar cells. This systemic reaction is linked to activation of the transcription factor NF-κB, occurring early in the course of experimental pancreatitis. The canonical NF-κB signaling pathway regulates cytokine production by acinar cells and thus triggers inflammatory cell recruitment [6]. Treatment with a PI3K inhibitor decreases the nuclear translocation of NF-κB in thyroid tissue associated with severe AP [7]. The inhibition also reduces the activation of trypsinogen and cathepsin B in rodent models of pancreatitis (reviewed in [7]). However, it does not block NF-κB activation in acinar cells directly, but prevents neutrophil infiltration in the pancreas, leading to the speculation that PI3K inhibitors selectively block inflammatory cell function in AP [5]. In line with these findings, novel treatment strategies aim at PI3K inactivation to ameliorate the outcome of AP [7].

Akt inhibitor: a double-edged sword?

The study presented by Chen, Malagola *et al* [1] points to the other side of this treatment coin. Akt promotes G1-S phase cell cycle progression by stabilizing cyclin D1, a downstream canonical effector of the Akt pathway. The authors therefore hypothesize that inactivation of either PI3K or Akt signaling could impair acinar cell proliferation and thus limit pancreatic regeneration. This particular outcome would be a significant negative side-effect of PI3K–Akt inhibitor-mediated therapy in AP.

Morphologically, the time course of AP consists of three phases: acute inflammation, regeneration and refinement [8]. Once the causative factors have been treated or reduced, the exocrine pancreas often fully recovers its structure and function. Proliferation of the different cellular compartments is crucial for the complete regeneration of the pancreas. The effect of a Pan-Akt inhibitor, MK2206, and of induced *Akt1* genetic ablation shown by Chen, Malagola *et al* [1] indicates a reduction in the Ki67-positive acinar cell population, leading to a delayed pancreatic regeneration and prolonged de-differentiation after AP.

Additionally, major events of AP are ADM characterized by the formation of tubular complexes and de-differentiation of acinar cells together with recruitment of inflammatory cells. Moreover, Chen, Malagola *et al* [1] successfully show that Akt1, being abundantly expressed in acinar cells and significantly increased in pancreatitis mice, is probably the major isoform responsible for the impaired acinar cell proliferation and associated ADM formation. On the other hand, interstitial cell number remains unaffected following AP, indicating a partial redundancy of Akt isoforms.

The finding of prolonged ADM formation and de-differentiation might also be relevant to the results reported by Kong *et al* [8], that pancreas regeneration

requires a coordinated proliferation transition between mesenchymal, progenitor-like and acinar cells. Prior to a 'proliferative transition', acinar cells are able to form pancreatic intraepithelial neoplasia (PanIN) - like lesions. However, once the cells undergo a 'proliferative transition', they become highly refractory to the PanIN formation. In this context, a study has shown that in response to an oncogenic signal, PanIN-like lesions occurring in areas of ADM (so-called 'mucinous tubular complexes') can act as a significant precursor of pancreatic ductal adenocarcinoma (PDAC) [9].

In contrast, apart from observing significant ADM lesions, Chen, Malagola *et al* [1] did not detect any PanIN or extensive mucinous tubular complex transformation upon MK2206 treatment in caerulein-induced mice pancreata. This further underscores the mandatory requirement of an oncogenic event to induce PanIN or persistent mucinous tubular complex formation in mouse models [10]. Without an oncogenic mutation, pancreatitis-induced ADM is a reversible process (metaplasia) and can differentiate back into acinar cells once inflammation is resolved. The absence of PanIN or PanIN-like lesions weakens the claim by Chen, Malagola *et al* [1] that therapy with an Akt inhibitor represents a risk for the development of PDAC. Perhaps, a time point later than hours might also help to answer the question if PDAC precursor lesions could form at all. A follow-up study would be required to answer this open question.

Blocking Akt signaling usually gives rise to a prominent inflammatory influx supporting ADM formation. However, the genetic and drug-mediated models Chen, Malagola *et al* [1] used did not trigger any significant additional inflammation, except for a trend in macrophage infiltration. Nevertheless, they observed exacerbated ADM formation. This adds a new finding that ADM formation might not be dependent solely on the degree of inflammatory cell influx, but that there are additional factors contributing to the metaplastic reaction.

Open questions

The study by Chen, Malagola *et al* [1] leaves some questions unanswered. First, it would be interesting to know the effect of Akt inhibition on acinar cell death pathways (apoptosis/necrosis/necroptosis) in AP. Second, in addition to cyclin D, other downstream targets of NF-κB need further investigation to elucidate how Akt fine-tunes NF-κB signaling during acinar cell proliferation and its reprogramming toward ADM. In addition to the initial concern by Chen, Malagola *et al* [1] that using Akt inhibitors to downregulate the acute inflammatory phase of AP might also suppress the acinar cell proliferation, the effect of Akt blockade on remote organs also needs to be investigated. For example, one third of patients with a severe course of AP experience an acute lung injury [11]. Therefore, it creates an open question whether Akt inhibitor therapy can also decrease the proliferation of type II pneumocytes, which are indispensable for lung function and regeneration in the course of an AP-induced acute lung injury. Last but not least, the authors highlighted the plausible risks associated with PI3K–Akt pathway inhibitors. In future, therapeutic drugs for AP should be developed that only reduce inflammation but do not suppress acinar cell proliferation. This might be achieved by combining an Akt1 activator after the inflammatory phase to promote pancreatic regeneration. The findings of Chen, Malagola *et al* [1] consequently underscore a potential new and fine-tuned therapeutic strategy for AP.

Author contributions statement

RSJS and KS equally contributed in writing the commentary. Both authors approved the final version of the manuscript.

References

1. Chen R, Malagola E, Dietrich M, *et al*. Akt1 signalling supports acinar proliferation and limits acinar-to-ductal metaplasia formation upon induction of acute pancreatitis. *J Pathol* 2020; **250**: 42–54.
2. Roberts SE, Morrison-Rees S, John A, *et al*. The incidence and aetiology of acute pancreatitis across Europe. *Pancreatology* 2017; **17**: 155–165.
3. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology* 2013; **13**: e1–e15.
4. Lerch MM, Gorelick FS. Models of acute and chronic pancreatitis. *Gastroenterology* 2013; **144**: 1180–1193.
5. Singh VP, Saluja AK, Bhagat L, *et al*. Phosphatidylinositol 3-kinase-dependent activation of trypsinogen modulates the severity of acute pancreatitis. *J Clin Invest* 2001; **108**: 1387–1395.
6. Steinle AU, Weidenbach H, Wagner M, *et al*. NF-kappaB/Rel activation in cerulein pancreatitis. *Gastroenterology* 1999; **116**: 420–430.
7. Abliz A, Deng W, Sun R, *et al*. Wortmannin, PI3K/Akt signaling pathway inhibitor, attenuates thyroid injury associated with severe acute pancreatitis in rats. *Int J Clin Exp Pathol* 2015; **8**: 13821–13833.
8. Kong B, Bruns P, Behler NA, *et al*. Dynamic landscape of pancreatic carcinogenesis reveals early molecular networks of malignancy. *Gut* 2018; **67**: 146–156.
9. Aichler M, Seiler C, Tost M, *et al*. Origin of pancreatic ductal adenocarcinoma from atypical flat lesions: a comparative study in transgenic mice and human tissues. *J Pathol* 2012; **226**: 723–734.
10. Morris JP, Cano DA, Selkine S, *et al*. β-catenin blocks Kras-dependent reprogramming of acini into pancreatic cancer precursor lesions in mice. *J Clin Invest* 2010; **120**: 508–520.
11. Manohar M, Verma AK, Venkateshaiah SU, *et al*. Chronic pancreatitis associated acute respiratory failure. *MOJ Immunol* 2017; **5**: 00149.