Pancreatitis

Stopped clock promotes fibrosis in chronic pancreatitis

Dysfunction of the pancreatic clock contributes to fibrosis in chronic pancreatitis, according to new work. The findings suggest that targeting of circadian function has potential as a therapeutic strategy.

The pancreas is one of multiple peripheral organs with an internal circadian clock that influences physiology to synchronize function with external factors and other organ systems. The effects of the pancreatic clock on endocrine function have been well studied. However, little is known about the effects of the pancreatic clock in exocrine function or its influence on disease.

In their new study, Weiliang Jiang and colleagues focused on the role of the pancreatic clock in the pathophysiology of chronic pancreatitis. They first demonstrated that altered expression of pancreatic clock components was associated with fibrosis in human tissue, leading them to investigate the molecular mechanisms of this association in mouse models.

The researchers used two models of chronic pancreatitis in combination with mutations of the circadian clock genes *Bmal1* and *Clock*. Knockout of *Bmal1*, which is an essential component of the circadian clock, exacerbated features of chronic pancreatitis, whereas *Clock* mutation did not induce such profound changes. Similarly, disturbing the pancreatic clock with a restricted feeding paradigm increased pancreatic fibrosis in models of chronic pancreatitis.

"Our findings established a protective role for an intact pancreatic clock in chronic pancreatitis, while either genetic or environmental circadian disruption exacerbated pancreatic fibrogenesis and exocrine insufficiency," explains Jiang.

Examination of gene expression in fibrotic tissue revealed dysregulation of a circadian stabilizing loop that involves the *Bmal1* protein product BMAL1 and the nuclear receptors NR1D1 and RORα. This dysregulation led to a deficiency in BMAL1 and, consequently, activation of pancreatic stellate cells, which increased their expression of fibrosis-related genes.

The therapeutic relevance of these findings was demonstrated by use of the RORα agonist SR1078 in combination with melatonin to restore the circadian stabilization loop. This treatment attenuated fibrosis in the mouse models of chronic pancreatitis.

> "treatment attenuated fibrosis in the mouse models of chronic pancreatitis"

"Our study showed that reinvigorating the pancreatic circadian clock largely attenuated experimental chronic pancreatitis," says Jiang. "We hope our findings give new insights into the management and treatment of chronic pancreatitis."

Ian Fyfe

Original article: Jiang, W. et al. The pancreatic clock is a key determinant of pancreatic fibrosis progression and exocrine function. *Sci. Transl Med.* https://doi.org/10.1126/scitranslmed.abn3586 (2022)

In brief

IBD

Integrated systems approach to identify environmental factors in intestinal inflammation

Environmental factors have an effect on the onset and progression of inflammatory bowel disease (IBD). A new study published in *Nature* combines an integrated systems approach, consisting of zebrafish, mouse models and chemical databases, with machine learning to investigate the effect of environmental factors on intestinal inflammation. The approach found that propyzamide, a common herbicide, targets a T cell and dendritic cell signalling pathway (AHR–NF-κB–C/EBPβ) that regulates intestinal inflammation.

Original article: Sanmarco, L. M. et al. Identification of environmental factors that promote intestinal inflammation. *Nature* https://doi.org/10.1038/s41586-022-05308-6 (2022)

Colorectal cancer

Colonoscopy screening and risk of CRC

In a trial to assess the effects of population-based colonoscopy screening on risks of colorectal cancer (CRC), participants aged 55–64 years were randomly assigned (1:2) either to be invited to undergo a screening colonoscopy or to receive no screening. 10-year follow-up data for participants in Poland, Norway and Sweden — 28,220 were invited, of whom 42% underwent screening, and 56,365 were not invited — showed that in intention-to-screen analysis, the risk of CRC at 10 years was lower in the invited group (0.98%) than in the group assigned to no screening (1.20%). The risk reduction was 18% (risk ratio 0.82; 95% CI 0.70–0.93). The risk of death from CRC was 0.28% in the invited group and 0.31% in the group assigned to no screening (risk ratio 0.90; 95% CI 0.64–1.16). The researchers plan to release updated analysis at 15 years.

Original article: Bretthauer, M. et al. Effect of colonoscopy screening on risks of colorectal cancer and related death. *N. Engl. J. Med.* **387**, 1547–1556 (2022)

Gut microbiota

Follow-up of SER-109 for recurrent *C. difficile*

Earlier in 2022, a phase III trial showed that oral administration of the investigational microbiome therapeutic SER-109 was superior to placebo in reducing the risk of recurrent *Clostridioides difficile* infection (rCDI) by week 8 in patients with rCDI who had symptom resolution after antibiotic treatment. Now, 24-week follow-up (n=182 patients were randomized) has demonstrated durable reductions in rates of rCDI: 21.3% of the SER-109 group and 47.3% of the placebo group had rCDI after 24 weeks. SER-109 was well tolerated through 24 weeks.

Original article: Cohen, S. H. et al. Extended follow-up of microbiome therapeutic SER-109 through 24 weeks for recurrent *Clostridioides difficile* infection in a randomized clinical trial. *JAMA* https://doi.org/10.1001/jama.2022.16476 (2022)

COVID-19

Investigating two versus three doses of mRNA vaccine in patients with cirrhosis

Cirrhosis has been associated with decreased responsiveness to several vaccines. In a retrospective study of 26,082 patients with cirrhosis, participants who received three doses of a coronavirus disease 2019 (COVID-19) mRNA vaccine when Delta and Omicron were the predominant variants had an 80.7% reduction in COVID-19 incidence (95% CI 39.2–89.1, P<0.001) compared with matched controls who only received two doses.

Original article: John, B. V. et al. Third dose of COVID-19 mRNA vaccine appears to overcome vaccine hyporesponsiveness in patients with cirrhosis. *J. Hepatol.* https://doi.org/10.1016/j.jhep.2022.07.036 (2022)