Paris, January 22, 2018

Press information

Could the Biological Clock Be a Key Ally in the Fight Against Inflammatory Disease?

What if the symptoms and seriousness of certain inflammatory diseases were linked to time of day? Researchers from Inserm, Institut Pasteur de Lille and Université de Lille[1] have been working on this hypothesis, after noting that the seriousness and mortality associated with fulminant hepatitis were dependent on the time at which the disease was induced. Their study, conducted on human cells and mice, shows that the anti-inflammatory action of a biological clock protein could prevent the onset of fulminant hepatitis, by alleviating symptoms and increasing survival rates.

This research has been published in *Gastroenterology*.

Fulminant hepatitis is a serious disease which leads to rapid deterioration of tissue and liver function in the patient, associated with blood coagulation disorders and irreparable brain damage. Although fulminant hepatitis can be caused by different factors, overdose with medications containing acetaminophen continues to be the main cause of the disease. Accumulation of acetaminophen in the body can cause cellular stress, which gives rise to an abnormal immune system response. This is expressed by excessive inflammation, which destroys hepatocytes and the liver. Until now, no specific treatment for fulminant hepatitis has been identified, and the only solution is liver transplant within 24 hours following onset of symptoms. Researchers from Inserm, Institut Pasteur de Lille and Université de Lille are focusing on the mechanisms underlying inflammation specifically in fulminant hepatitis, with a view to identifying potential avenues of treatment.

Starting from the observation that immune functions vary during the day, the researchers examined a biological clock protein called Rev-erbα and its potential role in regulating inflammation in fulminant hepatitis. This protein notably targets adipose tissue, together with liver, skeletal muscle and brain cells. It plays a major role in developing and regulating their circadian rhythm, i.e. the repetition of their biological cycle every 24 hours.

This new research, conducted on human immune system cells and on mice, showed that the inflammation also follows a circadian rhythm. The researchers also observed that injecting a molecule potentiating the action of Rev-erbα reduced the inflammatory response which causes hepatocyte death in fulminant hepatitis. Mice having received the Rev-erbα-activating treatment demonstrated less severe forms of the disease, together with a higher survival rate. As the same results were observed *in vitro* on human cells, these data indicate new avenues to be explored with a view to potentially developing a treatment for acute fulminant hepatitis or able to slow the progression of symptoms in patients awaiting transplantation.

[1] Joint Research Unit 1011 nuclear receptors, cardiovascular diseases and diabetes (Inserm, Institut Pasteur de Lille, Université de Lille)

Fulminant hepatitis is not the only disease involving the circadian molecular mechanism inhibited by Rev-erbα. Other diseases such as peritonitis, diabetes or even atherosclerosis display a similar imbalance in the inflammatory response due to the abnormal accumulation of toxins in the body. Inserm researcher Hélène Duez affirms that: "the results of this study could open up new prospects in preventing these diseases. They also offer new avenues for researchers, notably in terms of potential improvements in quality of life and longevity among patients suffering from chronic inflammatory disease."

Sources

Nuclear Receptor Subfamily 1 Group D member 1 Regulates Circadian Activity Of NLRP3 Inflammasome to Reduce the Severity of Fulminant Hepatitis in Mice

Pourcet B1,3, Zecchin M1,3, Ferri L1, Beauchamp J1, Sitaula S2, Billon C2, Delhaye S1, Vanhoutte J1, Mayeuf-Louchart A1, Thorel Q1, Haas J1, Eeckhoute J1, Dombrowicz D1, Duhem C1, Boulinguiez A1, Lancel S1, Sebti Y1, Burris T2, Staels B1 & Duez H1*.

1European Genomic Institute for Diabetes (EGID), FR 3508, F-59000 Lille, France; Univ. Lille, F-59000 Lille, France; INSERM UMR 1011, F-59000 Lille, France; Institut Pasteur de Lille, F-59000 Lille, France.
2Department of Pharmacology and Physiology, Saint Louis University School of Medicine, St. Louis, MO, USA. The Scripps Research Institute, Jupiter, FL, USA.
3These authors contributed equally to this work

Gastroenterology: https://doi.org/10.1053/j.gastro.2017.12.019

Researcher contacts

Hélène Duez
Inserm Unit 1011 "Nuclear receptors, cardiovascular diseases and diabetes"
Team "Nuclear receptors in metabolic syndrome"
Email: helene.duez@pasteur-lille.fr
Tel.: +33 (0)3 20 87 77 93

Benoit Pourcet
Inserm Unit 1011 "Nuclear receptors, cardiovascular diseases and diabetes"
Team "Nuclear receptors in metabolic syndrome"
Email: benoit.pourcet@pasteur-lille.fr
Tel.: +33 (0)3 20 87 71 25

Press contact

presse@inserm.fr

Access the Inserm press room