New research links body clocks to chronic lung diseases

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(Medical Xpress)—The body clock's natural rhythm could be utilized to improve current therapies to delay the onset of chronic lung diseases.

Scientists at The University of Manchester have discovered a rhythmic defence pathway in the lung controlled by our body clocks, which is essential to combat daily exposure to toxins and pollutants.

Internal biological timers (circadian clocks) are found in almost all living things driving diverse processes such as sleep/wake cycles in humans to leaf movement in plants. In mammals including humans, circadian clocks are found in most cells and tissues of the body, and orchestrate daily rhythms in our physiology.

The research team's ground breaking findings, which are being published in *Genes & Development*, have for the first time found that the circadian clock in the mouse lung rhythmically switches on and off genes controlling the antioxidant defense pathway. This 24 hourly rhythm enables the lungs to anticipate and withstand daily exposure to pollutants.

The research was led by Dr Qing-Jun Meng from The University of Manchester who is also a Medical Research Council (MRC) Research Fellow. He has been studying body clocks for a number of years and has been awarded an MRC Career Development Award to establish the relationship between the disruption of circadian rhythms and the susceptibility to human diseases, especially those associated with old age.

Dr Meng said: "We used a mouse model that mimics human pulmonary fibrosis, and found that an oxidative and fibrotic challenge delivered to the lungs during the night phase (when mice are active) causes more severe lung damages than the same challenge administered during the day which is a mouse's resting phase."

This means that the rhythm of this lung clock gives an indication of more suitable times of the day for drugs to be administered to patients suffering from oxidative/fibrotic diseases such as pulmonary fibrosis, asthma, chronic obstructive pulmonary disease.

Dr Meng continued: "Our findings show that timed administration of the antioxidant compound sulforaphane, effectively attenuates the severity of the lung fibrosis in this mouse model."

In other words the research suggests that taking drug treatments for oxidative and fibrotic diseases according to the lung clock time could increase their effectiveness, which would allow a lower dosage and consequently reduce side effects.

Dr Vanja Pekovic-Vaughan, who was part of the University's research team, said: "This research is the first to show that a functioning clock in the lung is essential to maintain the protective tissue function against oxidative stress and fibrotic challenges. We envisage a scenario whereby chronic rhythm disruption (e.g., during ageing or shift work) may compromise the temporal coordination of the antioxidant pathway, contributing to human disease."

This latest study is part of on-going research that is exploring how chronic disruption to body clocks by changes like ageing or shift work contribute to a number of conditions such as osteoarthritis, cardiovascular disease, breast cancer, and mood disorder.

Dr Meng said: "Our next step is to test our theory that similar rhythmic activity of the antioxidant defence pathway also operates in human lungs. This will enable us to translate our findings and identify the proper clock time to treat chronic lung diseases that are known to involve oxidative stress.

"Funded by an MRC Fellowship Partnership Award, we have teamed up with GlaxoSmithKline to explore the potential of utilizing the body clock mechanisms to improve the efficiency of the current antioxidant compounds for diseases. Timing the delivery of drugs - so-called 'chrono-therapy' or 'chrono-pharmacology' - has already demonstrated clinical benefits in treatment of cancer and arthritis," he said.

Professor Stuart Farrow, a Director in the Respiratory therapy area at GSK (who is also the industrial partner for Dr Meng on the MRC Fellowship Partnership Award), commented: "Chronic lung diseases are prevalent and debilitating, and continue to be an important area of unmet medical need. This exciting new research reveals an opportunity to harness the body clock to provide valuable benefit to patients."

More information: Gossan, Nicole; Zhang, Feng; Guo, Baoqiang; Jin, Ding; Yoshitane, Hikari; Yao, Aiyu; Glossop, Nick; Zhang, Yong Q; Fukada, Yoshitaka; Meng, Qing-Jun. "The E3 ubiquitin ligase UBE3A is an integral component of the molecular circadian clock through regulating the BMAL1 transcription factor." N A R, eScholarID:220750

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