

Controlling the peripheral clock might be a new treatment strategy in allergy and immunology

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Virtually all organisms on Earth maintain an internal rhythm that oscillates approximately 24 hours per cycle.¹ This is known as the endogenous circadian system.² The master clock of the circadian rhythm is located in the suprachiasmatic nuclei in the anterior hypothalamus,³ and it is oriented to the external environment through the retinohypothalamic tract, receiving light information from the eye.⁴ Importantly, the circadian clock system influences most peripheral tissues, including immune and structural cells.³ For example, in human blood numbers of naive, central memory, and effector memory T cells increase at night.³ It is well known that allergic symptoms can worsen at nighttime, particularly in the still-dark hours of early morning,³ and mouse models have demonstrated circadian rhythm in allergic responses.⁵ Nocturnal peaks of signals, such as cortisol and histamine levels in blood, were implicated in those circadian variations of allergic responses⁶; however, the precise mechanisms have remained unclear.

The circadian clock is guided by an interaction of genes that results in a 24-hour autoregulatory feedback loop.⁷ There are 2 interlocking phases of this transcriptional-translational feedback loop, which contains *BMAL1*, *CLOCK*, E-box promoter elements, Period (*PER1-3*), cryptochrome (*CRY1/2*), *NR1D1* (Rev-erb α), and retinoic acid–related orphan receptor A (*RORA*).² Gradually, PER and cryptochrome proteins start to degrade, after which suppression on BMAL1 and CLOCK is relieved. The timing regulation produced by the system synchronizes peripheral clocks,¹ inducing rhythmic expression of approximately 10% of all genes in each peripheral cell.²

Murine bone marrow–derived mast cells (BMMCs) assessed after cell activation have shown circadian variations in the

expression of cytokine mRNA and Fc ϵ RI α .³ Prostaglandin E₂³ and monocyte chemoattractant protein 1 (CCL2)⁴ have been reported to be involved in circadian responses in the immune system as well. These results suggest circadian clock genes might be involved in IgE-mediated allergic reactions. Nakao et al⁸ report on molecular mechanisms of the circadian clock in BMMCs in association with nocturnal IgE-mediated allergic reactions. In particular, they demonstrate that reduction of Fc ϵ RI signaling occurs when PER2 expression is increased in active-phase mice. They speculate that because PER2 inhibits CLOCK/BMAL1 activity, which regulates Fc ϵ RI β expression levels by binding to the E-box sequence in the promoter, upregulation of PER2 results in reduction of Fc ϵ RI signaling.

In the current issue of the *Journal*, Nakamura et al⁹ find pharmacologic increases of PER2 in mast cells and basophils, which imply shifting the molecular clock to times when Fc ϵ RI signaling was reduced in those cells downregulated IgE-mediated allergic reactions. The authors used PF670462, corticosterone, and aminophylline to upregulate PER2, which suppressed Fc ϵ RI signaling. Through bioluminescent emission of PER2^{LUC} BMMCs, they show circadian clock rhythms in these cells were not influenced by IgE sensitization. This suggests that the phenomenon underlying suppression of IgE-mediated reactions might relate to downregulation of Fc ϵ RI expression levels on the cell surface; in fact, the authors found an overexpression of PER2 in BMMCs suppressed Fc ϵ RI α expression, as well as IgE-mediated degranulation. Like glucocorticoids, cyclic AMP (cAMP) is associated with allergic reactions and affects circadian rhythm. On cAMP stimulation, cAMP-response element–binding proteins have been found to increase *PER2* gene transcription, thus maintaining circadian oscillation.¹⁰ In the present study the authors find that aminophylline increased PER2 levels, which led to reductions of Fc ϵ RI α expression and IgE-mediated degranulation in BMMCs. Collectively, PER2 in immune cells appears to have an antiallergic function that provides a novel view of the pharmacologic molecular mechanism of glucocorticoids or cAMP (aminophylline) in allergic reactions.

Although we know immune cells and tissues from mice possess local circadian clocks that operate autonomously, even in the absence of endocrine regulations,⁴ the effect of glucocorticoids and cAMP on the immune system is substantial. Thus precise analysis to investigate the regulation mechanism of these “clock modifiers,” or pharmacologic treatments that affect circadian rhythm, will be required in the near future. For example, how do glucocorticoids, which are often prescribed as a treatment option in allergic patients, affect levels of nuclear factor κ B, which was used in this study to reset the circadian clock? Reports of non-IgE-mediated allergies are on the increase.¹¹ Assessing the association between circadian oscillation and these diseases might further our understanding of their pathophysiology.

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The circadian system provides a unique vantage from which to study the immune system. However, our challenge has just begun, and there are many pieces we need to gather to continue this investigation. In particular, clarifying the roles and synchronicity of local circadian clocks among both immune and structural cells is important. A better understanding of the circadian system might influence the time of day in which we draw blood or pursue medical tests. It might provide a rationale for chronotherapy, or a circadian-influenced treatment schedule of medications or immunotherapy, and chrononutrition, which takes into account the relationship between food and the circadian clock system.² Harmonizing advanced study in allergy and immunology with chronobiology can positively affect our future diagnoses, therapeutic measures, and means of disease prevention.

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