Clockwork allergy: How the circadian clock underpins allergic reactions

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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Activity Objectives:

1. To explain how the circadian clock is regulated.
2. To identify allergic processes that vary according to circadian rhythms.
3. To explain the mechanisms that regulate circadian rhythms in allergic cells.

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Allergic disease is characterized by marked day-night changes in the clinical symptoms and laboratory parameters of allergy. Recent reports suggest that the circadian clock, which drives a biological rhythm with a periodicity of approximately 24 hours in behavior and physiology, underpins a time of day–dependent variation in allergic reactions. New studies also suggest that disruption of clock activity not only influences temporal variation but can also enhance the severity of allergic reactions and even increase susceptibility to allergic disease. These findings suggest that the circadian clock is a potent regulator of allergic reactions that plays more than a simple circadian timekeeping role in allergy. A better understanding of these processes will provide new insight into previously unknown aspects of the biology of allergies and can lead to the application of clock modifiers to treat allergic disease. Finally, this area of research provides a novel opportunity to consider how modern lifestyles in the developed world are changing the clinical manifestations of allergy as our society quickly transforms into a circadian rhythm–disrupted society in which sleeping, working, and eating habits are out of sync with endogenous circadian rhythmicity. Such findings might reveal lifestyle interventions that enable us to better control allergic disease. (J Allergy Clin Immunol 2018;142:1021-31.)

Key words: *Circadian clock, period2, allergy, mast cell, chronotherapy*

The circadian rhythm is a biological rhythm with a periodicity of approximately 24 hours and is observed in the behavior and physiology of virtually all living organisms. The word *circadian* is derived from the Latin *circā* ("about") and *diēs* ("a day"), meaning about a day. Circadian clocks are the endogenous time-keeping mechanisms that drive circadian rhythms.[1-3] Circadian clocks generate robust approximately 24-hour rhythms, even in the absence of external inputs, but can adjust their timing in response to environmental cues, such as light, meal timing, exercise, and strong social interactions.

It is well documented that allergic diseases exhibit a circadian oscillation. Many symptoms and laboratory parameters in

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Abbreviations used
AD: Atopic dermatitis
AQP3: Aquaporin 3
BMAL1: Brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1
CCG: Clock-controlled gene
CK: Casein kinase
CLOCK: Circadian locomoter output cycles kaput
Cry: Cryptochrome
PCA: Passive cutaneous anaphylaxis
Per: Period
SCN: Suprachiasmatic nucleus
TEWL: Transepidermal water loss

patients with allergic diseases show marked day-night changes.[4,5] For instance, in most patients with allergic rhinitis, symptoms worsen overnight or early in the morning ("morning attack"), thereby compromising nighttime sleep and resulting in poor daytime quality of life.[4] However, until recently, the precise mechanisms underlying these observations have remained enigmatic.

New studies reveal that the immune system is fundamentally connected to the circadian clock system.[6-10] As a type of immune response, an allergic reaction is also intrinsically under the control of the circadian clock.[11-13] This review summarizes recent advances in our understanding of clock-controlled allergic reactions, the effect of circadian disruption on allergy, and the potential application of clock modifiers to control allergic disease.

MOLECULAR CLOCKS TICK-TOCK INSIDE OF MAMMALIAN CELLS

Virtually all living organisms are subjected to 24-hour periodic changes in their external environment driven by the rotation of the earth. These environmental changes include a light/dark cycle, changes in temperature and food availability, and risk of predator attack. Consequently, organisms have evolved internal timers referred to as circadian clocks that drive daily rhythms in behavior and physiology, enabling them to anticipate and adapt to daily alterations in the environment.[1-3]

In mammals circadian rhythms are generated from cyclic gene expression controlled by cell-autonomous and self-sustained molecular clocks within each cell.[2,3] These molecular clocks consist of interlocked transcriptional-translational feedback loops centered on the transcription factors brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1 (BMAL1) and circadian locomoter output cycles kaput (CLOCK) (Fig 1). BMAL1, which heterodimerizes with CLOCK, binds to E-box motifs throughout the genome and drives transcription of target genes, including their own repressors period 1 *(Per1)*, *Per2*, and *Per3* and cryptochrome 1 *(Cry1)* and *Cry2*. PER and CRY proteins form oligomers and enter the nucleus, where they inhibit BMAL1/CLOCK activity. This negative-feedback loop, in conjunction with multiple layers of posttranscriptional regulation, takes approximately 24 hours to be completed, which acts as a molecular oscillator controlling periodic expression of thousands of clock-controlled genes (CCGs) with E-box motifs in the promoter/enhancer regions. Most of the CCGs encode key regulators of various cellular pathways in metabolism and hormonal, neural, and immune functions. Indeed, Bmal1-deficient mice lack a functional molecular clock, leading to a loss of CCGs oscillation in most tissues and resulting in behavioral and physiologic arrhythmicity.[14]

In addition to this core loop, there is a stabilizing loop that regulates the timing and amplitude of Bmal1. This stabilizing loop is provided by the nuclear receptors retinoic acid–related orphan receptor (ROR) α and REV-ERBα *(Nr1d1)*. The BMAL1/CLOCK heterodimer activates transcription of RORα and REV-ERBα, which activates or represses BMAL1 transcription, respectively. Details of transcriptional regulation by the mammalian circadian clock, including dynamic control of chromatin remodeling on a daily basis, have been reviewed elsewhere.[15,16]

Molecular clocks regulate the timing of cellular activities by controlling a large proportion of CCGs in a cyclic manner. For instance, 1,403 (approximately 8.1%) genes out of a total of 17,308 genes expressed in mouse peritoneal macrophages oscillate in a circadian fashion.[17] These genes include many important regulators of pathogen recognition and cytokine secretion. This results in daily variation in the immune response to bacteria or viruses.[6-10]

Generally, cycling genes are expressed at high levels, and energy needed to synthesize and degrade mRNAs and protein levels of cyclic genes is as much as 2 times greater than that of noncyclic genes.[18] Thus highly expressed genes might be selected to be downregulated in a cyclic manner for energy conservation, and rhythmic gene expression might optimize the metabolic cost of global gene expression.[18]

Under constant conditions, molecular clocks autonomously oscillate with a periodicity of around 24 hours (free run, about 23.5 hours in mice), so that the phase needs to be adjusted every day to match the periodic environmental signals. Each component of a molecular clock can be regulated by nonclock proteins, such as nuclear hormone receptors (eg, the glucocorticoid receptor).[2,3] These regulations result in adjustments to a molecular clock's phase, amplitude, and period in response to inputs from signaling associated with temporally relevant events, such as light and feeding, as discussed below.

MULTICELLULAR CLOCKS ARE SYNCHRONIZED AT THE WHOLE-ORGANISM LEVEL

The human body consists of approximately 40 trillion cells, each having their own clock. How are the numerous cellular clocks coordinated within our body? In mammals the circadian clock system consists of the master oscillator, which is located in the suprachiasmatic nucleus (SCN) neurons of the hypothalamus (the central clock), and peripheral oscillators, which are present in virtually all cell types, including immune cells (peripheral clocks; Fig 2).[2,3] The SCN receives innervation from the retina, allowing it to be entrained by solar light/dark cycles. Actually, light signaling increases *Per* expression in the SCN neurons and induces phase shifts of the circadian rhythms. In turn, the central SCN clock transmits time-of-day information to peripheral clocks through the hypothalamus-pituitary-adrenal axis and the autonomic nervous system.[19,20] Thus the main function of the SCN clock is to organize stable phase relationships in the peripheral oscillators. This hierarchically organized system keeps the central and peripheral clocks in phase with each other and synchronizes temporal programs of physiology across many