

REVIEW ARTICLE

The circadian clock functions as a potent regulator of allergic reaction

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Abstract

Symptoms and laboratory parameters of allergic diseases exhibit prominent ~24-h variations. For instance, in most allergic rhinitis patients, symptoms worsen overnight or early in the morning. Accordingly, there are benefits to nighttime dosing of anti-allergy medications in such patients. Although the circadian pathophysiology of allergic diseases is well documented, the biological basis of this phenomenon remains poorly understood. Recent studies have begun to reveal that the internal timekeeping system termed the circadian clock plays a key role in temporal regulation of allergic reaction, and may therefore underlie the circadian pathophysiology of allergic diseases. Here, we review new knowledge that highlights the emerging role of the circadian clock as a potent regulator of allergic reactions. Given the strong influence of circadian rhythms on allergic diseases, we believe that research on how the time of day impacts allergic reaction which we may call 'chronallergy' will provide new insight into previously unknown aspects of the biology of allergies. Such knowledge should facilitate novel strategies for prevention and treatment of these diseases.

Many symptoms and laboratory parameters in allergic diseases exhibit prominent variations with a period of approximately 24 h (circadian rhythm; *circadian*, from the Latin *circā* ['about'] and *diēs* ['a day']) (1, 2). For instance, in most allergic rhinitis patients, symptoms worsen overnight or early in the morning called 'morning attack', thereby compromising nighttime sleep and resulting in poor daytime quality of life (3).

In the 4th or 5th century AD, Aurelianus Caelius noted the frequent nocturnal occurrence of asthma attacks (4), which may be associated with a 24-h rhythm in bronchial hyper-reactivity to allergens (5). Until recently, however, the precise mechanisms underlying these observations have remained enigmatic.

New studies are beginning to reveal that the 'circadian clock', the fundamental timing mechanisms by which living organisms fit their physiology to daily alterations in the environment (6–8), plays a key role in the circadian pathophysiology of allergic reaction (9–12). Here, we briefly overview the machinery that governs the circadian clock and summarize new knowledge that highlights an emerging role of the circadian clock as a potent regulator of allergic reaction. In particular, this review primarily addresses circadian regulation of IgE/mast cell-mediated allergic reaction; the IgE/mast cell axis plays a central role in allergy, and most

of the new studies in this area have focused on this topic (9–11).

It is becoming increasingly clear that several general immune responses, such as the innate immune reaction (13, 14), leukocyte trafficking (15–17), T-cell development (18), and protection against pathogens (19), are heavily influenced by the circadian clock. For a detailed overview of the circadian regulation of aspects of immunity other than allergy, we encourage the reader to consult several excellent reviews published recently (20–25).

What is the circadian clock?

Virtually every organism on the earth undergoes ~24-h oscillations in behavior and physiology such as sleep–wake cycles, body temperature, and hormonal secretions, referred to as 'circadian rhythms', which are driven by endogenous clocks (6–8). The biological clock enables organisms to anticipate and respond to changes in the external environment imposed by solar time.

The mammalian circadian clock system consists of the central oscillator, located in the suprachiasmatic nucleus (SCN) of the hypothalamus, and peripheral oscillators present in

virtually all cell types (Fig. 1). Light activates a specific group of photoreceptors in the retina that are connected to the central SCN clock, which entrains peripheral circadian clocks via neural and endocrine pathways.

The molecular mechanisms of rhythm generation are cell autonomous and highly conserved in the SCN and peripheral cells. These rhythms are created and maintained by transcriptional–translational feedback networks consisting of several ‘clock genes’, including *Clock*, *Bmal1*, *Period* (*Per*), and *Cryptochrome* (*Cry*) (6–8). Briefly, the core loop consists of two transcription factors, CLOCK and BMAL1, that heterodimerize and bind to E-box (CANNTG)-containing sequences in a number of genes, including the three *Per* genes (*Per1*, *Per2*, and *Per3*) and the two *Cry* genes (*Cry1* and *Cry2*). The PER and CRY proteins form a repressor complex, which in turn inhibits CLOCK/BMAL1-mediated activation of *Per* and *Cry*. This negative feedback loop, in conjunction with additional post-translational modifications, generates the ~24-h oscillations of CLOCK/BMAL1 activity. The CLOCK/BMAL1 complex activates expression of not only *Per* and *Cry*, but also other genes containing E-box elements in their promoter regions termed clock-controlled genes (CCGs), in a circadian manner. In general, CCGs are key transcription factors, enzymes, and molecules involved in a variety of important physiological processes (e.g., the

nuclear receptors or rate-limiting enzymes involved in cellular metabolic pathways) including immune functions. For instance, in mouse macrophages, CLOCK/BMAL1 binds to the E-box(-like) elements in the promoter of the *Toll-like receptor* (*Tlr*) 9 and regulates its expression in a circadian manner, thereby mediating temporal regulation of TLR9-associated innate immune responses in mice (26).

Circadian nature of allergic diseases: chronobiology and chronotherapy

Symptoms and laboratory parameters of allergic diseases such as allergic rhinitis, asthma, and chronic urticaria exhibit prominent circadian variations. Documentation of this phenomenon has expanded rapidly since the early 1960s, possibly because the concept of the biological clock in organisms including mammals was established at a Cold Spring Harbor Meeting held in 1960; subsequently, allergists became aware of the importance of the biological clock in allergic diseases (27).

As noted above, symptoms of allergic rhinitis, including sneezing, runny nose, blocked nose, and itchy nose, exhibit circadian rhythms, worsening overnight or early in the morning (1, 3, 28). Consistent with this, there are circadian variations in nasal reactivity to methacholine and the activity of eosinophils and basophils in the nasal mucosa, all of which

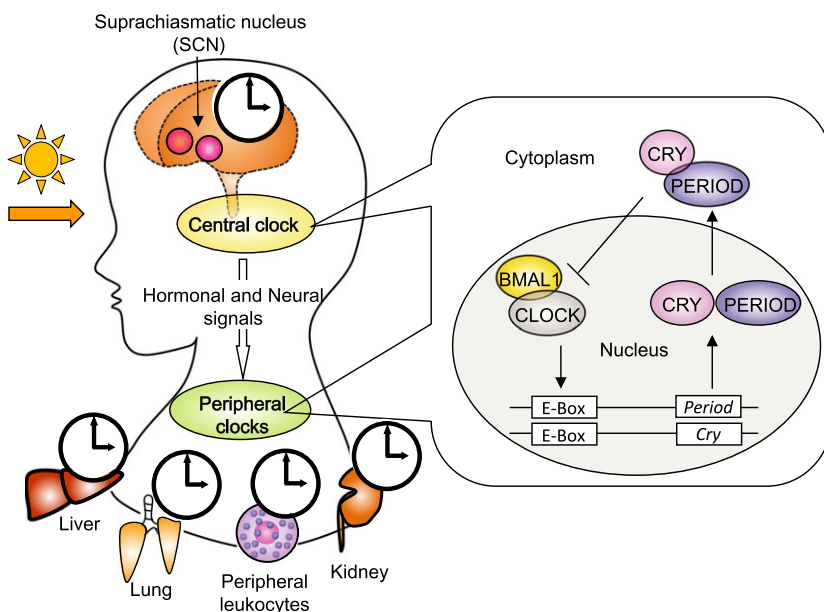


Figure 1 A canonical model of the mammalian circadian clock. The mammalian circadian clock consists of the central oscillator, located in the suprachiasmatic nucleus (SCN) of the hypothalamus, and peripheral oscillators present in virtually all cell types. Light activates a specific group of photoreceptors in the retina that are connected to the central SCN clock, which synchronizes and entrains peripheral circadian clock via neural and endocrine pathways. At the molecular level, CLOCK and BMAL1 heterodimers activate transcription of *Period* (*Per*) and *Cryptochrome* (*Cry*) genes. PER and CRY proteins in turn inhibit their own

expression by repressing CLOCK/BMAL1 activity. This negative feedback loop, with additional post-translational modifications, generates ~24-h oscillations of clock protein levels and activity, which is translated into circadian behavior and physiology. The molecular mechanisms of rhythm generation are cell autonomous and highly conserved in the SCN (the central clock) and peripheral cells (the peripheral clocks). Please note that this model is classical and recent new data reveal that the molecular clock consists of more complicated network of clock genes (references 6–8).

are higher in the early morning than at other times (29). Likewise, patients with asthma experience nocturnal exacerbations (1), which are associated with circadian rhythms in bronchial reactivity to allergens such as house dust (5) and the activity of alveolar eosinophils, which peak significantly at midnight or during the early morning (30). Patients with chronic urticaria are most bothered by symptoms in the evening (2), probably due to a prominent circadian pattern of intradermal skin reactions to histamine or house dust; the response is elevated in the afternoon, peaks in the evening, and exhibits a morning trough (31). Thus, the circadian rhythm is inextricably linked to the pathophysiology of allergic diseases, although the precise mechanisms remain poorly understood.

Accordingly, allergic diseases are among the best suitable targets for chronotherapy, that is, the use of circadian rhythmic cycles in the application of therapy to maximize effectiveness and minimize side-effects (32). In allergic rhinitis, there are benefits to nighttime dosing of anti-allergy medications. For example, the antihistamine mequitazine has exhibited improved efficacy when administered in the evening compared with morning dosing (1). In patients with nocturnal asthma, the optimal timing of steroid treatment is early evening, accompanied by a significant increase in FEV₁ and a reduction in airway inflammatory cells relative to controls (1, 33, 34). Similarly, evening dosing of long-acting bronchodilators in nocturnal asthma achieves maximum efficacy at night (1). Hence, many other classes of medications have been explored for chronotherapy of allergic diseases.

IgE/mast cell-mediated allergic reaction exhibits circadian rhythms, relying on the normal circadian clock activity

The IgE/mast cell axis plays a central role in allergic diseases, including allergic rhinitis, asthma, urticaria, and food allergy (35–38). Previous studies have shown that the IgE/mast cell-mediated allergic reaction exhibits circadian variations in both mice and humans. For instance, anaphylactic sensitivity in the pinna of mouse is subjected to diurnal variation (39). The magnitude of cutaneous hypersensitivity reactions to allergens in patients with nocturnal asthma also exhibits a circadian rhythm (40). Although rhythmic humoral signals such as cortisol from the adrenal gland and rhythmic activity of the autonomic nerves have been implicated in diurnal variations (40), the precise cellular and molecular mechanisms underlying circadian regulation of IgE/mast cell-mediated allergic reaction remain poorly understood.

Recent studies demonstrated that mast cells, like other peripheral cells, possess a functional molecular clock. Core clock genes such as *Per1*, *Per2*, *Bmal1*, *Rev-erba*, and *Dbp* are expressed in a rhythmic circadian manner in mouse bone marrow-derived cultured mast cells (BMMCs), mouse jejunal mast cells, and human intestinal mast cells (9, 41, 42). In addition, genes expressed exclusively or predominantly in mast cells, such as *Mcpt-5*, *Mcpt-7*, tryptase, and *FcεRIα*, also exhibit robust circadian oscillations (42). Furthermore, circadian variations in histamine release, cysteinyl leukotriene

production, and IL-6/IL-13 expression occur in mast cells following IgE-mediated activation (9, 41). Most recently, IgE-dependent release of chemokine CCL2 was also shown to exhibit a circadian variation associated with rhythmic phosphorylation levels of ERK1/2 in human intestinal mast cells (43). These results suggest that mast cells contain their own clockwork that may be involved in their circadian functions.

Several *in vivo* studies provide direct evidence that the circadian clock drives daily rhythms in IgE/mast cell-mediated allergic reaction. A time of day-dependent variation in passive cutaneous anaphylactic (PCA) and passive systemic anaphylactic (PSA) reactions, which are IgE/mast cell-dependent allergic reactions, is present in wild-type mice, but absent in *Per2*-mutated mice (9). Likewise, a time of day-dependent variation in PCA or PSA reaction is present in wild-type mice, but absent in mice that have undergone mechanical disruption of the central SCN clock or in mice with adrenalectomy (9, 10). Furthermore, no time of day-dependent variation in the PCA reaction is present in aged mice, which tend to have aberrant circadian clock activity (9). These findings strongly suggest that the circadian clock plays a key role in the generation of daily rhythms in IgE/mast cell-mediated allergic reaction (Fig. 2). A possible mechanism how the SCN disruption or adrenalectomy blunts a time of day-dependent variation in PCA or PSA reaction in mice is discussed later.

The mast cell-intrinsic clock may primarily contribute to the generation of a time of day-dependent variation in IgE/mast cell-mediated allergic reaction

Following the discoveries described above, the relative contribution of systemic (e.g., neuronal and endocrine) and local (e.g., mast cell) clocks to the temporal regulation of IgE/mast cell-mediated allergic reaction remained unclear. In this regard, a very recent study showed that the mast cell-intrinsic clock may be a primary driver of the daily rhythm of the PCA reaction. Mast cell-deficient mice reconstituted with BMMCs generated from *Clock*-mutated, but not from wild-type, mice lacked the daily rhythms of the PCA reaction despite having intact daily profiles and levels of serum corticosterone (11). *CLOCK* protein appears to be a key molecule linking the circadian clock and IgE-mediated signaling in mast cells. Specifically, *CLOCK*, whose activity changes across the circadian day, promotes expression of β subunit of *FcεRI* (*FcεRIβ*) in mast cells via chromatin modifications around the promoter region of *FcεRIβ* (11). Because *FcεRIβ* is a modifier of surface expression and signaling of *FcεRI* (35, 36, 44), *CLOCK* may fine-tune *FcεRI* expression and signaling in mast cells in a circadian manner. A model based on these findings is summarized in Fig. 3, but other mechanisms may be also involved in the temporal regulation of IgE/mast cell-mediated allergic reaction.

How do mast cells tell time in our body?

The *in vivo* findings suggest that the peripheral, but not systemic, circadian clock in mast cells makes the primary

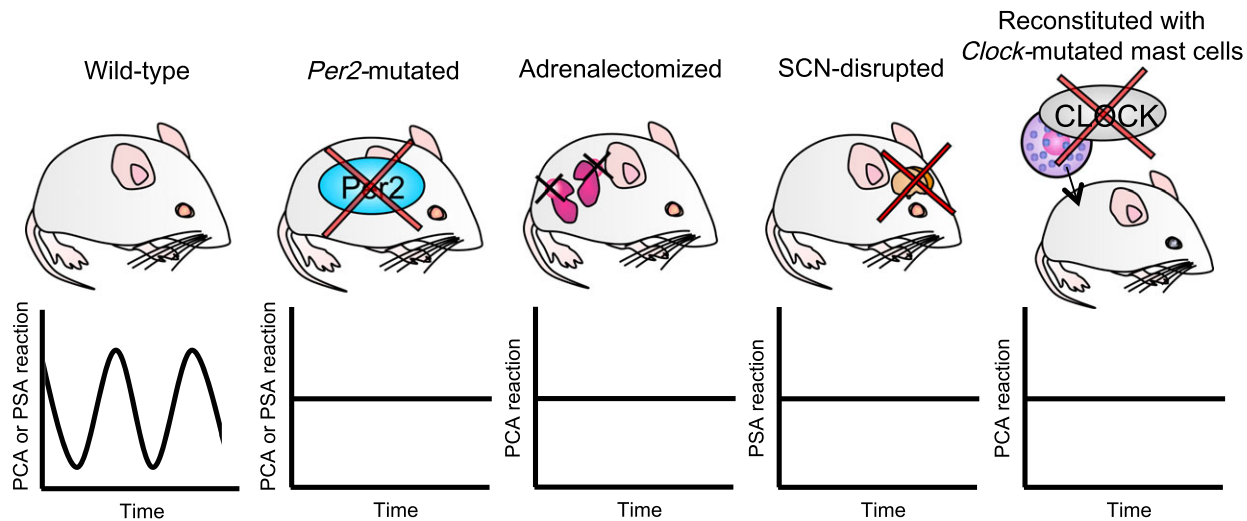


Figure 2 The circadian clock times the IgE/mast cell-mediated allergic reaction. Wild-type mice exhibit a time of day-dependent variation in passive cutaneous anaphylactic (PCA) and passive systemic anaphylactic (PSA) reactions. This daily variation was absent in *Per2*-mutated mice, adrenalectomized mice, SCN-disrupted mice, and mast cell-specific *Clock*-mutated mice (references 9–11). The

absence of daily rhythms in PCA or PSA reaction observed in SCN-disrupted or adrenalectomized mice can be attributed to the loss of synchronicity of the mast cell clockwork, possibly induced by aberrant release of corticosterone and subsequent uncoupling of the IgE-mediated response at the population level in mast cells.

contribution to the generation of the daily rhythms of the PCA reaction (11). These results imply that failure of individual mast cells to synchronize with systemic timing cues would lead to damping of the ensemble rhythm at the population level and might result in uncoupling of the IgE-mediated response. Large numbers ($\sim 10^{12}$) of mast cells are present in our body. Thus, each mast cell clock must be tightly synchronized by internal timing signals to generate the net circadian IgE response. However, it remains unclear how mast cells tell time *in vivo*.

The recent study cited above (11) also addressed this issue. Bioluminescence emission from mast cell-deficient mice subcutaneously reconstituted with BMMCs generated from *Per2^{LUC}* knock-in mice, which express PER2 as a luciferase fusion protein (PER2^{LUC} BMMCs) (45), showed a time of day-dependent variation in PER2^{LUC} protein in wild-type or sham-operated mice, with a peak at 10:00 PM. Adrenalectomy of the mice abolished the circadian variations in PER2^{LUC} protein levels in mast cells (11). Additionally, corticosterone induces *Per1* and *Per2* mRNA expression in wild-type BMMCs (11). Thus, humoral factors derived from the adrenal gland, such as corticosterone, are likely to play a critical role in synchronizing the mast cell clockwork *in vivo*.

Release of humoral factor(s) such as corticosterone from the adrenal gland exhibits circadian rhythms driven by the central SCN and adrenal clocks (46). Therefore, the absence of daily rhythms in the PCA or PSA reaction observed in SCN-disrupted or adrenalectomized mice (9, 10) can be attributed to loss of synchronicity of mast cell clockworks, likely due to aberrant release of corticosterone and subsequent uncoupled IgE-mediated response at the population level in mast cells (Fig. 3). Please note again that, at present,

this notion is a working hypothesis, and it remains unclear precisely how mast cells tell time *in vivo*.

Why does IgE/mast cell-mediated allergic reaction exhibit circadian rhythms?

One fundamental question is why circadian control of IgE/mast cell-mediated allergic reaction evolved in mammals. IgE/mast cell-mediated allergic reaction is thought to be the body's first line of defense against macroparasites such as helminth worms and biting arthropods (they can be vectors for bacteria or viruses that are lethal to humans), and these stimuli may provide an evolutionary driving force to maintain allergy (47). Like almost all animals and plants, most parasites and biting arthropods exhibit circadian rhythms in their behaviors (48). Therefore, it is possible that the circadian control of IgE/mast cell-mediated allergic reaction evolved to deal with macroparasites and biting arthropods that themselves behave in a circadian manner. Thus, our immune system might anticipate and prepare for the risk of attack by macroparasites and biting arthropods during our resting phase by enhancing the IgE/mast cell-mediated reaction at that time.

Future directions

A number of issues regarding circadian regulation of allergy remain to be addressed:

- 1 Evidence has accumulated that the circadian clock regulates IgE/mast cell-mediated allergic reaction (9–11), but the underlying cellular and molecular mechanisms are not fully understood.

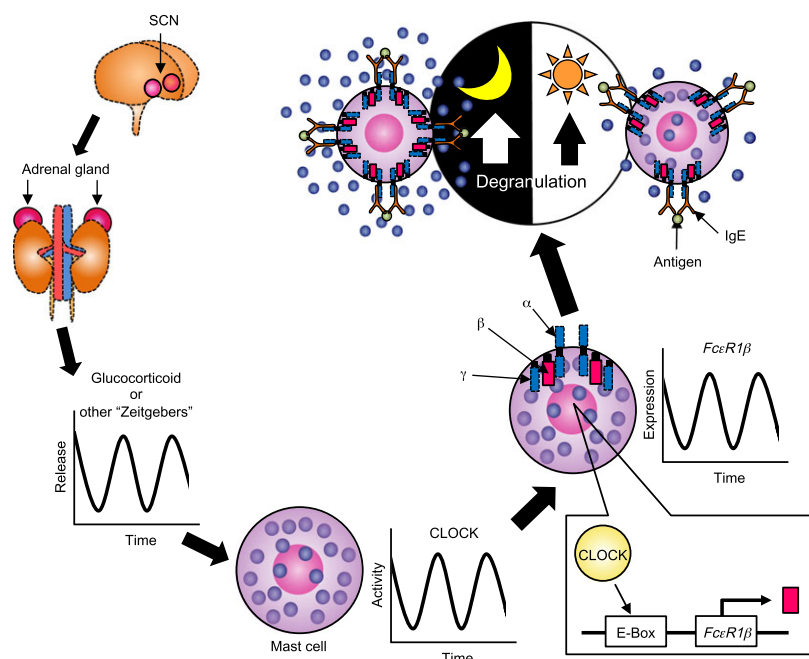


Figure 3 The mast cell clock, entrained by the SCN and adrenal clocks via endocrine pathways, may temporally gate FcεRI expression and signaling, thereby generating a marked day–night variation in IgE/mast cell-mediated allergic reactions. The mast cell-intrinsic clock primarily contributes to the generation of the daily rhythms in IgE-mediated degranulation in mast cells. At the molecular level, CLOCK protein, whose activity changes across the circadian day, promotes expression of FcεRIβ in mast cells. Because FcεRIβ is a modifier of surface expression and signaling of FcεRI, CLOCK can

fine-tune FcεRI expression and signaling (degranulation) in a circadian manner. In addition, mast cell clocks are synchronized by humoral factor(s) released from the adrenal gland. Because the release of humoral factor(s) from the adrenal gland is temporally regulated by the SCN and adrenal clocks, circadian IgE/mast cell-mediated allergic reaction may require tight coupling of the SCN/adrenal/mast cell clocks. Please note that, at present, this model is a working hypothesis based on the recent literatures (references 9–11).

- 2 The specific roles in allergic diseases of the molecular clocks present in immune cells, such as T cells (49, 50), eosinophils (42, 43), basophils (12), macrophages (51), or type-2 innate immune cells, or in organs, such as the lung (52) and skin (53), remain to be investigated. In addition, it is not fully understood how the peripheral clocks in these immune cells or organs are synchronized to systemic timing cues.
- 3 Few epidemiological and clinical studies have investigated circadian involvement in the predisposition, etiology, maintenance, and progression of allergic diseases; by contrast, many studies have described the effect of circadian rhythms in cancer, diabetes, and cardiovascular disease (21). For instance, night-shift workers with aberrant circadian rhythms exhibit an increased risk of breast cancer (54). Hence, more human studies are clearly needed to determine how strongly the circadian clock (or its disruption) influences the predisposition, etiology, maintenance, and progression of allergic diseases.
- 4 The relationships between the circadian clock and allergic reactions can be bidirectional. Several studies have shown that inflammatory stimuli such as TNF-α modulate expression of core clock genes (55). Therefore, it is important to determine whether immune signals generated at

the sites of allergic inflammation affect the period length, phase, or amplitude of the molecular clock machinery, thereby modulating the circadian nature of allergic inflammation.

- 5 In normal subjects, the peripheral circadian clock regulates circadian variability in local physiology, such as nasal or bronchial responsiveness to environmental stimuli, on a day-to-day basis (6–8). The airways of patients with allergic rhinitis/asthma or the skin of patients with chronic urticaria may be more sensitive to the output of the molecular clock; alternatively, the amplitude of the clock might be increased in allergic airways or skin (33). Therefore, it is important to investigate the status of the local circadian clock in allergic lesions; the resultant knowledge should provide novel insights into the essence of allergic diseases.
- 6 New strategies for treatment and prevention of allergic diseases should be explored based on the accumulating knowledge about the critical roles of the circadian clock in allergic reaction. For instance, because the circadian clock temporally gates signaling via the FcεRI in mast cells (11), pharmacologically resetting the molecular clock in mast cells to times when FcεRI signaling is reduced may inhibit IgE-mediated allergic reactions. In addition,

because transcriptional factor E4BP4 (NF-IL3), which is a transcriptional target of the CLOCK/BMAL1 complex (6–8), is shown to be a key regulator of IgE class switching (56), selective modulation of the circadian clock activity in B cells might help prevent sensitization to allergens.

Concluding remarks: Toward 'chronoallergy'

Recent studies have shown that the circadian clock significantly impacts allergic reaction. These findings provide novel insight into the pathophysiology of allergic diseases. Given the accumulating evidence and strong influence of circadian rhythms in allergic diseases, we predict that 'chronoallergy' will become an important field aimed at revealing the essence of allergic diseases and facilitating the development of new strategies for prevention and treatment of these diseases.

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Conflict of interest

The authors declare no financial or commercial conflict of interest.

Author contributions

A.N, Y.N, and S.S. wrote the paper. All authors reviewed the manuscript.

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