International Immunology, Vol. 32, No. 11, pp. 703–708
doi:10.1093/intimm/dxaa048
Advance Access publication 25 July 2020

Immune-enhancing effects of glucocorticoids in response to day–night cycles and stress

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Received 3 April 2020, *editorial decision* 20 July 2020; *accepted* 20 July 2020

Environmental cues such as the day–night cycle or stressors trigger the production of glucocorticoids (GCs) by the adrenal cortex. GCs are well known for their anti-inflammatory effects that suppress the production of inflammatory cytokines and induce the apoptosis of lymphocytes. Recent studies in mice, however, have revealed pro-inflammatory effects. The diurnal oscillation of GCs induces the expression of IL-7 receptor α (IL-7Rα) and C–X–C motif chemokine receptor 4 (CXCR4) at the active phase, which drives the diurnal homing of T cells into lymphoid organs. This accumulation of T cells at the active phase enhances T-cell priming against bacterial infection and antigen immunization, leading to an increase of effector CD8 T cells and antibody production. GCs induced by moderate stress trigger the homing of memory CD8 T cells into the bone marrow and support the maintenance and response of these cells. Thus, endogenous GCs have a self-defense function to enhance adaptive immune responses. By contrast, strong stress induces even higher GC levels and causes chronic inflammation and autoimmunity. Because GCs can enhance the differentiation and function of T-helper 2 (T_h2) and T_h17 cells, high stress-induced GC levels might enhance inflammation via T_h17 cell differentiation. Overall, the positive and negative effects of GCs may regulate the balance between normal immune responses and susceptibility to infections and inflammatory diseases.

Keywords: circadian rhythm, CXCR4, IL-7R, memory T_h2, T_h17

Introduction

The body is constantly receiving environmental cues and stressors, such as the 24-h day–night cycle, hunger and psychological stress. When we respond to these stressors to change behavior and biological activity, the central nervous system directs hormone secretion, which modifies the expression of genes in various cells including immune cells. Interestingly, recent studies have showed that environmental cues and stressors affect immune responses against foreign antigens. Glucocorticoids (GCs) are one of the mediators connecting stressors and the immune system. GCs are a class of steroid hormones produced by the adrenal cortex. They have strong anti-inflammatory effects and are used in treatments for allergies, chronic inflammation and autoimmune diseases. However, recent studies have also suggested that endogenous GCs have immune-enhancing effects, promoting the maintenance and response of lymphocytes. In this article, we will introduce the immune-enhancing effects of GCs and propose the idea that GCs balance immunity and tissue repair.

GC production is controlled by two major stimuli: circadian rhythms and stress (1). The 24-h light/dark cycle induces oscillations of GC concentration in serum. GCs show diurnal fluctuation with a peak at early morning and nadir at night in diurnal animals like humans, whereas nocturnal animals like rodents show the opposite pattern. Light and dark stimuli to the eyes induce the circadian rhythm for the expression of clock genes in neurons of the suprachiasmatic nucleus, which innervate the paraventricular nucleus (PVN) in the hypothalamus. The PVN secretes corticotropin-releasing hormone (CRH), which triggers the anterior pituitary to secrete adrenocorticotropic hormone (ACTH) into the bloodstream. Finally, ACTH stimulates the adrenal cortex to produce GCs. In addition to this circadian rhythm, CRH production is induced by stresses such as hunger, physical restraint, enforced swimming, surgery, inflammation, infection and autoimmunity, leading to an increased production of ACTH and GCs.

GCs bind to cytoplasmic glucocorticoid receptor (GR) (2). GR consists of multiple domains including the N-terminal activation function-1 (AF-1) domain, DNA-binding domain and ligand-binding domain. After GC–GR binding in the cytoplasm, GR dimerizes, translocates into the nucleus and binds to specific DNA sequences known

as glucocorticoid response elements (GREs) to activate or suppress transcription of the target genes. Furthermore, GR directly interacts with other transcription factors, such as nuclear factor κB (NF-κB), activator protein 1 (AP-1), mitogen-activated protein kinase (MAPK), signal transducers and activators of transcription (STATs) and T-box expressed in T cells (T-bet), to augment or inhibit their functions.

GCs influence the biological activities of various organs/tissues such as nerves, liver, adipose tissues and muscle. GCs enhance hepatic gluconeogenesis by inducing the expression of metabolic enzymes and lipolysis in adipose tissues to release fatty acids and glycerol, which are gluconeogenic precursors and energy for the gluconeogenic pathway (3). They also drive the circadian rhythm of gluconeogenesis and lipolysis. In addition, GCs can promote the effects of other hormones and neurotransmitters, such as adrenaline and noradrenaline, a phenomenon known as the permissive effect (3, 4).

Immunosuppressive effects of GCs

GCs are well known for their strong immunosuppressive effects and are widely used in treatments for allergies and autoimmune diseases. There are two lines of experimental observations that support the immunosuppressive effects of GCs. First, GCs repress the expression of inflammatory cytokines such as interleukin-1 (IL-1), IL-2, IL-6, IL-8, IL-12, IL-18, tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) by binding to negative GREs and inhibiting the activation of NF-κB and AP-1 (5–8). Second, they can induce the apoptosis of lymphocytes (9). Thus, treatment with synthetic GCs reduces the production of inflammatory cytokines and the count of lymphocytes in lymphoid organs (9).

Similarly, previous studies with mouse models have showed that endogenous GCs strongly attenuate inflammatory responses by the innate immune system. GR-deficient macrophages and dendritic cells showed a higher expression of IL-1β, IL-6, TNF-α and cyclooxygenase-2 (COX-2) after stimulation, and sepsis caused a high mortality of mice with GR deficiency specifically in macrophages or dendritic cells (10, 11). In lungs, higher levels of GCs at the active phase in mice suppressed C–X–C motif chemokine ligand 5 (CXCL5) production by the epithelium through GR binding to negative GREs, leading to a circadian change of neutrophil mobilization and inflammatory cytokine expression with a peak at the rest phase and a nadir at the active phase (12).

In addition to the induction of lymphocyte apoptosis, GCs suppress T-helper 1 (T_h1) cell differentiation by inhibiting IL-12 and IL-18 production from antigen-presenting cells, thereby attenuating STAT4 and T-bet signaling (13–16). GCs also reduce IFN-γ production by T_h1 and natural killer (NK) cells. Kugler *et al*. reported that after infection with *Toxoplasma gondii*, IFN-γ and TNF-α are highly produced by the T_h1 cells of mice in which GR deficiency occurs specifically in T cells and that those mice exhibited higher mortality (17). Quatrini *et al*. found that GR-deficient NK cells express higher amounts of IFN-γ after IL-12 and IL-18 stimulation and that GR-deficient NK cells express programmed cell death 1 (PD-1) at lower levels in mice infected with murine cytomegalovirus (MCMV) (18, 19). This PD-1 reduction might cause excessive inflammation after MCMV infection, leading to accelerated IFN-γ production and higher mortality. Thus, GCs are critical for suppression of the innate immune response and cell-mediated cytotoxicity.

Immune-enhancing effects

Induction of cytokine receptors to enhance T-cell survival

In contrast to the immunosuppressive effects of GCs, some studies have suggested that endogenous GCs have immune-enhancing functions. Although GCs inhibit the production of inflammatory cytokines, it is reported that GCs promote the expression of cytokine receptors for IL-2, IL-6, IFN-γ, granulocyte/macrophage colony-stimulating factor (GM-CSF) and TNF-α (20).

In addition, Franchimont *et al*. identified IL-7 receptor α (IL-7Rα) as one of the target genes induced by GCs in T cells (21). IL-7Rα forms a heterodimer with the common γ-chain (γc). IL-7 binding to IL-7R induces the phosphorylation of STAT5 and phosphatidylinositol (PI) 3-kinase, which enhances the survival and proliferation of T cells, immature B cells and innate lymphoid cells (22–24). Franchimont *et al*. also showed that IL-7Rα induced by GCs up-regulates IL-2Rα expression on T cells to promote T-cell survival (21). Lee *et al*. investigated how GCs induce IL-7Rα expression and identified conserved non-coding sequence (CNS)-1 at 3.6 kb upstream of the promoter in the IL-7Rα locus (25). CNS-1 contains conserved NF-κB and GRE motifs. Furthermore, Abe *et al*. reported that TNF-α and GCs activate IL-7Rα transcription through CNS-1 and that CNS-1-deleted mice show reduced IL-7Rα expression in peripheral T cells, resulting in an impaired maintenance of T cells (26). These findings all suggest that GCs support T-cell maintenance in the periphery (Fig. 1).

Diurnal change of T-cell distribution and immune responses

Because the GC concentration in serum changes in concord with circadian rhythms, it is possible that the diurnal change of GCs might control T-cell function through IL-7Rα expression. To address this question, we generated GRE mutation (GREm) mice with point-mutations in two GREs of CNS-1 and analyzed them together with mice in which GR deficiency was specifically in T cells (CD4Cre GRcKO) (27).

First, we checked the IL-7R expression in T cells and found that IL-7R expression fluctuates during the course of the day in correlation with the oscillation of GCs in serum. To test whether the diurnal change of IL-7R expression affects T-cell functions, we compared the T-cell distribution among tissues, because the T-cell count in peripheral blood shows a diurnal change in humans (28, 29). We found that mouse blood contains a large number of T cells at daytime compared with night, whereas more T cells accumulate in the spleen, lymph nodes and Peyer's patches at night compared with daytime. Interestingly, the diurnal oscillations of IL-7R expression and T-cell numbers in blood and lymphoid organs are lost in CD4Cre GRcKO and GREm mice, suggesting that the IL-7R signal elevates T-cell migration into lymphoid tissues at night.

It is reported that cortisol and epinephrine control the diurnal change of T cells in blood by inducing chemokine receptor C–X–C motif chemokine receptor 4 (CXCR4) and that the IL-7 signal up-regulates CXCR4 expression on T cells (29, 30). We observed that CXCR4 expression on T cells exhibits a diurnal change and that this diurnal oscillation is lost in CD4Cre GRcKO and GREm mice. We also found that the diurnal change of the T-cell distribution was impaired in mice with T-cell-specific CXCR4 deficiency. These results indicate that CXCR4 expression regulated by IL-7R and GCs drives the diurnal change of the T-cell distribution (Fig. 2).

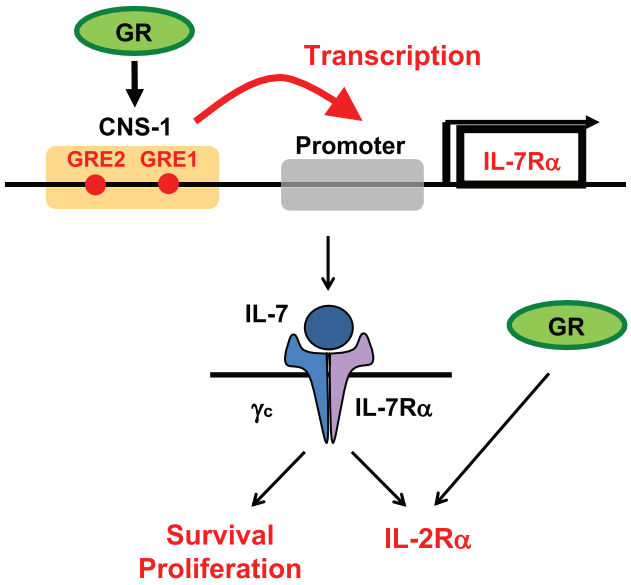

Fig. 1. Glucocorticoids up-regulate IL-7Rα transcription through conserved non-coding sequence 1 (CNS-1) and glucocorticoid response elements (GREs) in the IL-7Rα gene locus. CNS-1, which is upstream of the IL-7Rα promoter, contains two GRE motifs. Glucocorticoid receptor (GR) binding to these GREs activates IL-7Rα transcription. The induced IL-7Rα enhances T-cell survival and proliferation. A synergistic effect of GR and the IL-7R signal enhances IL-2Rα expression in T cells and helps T-cell survival through the IL-2 signal.

Because antigen presentation and T-cell priming take place in lymphoid organs, we hypothesized that the difference in T-cell accumulation at daytime and night might influence immune responses against antigens. We infected mice with ovalbumin (OVA)-expressing *Listeria monocytogenes* at daytime or night and observed that infection at nighttime, when T-cell accumulation in the lymphoid organs was promoted compared to daytime, induced a greater generation of effector CD8 T cells than daytime infection. Moreover, immunization with a soluble antigen at night enhanced the differentiation of follicular helper T (Tfh) cells and formation of germinal centers. By contrast, the enhanced response at night was abolished in CD4Cre GRcKO and GREm mice. Similar to our results, Suzuki *et al.* reported that the signal from β2 adrenergic receptor (β2AR, which binds epinephrine) augments the activities of CC chemokine receptor 7 (CCR7) and CXCR4 and retains T and B cells in lymph nodes at night (31).

In addition, Druzd *et al.* found that a clock gene, brain and muscle *ARNT*-like 1 (BMAL1), induces a high expression of CCR7 and low expression of sphingosine-1-phosphate receptor 1 (S1PR1) in mice at night, which drives the accumulation of T and B cells in lymph nodes (32). They further demonstrated that the accumulation of T and B cells in lymph nodes at night enhances humoral immunity by Tfh and

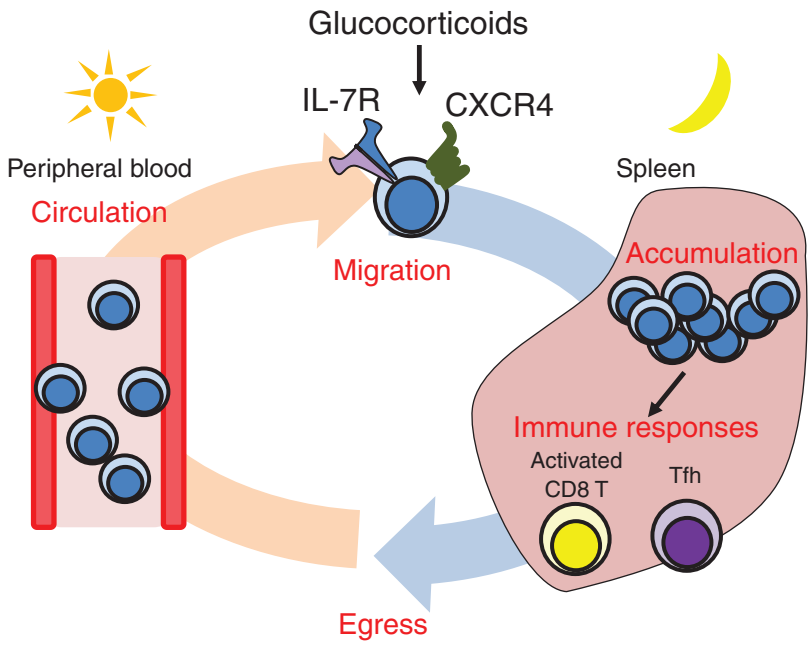

Fig. 2. The diurnal oscillation of IL-7Rα and CXCR4 expression induced by glucocorticoids (GCs) controls the diurnal rhythm of the T-cell distribution and immune responses. In mice, T cells egress from lymphoid organs and circulate in blood during the daytime. Higher GC levels at night up-regulate IL-7R and CXCR4 in T cells and induce T-cell migration into lymphoid organs. The accumulation of T cells enhances T-cell priming and the generation of activated CD8 T and follicular helper T (Tfh) cells.

germinal center B cells and autoimmunity mediated by T_h17 cells in experimental autoimmune encephalomyelitis (EAE) (31, 32).

Although BMAL1 and β2AR control the circadian rhythm of T-cell recirculation via CCR7 and S1PR1, GR seems to be critical for the diurnal cycle of the T-cell distribution via CXCR4. One explanation is that GCs might up-regulate the β2AR expression in T cells and thereby enhance the retention of T cells within lymphoid organs. It is reported that GCs increase the expression and function of adrenergic receptors (33–35). Thus, GR deficiency might reduce the β2AR signaling in T cells. Another explanation is that GCs affect the circadian oscillation expression of some clock gene genes such as PER1, PER2, NFIL3 and REV-ERB (36). Additionally, it is reported that GRE motifs are present in the Per1 and Nfil3 loci and involved in their expression. Therefore, GR deficiency might attenuate the feedback loop of clock genes and the diurnal cycle of T-cell recirculation mediated by CCR7 and S1PR1. Taken together, GCs as well as adrenergic nerves and clock genes enhance adaptive immunity by controlling the diurnal oscillation of the T-cell distribution between blood and lymphoid organs. However, how GCs control adrenergic signaling and clock genes remains to be clarified.

GCs enhance the T-cell response not only by controlling the diurnal change of the T-cell distribution but also by promoting T-cell proliferation. Because GCs increase IL-2Rα expression through the IL-7R signal and enhance IL-2-mediated survival, GR promotes T-cell proliferation by T-cell antigen-receptor (TCR) and IL-2 stimulation *in vitro* (27).

Furthermore, GCs influence the differentiation of certain T-helper cell subsets (37). As mentioned above, GCs strongly inhibit T_h1 differentiation and IFN-γ production, and the administration of GCs rapidly eliminates T_h1 cells (38). In contrast, GCs enhance the differentiation and function of T_h2 cells. Ramirez *et al*. reported that rat T cells cultured in T_h2-skewed conditions produce greater amounts of IL-4, IL-10 and IL-13 when stimulated with concanavalin A (ConA) and dexamethasone (a synthetic GC) than with ConA alone (39). Indeed, we observed that the differentiation of IL-4-producing and IL-13-producing CD4 T cells from GR-deficient mice is impaired in T_h2-skewed culture conditions, which suggests that endogenous GCs enhance the differentiation of T_h2 cells by a ligand-dependent mechanism (27). *In vivo*, IL-4 transcription in Tfh cells and the production of IgG1 and IgG2b were decreased in CD4Cre GRcKO mice after immunization with a soluble antigen, suggesting that GCs promote the differentiation of T_h2 and Tfh cells. We also found that the numbers of Tfh cells and IgG1-expressing B cells are reduced in Peyer's patches of CD4Cre GRcKO mice, suggesting that GCs promote a humoral immune response in mucosal tissues.

Some effector T_h2 cells differentiate into memory T_h2 cells and are maintained in the periphery for a long period (40). IL-7R is highly expressed on memory T cells, and the IL-7 signal is important for their long-term survival. We found that a high level of GCs at night up-regulates IL-7Rα expression on memory T_h2 cells in mice (27). Because of the reduced IL-7R expression, the maintenance of memory T_h2 cells in CD4Cre GRcKO and GREm mice is attenuated, indicating that the IL-7R expression induced by GCs supports the survival of memory T_h2 cells. Thus, GCs enhance both the differentiation of T_h2 cells and the maintenance of memory T_h2 cells, which may cause the resistance of inflammatory diseases to GC treatments.

Stress enhances bone marrow-mediated immune responses and inflammatory diseases

The secretion of endogenous GCs is elevated by nutritional and psychological stress. Collins *et al*. found that dietary restriction (DR) induces memory CD8 T cells to egress from the spleen and migrate into the bone marrow of mice infected with *Yersinia pseudotuberculosis* (41). They also showed that DR increases the level of corticosterone in serum and that the DR-mediated accumulation of memory CD8 T cells in the bone marrow is lost in adrenalectomized mice. Interestingly, DR or the administration of dexamethasone up-regulates B-cell lymphoma 2 (Bcl-2) expression in memory CD8 T cells. Furthermore, they found that DR induces CXCR4 expression on memory CD8 T cells and that the deficiency of CXCR4 or S1PR1 impairs the accumulation of memory CD8 T cells, suggesting that the increase of memory CD8 T cells in the bone marrow is mediated by CXCR4-induced homing and S1PR1-induced egress. They also demonstrated that DR enhances protection from secondary bacterial infection, suggesting that moderate stress might be advantageous for the response of memory CD8 T cells through GC-mediated mechanisms.

Strong stress sometimes causes immune disorders such as chronic inflammation and autoimmunity. Qiu *et al*. reported that restraint-stress causes severe damage of the gut in a dinitrobenzene sulfonic acid-mediated colitis model and that the depletion of CD4 T cells ameliorates the tissue damage, suggesting that stress causes strong inflammation through T-helper cell activity (42). Arima *et al*. showed that stress induced by sleep disturbance leads to gastrointestinal damage and the sudden death of mice after the transfer of pathogenic T cells that had been stimulated with myelin oligodendrocyte glycoprotein (MOG) peptide (43). The inflamed vessels secreted inflammatory cytokines and chemokines in the central nervous system and triggered the infiltration of auto-reactive T-helper cells.

Recently, Inokawa *et al*. reported that long-term disruption of the day–night cycle in mice reduces lifespan, induces the expression of genes related to inflammatory and autoimmune diseases and increases the number of T_h17 cells (44). Thus, excessive stress might cause inflammation via T_h17 cells. Previous studies reported that dexamethasone promotes the differentiation of mouse T cells and human peripheral blood mononuclear cells in culture. De Castro Knoner *et al*. showed that GCs increase T_h17 differentiation and retinoic acid receptor-related orphan receptor C (RORC) expression via the inhibition of IL-2 production, suggesting that GCs have the potential to enhance the differentiation and function of T_h17 cells (45). Related to these observations, Marchetti *et al*. reported on transgenic mice expressing GR antisense RNA (46). They found that such mice exhibit milder inflammation in an EAE model, suggesting that GCs promote the development of the disease by enhancing the T_h17 cell function that is critical for EAE development. Taken together, stress-induced GCs promote the differentiation and function of T_h17 cells, which might

cause inflammation. Therefore, higher GC levels in stress conditions might have positive effects on immune protection against infection.

Above, we explain that GCs have both positive and negative effects on immune response. Although GCs suppress the activities of T_h1 and NK cells, when produced at the active phase or under stress conditions, they can enhance cell-mediated immunity through CD8 T cells. Moreover, GCs might enhance the differentiation and function of T_h17 cells. These positive effects on T_h17 cells might cause the resistance against GC treatments in asthma and colitis (47, 48). On the other hand, GCs are effective at suppressing the pathogenicity of T_h17 cells in psoriasis (49). Thus, whether GCs work positively or negatively might depend on the conditions of the inflammation and the microenvironment of the effector cells. For example, IL-7R might inhibit the apoptosis of T cells induced by GCs and enhance the immune responsiveness of T cells (21, 27). In other words, IL-7 from the immune microenvironment might switch the effects of GCs from negative to positive. In addition, cytokines such as IL-6 might enhance the positive effects of GCs on T_h17 cell differentiation and exacerbate the consequent inflammation (50, 51). Future work is needed to clarify which factors modulate the positive and negative effects of GCs in inflammatory diseases.

Conclusions

Most studies about GCs in immunity have described immunosuppressive effects such as the inhibition of inflammatory cytokine expression, induction of lymphocyte apoptosis and impairment of the immune response by T_h1 and NK cells expressing IFN-γ. However, recent studies have focused on the positive effects of endogenous GCs. Endogenous GCs enhance the maintenance, distribution and immune response of lymphocytes via the expression of cytokine and chemokine receptors. The peak of GCs produced at the active phase enhances T-cell migration into lymphoid tissues via IL-7R and CXCR4, and this accumulation of T cells promotes priming against bacterial infection. Furthermore, clock genes and adrenergic receptors contribute to the accumulation of T and B cells in lymphoid tissues at the active phase. These effects drive the diurnal oscillation of the lymphocyte distribution, bacterial rejection and humoral immunity.

Because GCs enhance the differentiation of T_h2 cells, IL-4 production from Tfh cells and IL-7R induction in memory T_h2 cells, GCs also contribute to the humoral immune response and maintenance of memory T_h2 cells. GCs induced by DR may collect and maintain memory CD8 T cells in the bone marrow, which helps trigger secondary responses against infection.

In contrast, excessive stress induces high and sustained levels of GCs, which may cause inflammation via T_h17 cells. These phenomena imply that physiological levels of GCs support the survival and response of lymphocytes, whereas pathological levels may induce inflammation and autoimmune diseases. Thus, GCs have both negative and positive functions in the immune system depending on their concentration and duration. Further studies are needed to reveal the mechanism in detail for how GCs enhance inflammation and autoimmunity via interactions with circadian rhythms and the sympathetic nervous system.

Funding

This work was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Numbers 16K15288 (K.I.) and 18K15184 (A.S.). K.I. was supported by a grant from the Naito Foundation and by a grant from the Uehara Memorial Foundation. A.S. was supported by a 2016 grant from the Shimizu Foundation for Immunology and Neuroscience, by a grant from the Takeda Science Foundation and by a grant from the Ichiro Kanehara Foundation for the Promotion of Medical Sciences and Medical Care for 2018. This work was also supported by the Joint Usage Research Center program of the Institute for Frontier Life and Medical Sciences, Kyoto University.

Conflicts of interest statement: the authors declared no conflicts of interest.

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