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The Potential of Circadian Realignment in Rheumatoid Arthritis

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Abstract

In this short review, we discuss evidence supporting the modulation of peripheral circadian systems as a therapeutic strategy for rheumatoid arthritis (RA). We first review the role of proinflammatory cytokines and oxidative stress, two of the primary mediators of chronic inflammation in RA, and their regulation by circadian clock machinery. We further highlight the role of environmental and metabolic signals in regulating the central and peripheral circadian clocks, with an emphasis on seasonal variations in photoperiod and rhythmic metabolic input, respectively. Finally, we hypothesize that the entrainment and realignment of peripheral clock rhythms have the ability to modulate these mediators, improving clinical outcomes in RA patients. Our discussion emphasizes the use of light therapy and time-restricted feeding for entraining peripheral clocks either via the entrainment of the central circadian clock in suprachiasmatic nuclei (SCN) or directly by uncoupling the peripheral circadian clocks from SCN. In doing so, we highlight the use of nonpharmacologic interventions as a potential strategy for improving clinical outcomes in chronic inflammatory conditions such as RA.

Keywords

rheumatoid arthritis; proinflammatory cytokines; circadian realignment; time-restricted feeding; seasonality

I. THE PATHOLOGY OF RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a systemic autoimmune disease primarily characterized by joint inflammation, resulting in joint damage and loss of function. Recent surveys estimate that >1.5 million American adults (aged 18 and over) have RA,¹ creating a multifaceted societal burden with an economic cost, accounting for hospitalization and loss of work, estimated to be almost \$40 billion annually in the United States alone.²

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Synovial inflammation, hyperplasia, and the production of antibodies, cartilage, and bone destruction are characteristic of RA,³ and cluster of differentiation 4 (CD4⁺) T cells, B cells, and macrophages are the primary cellular effectors of synovitis in RA. These infiltrate the synovial membrane and release cytokines, matrix-degrading enzymes, metalloproteinases, prostaglandins, reactive oxygen intermediates, and proteases that cause synovitis and destroy articular structures.⁴ Anticyclic citrullinated peptide (CCP) antibody positive patients who have severe, active disease often have extra-articular organ involvement, which is associated with increased mortality. RA is associated with a high risk for development of cardiovascular disease, susceptibility to infections, depression,⁵ reduced life expectancy,⁶ and significant socioeconomic burden.² Disease pathogenesis is thought to involve complex interactions between both genetic and environmental factors.³ Although genome-wide analyses have identified specific genes (such as Major Histocompatibility Complex, Class II, DR Beta 1 [HLA-DRB1]) that are involved in immune regulation among RA patients, environmental interactions (such as smoking and photoperiod) have also been implicated in the pathogenesis of RA.^{7,8} A higher incidence of RA among females has also been documented³ as well as latitude-dependent stratification of the disease.⁹ Despite recent advances, a substantial molecular- and systems-level understanding of the mechanisms underlying the onset and progression of disease pathology is yet to be developed.

A striking feature of RA pathophysiology is the circadian variation in the manifestation of disease symptoms, with patients suffering from increased stiffness, joint pain, and functional disability in early morning hours.¹⁰ The variation in symptom severity is correlated with circadian production of biomarkers such as proinflammatory cytokines and endogenous glucocorticoids.¹⁰

A. Inflammatory Mediators of RA

1. Proinflammatory Cytokines—Inflammation-induced synovitis and joint damage in RA are mediated by a number of cellular and soluble factors.¹¹ Cytokines, however, are the most important molecular mediators in rheumatoid pathobiology, functioning in overlapping, synergistic, and inhibitory capacities and initiating and establishing a state of chronic inflammation.¹² Synovitis and joint damage are largely facilitated by macrophage-derived cytokines, particularly, interleukin (IL)-1 β , IL-6, and tumor necrosis factor (TNF)- α ,¹² in both RA as well as in animal models of the disease.¹³ These cytokines induce the production of matrix-degrading neutral proteases in synovial fibroblasts, osteoclasts, and chondrocytes, leading to cartilage, bone, and periarticular tissue destruction. Recent investigations have also established the presence of T-cell cytokines. Although RA is primarily considered to be a T helper (Th)-1 cytokine-mediated disease, synovial specimens of patients exhibit highly heterogeneous cytokine profiles, with Th-1, Th-2, Th-10 cytokines being detected.¹⁴ Additionally, immune cell differentiation and maturation in the rheumatoid synovium are also driven by cytokines.

Cytokines have both local and systemic effects. Locally, they up-regulate the production of adhesion molecules on endothelial cells, enhance the migration of leukocytes to the inflamed synovium, contribute to synovial vascularization, and augment the production of reactive oxygen species (ROS), reactive nitrogen intermediates, and prostaglandins.¹² Systemically,

cytokines induce the production of acute phase proteins in the liver. These cytokines are largely anti-inflammatory, such as IL-1 receptor antagonist (IL-1Ra). Other cytokines, such as IL-6 and IL-11, produce both proinflammatory and anti-inflammatory effects. Moreover, the cytokine network is also self-regulated via the production of cytokines such as IL-10 that have anti-inflammatory effects.¹²

TNF- α is a potent autocrine and paracrine inducer of proinflammatory cytokines, including IL-1, IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor.¹⁵ Excessive TNF- α production is observed at the site of inflammation in both animal models and human subjects, and its inhibition has shown to reduce disease severity in RA clinical trials.¹³ Additionally, TNF- α indirectly participates in the feedback inhibition of inflammation by promoting glucocorticoid secretion via the activation of the hypothalamic-pituitary-adrenal (HPA) axis.¹⁶

Substantial concentrations of both IL-1Ra and IL-10 have been found in the rheumatoid synovium, and several members of the IL-1 superfamily have been implicated in the pathogenesis of RA. IL-1 consists of two inflammatory agonists, IL-1 α and IL-1 β , along with the naturally occurring IL-1Ra.¹² IL-1Ra, competitively binds to the IL-1 receptor but fails to activate an inflammatory response, thus inhibiting the proinflammatory effects of IL-1. The importance of IL-1Ra in controlling inflammation has been established in a number of animal models of inflammatory disease. Immunohistology indicates that IL-1 is present in 90% of cells in the cartilage-pannus junction, with most being macrophages. Additionally, 65% of the chondrocytes in the articular cartilage layer adjacent to the pannus also present IL-1. Moreover, <10% of the cells in these locations present IL-1Ra.¹² The importance of this balance between proinflammatory and anti-inflammatory cytokines in RA pathogenesis has been recognized.¹⁷ Transgenic mice deficient in IL-1Ra production have a faster onset of collagen-induced arthritis (CIA) with increased severity, whereas those with augmented IL-1Ra production are more resistant to CIA.¹⁸

2. Oxidative Stress in RA—ROS produced by cells in response to various physiological and environmental stimuli are critical mediators of the immune response. ROS produced by phagocytes are thought to be important for the priming of the immune system and mounting an effective inflammatory response.¹⁹ ROS exposure has been known to activate phagocytic neutrophils and macrophages via the nicotinamide adenine dinucleotide phosphate-oxidase system.²⁰ On the other hand, it has been observed that T cells become hyporesponsive to growth and apoptosis stimuli when exposed to oxidative stress.²¹ ROS have also been implicated in increasing the risk of developing autoimmune diseases, due to the correlation between oxidative stress and associated inflammatory disease activity in investigations of systemic lupus erythematosus as well as RA.¹⁹ Analyses of oxidative stress in synovial fluid and synovial tissue in RA have revealed oxidative damage of cartilage tissue, extracellular matrix components,²² and DNA.²³ Furthermore, ROS have been associated with mutations in the tumor-suppressor gene *p53* in RA fibroblast-like synoviocytes (FLS) that may partially explain their modified phenotype and hyporesponsiveness to apoptotic signaling.²⁴ Free radicals are also believed to mediate the inflammatory response in combination with proinflammatory cytokines. For instance, the release of peroxide ions by osteoclasts, which contributes to cartilage and bone degradation, is significantly enhanced in the presence of

proinflammatory cytokines.²⁵ Consequently, inhibition of proinflammatory cytokines is linked to a decrease of ROS in CIA mouse models and vice versa.^{26,27}

The prevailing oxidative stress is possibly caused by a defective antioxidant response that may lead to the role of ROS in RA pathogenesis. Recent investigations have identified the significant role of the transcription factor, nuclear factor erythroid 2–related factor 2 (Nrf2) in regulating the antioxidant defense system and possibly the anti-inflammatory response in RA.^{28,29} It was recently shown that Nrf2 signaling is up-regulated in synoviocytes isolated from joints of both RA and CIA mice. Moreover, the severity of cartilage damage, oxidative damage, and the incidence of spontaneous fractures was greater in Nrf2 knockout mice than in wild-type controls,²⁹ whereas Nrf2 deficiency accelerated the induction of the disease with an enhanced proinflammatory response associated with increased oxidative stress.²⁸

II. RA AND CIRCADIAN RHYTHMS

In mammalian organisms, the circadian machinery (i.e., the biologic time-keeping mechanisms that maintain 24-h oscillations in cellular and physiological processes) is organized as a hierarchical, interconnected network of clocks. The peripheral clocks are distributed across all cells and are synchronized within and across tissues and organs. The master, or central, clock in SCN is mainly linked to a light/dark cycle and synchronizes the network of peripheral clocks by controlling timing of feeding and activity cycles.^{30,31} The central and peripheral circadian clocks regulate interactions among endocrine, immune, autonomic, and central nervous systems³² in a precise temporal manner and coordinate the diurnal variation of important mediators of rheumatoid pathophysiology. These mediators include immune cell infiltration, the expression of proinflammatory cytokines IL-1 β , IL-6, and TNF- α ; neuroendocrine hormones, cortisol (corticosterone in rodents) and melatonin, mediators of oxidative stress, and neurotransmitters such as norepinephrine.³⁰

The ubiquity of circadian rhythms indicates that these periodic processes are not simply a passive adaptation to external stimuli but, rather, evolutionarily conserved because they confer adaptive advantages by means of anticipatory control mechanisms.³³ Circadian rhythms have a direct impact on the systemic regulation of energy metabolism and immune,³⁴ hormonal,³⁰ and cardiovascular functions.³⁵ Their chronic disruption increases susceptibility to inflammatory and metabolic disorders,^{34,36} indicating a protective role for circadian rhythms against incidence of disease.

In healthy subjects, these rhythms are tightly coupled to one another and appropriately regulate the core physiological processes that maintain homeostasis. However, under conditions of chronic inflammation, as seen in RA, it is believed that an imbalance in these compensatory mechanisms results in the onset and prevalence of disease symptoms.^{12,37} Moreover, the imbalance might also be responsible for the incidence of systemic comorbidities and extra-articular manifestations that are associated with RA.^{38,39} Therefore, although suppression of biological rhythms is an energy-preserving mechanism that is beneficial under stress,⁴⁰ the effects of long-term disruption of rhythms are pathologic,⁴¹ leading to worse outcomes and delayed recovery.⁴² Recent evidence supported the potential of using circadian systems as a therapeutic target.⁴³

The significance of circadian rhythms has become apparent in many chronic inflammatory diseases, including RA. Circadian variation of clinical symptoms, such as joint pain and morning stiffness, has been well documented in RA patients and serves as a diagnostic indicator. Disease activity is high in the early morning hours and is milder in the evening.³² The circadian dynamics and phase relationships between proinflammatory cytokines and cortisol (the balance between inflammatory mediators and anti-inflammatory processes) have served as the basis for explaining the circadian manifestation of RA signs and symptoms, because they are well correlated with the daily aggravation of disease activity.¹⁰ Consequently, the circadian dynamics between the HPA axis and key immune system mediators (endogenous glucocorticoids, proinflammatory cytokines, and hormones such as melatonin) have received much research attention.

In healthy individuals, the expression of the proinflammatory cytokines TNF- α and IL-6 peaks during the end of the rest phase (~3:00–6:00 am) and is inversely related to cortisol's rhythms,⁴⁴ but RA patients with mild to moderate disease activity exhibit peak cytokine levels later in the morning hours (i.e., the levels are phase delayed). In addition, cytokine levels remain elevated, by up to tenfold in RA patients for a longer duration, resulting in the broadening of TNF- α and IL-6 peaks.¹⁰ This is summarized schematically in Fig. 1A. Increased cytokine expression in response to inflammation activates the HPA axis, leading to increased production of corticotropin-releasing hormone, adrenocorticotrophic hormone, and subsequently cortisol, which eventually modulates the expression of the proinflammatory cytokines. Cortisol and its glucocorticoid analogs, such as dexamethasone, are considered to be immune “permissive” at low concentrations because they up-regulate proinflammatory receptors (IL-1R1, the gp130 subunit of the IL-6 type receptors, IFN- α R, IFN- γ RI, IFN- γ RII, and TNF receptor family members)⁴⁵ but also immune “suppressive” since, at higher concentrations, they inhibit T-lymphocyte activity and the transcription of numerous proinflammatory cytokine genes.⁴⁶

Although the circadian rhythm of cortisol remains largely unperturbed in RA patients with mild to moderate disease activity, its rhythm can be significantly disrupted in patients with high disease activity. Elevated cortisol levels in patients with high RA activity are associated with a blunted cortisol diurnal rhythm, whereas salivary cortisol levels in patients with high disease activity were higher in the inactive phase when compared to controls (Fig. 1B).^{10,47–49} It is widely believed that cortisol levels are inadequately low in response to prevailing proinflammatory cytokine levels—a phenomenon termed adrenal insufficiency.⁵⁰ Similar observations, including phase shifts, have been reported with respect to corticosterone rhythms in animal models of adjuvant-induced arthritis.^{51,52} It has been postulated that circadian coupling between neuroendocrine and immune system mediators has been evolutionarily conserved to optimize temporal energy requirements.¹⁰ Thus, the observed misalignment or uncoupling between the circadian characteristics of the cytokines and HPA axis hormones in RA might represent a pathological adaptation to the chronic disease state facilitated by the relevant evolutionarily conserved pathways. Therefore, it is apparent from the above discussion that the diurnal rhythms of the HPA axis hormones are closely linked to those of the proinflammatory cytokines and are of prime importance in RA pathophysiology.

A strong association between circadian rhythms and oxidative stress has been found in a number of diseases such as cancer, diabetes, and neurodegenerative disease.⁵³ To our knowledge, no studies have yet tried to elucidate the link between oxidative stress and circadian rhythms in RA pathophysiology. However, it has been argued that in diseases such as RA, with alterations in both circadian rhythms and anti-oxidant signaling, patients may benefit from treatments targeting both of these components of disease pathophysiology together.⁵³

III. REGULATION OF CYTOKINES AND OXIDATIVE STRESS RESPONSE BY COMPONENTS OF THE MOLECULAR CLOCK

Multiple studies have explored the regulatory links between circadian clock components and inflammatory mediators.^{54,55} Immune cells are known to have a functional molecular clock and exhibit circadian cytokine expression independently of systemic cues, strongly suggesting circadian clock control of proinflammatory cytokine expression.⁵⁶ For instance, Keller et al.⁵⁷ found that lipopolysaccharide (LPS)-stimulated murine splenic macrophages exhibited circadian rhythms in TNF- α and IL-6 expression, independently of systemic glucocorticoid concentrations or circadian fluctuations in the cellular constitution of the spleen cells.⁵⁷ Genome-wide transcriptional analysis revealed that important regulators of the LPS-induced response, that include components regulating LPS binding to toll-like receptor 4, components of the mitogen-activated protein kinase pathway controlling multiple downstream levels including transcription factor activation (e.g., ERK1 [extracellular signal-regulated kinase 1]), and components regulating cytokine transcription (NF- κ B [nuclear factor kappa-light-chain-enhancer of activated B cells], JUN [Jun Proto-Oncogene], FOS [Fos Proto-Oncogene]), mRNA stability (ELAVL1 [ELAV Like RNA Binding Protein 1], SFPQ [Splicing Factor Proline And Glutamine Rich]), and protein processing (ADAM17 [ADAM metalloproteinase domain 17]), were regulated by circadian clock genes.⁵⁷ These results strongly suggest that an internal peripheral circadian clock additionally regulates the inflammatory response of immune cells. Moreover, the expression of core clock components, such as cryptochrome (CRY), REV-ERB α (or nuclear receptor subfamily 1, group D, member 1 [NR1D1]),⁵⁸ Period (PER),⁵⁹ and aryl hydrocarbon receptor nuclear translocator-like protein 1 (BMAL), has been shown to regulate proinflammatory cytokine expression both *in vitro* and *in vivo*. Absence of CRY led to increased expression of proinflammatory cytokines such as IL-6 and TNF- α in *in vitro* studies with fibroblasts and macrophages.⁵⁴ This is supported by *in vivo* studies in which CRY deletion resulted in increased cytokine expression and exacerbated disease symptoms in mouse models of RA.^{54,60} Another core clock component, Bmal1, is also shown to have an anti-inflammatory function in monocytes and macrophages when challenged with an immune stimulant.^{55,58} Additionally, TNF- α and IL-1 β can suppress the expression of the circadian gene *Per* as well as the clock-controlled genes *D site of albumin promoter [albumin D-box]-binding protein (Dbp)*, *thyrotroph embryonic factor (Tef)*, and *hepatic leukemia factor (Hlf)*.^{61,62} Haas and Straub²⁵ also found that TNF- α inhibited the expression of *Clock*, *Per1*, and *Per2* in synovial tissue cells isolated from osteoarthritis patients, whereas TNF- α and IL-1 β increased the expression of these genes in RA synoviocytes.²⁵ Persistent disruption of the circadian rhythms has been closely associated with diseases in which chronic inflammation

is among the principal pathological features,⁶³ and elements of the immune system implicated in the chronic inflammation have been shown to be under circadian control. Kouri et al.⁶⁴ found clock gene expression to be disrupted in synoviocytes isolated from RA patients, with increased expression of REV-ERB α and the relative phase differences between BMAL1 and PER1 to be altered.

A number of studies demonstrate that clock genes can regulate the expression of key mediators of the oxidative stress response, such as *Nrf2*.^{65,66} For example, *Bmal1*-deficient mice exhibit increased ROS accumulation through an NRF2-dependent mechanism,⁶⁵ whereas *Per* deficiency increased susceptibility to hydrogen peroxide-mediated oxidative damage in *Drosophila melanogaster*.⁶⁷ Circadian clock associated 1, a core clock regulator, has been shown to diurnally regulate the expression of ROS genes.⁶⁸ The expression of the core circadian genes is also linked to ROS accumulation and sensitivity to oxidative damage. Furthermore, it has been shown that oxidative stress can reset the circadian clock through the *Nrf2* and NF- κ B signaling pathways, among others.⁶⁹

Given the importance of the bidirectional cross-regulating function of the molecular clock machinery and major antioxidant and inflammatory signaling pathways, a number of studies capitalized on the effects of timed pharmacologic intervention as a model for the management of chronic conditions.⁷⁰ Preliminary studies indicate that treatment with prednisolone was much more effective when given during the rising phase of TNF- α (2:00 am) rather than in the descending phase (7:30 am).⁷¹ Such studies highlight the significance of circadian cross regulation of the neuroendocrine and immune systems. Thus, the interplay between the circadian clock components and the mediators of chronic inflammation is an important determinant of RA pathophysiology.

IV. CIRCADIAN CLOCK INTEGRATES ENVIRONMENTAL AND METABOLIC CUES

A. Photic Entrainment of the Molecular Clock and Seasonality as Immune Response Modulator

Complex multifactorial diseases such as autoimmune, cardiovascular, and psychiatric disorders are known to exhibit seasonal patterns in incidence and symptom severity.^{72,73} Seasonal cycles are also commonly observed in most acute infectious diseases.⁷⁴ In the case of autoimmune illnesses such as RA, it is hypothesized that the underlying physiological immune response shows considerable seasonal dependence that results in observed patterns of disease prevalence.

A number of rheumatic diseases exhibit seasonal variation.⁷³ Exacerbations in disease activity of RA, Wegener's granulomatosis, and systemic vasculitis are observed in the winter and spring months, whereas incidence of gout attacks is highest in the spring.⁷³ Accordingly, seasonal variation in the production of a number of self-reactive antibodies has been reported, including anti-Jo-1 and antinuclear recognition particle autoantibodies.⁷⁵ Seasonality is primarily associated with the length of the photoperiod; in temperate regions, the duration of the light phase in the light/dark cycle varies throughout the year. The

photoperiod, or length of the illuminated day fraction, exhibits seasonal fluctuations such that it increases between winter and summer and then decreases toward the winter season. Photoperiod is a potent entrainer of circadian dynamics and capable of regulating numerous seasonal physiological changes.⁷⁶ Electrophysiological studies on rodent hypothalamic explants concluded that photoperiodic information is encoded in SCN neuronal activity.^{77–80} More compressed neuronal electrical activity observed in shorter photoperiods promotes greater synchrony among the neuronal population and results in higher-amplitude SCN electrical rhythms. Given the ability of SCN to entrain circadian dynamics to the daily light/dark cycle and their reputed role in moderating photic signal transduction to the periphery by a variety of mechanistic pathways, it is likely that SCN seasonal encoding of photoperiod changes may account for a variety of observed seasonal alterations in endocrine, immunological, and molecular activity.

SCN-projecting retinal ganglion cells (RGCs) present within the retina function as photoreceptors that communicate light/dark cycle information to SCN.⁸¹ The photic cues relayed to SCN are then translated into neuronal, metabolic, or hormonal signals that subsequently coordinate the timing of various physiological processes such that they are in synchrony with the environment, displaying a periodicity that parallels 24-h daily fluctuations of light and darkness.⁸² As discussed in previous sections, humoral neuroendocrine mediators such as cortisol and melatonin that are known to display pronounced circadian rhythmicity⁸³ are in part regulated via SCN, because SCN-lesioned rats display a loss of the day/night variation in melatonin concentration⁸⁴ and elevated corticosterone levels.⁸⁵ Apart from humoral signaling, autonomic nervous system pathways relay photic information to the periphery. An electrophysiological study conducted using male Wistar rats found that acute light exposure enhanced efferent activity in the adrenal, hepatic, pancreatic, renal, and splenic branches of the splanchnic nerve and suppressed activity in the gastric, hepatic, and pancreatic branches of the vagus nerve.⁸⁶ In contrast, both SCN-lesioning and adrenal denervation abolished the photic stimulatory responses, again underscoring the involvement of the SCN-sympathetic nervous system in relaying light information to the periphery.⁸⁷

Notably, seasonal variation of photoperiod has been found to influence the circadian rhythms of cortisol, melatonin, and proinflammatory cytokines, such as TNF- α . In comparing the effect of different winter photoperiods on the circadian rhythms of various neuroendocrine mediators in RA patients from regions of different latitude, Cutolo et al.⁷ found the circadian peak of melatonin and TNF- α to be significantly higher in RA patients from a region with higher latitude (shorter photoperiod) in comparison to age-matched controls. No seasonal variation in cortisol was observed in this study on RA patients. Although there is a dearth of large cohort studies on the effect of seasonality in RA patients, a number of large studies have found cortisol levels in healthy subjects to be highest in months of winter and early spring and lowest in summer months.^{88–90} Given its immunomodulatory roles and circadian rhythmicity, cortisol can therefore indirectly entrain immune activities such as cytokine production dynamics to the external light/dark cycle.⁹¹

In a recent study by Hand et al.⁹² on CIA mice, diurnal variation in symptomatic indicators of disease activity (such as paw edema) as well as inflammatory cytokine expression was

demonstrated, and a functional circadian clock was found in peripheral immune cells. Proinflammatory markers and severity of disease symptoms showed a marked increase during the light phase and decreased through the dark phase. Furthermore, exposure to constant light conditions disrupted circadian clock gene expression and resulted in increased proinflammatory cytokine expression and disease activity, accompanied by a loss in the diurnal variation in symptom severity. Similarly, in another study, exposure to constant darkness was found to reduce acute gastric and colonic inflammation in rats with acetic acid colitis and ethanol-induced gastric ulcers.⁹³ Considering the importance of light in regulating both central (SCN) and peripheral circadian clock expression as well as important inflammatory signaling pathways, the use of nonpharmacological light-therapy-based strategies (such as exposure to artificial light at specific times of the day and to varying photoperiods) may have clinical benefit for treatment of chronic inflammatory diseases such as RA. We hypothesize that a realignment of the circadian rhythms of neuroendocrine and immune mediators, such as cortisol, and various proinflammatory and anti-inflammatory cytokines may enable the host to resolve the chronic inflammatory response and lead to amelioration of RA symptoms. Such photic treatments have previously been used for the treatments of sleep disorders, in which exposure to bright light has been found to reset the phase of misaligned circadian rhythms when administered shortly before awakening or shortly before sleeping.⁹⁴ In a study by Song et al.,⁹⁵ patients with seasonal affective disorder (SAD), a condition primarily associated with photoperiod-induced circadian phase shifts in important immunomodulatory mediators, had significantly enhanced Th1-type inflammatory responses in winter months. Bright light therapy during the course of 4 wk was found to normalize the inflammatory response in these patients with SAD by decreasing the production of proinflammatory cytokines IL-1 β , TNF- α , and IFN- γ ; suppressing macrophage activity; increasing the release of anti-inflammatory cytokine IL-10 in mitogen-stimulated blood; and reversing the reduced lymphocyte proliferation and IL-2 production found in these patients.⁹⁵

B. Metabolic Modulation of Antioxidant and Inflammatory Responses

A growing body of research demonstrates a crucial link between immune and metabolic systems, with many critical immune regulatory elements located within an array of metabolic signaling networks.⁹⁶ Critical activities such as the proliferation, activation, and differentiation of immune cells are dependent on the metabolic state of these cells,⁹⁷ whereas metabolic signaling mediators regulate both housekeeping and effector functions of immune cells and the immune system.⁹⁸

Mammalian target of rapamycin (mTOR) is a serine/threonine kinase involved in integrating metabolic cues in the form of amino acids and growth factors,⁹⁹ whereas the sirtuin (SIRT) family is a set of Nicotinamide adenine dinucleotide (NAD) +-dependent class-III histone deacetylases implicated in regulating a number of critical physiological processes, including inflammation. Both of these evolutionary conserved signaling molecules have recently been the subject of much research effort for their role in immune cell metabolism.^{99,100}

mTOR links nutrient availability with cellular function by promoting *de novo* protein, lipid, and nucleotide synthesis in the presence of an adequate supply of oxygen, amino acid,

glucose, and growth factors.¹⁰¹ mTOR signaling has been implicated in the activation of T cells of the adaptive immune system by enabling them to switch from a catabolic to anabolic state via the downstream activation of the proteins involved in glycolysis, nutrient uptake, and the pentose-phosphate pathway.⁹⁹ Evidence suggests that mTOR can also regulate the innate immune system. Cytokine and immunologically relevant growth factor receptors promote mTOR activation,⁹⁹ and mTOR inhibition promotes proinflammatory cytokine (IL-12, IL-1 β) expression via NF- κ B activation and suppresses anti-inflammatory cytokine (IL-10) expression via the inactivation of signal transducer and activator of transcription (STAT) 3.^{102,103}

The SIRT family functions as diet-sensitive, anti-ageing proteins that can regulate metabolism across a number of tissues. Similar to mTOR, SIRT1 and SIRT6 also regulate the catabolic to anabolic shift during T-cell activation by promoting fatty acid oxidation and inhibiting glycolysis.¹⁰⁴ Furthermore, SIRT6 is a prominent inhibitor of glycolysis, and it has been observed that SIRT6 knockout mice die of hypoglycemia and persistent inflammation. SIRT1 can suppress the transcription of a number of NF- κ B target genes,¹⁰⁵ and TNF- α treatment has been shown to induce SIRT1 expression *in vitro*,¹⁰⁰ suggesting a role for SIRT1 in regulating cytokine expression.

mTOR and SIRT are also involved in bidirectional feedback loops with oxidative stress-related signaling pathways. Inhibition of the PI3K/AKT (AKT Serine/Threonine Kinase)/mTOR axis increases accumulation of ROS and augments KEAP1 (Kelch Like ECH Associated Protein 1)/NRF2 pathway activity,¹⁰⁶ and hydrogen peroxide, a major marker of oxidative stress, can inhibit mTOR signaling.¹⁰⁷ Similarly, conditions of oxidative stress lead to SIRT1 up-regulation and possible activation of SIRT3, and SIRT7 knockout increased sensitivity to oxidative stress in mice.¹⁰⁸

Several recent studies investigated the effects of mTOR and SIRT signaling in humans *in vitro* and animal models of RA. Inhibition of the mTOR signaling pathway led to a significant suppression of RA FLS invasion¹⁰⁹ and protected against osteoclast-mediated bone and cartilage loss.¹¹⁰ Overexpression of SIRT6 in a mouse model of CIA was found to suppress the activity of NF- κ B proteins, leading to inflammation and bone destruction.¹¹¹ SIRT1 expression is essential to the maintenance of cartilage homeostasis,¹¹² is upregulated in the RA synovium, and correlates with apoptosis resistance in RA synovial fibroblasts.¹¹³

Recent evidence has demonstrated that metabolism and food intake can regulate the expression of the circadian clock in peripheral tissues.¹¹⁴ Time-restricted feeding (tRF; i.e., restricting the time and duration of food availability without calorie reduction) has been shown to influence peripheral clock rhythms and enable the entrainment of molecular clocks in the periphery, likely independently of the central circadian pacemaker, SCN.¹¹⁵ Interestingly, feeding during the rest phase minimally affects SCN rhythmicity but reverses the phase of circadian clocks in peripheral tissues.¹¹⁶ Although such inversion of feeding patterns had beneficial effects on tumor growth in mice,¹¹⁷ reversing the feeding patterns in healthy animals compromised their response to subsequent trauma.¹¹⁸ Thus, tRF can uncouple SCN oscillators from those in the periphery, and physiological activities normally synchronized by SCN can be phase shifted to the time of food availability via metabolic

cues.^{115,119} Given that mTOR and SIRT are critical in integrating metabolic cues to modulate cellular function, one might suspect that tRF influences the signaling of these molecules. Indeed, a high-fat diet under a tRF regimen has been shown to reinforce mTOR and AMPK signaling,¹²⁰ oscillations of circadian genes, and expression of their target genes. tRF also uncouples mTOR circadian rhythms from the canonical circadian clock genes.¹²¹ Increased hypothalamic mTOR expression also negatively regulates food intake and body weight.¹²² In a study by Oyama et al.,¹¹⁸ reversal of feeding patterns led to a decrease in the expression of SIRT1.¹¹⁸ Moreover, both mTOR and SIRT1 can directly regulate, and can be regulated by, the expression of the core clock components, establishing a bidirectional feedback by which metabolic signals might be relayed to the circadian clock.^{123–125}

It has been suggested that interventions that take advantage of the metabolic networks involved in the immune response could improve the inflammatory features in RA.¹²⁶ Thus, as depicted schematically in Fig. 2, it is hypothesized that rhythmic metabolic inputs that can modulate the expression of these key metabolic signaling molecules could subsequently entrain the expression of core clock components. This might eventually lead to a realignment of the disrupted rhythmic expression of antioxidant and inflammatory mediators in RA and enable the host to mount a beneficial and self-limiting immune response at least in the short term, thus contributing to an overall improvement in disease symptoms and comorbidities.

V. CONCLUDING REMARKS

In this brief review, we highlight the contribution of immune system mediators and key redox signaling pathways to RA pathophysiology. Furthermore, we underscore the central position of the circadian clock in coordinating the functions of these signaling pathways. We hypothesize that the restoration of disrupted circadian rhythms in RA may alleviate disease symptoms and lead to an improved host response. Moreover, we propose that nonpharmacologic interventions in RA may possess significant potential in reestablishing circadian rhythmicity and providing therapeutic benefit. Such a treatment strategy would take advantage of the inherent physiological feedback systems of the host to alleviate disease symptoms. This is in keeping with the concept of allostasis, which, having recently emerged as a useful paradigm,¹²⁷ suggests that health can be described by a state of dynamic equilibrium aimed at restoring predictive fluctuations and broader defense mechanisms.¹²⁸ It implies that the body's physiological systems integrate information from multiple temporal and spatial scales to predictively optimize function. Therefore, the allostatic viewpoint suggests that the brain coordinates both low-level peripheral mechanisms as well as higher-level behaviors. Accordingly, this paradigm advocates a more holistic approach toward understanding disease pathology and treatment rather than solely emphasizing dependence on pharmacologic restoration of low-level mechanisms, which may interfere with functioning of broader systemic mechanisms already engaged as a result of the host's endogenous response to the disease. It has been observed that diseases such as RA have strong systemic components that predispose or contribute to development of disease.¹²⁸ Therefore, interventions that account for these broader systemic regulatory mechanisms in the host may be beneficial in treating complex diseases that are systemic in nature. However, although the ability to modulate immune signaling pathways with metabolic and

environmental inputs via the core clock machinery seems promising in principle, the efficacy of such a nonpharmacologic intervention is yet to be determined.

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FIG. 1.

(A) A summary of the circadian features of disease symptoms and proinflammatory cytokines in RA patients. (B) Schematic comparison of the circadian dynamics of cortisol in patients with RA and healthy controls.

FIG. 2.

(Top) RA is thought to arise from an imbalance in multiple compensatory pathways involved in immune, oxidative stress, and neuroendocrine signaling, resulting in primary symptomatic features, such as synovitis and the incidence of a host of systemic complications including cardiovascular disease and metabolic syndrome. This imbalance could result in peripheral clock disruption, which can give rise to altered neuroendocrine, immune, and metabolic signaling and further contribute to the development of systemic complications. (Bottom) Metabolic and photic inputs such as tRF and photoperiod-based intervention can realign the peripheral circadian clocks and regulate the inflammatory response via various signaling pathways, mediating cross communication among neuroendocrine, metabolic, autonomic nervous, and immune systems. This could potentially enable the host to restore allostatic balance, leading to amelioration of disease symptoms and improvement in systemic complications.