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## Molecular Clock and Autoimmune Diseases; An Approach to Rheumatoid Arthritis; A Review

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### A B S T R A C T

Circadian clock refers to a biological cycle that fluctuates in a period of ~24 hours. These cycles are supported by a molecular clock and provide a temporal time-related matrix that ensures the collocation of homeostasis processes with the course of environmental changes. Here in this mini-review, we are going to summarize all recent finding from the last five years till date in the field of circadian and evolutionary clock research in approach to rheumatoid arthritis as the world's most prevalence autoimmune disease with rate of over 76 million in world population and prevalence of near 0.6% of US which is almost 1.29 million people in the year 2015. Rheumatoid arthritis shows a verity of symptoms besides morning stiffness and increased joint pain in the early morning. This morning joint and stiffness aca correlate to an elevated level of pro-inflammatory cytokines include interleukin-6. The circadian clock has a regulatory role in activity and expression of proteins and their gene which comes under cycle which takes part in autoimmune disease expression and progression, such as fat-derived adipokines and few nuclear receptors. Based on current knowledge which expanding each and every moment we know the pathways that how inflammatory responses regulated base on that working in a new age in the treatment of autoimmune disease especially rheumatoid arthritis.

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### Methodology

One of the objectives to write this mini-review was to summarize all recent techniques in understanding and diagnosis of rheumatoid arthritis (RA) besides treatment options and

correlate this to the main phenomena. The RA is the world's highest prevalent autoimmune disease, based on WHO data released and Arthritis Foundation-USA (Leverone, D., & Epstein, B. J. 2010).

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First covered both the circadian clock and rheumatoid arthritis from A to Z, from their basis to the advanced molecular level so that it will be clear for the reader what we going talk about. For this purpose, all related data from the last 6 years from 1<sup>st</sup> Jan 2012 to 30th Dec 2018 has been retrieved from Pubmed and Scopis, repeated, overlapped or unrelated articles to the topic have been removed and rest considered for the following review.

## Introduction

Molecular clock or circadian rhythms are behavioral and physiological cycles in humans which have been noticed since 400 BC and also observed and reported in animals and plants. Peripheral clock in coordination with the central clock creates rhythmic expressions of a gene in specific organs or tissues on different bases either physiological or behavioral in responses to changes in the environment. Anyhow by the world going toward more and more modernization and industrialization, many activities interrupt the normal routine of endogenous homeostasis in the circadian clock. This changes which affected daily routine and lifestyle has direct link to increased rate of cancer and many other diseases which endanger human being (Fu, L., & Kettner, N. M. 2013) Studies and trials on animal models and human have shown that progress and development of cancer is so tightly related to loss of homeostasis and circadian clock in term of immune system functionality, energy balance and aging which are sponsored by cellular functions which are vital to suppress tumors via interfering such as cell metabolism, DNA damage responses, and also proliferation (www.painpathways.org/matt-iseman/).

### 1. Rheumatoid Arthritis:

First, let discuss rheumatoid arthritis (RA) and its symptoms, diagnostics and different approaches in treatments then we'll talk about its molecular causes and that how it is related to gene clock. In primary stages, an individual will not see joint swelling or redness but another feeling may appear

like: joint pain and stiffness in the morning which persists for more than 6 weeks and not relieving in less than 30 min. the other complains can be list out like more than one joint affected, small joints such as wrists and other small joints in hand and feet included and affect both sides of the body; for example, both wrists or both knees. Besides pain individuals may experience fatigue, light fever and loss of appetite (<https://www.ra.com/>) Symptoms in RA at the beginning can be episodic and if the gap between each appearance reduced and symptoms consistently remain for days to even months will be called a flare. Persist inflammation will cause a problem all over the body like **Eyes:** keratoconjunctivitis sicca, subconjunctival hemorrhage, photophobia and hypermetropia. **Mouth:** Xerostomia, gingivitis **Skin:** Rheumatoid nodules **Lungs:** Pneumonitis which can lead to dyspnea. **Blood vessels:** Vasculitis which can lead to neuropathy or in other organs like the skin. **Blood:** Anemia (Nkemdilim, O. C, and *et al*, book).

#### 1.1. RA Treatment and Medication:

The first rule in RA treatment is the earlier, the better. So the first step will be to stop or reduce inflammation in the shortest time possible. After that, the doctor will work on controlling joint damage by preventing or slowing it down. There is a different type of medicines for treatment or control of RA. Some of them advised symptomatic management and ease pain and others to slow down the course of illness and suppress the progress of structural damage. Drugs like NSAIDs (Nonsteroidal anti-inflammatory drugs) are the first choice in pain management such as ibuprofen, ketoprofen, naproxen sodium or diclofenac sodium or potassium. For patients who have stomach ulcers, celecoxib is the safest option which is designed to be stomach-friendly. These medications available in the form of tablets, capsules or patches or even in the form of gels for topical applications directly on joints. The other families of drugs which help in slowing down the progress of the disease, are corticosteroids such as prednisolone, methylprednisolone and prednisone. They are

rapid-acting anti-inflammatory medication. They take RA's damaging process compliant while hold back to DMARDs or NSAIDs takes responsibility and effect. DMARDs (Disease-modifying anti-rheumatic drugs) like HCQ (Hydroxychloroquine), Azathioprine, sulfasalazine, leflunomide, cyclophosphamide, and Methotrexate can be taken orally or in the form of an infusion or injection to be administered. A new approach in modern treatment includes JAK inhibitors which are a subcategory of DMARDs and block JAK's (Janus kinase) pathways, which is included in the human's immune system and responses. Drugs like: Ruxolitinib and Tofacitinib are two famous examples which are taken by mouth. There is no need for surgery in RA treatment unless surgery for replacing the damaged joint. Knee and hip replacement are more common (Kumar, P., & Banik, S. 2013).

## 2. Molecular Pathways and Treatment Options:

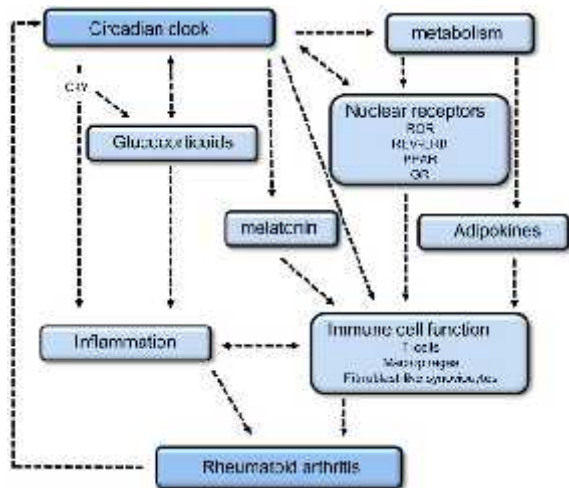
Brief relation between molecular clock and autoimmune disease in approach to RA, the world's first and most autoimmune disease with the highest prevalence. The first in line class of medication which advised blocking output of genes by-product is synthetic glucocorticoids like Dexamethasone and Prednisone. Hence long usage of synthetic glucocorticoids is associated with number of side effects such as metabolic imbalance, risk of diabetes mellitus (DM) and immune suppression. Therefore with the help of molecular biologists and molecular medicine specialists, a new line of the drug is designed likes PPARs (peroxisome proliferator-activated receptors) and RORs (Retinoic acid receptor-related orphan receptors) which had significant results in clinical trials and now in clinical use. These medications contributed to pathogens in RA. For example, Thiazolidinediones from a large family of synthetic PPAR gamma ligands which have anti-diabetic properties too that can be used in type 2 DM management (Bougarne, N., and *et al* 2018).

## 3. Novel Therapeutics by Targeting Circadian Clock Pathways:

A complete understanding of the pathway that how circadian clockworks and regulate the inflammatory pathways, give novel therapy options for treatment of autoimmune diseases, RA and another type of inflammatory abnormalities. Provide its role in T cell function, ROR can be one target. A new and noble synthetic ligand (SR1001) synthesized for alpha ROR and gamma ROR which restrain differentiation of TH17 cell and also decrease the gravity of rodent experimental autoimmune acute disseminated encephalomyelitis (ADEM), which is an autoimmune disease caused by TH17 cell (Solt, L. A., Kumar, and *et al* 2011). Studies and clinical trials have been elucidating that omega-3 fish oil and turmeric can have beneficial effects in the management of RA pains and morning stiffness (Laino, C. H. (2017, April), Zhang, Y., and *et al* 2018).

## 4. Immune System and Molecular Clock:

The circadian clock modulates different orientations of the immune system, which result, immune responses sometimes show assessable circadian variants. Many pieces of evidence highlighted the role and function of the circadian clock towards the immune system. Trials have suggested that the immune system of human cellular organelles starts inflammatory pathways that are precisely modulated by a molecular clock. This pathway includes mast cells, eosinophils, natural killer cells, basophils, macrophages and T lymphocytes. Still, the main cell lines that dominate molecular clock disease expression in rheumatoid arthritis persist unclearly. CD4+ T lymphocyte is the primary base in the rhythmic IL-6 secretion, which is known as the main intervener of rheumatoid arthritis with a fundamental function in support and disorders initiation. it has been determined that CD4+ T lymphocytes hold a molecular oscillator which gives rhythmic answers to activate stimuli, as a result, modify cytokine secretion and cell proliferation. Figure [1] (Bollinger, T., and *et al* 2011, Fortier, E. E., and *et al* 2011).



**Fig. 1: Connection between the Molecular Nature of the Immune System and Circadian Clock which Contribute to RA's Mechanism Online License Transfer (Gibbs, J. E., & Ray, D. W. 2013)**

## 5. Circadian Clock and RA:

Interruption of circadian clock's rhythm and RA in the latest research have shown that an interesting two-way connection amidst the inflammation and circadian. Any disturbance in the rhythmic function of the clock has an influence on the immune system hence can have a negative impact on RA pathogenicity. Vice versa, inflammation can directly modify the expression of genes of the clock (Coogan, A. N., & Wyse, C. A. 2008). Jet-lag is the best example that can explain the disruption of the circadian clock, an outcome of desynchrony amid the internal clock of body and environment, which consequent in the requirement for resetting of the clock. Depending on how many time zones you crossed by your flight and which direction it may take a few days for the body clock to resynchronize. Shift workers too have the same experience. These constant changes of working hours are can be health hazard and can lead to increase the number of chronic disorders like cancer, CVS diseases (cardiovascular system), MS (metabolic syndromes) including diabetes, hyperlipidemia and irritable bowel syndrome

(Wang, X. S., and *et al* 2011, Sosa, M. M. J. 2013). The endocrine system's circadian control had been linked to mediating the timing of signals from the central nervous system throughout the body. Hormones and to be exact two hormones have a role as circadian agents: melatonin and glucocorticoids. Both of them have a very important role in inflammation and mediating and regulation of immune responses and may play a vital role in RA pathogenesis.

### 5.1. Melatonin:

This hormone mainly secreted by the pineal gland but it will also have secreted in lesser amount by the retina, intestine, skin, Harderian Glands, leukocytes and bone marrow. The suprachiasmatic nucleus (SCN) maintains the synthesis of melatonin by suppression of the pineal gland's noradrenergic stimulation. Melatonin only synthesized and secrete during the night. Melatonin has a variety of roles in immune system responses. And it is also known as cytokines' pro-inflammatory modulator that suppresses the proliferation of synoviocytes which is a fibroblast-like structure and also maintains leukocyte function (Radogna, F., and *et al* 2010, Nah, S. S., and *et al* 2009). Fascinatingly, RA patients have fluctuated levels of circulating melatonin which can be core proof of melatonin action (Sulli, A., and *et al* 2002).

### 5.2. Glucocorticoids:

Endogenous anti-inflammatory agents called glucocorticoids (in human cortisol and in rodents corticosterone) circulating levels differ throughout the 24 hrs. In a circadian manner, its highest level is just before waking up in mammals. Unlike nocturnals, glucocorticoid's circulating level regulated by circadian clock via the neural connection between the hypothalamus's paraventricular nucleus and central clock of the suprachiasmatic nucleus (SCN), the exact central control site for the hypothalamic-pituitary-adrenal axis. Glucocorticoids can be seen everywhere throughout the body as their GR (glucocorticoids receptors) are ubiquitous, a transcription factor that is activated by a ligand, belonging to the

superfamily of the nuclear receptor. In RA patients, the normal high level of cortisol expresses nearly 40 min later after waking up in IL-6 levels (Perry, M. G., and *et al* 2009).

### 5.3. Glucocorticoids Receptors:

Glucocorticoid receptors protein has three isoforms including  $\alpha$ ,  $\beta$ , and  $\gamma$ , of which glucocorticoid receptor alpha is the most widely available isoform and present in most actions (Perry, M. G., and *et al* 2009). Furthermore, the circadian clock can do post-transcriptional alteration on glucocorticoids receptors protein and will affect its functions. This includes glucocorticoids receptors interaction with NF  $\kappa$ B (Nuclear Factor kappa-light-chain-enhancer B cells) protein, which results in the anti-inflammatory activity of glucocorticoids. Clock and BMAL (Brain muscle ARNT-like) proteins can do acetylation of a lysine residue in the joint area of the glucocorticoid receptors, which can selectively diminish the competence of glucocorticoid receptor to bind to glucocorticoids responses factors. The naturally being periodic fluctuation in BMAL-Clock levels resulting in translation into circadian oscillation in the acetylation of the glucocorticoids; for example, mononuclear cells in man's peripheral blood, acetylated glucocorticoids are approximately 3 times higher in day time (Charmandari, E. and *et al* 2011, Gibbs, J. E. & Ray, D. W. 2013).

### 5.4. Nuclear Receptors:

Transcription factor which is dependent on ligands called nuclear receptors, which maintain gene expression by straight binding to DNA response factors. More than half of the families of nuclear receptors show rhythmic expression in a definite organ or tissue (Yang, X., and *et al* 2006) and many may respond back directly to the clock itself.

### 5.5. Retinoid-related Orphan Receptors:

RORs are a member of the nuclear receptors family with 3 members, including ROR  $\alpha$ ,  $\beta$ , and  $\gamma$ , of which the later one has two isoforms,  $\gamma_1$  and  $\gamma_2$ . ROR genes transcription is rhythmic, and proteins of ROR have a great and proofed role in the circadian clock by transcriptional control on

brain muscle ARNT-like or BMAL; studies on rodents showed that mice with ROR  $\alpha$  and deficiency express aberrant circadian behavior. ROR  $\alpha$  has an important role in assisting T cells differentiation into TH 17 cells.

### 5.6. Peroxisome Proliferator-activated Receptors:

PPARs are a subclass of nuclear receptors that tightly related to the circadian clock. PPARs are regulators of transcription that activated by ligands, in that act through forming heterodimers with RXRs (retinoic acid receptors) and binding to desired regions on target genes. All three PPARs,  $\alpha$ ,  $\beta$ , / and  $\gamma$  are organ or tissue-specific in circadian clock's expression. Modulating the circadian clock both way in terms of PPARs function and expression is multifarious.

### 5.7. Adipokines:

The molecular clock is basic in the maintenance of metabolic processes; regulating the expression of involved genes in metabolic pathways but also responding to metabolic cues (Konturek, P. C., and *et al* 2011). Interruption of the circadian clock has harmful effects on metabolism and is an aggravating factor in the occurrence of metabolic disorders, which itself is comorbid with the risk of developing RA (Gremese, E., & Ferraccioli, G. 2011, Nakao, A., and *et al* 2015). The clock has a direct responsibility in regulating processes that give to the pathogenesis of rheumatoid arthritis, like the making of inflammatory cytokines by immune cells. However, adipokines which modulate by the clock and nuclear receptors contribute to mechanisms integrated for the progression of the disease, such as inflammation and activation of T cell. A better understanding of how the circadian clock-related and control the immune system, and its involvement results in pathogenicity, is likely to guide us towards the noble therapeutic target for treating all kinds of inflammatory not only RA related inflammatory (Cope, A. P., and *et all* 2007).

## 6. An Anti-inflammatory and Healthy Diet and Self-care:

Despite the lack of special “diet” for RA patients, but scientists have observed and identified a few foods that are rich and antioxidants and can help to treat, prevent or reduce the inflammation. Many of such foods that are on the list are part of the Mediterranean diet which have more focus on fish, fresh vegetables and fruits and of course olive oil, among other food items. It is also very vital and important to exclude or decrease to a minimum of all types of junk food and over-fried food that worsen inflammation. The other important factor in pain management and RA treatment is rest, especially when joints are in extreme pain, stiff or swollen state. Rest will manage the fatigue and inflammation which co-presence with flare. Short breaks in working hours throughout the day is the best option to save energy and protect joints. Physical activity too can be part of treatment as it is so beneficial. It should consist of low impact aerobics and with concern on flexibility and muscle strengthening. The schedule should be tailor-made and be unique and special depending on everyone’s condition and symptoms. The best person to design such a schedule is a physical or rehabilitation therapist. Sometimes hot baths advised for stiff joints and ice-cold bath suggested for severe pain; as it can numb painful areas and reduce the inflammation. Options such as topical treatment such as salicylates, capsaicin or NSAIDs gel, creams or patches can be used over painful muscle or joints. Alternative medicines also have also treatments to offer in regards to RA, such as yoga, meditation, breathing techniques and massage therapy. In recent years’ acupuncture and acupressure also considered as an option when there are no long-lasting effects of NSAIDs has seen and pain still persists. The concept of acupressure is the same as acupuncture but the only difference is that specialists applying pressure instead of acupuncture needles at those Meridians or special points of the body (Bekkers, M. B., and *et al* 2015).

## Conclusion

Rheumatoid Arthritis for a long time known to be circadian clock constituent not just only by symptoms, but in the sense of disease biomarkers. It’s been nearly a decade that the importance of the biological and circadian cycles in maintaining the immune system confirmed and recognized. In recent years by advancing molecular science and development of equipment scientist achieved a great milestone in the treatment of RA as the world’s leading autoimmune disease. Maintaining the circadian rhythm is the most important and vital thing in homeostasis for a normal and healthy human being. As studies found only 5-10% of cancers have genetic background and the rest are de novo and results from disruption of the circadian clock (Anand, P., and *et al* 2008). The prevalence of cancer elevating due to changes in lifestyle toward lesser activity, high consumption of fried and junk food, full-fat dairy products and processed meats especially in developing countries (Jemal, A., Bray, F., and *et al* 2011). Unfortunately, cancer can’t be diagnosed in primary stages due to a lack of known biomarkers and obvious symptoms (Verma, M., & Srivastava, S. 2003, Saunders, N. A., and *et al* 2012). Recent reports show that disruption of endogenous circadian homeostasis is a noble yet separate risk factor for cancer. Furthermore, as a key factor in mammalian physiology interruption of circadian clock’s work likely express inform of cancer development and progress induced by formerly pinpointed endogenous and exogenous cancer risk factor such as wrong diet, tobacco, high alcohol consumption, viral fevers and infections, air and water pollutions, aging, endocrine system dysfunction, metabolic syndromes and immune deficiencies (Zangeneh Pour Zadeh, A., and *et al* 2016, Rosa, L. M. D. 2011). Although still in the beginning, recent progress and developments strongly advised that in vivo clock-controlled physiological capabilities include tumor suppressor and anticancer treatment responses. Therefore; the circadian clock of mammalian, furnish an irreplaceable and unique system to study deeper about cancer mechanism and anticancer chronotherapy at the organ, tissue, cellular or even

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molecular *in vivo* levels like clinical trials and studies have great noteworthy impact on human health and lifestyle in the future by advancing both cancer treatment and prevention.

**Conflict of Interest:**

The authors declare that there is no conflict of interest regarding the current paper.

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## ساعت مولکولی و بیماری های خودایمنی با رویکرد به آرتروز روماتیسمی

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### چکیده

ساعت مولکولی به چرخه‌ای زیستی اشاره دارد که با دوره متناوب بیست و چهار ساعت تغییر میکند. این چرخه‌ها با یک ساعت مولکولی پشتیبانی و یک ماتریس وابسته به زمان را فراهم می‌کنند که تلفیق فرایندهای هموستازی با تغییرات محیط تضمین می‌کند. در اینجا قصد داریم در یک مقاله مروری همه یافته‌های اخیر در پنج سال گذشته تا به امروز در زمینه تحقیقات ساعت مولکولی و تکامل آن در زمینه و نقش آن در آرتروز روماتوئید به‌عنوان شایع‌ترین بیماری خود ایمنی در جهان با میزان بیش از ۷۶ میلیون نفر در جهان و شیوع تقریباً ۰.۶ درصد در امریکا که در سال ۲۰۱۵ به حدود ۱،۲۹ میلیون نفر رسیده است، را بررسی کنیم. علائم آرتروز روماتوئید شامل خشکی صبحگاهی مفاصل و افزایش درد مفاصل در آغاز صبح است. خشکی صبحگاهی مفاصل با سطح بالای سیتوکین‌های پیش التهابی شامل اینترلوکین-۶ در ارتباط است. ساعت مولکولی دارای نقش نظارتی بر فعالیت و بیان پروتئین‌ها و ژن‌ها مانند آدیپوکین‌های حاصل از چربی و گیرنده‌های چند هسته‌ای، که به‌عنوان چرخه‌ای در بیان و پیشرفت بیماری‌های خود ایمنی شرکت می‌کنند، می‌باشد. براساس دانش فعلی که در هر لحظه در حال پیشرفت است، مسیرهای بیولوژیکی که در آن چگونگی پاسخ‌های التهابی بر اساس کارشان در درمان بیماری‌های خود ایمنی به ویژه آرتروز روماتوئید استفاده می‌شود، را می‌دانیم.

واژگان کلیدی: بیماری‌های خودایمنی، سرطان، ساعت زیستی، گیرنده های هسته ای، آرتروز روماتیسمی

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