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*Review article*
*מאמר סקירה*

# Timing is everything: Overview and possible implications of the circadian rhythm in the skin

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ת ק צ י ר

בשנים האחרונות נחקרה רבות חשיבות השפעתו של השעון הצירקדי על התפקוד בכלל ועל עור האדם בפרט. מקצב פנימי זה, שאורכו כ-24 שעות, שולט על מגוון התנהגויות ותהליכים ביולוגיים, ותכליתו לסנכרן את תפקוד הגוף עם סביבתו. את המאמר פותחת הצגה קצרה של המנגנון המולקולרי של השעון המרכזי במוח. עיקר המאמר מוקדש להשפעתו של מנגנון זה על העור ועל השעון הפריפרי שבו, אותו שעון המבקר תהליכים מרכזיים בתפקוד העור, כגון חלוקת תאים, חדירות חומרים לגוף והגנה מפני נזקי הסביבה. חותמים את המאמר פירוט יישומים אפשריים של ידע זה ובחינת ההשערה כי טיפולים דרמטולוגיים, לרבות טיפול פוטותרפי בים המלח, חייבים להתחשב במקצב הפנימי של העור על מנת לקבל תגובה נאותה.

*מילות מפתח:*
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A B S T R A C T

In the last decade, numerous studies have demonstrated the pivotal role of the circadian rhythm in general, and the internal peripheral clock of the skin in particular. This 24 hour oscillation mechanism governs our everyday functions to synchronize our functions with our environment. This mini review outlines the molecular principles underlying this biological timekeeping mechanism. In addition, it is focused on the circadian rhythmic action in the skin, suggesting that normal functions of this vital tissue, such as permeation, protection from environmental stressors and regeneration are modulated by it. Finally, possible implication of this knowledge to dermatological therapy and Dead Sea phototherapy are suggested.

*Keywords:*
Circadian rhythm
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## 1. Circadian rhythm

All light-sensitive organisms, from cyanobacteria to humans, possess an internal clock, which responds to light-dark cycles (LDC) of approximately 24 hours. Originating from the Latin term *circa diem*, about a day, the circadian rhythm governs our everyday life, for example, when we sleep and eat (McClung, 2006). The first scientific reference of a circadian rhythm dates back to 1729, when Jean-Jacques d'Ortous de Mairan observed that the leaf movement of the plant *Mimosa pudica* does not occur solely in response to sunlight but continues when the plant is transferred to complete darkness. Since this 18th century observation, circadian rhythms have been studied extensively, with a high rate of publications growing over the last sixty years, reaching approximately 2,000 publications per year for over a decade. Importantly, the 2017 Nobel Prize in Physiology or Medicine was awarded to Jeffrey C. Hall, Michael Rosbash and Michael W. Young for their "discoveries of molecular mechanisms controlling the circadian rhythm", indicating how profound and significant this area of research is.

Several criteria must take place in order to consider an oscillatory pattern as circadian. First, the rhythm should have a period of approximately 24 hours. Second, the rhythm can be

entrained or synchronized by an external stimulus. Third, the rhythm must be self-sustained and to continue upon removal of the stimulus. The cycle of the rhythm can be shifted but without altering its duration. Finally, it must maintain its period independent of temperature changes in the physiological range (temperature compensation) (Lowrey and Takahashi, 2011).

The external signal responsible for entraining the circadian rhythm is called a zeitgeber, a German term meaning "time giver" (Daan and Aschoff, 2001). The strongest environmental zeitgeber is light. In mammals, light is transferred through the retina into the central clock located in the suprachiasmatic nuclei (SCN) in the hypothalamus (Figure 1). The SCN receives light signals and interprets them into a neurological and endocrinal signals sent to peripheral organs and tissues, thus synchronizing all peripheral clocks (Bhadra et al., 2017). Initially, it was thought that light signals were received and interpreted into both visual sight and entrainment of the circadian clock by the same cells and photoreceptors in the retina. However, this hypothesis was found to be incorrect, as mice lacking rod and cone cells in the retina (cells that are responsible for visual sight) retained circadian entrainment by light. This phenomenon was abolished by removal of the eyes (Freedman, 1999). In humans, blindness is often accompanied by circadian arrhythmia and sleep disorders. However, some blind individuals that lack a functional outer retina are still able to sense light and maintain a normal circadian rhythm, indicating that indeed there are "non-visual" photoreceptors (Zaidi et al., 2007).

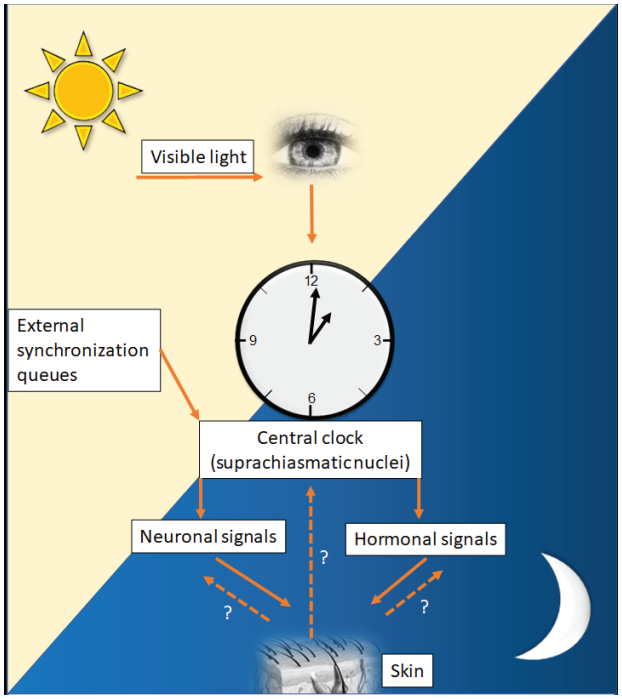


**Figure 1:** Hierarchy and reciprocal interactions between the environment, central and peripheral clock

Although visible light is the key zeitgeber, several other external signals may modulate the internal rhythm. The classical example is the reciprocal action of metabolic queues and the internal clock; it is well established that energy intake is regulated by the circadian regulation. For instance, mammals consume the majority of caloric intake and water during their waking period and ablation of the SCN destroys rhythmicity in both eating and drinking patterns (Stephan and Zucker, 1972).

On the other hand, food consumption is considered an external regulator of the central and peripheral clock, possibly due to a shift in energy-dependent gene expression or indirectly due to an anticipatory activity (Mistlberger, 2009). Wehrens et al. demonstrated that a 5-hour delay in meals in healthy volunteers played a role in synchronizing peripheral circadian rhythms (Wehrens et al., 2017). Of note, several recent studies have shown that food intake and energy balance may modulate even the central circadian clock by an indirect action of hormonal action of ghrelin or by direct action of energy-sensing enzymes, respectively (reviewed in Albrecht, 2012). Other external signals, such as smell and sound can also influence the internal rhythm (Emery and Francis, 2008).

At the molecular level, the clock is maintained by a transcription-translation feedback loop (TTFL). The transcription factors CLOCK and BMAL1 dimerize and promote the transcription of Period (per1-3) and Cryptochrome (Cry1/2) genes by binding to their E-box promoter elements. PER and CRY proteins in turn form complexes in the cytoplasm, that at a certain threshold migrate back into the nucleus and inhibit CLOCK/BMAL1 action, thereby inhibiting further transcription of PER and CRY (Figure 2). PER/CRY complexes are subjected to post-translational modifications leading to a delayed proteasomal degradation that removes the inhibition on CLOCK and BMAL, allowing the feedback loop to restart again. Thus, this negative feedback loop creates oscillation loop of approximately 24 hours (Robinson and Reddy, 2014). This primary TTFL is further sustained and fine-tuned by additional secondary feedback loops (Preitner et al., 2002). One such accessory loop involves the retinoic acid receptor-related orphan receptors, REV-ERBα/β and RORα, which bind to enhancer elements on the Bmal1 promoter to inhibit or promote transcription, respectively. Reciprocally, the BMAL1/CLOCK complex acts directly on the REV-ERBα gene (Preitner et al., 2002). Of notice, It is estimated that approximately 10% of all downstream genes exhibit a circadian expression, differing between tissues (Lowrey and Takahashi, 2011).

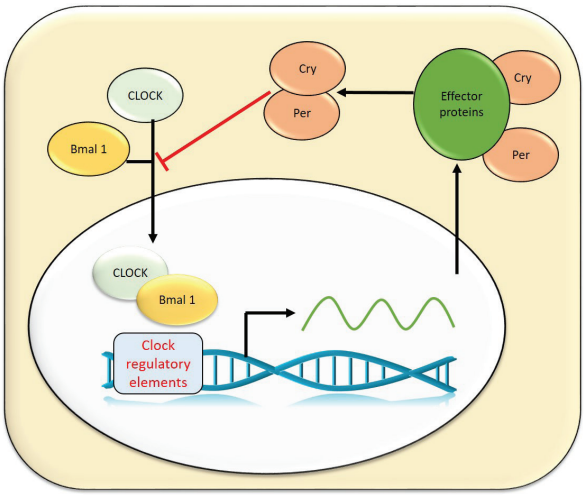


**Figure 2:** Molecular mechanism of the oscillating rhythm

Circadian rhythms are evolutionarily conserved, enhancing fitness and proper responses by synchronizing biological activity with the external environment. While synchrony with the environment is advantageous, it follows that being out of phase may be detrimental (Robinson and Reddy, 2014). Indeed, circadian rhythm disruption can lead to various disorders and higher incidence of disease. Much of our knowledge on circadian clocks in mammals originates from mouse models and from studies on shift workers who experience sleep deprivation and exposure to light-at-night (LAN). These studies establish a link between circadian disruption and sleep disorders, depression, schizophrenia (Karatsoreos, 2014; Wulff et al., 2010), metabolic disorders, diabetes, obesity (Huang et al., 2011; McHill et al., 2014), cardiovascular events (Takeda and Maemura, 2011) and cancer (Lengyel et al., 2013; Papagiannakopoulos et al., 2016).

It is widely accepted that the endogenous circadian rhythms influence neurobehavioral functions (Goel et al., 2013). Interestingly, the hypothesis that psychological factors can modulate the circadian rhythm has recently gained substantial evidence. For instance, several studies have linked stress response, mediated by the hypothalamus-pituitary-adrenal axis and the autonomic nervous system to the circadian rhythm. Secreted from the adrenal cortex, cortisol display a circadian oscillation peaking prior the onset of the active phase. In addition, Oishi et al. (2005) have demonstrated that approximately 100 rhythmic genes' oscillation in murine liver were lost in adrenalectomized animals (Oishi et al., 2005). Another evidence of the reciprocal and complex interaction between psychological factors and the circadian clock is based on recent findings that linked disrupted circadian clocks to neuropsychiatric disorders, particularly depression, mania, and schizophrenia (Karatsoreos, 2014). Typically, a disruption in the sleep-wake cycle is evident in those patients. Intestinally, the antidepressant drug agomelatine is actually a melatonin agonist, which acts as a circadian "resynchronizer" in models of depression (Koresh et al., 2012). The beneficial effect of lithium, a widely used drug in mania patients, have also been suggested to modulate the circadian clock (Klemfuss and Kripke, 1995). Overall, stress as well as other psychological factors are to be considered as biological clock modulators.

## 2. Circadian rhythm in the skin

In addition to being synchronized by the master clock, peripheral organs also contain a local clock, acting at the tissue/organ level according to its physiological activity (Janich et al., 2014). One such tissue is the skin, harboring a robust self-autonomous internal clock. The skin is a complex tissue, encompassing the organism and creating a barrier between the body and the environment. Skin, being an outer layer, is exposed to various external cues such as light, temperature, pollution, microbes etc. Due to its complexity and multicellular composition, the local rhythm should be separated to the different cellular compartments rather than the whole tissue. Indeed, circadian rhythm has been identified in various cell types in the skin, including keratinocytes, fibroblasts, melanocytes, epidermal stem cells, sebaceous glands and hair follicles (Plikus et al., 2015; Zanello et al., 2000). It seems that each cell type contains a specific circadian oscillator which acts according to a designated activity and to the diversity of skin functions (Plikus et al., 2015). The skin's pH, stratum corneum capacitance and hydration, transepidermal water loss, epidermal differentiation, DNA damage repair and sebum secretion are some of the skin functions that are controlled by circadian rhythms (Plikus et al., 2015). Altogether, human skin barrier functions are stronger during the day, suggesting that skin permeability is higher during the night, in our less-active state (Figure 3).

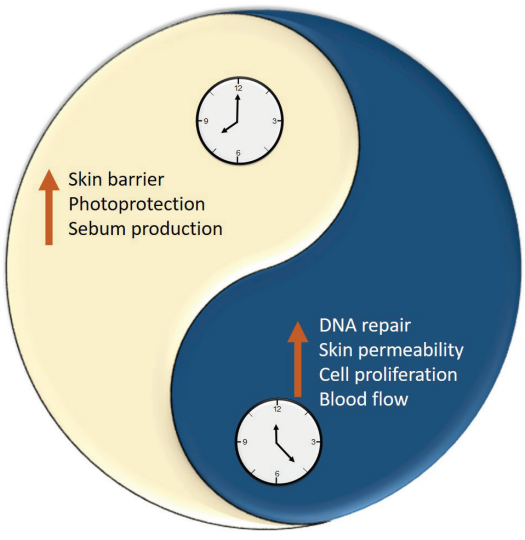


**Figure 3:** The rhythmic regulation of the skin

It has been postulated that skin is able to directly receive light signals and thus entrain the circadian clock by an extraocular phototransduction (Figure 1). One study suggested that light pulses, presented to the popliteal (behind the knee) region, were able to phase shift the circadian rhythm in the entire body (Campbell and Murphy, 1998). However, this result was not corroborated by subsequent studies. Nonetheless, various skin cells possess several photoreceptors, including rhodopsin, melanopsin, neuropsin, panopsin and peropsin (Buhr et al., 2015; Haltaufderhyde et al.; Provencio et al., 2000; Regazzetti et al., 2018; Toh et al., 2016). These diverse photoreceptors receive light signals of different wave lengths and influence local clocks in the numerous cell types to execute various physiological functions of the skin, such as calcium mobilization, early melanin synthesis and immediate pigment darkening (IPD) (de Assis et al., 2018; Regazzetti et al., 2018; Wicks et al., 2011).

Many of studies regarding circadian rhythms and the skin are performed in mice. Paradoxically, mice are nocturnal animals, keeping resting-active cycles opposite to that of humans. Additionally, in nature, mice's skin is coated by hair, thereby supplying another layer of protection against damage or UVR. Nevertheless, the bulk of data obtained from mice serves to unfold the various skin functions that are circadian, keeping in mind that the effect in humans should not be considered as the mirror image of the time in mice, rather that each rhythmicity in humans should be tested for and elucidated. One example for this is DNA damage response; Nucleotide excision repair (NER) is a form of repair that responds to specific DNA bulky lesions that are caused by UVR and some chemotherapies such as cisplatin, that cause covalent linkage of adjacent pyrimidines: cyclobutane pyrimidine dimers (CPD) and 4–6 photoproducts (Ndiaye et al., 2014).

Xeroderma pigmentosum A (XPA) is part of the NER mechanism and was found to be expressed rhythmically in the brain, liver and skin of mice (Gaddameedhi et al., 2011; Kang et al., 2009; Sancar et al., 2010). Indeed, mutation in this gene may cause a life threatening skin disorder, in which the patients accumulate massive DNA damage to their skin resulting in numerous cancer formation throughout the body and consequently premature death. XPA expression and activity are highest during the late afternoon and low during the early morning hours. This is in contrast to cell proliferation in skin of mice. There seems to be a temporal regulation separating cell proliferation (i.e. DNA replication) and NER (Gaddameedhi et al., 2011), therefore (and quite intuitively) mice epidermis is more sensitive to UVB-induced DNA damage at night, when DNA replication is high and NER is low (Gaddameedhi et al., 2011; Plikus et al., 2015). In human skin, this issue is more complex and depends on the specific cell type in question. For example, there is a difference in the timing of DNA damage response (DDR) and DNA replication between differentiated keratinocytes and epidermal stem cells. However, unlike mice, there is no temporal segregation between these two processes and similar to mice, human skin is most protected against UVR during the light hours (Janich et al., 2014).

Exposure to UVR and accumulation of DNA damage is one process that promotes transformation and can lead to tumorigenesis. Additionally, reactive oxygen species (ROS) maintain another avenue of transformation by impairing DNA integrity. Homeostasis of ROS is integral to avoid oxidative stress, which results due to imbalance between ROS production and accumulation and the cellular antioxidant pathways. ROS are generated endogenously by mitochondrial oxidative metabolism and play an important role in signaling pathways such as proliferation and survival (Ray et al., 2012). Notwithstanding, ROS are also produced exogenously by UVR and exposure to xenobiotic factors, and this can shift the balance toward an excess of ROS, which is deleterious to cells as these molecules can react and damage DNA, RNA, proteins and lipids (Ndiaye et al., 2014). ROS levels and their counteract antioxidant pathways are subjects of circadian rhythms and exhibit a peak in the morning hours in diurnal animals (Ndiaye et al., 2014). Alternatively, circadian disruption leads to accumulation of ROS and to oxidative stress (Kondratov, 2006; Matsui et al., 2016). Circadian rhythm disruption, as well as oxidative stress, contributes both to oncogenesis and to aging. Bmal1 knockout mice exhibit symptoms of premature aging and reduced lifespan.

Additionally, these mice displayed deficiency in hair regrowth and a severe decrease over time in their subcutaneous adipose tissue (Kondratov, 2006). ROS promotes skin aging by increasing the amount of senescence, decreasing proteasome activity (Hwang et al., 2007) and by decreasing collagen synthesis and promoting collagen degradation. Collagen fragments further increase ROS accumulation thereby creating a feedback loop with deleterious effects on skin elasticity and hydration (Ahsanuddin et al., 2016; Hwang et al., 2007). At the organismal level, circadian rhythm disruption is related with sleep disorders (Johansson et al., 2016) and poor quality of sleep is associated with skin aging (Oyetakin-White et al., 2015).

As the skin is exposed to environmental factors that promote ROS formation, it also possesses several protective mechanisms to reduce oxidative stress. The skin is able to retain and synthesize

several molecules with protective properties, among them are serotonin, melatonin, vitamin D and vitamin A (Ndiaye et al., 2014). Melatonin is secreted from the pineal gland during the dark phase of the circadian rhythm as well as from peripheral organs such as bone marrow, gastrointestinal and skin cells (Gutierrez and Arbesman, 2016). In the skin, melatonin synthesis depends on the transformation of tryptophan to serotonin to melatonin (Ndiaye et al., 2014). Both serotonin and melatonin are subject to circadian rhythms and their relative concentrations in human melanocytes has been shown to indicate the length of the day and night. Higher melatonin levels correspond to long nights and short days, while high serotonin levels in the presence of melatonin reflect short nights and long days, a possible mechanism for regulating seasonal rhythmicity (Iyengar, 1994). Melatonin has antioxidant and anti-carcinogenic activities, its derivatives act as ROS scavenging molecules, protecting the cells against oxidative stress. Concomitant with UVR increasing the amount of ROS in cells (Ahsanuddin et al., 2016), it also enhances melatonin metabolism in a dose dependent manner, thereby enabling a defense mechanism (Fischer et al., 2006). Notably, topical administration of melatonin to the skin prior to UVR exposure, significantly reduces the amount of UV-induced erythema (Iyengar, 1994).

Regeneration of skin and hair is tightly linked with cell cycle and proliferation of cells, processes that are regulated by circadian rhythms. A study performed on human epidermis throughout the day identified a circadian regulated transcription factor, Krüppel-like factor 9 (Klf9), as responsible for keratinocytes proliferation. Klf9 gain and loss-of-function experiments revealed a strong anti-proliferative effect of keratinocytes *in vitro* (Spörl et al., 2012), demonstrating that loss of circadian rhythmicity greatly affects the proliferative potential of these cells. A study performed on hair follicle growth in mice showed a daily mitotic rhythm, which appears to depend on circadian synchronization of the G2/M cell cycle checkpoint (Plikus et al., 2013). Thus, by timing γ-radiation to the time of the day with lowest mitotic activity, a dramatic radioprotective effect was achieved in wild-type (WT) mice, and radiation-induced hair loss was largely prevented. This radioprotective effect was lost in circadian mutants (Plikus et al., 2013). Importantly, loss of Bmal1 led to changes in the number of dormant bulge stem cells, and premature epidermal ageing (Janich et al., 2011). Hair loss and hair graying are associated with aging. Functional clock is essential both for the hair regeneration cycle (Kondratov, 2006) as well as for pigmentation of hair and melanocytes (Hardman et al., 2015).

Circadian arrhythmia results in wound healing defects, as was noted in several circadian mutants: NONO, Per1/2 and Bmal1 null mice (Kowalska et al., 2013; Plikus et al., 2015). Reciprocally, a recent study found that there are implications to the time in which a wound or burn is inflicted during the 24 hours of the day. Mouse fibroblasts express cytoskeleton proteins such as actin rhythmically, thereby the mobility of cells varies in a circadian manner. The migration and adhesion of fibroblasts are actin-dependent processes necessary for wound healing. Thus, a wound inflicted during the active period of the day healed faster than a wound inflicted during rest (Hoyle et al., 2017). Importantly, this was found to be relevant to humans, as analysis of clinical data obtained from the international Burn Injury Database (iBID), indicated a similar pattern for burn healing in humans (Hoyle et al., 2017). This finding makes evolutionary sense, as animals and humans are more likely to suffer an injury during their active state rather than during their resting period. However, these clinical results should be regarded with care, as multiple factors can contribute to this phenomenon, including better healthcare during the day.

## 3. Possible implications and final remarks

The skin can be used as a diagnostic tool for disorders with circadian rhythm disruptions. For example, skin fibroblasts from patients with chronic schizophrenia, displayed loss of rhythmic expression of CRY1 and PER2 compared to cells from healthy controls (Johansson et al., 2016). Additionally, hair follicles can be used as a non-invasive method for assessing the circadian rhythm in humans and harnessed as a diagnostic tool for circadian arrhythmia-related diseases (Akashi et al., 2010).

The current knowledge on biological rhythm, its pivotal function and importance in the skin raise the question: Does dermatological treatments should be synchronized with the endogenous clock of the skin or cellular compartment of interest? For instance, if skin permeation is enhanced at the night, the safety and systemic absorption of topical compounds with low therapeutic index should be assessed at night. Alternatively, treatment regimen should be restricted to the day. By the same logic, the use of wound healing substrates could be augmented by topical application at daytime, when the tissue is presumably more prone to healing queues.

Phototherapy is routinely used to treat or to reduce the severity of several immune-based skin disorders, including psoriasis, vitiligo and atopic dermatitis. A synthetic light source or controlled exposure to the sun, such as in the Dead Sea, are used (Brandwein et al., 2018). For instance, a clinical study

performed by Harari et al. demonstrated almost 95% clearance in patients with atopic dermatitis following a daily five hour sun exposure for four weeks (Harari et al., 2000). However, the exact molecular mechanism is not fully elucidated. Thus, another question that should be asked regarding the rhythmic skin: Does phototherapy influence and possibly act by normalizing the local/central rhythm? A new finding correlated the success rate of Dead Sea phototherapy with serum vitamin D (Harari et al., 2011), a known modulator of the internal circadian rhythm (Cheng et al., 2017; Gutierrez-Monreal et al., 2014). Interestingly, Hirotsu et al. have recently demonstrated that sleep deprivation in mice may worsen psoriasis manifestation (Hirotsu et al., 2012).

Significant increases were observed in the level of several pro-inflammatory cytokines, such as IL-1β, IL-6 and IL-12 after sleep deprivation. Importantly, their levels were normalized after a 48 hour recovery period in animals that were permitted to sleep. This may suggest that restoration of normal circadian clock could enhance psoriasis treatment. Another possible influence of the Dead Sea climatotherapy on the circadian clock may be derived from patient relaxation. As stress is linked to both circadian regulation and the manifestation and severity of inflammatory skin disorders (Alexopoulos and Chrousos, 2016), it is expected that the calming environment may benefit the outcome of the treatment.

Circadian rhythms are greatly conserved throughout evolution, and have evolved to synchronize us with our surrounding environment and thus provide a selective advantage and greater fitness. It is clear that modern life styles adversely affect the integrity and potency of our circadian clock. However, if we could minimize our exposure to light-at-night (LAN), restrict our eating to 11 hours during the 24 and refrain from shift work, we will boost our circadian clock and reduce the risk of developing circadian arrhythmia-related diseases.

To summarize, the increasing knowledge obtained in the last few years on the skin's circadian clock could start a new era in personalized medicine. In our opinion, it will not be long until topical treatment will be synchronized to the patient's internal clock.

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