Circadian Clock to Skin /Cancer

Subjects: Pharmacology & Pharmacy
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Over the years, the circadian regulation of drug metabolism and processing has been employed in the treatment of a range of disease states, including diabetes, hypertension, peptic ulcers, and allergic rhinitis . There is also interest in using chronotherapeutic approaches for skin disease, including psoriasis and atopic dermatitis . Although time-dictated drug administration had been demonstrated many decades ago, its application in cancer treatment was limited due to insufficient mechanistic data supporting experimental results and inconsistency among clinical trials.

Keywords: DNA repair ; circadian clock ; skin biology ; skin cancer ; genotoxicity ; cell cycle ; UV radiation

1. The Circadian Clock

Though circadian (Latin for “about a day”) behaviors have been recognized and observed in organisms for centuries, it was not until the late 1970s that a genetic basis for circadian rhythms was found. Thus, as is true for understanding many aspects of biochemistry and physiology, model organisms were key to elucidating the molecular mechanism of the circadian clock. The isolation of a Drosophlia mutant with altered circadian behavior (known as period) in the 1980s ultimately led to the cloning and characterization of both the period gene and other circadian clock components. In the 1990s, the development of the first knockout mice lacking evolutionarily conserved clock genes [1] initiated a field of research that continues today, revealing a seemingly unending number of systems and pathways that are controlled in part by the body’s circadian clock.

[2]. The light that is sensed by the retina, therefore, allows for entrainment, or synchronization, of daily rhythms to the 24 h light-dark cycle which occurs because of the earth’s rotation. Then, via neuronal and hormonal signaling, the SCN sends signals to other peripheral organs to keep tissues synchronized to the master clock in the brain. Ultimately, these processes affect aspects of physiology that display circadian rhythmicity in humans, including blood pressure, body temperature, and the release of the hormones cortisol and melatonin.

The PER and CRY proteins are eventually degraded, which allows the CLOCK-BMAL1 to promote transcription again, thus resetting the clock. In addition to this core TTFL, CLOCK-BMAL1 also activates the transcription of the retinoic acid-related orphan nuclear receptors REV-ERB and ROR. Thus, via controlling the abundance of BMAL1, this secondary loop also influences circadian rhythm. Thus, the clock is under many levels of regulation, which allows for various inputs like light, feeding, and temperature to modulate clock activity.

With the genetic basis of circadian rhythms well-established, understanding how genetic and environmental disruptions of the clock affects physiology and disease risk becomes an important issue that remains to be fully explored. Though a number of circadian rhythm disorders exist, including various sleep–wake rhythm disorders, the molecular basis for these pathologies is largely unknown. However, mutations in PER2 are responsible for familial advanced sleep phase syndrome [3]. Humans that travel across time zones or that work night shifts may also exhibit symptoms associated with clock disruption.

Some experimental and observational data indicate that this type of work might lead to circadian disruption at the cellular and hormonal level. Hormonally, circadian disruptions can interfere with essential processes such as the regulation of metabolism, sleep growth factors, and other diurnal-cycle behavioral and physiological process adaptations [4][5]. At the cellular level, circadian rhythms are in partly responsible for regulating cell synthesis, mitotic mechanisms, DNA repair, and elements of the apoptotic cascade [5][6]. , it is perhaps not too surprising that disruptions to the clock will affect cell function and ultimately disease pathology.

2. The Skin Circadian Clock

Though early analyses of circadian biology in animals focused on internal organs, such as the liver and heart, the skin has also been found to be under circadian control. Below, we review studies that addressed the molecular aspects of the clock in the skin before discussing the factors concerning clock function in the skin and the physiological processes that have been shown to be under circadian control.

Later studies showed that primary cultures of such cells could be synchronized with the glucocorticoid dexamethasone to monitor changes in clock gene expression over a couple of days [7]. Bjarnason and colleagues were the first to examine clock gene expression in tissue biopsies from the oral mucosa and skin from healthy adult males [8] and showed that the expression of Per1, Cry1, and Bmal1 at the mRNA level oscillated and peaked in early morning, late afternoon, and night, respectively. transduced fibroblasts isolated from skin biopsies from different donors with a lentiviral vector expressing a Bmal1 promoter and luciferase construct to monitor oscillations in circadian bioluminescence from fibroblasts [9]. The authors found widely variant circadian periods among different cell lines, suggesting that though the core clock machinery may be expressed in skin cells, its function likely varies due to additional genetic factors.

Whereas previous studies examined the expression of only a small number of genes, Spörl et al. were the first to take a more unbiased look at global gene expression throughout the day [10]. Using epidermal tissue obtained from suction blisters generated at three different times of the day (9:30 a.m., 2:30 p.m., and 7:30 p.m.), the authors carried out whole-genome microarray analyses of gene expression and observed hundreds of transcripts that displayed rhythmic expression. In addition to providing further support for the idea that the epidermis is under circadian control, their approach enabled the researchers to identify a transcription factor (Krüppel-like factor 9, or Klf9) that regulates the expression of several circadian output genes and is, itself, expressed in a rhythmic manner.

Using hair follicle cells that remain attached to hairs plucked from either the head or chin, Akashi and colleagues demonstrated that the circadian phase of clock gene expression could be readily and accurately measured by RT-qPCR [11]. A similar approach using beard follicle cells supported the observation that hair follicles can be used to monitor the expression of clock gene expression at the mRNA level [12]. One study, using pubic hair follicles from nurses working either day or night shifts, found that Per2 exhibited partially reduced expression in the morning relative to daytime working nurses [13]. An additional study examining Per3 and Nr1d2 expression in beard follicle cells from a small number of individuals working either a one-night shift or continuous night shifts further revealed altered gene expression [14], though significant variation between individuals was observed.

In addition to altered circadian rhythms caused by shift work, the relation between clock gene expression in the skin and disease states was examined. demonstrated that the circadian period length could be readily monitored in this tissue system and that older individuals with severe dementia retained clock oscillation in a manner similar to those of young and healthy subjects even though the dementia patients showed abnormal circadian behavior [15]. Altered circadian rhythms may also contribute to other diseases, such as cancer; therefore, an important issue in the cancer biology field is whether clock disruption influences carcinogenesis and whether tumors display altered clocks. Using skin biopsies of malignant melanoma and nonmalignant naevus tumors, Lengyel et al. reported that the expression of several Per and Cry genes was reduced by 30–60% relative to normal adjacent skin, whereas Clock was upregulated in nontumorous cells of melanoma biopsies [16].

Because of its abundance and ease of access, the skin has also been explored as a potential source of circadian biomarkers that could inform clinical decision making. Using the epidermis from skin punch biopsies obtained from human subjects sampled every 6 h across a 24 h period, the Hogenesch lab identified and characterized genes that displayed circadian rhythmicity [17]. Then, using bioinformatics approaches and additional skin samples from a larger population of 219 individuals at a single time point, the authors were able to identify a set 29 genes that could be used to determine a circadian phase to within 3 h. More recent work from the same group took advantage of additional gene expression datasets [10][18] and reported that the clock was more robust in the epidermis than the dermis regardless of body site, age, or gender [19]. This work further refined a 12-gene expression signature that reports molecular clock phase and developed an app (SkinPhaser) to test biomarker performance in new datasets.

Though the genetic disruption of circadian clock genes in mice proved that the clock affects various aspects of skin physiology, several studies found that additional factors can influence skin clock behavior (Figure 4). Interestingly, a recent study found that even in the absence of BMAL, skin and other tissues exhibited 24 h oscillations of the transcriptome and proteome over a few days in the absence of light, temperature, or other exogenous drivers [20]. Thus, even in the absence of a key clock gene, there may be other mechanisms that can be used to drive circadian rhythmicity.

Animal studies have found that light stimulation rapidly activates hair follicle stem cells via M1-type photosensitive retinal ganglion cells that signal to the SCN via melanopsin [21]. Efferent sympathetic nerves are then activated to release norepinephrine in the skin, which promotes hedgehog signaling to activate hair follicle stem cells. Whether skin cells and peripheral tissues possess their own capacity to sense light and regulate the clock remains controversial [22]. However, a recent study identified a population of melanocyte precursor cells in hair follicles that express the photopigment neuropsin (OPN5) and found that OPN5 influenced the entrainment of skin organ cultures of mouse skin exposure to violet light ex vivo [23].

Interestingly, as altered sleep schedules are known to affect various aspects of circadian physiology [24], a study in which dermal fibroblasts were isolated from the skin of idiopathic hypersomnia (IH) patients and cultured in vitro revealed dampened expression of BMAL1, PER1, and PER2 [25]. Furthermore, a BMAL1 promoter-containing luciferase reporter was used in primary fibroblasts from IH patients to show that the cells displayed a prolonged circadian period length [26].

Food is another factor affecting various organ clocks. A recent study using mice showed that time-restricted feeding (RF) shifted the circadian phase and changed the expression of about 10% of the skin transcriptome [27]. However, the pancreatic hormone insulin, which is rapidly secreted in response to feeding, was shown to affect clock gene expression and circadian phase in hair follicles cultured ex vivo [28]. Thus, feeding-induced insulin release may be involved in resetting the clock in skin and other peripheral clocks.

Studies have further suggested that the process of tumorigenesis may be related to the circadian clock in the skin. For example, the overexpression of the oncogene Ras was found to disrupt the clock and increase circadian length [29]. Disruption of PTEN was similarly found to cause constitutive activation of BMAL1 in hair follicle stem cells [30]. Moreover, the presence of a tumor in the skin may also affect the skin circadian clock, as was shown when melanoma cells were injected into mouse skin [31].

For example, cell cycle progression [32], keratinocyte proliferation [10], and stem cell function [33][34] have all been reported to show rhythmicity that likely influences reported circadian differences in processes, such as wound healing, through a variety of mechanisms [35][36][37][38]. Similarly, the clock has even been reported to affect hair follicles [39], such that hair growth is reported to occur faster in the morning [40] and be disrupted by the loss of core circadian genes [41][42]. Interestingly, genes encoding antimicrobial peptides [43], susceptibility to infection by herpes simplex virus 2 (HSV-2) [44], and induction of interferon-sensitive genes (ISGs) important in immune responses [45] have all been shown to be under circadian control.

Ultimately, altered circadian rhythms likely increase skin disease susceptibility. For example, experimental studies in mice have shown that genetic disruption of the circadian protein CLOCK promotes dermatitis [46]. Ionizing radiation-induced dermatitis, which commonly occurs in patients undergoing radiation therapy for cancer, is also stronger when the clock is disrupted by either an environmental disruption that mimics rotating shiftwork or by genetic disruption of Per1/2 [47]. Clock disruption leads to other skin conditions, such as psoriasis and time of treatment by the Toll-like receptor 7 ligand imiquimod

3. The Circadian Clock and Disease Treatment

Over the years, the circadian regulation of drug metabolism and processing has been employed in the treatment of a range of disease states, including diabetes, hypertension, peptic ulcers, and allergic rhinitis [48]. Although time-dictated drug administration had been demonstrated many decades ago, its application in cancer treatment was limited due to insufficient mechanistic data supporting experimental results and inconsistency among clinical trials. However, the timed administration of anti-cancer drugs is rapidly gaining attention as studies with animal and human models unveil molecular intricacies in the circadian control of biological pathways. Thus, more work is needed to understand how optimizing the timing of drug treatment can improve the treatment of skin diseases.

The realization that the circadian clock machinery affects virtually all aspects of physiology, disease pathogenesis, and treatment has led to interest in manipulating the circadian clock with small-molecule compounds [49][50][51]. Indeed, several compounds have been discovered or developed over the past few years that target specific components of the clock machinery (Figure 7), and animal studies have begun to show therapeutic benefits in metabolic disorders.

There have been a few studies that have explored the use of these compounds in treating various skin conditions. [52] and inhibit skin tumors induced by the chemical carcinogen DMBA [53]. Another study demonstrated that topical application of the ROR inverse agonist SR1001 on mouse skin was able to reduce inflammation induced by irritants [54]. Finally, a recent study showed that the CRY stabilizer KL001 altered the expression of proliferation and apoptotic genes and prolonged anagen in hair follicles ex vivo [55].

Other recently developed compounds that remain to be explored for use in the skin include the cryptochrome inhibitor KS15 [56][57], the REV–ERB antagonist SR8278 [58], and the ROR agonist SR1078 [59]. Given that the circadian clock regulates the expression of the NER gene XPA, it may be possible to manipulate the clock machinery in human skin pharmacologically to increase XPA expression transiently during maximum sun exposure to limit erythema and mutagenesis. There has long been interest in incorporating DNA repair enzymes into topical sunscreens to prevent skin cancers [60][61]; consequently, small-molecule circadian clock modulators potentially offer a new way to increase DNA repair efficiency by promoting the expression of XPA and other DNA damage response genes.

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