Plant's Immunity and Circadian Rhythms

Subjects: Plant Sciences

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The circadian clock is an endogenous time keeping mechanism found in living organisms and their respective pathogens. Numerous studies demonstrate that rhythms generated by this internal biological oscillator regulate and modulate most of the physiological, developmental, and biochemical processes of plants. Importantly, plant defence responses have also been shown to be modulated by the host circadian clock and vice versa.

Plant's Immunity,Circadian Rhythms,Plant pathogens

1. Introduction

Plant pathogens cause 40% of crop losses worldwide [1][2]. Viruses, fungi, nematodes, parasitic plants, and bacteria constitute the major agricultural pathogens. In spite of plants' multi-layered defence systems, the relentless evolution of pathogens ensures a continuous "arms race" to maintain disease resistance [3][4][5]. Along with many other metabolic processes, pathogen defence is also regulated by the plant circadian system [6][7][8]. The plant circadian clock is a pervasive biological timer that contributes towards growth, development, and health [9][10]. Although there have been multiple studies examining how the plant circadian clock responds during abiotic stress, little is known about the interconnection between biotic stress and the circadian clock [11]. It is also important to acknowledge the role of light, which has an important influence on plant/pathogen interactions [12].

The capacity of the plants to tolerate or to prevent a pathogen attack is described as their "innate immunity" [13]. Plants prioritize defence responses over their normal cell functions following infection by a pathogen [13][14]. Physical barriers of a plant such as its cuticle serve as the first line of defence in case of a pathogen attack. These structures prevent and avoid pathogen and pest invasion. In case of a pathogen attack, changes occur in the cuticle which are recognized by the plant and it immediately initiates defence responses [14].

Pathogens typically secrete Pathogen-Associated Molecular Patterns (PAMPs) when in proximity to the plant host. PAMPs are essential for pathogenicity and can be found in either physical structures or exudates such as saliva or honeydew in the case of insects [15][14]. PAMPs released by the pathogen are recognized by specialized receptor proteins known as Pattern Recognition Receptors (PRRs) present either in the plant cell/plasma membrane or within the cell in the cytoplasm. PRRs are a diverse group of proteins whose specificity is derived from the target recognised. For instance, the FLS2 PRR recognizes bacteria that produce flagellin [14]. The initial interaction between PAMPs and PRRs triggers a number of plant defence responses such as the closing of stomata to avoid pathogen invasion [15][14][16]. If the pathogen progresses within the plant cell, polymorphic Nucleotide-Binding and Leucine-Rich Repeat (NB-LRR) proteins present inside the host cell interact with specific effector molecules

released by the pathogens. NB-LRRs are encoded by Resistance (R) genes in plants and confer resistance to specific pathogens [15][16]. Following this a series of defensive reactions occur starting from the production of pathogenesis-related proteins, structural cell wall changes, and synthesis of phytoalexins, concluding with the initiation of the hypersensitive response (localized cell death at the site of invasion) [17][18].

Phytohormones play a crucial role in plant defence, particularly Salicylic Acid (SA) and Jasmonic Acid (JA) [19]. Plants synthesize different phytohormones dependent upon pathogens' mode of attack. For example, the SA pathway is only effective against biotrophs [13][20]. SA contributes to both local and Systemic-Acquired Resistance (SAR) and is synthesized by plants in response to pathogen attack. Plants with impaired SA signalling or synthesis are more susceptible to disease [20]. The accumulation of SA induces cell wall strengthening, ion fluxes, the production and accumulation of phenolics, and the activation of R and other defence-related genes. These responses ultimately lead to the Hypersensitive Response that results in programmed cell death [13][20][21].

To combat nectrotrophic pathogens, plants synthesize JA which acts via an ethylene-mediated pathway [13][19]. JA is endogenously produced, and is a conjugate between isoleucine and methyl ester which are derivates of a fatty acid class known as the jasmonates. Although the exact mechanism behind the activation of the JA pathway remains unclear, polypeptide signal molecules such as systemin and oligosaccharides hydrolysed after damages caused by the pathogens, are speculated to trigger the JA pathway into action [22]. Although the JA and SA pathways have been shown to be antagonistic, some pathogens induce both pathways [19].

2. Modulation of Plant's Immune Responses by the Circadian Clock

Scientific evidence is growing in support of the regulation of plant–pathogen interaction by the circadian clocks of both the pathogen and the plant. Studies supporting that the plant immunity indeed is regulated by its circadian clock are briefly documented here [8][23]. A microarray data study concluded that many genes responsible for PTI or PAMP-triggered immunity, like FLS2, express rhythmically in Arabidopsis. Pathogen responsive genes, such as glycine-rich RNA binding protein (GRP), found in barley and many other crops also show circadian regulation [8]. GRP directly binds with PAMPs released by the pathogen, thus enabling the plant to recognize the pathogen and initiate PTI [24]. When attacked by a fungal pathogen, two GRPs namely HvGRP2 and HvGRP3 of barley were expressed at a higher rate, their respective levels varied when barley was placed in a light/dark cycle of 16/8 h respectively. Likewise, in Arabidopsis, AtGRP7 (also a member of GRP) was shown to influence the stomatal opening, response towards stresses and flowering and proved to be regulated by the circadian clock. It has been shown to work with CCA and LHY to control the stomatal defence response of plants [8].

The major defence mechanism of plants against specific pathogens is the R (resistance) gene system, which has also been shown to be influenced by the circadian system. Impaired clock mutants of Arabidopsis show a defect in the R gene and even basal resistance [25]. For instance, Goodspeed et al. [26] experimented on Arabidopsis plants attacked by an herbivore (cabbage loopers). They concluded that cabbage loopers almost always prefer to feed on arrhythmic plants proving that the circadian clock increases resistance towards herbivore attack mainly through

affecting the SA and JA pathways [27]. One of the six acyl-coa-binding proteins (ACBP) in Arabidopsis, ACBP3, was studied to better understand its role in the resistance and plant defence; the same protein was found to be regulated by the circadian clock [28].

The morning phased *CCA1* and *LHY* genes positively regulate plant resistance against oomycetes and bacterial pathogens like *P.syringae*. CCA1 regulates the plant–pathogen interaction by contributing to resistance responses. Plants lacking *CCA1* show increased susceptibility at evening while being highly resistant in the morning. These rhythmic susceptibilities during the course of 24 hours were not visible in *CCA1-ox* mutants, thus indicating a relationship between CCA1 and plant immunity [29]. Similarly, resistance against downy mildew is impaired in *cca1* seedlings whereas overexpression of *CCA1* led to improved resistance [5]. Characterization of the tomato gene *DEA1* (which is expressed upon infection by the late blight pathogen *Phytophthora infestans*) showed that *DEA1* is modulated by both the circadian clock and light [30]. Some experiments conducted on plant defence pathways via stomata suggest that clock genes control resistance towards bacterial pathogens through stomatal opening timing. For example, Arabidopsis showed resistance towards *P.syringae* at night. However, plants can close stomata actively during bacterial invasion to restrict entry upon PAMP recognition. Crucially, *CCA1* and *LHY,* both regulate this gating response of stomatal opening and closing [8].

The interplay between the circadian system, light, and pathogen resistance has also been explored. One of the studies explored the links between red light and resistance showed by Arabidopsis towards *P. syringae pv*. *tomato* DC300. Plants showed increased susceptibility just before midnight. RNA-seq analysis showed that red light-triggered resistance responses regulated by the circadian clock and therefore, increased the chance of survival against pathogens. Furthermore, it was revealed that the circadian regulated genes interacted with various plant hormones, phytochromes, and induced the SA mediated defence responses [31]. Another study conducted on comparing the activity of flagellin-sensing2 (a PRR that recognizes bacterial flagellin) in wild type and arrhythmic mutants of Arabidopsis plants concluded that when infected with *Pseudomonas syringae* in the morning the expression of FLS2 was stronger in the wild type and not in the mutants [32][33].

Interestingly, some studies have revealed that plants anticipate possible infection using their circadian clocks [25]. Time of the day and circadian rhythms directly play a role in the functionality of host's immune system and therefore they also affect the virulence of pathogens, intensity of infection, colonization and damage to host cells, and the overall outcome of host–pathogen relationship [34]. The circadian clock in a way decides the most appropriate time of the day for efficient plant immune responses [29]. Plants show enhanced resistance towards pathogens during daytime hours compared to the night. Importantly, plants' defence system exhibits circadian oscillations even in the absence of a pathogen [35]. For instance, Arabidopsis infected by *P. syringae* DC3000 showed increased tolerance towards infection at certain times of the subject day, i.e., in the morning. These temporal regulations help plants to not only better respond but anticipate when the next infection may occur [36].

Conversely, pathogen–plant interactions can often reset the plant's circadian clock, resulting in the reallocation of the limited resources used for the development and growth of the plant [8]. For example, experiments using *Paulownia fortunei* concluded that circadian gene expression was altered when infected with the Paulownia

Witches' Broom phytoplasma [6]. Similarly, pathogens can manipulate hormone signaling thus altering the plant's circadian system. Effectors of *P. syringae* cause the production of abscisic acid and auxins, both of which are regulated by the clock and which can also regulate clock function. SA and JA signaling can also be manipulated by pathogens [8]. Importantly, minor alteration in clock genes can cause a change in the plant's defence responses [37]. Following a very localized infection at a single leaf in Arabidopsis, it was observed that the amplitude of the circadian clock slowed down and period length increased even in the distant un-infected tissues [11]. When treated with the defence phytohormone SA, the same results were noticed [11]. Another study completed using susceptible eds4 Arabidopsis concluded that *eds4* seedlings showed altered clock responses compared to the wild type Arabidopsis plants [38]. *eds4* seedlings were less sensitive towards the red and white light, their flowering time was accelerated, and their leaf movement had a longer period as compared to wild type controls. Other circadian responses and clock profiles were also altered in the *eds4* plants. The same study found that a bacterial infection induces substantial reconfiguration in the circadian clock genes expression for example downgrading of the morning phased genes, resulting in an increase of bacterial infection and susceptibility of host plant [38].

3. Interactions between the Circadian System, Light, and Plant Defence

Light has a crucial role in both plant growth and response towards pathogen attack, whilst also serving as one of the primary zeitgebers that entrain the circadian system [10][39]. The regulation of plants' defence by light and the circadian system allows plants to anticipate periods of likely infection and thus periodically increase their resistance [12]. Although additional work is needed to understand these interactions—particularly in natural or field settings—it is of interest to discuss the interplay between light, circadian signalling, and plants' immune response [12].

Light and the circadian system both contribute to innate immunity—in part by contributing to the maintenance of the physical barriers that restrict pathogen ingression. For example, stomatal opening is regulated by both light and the clock. Inoculation with pathogenic bacteria via direct infiltration (bypassing stomata) negates the contribution of the circadian system to innate immunity, although light maintained a significant contribution [12][17][39].

Plants show attenuated defence responses towards viral, fungal, and bacterial pathogens when grown in the dark [8][31]. Indeed, a direct link between light and plant–pathogen compatibility is becoming more evident in studies particularly regarding SA and other defence mechanisms of plants [12]. Light quality, fluence rate, and duration influence plants' immunity and defence by regulating the sensitivity of plants towards SA, development of the HR, and expression of pathogenesis-related genes[5][17][40]. Inoculation with *Pseudomonas syringae pv. maculicola,* during the day, induces a more substantial response compared to plants inoculated at night. The dependence of the SA signalling pathway on light irradiation is one possible explanation of these data [5]. Similarly, the JA pathway is also modulated by light. Red and Far-Red (or the R/FR ratio) regulate the activation of JA. phyB mutants, which have impaired red/far-red responses, were found to be more prone to infection caused by the fungus *Fusarium oxysporum* [5].

In some cases, the chloroplast electron transport chain drives the production and physiological functions of several reactive oxygen species (ROS) that contribute to plant defence [41]. Rapid production of ROS is a first-line defence response, and the interplay between cellular redox state and the circadian clock ensures an equilibrium between plant growth and immunity [42][29]. Importantly, Arabidopsis mutants lacking nonphotochemical quenching also lack PTI [5]. When infected with avirulent strains of *Pseudomonas syringae*, Arabidopsis plants maintained in constant darkness showed increased bacterial infection and decreased resistance in comparison with Arabidopsis plants grown in the presence of light and infected with the same bacteria [41]. Impaired photosystem function and reduced light input similarly have a positive impact on the susceptibility of *Nicotiana benthamiana* towards the Turnip Mosaic Virus (TVC) [5].

HR and ETI particularly require light signalling for activation [12][39]. Arabidopsis infected with TVC and grown in the dark showed a reduced HR and a suppressed resistance in comparison to the ones treated in the light [43]. The study of the TVC pathosystem revealed that photoreceptors cryptochrome1, cryptochrome2, phototropin1, and phototropin2 are required for mediation of HR conferred by R gene termed as HRT [5]. Various experiments using maize, transgenic tomatoes, rice, and Arabidopsis mutants hint at a link between light and HR [39]. For example, phytochromes are thought to play a role in PRR gene expression. Plants with the varying activity of phytochrome A and B were grown in darkness and high fluence white light respectively. Those which were grown in darkness had no expression of HR and PRR when treated with SA, while those in the light had a proper expression. Plants lacking phytochromes A and B similarly demonstrated complete loss of PRR expression, indicating their role in this important defence signalling pathway [17]. In addition, the blue light photoreceptor cryptochrome1 is required for defence against bacterial infection only under continuous light and not when the plant is under short daylight conditions [5].To test this hypothesis further, Arabidopsis was infected with *Pseudomonas syringae*, the results demonstrated a clear connection between the accumulation of SA and the presence of light [12].

4. Conclusions

A successful plant pathogen infection requires a virulent pathogen, a susceptible host, and environmental conditions favouring the pathogen [12]. Through various experimentation, it has been established that plants' innate immunity involves crosstalk across multiple pathways including light signalling and the circadian clock [44]. As circadian rhythms have beneficial effects upon physiological, developmental and biochemical processes of living organisms, it is apparent that they also influence drug efficiency and disease treatments. Various mechanisms have been hypothesized on how the circadian system contributes to plants' immunity and defence as both adaptive and innate immunities are modulated by the circadian system [39]. Unravelling the mechanisms underlying the relationship between the circadian system and plant immunity carries great importance for plant health and disease management [45][46]. The emerging field of chrono-immunotherapy (synchronizing time of medicine with the circadian clock of the body to optimize treatment) demonstrates the utility of this approach in treating disease [45]. As a consequence, efforts to improve the efficiency of plant defense responses using targeted interventions within the circadian system should be explored further. Our understanding of the circadian clock controlling the plant

defense in different ways provides a foundation for future work [46][47][48]. The synchronization of disease treatment and plants' internal clock could result in efficient disease control and decreased crop yield losses [46][49].

References

1. Strange, R.N.; Scott, P.R. Plant Disease: A Threat to Global Food Security. Annu. Rev. Phytopathol. 2005, 43, 83–116.
2. Scala, V.; Pucci, N.; Loreti, S. The diagnosis of plant pathogenic bacteria: A state of art. Front. Biosci. 2018, 10, 449–460.
3. Mansfield, J.; Genin, S.; Magori, S.; Citovsky, V.; Sriariyanum, M.; Ronald, P.; Dow, M.; Verdier, V.; Beer, S.V.; Machado, M.A.; et al. Top 10 plant pathogenic bacteria in molecular plant pathology. Mol. Plant Pathol. 2012, 13, 614–629.
4. George Agrios. Plant Pathology; Elseiver: San Diego, CA, USA, 2005; pp. 4–42.
5. Hua, J. Modulation of plant immunity by light, circadian rhythm, and temperature. Curr. Opin. Plant Biol. 2013, 16, 406–413.
6. Fan, G.; Dong, Y.; Deng, M.; Zhao, Z.; Niu, S.; Xu, E. Plant-Pathogen Interaction, Circadian Rhythm, and Hormone-Related Gene Expression Provide Indicators of Phytoplasma Infection in Paulownia fortunei. Int. J. Mol. Sci. 2014, 15, 23141–23162.
7. Karapetyan, S.; Dong, X. Redox and the circadian clock in plant immunity: A balancing act. Free. Radic. Biol. Med. 2018, 119, 56–61.
8. Lu, H.; McClung, C.R.; Zhang, C. Tick Tock: Circadian Regulation of Plant Innate Immunity. Annu. Rev. Phytopathol. 2017, 55, 287–311.
9. Farré, E.M. The regulation of plant growth by the circadian clock. Plant Biol. 2012, 14, 401–410.
10. Oakenfull, R.J.; Davis, S.J. Shining a light on the Arabidopsis circadian clock. Plant Cell Environ. 2017, 40, 2571–2585.
11. Li, Z.; Bonaldi, K.; Uribe, F.; Pruneda-Paz, J.L. A Localized Pseudomonas syringae Infection Triggers Systemic Clock Responses in Arabidopsis. Curr. Biol. 2018, 28, 630–639.e4.
12. Roden, L.C.; Ingle, R.A. Lights, Rhythms, Infection: The Role of Light and the Circadian Clock in Determining the Outcome of Plant–Pathogen Interactions. Plant Cell 2009, 21, 2546–2552.
13. Spoel, S.H.; Dong, X. Making Sense of Hormone Crosstalk during Plant Immune Responses. Cell Host Microbe 2008, 3, 348–351.
14. Malik, N.A.A.; Kumar, I.S.; Nadarajah, K. Elicitor and Receptor Molecules: Orchestrators of Plant Defense and Immunity. Int. J. Mol. Sci. 2020, 21, 963.

15. Miller, R.N.G.; Alves, G.S.C.; Van Sluys, M.-A. Plant immunity: Unravelling the complexity of plant responses to biotic stresses. Ann. Bot. 2017, 119, 681–687.
16. Jones, J.; Dangl, J. The plant immune system. Nature 2006, 444, 323–329.
17. Genoud, T.; Buchala, A.J.; Chua, N.-H.; Métraux, J.-P. Phytochrome signalling modulates the SA-perceptive pathway in Arabidopsis. Plant J. 2002, 31, 87–95.
18. Greenberg, J.T.; Yao, N. The role and regulation of programmed cell death in plant-pathogen interactions. Cell. Microbiol. 2004, 6, 201–211.
19. Tamaoki, D.; Seo, S.; Yamada, S.; Kano, A.; Miyamoto, A.; Shishido, H.; Miyoshi, S.; Taniguchi, S.; Akimitsu, K.; Gomi, K. Jasmonic acid and salicylic acid activate a common defense system in rice. Plant Signal. Behav. 2013, 8, e24260.
20. Loake, G.; Grant, M. Salicylic acid in plant defence—the players and protagonists. Curr. Opin. Plant Biol. 2007, 10, 466–472.
21. Bechtold, U.; Karpinski, S.; Mullineaux, P.M. The influence of the light environment and photosynthesis on oxidative signalling responses in plant-biotrophic pathogen interactions. Plant Cell Environ. 2005, 28, 1046–1055.
22. Ruan, J.; Zhou, Y.; Zhou, M.; Yan, J.; Khurshid, M.; Weng, W.; Cheng, J.; Zhang, K. Jasmonic Acid Signaling Pathway in Plants. Int. J. Mol. Sci. 2019, 20, 2479.
23. Westwood, M.L.; O'Donnell, A.J.; De Bekker, C.; Lively, C.M.; Zuk, M.; Reece, S.E. The evolutionary ecology of circadian rhythms in infection. Nat. Ecol. Evol. 2019, 3, 552–560.
24. Sharma, M.; Bhatt, D. The circadian clock and defence signalling in plants. Mol. Plant Pathol. 2014, 16, 210–218.
25. Wang, W.; Barnaby, J.Y.; Tada, Y.; Li, H.; Tör, M.; Caldelari, D.; Lee, D.-U.; Fu, X.-D.; Dong, X. Timing of plant immune responses by a central circadian regulator. Nat. Cell Biol. 2011, 470, 110–114.
26. Goodspeed, D.; Chehab, E.W.; Min-Venditti, A.; Braam, J.; Covington, M.F. Cozzarelli Prize Winner: Arabidopsis synchronizes jasmonate-mediated defense with insect circadian behavior. Proc. Natl. Acad. Sci. USA 2012, 109, 4674–4677.
27. Goodspeed, D.; Chehab, E.W.; Covington, M.F.; Braam, J. Circadian control of jasmonates and salicylates. Plant Signal. Behav. 2013, 8, e23123.
28. Zheng, S.X.; Xiao, S.; Chye, M. The gene encoding Arabidopsis acyl-CoA-binding protein 3 is pathogen inducible and subject to circadian regulation. J. Exp. Bot. 2012, 63, 2985–3000.
29. Zhang, J.; Ren, Z.; Zhou, Y.; Ma, Z.; Ma, Y.; Hou, D.; Xu, Z.; Huang, X. NPR1 and Redox Rhythms: Connections, between Circadian Clock and Plant Immunity. Int. J. Mol. Sci. 2019, 20,

1211.

30. Weyman, P.D.; Pan, Z.; Feng, Q.; Gilchrist, D.G.; Bostock, R.M. A Circadian Rhythm-Regulated Tomato Gene Is Induced by Arachidonic Acid and Phythophthora infestans Infection. Plant Physiol. 2005, 140, 235–248.
31. Yang, Y.; Wang, M.-M.; Yin, Y.-L.; Onac, E.; Zhou, G.-F.; Peng, S.; Xia, X.-J.; Shi, K.; Yu, J.-Q.; Zhou, Y. RNA-seq analysis reveals the role of red light in resistance against Pseudomonas syringae pv. tomato DC3000 in tomato plants. BMC Genom. 2015, 16, 120.
32. McWatters, H.; Devlin, P. Timing in plants—A rhythmic arrangement. FEBS Lett. 2011, 585, 1474–1484.
33. Korneli, C.; Danisman, S.; Staiger, D. Differential Control of Pre-Invasive and Post-Invasive Antibacterial Defense by the Arabidopsis Circadian Clock. Plant Cell Physiol. 2014, 55, 1613–1622.
34. Costantini, C.; Renga, G.; Sellitto, F.; Borghi, M.; Stincardini, C.; Pariano, M.; Zelante, T.; Chiarotti, F.; Bartoli, A.; Mosci, P.; et al. Microbes in the Era of Circadian Medicine. Front. Cell. Infect. Microbiol. 2020, 10, 30.
35. Mishra, S.; Digennaro, P. Root-knot nematodes demonstrate temporal variation in host penetration. J. Nematol. 2020, 52.
36. Bhardwaj, V.; Meier, S.; Petersen, L.N.; Ingle, R.A.; Roden, L.C. Defence Responses of Arabidopsis thaliana to Infection by Pseudomonas syringae Are Regulated by the Circadian Clock. PLoS ONE 2011, 6, e26968.
37. Bendix, C.; Marshall, C.M.; Harmon, F.G. Circadian Clock Genes Universally Control Key Agricultural Traits. Mol. Plant 2015, 8, 1135–1152.
38. De Leone, M.J.; Hernando, C.E.; Romanowski, A.; Careno, D.A.; Soverna, A.F.; Sun, H.; Bologna, N.G.; Vázquez, M.; Schneeberger, K.; Yanovsky, M.J. Bacterial Infection Disrupts Clock Gene Expression to Attenuate Immune Responses. Curr. Biol. 2020, 30, 1740–1747.e6.
39. Griebel, T.; Zeier, J. Light Regulation and Daytime Dependency of Inducible Plant Defenses in Arabidopsis: Phytochrome Signaling Controls Systemic Acquired Resistance Rather Than Local Defense. Plant Physiol. 2008, 147, 790–801.
40. Pink, B.; Mueller, M.J.; Berger, S. Light conditions influence specific defence responses in incompatible plant?pathogen interactions: Uncoupling systemic resistance from salicylic acid and PR-1 accumulation. Planta 2004, 219, 673–683.
41. Gallé, Á.; Czékus, Z.; Bela, K.; Horváth, E.; Ördög, A.; Csiszár, J.; Poór, P. Plant Glutathione Transferases and Light. Front. Plant Sci. 2019, 9, 1994.

42. Brody, S. Circadian Rhythms in Fungi: Structure/Function/Evolution of Some Clock Components. J. Biol. Rhythm. 2019, 34, 364–379.
43. Chandra-Shekara, A.C.; Gupte, M.; Navarre, D.; Raina, S.; Raina, R.; Klessig, D.; Kachroo, P. Light-dependent hypersensitive response and resistance signaling against Turnip Crinkle Virus in Arabidopsis. Plant J. 2006, 45, 320–334.
44. Moghaddam, M.R.B.; Ende, W.V.D. Sweet immunity in the plant circadian regulatory network. J. Exp. Bot. 2013, 64, 1439–1449.
45. Martinez, M.; Helm, B. The influence of biological rhythms on host–parasite interactions. Trends Ecol. Evol. 2015, 30, 314–326.
46. Seifalian, A.; Hart, A. Circadian Rhythms: Will It Revolutionise the Management of Diseases? J. Lifestyle Med. 2019, 9, 1–11.
47. Rijo-Ferreira, F.; Takahashi, J.S. Genomics of circadian rhythms in health and disease. Genome Med. 2019, 11, 1–16.
48. Zhang, R.; Lahens, N.F.; Ballance, H.I.; Hughes, M.E.; HogenEsch, J.B. A circadian gene expression atlas in mammals: Implications for biology and medicine. Proc. Natl. Acad. Sci. USA 2014, 111, 16219–16224.
49. Scheiermann, C.; Gibbs, J.; Ince, L.; Loudon, A.S.I. Clocking in to immunity. Nat. Rev. Immunol. 2018, 18, 423–437.

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