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Opinion

Development of a circadian immune system

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Circadian rhythms are key regulators of immune functions. These endogenous oscillations help to maintain immune homeostasis, regulate responses to pathogens, and shape vaccine efficacy. Recent studies further indicate that they are of clinical relevance for cancer immunotherapies. While circadian immune rhythms are thus recognized to be important in adults, it is unknown at what developmental stage these rhythms begin to manifest. In this opinion article we review the development of circadian rhythms in the immune system in both rodents and humans, with a focus on their interactions during the perinatal period. Understanding their emergence in early life may help guide time-based clinical interventions for infants.

Highlights

Circadian rhythms emerge early during development and further mature postnatally.

Maternal circadian rhythms influence neonatal immunity through fatty acids in breast milk, regulating the immunosuppressive function of neonatal myeloid-derived suppressor cells.

Mothers with circadian rhythm disruption confer increased susceptibility to inflammatory disorders in their offspring.

Circadian rhythm disruption in parents induces long-term immune consequences in the offspring, persisting into adulthood.

Significance

Circadian rhythms are key regulators of immune functions in adults. However, it is unknown at what developmental stage these rhythms begin to manifest themselves in the immune system. Understanding their emergence in early life may help guide time-based clinical interventions for infants.

Circadian rhythms in the perinatal period

Circadian rhythms (see Glossary) are generated by an intrinsic ~24 h cycle that is synchronized by environmental cues. These oscillations are essential for maintaining homeostasis and regulate multiple physiological processes in organisms (Box 1) [1,2]. Within the immune system, circadian oscillations regulate immune cell distribution and function across the body and thus the response to insults, pathogens, and malignant cells [3–5].

While circadian rhythms in the adult immune system are under extensive investigation, their patterns and relevance during the development of an organism remain largely unexplored. The **perinatal period** represents a critical time window for immune programming in humans, laying the foundation for immune competence later in life [6,7]. Any process that impacts the immune system on such a large scale as do circadian rhythms is thus vital to study at an early stage. Investigation of the ontogeny and etiology of immune fluctuations will help us to understand how circadian rhythms shape immune development and function, and whether and how they impact the mature immune system.

This opinion article aims to provide insights into the crosstalk between the development of the body's circadian rhythm and perinatal immunity. We summarize and compare the profiles of circadian rhythms and immune function in early life and adulthood. Drawing on recent studies, we focus on the influence of circadian rhythms on neonatal immune development, with particular emphasis on a maternal contribution. Finally, we explore how a better understanding of a circadian immune system in early life may inform clinical applications to enhance neonatal immunity and attenuate susceptibility to infections in both term and preterm infants.

Development of circadian rhythms

Development of circadian rhythms in humans

The human circadian system begins to develop during fetal life and continues to mature throughout infancy and childhood. The **suprachiasmatic nucleus (SCN)**, the central circadian pacemaker of the body, can be identified histologically by approximately gestational weeks 18–20, but remains functionally immature at birth [8,9]. During gestation, the fetus therefore relies heavily on maternal

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Box 1. Circadian rhythms

Circadian rhythms are governed primarily by circadian clocks located in the brain and peripheral tissues. The SCN of the hypothalamus is an endogenous circadian clock that functions as the central pacemaker of the body. It receives light cues through the retinohypothalamic tract to align to the external environment and synchronizes clocks in peripheral tissues [53]. At the molecular level, circadian rhythms are controlled by a network of circadian transcription factors, including **BMAL1** (basic helix–loop–helix ARNT like 1), CLOCK (circadian locomotor output cycles kaput), CRY1/2 (cryptochrome circadian regulator 1/2), PER1/2/3 (period circadian regulator 1/2/3), NR1D1/2 (nuclear receptor subfamily 1 group D member 1/2, also known as Rev-Erbα/β), and DBP (D-site-binding protein) [5]. These clock genes/proteins form several transcription–translation feedback loops that maintain ~24 h timing and coordinate circadian rhythms across organs. Circadian clock genes regulate the temporal expression of downstream targets known as clock-controlled genes, including immune factors such as TNF (tumor necrosis factor), IL-1β (interleukin-1β), and CXCR4 (C-X-C chemokine receptor type 4), thereby exerting circadian control into cytokines and chemokines, key regulators of the immune system [54].

circadian cues for temporal information. Transplacental signals such as **melatonin**, **cortisol**, and temperature rhythms provide entrainment input to the developing fetal SCN as well as to peripheral organs. These signals are thought to drive the emergence of fetal rhythmic physiology, including daily variations in fetal heart rate and respiratory movements, even in the absence of endogenous SCN rhythmicity [10]. After birth, maternal influences persist through lactational signals, even though the infant starts to receive external **zeitgebers** such as light. While these external cues gradually synchronize the neonatal SCN, maternal cues continue to play a significant role, including the transmission of biological rhythms via breast milk, as well as via behavioral interactions [10–12]. Human milk exhibits diurnal variation in bioactive components, including cortisol, immunoglobulins, cytokines, and melatonin [11]. These components contribute not only to metabolic regulation but also to the sleep–wake organization and immune priming of the infant. By 1–3 months of age, infants begin to produce melatonin endogenously, and plasma cortisol starts to show a stable circadian rhythm, in parallel with the emergence of more consolidated sleep–wake cycles and core body temperature rhythms [13,14]. However, full maturation of the circadian system takes well into the first year of life and beyond to develop, with substantial individual variability influenced by genetic background, maternal behavior, and environmental light exposure [10].

Development of circadian rhythms in rodents

Due to the practical and ethical limitations in human studies, preclinical mouse models have become essential for understanding the temporal dynamics of circadian rhythm development in molecular detail. In mice, the early life stage typically spans from **embryonic day** 18 (E18) to **postnatal day** 21 (P21), covering the late embryonic, neonatal, and infant periods. When it comes to weaning, which occurs around P21, mice are considered juveniles. By ~8 weeks, mice mature into adults. During the mid-gestation period (i.e., E10–12), rhythmic gene expression is minimal or absent, with no detectable oscillations of canonical clock genes in most tissues, including the fetal heart [15]. However, by E15–19, endogenous circadian rhythmicity emerges in several tissues (Figure 1). As early as E15.5, *Per2* expression becomes detectable in the fetal SCN, as shown by bioluminescence rhythms in isolated SCN explants [16]. By E17, *Per1* also exhibits circadian oscillation in the SCN [17]. Notably, early rhythmic activity in the fetal SCN emerges before the canonical molecular clock is fully developed, and appears to be driven by maternal circadian cues [18]. Transcriptomic data from fetal heart and cardiomyocytes at this stage reveal oscillations in circadian clock genes such as *Bmal1*, *Cry1*, *Per2*, *Per3*, *Nr1d2*, and *Dbp*, indicating a key developmental transition of rhythmicity in peripheral organs (Figure 1) [15]. Similarly, in the fetal retina (E16), *Bmal1* and *Cry1* genes display rhythmic expression, with detectable BMAL1 protein, despite the lack of direct light input [19]. Metabolic organs such as the liver and kidney begin to exhibit oscillations of core clock genes shortly before birth, though the amplitudes remain lower than those observed in adulthood [20,21]. After birth, circadian rhythms progressively develop across different tissues, gradually aligning with adult-like oscillatory patterns. In the SCN, the clock genes *Bmal1*, *Cry1*, *Per1*, *Per2*, and *Nr1d1* are oscillatory shortly after birth,

with some genes such as *Per1* and *Per2* exhibiting clear rhythmicity as early as P3. These rhythms gradually stabilize within the first 2 postnatal weeks [17,22,23]. During this developmental window, arginine vasopressin and vasoactive intestinal peptide neurons, essential for SCN network function, exhibit temporal and spatial transcriptional patterns, indicating that SCN circuitry and core clock gene rhythms develop in parallel [24]. A similar trajectory is observed in the heart, with clear developmental phase shifts occurring during early postnatal stages [22]. By contrast, peripheral organs such as the liver, kidney, and adrenal gland exhibit a slower pace of rhythm maturation (Figure 1). At P3–7, these tissues still display low-amplitude and desynchronized clock gene expression, which gradually transition to more adult-like rhythms only after P10 [21,25–27]. Interestingly, the ovary shows detectable time-of-day-dependent fluctuations in core clock genes as early as P7 [28], suggesting that rhythmic regulation is already active in reproductive tissues during early postnatal development. Although no specific time point has been confirmed for the full and functional maturation of circadian rhythms, oscillatory gene expression becomes more robust across tissues by adolescence (around P28) [27]. By adulthood, circadian rhythms are robust and functionally aligned, due to a gradual and organ-specific maturation process throughout early life. Similar to humans, maternal cues also influence early rhythms in rodents. This aspect is discussed specifically in the context of the rhythmic regulation of downstream physiological systems in the immune system.

Development of the immune system

Immune development is recognized as unfolding in a layered manner, with distinct waves of hematopoiesis beginning early in embryonic and fetal life. Certain fetal-derived (tissue-resident) immune cells – such as microglia, alveolar macrophages, epidermal T cells – persist into adulthood. Hematopoiesis originates in the yolk sac, transitions to the **fetal liver**, and ultimately establishes definitive immune cell production in the bone marrow and thymus [29–31]. Throughout gestation, the fetal immune system stays in a tolerant state to allow maintenance of pregnancy, with weak responsiveness to external stimuli. Passive immunity is primarily provided by **maternal IgG antibodies** that are transferred across the placenta via neonatal Fc receptors [32].

At birth, the immune system undergoes a dramatic shift, adapting from the sterile intrauterine environment to the microbially rich external world. This transition requires a tightly coordinated balance of immune tolerance and activation to ensure a safe adaptation to environmental antigens. Perinatal disturbances, such as preterm birth or infections, can disrupt this balance and contribute to impaired immune function and long-term immunological consequences [6,7,33].

In the early postnatal period, **neonates** rely primarily on innate immunity. However, limited immune responses, such as dampened neutrophil function, cytokine production, and natural killing capacity, renders neonatal innate immunity less effective [34]. The neonatal development process is guided by distinct transcriptional programs, which differ from those in adults. Consequently, both functional and phenotypic differences have been described in various murine and human immune cell subsets compared with those in adults (Table 1). During the first weeks and months of life, immune development follows a rapid trajectory [35], with exposure to various antigens shaping immune memory and strengthening long-term immunity. It is significantly supported by maternal-derived components such as secretory IgA and immune cells in breast milk [36,37]. Thus, investigating the developmental mechanism and influencing factors behind neonatal immunity is key to create more effective interventions to improve health outcomes in early life.

Circadian rhythms in immune parameters during development

Physiological processes are firmly interlinked with circadian rhythms in adults, ensuring synchronization with the external environment and across organs. However, the relationship between

Glossary

BMAL1: an essential component of the circadian clock; loss of BMAL1 abolishes circadian rhythmicity at the molecular level.
Circadian rhythms: endogenous biological rhythms with approximately a 24 h period. These oscillations occur even in the absence of external cues (Zeitgebers).
Cortisol: an endogenous glucocorticoid hormone in humans, produced by the adrenal glands in a circadian manner; it regulates metabolism, immune responses, and stress responses.
Dams: pregnant or lactating female animals in preclinical research, particularly mice.
Docosahexaenoic acid (DHA): a long-chain omega-3 fatty acid essential for brain and eye development and anti-inflammatory processes; it is obtained primarily from breast milk during the perinatal period.
Embryonic day: number of days post-fertilization.
Fetal liver: the primary site of hematopoiesis during embryonic and fetal development in the mouse; after birth, the bone marrow takes over this function.
Maternal antibodies: antibodies generated by the mother in response to antigens; they can be passively transferred to offspring via the placenta (IgG) or through breast milk (IgA) to provide early-life immunity.
Melatonin: a hormone produced in a circadian manner by the pineal gland; it regulates sleep–wake cycles and other physiological processes, including immunity.
Myeloid-derived suppressor cells (MDSCs): a heterogeneous population of immature myeloid cells with immunosuppressive functions.
Neonate: a newborn infant, typically defined as a baby within the first 28 days of life after birth.
Peak phases: the time points at which a biological process reaches its maximum level in a circadian cycle.
Perinatal period: in mice, the period is typically defined from late gestation (approximately E17–E19) to the early postnatal period (typically until P7–P10), which is critical for fetal-to-neonatal transition; in humans, it is defined as the period from the 22nd week of gestation to postnatal day 7, followed by the neonatal period, which extends to postnatal day 28.

circadian rhythms and the immune system in early life is unclear. Maternal circadian rhythms during pregnancy not only synchronize fetal clocks and shape metabolic programming, but also exert critical influence over the intrauterine immune environment, particularly through the placenta [20]. In mice with disrupted circadian rhythms, increased expression of Iba1 and CD11b – markers of activated macrophages and microglia – in the placenta suggests the presence of a proinflammatory environment [38]. These findings raise the possibility that intact maternal circadian clocks may be essential for maintaining a healthy immune milieu within the placenta, thereby supporting a successful pregnancy. Given the extensive interactions between placenta and fetus, the regulated inflammatory environment in the placenta may influence neonatal immune system development (Figure 2, Key figure). The importance of the role of maternal circadian rhythms on fetal immunity is further supported by a study using conditional uterine *Bmal1*-deficient mice – progesterone receptor (*Pgr*)-*cre:Bmal1*^{flox}, *Bmal1*^{cKO} mice – in which disruption of uterine clock function results in fetal resorption and miscarriage after normal embryo implantation. In these animals, development of maternal blood spaces is impaired, leading to defective placental vascularization and compromised maternal–fetal exchange [39]. In addition to affecting placental structure, circadian rhythms also regulate the function of P-glycoprotein during late gestation, a key efflux transporter that modulates the transfer of multiple substances critical for fetal protection and development [40]. Furthermore, the uterine immune environment is closely linked to maternal circadian rhythms. In *Bmal1*^{cKO} placentas, uterine natural killer (NK) cells – especially the CD161^{+} subset associated with immune tolerance and vascular remodeling – are markedly reduced in the

Peroxisome proliferator-activated receptor γ (PPARγ) pathway: a signaling pathway mediated by PPARγ, a nuclear receptor involved in lipid metabolism, adipogenesis, and immune regulation.
Postnatal day: number of days after birth.
Suprachiasmatic nucleus (SCN): the central circadian clock located in the hypothalamus; it receives light signals from the retina and synchronizes peripheral clocks.
Zeitgebers: external environmental cues that synchronize circadian rhythms, including light, temperature, and food intake.

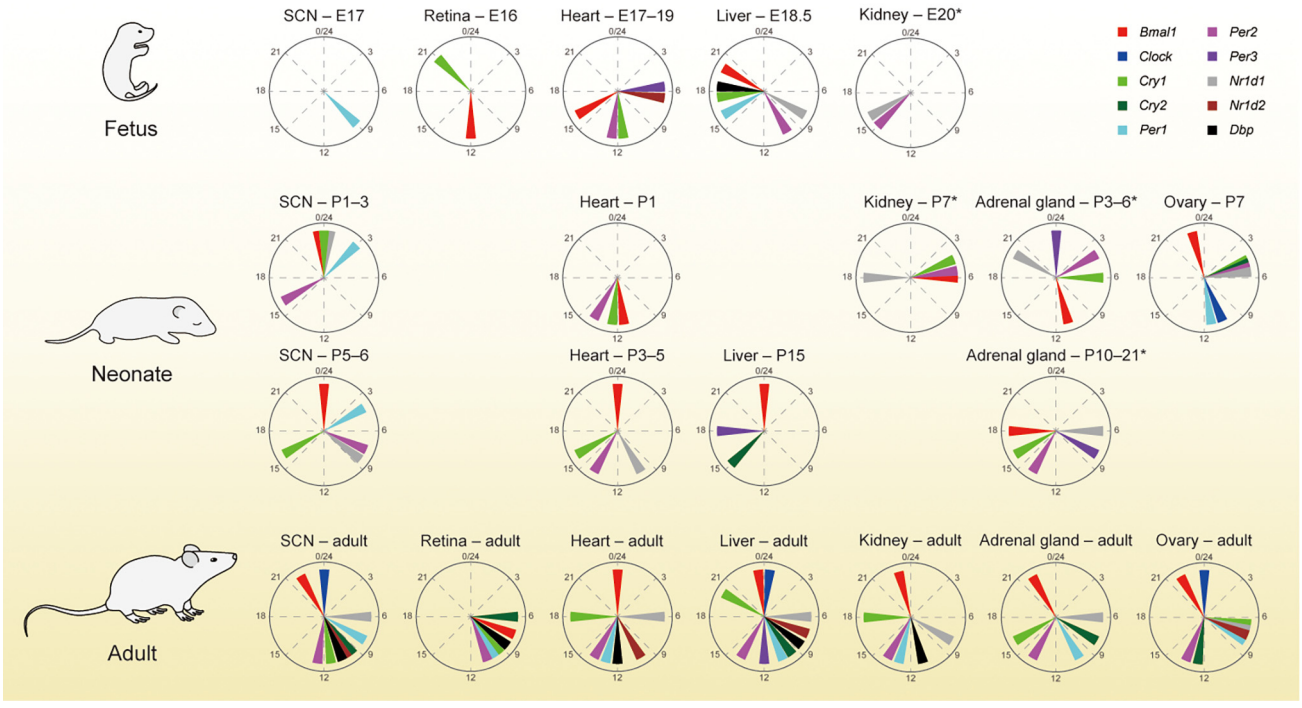

Figure 1. Development of circadian rhythms. Developmental timeline of circadian clock gene expression across multiple organs in rodents, spanning fetal, neonatal, and adult stages. The radial plots represent the approximate **peak phases** of core clock gene expression within a 24 h period (ZT0–ZT24; ZT: Zeitgeber time, where ZT0 refers to lights on and ZT12 to lights off). Data are compiled from multiple published meta-data sources: SCN (E17 [17], P1–3, P5–6 [17,22], adult [78,79]), retina (E16 [19], adult [80,81]), heart (E17–19 [15], P1, P3–5 [22], adult [82,83]), liver (E18.5 [20], P15 [26], adult [84–86]), kidney (E20, P7 [21], adult [82]), adrenal gland (P3–6 [25], P10–21 [25,27], adult [87,88]), ovary (P7 [28], adult [89]). Asterisks (*) indicate data from rats; all other data are from mice.

Table 1. Immune system comparison between neonates and adults

Parameters	Mice		Human	
	Age/stage	Functional profile	Age/stage	Functional profile
Neutrophils	E13–14 [55–57]	Reduced chemotaxis, adhesion, transmigration, and antimicrobial activity	Cord blood and newborns [57–59]	Reduced rolling and adhesion, reduced NLRP3 inflammasome activation; noncanonical NF-κB signaling pathway
	Adult [60]	Fully functional; proinflammatory phenotype	Adult [57–59]	Canonical NF-κB signaling pathway
Monocytes/macrophages	P7 [61]	Mainly CD206^{hi} macrophages in CNS	Newborns [36,62]	Lower rates of aerobic glycolysis; S100-alarmins as alternative age-specific mechanism of immune regulation
	Adult [61]	Mainly MHCII^{hi} macrophages in CNS	Adult [36,62]	Higher rates of aerobic glycolysis
Dendritic cells (DCs)	P7 [63,64]	Limited plasmacytoid DCs; lower frequency of cDCs; reduced antigen presentation	Newborns [64]	cDC2 from fetal spleen respond differently to various PAMPs; higher production of anti-inflammatory cytokines
	Adult [63,64]	More plasmacytoid DCs; higher frequency of cDCs; efficient antigen presentation	Adult [64]	Higher production of inflammatory cytokines
Innate lymphoid cells	P0–3 [65]	ILC1 with high cytotoxicity	Newborns [66]	ILC1-like and ILC3-like functionally immature; ILC2 fully functional
	Adult [65]	ILC1 with low cytotoxicity and high memory potential	Adult [67]	Regulate effector cell activity
NK cells	P7 [68]	Immature phenotype; highly proliferative	Newborns [69]	Phenotypically formed but functionally reduced
	Adult [68]	Mature phenotype	Adult [69]	Mainly mature NK cells
CD4$^+$ T cells	P7 [70]	Differentiated into Th2 and Th17 cells; stronger activation; higher proliferation	Newborns [71,72]	Th2-biased; increased sensitivity to low antigen doses; equipped to respond to TLR1 and TLR2 ligands
	Adult [70]	Differentiated into Th1 and Treg cells	Adult [73]	Classical adaptive response; TCR-dependent activation
CD8$^+$ T cells	P0–10 [74]	TCR-independent activation; inflammation-dependent activation	Newborns [72]	Innate-like response; more responsive to innate cytokine stimulation, equipped to respond to TLR2 and TLR5 ligands
	Adult [74]	Classical adaptive response; TCR-dependent activation	Adult [73]	Classical adaptive response; TCR-dependent activation
B cells	P6–8 [75,76]	Mainly B-1 cells; limited antibody diversity (IgM); IL-10 production	Newborns [77]	Mainly mature, naïve CD5$^+$ B cells; accelerated responsiveness to stimulation; facilitated IgA class switching
	Adult [75,76]	Mainly B-2 cells; various antibodies (IgG, IgA, IgE)	Adult [77]	Increasing frequencies of memory B cells and plasma blasts

spongiotrophoblast layer, indicating that circadian regulation is critical for establishing proper immune conditions at the fetal–maternal interface [39].

Beyond its role in ensuring pregnancy and shaping the intrauterine immune environment, maternal circadian rhythms are emerging as a key factor in regulating fetal and neonatal immune development. A recent study demonstrated that maternal circadian rhythms actively shape neonatal immune homeostasis through the metabolic programming of regulatory myeloid cells [41]. The researchers established a model of maternal circadian rhythm disruption by altering the environment with repeated 8 h light–dark phase advances every 2 days from E10.5 until birth. Neonatal mice born to these circadian rhythm-disrupted **dams** exhibit increased susceptibility to inflammatory disorders, including necrotizing enterocolitis and sepsis, due to impaired immunosuppressive function of **myeloid-derived**

Key figure

Influence of maternal rhythms on neonatal immunity

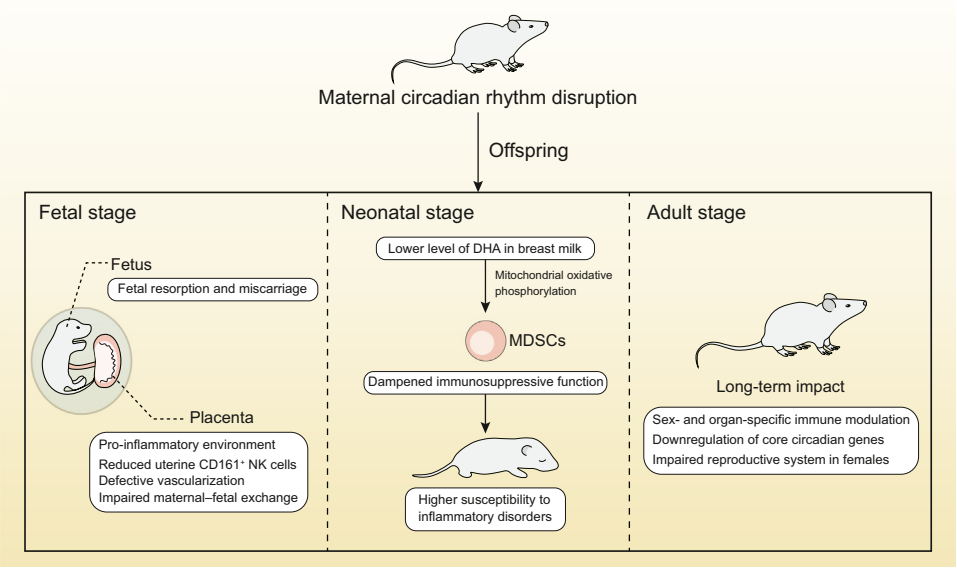

Figure 2. Maternal circadian disruption impacts immune development across offspring life stages. Disruption of maternal circadian rhythms alters immune trajectories in offspring from fetal to adult life. In the fetal stage, impaired uterine immunity and placental function contribute to pregnancy loss. In neonates, reduced docosahexaenoic acid (DHA) in breast milk and mitochondrial dysfunction compromise myeloid-derived suppressor cell (MDSC)-mediated immunosuppression, increasing susceptibility to inflammation. In adulthood, long-term consequences include sex- and tissue-specific immune alterations, downregulation of core clock genes, and reproductive deficits in females.

suppressor cells (MDSCs). Several altered components in the breast milk and serum of dams with disrupted circadian rhythms, particularly an overall reduction in **docosahexaenoic acid (DHA)**, contribute to postnatal immune modulation in the offspring [41]. DHA, an essential maternally derived fatty acid, acts through the **peroxisome proliferator-activated receptor γ (PPARγ) pathway** to regulate mitochondrial oxidative phosphorylation and metabolic fitness of MDSCs. Both perinatal DHA supplementation and adoptive transfer of functional MDSCs can restore the immunosuppressive function of MDSCs and rebalance the neonatal immune system. This study highlights the role of the maternal circadian rhythm in training neonatal immunity during the critical developmental time window [41].

Notably, this early circadian disruption appears to have long-term consequences on the immune system. Circadian rhythm disruption in parents changes the cytokine responses upon lipopolysaccharide stimulation in adult offspring in a sex-dependent manner: male offspring show increased *Il1* and decreased *Tnfα* expression in the spleen, while female offspring exhibit reduced *Il6* expression in the hypothalamus and increased serum bactericidal capacity under inflammatory conditions [42]. Furthermore, cytokine and chemokine signaling pathways in the ovaries of female offspring are upregulated, alongside downregulation of core circadian clock genes. In addition, impaired ovarian follicle development and oocyte maturation suggest potential transgenerational effects of maternal chronodisruption [43]. Collectively, these recent findings highlight the critical importance of maternal circadian signaling for neonatal immune

development. However, it remains unclear whether the development of circadian rhythms and the immune system are synchronized during early life, or whether one influences the other. Future studies are thus necessary to elucidate the mechanistic links between onset of circadian oscillations and the development of immune functions.

Relevance of circadian immune development in early clinical interventions

Circadian rhythms govern immune responses

Circadian rhythms critically regulate immune responses, shaping activity and function of immune cells throughout the day. In murine models, recent research has demonstrated that circadian rhythms govern various immune processes, including leukocyte trafficking, antigen presentation, and cytokine secretion [3,4]. In humans, both innate and adaptive immunity exhibit strong time-of-day differences, as observed in both children and adults. Studies on vaccination timing generally show that morning administration elicits a stronger immune response than evening vaccination, resulting in enhanced antibody production, more robust cellular immunity, and lower breakthrough infection rates [4,44–47]. Similarly, in cancer immunotherapy, circadian timing of immune checkpoint inhibitor and chimeric antigen receptor (CAR)-T cell infusion influences therapeutic outcomes [48,49]. Across both humans and rodents, peak immune responsiveness aligns with the onset of the behavioral activity phase, likely reflecting shared mechanisms such as rhythmic immune cell trafficking, proliferation, and germinal center formation [4].

Circadian immune interventions in early life

Infections early in life, such as pneumonia, sepsis, and meningitis, are leading causes of morbidity and mortality in neonates. Vaccination has become a cornerstone of preventive healthcare, actively inducing protective immunity in a safer and more effective manner early on. Traditionally, the neonatal immune system has been regarded as poorly responsive to vaccines. However, emerging evidence challenges this view. Indeed, neonates exhibit robust immune responses to certain vaccines, including bacillus Calmette–Guérin (BCG), oral polio (OPV), and hepatitis B vaccines – comparable with, if not stronger than, responses in older infants. Additionally, promising serological responses have been observed for other vaccines not yet licensed for neonatal administration, such as those targeting rotavirus, diphtheria, and tetanus [50–52]. Despite this immunological potential, neonatal vaccines do not yet target the primary pathogens responsible for the most severe early-life infections [50]. This highlights the need for tailored vaccination strategies that align with the unique physiology of neonatal immune development. While maternal vaccination is a crucial strategy for enhancing neonatal protection through vertical antibody transfer, an emerging concept is to optimize vaccine timing in neonates based on circadian immune regulation. Given the time-of-day-dependent efficacy observed in adults and older children, it is plausible that the neonatal immune system may also exhibit circadian variation. However, the precise onset of circadian immune oscillations in neonates remains unclear, making the optimal timing of early-life vaccinations difficult. Further research is needed to determine whether aligning neonatal vaccination schedules with circadian immune peaks could enhance vaccine efficacy and long-term immune protection.

Beyond optimizing neonatal interventions, current findings also underscore the importance of stable maternal circadian rhythms for offspring health. Experimental evidence shows that circadian disruption in mothers can adversely influence immune development in their offspring during both the prenatal and postnatal periods [38,39,41]. Therefore, promoting regular light–dark cycles and daily routines during pregnancy and early postpartum may represent an accessible strategy for optimal immune development in the offspring. Integrating circadian health into maternal education could offer a simple yet powerful approach to support the long-term wellbeing of children.

Concluding remarks

Circadian rhythms are increasingly recognized as key regulators of immune function in adults, yet their role during early life remains poorly understood. In this opinion article we highlight emerging evidence indicating an essential role of the circadian clock in early life, especially from the maternal side. Maternal circadian signals transmitted through the placenta or through breast milk contribute to maintaining a protective environment and help fine-tune the specific and time-dependent needs of both the fetus and the neonate. Disrupting rhythmicity during this delicate time of life most likely has long-term impacts on immune homeostasis and reproductive health of adult offspring, but many fundamental questions still remain unanswered (see Outstanding questions), particularly regarding the ontogeny of immune circadian rhythms and their synchronization with maternal and environmental signals. Addressing these knowledge gaps will guide the development of clinical interventions to enhance neonatal immunity and long-term health outcomes.

Outstanding questions

At what time point during development do circadian rhythms in the immune system become apparent and functionally relevant?

Which factors are required for the appearance of circadian immune rhythms during development?

What is the influence of maternal and (potentially) paternal factors compared with neonatal factors in the development of immune rhythms in the offspring?

Can circadian rhythms in the immune system in early life be exploited clinically: for example, by timed vaccinations?

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Declaration of interests

The authors have no interests to declare.

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