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Circadian Perturbations in Immune Cell Trafficking

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Abstract

Immune cells form the first line of defence and are important for their properties like pathogen clearance, phagocytosis, inflammation, and tissue remodeling. Innate and adaptive immunity together work in synchrony to regulate several pro- and anti-inflammatory processes. Detection of multiple clues is the key during immune cell migration wherein: the chemokines (chemo-attractant cytokines) are extensively investigated to decipher the intricacies of migration and homing. Chemokine receptors (CXCR4, CCR2, CXCR7, etc.) expressed by the immune cells are sensitive to their ligands (CXCL12, CCL2, CXCL13, etc.) released from the site of infection. On the other hand, the circadian control of innate and adaptive immune responses is widely reported in which a state of chronodisruption hampers the organ/tissue-specific homing of immune cells. The same can affect the physiological outcome of therapeutic intervention and, hence, a profound understanding of circadian circuits controlling immune cell trafficking can provide a better understanding of disease progression and planning the course of therapy. Skewed immune cell trafficking can vary extensively as per the disease wherein the role of chronodisruption can be crucial. This review focuses on factors regulating immune cell migration and the aberrations caused due to circadian perturbations.

Keywords: Circadian, Chemokines, Chrodisruption, Monocyte Homing

1. Introduction

Monocytes, neutrophils, T cells, and B cells migrate from their secondary lymphoid organs into the circulation and return to perform their routine scavenging activities as well as to poozle out traces of inflammatory signals[2–4]. Once matured these cells are sensitive to chemokine signaling that results in their subsequent migration commensurate to the concentration gradient of their respective ligands. Neutrophils and monocytes are usually the first responders to reach the site of infection and to recruit other immune cells by release of cytokines for triggering the downstream cascade[5,6]. Circadian clocks drive the daily oscillation in the behavior and physiology of organisms[7]. They are the cell-, tissue- or organ-specific clocks that can impact the responsiveness, localization, and activity of immune cells. Compelling evidence for the circadian rhythmicity and the underlining mechanisms that orchestrate an immune response during pathogen exposure or tissue repair exists[8]. The migration and localization of immune cells during surveillance, tissue repair, or disease pathogenesis have been individually as well as collectively reported for their circadian control[9]. Hence, the chronobiology of immune cell migration in health and disease is currently under focus and forms the core of this review article (Figure 1).

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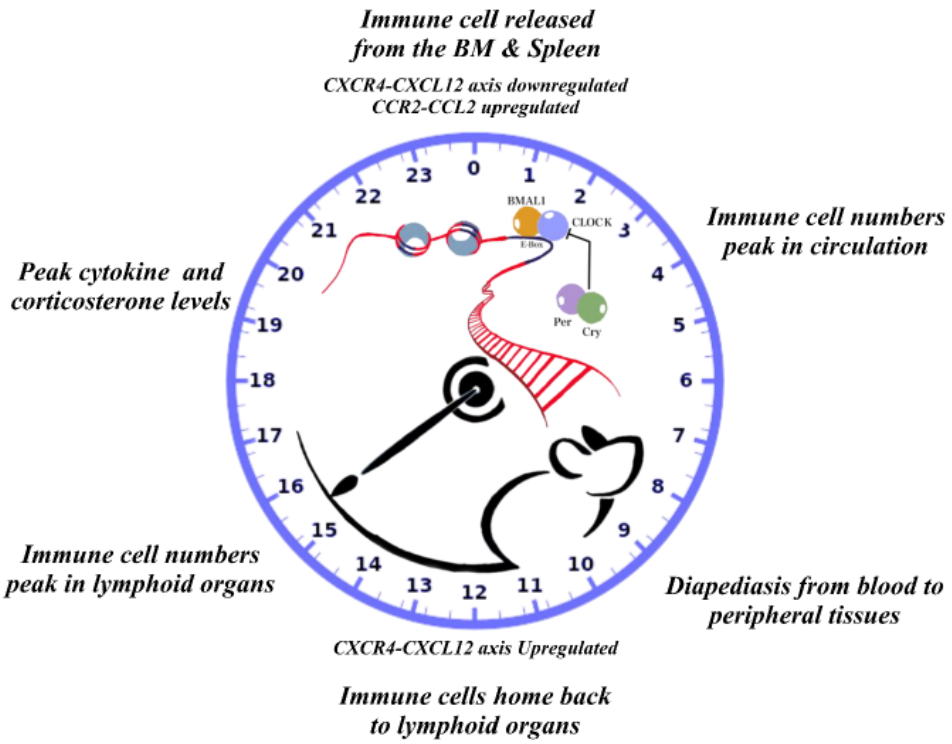

Figure 1. Circadian biology of immune cell trafficking in rodents. Note the regulatory role of Core (BMAL 1 and CLOCK) clock genes.

2. Update on Lymphocyte- and Monocyte Migrations

Fundamentally, monocytes are crucial in tissue homeostasis, resolution of inflammation, and imparting immunity. Monocytes are highly plastic in nature and can differentiate into macrophages or dendritic cells according to their micro-environmental clues[10]. Recruitment of monocytes usually begins with their diapedesis from the vascular endothelium and its subsequent downstream events[2] (Figure 2). Tumor Necrosis Factor-α (TNF-α) or Interleukin-1β released by the tissue macrophages stimulate the endothelial cells to induce expression of adhesion molecules like E & P selectin, intracellular adhesion molecule -1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)[5,11]. These molecules interact with the surface proteins expressed on the monocytes and induce firm adhesion to endothelium, regulated by C-C & C-X-C chemokines and very late antigen-4 (VLA-4). Immergence of monocytes from bone marrow is orchestrated by CXCR4-CXCL12 and CCR2-CCL2 axis wherein CCL2 is known to desensitize its migration towards the ligand (CXCL12)[12]. Monocyte recruitment is a multistep process and follows a series of immune and endothelial cell interactions preceding the transmigration step. Upon adhesion, the monocytes crawl onto the endothelial lining to find an appropriate site of extravasation assisted by the ICAM-1 receptor[13] wherein they undergo paracellular or transcellular migration across the endothelial lining. Herein, endothelial VCAM-1 and ICAM-1 elevate intracellular Ca^{+2} concentration and cause the loosening of tight junctions resulting in cell migration[14,15]. A detailed compilation of the chemokines, their site of expression, and their function/s are detailed in Table 1.

Naïve T cells originate from the secondary lymphoid organs and have been reported to home from blood to lymph nodes[16]. T cells undergo activation and migrate by following the chemokine gradient to the site of inflammation. This event is preceded by extravasation of T cells from the blood vessels/lymph nodes, a process mediated by L-selectin[17]. An inflamed endothelium expresses E & P selectins that arrest rolling and diapedesis of the cells[18]. It is noteworthy that the patients of Multiple Sclerosis and Rheumatoid arthritis have significantly upregulated CCR5 & CXCR3 in Th1 cells and more

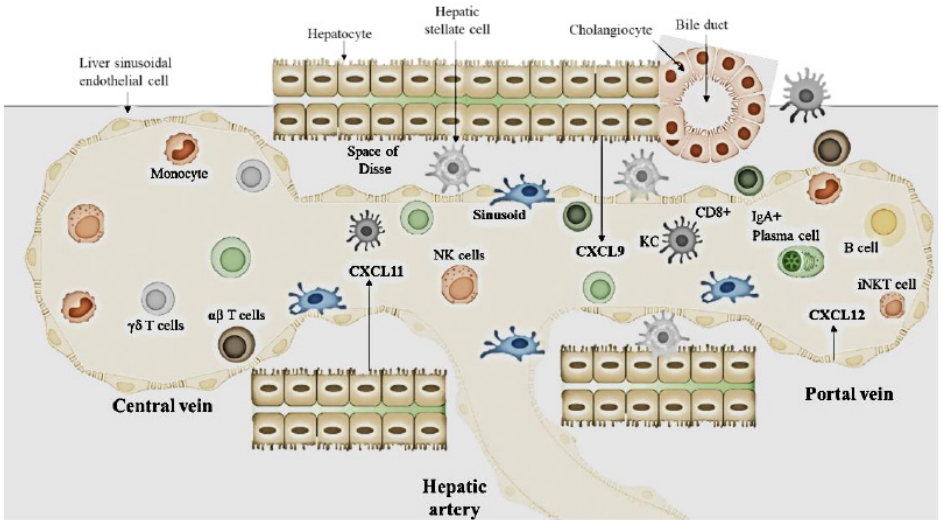

Figure 2 Sequence of events in monocyte homing viz., rolling, arrest and extravasation (diapedesis) of monocytes to the inflamed tissue.

Table 1. Chemokines regulating monocyte migration

Class	Common name	Gene name (mouse)	Expressed on	Function	Reference/s
Chemokine receptors	CCR1	*Ccr1*	Monocytes	Arrest	(22)
	CCR5	*Ccr5*	Monocytes	Spreading, arrest, transmigration	(23)
	CCR2	*Ccr2*	Monocytes	Adhesion, transmigration	(2)
Selectins	E- selectin	*Sele*	EC	Rolling	(24)
	P- selectin	*Selp*	EC	Rolling, arrest	(25)
	L-selectin	*Sell*	Monocytes	Rolling, signalling	(5)
Integrins	LFA-1	*Itgal, Itgb2*	Monocytes	Patrolling, locomotion, arrest	(3,14,26)
	Mac-1	*Itgam, Itgb2*	Monocytes	Arrest, locomotion, transmigration, activation	(3)
	VLA-4	*Itga4, Itgb1*	Monocytes	Adhesion, transmigration	(3)
Immunoglobulin superfamily	ICAM-1	*Icam1*	EC	Adhesion, transmigration	(3)
	ICAM-2	*Icam2*	EC	Adhesion, transmigration	(10)
	MCAM	*Mcam*	EC	Transmigration	(27)
	JAM-A	*F11r*	EC	Transmigration	(26)
	JAM-B	*Jam2*	EC	Transmigration	(6)
	JAM-C	*Jam3*	EC	Reverse transmigration	(6,28)
	JAML	*Amica1*	Monocytes	Arrest, transmigration	(11)
	VCAM-1	*Vcam1*	EC	Arrest	(3)
	PECAM-1	*Pecam1*	EC, monocytes	Transmigration	(29)
	Poliovirus receptor	*Pvr*	EC, monocytes	Transmigration	(30)
	MIC2	*Cd99*	EC, monocytes	Transmigration	(31)
	ICD99L2	*Cd99l2*	EC, monocytes	Transmigration	(32)
Other(s)	VE- cadherin	*Cdh5*	EC	Transmigration	(33)
	Eph A1, -2	*Epha1*	Monocytes	Transmigration	(34)
	Eph B1–4	*Ephb1*	Monocytes	Transmigration	(34)

Table 2. Key molecules regulating, lymphocyte migration

Class	Common name	Role in Lymphocyte migration	References
Selectins	L-selectin (CD62L)	Homing to lymph nodes and Peyer's patches	(35)
	E-selectin (CD62E)	Homing of memory and effector cells to skin and sites of inflammation	(36)
	P-selectin (CD26P)	Homing of memory or effector (Th1) cells to sites of inflammation; platelet-mediated interaction with venules that express peripheral-node addressin	(18,37,38)
Selectin ligands	Sialyl-LewisX (sCD15)	Function depends on the presentation molecule	(39,40)
	P-selectin glycoprotein ligand 1	Homing of memory and effector (Th1) cells to inflamed tissue; binding to activated platelets	(37,41)
	Peripheral node addressin	Homing of naive T cells and central memory cells to lymph nodes	(16,42)
	Cutaneous lymphocyte antigen	Homing of memory and effector cells to inflamed skin	(36,43)
α4 Integrins	α4β1 (VLA-4)	Homing of memory and effector cells to inflamed tissues, especially lung	(44,45)
	α4β7	Homing of all lymphocytes to gut and associated lymphoid tissues	(46,47)
Immunoglobulin superfamily	ICAM-1 (CD54)	Critical endothelial ligand for β2 integrins	(13,48,49)
	VCAM-1 (CD106)	Homing of memory and effector cells to inflamed tissue	(36,50,51)
	Mucosal addressin-cell adhesion molecule 1	Homing of all lymphocytes to gut and associated lymphoid tissues	(17,52)
β2 Integrins	αLβ2 (LFA-1, CD11αCD18)	Homing of all lymphocytes to lymph nodes, Peyer's patches, and most sites of inflammation; adhesion to antigen-presenting cells	(1,40)

prominently in T cells[19,20]. The Naïve T cells exhibit high levels of CCR4, CCR8, and CXCR4 and a circadian cyclicity that can impact their migration and organ-specific interactions in healthy and diseased individuals[21] (Figure 2). The various types of cell adhesion and signaling molecules and their regulatory roles in immune functions and homing are presented in Table 2.

3. Circadian Control of Immune Cell Trafficking

A gamut of immunological events *viz*., expression of recognition receptors, secretion of coagulation factors, and release of histamine or cytokines have been reported to have a circadian control[53]. Also, the phagocytic activity of macrophages is known to exhibit circadian oscillations. The altered Period 1 expression of Natural Killer cells affects its ability to make Interferon γ or killing of the target cells. In macrophages, manipulation of Rev-erbs suppresses CX3CR1, CCL2, CCL5, IL12, and IL6 resulting in a subdued inflammatory response[54,55]. The photoperiodic cues have been implicated in entrain cyclic homing of hematopoietic stem cells (HSCs) to skeletal muscles and bone marrow. In mice, BMAL-1, a key clock gene, has been implicated in regulating multiple immune functions including monocyte homing. A study reports that homing behavior was completely abolished in BMAL1$^{-/-}$ mice underlining the importance of the regulatory role of a core clock gene. The central clock collects cues from the environment that regulates the expression of CXCL12 which translates into control of the rhythmic egress of cells into the periphery[56]. Another evidence of a clock-controlled influx of neutrophils into the lungs is suggested by BMAL1$^{-/-}$ bronchiolar epithelial club cells that abrogate the rhythmic cyclicity. Also, during acute inflammation, the release of CXCL5 from the club cells in the lungs has been found to be different in the active (night) *vs* inactive (day) phases of mice. The rhythmicity of IL-7R and CXCR4 in T cells has been attributed to the circadian cyclicity of glucocorticoids[57]. Herein, it may be noted that high levels of T cells in the resting phase of the mouse correlate with low IL-7R. Conversely, the active (night) phase of mice

recorded high IL-7R and an accumulation of T cells in the spleen and lymph nodes[58]. The rhythmic oscillations of cell adhesion molecules ICAM-1, ICAM-2, and VCAM-1 are well-known in lymphoidal and non-lymphoidal tissues. These molecules exhibit pro-migratory properties and, therefore, circadian control of their expression can play a subtle modulatory role resulting in long-lasting physiological implications in health and disease. Silencing of the cellular clock in leukocytes has been reported to result in an altered time-specific response that is governed by chemokine receptor (eg., CXCR4). However, selectins (E & P- Selectins) have been reported to display a tissue-restricted circadian oscillation in the liver that needs further investigation[59]. Currently, alterations of Reverb have been reported to be beneficial in both atherosclerosis[60] and cancer[61]. Also, stabilizing cry gene expression has been reported to manifest anti-inflammatory activity. These reports provide an intriguing update on immune cell trafficking and humoral-organ crosstalk that can undergo subtle changes due to alterations in circadian rhythms. Taken together, an optimal immune response can vary in conditions of circadian perturbations and chronodisruption that need further clarity.

4. The Way Forward

A better understanding of drug-based targeting of circadian oscillations and bringing about corrective changes in their rhythms can be a novel approach to treating metabolic diseases. It would be intriguing to decipher the time for administration of chrono-modulatory drugs because, more than the dose, the timed administration of the drug is vital to orchestrating desired physiological/therapeutic response. An improved understanding of the circadian basis of disease and lifestyle disorders can help in addressing many unanswered questions. Further, clarity on the complex interplay between the intrinsic cellular clocks of immune cells and the oscillations of the target tissue can open new research avenues in the field of chrono-medicine.

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