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Title: The Interplay between Mast Cells, Pineal Gland and Circadian Rhythm: Links Between Histamine, Melatonin and Inflammatory Mediators

Running Title: Mast Cells, Pineal Gland and Circadian Rhythm

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Abbreviations
AANAT = aralkylamine *N*-acetyltransferase; **Ags** = antigens; **Akt** or **PKB** = protein kinase B; **AHR** = airway hyperresponsiveness; **ASMT** = Acetylserotonin O-methyltransferase; **BMAL1** =

brain and muscle ARNT-like 1; **BMCMCs** = bone marrow-derived cultured mast cells; **BMMCs** = bone marrow-derived mast cells; **C5a** = anaphylatoxin complement 5a; **cAMP** = cyclic adenosine monophosphate; **$Ca_V1.3$** = L-type voltage-gated Ca^{2+} channels; **CCA** = cholangiocarcinoma; **CFTR** = cystic fibrosis transmembrane conductance regulator; **CLCA1** = chloride channel accessory 1; **CLOCK** = circadian locomotor output cycles kaput; **COPD** = chronic obstructive pulmonary disease; **COX** = cyclooxygenase; **CRISPR/Cas9** = clustered regulatory interspaced short palindromic repeat/CRISPR associated protein-9 nuclease; **CRY** = cryptochrome; **CXCL** = C-X-C motif chemokine ligand; **CXCR** = C-X-C motif chemokine receptor; **DARPins** = designed ankyrin repeat proteins; **dCREB2** = Drosophila cAMP response element binding protein 2; **DIDP** = diisodecyl phthalate; **ENU** = N-ethyl-N-nitrosourea; **ERK** = extracellular-signal regulated kinase; **FcεRI** = high affinity receptor for the Fc region of immunoglobulin E; **GOB5 or CLCA1** = chloride channel accessory 1; **Gβγ** = βγ subunits of G protein; **GPER** = G-protein-coupled estrogen receptor; **HDC** = histidine decarboxylase; **HIF-1α** = hypoxia-inducible factor-1alpha; **HIOMT** = hydroxyindole-O-methyltransferase; **HMC** = human mast cell; **HO-1** = heme oxygenase 1; **HR** = histamine receptors; **IBS** = irritable bowel syndrome; **IEC** = intestinal epithelial cell; **IgE** = immunoglobulin E; **IκBα** = Inhibitor of the nuclear transcription factor NF-κB; **IL** = interleukin; **IL-1RL1** = interleukin-33 receptor 1; **IL-1RacP** = interleukin-33 receptor 1 accessory protein; **ILC2** = innate lymphoid cells group 2; **IPF** = idiopathic pulmonary fibrosis; **LPS** = lipopolysaccharide; **LT** = leukotrienes; **Lyn** = tyrosine-protein kinase; **MAPK** = mitogen-activated protein kinase; **MCs** = mast cells; **MCP1**= monocyte chemoattractant protein 1; **MMCP6** = mouse mast cell protease-6; **MRGPRX2** = Mas-related G protein coupled receptor X-2; **MT** = melatonin receptors; **NAD(P)H** = nicotinamide adenine dinucleotide (phosphate); **NAT** = N-acetyltransferase; **NECA** = 5'-N-ethylcarboxamido-adenosine; **NF-κB** = nuclear factor binding near the κ light chain gene in B cells; **NGF** = nerve growth factor; **NLRP3** = NLR pyrin domain containing 3; **NLS** = nuclear localization signal; **NQO** = NAD(P)H-quinone oxidoreductase 1; **Nrf2** = nuclear factor erythroid-derived factor 2; **OTC** = over-the-counter; **OCT3** = organic cation transporter 3; **OEA** = oleoylethanolamide; **OGG1** = 8-oxoguanine DNA glycosylase 1; **PBC** = primary biliary cholangitis; **PDTC** = pyrrolidine-dithiocarbamate; **PER** = period; **PGD2** = prostaglandin D2; **PKA/B** = protein kinase A/B; **PMACI** = phorbol 12-myristate 13-acetate plus calcium ionophore A23187; **PSC** = primary sclerosing cholangitis; **RBL** = rat basophilic leukemia; **REM-SD** = rapid eye movement sleep deprivation; **rhIL-1β** = recombinant human interleukin-1 beta; **ROS** = reactive oxygen species; **Ryr** = ryanodine receptor; **SCF** = Stem cell factor; **SCN** = suprachiasmatic nucleus; **SELEX** = systematic evolution of ligands by exponential enrichment; **SOD1** = copper-zinc superoxide dismutase 1; **ST2** = suppressor of tumorigenicity; **STAT1** = signal transducer and activator of transcription; **Syk** = spleen tyrosine kinase; **TALEN** = transcription activator-like effector nucleases; **TBI** = traumatic brain injury; **TGF-β** = transforming growth factor beta; **Th1/2** = T-helper subsets 1/2; **TMN** = tuberomammillary nucleus; **TNFα** = tumor necrosis factor alpha; **TSLP** = thymic stromal lymphopoietin; **VEGF** = vascular endothelial growth factor; **VH** = visceral hypersensitivity; **WAS** = water avoidance stress; **WT** = wild type.

Abstract

Our daily rhythmicity is controlled by a circadian clock with a specific set of genes located in the suprachiasmatic nucleus in the hypothalamus. Mast cells (MCs) are major effector cells that play a protective role against pathogens and inflammation. MC distribution and activation are associated with the circadian rhythm via two major pathways, IgE/FcεRI- and IL-33/ST2-mediated signaling. Furthermore, there is a robust oscillation between clock genes and MC-specific genes. Melatonin is a hormone derived from the amino acid tryptophan and is produced primarily in the pineal gland near the center of the brain, and histamine is a biologically active amine synthesized from the decarboxylation of the amino acid histidine by the 1-histidine decarboxylase enzyme. Melatonin and histamine are previously reported to modulate circadian rhythms by pathways incorporating various modulators in which the nuclear factor binding near the κ light chain gene in B cells,NF-κB, is the common key factorNF-κB interacts with the core Clock genes and disrupts the production of proinflammatory cytokine mediators such as IL-6, IL-13, and TNF-α. Currently there has been no study evaluating the interdependence between melatonin and histamine with respect to circadian oscillations in MCs. Accumulating evidence suggests that restoring circadian rhythms in MCs by targeting melatonin and histamineNF-κB may be promising therapeutic strategy for MC-mediated inflammatory diseases. This review summarizes recent findings for circadian-mediated MC functional roles and activation paradigms, as well as the therapeutic potentials of targeting circadian-mediated melatonin and histamine signaling in MC-dependent inflammatory diseases.

1. Introduction

Mast cells (MCs) are derived from multipotent hematopoietic progenitor cells in the bone marrow and involved in innate immunity[1]. The migration of MC progenitors into target tissues and their proliferation and activation are critically regulated by stem cell factor (SCF) recognized by its receptor c-Kit, a type III tyrosine kinase broadly expressed on mature MCs[2]. Other factors contributing to MC abundancy and localization and/or phenotypic characteristics are transforming growth factor-β (TGF-β)[3]; integrins[4]; C-X-C motif chemokine receptors including CXCR2, CXCR3, CXCR4, and CXCR5[5]; and selected interleukins such as (IL)-3[6], and IL-33[7]. MCs are historically considered key effector cells of allergic reactions employing the immunoglobulin (Ig)E-mediated activation pathway[8]. MCs are associated with regulation of immunity and inflammation by releasing important inflammatory mediators, including predominantly histamine, vascular endothelial growth factor (VEGF), IL-6, and IL-8[9]. There is also evidence indicating the expression of sex hormone receptors including estrogen, estradiol, and progesterone receptors in human MCs[10]. Activation of MCs is generally classified into two mechanisms based on the link to the adaptive immune system. The most extensively studied mechanism is the antigen-specific immunoglobulin E-bound/high affinity receptor for the Fc region of immunoglobulin E (IgE/ FcεRI)-mediated signaling which plays a central role in allergic responses and diseases[8]. The most recently discussed paradigm independent of the adaptive immune system is the IL/ suppressor of tumorigenicity (IL-33/ST2)[11]. There are studies supporting an emerging role of MCs activation following IgE-independent pathways in non-allergic diseases such as late-stage asthmatic response, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), and lung cancer[12].

Recent research has clarified that MC quantity and activity are controlled by daily rhythmic variation[13], a circadian clock under the regulation of a specific set of clock genes such as *circadian locomotor output cycles kaput (Clock)*, *brain and muscle ARNT-like 1* (*Bmal1)*, *Period* (*Per1/2,* and *Cryptochromes (Cry1/2)*, and environmental factors, such as light intensity and nutritional input[8]. The circadian clock is an internal cellular time-keeper cycle located in the suprachiasmatic nuclei (SCN), a bilateral structure in the anterior part of the hypothalamus. It is driven by a series of cell-autonomous clock genes and responsible for the coordination of almost all physiological activities[14]. The components of the mammalian circadian clock including a central pacemaker in the brain's SCN and peripheral clocks in the cells of most organs and tissues, as well as their connections to major processes in pathophysiological and metabolic systems were identified using the well-characterized *Mus musculus* mouse model[15]. *Clock* was the first gene identified in the circadian rhythm using C57BL/6J male mice treated with a single injection of N-ethyl-N-nitrosourea (ENU)[16]. From this foundational discovery in 14, a series of mouse circadian clock and clock-related genes were identified including *Bmal1, Per1/2/3, Cry1/2, casein kinase (CK1ε and CK1δ), differentiation of human embryo chondrocytes (Dec1/2), RAR-related orphan receptor (Rorα, Rorβ, and Rorγ), nuclear receptor subfamily 1 (NR1D1 or Rev-erbα), Neuronal PAS domain protein 2 (NPAS2), Timeless (Tim)*, and *F-box and leucine-rich repeat protein 3 (Fbxl3)*[17]. The core loop of the circadian clock contains two nuclear transcription factors, CLOCK and BMAL1, binding as a heterodimer to the E-box elements in *Per1/2/3* and *Cry1/2* genes and activating the *Per1/2/3* and *Cry1/2* transcriptions. In the cytoplasm, PER and CRY proteins form an active repressor complex acting on the CLOCK/BMAL1 negative feedback loop which in turn inhibits *Per1/2/3* and *Cry1/2* expressions[18]. The transcriptional-translational feedback network plays an important role in the generation and maintenance of circadian rhythm.

Located near the center of the brain, the pineal gland is a very small organ producing melatonin (*N*-acetyl-5-methoxytryptamine), which helps maintain circadian rhythm and regulate reproductive hormones[19]. Melatonin is a hormone derived from the amino acid tryptophan with potential applications for early prevention of neurodegenerative diseases[20] and human diseases of the biliary tract[21] including primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and cholangiocarcinoma (CCA). It also possesses strong anti-oxidant capacity and activates two high-affinity G-protein-coupled receptors in mammals, MT1 and MT2, which in turn inhibit downstream processes such as forskolin-stimulated cyclic adenosine monophosphate (cAMP) production[22,23]. Melatonin is one of several neurotransmitters and neuromodulators participating in the regulation of circadian rhythms, especially in the sleep-wake pattern[24]. Aberrant timed melatonin production has a strong connection to the non-24h sleep-wake disorder, advanced sleep phase syndrome, and delayed sleep phased syndrome[25]. Actions at the two melatonin receptors MT1 and MT2 lead to sleep promotion by inducing sleep-like brain waves, as well as the improved phase shift of circadian oscillations[26].

Histamine (2-(1H-imidazol-4-y)ethanamine) is a biologically active nitrogenous-based compound synthesized from the decarboxylation of the amino acid histidine by the l-histidine decarboxylase (HDC) enzyme. Both histamine released by MCs and HDC play an important role in inflammatory responses[27]. Histamine binds to four protein-coupled histamine receptors (HR), H1-4HR in which H1-3HR are expressed in brain[28]. Though histamine was first reported in the brain half a decade ago, only recently have researchers discovered histamine's role as a key wake-promoting neurotransmitter in the sleep-wake behavior[29]. Valko *et al.* reported a 41% reduction of histamine neurons in the tuberomammillary nucleus (TMN) of traumatic brain injury (TBI) victims. They also suggested the inverse correlation between histamine signaling and sleep need[30].

This finding was further confirmed by a ~36% loss of histamine immunoreactive neurons in the TMN of adult male Sprague-Dawley rats that underwent electroencephalography/electromyography[31]. While studying larval zebrafish, that possess a mutation in HDC gene leading to deficiency of histamine production, Prober *et al.* found contradicting data that the zebrafish experienced remarkably normal sleep-wake patterns[32]. Nevertheless, there is rapidly growing evidence to identify histamine as an important neuromodulator of the sleep-wake behavior and potential targets in allergic diseases and epilepsy therapy[33].

2. Mechanisms of circadian rhythm-mediated MC activation

2.1. Circadian clock in MCs

The connections between MCs and the circadian clock were first reported in the rat-thyroid gland[13] and have been extensively studied since then[34]. Mouse jejunal MCs from peripheral blood was isolated to study the robust oscillation between circadian clock genes (*Per1/2*, *Clock*, and *Bmal1*) and MC specific genes (*Mcpt-5/7, c-Kit,* and *FcεRIα*). In purified human MCs from intestinal tissue samples, similar circadian variations were also observed between the clock genes (*Per1/2* and *Bmal1*) and MC related genes (*FcεRIα* and *Tryptase*)[35]. Downstream targets of circadian functions in MCs are pro-inflammatory cytokines such as TNF-α[36], IL-1β[37], and chloride channel accessory 1 (CLCA1 or GOB5)[36]. There is a significant number of studies focusing on mechanisms underlying the modulation of the circadian clock and MC functions, of which IgE/FcεRI- and IL-33/ST2-mediated MC activation are the two main pathways[34,38]. The promoter regions of β subunit of the Fc receptor for IgE (FcεRIβ) and IL-33 receptor (ST2) bind CLOCK with high affinity leading to a circadian rhythm-dependent MC activation (**Figure 1**)[39]. Other activation paradigms include H1-H4 HRs[40-42], Mas-related G protein coupled receptor X-2

(MRGPRX2)[43], the 8-oxoguanine DNA glycosylase 1 (OGG1)[44], and MC-possessed potentiation form, which is not related to the adaptive immune system[11].

2.2. IgE/FcεRI-mediated MC pathway

The FcεRI receptor is an αβγγ tetramer on the surface of MCs and basophils with one α chain for IgE binding and one β and two γ for signal amplification and transduction[45]. In MCs, FcεRIα and FcεRIβ are the key IgE receptors with high binding affinity in addition to FcγRII, FcγRIII (in mice only), and Galectin-3[34]. Human and mouse MCs with high oscillating concentration of IgE possess a high number of FcεRI receptors on the surface since the binding of IgE to FcεRI protects these receptors from being internalized and degraded which stabilizes them[46]. Other researchers proposed that the IgE-dependent circadian synthesis and release of cytokines and chemokines in MCs are mediated indirectly by clock genes through the activation of various signaling molecules such as the extracellular-signal regulated kinase (ERK1/2)[47], p38 mitogen-activated protein kinase (MAPK)[48], and protein kinase B (Akt or PKB)[48].

In allergic reactions, MC activation was reported to follow the IgE/FcεRI signaling pathway[8,49]. The significant amplifying role of FcεRIβ for IgE-mediated MC functions was identified using a mouse model repeating the tissue distribution of human FcεRI trimeric and tetrameric forms[50]. However, the first evidence identifying the direct link of IgE antibodies in MC-mediated reaction under the regulation of circadian rhythms was published by Nakamura *et al.* in a study on cutaneous anaphylactic reactions[51]. Utilizing a loss-of-function mutation of *Per2* (mPer2$^{m/m}$) mouse model, the authors reported an aberrancy in the daily variation of serum corticosterone and a reduction in the bone marrow-derived MCs (BMMCs) sensitivity to the glucocorticoid inhibition both *in vitro* and *in vivo* suggesting *Per2* may regulate MCs. Furthermore, the inhibitory effect of dexamethasone on IgE-mediated β-hexosaminidase release in BMMCs was

not observed for the mPer2$^{m/m}$ mice as opposed to the wild-type (WT)[51]. Consistent data was presented showing expression levels of several clock genes, such as *Per1/2, Bmal1, Rev-erb,* and *Dbp* oscillated in murine BMMCs. Specifically, the expression of IL-13 and IL-6 mRNA exhibits circadian rhythms upon the stimulation of synchronized BMMCs with high affinity IgE receptor FcεRIα[52]. The result indicated the IgE/FcεRIα signaling pathway as the underlying mechanism for MC activation under regulation of the circadian clock (**Figure 1**).

The details of temporal regulation of IgE-mediated activation in MCs remained elusive until Nakamura *et al.* reported a novel regulatory mechanism suggesting IgE-mediated degranulation in MCs is primarily driven by the peripheral circadian clock in allergic reactions both *in vivo* and *in vitro*[39]. The authors observed circadian oscillation in mRNA expression of *Per2* and *FcεRIβ* in WT bone marrow-derived cultured MCs (BMCMCs), but not in *Clock*-mutated (*Clock*$^{\Delta 19/\Delta 19}$) BMCMCs, indicating that the *Clock* mutation in MCs accounts for the significant disruption of temporal variation in IgE/FcεRIβ - mediated degranulation of MCs. However, that phenomenon was not observed in the same experiments using *Clock*-deleted (*Clock* siRNA treated) BMCMCs, a model with less severe interference to the circadian rhythmicity. The authors stated that *Clock* binds to the promoter of *FcεRIβ* based on two key findings (i) the reduction of *FcεRIβ* mRNA expression level in association with the decrease of IgE-mediated β-hexosaminidase in *Clock*$^{\Delta 19/\Delta 19}$ BMCMCs, and (ii) the *FcεRIβ* promotor activity enhancement due to Clock overexpression in WT BMCMCs[39]. Different approaches for potential pharmacological drugs treating IgE/FcεRI-mediated allergic reactions were proposed by targeting the MC molecular clock[53], as well as using anti-IgE monoclonal antibodies, designed ankyrin repeat proteins (DARPins), and fusion proteins[54].

2.3. IL-33/ST2-mediated MC pathway

IL-33 is a member of the Toll/IL-1 cytokine family localizing in the nucleus and is expressed by different immune cells including MCs[55]. IL-33 induces large synthesis of cytokines and chemokines by MCs such as IL-5 and IL-13 in group 2 innate lymphoid cells (ILC2s) [56]; IL-8 and IL-13 in human umbilical cord blood-derived MCs[57]; and T-helper subsets 1 and 2 (Th1 and Th2) in human CD^{34+} MCs[58]. IL-33 promotes the production of cytokines in human and mouse MCs through various pathways involving binding of antigens (Ags) to IgE-bearing MCs via high-affinity FcεRI[59], anaphylatoxin complement 5a (C5a), adenosine, SCF, and nerve growth factor (NGF).[60] In contrast, Martin *et al.* proposed the dampening effect of IL-33 on proinflammatory signaling as evidenced in the suppression of prototypic NF-κB-triggered gene expressions including IκBα, TNF-α, and cRel [61]. The interaction between IL-33 and the p50 subunit of NF-κB is constitutive with no significant enhancement in the p50 signal after stimulating human HEK293RI cells with recombinant human interleukin-1 beta (rhIL-1β), a classical activator of the NF-κB signaling pathway. Upon stimulation, the N-terminal part containing amino acids 66-109 of IL-33 interacts with the N-terminal Rel homology domain of the NF-κB p65 subunit leading to a remarkable decrease in binding affinity of p65 to its cognate DNA after IL-33/p65 nuclear translocation. However, the suppressing effect of IL-33 on the NF-κB activity is prominent at low concentration of p65 and can be overcome when p65 abundance exceeds the inhibitory capacity of IκBα [61].

Both IL-33 and ST2 expression levels are significantly elevated in human asthma suggesting the crucial role of the IL-33/ST2 axis in genetic susceptibility[62]. It is worth noting that the efficiency of this pathway significantly depends on the binding affinity of IL-33 to ST2[63]. The IL-33/ST2 axis has been recognized as one important signaling pathway in various systems and

diseases including the central nervous system[64], innate and adaptive immune responses[65], organ fibrosis[66], allergic inflammation[67] and neuroinflammation[68]. IL-33/ST2 signaling promotes liver steatosis, inflammation, and fibrosis due to the significant elevation of procollagen-α1 and IL-13 mRNA expression in high-fat diet-fed ST2-knock out mice compared to BALB/c mice[69]. The activation of ST2 by IL-33 was proposed to be the underlying mechanism for the maturation of human MCs[70]. The elevated production of IL-6 and IL-13 by mouse BMMCs via IL-33/ST2 pathway is independent of the IgE/FcεRI signals indicating potentials roles of this pathway in studying MC degranulation and survival in the absence of IgE[7]. However, the IL-33/ST2 axis also improves the IgE-dependent responses to inflammation as shown in the elevation of CXCL8 concentration in IL-33-stimulated human MCs cultured with fibroblasts[60]. In a study on asthma, the protective role of MC-dependent IL-33/ST2 pathway as dampening effect on airway hyperresponsiveness (AHR) in MC-deficient C57BL/6Kit$^{W\text{-}sh}$ mice was identified[71].

Kawauchi *et al.* evaluated the fluctuation of IL-6, IL-13, and TNFα concentrations with time and the association between ST2 and *Clock* expressions in WT and *Clock*-mutated (Clock$^{\Delta 19/\Delta 19}$) BMMCs[36]. They suggested that CLOCK protein is a novel modulator for the temporal regulation of IL-33/ST2 axis in MCs; however, the authors were not able to exclusively attribute the temporal IL-33/ST2 signaling to *Clock* gene. There are previously published data on the interactions between CLOCK and NF-κB that can interfere with the circadian rhythmicity of IL-33/ST2 pathway (**Figure 1**) [72,73].

The biological outcome of the IL-33/ST2 axis is profoundly controlled by the quality and abundance of ST2 expression depending on the cell types. So far, MCs are considered as the only cell type that constitutively express high levels of ST2 independent of tissues specificity, therefore they provide critical checkpoints for IL-33 signaling in innate immune cells[74]. IL-33 expression[75]

and MC infiltration[76] have been associated with both good and poor prognosis depending on the cancer and tumor type and tissue localization. IL-33 promotes tumor progression by altering the tumor microenvironment and inducing angiogenesis whereas the anti-tumor effect of IL-33 largely correlates with the activation of immune effector cells[75]. Research on the dual importance of IL-33/ST2 axis in MCs as tumor-promoting and tumor-suppressing roles has quickly progressed to decipher this dichotomous effect to avoid putative false therapeutic drugs targeting the IL-33/ST2 axis in MCs.

3. Effects and action mechanisms of melatonin and histamine in MCs

Notwithstanding the extensive research on the roles and functions of melatonin and histamine individually, so far only one study has evaluated their interdependence under circadian rhythms. Prober. *et al.* used TALEN (Transcription Activator-Like Effector Nucleases) and CRISPR/Cas9 (Clustered Regulatory Interspaced Short Palindromic Repeat/ CRISPR associated protein-9 nuclease) technology to generate null mutation in arylalkylamine N-acetyltransferase 2 (*aanat2*) zebrafish to suppress the production of melatonin in the pineal gland. They observed that the nighttime sleep activity of the *aanat2*$^{-/-}$ group significantly decreased by half while the daytime activity was drastically increased by three-fold.[77] In contrast, increased sleep and decreased night activity in larvae were reported when treated with adenosine receptor agonist 5'-N-ethylcarboxamido-adenosine (NECA) and H1R antagonist pyrilamine. This indicated that histamine and melatonin act parallel in regulating sleep-wake patterns[77]; however, the mechanism for the interdependence of melatonin and histamine in circadian rhythms remains elusive, and at the time of this review no such evidence has been reported in MCs. Therefore, we will discuss MC regulation with respect to melatonin and histamine separately in this section.

3.1. Melatonin: The pineal gland hormone and MCs

The effects of melatonin on different cells related to innate immunity have been reported[19]. The circadian synthesis of melatonin is best known for its key role in mediating sleep patterns and is under regulation of the daylight-darkness cycle[78]. The absence of pineal melatonin was reported to abolish the daily mRNA expression of clock genes, such as *Rev-erbα*, *Bmal1*, *Per 1/2*, and *Cry1/2* in testes of Wistar rats[79]. After pinealectomy, the daily expression profiles of melatonin-forming enzymes Aanat and Acetylserotonin O-methyltransferase (Asmt), MT1, MT2, and clock genes (*Clock*, *Bmal1*, *Per1/2*, and *Cry1/2*) were significantly altered. However, these changes were partially or completely re-established by treatment with melatonin in accordance with the maturational stage of the meiotic cellular cycle and the hour of the day[80]. (**Figure 2**). Recently, new perspectives on the role of melatonin as a chronobiotic, an internal synchronizer of the circadian clock and seasonal rhythmicity, have attracted increasing interest and provided potential treatments for many sleep disorders with significant enhancement in sleep quality[81].

The first evidence for the release of melatonin by both resting and stimulated rat basophilic leukemia (RBL)-2H3 MCs was published by Maldonado *et al.*[82]. After chemical stimuli, the melatonin secretion in RBL-2H3 culture supernatants was significantly elevated compared to unstimulated cells, supporting MC melatonin production. The activities of key enzymes N-acetyltransferase (NAT, which regulates the biosynthetic pathway of serotonin and its derivatives including melatonin) and hydroxyindole-O-methyltransferase (HIOMT, which catalyzes melatonin synthesis), are significantly increased in the stimulated cells. Furthermore, the expression of melatonin membrane receptors MT1 and MT2 in both unstimulated and stimulated cells was observed indicating the modulatory effect of melatonin on MC-mediated inflammatory pathways[82]. With the intravenous administration of melatonin before and after the

lipopolysaccharide (LPS) injection, the number of MCs in the small intestine, but not liver, were reported to pronouncedly decrease[83]. Pineal melatonin synthesis was decreased with the increase in pineal calcification and MC activity[84]. An inversely proportional relationship between melatonin levels and the number of MCs was also reported in four separate rat groups treated with cisplatin ± melatonin/quercetin[85]. Melatonin was proposed to suppress the differentiation and possibly the proliferation of MCs, indicating an inhibitory role of melatonin in the accumulation of MCs in frog testis[86]. The testicular melatonin level was positively correlated with the expressions of antioxidant enzymes such as copper-zinc superoxide dismutase 1 (SOD1), peroxiredoxin 1, and catalase and negatively correlated with the generation of reactive oxygen species (ROS) in human mast cell (HMC-1) line[87]. The finding suggested melatonin might act as a protective agent against oxidative stress in testicular MCs. The protective roles of melatonin in MC degranulation in the dermis[88] and in bladder [89] in chronic water avoidance stress (WAS) condition were reported, and the abundancy of MCs in the WAS plus melatonin group was significantly lower than the WAS only control.

Melatonin is a key mediator which recognizes potential damages and risk status in MCs and macrophages via NF-κB[90] and Signal Transducer and Activator of Transcription (STAT1)[91] signaling pathways, respectively. During anti-inflammatory actions, the NF-κB pathway controlled by AANAT enzyme is responsible for the synthesis of endogenous melatonin by activated MCs[90,92,93]. Melatonin was confirmed as a cytoprotectant modulated by phorbol 12-myristate 13-acetate plus calcium ionophore A23187 (PMACI) through the NF-κB pathway[94]. However, the mechanism of melatonin activation in reducing inflammatory toxicity remains unclear. In quest of elucidating this mechanism, Maldonado *et al.* identified that in the PMACI stimulated MCs, the significant increase of TNF-α, IL-6, and endogenous melatonin levels was

recorded at 82%, 68%, and 63% higher than the unstimulated MCs. More importantly, pre-treatment with exogenous melatonin before PMACI stimulation decreased the levels of TNF-α, IL-6, and endogenous melatonin by 60%, 55%, and 33% in a dose-dependent manner. The authors proposed that melatonin treatment prevented the phosphorylation of IκB protein which is an inhibitor of NF-κB, stabilizing it and consequently inhibiting the activation of NF-κB[93]. Diisodecyl phthalate (DIDP), a chemical widely used as an eco-friendly plasticizer, enhanced the activation of NF-κB in mouse skin MCs.[95] This effect was counteracted significantly when treated with melatonin as shown in the elevated expression of redox sensor–nuclear factor erythroid-derived factor 2 (Nrf2), decreased expression of thymic stromal lymphopoietin (TSLP), and up-regulation of antioxidant genes–heme oxygenase 1 (HO-1) and Nicotinamide adenine dinucleotide (phosphate) NAD(P)H-quinone oxidoreductase 1 (NQO)[95]. Using *aanat2*$^{-/-}$ zebrafish larvae lacking melatonin, Ren *et al.* suggested endogenous melatonin promotes migration of neutrophils through cytokine signaling, in particular the downregulation of inflammatory cytokines IL-1β and IL-8[96]. Recently, melatonin was reported to disrupt the IL-1β/NF-κB/NLRP3 inflammasome positive feedback loop leading to the inhibition of NLR pyrin domain containing 3 (NLRP3), p20, and IL-1β synthesis[97]. In intestinal epithelial cells (IECs), activation of NF-κB enable transcriptions of numerous genes in a rhythmic fashion[98]. In microbial metabolism, NF-κB pathway modulates the regulation of melatonin in a circadian pattern. The expression of circadian clock proteins is controlled by a positive feedback inhibition involving Bmal1/Clock transcription factors[99]. The regulatory mechanism between melatonin and the pathways involving NF-κB and its signaling mediator IκBα may provide new insight for diagnosis and treatment of allergic and intestinal diseases (**Figure 2**).

In the past three decades, there has been growing evidence supporting the production of extra-pineal melatonin in the brain, retina, skin, gastrointestinal tract, and by activated immune-competent cells. The coordination in the synthesis of melatonin by pineal gland and extra-pineal glands is fundamental in the regulation of the immune-pineal axis model[100]. This model extends the bidirectional communication hypothesis on the immunological roles of pineal and extra-pineal melatonin proposed by Skwarlo-Sonta in 2003 [101]. The central component of the immune-pineal axis is the NF-κB family containing homo- or heterodimers of five subunits including p50, p52, p65 (RelA), RelB, and cRel. The nuclear translocation of NF-κB is promoted by the release of the inhibitory protein IκB leading to the exposure of the nuclear localization signal (NLS)[100]. The κB sequence was reported to be present in the promoter and the first intron of the gene that codifies AANAT, a key enzyme in melatonin synthesis, indicating NF-κB is a putative regulator of AANAT expression. Depending on the identity of the NF-κB dimers and the cellular microenvironment, the rhythmic production of melatonin can be switched from the pineal gland to immune-competent cells. In particular, the homodimer p50/p50 blocks the *Aanat* transcription meanwhile heterodimers containing cRel is connected to the enhancement of *Aanat* transcription [102]. The inhibition of NF-κB activity is crucial for the reinstatement of melatonin production in the pineal gland.

3.2. MC regulation and histamine

The link between the central histaminergic system and circadian oscillation accounts for the rhythmicity regulation of various behavioral and hormonal parameters including histaminergic morphology and neuronal activity[103]. The first evidence directly connecting histamine in behavior and sleep-wake control was reported using an $HDC^{-/-}$ mouse model. They found the $HDC^{-/-}$ mice, compared to the WT control group, experienced a deficit of waking at lights-off and lower sleep

latencies upon stimulation[104]. The mRNA expression levels of clock genes in HDC$^{-/-}$ mice such as *Per1/2* and *MAL1* in 24-hr profiles appeared intact in the SCN, but were drastically disrupted in the brain areas outside the SCN, including the cortex and striatum. This suggests that the involvement of histamine in mediating circadian rhythm possibly depends on an output pathway or a feedback route[33]. Researchers have proposed mechanisms by which histamine mediates the circadian clock by acting through processes including HRs, such as the H1HR/Gβγ/cAMP/PKA/CFTR pathway[105] and the H1HR/Ca_V1.3/RyR pathway[106]. Rezov *et al.* utilized mice lacking key HRs, H1HR and H3HR (*Hrh1*$^{-/-}$ and *Hrh3*$^{-/-}$) to examine the contribution of these two receptors in the histamine-mediated circadian oscillation. In contrast, they found no substantial changes in the expression of *Per1/2* and *Bmal1* in any of the tested brain structures, suggesting the H1HR and H3HR receptors do not affect the expression patterns of the core clock genes. However, H3HR possibly contributes to the significant decrease in the amplitude of free-running activity rhythm[107]. In a study of chronic rapid eye movement sleep deprivation (REM-SD), the up-regulation of HDC leading to elevated histamine release accounts for maintaining wakefulness[108].

To elucidate the underlying mechanisms of the circadian function of MCs, MC mediators such as cytokines, histamine, interleukins, and TNF-α were evaluated in which histamine has emerged as a potent downstream target[8]. The levels of blood histamine, thyroid histamine, and thyroid MCs follow a consistent 12-hour rhythmic manner with peaks of each variables observed at different times[13]. In research conducted on MC-deficient W/Wv mice, plasma histamine levels at steady state oscillated under the influence of MC-intrinsic circadian clock. The authors indicated that organic cation transporter 3 (OCT3), which is responsible for the delivery of cytosolic histamine in MCs, is linked to the expression of *Clock* suggesting OCT3 is a *Clock*-control gene[109].

Blasco *et al.* recently studied gut MCs in stroke-induced male C57BL/6J mice and observed a significant increase of MC number and histamine receptor expression with aging. These changes lead to the elevated levels of MC-released mediators as a part of peripheral inflammatory response, such as IL-6, TNF-α, and especially histamine[110]. MC-mediated histamine plays a key role in the activation of the NF-κB signaling pathway in inflammatory reactions[111]. In LPS treated aged F-344 rats, the release of histamine activated the MC-mediated NF-κB factor proving the major role of MC/histamine/NF-κB axis in acute inflammation[112]. Recently, components of the MC-histamine autocrine loop was presented suggesting the NF-κB phosphorylation is activated because of interactions between MCs and inflammatory stimuli[113].

The histamine released by MC degranulation binds to one of the four G-protein-coupled HRs expressed on MCs. Pretreatment with an H1HR blocker reduced the cortisol secretion level of histamine and degranulation of brain MCs in dogs passively sensitized with IgE[114]. Inhibition of H2HR in multi-drug resistant knockout mice ($Mdr2^{-/-}$) decreased liver damage, in particular large ductal PSC-induced damage[115]. In a study on irritable bowel syndrome (IBS), the G-protein-coupled estrogen receptor (GPER) was postulated to co-localized with MC markers, including histamine and substance P in human and rat colonic tissues. The levels of colonic histamine and MC degranulation were elevated in visceral hypersensitivity (VH)-induced rat; however, the effect was reversed following pretreatment with GPER antagonist G15[116]. Misto *et al.* reported that fasting activates the histamine release from MCs, and consequently induces liver H1HR, triggering the biosynthesis of oleoylethanolamide OEA in liver[117].

4. Therapeutic potentials targeting circadian MC-mediated histamine/melatonin

4.1. The key factor: NF-κB

The circadian-mediated behaviors of melatonin and histamine in MCs are involved in different pathways with various factors including NF-κB which stands out as the common key player. When Sen and Baltimore first identified NF-κB[118], a nuclear factor binding near the κ light-chain gene in B cells in 1986, scientists did not realize the impact of this factor on human pathobiology[119]. NF-κB comprising of dimers of Rel family members is a major signaling component in the immune system, cancer, and rapid inflammatory response[120]. The roles of NF-κB in different signaling pathways modulating the SCN circadian pattern have been evaluated extensively. Marpegan *et al*. reported the blocking effect of pyrrolidine-dithiocarbamate (PDTC), an inhibitor of NF-κB, on the light-induced phase in hamsters suggesting the connection of Rel/NF-κB family proteins to the modulation of circadian clock[121]. Similar research in Drosophila nervous system demonstrated the circadian oscillation of cAMP response element binding protein 2 (dCREB2)/NF-κB activity *in vivo*[122]. There are previously published findings on the interactions between NF-κB factor and the core *Clock* genes such as *Bmal1*, *Cry1/2*, and *Clock* that can interfere with the circadian rhythmicity. Narasimamurthy *et al.* further proposed that the phosphorylation of Cry proteins elevated the cAMP synthesis leading to the activation of NF-κB[73]. *RelB* and *Clock* were reported to function as a negative and positive regulator of NF-κB-mediated pathway in circadian oscillation, respectively[123,124]. A circadian pattern in the accumulation of nuclear p65, one component of NF-κB, in serum-shocked fibroblasts was observed[125]. Mouse MC protease-6 (MMCP-6) and MMCP-7 induced IL-33 release in the midbrain and striatum by activation of NF-κB[126]. Based on these findings, many compounds have been extensively

investigated to impose various regulatory effects on NF-κB signaling pathway in MCs and play a role as potential therapeutic drugs in MC-mediated inflammatory reactions as shown in **Table 1**.

4.2. Alternative factors

In IgE- and IL-33-mediated MC activation pathways, synthetic compounds able of modulating the components (casein kinase 1δ/ε and REV-ERBα) and modifiers (glucocorticoids) of clock gene expression are potential therapeutic targets[8]. Evidence for the inhibitory effect of HMG-CoA reductase (statin) on the activation of MCs via IgE-mediated pathway was supported by the reduction in the synthesis of inflammatory mediators (histamine, tryptase, proteoglycans) and cytokines (IL-4, IL-6, TNF-α, and IFN-γ)[127]. Short-chain fatty acids (SCFAs) such as butyrate is an effective inhibitor of both IgE-dependent and IgE-independent pathways by down-regulating the release of allergen-induced histamine [128]. SR9009, a synthetic agonist of the nuclear receptor REV-ERBs, was used to inhibit MC activation independent of circadian rhythm activity[129]. Human MRGPRX2 activating the release of histamine is at the center of the extensive research as a potential target to prevent allergic reactions through an IgE-dependent pathway[130,131]. Suzuki *et. al*. employed modified systematic evolution of ligands by exponential enrichment (SELEX) approach to select aptamer-X35 as an inhibitor of histamine release from MCs via MRGPRX2 pathway[132]. Paeoniflorin was proposed as a novel inhibitor of MRGPRX2 in C48/8-induced allergic response both *in vitro* and *in vivo*[133].

The development of therapeutics based on H1HR antihistamines and H2HR-targeting "blockbuster" is at the center of the search for effective treatments for allergies, liver diseases, and gastrointestinal disorders[134]. In the study by Kennedy *et al.*, the authors observed an elevation of H1/H2HR and MC presence in human PSC and CCA and a decrease of liver and biliary damages and fibrosis when $Mdr^{-/-}$ mice were treated with H1HR, H2HR or both antagonists[135]. In the human

brain, [^{11}C]doxepin, a potent antagonist of histamine receptor H1HR, was examined to visualize the neuronal histamine release as a consequence of circadian rhythms[136]. Of the four histamine receptors, the H3HR has shown a promising potential for prevention and treatment of sleep-wake disorders, due to its favorable properties and location [24]. Diphenhydramine and doxylamine are the two most common over-the-counter (OTC) antihistamines offering benefits to sleep onset and sleep maintenance[137]. However, more research is required to address the tolerance for sleep-promoting pharmacodynamics effect and possible adverse effects such as next-day sedating, paradoxical reactions, and increased risk of cognitive impairment in the elderly.

Recently, exposure of IgE-activated RBL-2H3 MCs to tricin, a flavone in rice bran, suppressed production of TNFα, IL-4, leukotrienes (LT) B_4, LTC_4, and prostaglandin E_2 by significantly decreasing the phosphorylation of the tyrosine-protein kinase (Lyn) and spleen tyrosine kinase (Syk)[138]. This suggested that the Lyn/Syk axis as a new potential target for prevention of IgE-mediated allergic reactions.

4.3. The emergence of complementary and herbal medicines

Herbal medicine is a fast-growing field and provides an important research direction on the prevention and treatment of MC-mediated inflammatory diseases. (-)-Asarinin (Asa), a Chinese traditional herbal medicine purified from the roots of *Asiasari radix*, was reported to inhibit IgE-dependent and IgE-independent allergic pathways[139]. Hispidulin, another Chinese natural compound, attenuated the release of histamine and β-hexosaminidase in anti-dinitrophenyl IgE-sensitized RBL-2H3 MCs[140]. The fruits of *Poncirus trifoliata* (L.) Raf (Rutaceae) (FPT)[141] and the formulated ethanol extract of *Artemisia asiatica Nakai* (DA-9601)[142] inhibited NF-κB activation by preventing the degradation of IκB, nuclear translocation of NF-κB, and NF-κB /DNA binding in activated HMCs. An unspecified aqueous extract from leaves of *Eriobotrya japonica*

(LEJL) decreased the PMACI-induced activation of NF-κB in HMC-1 leading to the suppression of TNF-α, IL-6, and IL-8 gene expression and secretion[143]. Similar effect on the expression of IL-6 mRNA was observed when chelidonic acid in the rhizome of *Chelidonium majus* was tested as a potential treatment in MC-mediated inflammatory diseases[144]. Oral administration of *Prunus serrulata* (AEBPS) leads to the suppression of MC degranulation through the downregulation of NF-κB in RBL-2H3 MCs[145]. Sesamin, a lignan in sesame oil, has shown inhibitory effects on the production of histamine, TNF-α and IL-6 dependent on the activation of NF-κB[146]. Recently, the first phytomelatonin, a plant extract rich in melatonin, was successfully obtained from herbal mixed plants with the exact formulation are being patented at the time of this review[147]. This finding proposed a "green" approach for producing dietary supplement rich in phytomelatonin rather than synthetic melatonin.

5. Conclusions and future perspectives

There is a robust association between circadian rhythms and MC activation via the IgE/FcεRI- and IL-33/ST2-mediated signaling pathways. Melatonin and histamine are two important neuromodulators involved in the regulation of circadian oscillations via NF-κB, a common key factor. The interactions between NF-κB and core clock genes *Cry1/2*, *Clock*, and *Bmal1* disrupt the production of proinflammatory cytokines such as IL-6, IL-13, and TNFα and interfere with our daily rhythmic activity. Since there is currently only one study proposing the parallel acting mechanism between melatonin and histamine in regulating sleep-wake pattern, additional research is required to further elucidate the interdependence between melatonin and histamine in MC circadian rhythms. Although detailed mechanism remains elusive, current therapeutic approaches target NF-κB to restore circadian rhythms in MCs remain promising, and

these studies will undoubtedly foster a better understanding on the roles of melatonin and histamine in the prevention and treatment of MC-mediated inflammatory diseases.

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Figure legends

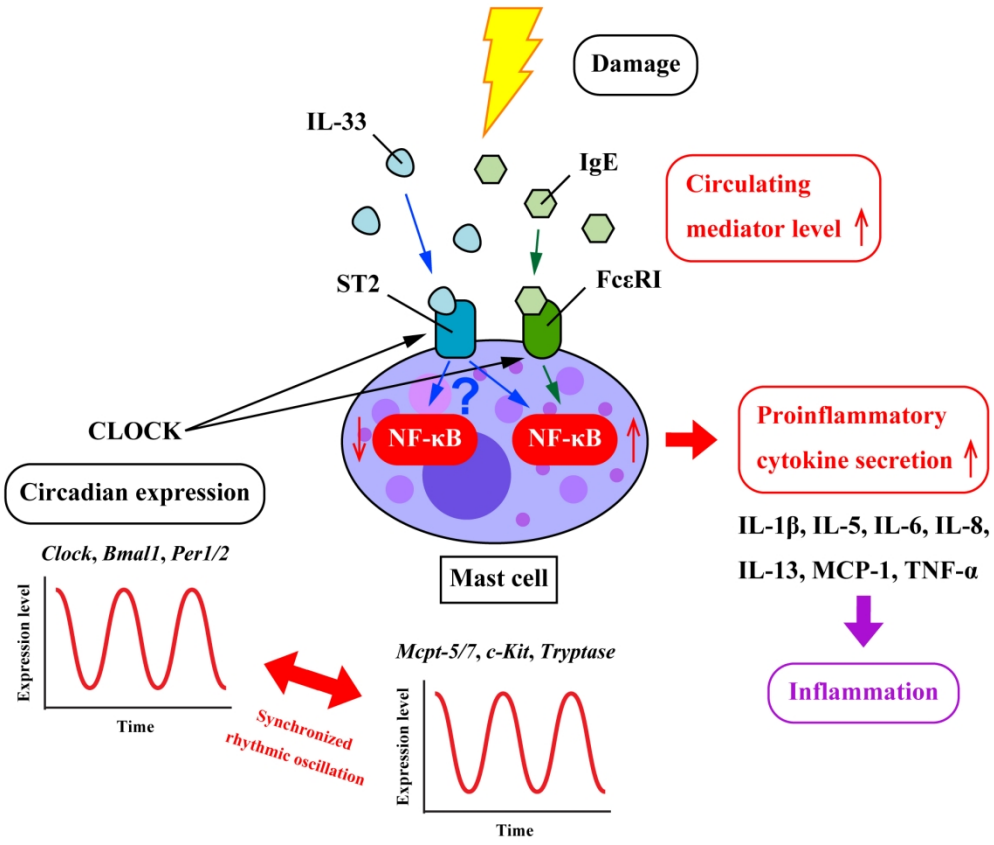
Figure 1. IgE/ FcεRI- and IL33/ST2-mediated MC activation pathways.

There is a robust oscillation between the circadian clock genes (*Per1/2*, *Clock*, and *Bmal1*) and MC specific genes (*Mcpt-5/7, c-Kit, FcεRI* and *Tryptase).* IgE/FcεRI- and IL-33/ST2-mediated MC activations are the two major pathways underlying the modulation of the circadian clock and MC functions. The promoter of β subunit of the Fc receptor for IgE (FcεRIβ) and IL-33 receptor (ST2) bind CLOCK with high affinity leading to a circadian rhythm-dependent MC activation.

Upon the binding of IgE and IL-33 to FcεRI and ST2 in MCs, the expression level of the nuclear factor NF-κB is significantly elevated leading to the increase in the secretion of proinflammatory cytokines such as TNF-α, IL-1β, IL-5/6/8/13, and MCP-1.

Figure 2. Therapeutic potentials targeting circadian MC-mediated melatonin

Melatonin is a hormone produced primarily in the pineal gland which helps maintain circadian rhythm and regulate reproductive hormones. Daily expressions of melatonin-forming enzymes (Aanat and Asmt), and melatonin receptors (MT1and MT2) are in synchronized rhythmic oscillation with expression of clock genes (*Clock*, *Bmal1*, *Per1/2*, *Cry1/2,* and *Rev-erbα*). Melatonin is also a key mediator which recognizes potential damages and risk status in MCs via NF-κB and STAT1 pathways. Binding of melatonin to MT1 and MT2 leads to the inhibition of NF-κB activation, which in turn down-regulates MC activation, proliferation, and differentiation. Based on these findings many compounds have been extensively investigated to impose various regulatory effects on NF-κB and melatonin in MCs and play a role as potential therapeutic drugs in MC-mediated inflammatory reactions.


Damage
IL-33
IgE
Circulating
mediator level
ST2
FcεRI
CLOCK
?
NF-κB
NF-κB
Proinflammatory
cytokine secretion
Circadian expression
IL-1β, IL-5, IL-6, IL-8,
IL-13, MCP-1, TNF-α
Mast cell
Clock, Bmal1, Per1/2
Expression level
Time
Synchronized
rhythmic oscillation
Mcpt-5/7, c-Kit, Tryptase
Expression level
Time
Inflammation

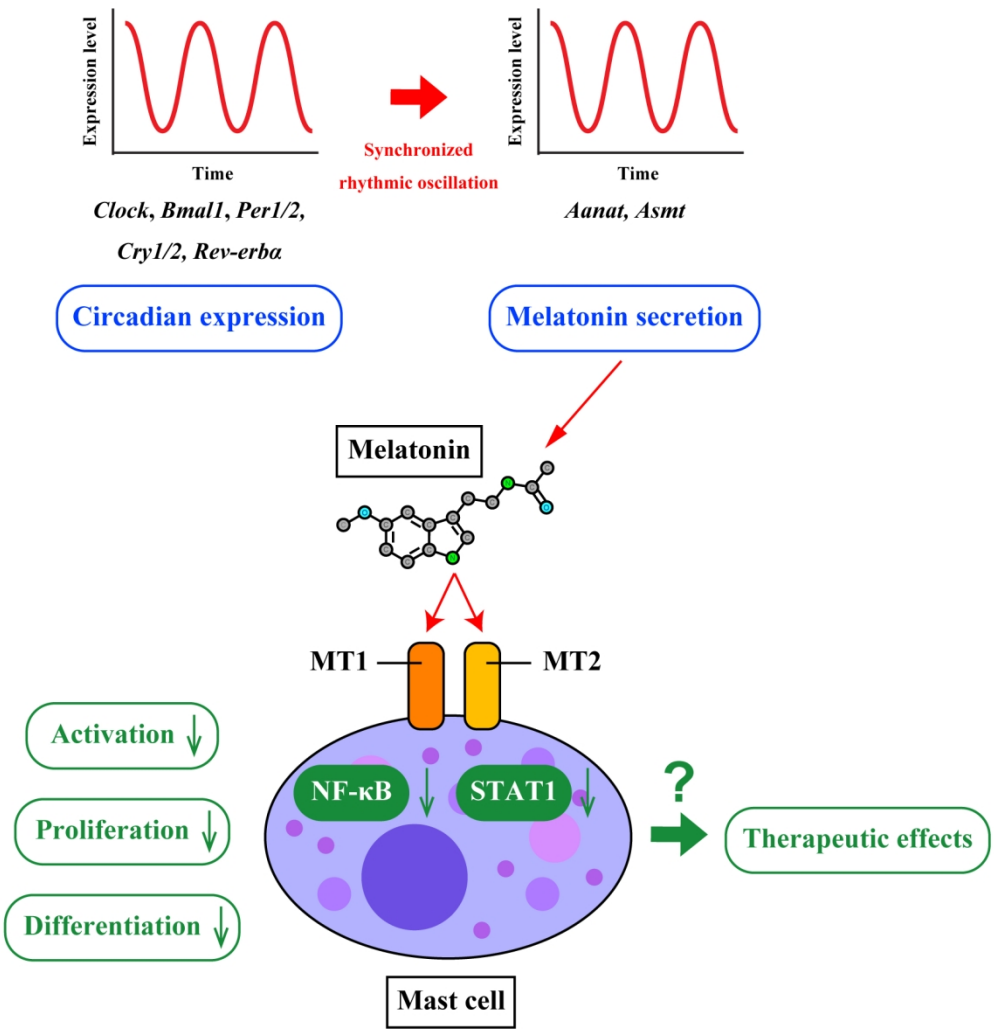

Expression level
Time
Clock, Bmal1, Per1/2,
Cry1/2, Rev-erbα
Synchronized
rhythmic oscillation
Expression level
Time
Aanat, Asmt
Circadian expression
Melatonin secretion
Melatonin
MT1
MT2
Activation
Proliferation
Differentiation
NF-κB
STAT1
?
Therapeutic effects
Mast cell

Table 1. Compounds targeting NF-κB in Mast Cells

Name	Year	Factors Decremented	Cell Lines
SC-236	2005	NF-κB, TNF-α, IL-6, IL-8, VEGF, COX-2, HIF-1α	HMC[148]
Quercetin	2007	NF-κB, p38 MAPK, TNF-α, IL-1β, IL-6, IL-8	HMC-1[149]
Gallotannins	2007	NF-κB, TNF-α, IL-1β, IL-6	HMC-1[150]
Flavonoids	2008	NF-κB, TNF-α, IL-1β, IL-6, IL-8, intracellular [Ca^{2+}]	MC-like RBL-2H3 cells and HMC-1[151]
Resveratrol	2009	NF-κB, TNF-α, IL-6, IL-8, COX-2, intracellular [Ca^{2+}]	HMC-1[152]
WECG	2010	NF-κB, histamine, TNF-α, IL-6	Rat peritoneal MCs and HMC[153]
WEEC	2011	NF-κB, p38 MAPK, histamine, TNF-α, IL-1β, IL-6	HMC-1[154]
Chrysin	2011	NF-κB, histamine, TNF-α, IL-1β, IL-4, IL-6	MC-based *in vitro* and *in vivo* models[155]
WESC	2012	NF-κB, histamine, TNF-α, IL-1β, IL-6, intracellular [Ca^{2+}]	HMC[156]
Houttuynia cordata Thunb	2013	NF-κB, TNF-α, IL-6, IL-8	HMC-1[157]
BiRyuChe-bang	2013	histamine NF-κB, TNF-α, IL-6, IL-8	Rat peritoneal MCs[158] HMC-1[158]
[6]-Shogaol	2013	histamine NF-κB, TNF-α, IL-6, IL-8	Rat peritoneal MCs[159] HMC-1[159]
Caffeic acid phenethyl ester	2014	NF-κB, Histamine, IL-1β, IL-6, IL-8	HMC-1[160]

Name	Year	Factors Decremented	Cell Lines
DHMEQ	2015	NF-κB, TNF-α, IL-6	RBL-2H3 MCs and BMMCs[161]
SG-HQ2	2015	NF-κB, Histamine, TNF-α, IL-1β, IL-4, IL-6	HMC and primary peritoneal MCs[162]
Cornuside	2016	NF-κB, Histamine, TNF-α, IL-6	Rat peritoneal MCs[163]
Nodakenin	2017	NF-κB, TNF-α, IL-1β, IL-6	HMC-1[164]
Berberine	2019	NF-κB, p38, TNF-α, IL-6, IL-13, MCP-1	Rat peritoneal MCs[165]
Nothofagin	2019	NF-κB, Histamine, TNF-α, IL-4, β-hexosaminidase	Cultured/isolated MCs[166]

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