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Potential role of melatonin in autoimmune diseases

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ABSTRACT

Autoimmune diseases are a broad spectrum of disorders involved in the imbalance of T-cell subsets, in which interplay or interaction of Th1, Th17 and Tregs are most important, resulting in prolonged inflammation and subsequent tissue damage. Pathogenic Th1 and Th17 cells can secrete signature proinflammatory cytokines, including interferon (IFN)-γ and IL-17, however Tregs can suppress effector cells and dampen a wide spectrum of immune responses. Melatonin (MLT) can regulate the humoral and cellular immune responses, as well as cell proliferation and immune mediators. Treatment with MLT directly interferes with T cell differentiation, controls the balance between pathogenic and regulatory T cells and regulates inflammatory cytokine release. MLT can promote the differentiation of type 1 regulatory T cells via extracellular signal regulated kinase 1/2 (Erk1/2) and retinoic acid-related orphan receptor-α (ROR-α) and suppress the differentiation of Th17 cells via the inhibition of ROR-γt and ROR-α expression through NFIL3. Moreover, MLT inhibits NF-κB signaling pathway to reduce TNF-α and IL-1β expression, promotes Nrf2 gene and protein expression to reduce oxidative and inflammatory states and regulates Bax and Bcl-2 to reduce apoptosis; all of which alleviate the development of autoimmune diseases. Thus, MLT can serve as a potential new therapeutic target, creating opportunities for the treatment of autoimmune diseases. This review aims to highlight recent advances in the role of MLT in several autoimmune diseases with particular focus given to novel signaling pathways involved in Th17 and Tregs as well as cell proliferation and apoptosis.

Abbreviations: AANAT, Arylalkylamine N-acetyltransferase; AMT, Acetyl-melatonin; AOPP, advanced oxidation protein products; AS, Ankylosing spondylitis; BAFF, B-cell-activating factor of TNF family; BASDAI, Bath ankylosing spondylitis disease activity index; BMT, Benzoyl-melatonin; CAMKIV, calcium/calmodulindependent kinase IV; CRP, C-reactive protein; EAE, experimental autoimmune encephalomyelitis; ERK, Extracellular signal regulated kinase; ESR, Erythrocyte sedimentation rate; GAD antibody, Glutamic acid decarboxylase antibody; GI, Gastrointestinal line; GPx, Glutathione peroxide; GSH, Glutathione; HIOMT, Hydroxyndole-O-methytransferase; HIS, 5-hydroxy-2'-isobutyl-streptochlorin; HO-1, heme oxygenase-1; IBD, Inflammatory bowel disease; ICA antibody, Islet cell antibody; IL, Interleukin; MAPK, mitogen-activated protein kinase; MDA, Malondialdehyde; MLT, Melatonin; MNs, myenteric neurons; MPO, Myeloperoxidase; MS, Multiple sclerosis; MSH, Melanocyte stimulating hormone; MSFC, MS functional composite score; MT1, MLT membrane receptors type 1; MT2, MLT membrane receptors type 2; MT3, MLT binds to the quinone reductase enzyme family; MTNRIB, MLT receptor type 1B; MSFC, Multiple sclerosis functional composite score; MyD 88, myeloid differentiation factor 88; NAA, N-acetylaspartate; NAT, N-acetyltransferase; NF-κB, Nuclear transcription factor kappa B; NK, Natural killer; NO, Nitric oxide; NOS, Nitric oxide synthase; Nrf2, nuclear erythroid 2-related factor 2; PBMCs, Peripheral blood mononuclear cells; PDC, pyruvate dehydrogenase complex; PDK4, pyruvate dehydrogenase kinase-4; RA, Rheumatoid arthritis; RF, Rheumatoid factor; RORα/RZR, Retinoid-related orphan nuclear hormone receptor; ROS, free radicals of oxygen species; RRMS, relapsing-remitting multiple sclerosis; SLE, Systemic lupus erythematosus; SLEDAI, Systemic lupus erythematosus disease activity index; 6-SMT, 6-sulphatoxymelatonin; SNP, Single-nucleotide polymorphism; SOD, Superoxide dismutase; SSc, Systemic sclerosis; TAC, Total antioxidant capacity; T1DM, Type 1 diabetes mellitus; Th1, T helper 1; TLRs, toll like receptors; TNF-α, Tumor Necrosis Factor-α; Tregs, Regulatory T cells; Tr1, type 1 regulatory; TOS, Total oxidant status; TPH, Tryptophan hydroxylases; UC, Ulcerative colitis

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1. Introduction

Autoimmune diseases are a category of complex diseases, characterized by the break in tolerance and inappropriate activation of the immune system, leading to a shift in the immune system towards a proinflammatory state, the production of autoantibodies and tissue destruction [1]. These diseases are involved in interactions between B and T cells, including CD4 + T helper (Th) cells, regulatory T cells (Tregs) and CD8 + T lymphocytes. CD4 + T cells can produce Th1, Th2, Th17 and Treg cells. Pathogenic Th1 and Th17 cells can secrete proinflammatory cytokines, including interferon (IFN)-γ and interleukin-17 (IL-17), however, Treg cells can suppress effector cells and dampen a wide spectrum of immune responses [2]. Th17 cells not only can produce IL-17 and IL-22, but also can recruit other inflammatory cell types, especially neutrophils, to mediate pathology in the target tissues [3]. Treg-mediated suppression occurs through inhibiting the production of IL-2 mRNA in the responder T cells and expressing granzyme A or B to kill target cells, *etc* [4]. Currently, Melatonin (MLT) has been found to play critical roles both in nonspecific immunity and specific immunity [5,6]. MLT can regulate responses of Th1, Th2, Th17, Tregs and B-cell. Moreover, many studies have reported that MLT has contributed to the development and pathogenesis of autoimmune diseases [7,8]. Thus, MLT is critical for maintaining peripheral immune tolerance and may serve as potential new therapeutic targets to prevent autoimmunity and tissue injury. In this review, we first review the biological source and functions of MLT, as well as its receptors. Then, we discuss the relationship between MLT and immune–inflammatory responses. Finally, we highlight recent advances in the role of MLT in several major autoimmune diseases, with particular focus given to novel signaling pathways involved in Th17 and Treg cells, as well as cell proliferation and apoptosis.

2. Biological source and functions of MLT

Melatonin (MLT), also named *N*-acety- 1-5-methoxytryptamine, is an avirulent indoleamine which can lighten skin color, inhibit melanocyte stimulating hormone (MSH) and modulate circadian rhythms [9]. MLT is made up of amino acid tryptophan, the main source of biosynthesis of MLT. With the help of tryptophan hydroxylase and decarboxylase, after the process of hydroxylation and decarboxylation, tryptophan synthesizes 5-hydroxytryptamine (serotonin). Further, the acetylation of serotonin by *N*-acetyltransferase (NAT) produces *N*-acetylserotonin, which is then methylated by hydroxyndole-O-methytransferase (HIOMT) to form MLT [10,11]. MLT and its derivatives can boost the activity of antioxidant enzymes and glutathione and scavenge free radicals of oxygen species (ROS) and thus act as free radical detoxifiers and antioxidants.

MLT is one of the major neuroendocrine hormones, which is mainly produced by the pineal gland and shows a remarkable functional versatility [10]. At night, pineal MLT is synthesized and then delivered into the peripheral circulation, which is then allowed to regulate the circadian day–night rhythm and seasonal bio-rhythms, including molt and pelage changes, prolactin secretion, thermoregulation, hibernation and body mass changes [10]. MLT also shows mitochondrial homeostasis, proliferation, apoptosis, metastasis, oncostatic [12–14], anti-aging [15] and immunomodulatory properties [16], as well as many other physiological functions [17], including an antioxidant activity, of which MLT could not only show direct free radical scavenging actions, but also enhance the activities of other antioxidative enzymes [18].

MLT is not just synthesized in the pineal gland, but also in a wide range of other tissues [19]. In retinal pigment epithelium, it has been found the existence expression of tryptophan hydroxylases (TPH), arylalkylamine *N*-acetyltransferase (AANAT) and HIOMT, which act as key enzymes involved in the process of MLT synthesis [20]. Moreover, the gastrointestinal line (GI) can produce MLT independently [21]. In addition, the presence of high concentrations of MLT has also been found in rat and human bone marrow [22], as well as in the presence of TPH, NAT and HIOMT activities in human peripheral blood mononuclear cells (PBMCs) and tumor-derived human cell lines, respectively [12–14,22,23].

3. MLT receptors

MLT actions concern three pathways: a receptor less radical scavenging action, a nuclear signaling and a G-protein mediated membrane signaling. MLT membrane receptors type 1, type 2 (MT1 and MT2), as two major membrane bound melatonin receptors, belong to the family of seven G protein-coupled transmembrane receptors. MT1 receptors are expressed throughout the body but predominantly in the brain. They are expressed in the thymus and the spleen, as well as in B cells, CD4, CD8 cells. MLT activates various different second messenger cascades after its binding to MT1/MT2 [24]. MLT binds to the quinone reductase enzyme family (also named as quinone reductase 2, MT3) was only demonstrated in hamsters and rabbits. Multiple roles and complexity processes of MLT are attributed to MT1, MT2 and MT3 which make them unique at the molecular level [25]. In addition, there are nuclear receptors of the retinoid-related orphan nuclear hormone receptor (RORα/RZR) family that play an indirect role in MLT actions. Nuclear receptors are expressed in human peripheral mononuclear cells (PBMCs), lymphocytes (Jurkat cells), U937 cells, CD4 and CD8 cells. Moreover, MT1 and MT2 affect related genes transcription through extracellular signal regulated kinase (ERK) pathways and CREP phosphorylation.

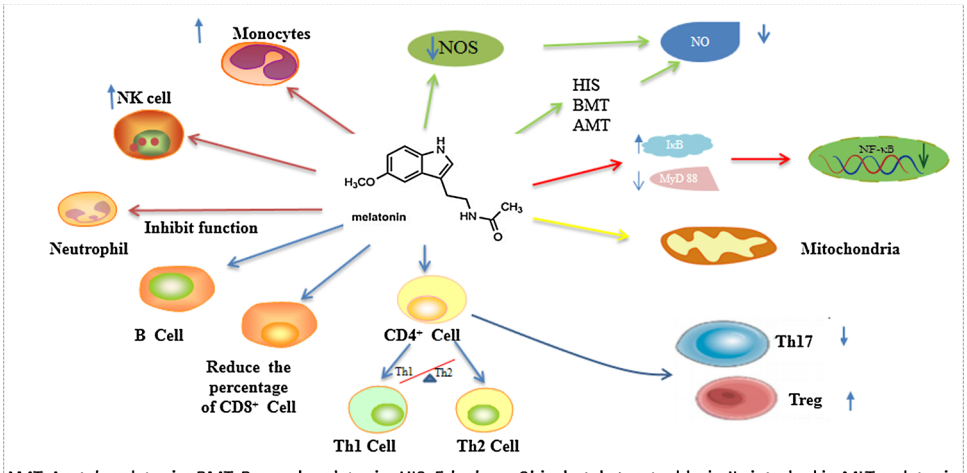
4. The role of MLT in immune modulation

Numerous studies have shown that MLT has a pleiotropic effect in regulating the immune system (Fig. 1).

In nonspecific immunity, MLT could dramatically inhibit neutrophil function both on immune response and cell migration process. The ERK signaling phosphorylation level which is involved in this migration process was significantly decreased when treated with MLT [26,27]. MLT could also inhibit intercellular adhesion of integrin-mediated granulocyte [28]. In the bone marrow and spleen, with dietary supplementation of MLT, the levels of natural killer (NK) cells and monocytes were significantly increased [5].

In specific immunity, MLT influences activation, differentiation, memory, and perhaps development of T cells. T cells express both membrane receptors and nuclear binding sites for MLT and the four enzymes involved in the synthesis of MLT from tryptophan are present in T cells which produce high levels of MLT [6]. The mRNA of MLT receptors in the thymus and spleen is expressed in the lymphocytes (CD4+, CD8+, double positive, double negative and B cells) [29]. Although the percentage of CD8 + T cells were reduced under MLT treatment [30], the percentage and absolute amount of these T cells were needed to consider the change of light/dark rhythm [31]. In addition, MLT can reduce the number of T effector memory cells (with CD44 expression) and its pro-inflammatory response [32]. Several studies revealed that high doses of MLT were directly toxic to human lung adencoarcinoma cells. The studies found that MLT increases apoptotic cell death and oxidative stress under co-culture conditions with human PBMCs [33].

MLT can regulate responses of Th1, Th2, Th17, Tregs and B-cell, which are important and complex in the immune system. MLT can inhibit Th1 responses, but promote Th2 responses showing that the balance of Th1/Th2 cells can be broken by MLT [32], but how MLT enhances Th1 or Th2 cell mediated immune responses is still in controversy. The key factor RORα of Th17 cells is a high-affinity for MLT, thus it can directly affect the differentiation of Th17 cells [34]. MLT reduced the production of IL-17, RORC and IL17A expression by human CD4 + T cells activated under Th17 polarizing conditions [7]. Moreover, MLT suppresses Th17 cell differentiation via Erk1/2 and C/



AMT, Acetyl-melatonin; BMT, Benzoyl-melatonin; HIS, 5-hydroxy-2′-isobutyl-streptochlorin;IL, interleukin;MLT,melatonin; MyD 88, myeloid differentiation factor 88; NK, natural killer; NO, Nitric oxide; NOS, Nitric oxide synthase; NF-κB, nuclear transcription factor kappa B; Th1, T helper 1; Tregs, Regulatory T cells;

Fig. 1. The effect of MLT on the immune system. MLT can inhibit neutrophil function, increase the levels of NK cells and monocytes, and regulate CD4+, CD8+ cells differentiation and B-cell activation. In addition, MLT can influence NO/NOS pathway, improve mitochondrial function, and inhibit the nuclear translocation of NF-κB, thereby regulating immune system.
AMT, Acetyl-melatonin; BMT, Benzoyl-melatonin; HIS, 5-hydroxy-2'-isobutyl-streptochlorin; IL, interleukin; MLT, melatonin; MyD 88, myeloid differentiation factor 88; NK, natural killer; NO, Nitric oxide; NOS, Nitric oxide synthase; NF-κB, nuclear transcription factor kappa B; Th1, T helper 1; Tregs, Regulatory T cells;

EBPα activation and boosts type 1 regulatory (Tr1) cell differentiation via Erk1/2 and ROR-α [7]. MLT also increased IL-10 production by human CD4 + T cells activated under Tr1 polarizing conditions [7].

MLT can enhance the immune response through influencing the concentration of cytokine. MLT has both pro and anti-inflammatory effects depending on the state of the cells [35]. At an early phase of inflammation, MLT may activate pro-inflammatory mediators such as TNF. At chronic inflammation, MLT can down-regulate pro-inflammatory mediators. Cytoprotective effects of MLT involve several prominent pathways/molecules including the nuclear factor NFκB, nuclear erythroid 2-related factor 2 (Nrf2) [36], mitogen-activated protein kinase (MAPK) [37] and toll like receptors (TLRs) [38,38]. Of these, NF-κB signaling is central to all pathways. Studies revealed that MLT decreases the levels of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6, and increases the secretion of anti-inflammatory cytokine including IL-2 and IL-10 [7]. MLT dose-dependently inhibits TNF-α and IL-1β expression through the PI3K/AKT, ERK, and NF-κB signaling pathways [8]. A novel MLT derivative, 5-hydroxy-2′-isobutyl-streptochlorin (HIS), is observed to have an effect on inflammatory responses by inhibiting the production of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 [39]. Moreover, MLT was also shown to induce Th17 cells to produce IL-17, although it had little influence on activated cells [40]. These studies suggested that MLT has a dual effect on cytokine secretion and multiple effects on the immune system.

Nitric oxide (NO) is known as an inflammatory regulator and mediator, synthesized by activated inflammatory cells through inducible nitric oxide synthase (NOS) and reactive oxygen species [41]. It has been shown that MLT can influence NO/NOS pathway and regulate the synthesis of NO [42,43], of which MLT could depress the expression of NOS both on mRNA level and protein concentrations [44]. It has also been demonstrated that HIS has affected the inflammatory responses by inhibiting the synthesis of NO [39]. In addition, benzoyl-melatonin (BMT) and acetyl-melatonin (AMT), two newly founded MLT derivatives, can also inhibit the production of NO [45].

Mitochondria have an important function on keeping the normal metabolism and cell homeostasis, if mitochondria began to malfunction, it could result in damage, even disease [46]. MLT can be regarded to have a protective role in mitochondria dysfunction, it can insulate pro-apoptotic Bax into mitochondria in an inactive form and thus reduce cell apoptosis [47], prevent mitochondrial dysfunction and restore the ATP production [48,49]. It has been demonstrated that treatment with MLT could decrease inflammatory factor, improve mitochondrial function and maintain metabolic activity [50,51].

Nuclear transcription factor kappa B (NF-κB) is an important group of the nuclear transcription factor proteins. NF-κB can regulate many genes which are related to immune function and inflammation, and play an important role in physiology and pathology. It has been shown that NF-κB is involved in many complex processes in our body, such as immune response, thymus development, embryogenesis, inflammation, acute response and cell proliferation [52–55]. MLT can suppress the expression level of NF-κB and therefore, repress inflammation [56,57]. Several studies have suggested that MLT could disarrange the translocation of NF-κB [58–60], inhibit or acetylate NF-κB p50 subunit, which may block the DNA binding activity of NF-κB both in vitro and in vivo [61–63]. Moreover, MLT could increase the cytosolic level of IκB, which is an endogenous inhibitor of NF-κB, and suppress the myeloid differentiation factor 88 (MyD 88) protein which is participate in a dependent signaling pathway, thus inhibiting the nuclear translocation of NF-κB [64].

5. MLT and autoimmune diseases

Several studies have addressed that MLT seems to be engaged in the pathogenesis of various autoimmune diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), inflammatory bowel disease (IBD), type 1 diabetes mellitus (T1DM), idiopathic thrombocytopenic purpura (ITP), ankylosing spondylitis (AS), systemic sclerosis (SSc), psoriasis and vitiligo (Table 1, Figs. 2 and 3).

5.1. Rheumatoid arthritis

RA is a chronic autoimmune disorder that primarily affects joints. It typically results in symmetry and invasive joint inflammation in foot

Table 1
Expression of melatonin in autoimmune diseases.

Disease name	Expression of melatonin	Increase/decrease/NSD compared with controls	Reference
RA	Serum	Increase	[74]
SLE	Serum	Decrease	[82,83]
	Plasma	NSD	[84]
MS	Serum	Decrease	[90]
T1DM	Salivary	Decrease	[118]
	Plasma	Decrease	[119]
AS	Serum	Increase	[122,123]
Psoriasis	Serum	Decrease	[128]

RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; MS, Multiple sclerosis; T1DM: Type 1 diabetes mellitus; AS: Ankylosing spondylitis; NSD: no significant differences.

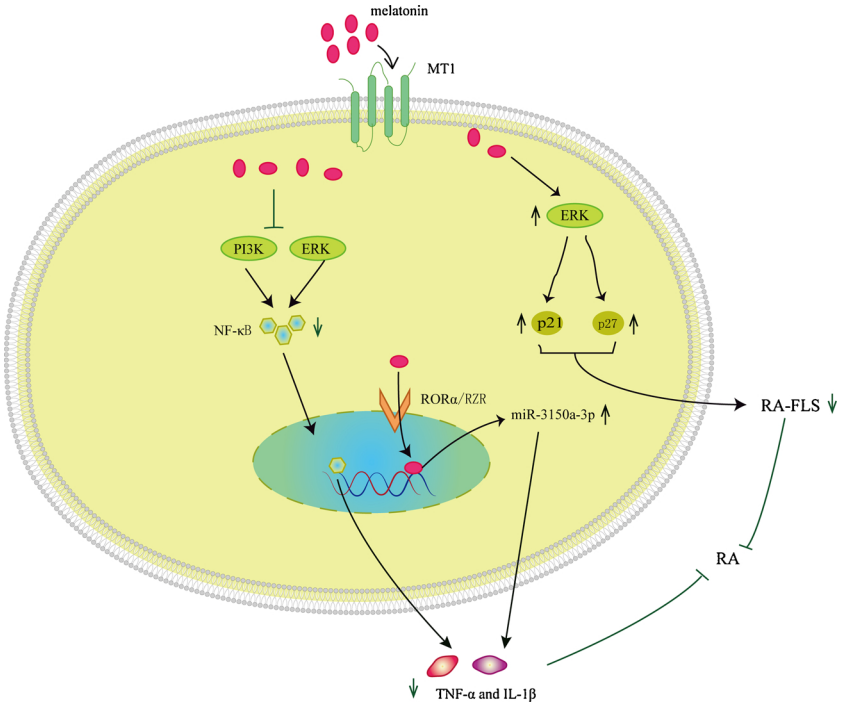


Fig. 2. The mechanisms underlying the effect of MLT on RA-FLS. MLT (at concentrations of 10 and 100μM) exerts the inhibitory effect of the proliferation of RA-FLS by activating P21 (CIP1) and P27 (KIP1) via ERK. In addition, MLT (0.2, 0.5, or 1 mM) treatment can suppress the PI3K/AKT, ERK, NF-κB signaling pathways, upregulate miR-3150a-3p levels to reduce the production of TNF-α and IL-1β.
ERK, Extracellular signal regulated kinase; IL, interleukin; RA-FLS, RA derived fibroblast-like synoviocytes; MLT, melatonin; MT1, MLT membrane receptors type 1; NF-κB, nuclear transcription factor kappa B.

and small joints, often accompanied with serum rheumatoid factor (RF) positive:, the enrichment of autoimmunity and immune complexes leading to joint deformity and loss of function [65].

There is conflicting data regarding the role of MLT in RA [66]. In animal models, MLT could increase the inflammatory response both on tissues and joints and promote the production of IL-6 and TNF-α [67]. Cardinali et al revealed that pinealectomized (unable to secrete MLT) rats could exhibit a significantly lower inflammatory response than the inflammatory and immune response of the highly MLT treated rats [68]. However, in the collagen-induced arthritis mouse model, MLT reduced paw swelling, bone erosion and cartilage degradation [8]. In adjuvant-induced arthritis rats, MLT possesses anti-inflammatory responses and it exhibited this action through Met-Enk release and the G protein-AC-cAMP transmembrane signal [69]. In addition, MLT (at concentrations of 10 and 100 μM) actives P21 (CIP1) and P27 (KIP1) via ERK exert the inhibitory effect of the proliferation of RA derived fibroblast-like synoviocytes (RA-FLS) [70]. RA-FLS takes critical roles in regulating inflammation and joint destruction and it can activate osteoclasts to enhance bone erosion. A recent study indicated that in synovial fibroblasts, MLT (0.2, 0.5, or 1 mM) treatment can suppress the PI3K/AKT, ERK and NF-κB signaling pathways, upregulate miR-3150a-3p levels to reduce the production of TNF-α, IL-1β and MT1 [8] (Fig. 2). In MLT-treated CIA mice, paw swelling was improved and the TNF -α, IL-1β production in serum was decreased, indicating that MLT alleviates disease activity in the CIA mouse model [8].

In addition, MLT can affect clock gene expression to exert its role. In mouse anti-type II collagen antibody-induced arthritis (CIA) model, MLT was injected intraperitoneally 5 times a week (10 mg / kg) for 2 weeks, CIA plus MLT animals have decreased mRNA and protein levels of Cry1 than CIA animals, showing that MLT can attenuate Cry1 gene expression in RA [67]. Cry1 can suppress cAMP production, suggesting that the lack of Cry1 may lead to elevated cAMP, increased PKA and NF-κB activation, and subsequently contribute to RA [71]. Moreover, a strong relationship between MLT secretion and IL-12 and NO production by macrophages has been found from RA patients, both in the synovial fluid and specific binding sites [72]. In addition, it has been demonstrated that the MLT receptor type 1B (MTNRIB) single-nucleotide polymorphism (SNP) is related with the RF in RA patients [73].

It has been observed that the serum MLT levels were significantly higher in RA patients than in healthy people and there is a positive correlation between the serum MLT levels with disease activity scores and the erythrocyte sedimentation rate (ESR) [74]. However, some studies reported conflicting results. Afkhamizadeh et al observed that the serum MLT levels in the morning do not relate with disease activity in RA patients, and they found that the newly diagnosed RA patients have a higher serum MLT values [75]. RA patients treated with 10 mg/day MLT showed a slowly developing antioxidant profile and increased ESR, but these do not affect the levels of pro-inflammatory cytokine or clinical symptoms, it may be a compensatory reaction [76]. Therefore, the anti-inflammatory and antioxidant actions of MLT involve many pathways, to indirectly or directly block NF-κB signaling and terminate the inflammatory responses. In addition, MLT can be associated with circadian clock genes (such as Cry1) to disrupt circadian rhythms and ultimately regulate the expression of pro-inflammatory cytokines. MLT may open new avenues to alleviate inflammatory joint symptoms in RA patients by inhibiting synovial proliferation and thus may become a kind of adjuvant therapy on RA in the future.

5.2. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a classical and complex autoimmune disease, characterized by a multitude of immune-complex deposition, autoantibody production and complement activation which causes tissue and organ damage [77].

In an animal model, Jimenez-Caliani et al observed that MLT decreased the levels of total serum IgM, IgG, anti-dsDNA antibodies and pro-inflammatory cytokines (IL-1β, IL-2, IL-6, IFN-γ and TNF-α), increased the production of IL-10 in female MRL/MP-fas mice, but had a contrary effect in males [78]. This gender-dependent effect of MLT may be owing to the modulation of sex hormones [79]. Oral treatment with MLT in the pristane-induced LN mice can block LN-related kidney injury by increasing TGF-β1, IL-6, Bax production and reducing CAT and SOD1 production [80].

It has been demonstrated that the MLT concentrations in SLE patients are changing with seasonal variations, of which the daily plasma MLT levels were higher in December than in June, but MLT levels were not related to clinical disease activity or manifestation [81]. Studies showed a lower MLT level in SLE patients compared to controls

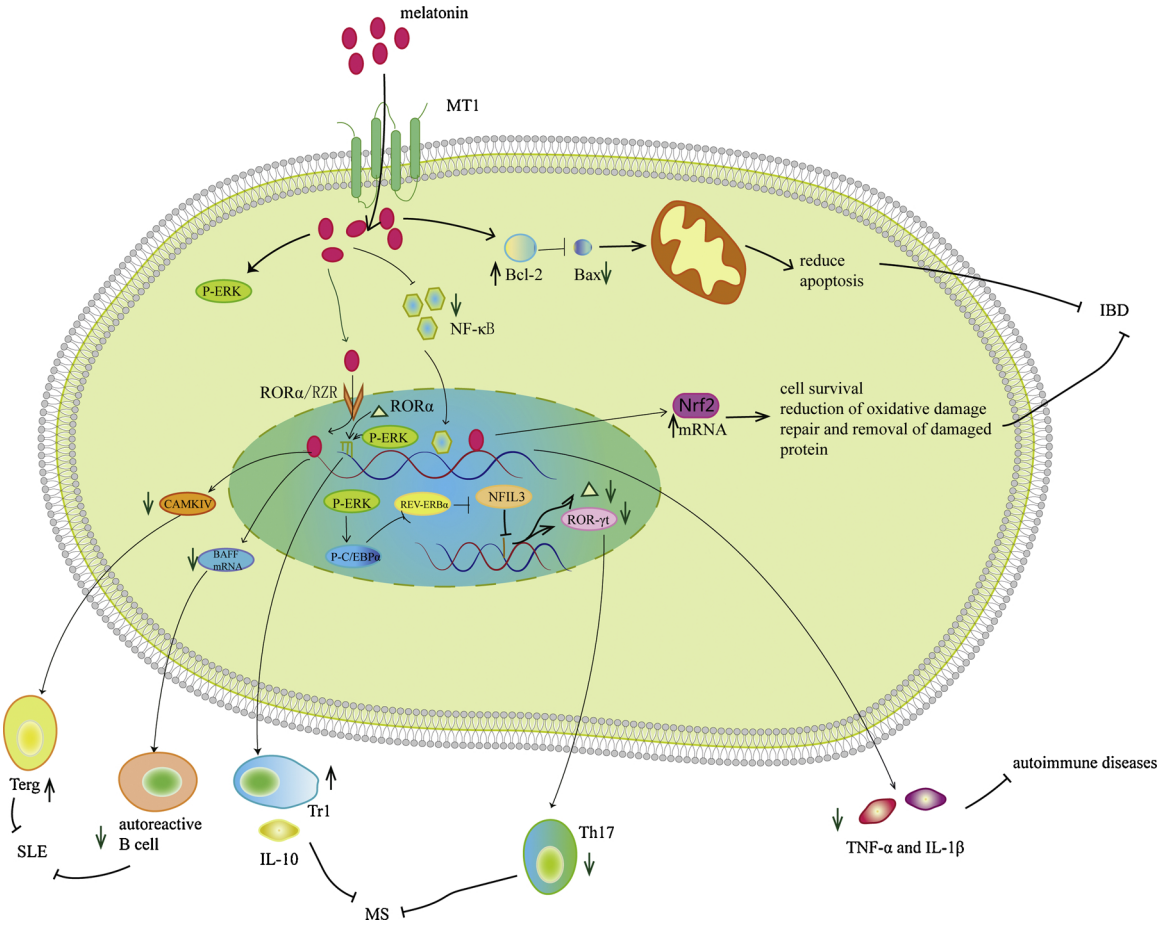


Fig. 3. The mechanisms underlying the effect of MLT on autoimmune diseases. Several pathways contribute to the pathogenesis of autoimmune diseases. First, MLT increases the recruitment of ROR-α to the Il10 promoter and consequently, Il10 transcription. MLT boosts Tr1 cell differentiation via Erk1/2 and ROR-α. Second, melatonin suppresses Th17 cell differentiation via the inhibition of ROR-γt and ROR-α expression through a NFIL3-dependent mechanism. Third, MLT up-regulates the number of Treg cells by silencing CAMKIV. Fourth, MLT down-regulates the expression of BAFF mRNA in PBMC and finally regulates B cell activation. Fifth, MLT treatment promotes Nrf2 gene and protein expression to reduce oxidative and inflammatory status. Sixth, MLT reduces the apoptosis of cells through decreasing the expression of Bax and preventing the loss of Bcl-2 proteins. Seventh, MLT reduces TNF-α and IL-1β through decreasing the activation of NF-κB.
BAFF, B-cell-activating factor of TNF family; CAMKIV, calcium/calmodulindependent kinase IV; ERK, Extracellular signal regulated kinase; IBD, inflammatory bowel disease; MLT, melatonin; MT1, MLT membrane receptors type 1; MS, multiple sclerosis; NF-κB, nuclear transcription factor kappa B; Nrf2, nuclear erythroid 2-related factor 2; ROR-α, Retinoid-related orphan nuclear hormone receptor; Il10, interleukin-10; IL-1β, interleukin-1β; SLE, systemic lupus erythematosus; TNF-α, Tumor Necrosis Factor-α; Tr1, type 1 regulatory; Tregs, Regulatory T cells;

[82,83], and Robeva et al found that MLT levels also correlated inversely with the systemic lupus erythematosus disease activity index (SLEDAI). However, in contrast to previous studies our recent study showed that MLT levels were not significantly different in SLE compared with controls [84]. Moreover, MTNR1B polymorphisms could affect the clinical features in SLE patients, and especially the susceptibility to leucopenia [85]. A vitro study evaluating the effects of MLT on leukocyte immune responses in SLE found that MLT has a dual role in the cells of patients versus controls [86]. MLT treatment had no effect on the frequency of FOXP3+ cells in PBMCs from healthy controls, whereas it elevated the mean fluorescence intensity of FOXP3 and the frequency of CD4+CD3+FOXP3+ cells in SLE patients [86]. They assumed that MLT may contribute to silencing of calcium/calmodulindependent kinase IV (CAMKIV, a putative MLT target), and after that up-regulate the number of Treg cells expressing FOXP3 [86]. MLT can down-regulate and up-regulate B-cell-activating factors of the TNF family (BAFF) mRNA expression in PBMC from lupus patients and healthy controls, respectively [86]. Study has showed that BAFF affected the capacity of the innate immune system to regulate B-cell activation in SLE [87]. Moreover, MLT inhibited IL-5 and IL-9 production [86]. Therefore, MLT may be involved in SLE pathophysiology by regulating cytokines, FOXP3 and BAFF signaling pathway (Fig. 3).

5.3. Multiple sclerosis

Multiple sclerosis (MS) is a common central nervous demyelinating disease, resulting in several of specific symptoms, including neuritis, retrobulbar neuritis, ophthalmoplegia and mental symptoms. Tregs, Th1, Th9, Th17, and Th22 cells are involved in disease development [88].

It has been found that MLT could reverse cuprizone-induced demyelination, by protecting the axon and increasing the numbers and activity of mitochondrial in MS mouse model [89]. MLT therapy ameliorated experimental autoimmune encephalomyelitis (EAE) severity by reduced mean clinical scores, compared to control EAE mice [90]. In addition, MLT can reduce procalcitonin levels in EAE mice [90]. A recent study in an EAE mouse model of MS explored its effect on oligodendrocytes metabolism and found that MLT increased myelin protein levels and remyelination [91]. And MLT treatment increased IL-4 level and reduced TNF-α and IL-1β level [91]. And high-dose MLT treatment increased N-acetylaspartate (NAA) levels more than in untreated EAE mice, demonstrating that MLT may reverse mitochondrial dysfunction [91]. Moreover, MLT suppressed pyruvate dehydrogenase complex (PDC) activity and increased pyruvate dehydrogenase kinase-4 (PDK4) levels suggesting the effect on modulating brain glucose metabolism

[91].

In the human body, MS patients showed that MLT levels and urine levels of 6-sulphatoxymelatonin (6-SMT, the major metabolite of MLT) are decreased, in comparison to healthy controls [90]. 6-SMT was also correlated with MS functional composite score (MSFC), disability and fatigue severity [92,93]. Treatment with MLT controls T effector Th1 and Th22 responses in PBMCs from MS patients while biasing the IL-10/Th1 cytokine balance toward a more protective profile [88]. In addition, MLT pathway genes are related to the risk of MS [94]. Farez et al observed MLT can affect the T cell differentiation, by which it can suppress the differentiation of Th17 cells (pathogenic) via the inhibition of ROR-γt and ROR-α expression through an NFIL3-dependent mechanism and promote the differentiation of Tr1 cell (protective) via Erk1/2 and the transactivation of the IL-10 promoter by ROR-α, though the MLT levels were negatively related with MS activity [7].

After MLT administration in relapsing-remitting multiple sclerosis (RRMS) patients, serum concentration of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and oxidative stress markers (lipoperoxides, nitric oxide catabolites) were decreased [88]. Kynurenine, N'-Formylkynurenine, dityrosine, carbonyl contents, and advanced oxidation protein products (AOPP) contents were decreased in the group treated with interferon beta plus MLT, indicating that combined administration of interferon beta-1b and MLT can be more effective in reducing oxidative stress in MS [95]. It has been shown that MLT could increase the levels of superoxide dismutase (SOD) and glutathione peroxide (GPx), and decrease the levels of malondialdehyde (MDA) [96]. MS patients under the treatment of natalizumab showed an increased MLT level, which also is associated with the increase of antioxidants and decrease of oxidative stress biomarkers, indicating that the effect of natalizumab may be due, in part, to the stabilization of MLT levels and its antioxidant effects [97]. MLT can increase the serum concentration of SOD activity and the total antioxidant capacity (TAC), and decrease the serum total oxidant status (TOS), thus reducing the symptoms of anxiety and insomnia and improving the sleep quality of MS patients [98,99]. Moreover, MLT may affect the function of TH1 cells by downregulating CD44 [100]. Thus, MLT can ameliorate MS by regulating Th1, Thr1, Th17, Th22 and by improving antioxidant effects and the sleep quality of MS patients (Fig. 3). It seems that MLT can be an effective and potential therapeutic option on the improvement in the quality of life of MS patients.

5.4. Inflammatory bowel disease

IBD is a group of special and complex intestinal inflammatory disease, including Crohn's disease, ulcerative colitis (UC) and indeterminate colitis. IBD can not only affect the colon and small intestine, but also have an effect on the mouth, esophagus and stomach. It is believed that the sleep disorders caused by MLT deficiency may be a potential trigger for disease flare of IBD.

In animal models, it has been shown that MLT treatment could decrease the levels of IL-6, IL-17, TNF-α, NF-κB, COX-2 and STAT3, it also clearly showed the anti-inflammatory function of MLT [101]. Marquez et al found that MLT could reduce the MPO activity in acute rats, but increase the MPO activity and the production of TNF-α in the chronic group [102], it showed that MLT may have an immunostimulatory effect in long-term diseases, such as IBD. Chamanara et al explored the roles of MLT in trinitrobenzene sulfonic acid (TNBS)-induced rat colitis, found that MLT improved histological damage, mucosal and weight loss. In addition, MLT increased TNBS-induced-downregulation of I-κB proteins and decreased up-regulation of NF-κB p65, MyD88 and TLR4, indicating that MLT inhibits TLR4/NF-κB signaling pathway to mediate the anti-inflammatory effects [103]. In 2,4-dinitrobenzene sulfonic acid (DNBS)-induced colitis animal model, DNBS group has decreased SOD activity and Nrf2 mRNA expression, increased MDA level, heme oxygenase-1 (HO-1) and myeloperoxidase (MPO) activity compared with control group [104]. MLT treatment reversed the SOD activity to a relatively high level, partly prevented increased MPO activity and MDA level, promoted Nrf2 gene and protein expression, leading to reduced oxidative and inflammatory status [104]. Moreover, MLT can protect the myenteric neurons (MNs, which can regulate motility and sensitivity of the intestine) from damage caused by inflammation and oxidative stress during colitis and may be mediated by the Nrf2-ARE pathway [104]. In addition, Mazzon et al observed that MLT could reduce the apoptosis of cells through decreasing the expression of Bax and preventing the loss of Bcl-2 proteins, and reduce inflammatory response through decreasing the activation of NF-κB and the phosphorylation of c-Jun [105].

In human body, it has been founded that the enterochromaffin cells were increased in the acute phase of UC, the c-reactive protein (CRP) levels were also decreased in MLT treatment patients, it may exist a beneficial reaction in the anti-inflammatory and defense mechanism [106]. MLT may become a useful treatment in the lower gut and gastrointestinal tract [107,108], can also be a supply treatment in IBD [109]. MLT can regulate Nrf2 mRNA expression and reduce the apoptosis of cells, thus, may become a new therapeutic regimen in IBD in the future (Fig. 3).

5.5. Type 1 diabetes mellitus

T1DM, also known as insulin-dependent diabetes mellitus, is a form of diabetes mellitus in which lack of insulin, and results in high blood sugar levels. The blood of the T1DM patients can be detected with a variety of autoimmune antibodies, such as glutamic acid decarboxylase antibody (GAD antibody), islet cell antibody (ICA antibody). These abnormal autoantibodies can damage the human islet β cell, which cannot be normal insulin secretion, so it highly possible related to immune abnormalities [110,111].

It has been shown that the levels of MLT were increased and the levels of insulin were decreased in streptozotocin induced rats, but insulin substitution could normalize the high expression of MLT, insulin receptor and adrenoceptor β 1, suggested the existence of a MLT-insulin antagonism [112,113]. However, Frankel et al observed that MLT did not affect the secretion of insulin from isolated mouse islets *in vitro* [114]. In addition, animal studier observed that MLT could regulate the vasoconstriction, treat the diabetes-induced functional and biochemical changes of aorta and corpus cavernosum [115,116]. Ozdemir et al demonstrated that MLT could decrease the retinal nitrotyrosine and MDA levels, and normalized the pathologic changes of retinal vascular, it showed a potential therapeutic effect on the retinopathy of diabetic rats [117].

In human body, it has been observed that the levels of MLT were significantly decreased in T1DM patients both on plasma and salivary [118,119]. Cavallo et al determined that MLT can decrease blood pressure, and prevent the complications of T1DM, such as hypertension and cardiovascular disease [120]. Perhaps the role of MLT in T1DM is still not clear, further studies are needed to find the relationship between MLT and T1DM.

5.6. Other autoimmune diseases

AS is a chronic inflammatory disease, characterized by the enthesitis of sacroiliac joints and the spine, the fibrosis and ossification of limbs and joints, intervertebral disc and adjacent connective tissue [121]. Some previous studies have shown that the serum MLT levels in AS patients were significantly higher than healthy controls, and correlated with Bath AS disease activity index (BASDAI) [122,123]. In addition, Senna et al [123] and Senel et al [122] confirmed that the serum MLT levels in AS patients were significantly higher than healthy controls and positively correlated with the disease activity. However, further studies are needed to clarify the relationship between MLT and AS.

SSc, also known as scleroderma, is a systemic autoimmune disease, characterized by localized or diffuse skin thickening and fibrosis,

resulting in skin sclerosis and vascular ischemia. It can affect the internal organs including the heart, lungs and other organs [124]. It has been observed that the MLT levels were decreased in SSc patients without circadian rhythm and the patients treated with MLT had no disease progression, thus suggesting that MLT could be regarded as a safe and effective treatment in SSc patients [125]. However, further studies are needed to support this view point.

Psoriasis is a common chronic inflammatory skin disease characterized by three important features including skin lesions, white scales, shiny film and punctate bleeding. The physiological mechanism of psoriasis is the abnormal proliferation and differentiation of the epidermis and the activation of the immune system [126]. It has been demonstrated that psoriasis shares a relationship with the deficiency of MLT [127]. Kartha et al observed that the levels of MLT are significantly decreased in psoriasis patients but are unrelated to depressive symptoms [128]. It suggested that the MLT agonists which could modulate MLT production can be an adjunctive therapeutic option in psoriasis.

6. Conclusion

In this review, we have highlighted the fact that MLT is involved in not only the modulation of the immune system but also oxidative stress production and has a role in reducing apoptosis. MLT has complex and specific functions in immune response through Nrf2, NFIL3, BAFF, and NF-κB, as well as MT1 and ROR-α. Moreover, MLT may regulate the expression of microRNAs (such as miR-3150a-3p) and other non-coding RNAs, which leads to the complexity of exploring its roles. MLT exerts activation and inhibition on inflammation based on the degree of inflammation and dosage (physiological or pharmacological), signifying its improved potential for the treatment of chronic inflammatory diseases. Therefore, MLT may serve as a potential new therapeutic target and provide new insight into the treatment of autoimmune diseases.

Declaration of Competing Interest

The authors declare that they have no competing interest.

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