Chapter 13
Sleep Hormone Melatonin, Inflammation and Aging

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13.1 Introduction

Aging is a progressive irreversible degenerative change in the structure and function of various tissues and organs with the growth of age, under the influences of many factors such as heredity, mental stress, and environmental pollution (Soto-Gamez and Demaria 2017; Bektas et al. 2018). Aging can be divided into physiological aging and pathological aging. The former refers to the state of natural aging of body function and metabolism over time, for example, protein degradation, tissue atrophy, decreased metabolic rate, and abnormal calcium metabolism (López-Otín et al. 2013; Verkhratsky 2019). The latter refers to the aging state caused by various diseases with the passage of age, like Alzheimer's disease (AD), Parkinson's disease (PD), cardiovascular and cerebrovascular diseases, infection-related diseases, and even cancers (Correa et al. 2018).

The original version of this chapter was revised: Acknowledgement statement has been updated. The correction to this chapter is available at https://doi.org/10.1007/978-3-031-22468-3_26

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A. Jagota (ed.), *Sleep and Clocks in Aging and Longevity*, Healthy Ageing and Longevity 18, https://doi.org/10.1007/978-3-031-22468-3_13

It should be noted that aging is mainly characterized by a weakened immune system accompanied by persistent inflammation, oxidative damage, and accumulation of advanced glycation end products (AGEs) (Basta 2008; Lian et al. 2020). Melatonin is primary secreted by the pineal gland in vertebrates, which is also destined to have a rhythmic secretion that can coordinate adaptive physiology (Cipolla-Neto and Amaral 2018). Moreover, melatonin has anti-inflammatory, antioxidant, and other activities (He et al. 2021, 2022; Bocheva et al. 2022; Xia et al. 2022), thus melatonin is thought to be a potential anti-aging substance. This chapter will mainly describe the roles of melatonin in inflammation and aging, as well as the involved mechanisms.

13.2 Aging and Inflammation

Actually, after birth, the body constantly carries out life activities such as nutrient metabolism, resists the threat of exogenous pathogens, removes own damaged components, and keeps the body in a state of balance (Cullum et al. 2020; Helman et al. 2020). The "free radical theory of aging" proposed in the mid-twentieth century (Harman 1956), that is, intracellular metabolism produces oxygen free radicals and leads to accumulated cell damage, which accelerates cell aging and supports the longevity hypothesis (Balaban et al. 2005). In addition to intracellular metabolism, chemical stimuli, heat sources, and ultraviolet radiation in the environment cause oxidative stress in cells (Finkel and Holbrook 2000). However, with the deepening of research, the telomere hypothesis that was proposed later causing aging has gradually been recognized by the public (Aubert and Lansdorp 2008), which links cellular aging with genomic changes and provides new research ideas for human aging and cancer (Aubert and Lansdorp 2008). Of not, as described in earlier, aging is formed by a variety of complex factors, and there are differences in various organisms; thus, it is hard to explain all aging phenomena with one theory currently.

The trend of global aging and the associated diseases during aging have become a challenge that cannot be ignored in the current human society (Partridge et al. 2018). Indeed, as the body becoming aging, the immune system undergoes a corresponding remodeling known as immunosenescence, resulting in long-standing chronic inflammation and weakened immune responses (Lian et al. 2020). Immunosenescence makes the elderly more vulnerable and more susceptible to various diseases. For instance, the coronavirus disease 2019 (COVID-19) pandemic predisposes the elderly, especially those older than 40 s, prone to adverse outcomes such as intensive care unit (ICU) admission or death (Chen et al. 2021a). Specifically, by assessing epigenetic aging in the blood of healthy people, non-severe and severe COVID-19 patients, researchers found that infection with COVID-19 might accelerate epigenetic clock and telomere attrition, promote epigenetic aging, and lead to post-COVID-19 syndrome (Cao et al. 2022).

In addition to changes in the immune status, metabolic disorders in the elderly also drive the progression of inflammation. For example, glycemic disorders in the elderly are prone to type 2 diabetes (T2D), and the imbalance of fat metabolism predisposes

the elderly to obesity and hyperlipidemia (Barbé-Tuana et al. 2020). With altered metabolism, aging organisms are accompanied by accumulation of AGEs, which bind to receptors and exacerbate tissue damage through the nuclear factor kappa-B (NF-κB) signaling pathway (Basta 2008).

Furthermore, aging causes an imbalance in the gut microbiota, which is interestingly gender specific, for example, decreased *Bifidobacterium* and increased *Blautia* and *Roseburia* in aged males, but the opposite was detected in aged females (Ma et al. 2020). The gut microbiome may act through inflammatory signaling, for instance, inhibition of caspase-1 shapes the fecal microbiome, with the increased relative abundances of *Akkermansia* spp. and *Blautia* spp., thereby favoring to lessen inflammation and rebalance the gut microbiota to protect the host (Wong et al. 2016). Studies also found that intestinal *Bifidobacterium* and *Roseburia* were negatively correlated with T2D, and *Blautia* was positively correlated with T2D (Gurung et al. 2020). These similar changes in gut microbiota provide us with interesting speculations about whether the imbalances in gut microbiome of the elderly interact with inflammatory diseases and metabolic disorders associated with immunosenescence. Of course, the relevant conclusions need to be experimentally confirmed.

On the other side, the persistent inflammatory responses in the aging population also exacerbate the aging of the body, and this process involves complex changes in a variety of immune cells. For example, $CD8^+$ T cells play an important role in controlling chronic infections, but studies have shown that persistent antigenic stimulation of inflammation leads to T cell exhaustion and that overexpression of programmed cell death (PD)-1 reduces the proliferative capacity of $CD8^+$ T cells (Hashimoto et al. 2018). In chronic persistent infection caused by Hepatitis B Virus (HBV), monocytes express high levels of PD-L1 and interleukin (IL)-10, and the suppressive monocytes induce natural killer (NK) cells to produce IL-10 and suppress T cell activation, including $CD4^+$ and $CD8^+$ T cells (Li et al. 2018). As mentioned earlier, senescence increases susceptibility to viruses, $CD4^+$ T cells are essential for antiviral infection, and enhance the lethality of $CD8^+$ T cells in the context of chronic infection by secreting IL-12 (Zander et al. 2019). Therefore, immunosenescence is further promoted by multiple cellular immune blunting due to chronic inflammation. The presence of leukocytes in the chronic inflammatory microenvironment continues to stimulate the body, locally induces fibrosis, and eventually leads to irreversible tissue damage and organ failure (Sebastiani et al. 2014; Eming et al. 2017; George et al. 2020).

More importantly, the immunosenescence of the elderly is accompanied by an impaired immune response to vaccination (Pawelec 2018), that is, due to changes in the degeneration of the thymus and the lack of naive T cells in the older adults, vaccination may not have the desired effect when the elderly disease occurs. However, persistent inflammation is not harmful absolutely in the aging population, and research suggests that a new balance of pro- and anti-inflammatory responses in some older adults, especially centenarians, contributes to longevity (Santoro et al. 2021). Considering that aging is a systemic event involving changes in the immunity, nutrient metabolism, and intestinal microecology, and also is related to the accumulation of aging markers in non-invasive biological fluids such as plasma and urine (Adav

and Wang 2021); therefore, the treatment of senile diseases requires consideration of multiple factors. Actually, the suboptimal responses of older people to vaccines have prompted scientists to develop more comprehensive treatments and interventions, for example, the use of autophagy enhancers, stem cell therapy, Chinese herbal medicine treatment, enhanced exercise, and other multi-faceted means (Shetty et al. 2018).

13.3 Melatonin and Aging

Melatonin is an indole hormone mainly secreted by the pineal gland in mammals with the multiple functions, including anti-oxidation, regulating sleep, modulating circadian rhythm, enhancing immunity, and suppressing tumor progression (Xia et al. 2019). Indeed, melatonin also plays an important role in the complex aging process of mammals (Boga et al. 2019). Interestingly, aging is accompanied by metabolic and physiological decline and has the characteristics of circadian rhythm disorder (Roenneberg et al. 2013; Nohara et al. 2019). Moreover, in most vertebrates, the link between aging and melatonin is that melatonin level decreases with age (Bubenik and Konturek 2011; Hardeland et al. 2012). There are two possible reasons for this: 1) The decreased density of β-adrenergic receptors leads to the weakening of melatonin synthesis in pineal gland during aging through downregulating the gene expression or phosphorylation of aralkylamine *N*-acetyltransferase (AANAT) (Suwazono et al. 2000; Jiang et al. 2017; Hohl et al. 2018); 2) the depletion of melatonin increases due to the metabolic events, resulting in changes in the overall content (Obayashi et al. 2014).

Importantly, it has been demonstrated that when the pineal gland of rats was excised to lower the production of melatonin, the accumulation of oxidative damage products accelerated their aging process (Kumazaki and Yoshida 1984). In contrast, when young pineal glands were transplanted into older animals or supplemented with exogenous melatonin, both significantly increased the life span of experimental animals (Kumazaki and Yoshida 1984; Doron et al. 2019). The study by Jauhari et al. also pointed out that AANAT knockout mice are an accelerated aging model (Jauhari et al. 2020), which further suggests that melatonin has an anti-aging effect. Moreover, age differences in the infection rate and severity of COVID-19 have been shown higher in the elder than in youth, and studies have linked this difference to melatonin (Zimmermann and Curtis 2020). Also, experiments have shown that children have higher levels of melatonin, which may be related to lower rates of COVID-19 infection. Therefore, these aforementioned findings suggest that low melatonin level could be considered as a biomarker of aging (Huffnagle and Noverr 2013; Obayashi et al. 2014; Brazao et al. 2017); and more importantly, melatonin might modulate aging process.

13.4 Regulatory Effects of Melatonin on Aging

13.4.1 Melatonin Slows Aging Through Antioxidant Function

The oxidative damage of aging originates from the "aging free radical theory." The vast majority of intracellular ROS comes from nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOXs) and mitochondrial oxidative phosphorylation (OXPHOS) (Balaban et al. 2005; Dan Dunn et al. 2015). Nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH) generate superoxide anion ($O_2 \cdot^-$) in the process of passing through the I and III sites of the mitochondrial electron transport chain (ETC) (Balaban et al. 2005). When the OXPHOS is disturbed by excessive cell inflammation, autophagy, and/or apoptosis, the balance is inclined to the production of ROS, which also called mitochondrial ROS (mtROS) (Dan Dunn et al. 2015). Likewise, oxidative damage causes changes in the morphology and physicochemical properties of senescent cells (Muñoz-Espín and Serrano 2014). Mitochondrial metabolism is also implicated in aging, for example, alterations in mitochondrial pyruvate dehydrogenase (PDH) activity lead to increased pyruvate, which in turn leads to mtROS production and promotes mitochondrial aging (Kaplon et al. 2013; Sun et al. 2016). In conclusion, mitochondria may play an important role in aging-induced oxidative damage.

Melatonin has anti-oxidative activity and its anti-oxidation efficacy dependently of direct and/or indirect means. As for the direct action, melatonin and its metabolites directly scavenge free radicals and ROS. For example, melatonin scavenges hydroxyl radicals (·OH) by tautomerization (Purushothaman et al. 2020). Therefore, melatonin has the potential to inhibit cancer by regulating angiogenesis by inhibiting the hypoxia-inducible factor 1α (HIF-1α)/ROS/vascular endothelial growth factor (VEGF) pathway (Cheng et al. 2019). The melatonin metabolite *N*(1)-acetyl-5-methoxykynuramine (AMK) also exhibits excellent scavenging efficiency for ·OH and $\cdot OOCCl_3$ (Galano et al. 2013). And for the indirect effects: (i) Melatonin upregulates glutathione (GSH) synthesis by stimulating antioxidant enzymes [e.g., glutathione reductase (GR)], which in turn carry out antioxidant activities (NaveenKumar et al. 2020). (ii) Melatonin restores immune cell functions, such as enhancing neutrophil phagocytosis and NETosis function and defending against infections (NaveenKumar et al. 2020). (iii) Melatonin neutralizes nitrogen-based poisons such as nitric oxide (NO) and chelates transition metals to resist oxidation (Reiter et al. 2016).

In view of the aforementioned role of mitochondria in oxidative damage, melatonin exerts an antioxidant effect through the melatonin–mitochondrial axis in the process of resisting infection, reducing tissue damage, thereby inhibiting or delaying tissue aging (Reiter et al. 2018). Actually, the oligopeptide transporter peptide transporter 1 and 2 (PEPT1/2) promotes the transport of melatonin to mitochondria (Fig. 13.1) (Huo et al. 2017). In addition, mitochondria express AANAT and *N*-acetylserotonin-*O*-methyltransferase (ASMT), which are involved in the production

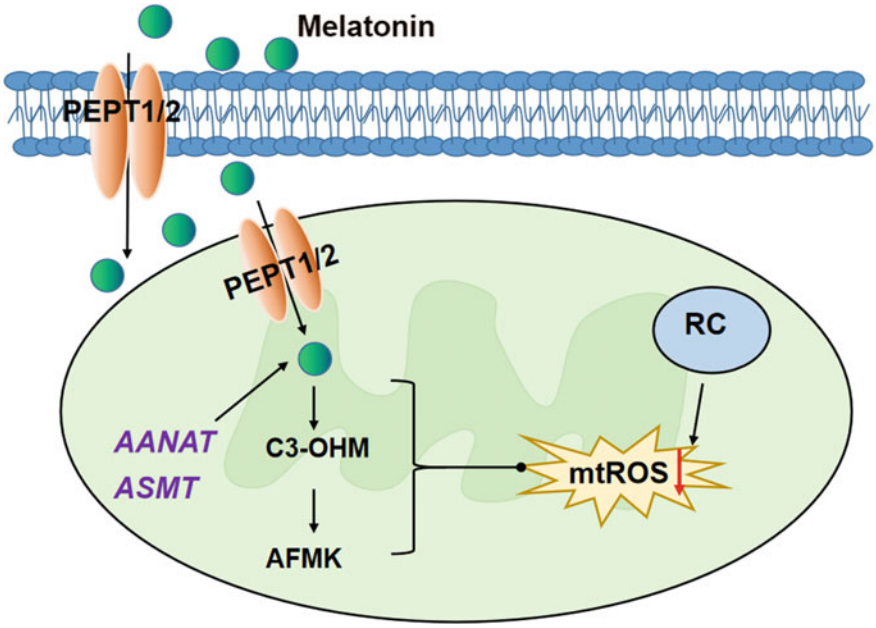

Fig. 13.1 Melatonin reduces oxidative damage and delays aging by inhibiting mtROS. Melatonin in mitochondria may rely on oligopeptide transporter PEPT1/2 transport or AANAT/ASMT-mediated synthesis. Melatonin and its metabolites C3-OHM and AFMK can reduce mtROS generated by mitochondrial RC, thereby reducing mitochondrial oxidative damage and inhibiting aging. *("↓" arrows represent decreases.) mtROS: mitochondrial ROS; AANAT: aralkylamine *N*-acetyltransferase; ASMT: *N*-acetylserotonin-*O*-methyltransferase; C3-OHM: Cyclic 3-hydroxymelatonin; AFMK: *N1*-acetyl-*N2*-formyl-5-methoxykynuramine; and RC: respiratory chain

of melatonin (Fig. 13.1) (Tan et al. 2013; Reiter et al. 2018). Melatonin reduces mtROS after entering mitochondria (Chen et al. 2020); its metabolite prevents mitochondrial permeability transition (MPT) and limits mitochondria-related apoptosis (Fig. 13.1) (Jou et al. 2019). Moreover, melatonin activates adenosine 5′-monophosphate-activated protein kinase α (AMPKα), attenuates dynamin-related protein 1 (Drp1)-dependent mitochondrial fission, restores the interaction of voltage-dependent anion channel 1 (VDAC1) and hexokinase 2 (HK2), prevents MPT pore (MPTP) opening and activation of PINK1/Parkin pathway, and ultimately blocks mitophagy-mediated cell death (Fig. 13.2) (Zhou et al. 2017). In addition, mitochondrial DNA (mtDNA) released into the cytoplasm activates the cyclic guanosine monophosphate–adenosine monophosphate synthase (cGAS)/stimulator of interferon genes (STING)/interferonregulatory factor 3 (IRF3) pathway, which mediates the inflammatory response in aging, and melatonin could reduce mtDNA to delay aging (Fig. 13.3) (Jauhari et al. 2020). Sirtuin 3 (Sirt3) is a mitochondrial nicotinic adenine dinucleotide (NAD) dependent deacetylase (Wang et al. 2019b), and melatonin reduces the acetylation of superoxide dismutase 2 (SOD2) through Sirt3–SOD2 signal and inhibits the generation of mitochondrial $O_2 \cdot^-$ (Fig. 13.3) (Pi et al. 2015).

Excessive oxidative stress will damage oocytes and thus affect reproductive function, which is also called ovarian aging (Tamura et al. 2020). Melatonin reduces the ROS level of oocytes through melatonin receptor 1 (MT1)/AMPK pathway, maintains mitochondrial membrane potential, and ultimately delays ovarian aging and improves fertility (Zhang et al. 2019a).

In conclusion, melatonin signaling, such as melatonin receptor MT1, melatonin transporter PEPT1/2, melatonin synthases AANAT and ASMT, and melatonin metabolite AMK, acts as the target of mitochondrial antioxidant through AMPK/Drp1, HIF-1α/ROS, cGAS/STING, SIRT3-SOD2, and other signals to reduce cellular and/or tissue senescence in the process of alleviating oxidative damage.

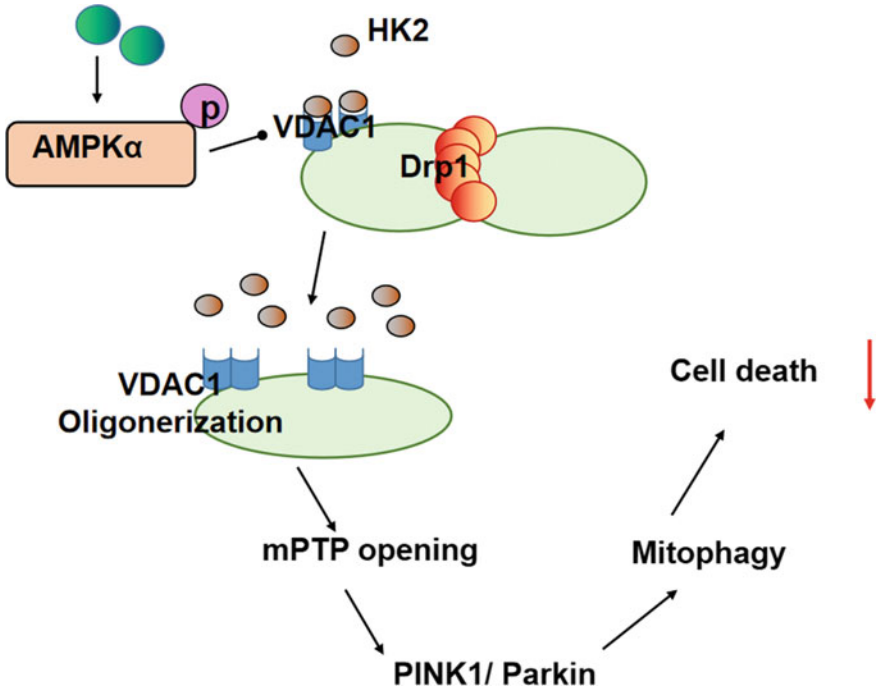

Fig. 13.2 Activation of AMPKα by melatonin inhibits mitochondrial fission and autophagy-induced cell death. Melatonin inhibits Drp1-induced mitochondrial fission by activating AMPKα, reverses VDAC1 oligomerization, promotes VDAC1-HK2 interaction, prevents mPTP opening and PINK1/Parkin activation, and ultimately prevents mitophagy-induced cell death. *("↓" arrows represent decreases.) Drp1: dynamin-related protein 1; VDAC1: voltage-dependent anion channel 1; HK2: hexokinase 2; and mPTP: mitochondrial permeability transition pore

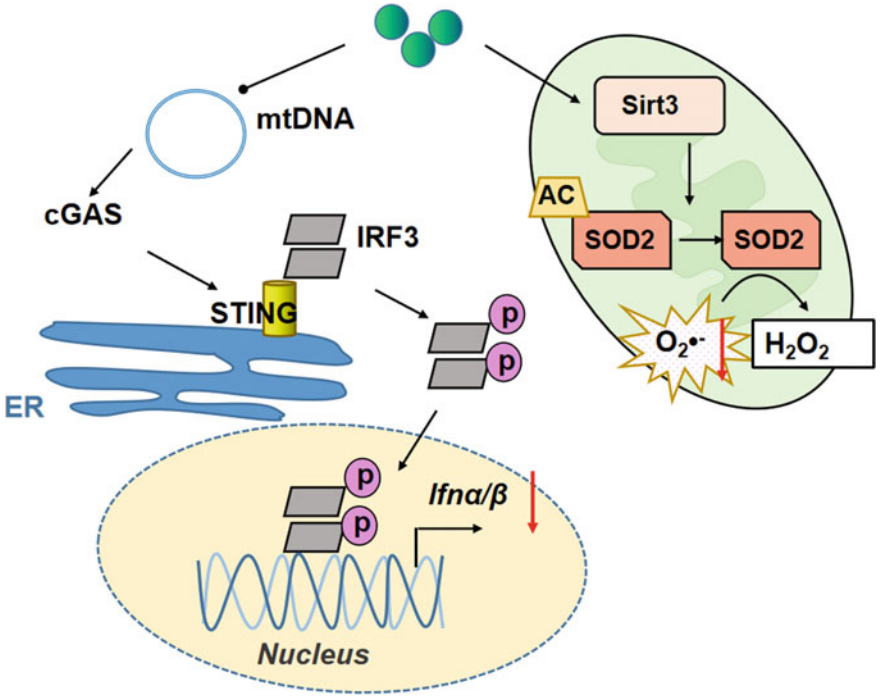

Fig. 13.3 Melatonin reduces mtDNA to suppress inflammation or promotes Sirt3 to reduce oxidative damage. The mtDNA released into the cytoplasm activates the cGAS/STING/IRF3 pathway and promotes Ifnα/β expression to mediate inflammatory responses during aging. Melatonin can reduce mtDNA, thereby inhibiting its cascade reaction and delaying aging. Melatonin promotes the deacetylation of SOD2 by enhancing the activity of Sirt3, thereby reducing mitochondria-derived $O_2\cdot^-$, reducing cellular oxidative damage, and delaying aging. *("↓" arrows represent decreases.) mtDNA: mitochondrial DNA; Sirt3: sirtuin 3; cGAS: cyclic guanosine monophosphate–adenosine monophosphate synthase; and SOD2: superoxide dismutase 2

13.4.2 Melatonin Delays Aging by Repairing DNA Damage

Another theory about aging is the "telomere theory." As cells becoming aging, the telomeres at the ends of eukaryotic chromosomes shorten or change structurally, leading to replication aging and chromosome instability, and consequently, universal cell aging causes qualitative changes in body aging (Aguado et al. 2020). Melatonin may target human cytochrome P450 1A1 (CYP1A1) gene-mediated 15-hydroxyeicosatetraenoic acid (15-HETE)/telomerase reverse transcriptase (TERT) pathway to regulate telomerase activity, improve telomerase activity, reduce DNA damage, and inhibit cell senescence (Xie et al. 2021). Melatonin also participates in epigenetic modification of genes, inhibiting gene silencing such as DNA methylation and lysine 9 trimethylation of histone H3 (H3K9me3), promoting transcription of activation genes such as acetylation of histone H3, promoting gene reprogramming,

further facilitating gene rejuvenation, and inhibiting cell aging (Yang et al. 2019). The prolongation of telomere and the stimulation of ribosome function by melatonin save the aging of endothelial tissue (Xie et al. 2021), retinal pigment epithelium (RPE) (Blasiak et al. 2016), ovary, and other tissues (Tamura et al. 2017). Therefore, the ability of melatonin in repairing DNA damage gives it the potential of delaying aging.

13.4.3 Melatonin Promotes Autophagy and Reduces the Accumulation of Harmful Substances During Aging

Autophagy is induced by the internal environment or external stress, which can guide the degradation of various substances and avoid the accumulation of damaged substances in the aging process (Glick et al. 2010). Therefore, impairing autophagy would promote the aging. In addition, lysosomal function declines with age, and the accumulation of damaged proteins or organelles induces senescence (Levine and Kroemer 2008; Lawrence and Zoncu 2019). Wong et al. concluded that autophagy defects, involving changes such as impaired nucleocytoplasmic transport and abnormal phase separation, are major risk factors for aging and some neurodegenerative diseases (NDDs) (Wong et al. 2020).

Melatonin prevents aging by regulating autophagy through inflammation-related signal pathways (Fig. 13.4). Melatonin blocks toll-like receptor 4 (TLR4)/protein kinase B (PKB or AKT)/mammalian target of rapamycin (mTOR) pathway to activate autophagy, thereby inhibiting neuro-inflammation and microglial apoptosis in T2D mice (Cui et al. 2021), or to promote mitophagy, reducing tumor cell viability and inhibiting tumors' growth (Shen et al. 2018). Melatonin also promotes mitophagy through SIRT3-SOD2 or AMPK/optic atrophy 1 (OPA1) signaling, which blocks caspase-9-induced mitochondrial apoptosis and maintains cellular homeostasis against cardiac injury (Pi et al. 2015; Zhang et al. 2019b). Melatonin can also activate the AMPK/Forkhead box O 3 (Foxo3) pathway to maintain mitochondrial redox homeostasis or inhibit NF-κB to promote autophagy, respectively, protecting chondrocytes and alleviating intervertebral disk degeneration (IVDD) (Chen et al. 2020, 2021b). Besides, melatonin attenuates AD, PD, Huntington's disease (HD), organophosphate-induced delayed neuropathy (OPIDN), amyotrophic lateral sclerosis (ALS), and other age-related NDDs. *Luo* and colleagues summarized the association between melatonin and aging-related NDDs via autophagy (Luo et al. 2020), which we would not discuss here again.

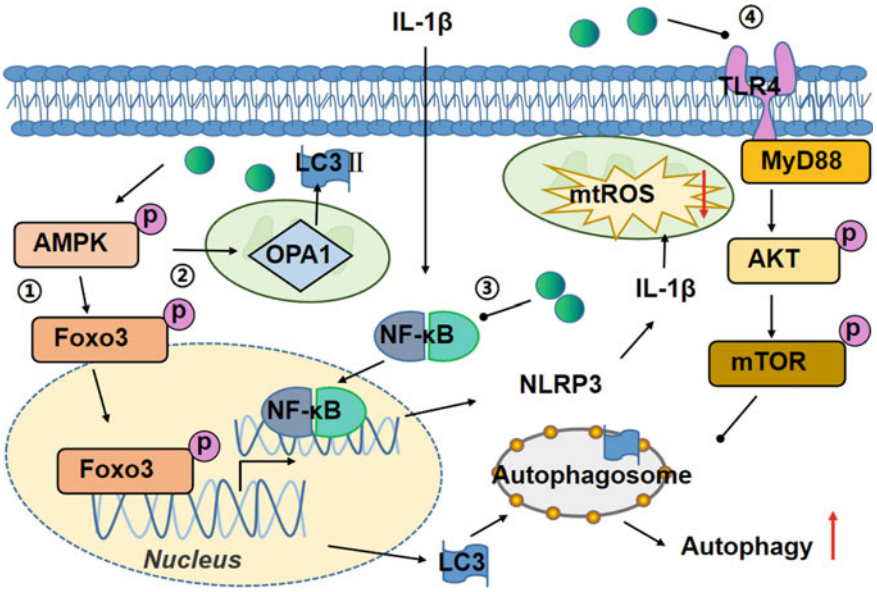

Fig. 13.4 Melatonin delays aging by promoting autophagy through inflammatory signaling. ① Activation of the AMPK/Foxo3 pathway by melatonin increases the expression of autophagy genes and promotes the expression of LC3, which promotes autophagy. ② Melatonin also promotes mitophagy by increasing the levels of LC3II and mito-LC3II through AMPK/OPA1 signaling. ③ IL-1β/NF-κB/NLRP3 activates a positive feedback loop to promote mtROS production, and melatonin mediates the disruption of the IL-1β positive feedback loop and inhibits mtROS production. ④ Melatonin inhibits the TLR4/AKT/mTOR pathway and promotes autophagosome generation to activate autophagy. *("↑" arrows represent increases, and "↓" arrows represent decreases.) Foxo3: Forkhead box O 3; LC3: microtubule-associated protein 1 light chain 3; OPA1: optic atrophy 1; and mtROS: mitochondrial ROS

13.4.4 Melatonin May Rescue Aging by Inhibiting Hyperactive Sympathetic Nerve Activity

In addition to facing changes in cellular aging and tissue dysfunction, both healthy aging and disease aging are accompanied by autonomic dysfunction, especially the overactive sympathetic nerve activity (SNA), which is innervated by projections from the paraventricular nucleus (PVN) of the hypothalamus and the rostral ventrolateral medulla (RVLM) of the brainstem (Balasubramanian et al. 2019).

Oral melatonin (30 mg/kg/day) for 15 days was shown to effectively inhibit sympathetic excitation, reduce baseline mean arterial pressure (MAP) and ROS levels in RVLM, and alleviate neurogenic hypertension, but the specific mechanism remains to be explored (Nishi et al. 2019). Study indicated that topical application of melatonin or its analog *N*-butanoyl-2-(2-methoxy-6H-isoindolo[2,1-a]indol-11-yl) ethanamine (IIK7) could reduce the intraocular pressure through MT2, and β-adrenergic agonists contribute to this effect; however, the co-localization of MT2 with the sympathetic

nervous system (SNS) was not observed in this article (Alarma-Estrany et al. 2008), so there may be other mechanisms involving in the aforementioned progress. At the end of the 20th, some studies focused on the effect of melatonin on the SNA and found that the SNS directly regulates the synthesis of melatonin in the pineal gland (Wurtman et al. 1964), and melatonin can be used as an endogenous mediator to participate in short photoperiods to inhibit peripheral SNA (Viswanathan et al. 1986). However, whether the role of melatonin in regulating the SNS is related to aging and the mechanism of how melatonin regulates the SNS remains an open question.

13.4.5 Melatonin Regulates Infection and Delays Aging by Modulating Gut Microbiota

Aging is accompanied by changes in host-microorganism homeostasis. This process is affected by factors such as diet, living environment, and lifestyle, as well as by the health status of the host. Ghosh et al. concluded that healthy aging and disease-related aging have both similar and distinct gut microbial changes (Ghosh et al. 2022). Among them, *Akkermansia*, *Butyricimonas*, *Christensenellaceae*, *Oscillospira*, and *Roseburia* increased in normal aging, but decreased in disease aging; *Ruminococcus* decreased in normal aging but increased in disease aging; Pathobionts, *Parabacteroides* are elevated in both normal and diseased aging, while short chain fat acid (SCFA) producers and *Bifidobacterium*, *Prevotella*, and *Eubacterium* are decreased in both normal and diseased aging (Ghosh et al. 2022). In addition, butyrate-producing *Faecalibacterium* and *Coprococcus* (Valles-Colomer et al. 2019) and *Lachnospiraceae* involved in the conversion of primary bile acids to secondary bile acids (Sorbara et al. 2020) are decreased in disease aging; *Anaerotruncus* associated with high cholesterol (Zhang et al. 2021) and *Coprobacillus* associated with the severity of COVID-19 (Zuo et al. 2020) are increased in disease aging (Ghosh et al. 2022). These above findings suggest that alterations in the gut microbiota during disease aging might affect host metabolism and make the host susceptible to infection. And the microbiota intervention with the same change trend in disease aging and healthy aging will become a new idea for regulating aging signals.

Melatonin modulates inflammatory responses in a microbe-dependent manner. For example, melatonin increases the abundance of probiotic *Bifidobacterium* and reduces the abundance of harmful bacteria such as *Desulfovibrio*, and has a relieving effect on oxazolone (Oxa)-induced colitis (Zhao et al. 2021). Melatonin blocks *Prevotella* lipopolysaccharide-induced nitric oxide and interleukin-6-induced host damage by inhibiting NF-κB and signal transducer and activator of transcription 1 (STAT1) activity (Choi et al. 2011). Furthermore, the whole metagenomic sequencing of gut microbiota in children with autism spectrum disorder (ASD) found decreased *Parabacteroides* in gut microbiota and decreased abundance of genes associated with melatonin and SCFAs in the ASD metagenome (Averina et al. 2020). Importantly,

Table 13.1 Melatonin affects microbiota with the same trends in healthy aging and diseased aging

Microbiota	Changes in healthy aging	Changes in disease aging	Melatonin effects	Reference
Bifidobacterium	↓	↓	↑	Zhao et al. (2021)
Prevotella	↓	↓	Inhibits *Prevotella*-LPS induced inflammation	Choi et al. (2011)
SCFA producers	↓	↓	↑	Lv et al. (2020)
Eubacterium	↓	↓	▲	Averina et al. (2020)
Faecalibacterium	↓	↓	▲	Averina et al. (2020)
Parabacteroides	↑	↑	▲	Averina et al. (2020)
Pathobionts	↑	↑	↓	Zhao et al. (2021)

*"↓" indicate decrease, "↑" indicate increase, "▲" indicate association

the metabolite genes of *Eubacterium*, *Faecalibacterium*, and *Roseburia* are mainly related to melatonin (Averina et al. 2020). Gut-derived plasma SCFAs showed significant circadian oscillations, possibly related to plasma melatonin (Swanson et al. 2020). Gut microbiota that produces SCFAs may promote melatonin receptor expression (Wang et al. 2019a), and melatonin supplementation can promote the abundance of SCFAs production-related flora and increase the production of SCFAs, finally alleviating neuro-inflammation (Lv et al. 2020). Therefore, melatonin may improve inflammation and ultimately affect the aging process by regulating the microbiota that commonly changes in healthy aging and disease aging (Table 13.1). However, whether there is a direct link between melatonin-gut microbiota-aging needs to be experimentally verified.

13.5 Conclusion

In conclusion, melatonin plays an important role in the complex aging process of mammals. For example, melatonergic signaling, including melatonin receptor MT1, melatonin transporter PEPT1/2, melatonin synthases AANAT and ASMT, and melatonin metabolite AMK might reduce cellular and/or tissue senescence through alleviating oxidative damage, promoting autophagy, and reducing the accumulation of harmful substances during aging. Notably, melatonin may curtail excessive inflammation and ultimately affect the aging process by regulating the microbiota that commonly changes in healthy aging and disease aging. Moreover, numerous reports

indicate that melatonin possesses anti-infection capability (He et al. 2021, 2022); and the susceptibility of pathogens increases during aging which may also be related to the decreased secretion of melatonin. Therefore, the melatonin level functions as a biomarker of aging and exogenous melatonin could be a potential age regulator.

Acknowledgements Our profound admiration and respect go to researchers in this field and in our laboratories, for their dedication and hard work. We apologize to scientists whose work is in this field if their papers are not cited owing to space limitations. This work was supported by Fundamental Research Funds for the Central Universities (SWU-KQ22068), Chongqing graduate research and innovation project (CYS18075), and College Student Innovation and Entrepreneurship Training Program Practical Project (S202110635157).

Compliance with Ethical Standards: This article does not contain any studies with human participants performed by any of the authors.

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