Commentary

Melatonin, macrophages and microbiota: Interactions

Russel J. Reiter

Department of Cell Systems and Anatomy**,** UT Health, Long School of Medicine**,** San Antonio, Texas 78229
Correspondence: reiter@uthscsa.edu, Tel: 210-567-3859

Running title: Functions of melatonin

Received: January 3, 2022; Accepted: March 23, 2022

ABSTRACT

This commentary summarizes and highlights the recent research reports of the group headed by Professor Wenkai Ren. Their research has been focused in two important investigative areas, namely, the role of melatonin in the regulation of macrophage polarization and the functional implications of melatonin for the gastrointestinal microbiota. Both these subjects are of high interest to melatonin biologists since both have significant implications in clinical and veterinary medicine.

Key words: immunomodulation, T cells, macrophage polarization, bacterial infection

Macrophages are an important component of the immune system and there is a growing body of evidence indicating their capacity to produce melatonin, but the molecular network to do so seems to be relatively dormant in healthy cells but is inducible under pathological conditions. Additionally, some immune cells express the classic membrane melatonin receptors, i.e., MT1 and MT2. Collectively, the findings implicate melatonin as an important endogenous immunomodulatory agent.

Ren et al. (1) demonstrated that melatonin is effective in orchestrating T cell activation and differentiation (especially for Th17 cells) which is largely dependent on both melatonin membrane and nuclear receptors. Mechanistically, melatonin inhibits the differentiation of Th17 cells by inducing the translocation of RORα from the nucleus or reducing the expression of RORα and RORγ through ERK1/2-C/EBPα-REV-ERBα-NFIL3 pathways (1). In addition to the effects of melatonin on T cells, they further (2) demonstrated that melatonin also has a significant role in macrophage biology due to its involvement in macrophage polarization: this includes the conversion of highly pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages. Melatonin inhibits pro-inflammatory macrophage polarization *via* STAT1, NF-κB, and NLRP3 pathways; whereas it enhances anti-inflammatory macrophage polarization by the activation of STAT6 (2). They found that melatonin reduces macrophage pro-inflammatory responses, especially for lowering IL-1β production, which is associated with enhanced mitochondrial functions and reprogramming of intracellular metabolism. This important work from Professor Ren's group (3) provides new insights into how melatonin determines macrophage phenotype.

To explore the intrinsic mechanism of melatonin-mediated inhibition of macrophage inflammation, they also compared the transcriptional profile between LPS/IFN-γ-stimulated macrophages with or without melatonin treatment. They found that treatment of macrophages with melatonin remodels signaling pathways which depends on interferon regulatory factor 7 (IRF7) (3). Mechanistically, melatonin acts via membrane receptor 1 (MT1) to increase heat shock factor 1 ((*Hsf-1*) expression, thereby transcriptionally inhibiting interferon (IFN)-γ receptor 2 (IFN-γR2) and ultimately causing defective canonical signaling events [Janus kinase (JAK) 1/2-signal transducer and activator of transcription 1(STAT1-IRF7]. These compelling works indicate the highly decisive roles of metabolites from amino acid metabolism (e.g., melatonin) in immune cell fate decision, and provide potential therapeutic targets to prevent and/or treat inflammatory diseases.

Their second field of investigation relates to the functional significance of melatonin in relation to gastrointestinal microbiota. Although compelling investigations indicate a link between melatonin and gut microbiota, the involvement of intestinal microbiota in melatonin-mediated physiology remains obscure. Ren et al. (4) reported that melatonin supplementation to weanling mice significantly improves body weight gain and intestinal morphology. Moreover, melatonin influences the community structure and metabolism of intestinal microbiota and reduces the bacterial load in enterotoxigenic *Escherichia coli* -infected weanling mice. Notably, in antibiotic-treated weanling mice and germ-free weanling mice, the influence of melatonin on these parameters is abolished. They also found that oral melatonin supplementation alleviates high fat diet-induced lipid accumulation and gut microbiota dysbiosis (5). The involvement of intestinal microbiota, especially intestinal microbiota-derived metabolites, in the regulatory function of melatonin on host metabolism is demonstrated with antibiotic exposure and fecal microbiota transplantation. These prospective studies for the first time clarify the modulatory effect of intestinal flora on the physiological functions of melatonin, and have important implications for use of melatonin in alleviating the weaning stress in farm animal production (e.g., pigs) and potentially children as well.

To explore the underlying mechanism as to melatonin's actions on bacterial physiology, Professor Ren's group conducted further experiments with *P. multocida*, a causative agent responsible for many economically-associated diseases in a wide range of hosts (6). Using RNA sequencing analysis, they found that melatonin down-regulates the expression of membrane transport and carbohydrate metabolism related genes. Furthermore, melatonin disrupts cell membrane integrity of *P. multocida*, which is evidenced by the increased release of intracellular contents. Most importantly, they determined that melatonin specifically targets the type II citrate synthase of Gram-negative pathogens through directly binding to the R300, D363, and H265 sites, accounting for its high selectivity against Gram-negative bacteria rather than Gram-positive bacteria or eukaryotes. Consistently, melatonin is efficacious in prevention and treatment the infections of *P. multocida*. These data indicate that type II citrate synthase represents an untapped target for development of novel antimicrobial agents against Gram-negative pathogens (6). In addition, they (7) also found that melatonin rescues colistin activity against colistin resistance gene (MCR)-positive pathogens both *in vitro* and *in vivo*. Mechanistic investigations demonstrated that the combination of colistin with melatonin enhances bacterial outer membrane permeability, promotes oxidative damage and inhibits the function of efflux pumps. This study has important implications for use of melatonin as potential adjuvants to restore the antibacterial activity of antibiotics and offers a cost-effective and novel strategy to overcome multidrug-resistant (MDR) pathogens.

In summary, two critically-important fields of research have been exploited by the work of Professor Ren and his colleagues. The results of these studies have applications in both veterinary and human medicine. The expectation is that their findings will be used as the foundation for subsequent studies in many other laboratories.

ACKNOWLEDGEMENT

No financial support was provided for this manuscript.

AUTHORSHIP

RJR conceived and wrote the commentary.

CONFLICT INTEREST

None

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Please cite this paper as:
Reiter, R.J. 2022. Melatonin, macrophages and microbiota: Interactions. Melatonin Research. 5, 1 (Mar. 2022), 52-54. DOI:https://doi.org/https://doi.org/10.32794/mr112500119.