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Interactions of Melatonin and MicroRNAs

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Abstract

MicroRNAs (miRNAs) are important players in the modulation of cellular functions and contribute substantially to epigenetic changes in the expression of genes. Moreover, the distribution of miRNAs via exosomes and ectosomes opens a vast field of intraorganismal communication, with the potential of spreading pathological deviations, but also curative effects induced by protective agents. Interactions between melatonin and microRNAs are of particular interest, as melatonin is a highly pleiotropic regulator of numerous functions in every organ. The effects of melatonin in correcting pathological alterations in miRNA composition are reviewed, along with the corresponding reversal of cell biological or physiological functions to normal. Additionally, knowledge on the influence of miRNAs on melatonin formation and expression of a melatonin receptor has been considered. The fields in which melatonin has been shown to influence miRNAs are as diverse as metabolic syndrome, liver steatosis, immunology, amyloid toxicity, progenitor cells, and cancer. Readers are encouraged to contribute to systematic studies on melatonin effects on miRNAs using modern RNA sequencing techniques.

Keywords: Cancer; Inflammation; Long noncoding RNA; Melatonin; MicroRNA; Neurodegeneration

Introduction

Epigenetic regulation receives increasing attention in cell biology and medicine. In melatonin research, this is an emerging field [1-3]. Among the multiple epigenetic changes, the contribution of microRNAs (miRNAs) as regulators of countless functions is of particular interest [4-9]. The number of mammalian miRNAs is in the range about one thousand, but their modulatory actions extend to the expression of, at least, half of the coding genes, because single miRNAs can sometimes interact with hundreds of mRNAs or their precursors, hnRNAs, or even with the respective antisense transcripts (asRNAs, which belong to the group of long noncoding RNAs, lncRNAs) [4-8]. Target mRNAs, asRNAs or hnRNAs are typically derived from genes that are dynamically regulated or others that are particularly important for the functional state of a cell. The typical and most frequently observed action concerns the silencing by Argonaute (AGO)-mediated duplex formation with the target, assembly of a silencing complex (RISC complex) followed by duplex cleavage. However, if an asRNA is the target, this may instead result in the elimination of a blockade. In addition to interactions with other RNAs, some miRNAs have been shown to also target specific toll-like receptors (TLRs) [9-11]. However, this is only possible with TLRs that are capable of binding single-stranded RNAs (ssRNAs) but not double-stranded RNAs (dsRNAs). Binding to TLR7 was first shown for the miRNAs Let-7c and miR-21 [10].

Discussion

MicroRNAs are also of utmost interest with regard to their modes of distribution from one cell to others. They may enter neighboring cells via gap junctions, but they can be also transmitted by exosomes and ectosomes. These are found in all body fluids and interact specifically with target cells [9,12]. Thereby, they are capable of transporting messages over a long distance in the body. As a consequence, the regulatory network in a body is considerably larger and more complex than previously believed.

The actions of miRNAs are not only of physiological relevance, but have an additional pathological dimension and contribute to dysregulation. Numerous diseases including cancer and even mood disorders display changes in composition and amounts of microRNAs. Transmission of dysregulated miRNAs by exosomes or ectosomes to recipient cells is actually discussed as part of disease spreading within the body [9]. In exosomes and ectosomes, miRNAs are typically enriched. One of the reasons is that these vesicles also contain larger RNAs, especially lncRNAs and circular RNAs (circRNAs) that act as miRNA “sponges” by binding a high amount of miRNA molecules [9,13,14].

Regulatory interactions of melatonin with miRNAs are of particular interest as the former acts as a highly pleiotropic regulator molecule that orchestrates countless body functions, both directly and indirectly via central and peripheral circadian oscillators [15,16]. Circadian oscillators and even melatonin synthesis are also subject to modulation by miRNAs [2,17-19]. Moreover, melatonin does not only act as a pineal hormone, but is synthesized in many extrapineal organs and in immune

cells [15,20]. The total amount of extrapineally formed melatonin exceeds those in the pineal gland and in the circulation by more than two orders of magnitude [15,21].

Melatonergic signaling can be affected by miRNAs, but the available information is still limited. The melatonin receptor MT_1 was downregulated in the context of type 2 diabetes by miR-29b, an effect that counteracted melatonin's beneficial role concerning obesity and metabolic syndrome [22]. Much more data are available for protective effects of melatonin that involve changes in miRNA expression. In a murine model of alcoholic liver disease, protection by melatonin enhanced miR-497 expression, which caused downregulation of the targets *Btg2* (B-cell translocation gene 2) and *Yy1* (Yin yang 1) [23]. Liver steatosis was reported to be ameliorated by melatonin via miR-23a [24]. In murine model of liver fibrosis, melatonin reduced primary sclerosing cholangitis by downregulating miR-200b in cholangiocytes and stellate cells [25]. Studies on miRNAs in Alzheimer's disease (AD) are of particular interest, because neuroinflammation, which is fueled by Aβ peptides and oligomers, can be partially reversed by melatonin [26]. In a rat scopolamine toxicity model of AD-like memory losses, melatonin reversed an increase of miR-124 and thereby corrected the level of the targeted *Egr1* (early growth response protein 1) mRNA [27]. In another AD model, $Aβ_{25-35}$ peptide added to primary cortical neurons caused downregulation miR-132, an effect that was also reversed by melatonin. The normalization of miR-132 is insofar of importance, as this miRNA transmits anti-apoptotic and other protective properties known from melatonin [28]. In neonatal brain inflammation induced in rats by bacterial lipopolysaccharide (LPS), this pro-inflammatory agent upregulated miR-34a, but downregulated miR-146a, and miR-126. Again, these changes were corrected by melatonin, along with reduction in ER stress and autophagy as well as reversal of sirtuin 1 downregulation [29]. With some likelihood, other data on inflammation may have resulted from transfer of miRNAs. In a study on the immune responsiveness, *in vitro* differentiated macrophages were exposed to exosomes from hepatocellular carcinoma cells [30]. The cancer cells had either remained untreated or were incubated with melatonin, which obviously changed the composition of the exosomal contents. Exosomes from melatonin-treated cells downregulated in the recipient macrophages the secretion of IL-6, IL-10, IL-1β, and TNF-α, whereas those from untreated cells upregulated these cytokines [30]. Unfortunately, the responsible miRNAs were not determined.

In the last years, actions of melatonin in progenitor cells have become of increasing interest and some of the respective studies have investigated the role of miRNAs in these effects. The protective, anti-oxidative role of melatonin was recently addressed in cardiac progenitor cells. Premature senescence of these cells was induced by hydrogen peroxide. This was prevented by melatonin, which safeguarded the expression of the lncRNA H19 and its derivative miR-675 [31]. In hair follicle cells of Cashmere goats, melatonin changed the relative expression of several miRNAs, in particular, let-7a, miR-96, miR-199a, miR-205, miR-203, miR-96, miR-199a, miR-96, miR-183, miR-183, and miR-199a [32]. In the murine spermatogonia cell line GC-1spg, melatonin-induced proliferation was suppressed by miR-16, which targets cyclin D1 mRNA [33]. In the same cell line, effects of melatonin on miRNAs were recently studied on the basis of deep sequencing [34]. The consequences were, in fact, profound, as 171 miRNAs were upregulated by melatonin, whereas 5 others were downregulated.

Melatonin is also known to exert oncostatic actions [35-37]. In this context, melatonin was reported to downregulate miR-155 in several human glioma cell lines, an effect that reduced *c-myb* (myeloblastosis protooncogene) expression, proliferation and migration [38]. In hypoxic PC-3 prostate cancer cells, melatonin was shown to inhibit angiogenesis, an effect of importance to cancer growth that was concluded to be mediated by miR-3195 and miR-374b [39]. A more detailed study in MCF-7 breast cancer cells revealed alterations in the expression of 22 miRNAs by either 1 nM or 100 nM melatonin [40]. Twelve miRNAs were significantly upregulated and ten others downregulated. According to the analysis of their 5'-utr sequences, the 22 miRNAs should be capable of targeting the remarkable number of 2029 mRNAs [40].

Conclusion

The study of interaction between melatonin and miRNAs is still in its infancy. To date, the available knowledge does not yet describe a coherent picture, since respective investigations are scattered over the various topics of melatonin research. Nevertheless, the findings already obtained are highly encouraging for continuing research more systematically in this direction. Moreover, it is important to remain aware of the remarkable, previously unforeseen potential of miRNA distribution via exosomes and ectosomes. While these processes may participate in the intraorganismal spreading of pathologies, one might, on the other hand, assume that variations in composition of exosomal and ectosomal miRNAs, if modulated by melatonin, will also spread beneficial or even curative messages within the body.

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