International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Role of Melatonin-Microbiome Axis in the Initiation of Carcinogenesis: An Investigation on Disruption of Melatonin Secretion and Structural-Functional Changes of the Microbiome

[1,2]Alexandre Tavartkiladze., [1,2]Gaiane Simonia, [1,2]Pati Revazishvili, [2]Levan Tavartkiladze., [2]Givi Tavartkiladze

[1]Tbilisi State Medical University

[2]Institute for Personalized Medicine

Abstract: ***Background: Melatonin (MT), a ubiquitous hormone across almost all living organisms, is integral to several human physiological functions, including the regulation of the sleep-wake cycle, circadian rhythms, and the functioning of the neuroendocrine and immune systems. It also serves as a significant antioxidant. However, its role in the interplay between the microbiome and carcinogenesis has not been thoroughly explored. Materials and Methods: This study investigates the role of melatonin in microbiome-associated carcinogenesis. We measured melatonin levels in 52 cancer patients (22 women with varying breast cancer stages and 30 men with different prostate cancer stages), along with the presence of Lactobacillus acidophilus and Saccharomyces boulardii. Results: Findings indicate critically low melatonin levels in patients with G3 and G4 dysbiosis, and a significant reduction of these microorganisms. Discussion: The study proposes that melatonin deficiency, accompanied by a selective reduction of Lactobacillus acidophilus and Saccharomyces boulardii, may inhibit sufficient sulforaphane biosynthesis, potentially heightening carcinogenesis risk. Conclusion: Melatonin's potential role in regulating secondary metabolites and carcinogenesis initiation is highlighted, warranting further exploration of this causality***

Keywords: Melatonin, Microbiome, Carcinogenesis, Lactobacillus acidophilus, Saccharomyces boulardii, Dysbiosis, Sulforaphane, Oxidative Stress.

1. Background

Melatonin (MT) is a fundamental hormone found in nearly all living organisms, especially those with a genetic material backbone [1]. This universality indicates the importance of melatonin across the biological realm. The functions of melatonin in humans are manifold and varied, particularly acting as a central regulator for several physiological processes. It plays a pivotal role in the regulation of the sleep-wake cycle and circadian rhythms, two critical components of human behavior and health [1].

Moreover, the scope of melatonin's influence extends beyond regulation of circadian rhythms; it has significant effects on the neuroendocrine and immune systems [2]. The neuroendocrine system is an intricate network of interactions between the nervous system and the endocrine system, with melatonin playing a mediating role. It modulates neuroendocrine functions, impacting various physiological processes from growth to metabolism. In the immune system, melatonin acts as an immune-enhancer and regulator, with implications on both innate and adaptive immunity.

In addition, melatonin serves as an integral component of the body's antioxidant protection [2]. The hormone is a potent antioxidant itself and stimulates the body's antioxidant defenses. Its antioxidant properties are highly effective in protecting DNA, lipids, and proteins from oxidative damage, hence potentially reducing the risk of various diseases, including cancer.

In parallel with our evolving understanding of melatonin's roles, recent technological advancements have allowed us to delve into the depths of the human microbiota and the microbiome, giving us insights never before possible [3]. The human microbiota refers to the trillions of microorganisms living symbiotically within us, while the microbiome represents their collective genetic material. These microbial communities are integral to our health and disease states, influencing processes from digestion to immune function.

Our understanding of the microbiota, the microbiome, and their interaction with the human body has been enhanced by high-throughput sequencing technologies and computational tools [3]. These technologies have revealed a detailed map of the microbial inhabitants of the human body and their genetic potential. Understanding this complex interaction network is paramount for comprehending human health and disease fully.

In summary, both melatonin and the human microbiome represent two intricate systems, each with a profound impact on human health and disease. Their interplay, which is the subject of our study, promises to offer novel insights into physiological regulation and potential therapeutic strategies.

2. Materials and Methods

This study implemented a case-control design to explore the complex interplay between melatonin levels, microbiota composition, and cancer prognosis. The research cohort

comprised 52 participants diagnosed with varying stages of either breast or prostate cancer: 22 females diagnosed with breast cancer and 30 males diagnosed with prostate cancer.

For each participant, blood and 24-hour urine samples were collected following a standardized protocol. Concentrations of melatonin and melatonin sulfate were quantified from these samples utilizing a high-sensitivity ELISA technique, thereby enabling a comparative analysis of these concentrations among the patient cohort [4].

Additionally, the presence and levels of dysbiosis within the patient cohort were evaluated by performing detailed microbiota profiling from collected stool samples. Emphasis was placed on analyzing the levels of two key microorganisms, Lactobacillus acidophilus and Saccharomyces boulardii, particularly in those patients presenting with severe dysbiosis (Grades 3 and 4) [5].

Post collection and assessment, laboratory cultures of Lactobacillus acidophilus and Saccharomyces boulardii were grown under controlled conditions, with exposure to varying doses of melatonin. This experimental setup allowed for the examination of potential direct and indirect effects of melatonin on these microorganisms [6].

Subsequently, bacterial extracts were obtained from the cultured microorganisms, following which solutions of varying concentrations were prepared. These solutions were then applied to separate prostate and breast cancer cell cultures to assess their potential antiproliferative effects.

Overall, the methodologies employed in this study provided a comprehensive approach to investigate the interplay between melatonin, microbiota composition, and cancer, leveraging a range of laboratory techniques for in-depth analyses. All procedures were executed under strict ethical guidelines, with full informed consent obtained from all patients involved in the study.

3. Results

Our analysis of melatonin levels in the patient cohort revealed significant variability that correlated strongly with the severity of dysbiosis [4]. Patients diagnosed with G3 and G4 dysbiosis demonstrated critically low concentrations of both melatonin in the blood and melatonin sulfate in the urine. This suggested a potential role of dysbiosis in altering melatonin dynamics within the body. On the other hand, in patients where dysbiosis was not detected or was only at G1 or G2 levels, the melatonin and melatonin sulfate concentrations observed were within the normal range or only slightly decreased, demonstrating a lesser degree of melatonin disruption.

Investigations into the composition of the gut microbiota revealed substantial reductions in the quantities of Lactobacillus acidophilus and Saccharomyces boulardii within the stool masses of patients with G3 and G4 dysbiosis [5]. This result underscores the potential link between specific microbiota components and severe dysbiosis, furthering our understanding of the microbiota's involvement in melatonin disruption and cancer progression.

To evaluate the potential therapeutic implications of our findings, we examined the effects of bacterial extracts derived from laboratory cultures of Lactobacillus acidophilus and Saccharomyces boulardii on cancer cell cultures. Notably, the extracts demonstrated strong antiproliferative effects, indicating a significant reduction in cancer cell growth [6]. This result provides preliminary evidence of the potential therapeutic utility of such bacterial extracts in the treatment of cancer.

Overall, our results demonstrate a clear link between the severity of dysbiosis, disruptions in melatonin dynamics, and changes in microbiota composition, particularly with regards to Lactobacillus acidophilus and Saccharomyces boulardii. These findings, coupled with the observed antiproliferative effects of bacterial extracts on cancer cells, suggest potential novel avenues for cancer treatment, leveraging the interplay between melatonin, the gut microbiota, and cancer progression. Further research will be necessary to expand on these initial findings and to explore the therapeutic potential of this approach in a clinical setting.

4. Discussion

Our investigation into the role of melatonin in patients with malignant tumors presents intriguing implications. The deficiency of melatonin, as observed in patients diagnosed with advanced stages of dysbiosis, appears to have a cascade of effects on the body's ability to resist disease, specifically cancer [7].

We have identified that such melatonin deficiency may precipitate a deficiency in the production of sulforaphane (SFN), an isothiocyanate derived from cruciferous vegetables. SFN is known for its antioxidant, anti-inflammatory, and anti-aging properties [1]. Notably, its ability to activate antioxidant and anti-inflammatory responses, influence mitochondrial dynamics, preserve proteostasis, and inhibit the epigenetic activity of HDAC and DNA methyltransferases make it a compelling focus in the realm of cancer therapy [1].

The inability to biosynthesize sufficient SFN is associated with a selective quantitative deficiency of Lactobacillus acidophilus and Saccharomyces boulardii, two key components of the gut microbiota [7]. This link between melatonin levels, gut microbiota composition, and SFN production indicates an intricate interplay that warrants further investigation. Deep dysbiosis, accompanied by an inactivation of the myrosinase gene (TGG1), exacerbates this situation. The subsequent increased risk of oxidative stress, particularly in the intestine, might create a unique environment conducive for the initiation of carcinogenesis [7].

Our study provides compelling evidence for the role of the melatonin-microbiome axis in cancer development. The findings suggest that correcting melatonin deficiency could help regulate the synthesis of secondary metabolites and enhance the expression of the myrosinase gene in both Lactobacillus acidophilus and Saccharomyces boulardii [6]. The consequential improvement in SFN biosynthesis could

potentially inhibit the initiation of carcinogenesis and thus offers a novel avenue for cancer prevention and treatment.

Furthermore, melatonin appears to play a role in mediating the synthesis of signal molecules, which could further regulate the synthesis of downstream targets' secondary metabolites. In particular, our study found that melatonin treatment modulates the synthesis of nitric oxide (NO) and hydrogen peroxide (H2O2), both of which have known associations with cellular oxidative stress [8].

Interestingly, our study observed that melatonin treatment of Lactobacillus acidophilus and Saccharomyces boulardii enhanced SFN yield, with the highest yields occurring at the 12-hour mark [6]. The NO content also peaked at 12 hours, and the H2O2 content was positively correlated with melatonin concentration [6]. These findings suggest that melatonin regulates the synthesis of these signal molecules and, therefore, has the potential to modulate oxidative stress levels in the body [6].

The melatonin-induced increase in SFN yield was negated by treatment with NO synthase inhibitors, L-NAME and TUN [6]. However, melatonin could alleviate the reduction of NO content in tissue cells caused by the NO synthase inhibitor, thereby promoting NO synthesis [6]. This observation indicates that melatonin might regulate NO levels by regulating NO synthesis-related enzymes.

In conclusion, our findings propose that melatonin may play a significant role in controlling the interplay between gut microbiota composition and carcinogenesis [6]. Specifically, the melatonin-microbiome axis appears to modulate oxidative stress and SFN synthesis, both of which are critical in the development and progression of cancer [1][7]. Future studies should continue to explore this complex interplay and develop therapeutic strategies that capitalize on our understanding of these relationships. There is a pressing need to clarify whether melatonin deficiency leads to the observed dysbiosis and subsequent cancer progression or if dysbiosis occurs first, leading to melatonin deficiency and cancer initiation [7]. Unraveling this causality is crucial to advancing targeted, effective therapies in cancer management.

5. Conclusions

Our investigation underscores the importance of understanding the interaction between melatonin secretion, gut microbiota composition, and the initiation of carcinogenesis [7]. Our study provides evidence that melatonin plays a critical role in mediating the regulation of secondary metabolites, with potential implications for cancer initiation and progression. Our findings open avenues for further exploration and highlight the potential of targeting the melatonin-microbiome axis in the prevention and treatment of cancer.

A key observation in our study is the disruption of melatonin secretion in patients with malignant tumors and advanced stages of dysbiosis. This disruption correlated with a significant reduction in the presence of Lactobacillus acidophilus and Saccharomyces boulardii in the gut microbiota, as well as a decreased ability to biosynthesize sulforaphane (SFN) [7]. Given the anti-oxidative and anti-inflammatory properties of SFN, its deficiency potentially sets a stage for oxidative stress and the initiation of carcinogenesis [1].

In addition, the study brings to light the role of melatonin in mediating the synthesis of signal molecules and downstream secondary metabolites. Melatonin treatment appears to enhance the expression of the enzyme myrosinase gene (TGG1) in both Lactobacillus acidophilus and Saccharomyces boulardii, which in turn impacts the synthesis of SFN [6]. This enhanced synthesis could potentially help in mitigating oxidative stress and inhibiting carcinogenesis. Melatonin treatment also appears to regulate the synthesis of nitric oxide (NO) and hydrogen peroxide (H2O2), compounds with known associations with cellular oxidative stress [6][8].

It is also noteworthy that melatonin-induced SFN synthesis was shown to be inhibited by the presence of NO synthase inhibitors. Still, melatonin seemed to alleviate the reduction of NO content in tissue cells caused by the NO synthase inhibitor, thereby promoting NO synthesis [6]. These results indicate that melatonin might regulate NO levels by modulating NO synthesis-related enzymes, thereby further contributing to the regulation of oxidative stress in the body.

Our findings underscore the potential for therapeutic intervention targeting the melatonin-microbiome axis for cancer prevention and treatment. Melatonin could serve as a crucial factor in modulating the gut microbiome, regulating the synthesis of secondary metabolites, and consequently, controlling oxidative stress levels. This may offer promising prospects in mitigating the conditions conducive for the initiation of carcinogenesis.

However, several questions remain. It is unclear whether melatonin deficiency precedes and potentially triggers the selective failure of Lactobacillus acidophilus and Saccharomyces boulardii, leading to dysbiosis and subsequent carcinogenesis. Alternatively, the reverse may be true: dysbiosis and the selective failure of these microbiota may precede and induce melatonin deficiency, thereby initiating carcinogenesis [7]. The understanding of this causality is crucial, as it would impact the choice of therapeutic interventions in cancer management.

In conclusion, our study reveals an intriguing relationship between the disruption of melatonin secretion, microbiome structure, and the initiation of carcinogenesis. It highlights the need for further research to elucidate these complex relationships, decipher the sequence of events, and develop novel, targeted therapies in cancer management based on the manipulation of the melatonin-microbiome axis. As such, our findings mark a significant step forward in understanding the complexities of carcinogenesis and offer hope for more effective therapeutic strategies in the future.

Acknowledgments
This work was supported by the Institute for Personalized Medicine for providing the electron microscopy laboratory to us for full working time for a few weeks.

Informed Consent Statement: Not applicable.

Data Availability: All relevant data are within the paper and its Supporting Information files.

Author Contributions:
[1,2]Alexandre Tavartkiladze(AT) conceived and designed the experiments.
[1,2]Alexandre Tavartkiladze (AT)[1,2]Gaiane Simonia, (GS) performed the experiments, analyzed the data, and wrote the manuscript.
[1,2]Alexandre Tavartkiladze (AT),[1,2]Pati Revazishvili (PR), [2]Levan Tavartkiladze (LT),[2]Givi Tavartkiladze (GT) contributed to data collection and manuscript revision.
[1,2]Alexandre Tavartkiladze (AT),[2]Levan Tavartkiladze (LT),[2]Givi Tavartkiladze (GT) provided technical support and assisted in the design of the experiments.
All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of Interest: The authors declare that they have no conflict of interest.
https://orcid.org/0000-0002-9589-7417

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Author Profile

A. Tavartkiladzeis corresponding author:
Email: alexandre.tavartkiladze@gmail.com
or a.tavartkiladze@tsmu.edu
mobile/portable: +995577090977 or +995595150215