Commentary

Daytime orexin and night-time melatonin regulation of mitochondria melatonin: roles in circadian oscillations systemically and centrally in breast cancer symptomatology

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ABSTRACT

This article reviews the recent proposed model of Reiter and colleagues in this journal on the role of circadian, pineal gland-derived melatonin in driving mitochondria melatonin production in the pathoetiology and pathophysiology of breast cancers. This uptake of melatonin is proposed to inhibit pyruvate dehydrogenase kinase, thereby increasing the production of acetyl-CoA from pyruvate, with acetyl-CoA being a necessary co-factor for the initiation of the melatonergic pathway within mitochondria. Consequently, this proposed model suggests that a circadian shift in metabolic regulation occurs in breast cancers, from daytime cytosolic glycolysis to a night-time, melatonin-driven mitochondria oxidative phosphorylation, with relevance to the early pathoetiology of breast cancers. This has a number of consequences and links well to wider breast cancer data showing a pathophysiological role for the aryl hydrocarbon receptor, cytochrome P450 (CYP)1B1, 14-3-3 protein, and microRNAs. The current article overviews such data in the context of pineal gland-derived melatonin's circadian regulation of the mitochondria melatonergic pathways in breast cancer cells as proposed by Reiter and colleagues, suggesting that daytime, wake promoting orexin and stress-induced gut dysregulation contribute to mitochondria dysfunction in wider breast cancer symptomatology.

Keywords: Breast cancer; pineal gland; mitochondria; pyruvate dehydrogenase complex; melatonin; N-acetylserotonin; orexin, glycolysis; oxidative phosphorylation.

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1. PINEAL AND MITOCHONDRIA MELATONIN IN BREAST CANCER

A number of recent studies have shown breast cancer susceptibility to be modulated by the circadian rhythm, with professions such as nursing that require high levels of shift-work having a heightened breast cancer risk (1). The recent publication by Reiter and colleagues proposes cellular mechanisms that may underpin such dysregulated circadian effects on the risk of breast and other cancers (2). These authors highlight the importance of high circulating, pineal gland-derived melatonin levels at night in shifting breast cancer cells from cytosolic glycolysis (Warburg effect) to ATP derived from mitochondrial glucose oxidation and oxidative phosphorylation. Concurrently, melatonin also promotes the conversion of pyruvate to acetyl-CoA, which the authors propose is mediated by the inhibition of pyruvate

dehydrogenase kinase (PDK) and therefore the disinhibition of the pyruvate dehydrogenase complex (PDC). The potentiation of acetyl-CoA has a number of consequences within mitochondria, including heightening oxidative phosphorylation and arylalkylamine N-acetyltransferase (AANAT)-driven melatonergic pathway activity. Importantly, given the presence of acetylserotonin O-methyltransferase (ASMT) in mitochondria (3), this suggests that pineal-derived melatonin will act to modulate local mitochondria melatonin production.

This model incorporates wider bodies of data pertaining to breast cancer pathoetiology and pathophysiology and also has a number of consequences. A corollary of this model is a circadian regulation of many melatonin-associated factors, including mitochondria located sirtuin-3 and sirtuin-3 induced superoxide dismutase (SOD2), thereby acting to improve the endogenous antioxidant status and better optimizing mitochondria functioning. In the context of breast cancer risk, the decreased melatonin synthesis in shift-workers means a decrease in pineal melatonin's ability to shift cancer cells to a non-neoplastic form of metabolism, including via the regulation of the mitochondria melatonergic pathway in breast epithelial cells.

This is an interesting and novel perspective, suggesting that breast cancer cells may be neoplastic by day and have a more normal cell phenotype at night, although only in the presence of adequate pineal gland-derived melatonin release. Given that most data on breast cancer cells are collected under daytime conditions, the article by Reiter and colleagues indicates that this approach is likely to miss the importance of circadian factors in the pathoetiology and pathophysiology of breast cancers. Some studies have indicated a role for circadian factors in breast cancer pathophysiology, including the suppressed and arrhythmic expression of the circadian genes, BMAL1 and PER2, in breast cancer cells. Variable core circadian clock oscillations have recently been shown to occur in breast cancer cell lines (4). These authors suggest that circadian gene oscillations may be more evident in the early stages of breast cancer development, as evidenced by the presence of circadian gene oscillations in low-, but not high-grade breast cancer cell lines (4). Such data suggests a role for alterations in circadian regulation in the pathogenesis of breast cancers. Notably, circadian genes can also act to regulate the circadian functioning of mitochondria, as evidenced in non-neoplastic cells (5). The interactions of such circadian gene changes with mitochondria functioning and melatonin's circadian effects in mitochondria will be an important area of further investigation.

2. INTEGRATING WIDER BREAST CANCER DATA

Recent data highlights the importance of intercellular communication in the pathophysiology of breast cancer cells, including via the release of exosomes that can drive aggressiveness in other tumor cells as well as altering the responses of cells in the tumor microenvironment (6). Exosomes can be part of a complex set of intercellular interactions, with the exosomes of macrophages exposed to chemotherapy-treated apoptotic breast cancer cells seemingly promoting breast cancer cell proliferation and metastases (7). Such data highlights the role that exosomes, from immune cells and breast cancer cells, play in breast cancer pathophysiology. It is of note that circadian melatonin modulates exosomal content, as evidenced in hepatocellular carcinoma exosomes, with the exosomes of melatonin treated cells modulating macrophage activity (8). Clearly variations in circadian melatonin production is likely to have impacts directly in breast cancer cells as well as in their interactions with other cells of the tumor microenvironment. Consequently, alterations in circadian melatonin can have significant impacts on the many cells, and their interactions, within the tumor microenvironment, which the work of Reiter and colleagues suggests may be mediated via alterations in mitochondria functioning.

Wider tumor microenvironment intercellular interactions are also important e.g. breast epithelial cells interact with other cells that are part of the tumor microenvironment, including neighbouring breast epithelial cells, fibroblasts and immune cells. All of these cells will show concurrent alterations arising from decreased pineal melatonin, including possible alterations in mitochondria melatonergic pathway activity. Clearly, suppression of pineal gland-derived melatonin will have impacts on many other cells and thereby modulate their interactions with, and influence on, breast cancer cell functioning. The role of pineal gland-derived melatonin in the regulation of melatonin synthesis in other cells is supported by data in rodents, where pineal melatonin positively regulates the circadian pattern of mRNA expression of the enzymes and receptors of the melatonergic pathway (9). It requires investigation as to whether pineal gland-derived circadian melatonin modulates the melatonergic pathway within the mitochondria of not only breast cancer cells but also other cells in the tumor microenvironment. The impacts of pineal and mitochondrial melatonin will have consequences for the levels of sirtuin-3 and other mitochondria regulators, with possible consequences for mitochondria functioning in an array of different cell types. It is long appreciated that the loss of pineal melatonin synthesis alters the circadian regulation of immune cells, where pineal gland-derived and the autocrine effects of melatonin can determine immune cell phenotype (10). The intercellular interactions of the tumor microenvironment add another layer of complexity to the effects of variations in pineal-derived melatonin in breast cancers.

A further layer of complexity arises from the number of factors that may act to regulate the melatonergic pathways within mitochondria. It is important to note that serotonin is the AANAT substrate for the synthesis of N-acetylserotonin (NAS), which is then enzymatically converted to melatonin by ASMT. NAS has similar antioxidant and anti-inflammatory effects to melatonin. However, NAS is also a brain-derived neurotrophic factor (BDNF) mimic via its activation of the BDNF receptor, TrkB (11). TrkB activation has trophic effects in breast cancer cells, with exosomal TrkB able to transfer aggressiveness to neighbouring tumor cells, reviewed in (12). As such, variations in the NAS/melatonin ratio, both in the pineal gland and breast cancer cells, is likely to have distinct, if not opposing, effects on breast cancer cell survival and proliferation.

The pathoetiology of breast cancers have long been associated with aryl hydrocarbon receptor (AhR) activation, including via the AhR increasing cytochrome P450 (CYP)1B1 within mitochondria, reviewed in (13). CYP1B1 leads to the 'backward' conversion of melatonin to NAS, suggesting that one of the important changes to occur in breast cancers is a shift to the trophic effects of NAS and the suppression of the inhibitory effects of melatonin. In non-tumor breast epithelial cells, there is a dramatic circadian variation in the ability of AhR ligands to induce CYP1B1, with the highest levels occurring at night and regulated by circadian genes (14). This requires investigation in breast cancer cells and other cells of the tumor microenvironment, as it suggests that any AhR ligand-induced CYP1B1 at night will act to heighten the NAS/melatonin ratio, thereby altering the trophic vs apoptotic effects of the melatonergic pathways in breast cancers. This also suggests that the protective effects of pineal gland-derived melatonin in breast cancers may be significantly compromised by night-time AhR activation.

As well as CYP1B1, a number of other factors can increase the NAS/melatonin ratio, including: ATP activation of the purinergic P2Y1 receptor; CYP2C19, which acts via O-demethylation; and the metabotropic glutamate receptor (mGluR)5, with the latter also raising CYP1B1 levels, reviewed in (12). It requires investigation as to whether any of these NAS/melatonin ratio modulators have any differential circadian interactions with breast cancers proliferation and apoptosis, including via the PDK/PDC pathway. As well as AANAT activity regulation by acetyl-CoA, the activity of AANAT requires its stabilization by 14-3-3

protein. 14-3-3 is expressed in mitochondria and is regulated by a number of microRNAs, including miR-451, miR-375 and miR-7, reviewed in (12). Consequently, the levels of melatonin synthesis are decreased in a number of cell types as a consequence of heightened levels of these miRNAs and their suppression of 14-3-3 (15,16). Alterations in 14-3-3 and miR-451 complicate the treatment of breast cancers (16), with effects likely mediated, at least in part, via increased miR-451 suppression of 14-3-3, leading to mitochondria melatonergic pathway inhibition. As to whether pineal gland-derived melatonin acts to regulate these 14-3-3 suppressing microRNAs, and thereby the 14-3-3 regulation of the mitochondria melatonergic pathway, will be important to determine. Figure 1 summarizes these processes.

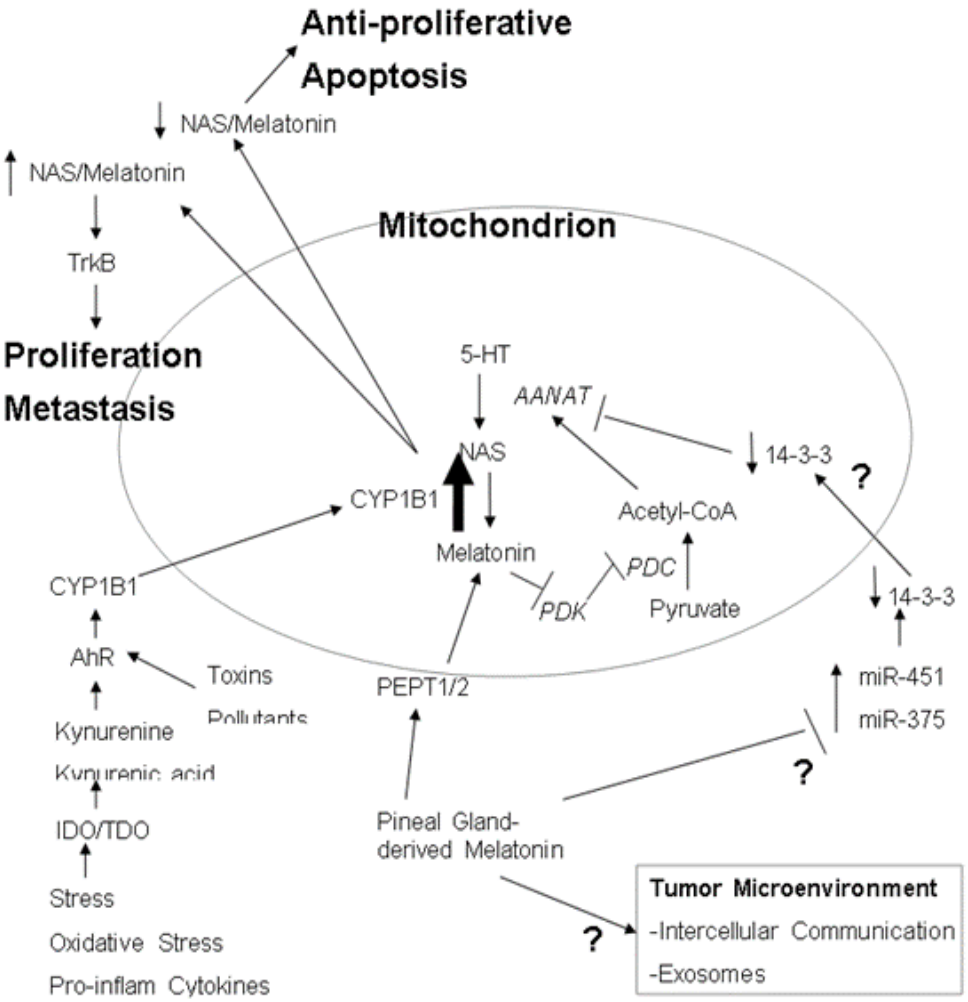

Fig. 1. The proposed anti-tumor pathways of melatonin.

Pineal gland-derived melatonin is taken into mitochondria by PEPT1/2 and acts to regulate mitochondria functioning via the suppression of PDK, thereby disinhibiting PDC and increasing the conversion of pyruvate to acetyl-CoA, which optimizes mitochondria functioning via the citric acid cycle whilst also acting as a necessary co-substrate for AANAT and melatonergic pathway activation. An increase in acetyl-CoA contributes to an increase in melatonin production in mitochondria, which can shift breast cancer cells from a metabolism based on cytosolic glycolysis (Warburg effect) to one of oxidative phosphorylation. A number of factors may complicate this circadian-driven alteration in mitochondria metabolism by melatonin, including increases in miR-451, miR-375 and miR-7, which can decrease 14-3-3.

If decreased 14-3-3 occurs in mitochondria it will prevent the stabilization of AANAT and therefore prevent mitochondria melatonergic pathway activation. Stress, oxidative stress and pro-inflammatory cytokines can increase IDO and TDO, leading to kynurenine and kynurenic acid, which activate the AhR, leading to CYP1B1's 'backward' conversion of melatonin to NAS. An increase, vs decrease, in the NAS/melatonin ratio may have dramatically opposing effects on breast cancer cell proliferation, metastasis and apoptosis. Pineal gland-derived melatonin is also likely to have impacts on the tumor microenvironment, including via exosomes released and in the mitochondria functioning of cells in the tumor microenvironment, including via mitochondria melatonergic pathway activation.

Abbreviations: 5-HT: 5-hydroxytryptamine; AANAT: aralkylamine N-acetyltransferase; AhR: aryl hydrocarbon receptor; CYP: cytochrome P450; IDO: indoleamine 2,3-dioxygenase; miR: microRNA; NAS: N-acetylserotonin; PDC: pyruvate dehydrogenase complex; PDK: pyruvate dehydrogenase kinase; PEPT: peptide transporter; TDO: tryptophan 2,3-dioxygenase; TrkB: tyrosine kinase receptor-B

3. DAYTIME MITOCHONDRIA REGULATION

As well as night-time reseting of mitochondria oxidative phosphorylation, a number of factors may similarly act to regulate daytime mitochondria oxidative phosphorylation, exemplified by the effects of orexin/hypocretin. Central oexin is produced in the perifornical area of the posterior lateral hypothalamus and is strongly associated with 'wake-promotion', in sharp contrast to the sleep-promoting effects of pineal gland-derived melatonin. However, orexin seems to have similar impact on mitochondria functioning as melatonin, including increasing PDC disinhibition and the production of acetyl-CoA, and therefore the activity of the mitochondria melatonergic pathway (17). As such the wake-promoting effects of daytime orexin may parallel the night-time effects of pineal gland-derived melatonin via the optimization of mitochondria functioning, driven at least partly via an increase in the activity of the mitochondria melatonergic pathway.

Hypothalamic orexin and pineal gland derived melatonin have some reciprocally inhibitory interactions, as shown in preclinical data (18,19), suggesting that the decrease in pineal gland melatonin in breast cancer associates with raised orexin levels that contribute to sleep disruption and circadian dysregulation in breast cancer patients (20). As such, the suppression of pineal gland-derived melatonin in the susceptibility to, and early course of, breast cancer may drive wider circadian dysregulation. The association of an initial increase in orexin will interact with stress responses, including via the sleep disruption and circadian dysregulation induced. Consequently, the alterations in the reciprocal interactions of melatonin and orexin will have temporal interactions with stress.

Stress is long-associated with the susceptibility to, and course of, breast, and other cancers (21). As well as shift-work, pineal gland-derived melatonin can also be suppressed by stress, ageing and an increase in immune-inflammatory activity (22). Some of the effects of stress are mediated via gut dysbiosis and increased gut permeability, thereby raising levels of circulating lipopolysaccharide (LPS), oxidative stress and immune-inflammatory activity (23). LPS can activate microglia, raising levels of inducible nitric oxide synthase (iNOS) and superoxide, which drives the synthesis of the highly toxic oxidant, peroxynitrite (24). Peroxynitrite is a major driver of acid sphingomyelinase (aSMase) and thereby long-chain ceramides (25). Long-chain ceramides increase apoptosis in orexin neurons and suppress orexin synthesis. As such, the initial increase in wake-promoting orexin in breast cancer may be reversed by the effects of stress, including via LPS and ceramide, leading to the loss of mitochondria oxidative phosphorylation by daytime orexin and night-time pineal gland-derived melatonin. This would suggest a significant alteration in central circadian regulation

in association with gut-linked stress processes in breast cancer. Such alterations will have significant impacts on mitochondrial functioning, both centrally and systemically, including changes in immune cell mitochondria and thereby in immune cell functioning (26).

Although ceramide is often regarded as useful in breast cancer, via its role in driving breast cancer apoptosis (27), its effects centrally will drive some of the circadian symptomatology often evident in breast cancer patients. Ceramide lowers levels of cell 14-3-3, leading to the loss of AANAT stabilization by 14-3-3 (28), thereby indicating that ceramide may act to suppress the mitochondria melatonergic pathway and its regulation of glycolysis and oxidative phosphorylation with consequences for circadian dysregulation. Clearly, the mitochondria melatonergic pathway would seem to be an important hub that is relevant to the pathogenesis of breast cancer, as well as in the central and systemic changes that underpin wider breast cancer symptomatology, including in hypothalamic orexin neurons. Stress effects in the regulation of the gut microbiome/permeability may be another crucial hub in breast cancer pathophysiology, both centrally and systemically, via the modulation of mitochondria functioning, thereby highlighting the importance of gut-mitochondria interactions (23).

4. CONCLUSIONS

Overall, the article of Reiter and colleagues provides a novel model that can integrate previous data as well as highlighting the need for further investigation on the role of pineal gland-derived melatonin in the pathoetiology and pathophysiology of breast cancer. The role of pineal- and mitochondria-derived melatonin in the regulation of PDK/PDC, acetyl-CoA, pyruvate and lactate will be important to determine. This may be of particular importance in the early pathogenesis of breast cancers. Wider bodies of data classically associated with breast cancer pathophysiology, including the AhR, CYP1B1, 14-3-3 and mitochondria plasticity may be intimately intertwined with such circadian processes, including putative shifts in the NAS/melatonin ratio. Variations in the NAS/melatonin ratio may allow for the melatonergic pathway to have proliferative or apoptotic consequences in breast cancers. The suppression of pineal-gland melatonin will contribute to an initial disinhibition of orexin and its wake-promoting effects, which may be countered by the heightened levels of central ceramide, as influenced by gut dysbiosis. Overall, the processes as highlighted by Reiter and colleagues focus on core aspects of cellular functioning, whilst hinting at the developmental complexity underpinning the pathogenesis of breast cancer cells.

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AUTHORSHIP

The manuscript was conceived and written by G. Anderson

CONFLICT OF INTEREST

The author declares no conflicts of interest in relation to this work

REFERENCES

1. Pham TT, Lee ES, Kong SY, *et al*. (2019) Night-shift work, circadian and melatonin

pathway related genes and their interaction on breast cancer risk: evidence from a case-control study in Korean women. *Sci. Rep*. **9** (1): 10982. doi:10.1038/s41598-019-47480-2.

2. Reiter RJ, Sharma R, Ma Q, Rosales-Corral SA, Acuna-Castroviejo D, Escames G (2019) Inhibition of mitochondrial pyruvate dehydrogenase kinase: a proposed mechanism by which melatonin causes cancer cells to overcome aerobic glycolysis, limit tumor growth and reverse insensitivity to chemotherapy. *Melatonin Res*. **2** (3): 105-119. doi:10.32794/mr11250033.
3. Suofu Y, Li W, Jean-Alphonse FG *et al*. (2017) Dual role of mitochondria in producing melatonin and driving GPCR signaling to block cytochrome c release. *Proc. Natl. Acad. Sci. USA* **114**: E7997-E8006.
4. Lellupitiyage Don SS, Lin HH, Furtado JJ, *et al*. (2019) Circadian oscillations persist in low malignancy breast cancer cells. *Cell Cycle*. **18** (19): 2447-2453. doi:10.1080/15384101.2019.1648957.
5. Neufeld-Cohen A, Robles MS, Aviram R, *et al*. (2016) Circadian control of oscillations in mitochondrial rate-limiting enzymes and nutrient utilization by PERIOD proteins. *Proc. Natl. Acad. Sci. U S A*. **113** (12): E1673-82. doi:10.1073/pnas.1519650113.
6. Groza M, Zimta AA, Irimie A, *et al*. (In press) Recent advancements in the study of breast cancer exosomes as mediators of intratumoral communication. *J. Cell Physiol*. doi: 10.1002/jcp.29096.
7. Yu X, Zhang Q, Zhang X, *et al*. (2019) Exosomes from Macrophages Exposed to Apoptotic Breast Cancer Cells Promote Breast Cancer Proliferation and Metastasis. *J. Cancer* **10** (13): 2892-2906. doi:10.7150/jca.31241.
8. Cheng L, Liu J, Liu Q, *et al*. (2017) Exosomes from melatonin treated hepatocellular carcinoma cells alter the immunosupression status through STAT3 pathway in macrophages. *Int. J. Biol. Sci*. **13** (6): 723-734. doi:10.7150/ijbs.19642.
9. Coelho LA, Andrade-Silva J, Motta-Teixeira LC, Amaral FG, Reiter RJ, Cipolla-Neto J. (In press) The absence of pineal melatonin abolishes the daily rhythm of tph1 (tryptophan hydroxylase 1), ASMT (acetylserotonin o-methyltransferase), and AANAT (aralkylamine n- acetyltransferase) mRNA expressions in rat testes. *Mol. Neurobiol*. doi: 10.1007/s12035- 019-1626-y.
10. Muxel SM, Pires-Lapa MA, Monteiro AW, *et al*. (2012) NF-κB drives the synthesis of melatonin in RAW 264.7 macrophages by inducing the transcription of the arylalkylamine-N-acetyltransferase (AA-NAT) gene. *PLoS One*. **7** (12): e52010. doi: 10.1371/journal.pone.0052010.
11. Jang SW, Liu X, Pradoldej S, *et a*l. (2010) N-acetylserotonin activates TrkB receptor in a circadian rhythm. *Proc. Natl. Acad. Sci. U S A*. **107** (8): 3876-81. doi: 10.1073/pnas.0912531107.
12. Anderson G (2019) Breast cancer: Occluded role of mitochondria N-acetylserotonin/melatonin ratio in co-ordinating pathophysiology. *Biochem. Pharmacol*. **168**: 259-268. doi:10.1016/j.bcp.2019.07.014.
13. Anderson G, Reiter RJ. (2019) Glioblastoma: role of mitochondria n-acetylserotonin/melatonin ratio in mediating effects of mir-451 and aryl hydrocarbon receptor and in coordinating wider biochemical changes. *Int. J. Tryptophan Res*. **12**: 1178646919855942. doi:10.1177/1178646919855942.
14. Qu X, Metz RP, Porter WW, Cassone VM, Earnest DJ. (2007) Disruption of clock gene expression alters responses of the aryl hydrocarbon receptor signaling pathway in the mouse mammary gland. *Mol. Pharmacol*. **72** (5): 1349-1358.
15. Pagan C, Goubran-Botros H, Delorme R, *et al*. (2017) Disruption of melatonin synthesis is associated with impaired 14-3-3 and miR-451 levels in patients with autism spectrum disorders. *Sci. Rep*. **7** (1): 2096. doi:10.1038/s41598-017-02152-x.

16. Wang W, Zhang L, Wang Y, *et al*. (2017) Involvement of miR-451 in resistance to paclitaxel by regulating YWHAZ in breast cancer. *Cell Death Dis*. **8** (10): e3071. doi: 10.1038/cddis.2017.460.
17. Liu Y, Zhao Y, Guo L. (2016) Effects of orexin A on glucose metabolism in human hepatocellular carcinoma in vitro via PI3K/Akt/mTOR-dependent and -independent mechanism. *Mol Cell Endocrinol*. **420**: 208-16. doi:10.1016/j.mce.2015.11.002.
18. Sharma R, Sahota P, Thakkar MM. (2018) Melatonin promotes sleep in mice by inhibiting orexin neurons in the perifornical lateral hypothalamus. *J. Pineal Res.* **65** (2): e12498. doi:10.1111/jpi.12498.
19. Mikkelsen JD, Hauser F, deLecea L, *et al*. (2001) Hypocretin (orexin) in the rat pineal gland: a central transmitter with effects on noradrenaline-induced release of melatonin. *Eur. J. Neurosci.* **14** (3): 419-425.
20. Borniger JC, Walker Ii WH, *et al*. (2018) A role for hypocretin/orexin in metabolic and sleep abnormalities in a mouse model of non-metastatic breast cancer. *Cell Metab.* **28** (1): 118-129.e5. doi:10.1016/j.cmet.2018.04.021.
21. Li P, Huang J, Wu H, *et al*. (2016) Impact of lifestyle and psychological stress on the development of early onset breast cancer. *Medicine (Baltimore).* **95** (50): e5529.
22. Pontes GN, Cardoso EC, Carneiro-Sampaio MM, Markus RP. (2007) Pineal melatonin and the innate immune response: the TNF-alpha increase after caesarean section suppresses nocturnal melatonin production. *J. Pineal Res.* **43** (4): 365-371.
23. Anderson G. (2019) Gut dysbiosis dysregulates central and systemic homeostasis via decreased melatonin and suboptimal mitochondria functioning: pathoetiological and pathophysiological implications. *Melatonin Res*. **2** (2): 70-85; doi:10.32794/mr11250022
24. Fetisova EK, Muntyan MS, Lyamzaev KG, Chernyak BV. (2019) Therapeutic effect of the mitochondria-targeted antioxidant skq1 on the culture model of multiple sclerosis. *Oxid. Med. Cell Longev.* **2019**: 2082561. doi:10.1155/2019/2082561.
25. Castillo SS, Levy M, Thaikoottathil JV, Goldkorn T. (2007) Reactive nitrogen and oxygen species activate different sphingomyelinases to induce apoptosis in airway epithelial cells. *Exp. Cell Res.* **313** (12): 2680-2686.
26. Rambold AS, Pearce EL. (2018) Mitochondrial dynamics at the interface of immune cell metabolism and function. *Trends Immunol.* **39** (1): 6-18. doi:10.1016/j.it.2017.08.006.
27. Moro K, Nagahashi M, Gabriel E, Takabe K, Wakai T. (2019) Clinical application of ceramide in cancer treatment. *Breast Cancer* **26** (4): 407-415. doi:10.1007/s12282-019-00953-8.
28. Pozuelo-Rubio M. (2010) Proteomic and biochemical analysis of 14-3-3-binding proteins during C2-ceramide-induced apoptosis. *FEBS J.* **277** (16): 3321-3342. doi: 10.1111/j.1742-4658.2010.07730.x.

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