

Review

Understanding the role of melatonin in cancer metabolism

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ABSTRACT:

Oncogenes alters metabolic pathways while the resulted metabolites, in turn, modifies the expression and production of oncogenes or tumor suppressors. Metabolic reprogramming has been considered as a consequence of oncogenes' activity more than a phenotypic change of cancer cells. Currently, three different metabolic alterations for cancer cells, i.e. an increased ability to acquire nutrients, preferred metabolic pathways or differentiation pathways, have been described. Melatonin is a molecule which has been extensively investigated since it was discovered more than 60 years ago. From the aggregation of melanophores to antioxidant chain reactions, melatonin has been proposed to be an important molecule affecting the physiology of mammals but also the biology of unicellular organisms. Thus, the decrease in melatonin synthesis in humans with age has been related to several diseases including neurodegeneration and cancer. For many years, it has been believed that melatonin crosses biological membranes easily to exert its functions. However, this notion has been challenged by recent discovery that majority of melatonin might cross biological membranes through glucose transporters. This initial observation has generated a new important idea about melatonin's function, that is, the membrane transportation of melatonin and glucose by the same transporter in cancer cells would be a new promising mechanism of this indole by either reprogramming glucose metabolism, impeding nutrients uptake or assigning preferred metabolic pathways in cancer cells. In this review, we will focus the role of melatonin as an antiproliferative agent, and its connection with metabolic changes due to melatonin competition with glucose.

Keywords: Melatonin, redox signaling, metabolism, glucose transporters, cancer, nutrients

1. MELATONIN: A REGULATOR OF HUMANS' PHYSIOLOGY.

Melatonin, the main product of pineal gland, was discovered in 1958 as a the hormonal factor that lightened the skin of tadpoles (1). This effect, that was the first biological function of melatonin, is far from the actual knowledge about the role of the indole. In the middle sixties, *Melatonin Res. 2019, Vol 2 (3) 76-104; doi: 10.32794/mr11250032*

Hoffman and Reiter found that seasonal fluctuations of melatonin synchronized reproductive activities in seasonal breeding animals (2). From then until now, almost every single knowledge about the indole has changed. Not only, it is questioned whatever the basic function in the cell is but also, where it can be found, and how it is synthesized. Melatonin has been found not only in amphibians or mammals but mostly in all vertebrates and some invertebrates, in pluricellular organisms and in some unicellular ones as bacteria, yeast or some aquatic algae [for review see (3)].

As the main product of the pineal gland, melatonin is produced from tryptophan in a consecutive enzymatic pathway. The initial signal for melatonin synthesis comes through sympathetic innervation from the suprachiasmatic nuclei (SCN). Then, melatonin is secreted from the pineal gland in a daily or seasonal rhythmic manner. The molecule is released at night with an inverse duration to the photoperiod, participating in the transmission of the circadian and seasonal message to the organism (4, 5). This daily rhythm of melatonin is considered the circadian mediator employed by the SCN to release the circadian message to target tissues (6). In fact, exogenously administered pharmacological doses of melatonin are able to synchronize circadian rhythms in rats and mouse with free-running circadian rhythms (7, 8). In humans, this pineal product has been used to readjust circadian rhythms, after time shifts derived from jet lag or shift work, sleep disorders, blind people or circadian-related mood disorders (9).

The pineal melatonin is rapidly distributed to target organs, tissues and cells of pluricellular organisms. High-affinity binding sites for melatonin were discovered in the late eighties by using ^{125}I -radiolabeled melatonin. Three affinity-binding sites were characterized as melatonin receptors. Melatonin receptor 1 (MT1) found in all vertebrates, mainly in the brain; MT2 found in all vertebrates, mainly in the retina and MT3, present in non-mammalian vertebrates. The low-affinity binding site, MT3, was lately identified as an enzyme, the quinone reductase II (10–12). Melatonin membrane receptors have seven transmembrane domains couple to G-inhibitory proteins and their activations low the levels of cAMP (10, 13). Activation of MT1 also alters diacylglycerol, inositol triphosphate (IP_3), intracellular Ca^{2+} , the activity of protein kinase C (PKC), the expression of *c-fos*, the phosphorylation of cAMP-responsive element (CRE)-binding protein (CREB) and increases phosphorylation of mitogen-activated protein kinase 1/2 and extracellular signal-regulated kinase 1/2. Activation of MT2 inhibits both forskolin-stimulated cAMP production and cGMP formation, activates PKC in the SCN and decreases calcium-dependent dopamine release in the retina (14). MT3 is also regulated by other compounds including resveratrol (15). Melatonin membrane receptors can dimerize as homo or heterodimers. In transfected HEK293 cells, MT1 and MT2 were able to form heterodimers MT1/MT2 or homodimers MT1/MT1 and MT2/MT2. After that, MT1 and MT2 were reported to dimerize with GPR50 (G-coupled protein 50) that does not bind melatonin but completely inhibits MT1 function (16). The physiological relevance of dimeric melatonin membrane receptors has been demonstrated in the retina. By using KO mice for MT1 and MT2 and the over-expression of a dominant negative MT2 in photoreceptors, the role of MT1/MT2 dimers in the enhancement of light sensitivity during the night was demonstrated (17). Finally, MT2 dimerization with serotonin receptors has also been found and it has been proposed of pharmacologic value in the treatment of depressive disorders (18).

Melatonin membrane receptors have been found, in addition to retina and brain, in many peripheral tissues as Harderian gland, spleen, testis, ovary, vascular system, gut, smooth muscle and some other cells of the immune system (5, 14). Thus, some of the biological activities of the indole has been related to its transduction signaling pathways.

However, melatonin exerts activities in tissues with low levels of membrane receptors. In fact, the discovery of melatonin in non-vertebrata, bacteria, unicellular eukaryotes and plants

suggest that the indole has gained many new functions during evolution (3, 19). Melatonin is produced in other tissues other than the pineal gland, including retina, Harderian gland, bone marrow, leukocytes, gut, some areas of the brain and skin (20). In these tissues, melatonin is only released after stimuli, as it is the case of postprandial stimulation from gastrointestinal tissue (21).

The discovery of melatonin in the dinoflagellate *Lingulodinium polyedra*, a unicellular organism, by Hardeland *et al.* in 1991 and its mediation in photoperiodic behavior suggested a common biochemical mechanism as the mediator of darkness in all organisms has changed the understanding of melatonin forever (22). Two years later, a direct free radical scavenging activity of this indole was discovered (23). Since then, many publications have reported either the ability of melatonin to scavenge free radicals and to protect cells from radicals insults or its function to increase antioxidant enzymes and alter the redox signaling in different types of cells (24–26). As a consequence of its antioxidant function, melatonin protects lipids, reducing lipid peroxidation and preserving the fluidity of the membranes (25, 27, 28), protects proteins from oxidative degradation (29) and protects nuclear and mitochondrial DNA from oxidative damage (30–32). The antioxidant activity of melatonin is mediated by a cascade reaction which leads to one melatonin molecule, at least, to scavenge up to 10 ROS/RNS. This cascade reaction generates several structurally different metabolites of melatonin including cyclic 3-hydroxymelatonin (C3-OHM) and N¹-acetyl-N²-formyl-5-methoxykynuramine (AFMK) and N-acetyl-5-methoxykynuramine (AMK). All these metabolites exhibit free radical scavenging activity too. This scavenging cascade reaction makes melatonin highly effective as a free radical scavenger and antioxidant (33). Melatonin modulates intracellular redox signaling by increasing antioxidant cellular defense, either enzymatic or non-enzymatic (3, 34, 35). The direct free radical scavenging activity is receptor-independent but the antioxidant effects of melatonin could be receptor-independent (36) or receptor-mediated (37, 38).

Melatonin production, as some other physiological factors, is affected by aging in organisms. For example, melatonin levels in human decay after middle age and this decline is probably associated with the loss of physiological integrity with aging. Thus, melatonin might be a major factor for human pathologies associated with aging including cancer, cardiovascular disorders and neurodegenerative diseases (26). In addition, several studies show that melatonin reduce the severity of a variety of age-related diseases by receptor-dependent and independent mechanisms that could participate simultaneously.

Although the researches on melatonin biological properties have increased during the last decades, some aspects remain to be clarified. For example, its role against tumor progression has been demonstrated in several tumors however, the molecular mechanisms may vary depending on the tissues and cell types, thus, some new aspects should be considered. In addition, to where and when melatonin is synthesized, how melatonin is transported inside cancer cells is poorly understood. The newly emerged evidence show that melatonin does not easily cross biological membranes as previously expected. It might share a well-known and regulated mechanism with one the principal molecules of life, the glucose, to pass biological membranes (39, 40).

Melatonin has been demonstrated to closely link to energy metabolism. Regulation of glucose metabolism by melatonin in peripheral tissues seems to involve clock genes since circadian disruption is associated with increased risk of diabetes and obesity. In fact, circadian misalignment, which occurs in sleep disorders, alters leptin levels and energy balance (41). In diet-induced obese rats, chronic melatonin treatment reduced the BW gain, visceral adiposity, blood triglycerides, serum insulin, homeostatic model assessment index and thiobarbituric acid reactive substances (42). Melatonin treatment also reduced serum free fatty acid levels, fasting

hyperglycemia, glycated hemoglobin (HbA1) in an experimental animal model of metabolic syndrome and type 2 diabetes mellitus (43). In rodents, the involvement of melatonin in glucose homeostasis, glucose uptake, insulin secretion or β -cell survival has been well documented (44).

In addition, direct effects of melatonin on specific tissue functions as glucose uptake or insulin secretion has also been reported. Melatonin activates insulin receptor substrate 1 (IRS-1) in mouse skeletal muscle cells, inhibits isoproterenol induced lipolysis and fatty acid transport in rat adipocytes or decreases glucose transporter type 4 (GLUT4) expression and glucose uptake in human brown adipocyte PAZ6 cell line (44).

Although, melatonin supplementation decreases body weight gain in several animal models, only small-scale human studies have demonstrated a modest effect (45, 46). MT1 knockout mice show increased insulin resistance, the development of type 2 diabetes and leptin resistance likely mediated by a down-regulation of leptin receptor transcription (47). Recently, melatonin has been recognized as an important modulator of metabolic diseases. Glucose intolerance and insulin resistance was described in pinealectomized animals (48) Melatonin is decreased in diabetic mouse models and melatonin treatment improved glucose control in high-fat-diet insulin-resistant mouse model (49). In humans, single dose of melatonin treatment seems to reduce morning and evening glucose tolerance, however, repeated administration over a 5-month period tends to have beneficial effects to decrease HbA1c levels and improves tissue response to metformin (50, 51). The role of melatonin receptors in glucose homeostasis has been studied in melatonin receptor knockout mice. MT1 knockout mice show a strong metabolic phenotype, including a high resistance to insulin (52). A single-nucleotide polymorphism (SNP) in the *MTNR1B* locus was associated with increased fasting plasma glucose levels and impaired insulin secretion, as well as increased risk of type 2 diabetes mellitus (T2DM) and gestational diabetes mellitus (53). The reports on the roles of melatonin in glucose homeostasis are sometimes inconsistent and it deserves to be further clarified.

Given the important role that glucose plays in cell physiology and the relevance of glucose metabolism in cancer cells, this review will focus on the interaction between melatonin and glucose transportation, particularly in cancer cells. In addition, the relevance of this transportation related to antiproliferative properties of melatonin will be discussed in detail.

2. RECEPTOR-DEPENDENT AND INDEPENDENT EFFECTS OF MELATONIN ON TUMOR CELLS

The nocturnal serum concentration of melatonin is inversely associated with the risk of breast, prostate, colorectal, lung, ovarian or cervical cancer (54–58). In addition, the reduction in serum melatonin levels by exposure to light at night (such as nocturnal workers) significantly increase the risk of breast cancer (59). Overall, melatonin reduces carcinogenesis and inhibits cancer cell growth, but antitumor actions of melatonin are sometimes required much higher levels than its night time concentrations (60).

Several human and murine breast, endometrial or ovarian cancer cells exhibit a bell-shaped pattern in response to melatonin with the inhibitory response restricted to the physiological range (61). However, some other cancer cells show a dose-responsive inhibitory property towards melatonin treatment (62). The question that arises now is what really constitutes a physiological concentration of melatonin, as it has been addressed by Tan and co-workers (63). In fact, melatonin levels in body fluids and cells are not necessarily in equilibrium to blood levels. In the bile (64) and cerebrospinal fluid of the third ventricle (65), melatonin concentrations are reported to be orders of magnitude higher than in the blood. There is also

evidence that some cell types, other than pineal gland or retina cells, have the synthetic machinery to produce this indolamine (66). Hence, cells may have elevated concentrations of the indolamine relative to the circulation (67). One aspect must be considered, melatonin blood levels are related to pineal gland, but most of the melatonin produced by other tissues is considered a self-consume product perhaps given a high oxidative metabolism, but this hypothesis is still to be clarified. Since melatonin is claimed to be highly lipophilic, it is also difficult to understand why it does not flux outside cells.

Since melatonin membrane receptors are expressed in tumor tissues (68, 69), the role of MT1 and MT2 in cancer cells proliferation have been studied. Ying *et al.* (70) originally found ¹²⁵I-melatonin specific binding sites in the membrane of a melanoma cells which are sensitive to melatonin, then pharmacologic and molecular approaches have been used to demonstrate their antiproliferative effects. Blask *et al.* (71) by using a perfusion *in vivo* model of breast cancer first identified that melatonin blood perfusion inhibited the growth of hepatoma 7288CTC cells. The decrease in cAMP caused by melatonin binding to its membrane receptors altered the uptake of lipoic acid and its further conversion in 13-hydroxyoctadecadienoic acid (13-HODE) resulting in a suppressive mitogenic response of the tumor. Interestingly, the pharmacologic designed inhibitors of melatonin receptor reduced melatonin's effect on tumor growth. Additional studies indicated that the antitumor effects of melatonin are more or less related to its activity modulating lipid metabolism. This fact suggests a potential link between oncostatic effect of melatonin and other nutritional factors which were observed in calorie restricted animals compared to those fed *ad libitum* (72). MT1 and MT2 were found in the prostate secretory epithelium and in transformed non-tumor RWPE-1 and tumor 22Rv1 cells (73). However, an inhibitory effect of melatonin in RWPE-1 cells was abolished by luzindole (a non-selective melatonin receptor antagonist) but not, by the selective MT2 receptor antagonist, 4-phenyl-2-propionamidotetraline (4-P-PDOT). This observation confirmed a correlation between MT1 expression and the inhibitory role of the indole in a nude mice xenograft model of LNCaP and PC-3 cells (74). Interestingly, the inhibitory effect was in a dose-dependent manner, which questions the exclusive participation of a receptor. Further experiments showed that the effect of melatonin depended more on androgen signaling than in the presence of MT1 receptors. Similar observations were found in pancreatic (75) or neuroblastoma cells (76). Molecular approaches related melatonin membrane receptors with its antiproliferative activity have been extensively performed in the *in vitro* condition. The overexpression of MT1 increased the inhibitory effects of melatonin on proliferation of estrogen receptor alpha (ERalpha)-positive (MCF-7) cells, but it did not induce a melatonin-sensitive phenotype in ERalpha-negative (MDA-MB-231) cells (77). Melatonin also significantly suppressed the invasive potential of MCF-7/6 and MCF-7/Her2.1 cells and repressed the protease activity of MMP-2 and MMP-9. Elevated expression of MT1 further enhanced, while luzindole abrogated, melatonin's anti-invasive effect. These suggest that melatonin's effect on cancer invasion is mediated, primarily through MT1 (78). Also, the expression of MT1 was higher in normal cells than that in cancer ovarian cells. Interestingly, the incubation of cells with melatonin (79) or the treatment of ovarian cancer bearing rats (80) upregulated MT1 expression. Since MT1 levels are reduced in ovarian cancer cells, melatonin feedback over its own receptor may play an important role in its oncostatic properties (81). Later on, Akbarzadeh *et al.* observed that melatonin reduced the growth of a cancer stem cell (CSCs) subpopulation of SKOV3 ovarian cancer cell line. Melatonin caused a marked decrease in the expression of stemness markers, decreased proliferation and induced apoptosis in both CSCs and SKOV3 cells. Since the inhibitors of melatonin receptors, such as luzindole, could not completely inhibit the anti-proliferative activity of the indole and melatonin decreased both

MT1 and MT2 expression but not their protein levels in both CSCs and SKOV3 cells, these results suggested that anticancer effects of melatonin only partially mediated by its specific receptors and other receptor-independent signaling pathways could not be excluded (82).

The silencing of melatonin membrane receptors was employed in few scenarios. Santoro *et al.* have discovered that melatonin increased p38-mediated p53 phosphorylation in cancer cells (83). They were the first using siRNAs to inhibit MT1 and MT2 in order to accurately prove the participation of melatonin membrane receptors in the antitumor properties. The results indicated that the inhibitory effect of melatonin on DNA damage caused by UVB irradiation was impaired in human colon carcinoma HCT116 cells and in MCF-7 cells by the depletion of either MT1 or MT2. In terms of growth, cells devoid of MT1 or MT2 responded in a lesser extent to melatonin in terms of proliferation, colony formation assay or the growth of tumor xenografts in nude mice. Moreover, melatonin's ability to phosphorylate p38 and p53 was reduced. However, intriguingly the exclusive elimination of melatonin receptors caused an increment in p38 and p53 phosphorylation and the treatment with melatonin reduced it. This apparent inconsistency was explained. Thus, MT2 signal transduction pathways cannot compete with the ability of melatonin to scavenge free radicals and to reduce p53 phosphorylation induced by UVB (84). However, it is noteworthy that even though there is still disagreement about the actual mechanism by which melatonin inhibits tumor growth, just few papers have clearly demonstrated the participation of melatonin membrane receptors, and only Santoro *et al.* used a genetic removal of the receptors to confirm their participations.

In addition to membrane receptors, melatonin antioxidant properties might be responsible for the inhibition of tumor growth. Several other antioxidants inhibit cancer growth and progression since redox signaling is implicated in initiation, promotion, and progression of cancer (85, 86). Melatonin, working as an antioxidant, has been found to decrease carcinogenesis since it prevents DNA damage caused by physical or chemical mutagens (31, 87, 88). The indole also inhibits cell growth of Chinese hamster ovary (CHO) cells by an antioxidant mechanism (89) and prostate cancer cells growth by mechanisms independent of membrane receptor (39, 90, 91). Melatonin also prevents cancer progression by inhibiting the expression and activity of proteases and reducing cell migration in glioma cells by antioxidant mechanisms (92), in hepatocarcinoma cells by an inhibition of NF-kappaB activity (93) and in oral cavity cancer cells by a histone deacetylation mechanism (94). Interestingly, melatonin was previously found to dock into the active site cleft of MMP-9 and to interact with key catalytic site residues reducing its catalytic activity (95). More recently, Trivedi *et al.* showed in a mouse model of colitis-associated colon carcinogenesis (CACC) that melatonin decreased the progression of CACC decreasing autophagy through the increased production of NRF2 and the associated antioxidant enzymes, NAD(P)H: quinone oxidoreductase (NQO-1) and heme oxygenase-1 (HO-1) in the colon (96). Interestingly, in this model, melatonin reduces markers of autophagy concomitant to a decrease of inflammation and oxidative stress in an *in vivo* condition.

In addition to its direct effect on cancer cells, melatonin also exhibits synergistic effects with several anticancer drugs, either by increasing their efficiency or reducing their toxicity (97). Cisplatin is a strong anticancer drug that is widely used to treat patients with bladder, head, neck, lung, cervix, endometrium or ovary cancer (98). Clinical utility of platinum compounds is limited because of its serious side effects, such as nephrotoxicity, neurotoxicity, and reproductive organ disorder. Since cisplatin triggers endoplasmic reticulum stress and mitochondrial reactive oxygen species (ROS), antioxidants were employed in combination with cisplatin to prevent tissues damage. When injected cisplatin with or without melatonin into 6-wk-old female mice, melatonin successfully rescued cisplatin-induced primordial

follicle loss via suppression the PTEN/AKT/FOXO3a signaling pathway in the ovary (99). Curiously, use of nonselective antagonist of MT1/MT2, luzindole, abolished protective effect of melatonin on ovarian injury caused by cisplatin while MT2 selectively 4-phenyl-2-propionamidotetralin did not. The results found suggest a role of MT1 in protection against cisplatin induced toxicity (81). The protective effects of melatonin on toxicities induced by doxorubicin were also observed in lymphatic tissue (100), myocardium (101, 102) and overall survival of animals based on its antioxidant properties and influencing mitochondrial homeostasis (103).

The effects of melatonin on the normal cell toxicity induced by anti-cancer drugs are easily understood in terms of its antioxidant and cytoprotective effects. Intriguingly, melatonin can also increase the efficacy of the same anticancer drugs. For example, melatonin increased the toxicity of cisplatin, doxorubicin or 5-fluorouracil (5-FU) in HeLa cervical carcinoma cells (104) or pancreatic cells by prooxidant activities (105). With poor mechanistic explanations, some of the resulting changes caused by melatonin treatment could be, from our point of view, the result of an increment of cancer cells death which may increase oxidative stress particularly in cancer cells. It was recently demonstrated that melatonin by itself can interact with DCFH-DA, the compound widely employed to measured melatonin pro-oxidant activity, increasing its fluorescence by a mechanism independent of free radicals production (106). It is clear that the mitochondrial functional impairment derived from apoptosis causes lately an increment in free radical production inside cells (107). If melatonin increases the toxicity of anti-tumor compounds in cancer cells, it might indirectly promote the production of free radicals as a consequence of apoptosis without producing any pro-oxidation by itself. A mechanistic study has indicated that the synergistic effects of melatonin and cisplatin on cancer cell toxicity are mediated by NFκB translocation. The p38 and JNK inhibitors, SB203580 and SP600125 interfered melatonin effect respectively, suggesting p38 and JNK mediate melatonin pro-apoptotic activity in cancer cells. However, the combination of cisplatin and melatonin did not modulate any signaling pathway related to the toxicity of cisplatin though there was an apparent increment of toxicity (108). Similarly, our group has found that melatonin enhances the toxicity of cytokines against prostate cancer cells (109) and increases the levels glutathione, as extensively demonstrated, altering redox signaling and reducing the constitutive activation of NFκB. NFκB is a survival factor constitutively activated in several types of cancer cells, including prostate cancer cells, due mainly to an increase oxidative status (110, 111). In addition, melatonin changes the phenotype of prostate cancer cells to a neuroendocrine-like phenotype. It is not clear how this phenotype alters tumor progression in the prostate, but it seems that heterogenic populations of neuroendocrine cells inside the tumor can either inhibit or promote the progression of the tumors. In one hand neuroendocrine-like cells do not divide, in the other hand, they produce bioactive products that promote the proliferation of neighbor cells (112). However, the phenotype changes caused by melatonin stimulated the toxicity of cytokines in prostate cancer cells (113).

Then it seems confusing how the indole promotes or inhibits the toxicity of anti-tumor drugs in cancer and normal cells, respectively, but it could be possible that the cellular context might account. This specific topic is controversial, and the results require a profound study and clarification in order to exploit the potential role of the indole in combination with anti-cancer drugs and these are summarized in Table 1.

Cell/tumor type	[Mel]	Effect(s) on cells	Mechanism(s) proposed by authors	Original Reference(s)
Breast cancer				
MCF-7, human estrogen-dependent breast cancer cells	1nM	Inhibits proliferation of estrogen-dependent cells	Membrane receptors; estrogen receptor	(115, 116)
	1nM	Increases sensitivity to tamoxifen	↓ estrogen receptor transactivation	(117)
	1nM	Inhibits cell invasion; no apoptosis detected; MT1 overexpression increases growth inhibition; anti-angiogenesis;	β1 Integrin/MT1/↓aromatase activity/↓VEGF/↓MDM2/DJ-1, KLF17, ID-1	(77, 118–123)
	10μM	Potentiates apoptosis induced by retinoids/all-trans retinoic acid	Not provided	(124, 125)
	10nM	Stimulates Ca ²⁺ -calmodulin; microfilament modulation	PKC/actin filaments	(126, 127)
	300μM	Sensitizes cells to doxorubicin-induced apoptosis	TRPV1 channels	(128)
	1nM	Sensitizes cells to docetaxel trioxide-induced apoptosis	↓BCL2, ↑BAD, ↑BAX	(129)
1nM	Sensitizes cells to arsenic trioxide-induced apoptosis	c-Myc, hTERT	(130)	
Colon cancer				
HT-29 human colon adenocarcinoma cells	1mM	Does not induce apoptosis <i>per se</i> /enhance apoptosis induced by flavone	Pro-oxidant	(131)
	1mM	Induces apoptosis/enhance proglumide-induced apoptosis	Antioxidative actions	(132, 133)
	1mM	Enhances 5-FU apoptosis	MT3	(134, 135)
	1mM-1nM	Melatonin or vitamin C do not enhance irinotecan-induced apoptosis (contrary to vitamins A/E)	N/A	(136)
SW480/LoVo colon cancer cells	0.1-1 mM	Enhances ursolic acid-induced apoptosis	MMP9/COX-2 modulation	(137)
HCT116 human colorectal cancer cells	10μM	Induces apoptosis and autophagy	MT1 upregulation	(138)
Caco-2 human colorectal cancer cells	1-10nM	Ultrastructural features of cytotoxicity	Not provided	(139)
RKO human colon carcinoma cells	2.5mM	Inhibits migration	↓Myosin light chain kinase	(140)
	0.2-1mM	Induces apoptosis	↓PrP ^C /PINK	(141, 142)

SNU-C5/WT human colorectal cancer cells	1mM	Enhances oxaliplatin-induced apoptosis		
Leukemia				
P388 leukemia	5nM	Sensitizes cells to doxorubicin	Inhibition of P-glycoprotein	(143)
HL-60 human promyelocytic leukemia cells	1mM	Induces apoptosis	↓BCL2↑BAX; independent	MT1- (144)
		Enhances H2O2-induced apoptosis	Not provided	(145)
	1mM	Enhances retinoic acid-induced apoptosis	Not provided	(146)
Jurkat Leukemia cells	1mM	Enhances radiation-induced apoptosis	TP53	(147)
	1-2mM	Induces apoptosis	MT1/MT2 independent	(148)
	250μM	Enhance doxorubicin-induced apoptosis	ROS-independent	(149)
Human acute myeloid leukemia cells from patient	1mM	Enhances etoposide-induced toxicity; does not alter apoptosis in HL-60, Jurkat, MOLT-4, Daudi, CMK, K562 cells	Not provided	(150)
Ramos, DoHH2, SU-DHL-4		Induces apoptosis; sensitivity: Ramos, DoHH2 > SU-DHL-4 > JURKAT	MT1/MT2 independent	(148)
MOLT-3 human T lymphoblast	1mM	Induces apoptosis	Caspase-dependent, independent	ROS- (151)
U937 human lymphoblast	1mM	Enhances hyperthermia-induced apoptosis; the same observed in HL-60, but not in K562 or MOLT-3 cells.	Caspase-dependent	(152)
Ovarian cancer				
Human ovarian cancer cells	100 μM	Inhibits proliferation	Not provided	(153)
Ovarian cancer cells	1mM		Not provided	(154)
HTOA ovarian cystadenocarcinoma cells	1μM	Enhances antiproliferation of CDDP	Not provided	(155)
SKOV3 human ovary adenocarcinoma cells	1-2mM	Do not induce apoptosis but enhance cisplatin-induced apoptosis; enhance laser irradiation-induced apoptosis; inhibits invasion and migration	ERK/p90RSK/HSP27	(82, 156, 157)
OVCAR-429 and PA-1 ovarian cancer cells	0.8 mM	Inhibition of cell proliferation with less than 5% apoptosis	↓CDK2/4	(158)
OVCAR-3 human ovary epithelial adenocarcinoma	1-2mM	Enhances inhibition of proliferation caused by cisplatin; avoids proliferation induced by cadmium	MT1-independent/ expression	ERα (159, 160)
Lung cancer				

A-549 human alveolar basal adenocarcinoma cells (NSCLC)	0.1-1mM	Enhances doxorubicin-induced apoptosis	Not provided	(161)
	1mM	Enhance UV-induced apoptosis	CCAR2-deficiency	(162)
	5-10mM	Induces apoptosis	↓HDAC1	(163)
	1mM	Enhances berberine apoptosis (also in H1299 cells)	hTERT inhibition	(164)
HEp-2 laryngeal cancer cells	0.1-1mM	Enhances doxorubicin-induced apoptosis	Not provided	(161)
H1795 NSCLC cells	1-10mM	Sensitizes cells to chemotherapy	↓EGFR	(165)
SK-LU-1 lung adenocarcinoma cells	2-10mM	Induces apoptosis	Not provided	(166)
	1-5mM	Enhances cisplatin-induced apoptosis	Not provided	(167)
Other cancer cell lines				
LNCaP Prostate cancer	1mM	Does not induce apoptosis but enhance apoptosis induced by TRAIL/TNFalpha	GSH/NE differentiation	(109, 113)
	1-3 mM	Induce apoptosis	ERK/p38MAPK/JNK activation	(168)
U87MG glioma cells	1-3mM	Induces apoptosis and enhance temozolomide induced apoptosis	↓TFAM, reduce mitochondrial transcription	(169)
A-431 human epidermoid carcinoma cells	0.1-5mM	Induces apoptosis	ROS production	(170)
Thyroid cancer cell lines (TPC-1, 8505c, ARO)	1-15mM	Inhibits proliferation and migration; induces apoptosis	↓p65 NFκB	(171)
SGC-7901 gastric cancer cells	1-5mM	Induces apoptosis	↓P-AKT, P-MDM2	(172)
	1-5μM	Induces apoptosis	↑miR-16-5p	(173)
Cal-27 and SCC-9 head and neck cancer cells	0.1-1mM	Enhances rapamycin-induced apoptosis and differentiation	mTOR, ROS formation	(174)

Table 1. The summary of the experimental evidences that links melatonin to different cancer cell lines.

Table 1 summarized the findings describing the anti-proliferative and/or pro-apoptotic actions of melatonin on cancer cells. As mentioned, in most of the cases melatonin enhances the pro-apoptotic effect triggered by other substances such as doxorubicin or other chemotherapeutic agents. Regarding the putative melatonin nuclear receptor RZR/RORα, it has been clearly demonstrated that this orphan nuclear receptor family do not bind melatonin so, as it has been recently suggested, results using the agonist of these receptors, CGP52608, should be reinterpreted and not related to melatonin functions (114). Thus, it has prompted us to exclude these results from the list shown in table 1.

3. MELATONIN AND MITOCHONDRIA, A SPECIAL RELATIONSHIP

Mitochondria offer the crucial intracellular location to extend the production of ATP from glucose oxidation, using O₂ as the final acceptor of electrons. Nevertheless, this benefit comes together with certain collateral damage, in terms of free radical overproduction, specifically

superoxide anion, $O_2^{\bullet-}$ (175). As a result, experimental evidences have confirmed that mitochondria are the major site for production of free radicals, particularly at complex I and complex III (176). Cells contain, however, weapons in the form of different intracellular antioxidant defenses, in charge of keeping this ‘physiological overproduction’ at low levels. Under normal conditions, these defenses will keep mitochondria healthy and consequently no respiratory damage or apoptosis will be triggered. Otherwise, if ROS overproduction is not conveniently counteracted, mitochondrial dysfunction, mitophagy or apoptosis would eventually occur. Consequently, mitochondrial involvement in the corresponding diseases has been referred as the “powerhouse of disease” (177, 178).

In the particular case, mitochondria has been one of the major targets of melatonin according to hundreds of reports, as it has been recently reviewed (179). In a review by Tan *et al.* it had proposed the hypothetical evolution in melatonin functions, deriving from an antioxidant to a circadian regulator, becoming a chemical expression of darkness (3) and more recently these authors also suggested that multiple experimental evidences make mitochondria as the origin for melatonin production (180). Finally, it was not surprising that a multiple laboratory study has determined that mitochondria are the synthetic sites for melatonin, as demonstrated by the presence of both, aralkylamine N-acetyltransferase (AANAT) as well as N-acetyl-serotonin O-methyltransferase (ASMT), the rate-limiting enzymes in melatonin synthesis from tryptophan (181). The same study has also demonstrated the presence of melatonin membrane GPCR receptor, MT1, at the outer mitochondrial membrane. Other studies have corroborated this results in oocyte’s, embryo or in plant mitochondria (182–184) and the same occur with chloroplasts in plants (185).

The question to be answered is whether the treatment of tumor cells with melatonin is related at some point with mitochondria. Melatonin has proved to be an effective neuroprotector, avoiding apoptosis in neurodegenerative disease models. Its antiapoptotic effects have frequently associated with its antioxidant ability, thus, this antioxidant effect might serve as a gate opener for apoptotic induction in tumor cells, when properly combined with chemotherapeutic agents that are not able to induce cell death by themselves alone (186). Furthermore, the abovementioned presence of MT1 in the outer mitochondrial membrane has been associated with the blockage of cytochrome c release from mitochondria and therefore with the anti-apoptotic effect observed in neurons (181). This is not the case for many cancer cell types in which melatonin still functions as an antioxidant, preventing rather than potentiating cell death (187, 188). In many other cell types, however, the subcellular scenario changes and melatonin has been reported to enhance cancer cell death when combined with other drugs.

Considering the evidence mentioned above, whether mitochondria are the major subcellular target for melatonin action also in cancer cells deserves further study, Mitochondria contribute to survival advantages of cancer cells. Alterations of mitochondrial antiapoptotic proteins have been found in several tumor types, and treatments based on the activation or inhibition of apoptotic-related gene product have been tested in clinical trials (189). In addition to apoptotic resistance, a disbalance of redox signaling in mitochondria is the feather of cancer cells which have increased levels of ROS but still under the control (190). In this regard, melatonin as mitochondrial targeted antioxidant has been tested in cancer cells. Melatonin, and its derivatives kynuramines participate in multiple mitochondrial associated processes including apoptotic-related mechanisms, ion disturbances, mutations in mitochondrial DNA and metabolic re-wiring (191, 192). Melatonin affects glucose uptake, TCA cycle and the activity of respiratory complexes I and IV, thus modulating oxidative phosphorylation (96, 193), as it

will be mentioned below. The suppression of aerobic glycolysis and Warburg effect of melatonin have been described in a human leiomyosarcoma model (194).

Beyond pure metabolic actions, Franco *et al.* have recently reported the modulatory effect of mitochondria transcription factor A (TFAM) in U87MG glioma cells (169), with an immediate impact on mtDNA transcription. Rough endoplasmic reticulum (RER) and mitochondrial cytochrome P450 1B1 (CYP1B1) mediates the antitumor activity of melatonin in neural cancer cells by converting it into N-acetyl-serotonin, the mediator of apoptosis triggering in these tumor cells (195). However, different action has been reported in some types of tumor cells, i.e., the pro-oxidant, ROS-generating effect, specifically occurred in the mitochondria, resulting in a decrease in mitochondrial membrane potential ($\Delta\psi_m$) and consequently, induction of cell death (196). This effect, totally opposed to the widely reported antioxidant activity in normal cells, could also be cell-type specifically and the underlying molecular pathway should be elucidated to select suitable tumor cells as the target of melatonin. Perhaps Huo *et al.* (197) have provided one of the clues to solve this complex scenario, namely the oligopeptide transporter PEPT 1/2 which usually expressed in the mitochondria. This transporter seemingly mediates the uptake of melatonin in mitochondria. The final equation, including the ability to synthesize melatonin as well as the expression of this or other transporters in mitochondria (91) might account for the differential effect of the indole on variety of tumor cells.

With some exceptions that show inconsistent results from specific tumor cells (e.g. MCF-7 or LNCaP cells), the apoptosis-triggering effect of melatonin when used alone appears to be cell-type restricted in HT-29, HCT116, SNU-C5/WT colon cancer cells (132, 133, 138, 141, 142) or in leukemia cell lines including HL-60 or Jurkat cells among others (144, 147–149). A few studies have also reported melatonin-induced apoptosis in lung cancer (163, 166), thyroid (171) or gastric cells (172). One of the major drawbacks of these studies is the extremely high concentration of melatonin used, which is largely over the high μM range, sometimes near to the 5-10 mM. This might have a limited impact in the *in vivo* conditions or in clinical trials and yet melatonin proves to be a very good antitumor agent in murine models, but molecular mechanisms associated to this oncostatic actions are not related with the induction of apoptosis (96, 198, 199). Our group have used a relatively high dose of melatonin (1-2 mM) in prostate cancer cell lines. The low solubility, using DMSO as vehicle, usually limits its maximal concentration. DMSO, rather than ethanol is by far the most commonly used solvent for preparing melatonin stock solutions and its final concentration in cell culture media for providing 1mM melatonin is usually excessive of 0.2-0.5% (over 50 mM), which has a tremendous side effect on cell viability (96). In this context, the enhancing/sensitizing effect of DMSO *per se* in pro-apoptotic effects of melatonin should not be ruled out. In the rest of publications (see Table 1), melatonin is shown to display sensitizing properties to many different apoptotic inducers, namely, doxorubicin, docetaxel, arsenic trioxide, 5-FU, ursolic acid, oxaliplatin, radiation, etoposide, hyperthermia, CDDP, cisplatin, cadmium, UV light, TRAIL/TNF α , temozolomide or rapamycin among others. Collectively all these data point out that the inclusion of melatonin in combination with either radiation or chemotherapy agents offers promising possibilities in cancer treatment. Nevertheless, except for some assays performed in the low micromolar range, the problem of high concentrations of solvents should be considered for *in vivo* experiments or clinical aims.

4. THE METABOLISM OF GLUCOSE IN CANCER CELLS

Of all the hallmarks of cancer, one has not received enough attention until recently. In fact, it was not included in Hanahan and Weinberg first review in 2000 (200) but afterwards, this issue was reemphasized in their review of 2011 (201). Since then, a new emerging hallmark at that time, reprogramming energy metabolism, is currently considered as a fundamental adjustment of proliferative cells to fuel their growth and division. Under aerobic conditions, normal cells employ glycolysis to convert glucose to pyruvate in the cytosol and then to shuttle it into mitochondria for ATP production via oxidative phosphorylation. Otto Warburg found, back in 1930, that even in the presence of oxygen, proliferative tumor cells reprogram their glucose metabolism limiting to glycolysis leading to a state that has been termed “aerobic glycolysis” (202, 203). Cancer cells must compensate for the lower efficiency of ATP production afforded by glycolysis relative to mitochondrial oxidative phosphorylation, in part by upregulating glucose transporters, notably *SLC2A1/GLUT1*, which substantially increases glucose import into the cytoplasm. A recent report published by our group (91) suggested that GLUT1 transporter might participate in melatonin uptake. This observation indicated a novel role of melatonin played in cancer cells.

Proliferating cells have a higher demand for nutrients which offer them the needed carbon and nitrogen elements necessary to growth and divide. In that sense, highly proliferative tumor cells showed metabolic adaptations to acquire necessary nutrients from a frequently nutrient-poor environment (204). In brief, tumor cells show an increased ability to acquire nutrients, assigned preferred metabolic pathways and altered differentiation programs in order to favor those pathways more efficient to create biomass.

Principal nutrients of mammalian cells are glucose and glutamine. Glucose is the main donor of carbons and glutamine offers in addition to carbons, nitrogen. Nutrients uptake is strictly regulated by growth factors in mammals, they do not import them in a constitutive manner (205). Cancer cells accumulated oncogenic alterations that make them independent of trophic factors in several cell functions including nutrients uptake (200). Genetic alterations that target PI-3K and its negative regulator PTEN increased glucose uptake and metabolism. Thus, the activating mutations or amplifications of receptor tyrosine kinase through the activation of PI-3K/AKT signaling pathways (206), the oncogenic activity of small GTPases as RAS (207) or transcription factors as C-MYC that activates the transcription of glutamine transporter ASCT2 and SN2 (208) will activate nutrients uptake. In fact, the deletion of RB family proteins has been shown to upregulate the uptake of glutamine via the E2F-dependent upregulation of ASCT2 and GLS1 (209). On the contrary, tumor suppressor genes decrease nutrients uptake.

While normal cells become quiescent in the absence of nutrients by auto-regulatory mechanisms, tumor cells do not have these regulatory systems, always keeping their high bioenergetic requirements and being addicted to what it is called “Warburg effect” (210). Otto Warburg described 90 years ago that cancer cells when grown in a glucose-rich culture medium, they convert pyruvate to lactate and released it to extracellular medium regardless of oxygen availability. Although, he firstly interpreted these results in a wrong way, considering that tumor cells suffered of an irreversible damage of respiration and the impairment of mitochondrial function, later it was demonstrated that tumor cells retain functional mitochondria and the ability to conduct oxidative phosphorylation (OXPHOS). Then, the metabolic switch in favor of glycolysis is an adaptive response of cancer cells in order to fulfill their biosynthetic demand. Now, this phenomenon is known as “Warburg effect” (211). In brief, in differentiated cells in presence of oxygen, glucose is predominantly used for energy

production by mitochondria while undifferentiated, highly proliferative cells, show a higher rate of glycolysis and an increased production of lactate, even in the presence of oxygen. When glycolysis is enhanced, only 2 ATP molecules are obtained from a molecule of glucose, instead of the 36 molecules of ATP obtained by OXPHOS (212). However, ATP production is never compromised in undifferentiated cells by glycolysis due to the fact that this process is multiple times faster than that of OXPHOS, providing sufficient energy for proliferation, high ratios of ATP/ADP and nicotinamide adenine dinucleotide (NAD)H/NAD⁺, and the necessary precursors of macromolecules for cell division (213). Moreover, by converting the excess of pyruvate to lactate, proliferative cells prevent accumulation of NADH and reduce ATP production and then a decrease in glucose metabolism free from feedback repression.

In general, glycolysis is not a single chain reaction of molecular events, but glycolytic metabolites derive in lateral biosynthetic pathways in cancer cells. Therefore, glucose-6-phosphate contributes to the pentose phosphate pathway in which glucose is oxidized to ribose-5-phosphate a structural component of nucleotides. Fructose-6-phosphate combine with the increment in glutamine uptake gives glucosamine-6-phosphate that participates in glycosylation of proteins and the synthesis of extracellular matrix components and finally, 3-phosphoglycerate is used by cancer cells as a precursor of serine, glycine, methyl donor groups and NADPH (204, 214, 215).

5. MELATONIN EFFECT ON GLUCOSE UPTAKE INHIBITS TUMOR GROWTH

In 2008, we proposed for the first time that facilitated diffusion or an active process rather than simple passive diffusion might be a dominating mechanism of melatonin uptake by prostate cancer cells (39). After that, we found that melatonin taken up in prostate cancer cells was mediated by a member of SLC2/GLUT proteins. In that way, melatonin competes with glucose for the same transporters and it leads to reduction of glucose uptake and inhibition of the proliferation and progression of cancer cells. Melatonin also modifies the expression of GLUT1 glucose transporter. These observations have been confirmed *in vitro* but also in animal models using the TRANsgenic Mice of Adenocarcinoma of the Prostate (TRAMP) mice. The evidence suggests a facilitative transportation of melatonin and this process may modify glucose metabolism to inhibit cancer cells proliferation (91).

Almost at the same time, Hill *et al.* (216) investigated glucose uptake and the production of lactate in breast tumor xenografts. They found a significantly shorter latency-to-tumor-onset and increased growth rate of tumors in tumor-bearing female nude rats exposed to dim light at night (dLEN). dLEN promoted also intrinsic resistance to tamoxifen. In addition, tumor glucose and O₂ uptake were increased in the mid-dark phase in vehicle-treated dLEN rats compared with vehicle-treated rats. Similarly, tumor glucose and O₂ uptake increased more than 3 times in dLEN rats. Interestingly melatonin alone reduced both glucose and O₂ uptake in vehicle or tamoxifen-treated dLEN rats. While tamoxifen has no effect on glucose uptake, melatonin reduced more than half the glucose uptake ($4.4 \pm 0.5 \mu\text{g}/\text{min}/\text{g}$ vs $1.6 \pm 0.1 \mu\text{g}/\text{min}/\text{g}$). Likewise, and maybe consequently, melatonin reduced the production of lactate (27.3 ± 1.1 vs $10.40.4 \text{ nmol}/\text{min}/\text{g}$). With these results, they implied that though the mechanism by which melatonin increases breast cancer responsiveness to tamoxifen is unknown, the participation of the indole in the inhibition of aerobic glycolysis might be implicated. In fact, glucose metabolism reprogramming is implicated in cell signaling pathways in breast cancer. Some phosphorylation pathways, pERK172, cAMP, SRC or IL-6 are activated in response to dLEN and somehow are connected to the potentiation of metabolism reprogramming. In addition, some mechanisms of chemoresistance are related to metabolic changes occurring

during the Warburg effect. However, we must carefully consider these results since a simple reduction of glucose uptake does not imply that melatonin modifies glucose reprogramming occurring in cancer cells a much more complex metabolic event.

Following year, the same group found an intrinsic resistance to doxorubicin in estrogen receptor alpha-positive (ER+) MCF-7 human breast cancer xenografts, grown in nude mice in which dLEN is present during the dark phase. While, the replacement of melatonin significantly restored doxorubicin sensitivity. Doxorubicin alone did not change the high rates of tumor glucose or O₂ uptake in xenografts versus those receiving vehicle. Rats bearing (ER+) MCF-7 human breast cancer xenografts receiving melatonin alone showed a significant reduction of glucose and O₂ uptake up to 66% compared with vehicle or doxorubicin-treated rats. This data confirmed previous work and shows how melatonin, by reducing glucose and O₂ uptake, lengthened tumor latency, tumor regression, suppressed tumor glycolysis and restored doxorubicin sensitivity. However, it is not clear if this is a consequence of melatonin activity on the phosphorylation of metabolic masters such as AKT or on the contrary, the modulation of glucose transportation is responsible for the changes in proliferating phosphorylation pathways (217).

Interestingly, the same group have developed a similar xenograft system by using androgen-independent prostate cancer cells. In this occasion, Dautchy *et al.* (2) found that the employment of blue-tinted rodent cages increased nighttime melatonin levels in nude rats. They found that the rates of tumor glucose uptake and lactate production were altered in rats in blue-tinted cages. In fact, glucose uptake and lactate production were suppressed by 46.8% and 29.3% compared with those in controls.

All these results have implied that physiologic melatonin alterations by dLEN or by stimulation of endogenous production with blue-tinted cages or by melatonin treatment at low physiologic doses (2.5µg/day) in mice can change the uptake of glucose and O₂ by tumor cells and the production of lactate and CO₂. Still, an increment of nutrients uptake by tumors is only one of three characteristics of metabolic reprogramming in cancer cells (204).

Other studies also indicate that melatonin, at high pharmacologic concentrations *in vitro* modify cancer cells proliferation by an alteration of glucose metabolism, i.e. reducing the glucose uptake and the production of lactate (218, 219).

Although melatonin at low physiologic or high pharmacologic concentrations seemed to reduce glucose uptake and lactate production, this did not mean that the indole affected metabolic reprogramming in cancer cells. All these papers claimed that melatonin affected Warburg effect. In addition to an increased ability to acquire nutrients by proliferating cells, Warburg effect also implies that nutrients follow preferred metabolic pathways and cells show altered differentiation programs in order to favor those pathways more efficient to create biomass. Neither of these has been clarified in these studies. In 2017, Hevia *et al.* (193) studied the actual effect of melatonin on glucose metabolism in androgen sensitive and insensitive prostate cancer cells, using an acute methodology based on ¹³C stable isotope-resolved metabolomics. The results have confirmed that melatonin reduces glucose uptake and lactate production and melatonin treatment drives glucose metabolism to OXPHOS. The isotopic enrichment of mitochondrial metabolites after culturing cells with ¹³C-glucose labeled and ATP levels indicated that the indole did not affect particularly at any stage of glycolysis or mitochondrial metabolism of glucose in either androgen sensitive or castration-resistant phenotype. The results suggest that melatonin may mainly target the process of glucose uptake rather than its metabolism in cancer cells. Even more, by studying glucose-6-phosphate dehydrogenase activity, authors demonstrated that melatonin also reduced the pentose phosphate pathway in prostate cancer cells (Figure 1).

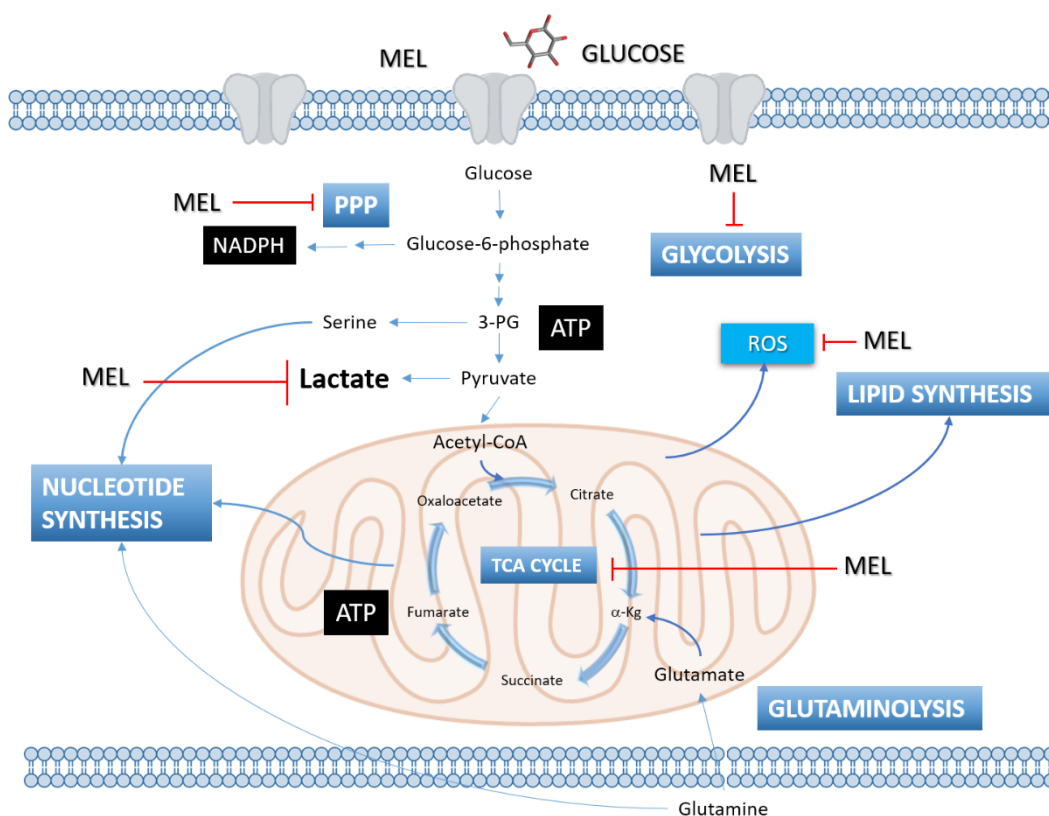


Fig. 1: The potential mechanisms that melatonin blocks the uptake of glucose in prostate cancer cells.

Cancer cells reprogram their metabolism to fabricate the highest possible biomass. They favor aerobic glycolysis increasing the production of lactate, re-wire glycolysis through pentose phosphate pathway sustaining reductive power inside the cells or increase lipid synthesis. Melatonin was proven by ^{13}C -isotopically labeled glucose that reduces glucose entrance that in turn, reduces lactate production and NADPH production in prostate cancer cells.

In summary, at least in this cellular model, melatonin reduces the glucose uptake and the production of lactate, but it does not imply that the indole modifies metabolic reprogramming in cancer cells because melatonin does not increase any other pathway alternative to glycolysis. Melatonin reduces the uptake of nutrients and then it reduces the proliferation and progression of tumor cells, and this is a relevant fact in cancer biology by itself.

6. CONCLUDING REMARKS

Melatonin is an important modulator of metabolic physiology, it influences insulin secretion, decreases blood glucose, and benefit to the prevention of hyperglycemia. Furthermore, polymorphisms of melatonin receptors have been associated with an increased risk of type 2 diabetes. Considering cancer cells, we have found that the indole upregulates IGFBP3, an inhibitor of insulin receptor, to reduce the proliferation of prostate tumors *in vivo* and it also reduces glucose uptake or lactate production. However, it seems that melatonin does not alter metabolic rewiring that occurs in cancer cells. Glucose metabolism in cancer cells plays a key role in progression and in oncogenic phenotype. Oncogenes altered metabolic pathways and metabolites change the expression or production of oncogenes or tumor suppressor genes, a vicious cycle. Given the relevance of glucose metabolism in cancer progression, the role of melatonin on glucose metabolism should be carefully investigated. Its

cross-talk with the role of the indole in phosphorylation pathways, i.e. AMPK, AKT or in cellular redox balance must be explored. In fact, the paradigm about melatonin and prostate cancer, for example, involves several pathways that might be related to glucose metabolism as it is shown in Figure 2. Melatonin is an endocrine factor with multiple cell and tissue targets, looking for a connection between all these factors would help to understand its actual role on human's health, particularly in cancer therapy.

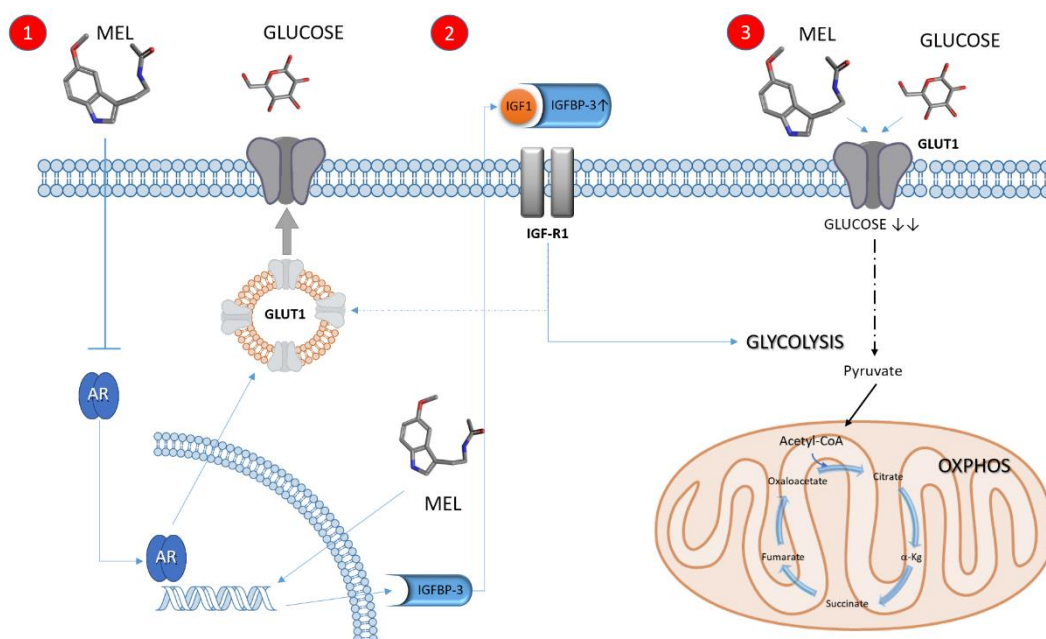


Fig. 2: Three different glucose-dependent mechanisms that likely mediate melatonin antiproliferative activity.

First, in hormone-dependent prostate cancer cells, melatonin reduces nuclear translocation and androgen signaling that likewise reduces the mobility of glucose transporters to cellular membranes and reduces glucose uptake. Second, melatonin by receptor-independent mechanisms transcriptionally increases the expression of IGFBP-3 protein that through the retention of IGF-1 might reduce glucose transporters and might reduce glycolysis. The last possibility is that melatonin simply by competing by glucose transporters reduces glucose entering and, in that way, it decreases the biosynthetic machinery of cancer cells. In all cases, melatonin reduces the proliferation, at least of prostate cancer cells and may be of other similar hormone-dependent tumor types.

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AUTHORSHIP

Rosa M. Sainz and Juan C Mayo have drafted and wrote the manuscript, Pablo Rodriguez and Jose I Garcia contributed to the discussion of melatonin metabolomics results, Rafael Cernuda has critical revised the manuscript and contributed to discussion, Isabel Quiros contributed to discussion and the editing of the manuscript.

CONFLICT OF INTEREST

The authors declared that they have no conflicts of interest to this work

REFERENCES

1. Lerner, A. B., Case, J. D. & Takahashi, Y. (1958). Isolation of melatonin, a pineal factor that lightens melanocytes. *J. Am. Chem. Soci.* **80**: 2587.
2. Hoffman RA, Reiter RJ (1965) Pineal gland: Influence on gonads of male hamsters. *Science* **148** (3677):1609–1611.
3. Tan DX, et al. (2010) The changing biological roles of melatonin during evolution: From an antioxidant to signals of darkness, sexual selection and fitness. *Biol. Rev.* **85** (3): 607–623.
4. Reiter RJ (1991) Melatonin: The chemical expression of darkness. *Mol. Cell Endocrinol.* **79** (1–3):C153-158.
5. Simonneaux V, Ribelayga C (2003) Generation of the melatonin endocrine message in mammals: A review of the complex regulation of melatonin synthesis by norepinephrine, peptides, and other pineal transmitters. *Pharmacol. Rev.* **55** (2): 325–395.
6. Pévet P (2002) Melatonin. *Dialogues Clin Neurosci.* **4** (1): 57–72.
7. Pitrosky B, et al. (1991) Effects of different doses and durations of melatonin infusions on plasma melatonin concentrations in pinealectomized Syrian hamsters: Consequences at the level of sexual activity. *J. Pineal Res.* **11** (3–4): 149–155.
8. Schuhler S, Pitrosky B, Kirsch R, Pévet P (2002) Entrainment of locomotor activity rhythm in pinealectomized adult Syrian hamsters by daily melatonin infusion. *Behav. Brain Res.* **133** (2): 343–350.
9. Bonmati-Carrion MA, et al. (2014) Protecting the melatonin rhythm through circadian healthy light exposure. *Int. J. Mol. Sci.* **15** (12): 23448–23500.
10. Reppert SM, et al. (1995) Molecular characterization of a second melatonin receptor expressed in human retina and brain: The Mel(1b) melatonin receptor. *Proc. Natl. Acad. Sci. USA* **92** (19): 8734–8738.
11. Dubocovich ML, Yun K, Al-Ghoul WM, Benloucif S, Masana MI (1998) Selective MT2 melatonin receptor antagonists block melatonin-mediated phase advances of circadian rhythms. *FASEB J.* **12** (12): 1211–1220.
12. Nosjean O, et al. (2000) Identification of the melatonin-binding site MT3 as the quinone reductase 2. *J. Biol. Chem.* **275** (40): 31311–31317.
13. Ebisawa T, Karne S, Lerner MR, Reppert SM (1994) Expression cloning of a high-affinity melatonin receptor from *Xenopus* dermal melanophores. *Proc. Natl. Acad. Sci. USA* **91** (13): 6133–6137.
14. Liu J, et al. (2015) MT 1 and MT 2 melatonin receptors: a therapeutic perspective. *Annu. Rev. Pharmacol. Toxicol.* **56** (1): 361–383.
15. Ferry G, et al. (2010) Old and new inhibitors of quinone reductase 2. *Chem. Biol. Interact.* **186** (2): 103–109.
16. Levoye A, et al. (2006) The orphan GPR50 receptor specifically inhibits MT1 melatonin receptor function through heterodimerization. *EMBO J.* **25** (13): 3012–3023.
17. Baba K, et al. (2013) Heteromeric MT1/MT2 melatonin receptors modulate photoreceptor function. *Sci. Signal.* **6** (296): ra89.
18. Kamal M, et al. (2015) Convergence of melatonin and serotonin (5-HT) signaling at MT2/5-HT2C receptor heteromers. *J. Biol. Chem.* **290** (18): 11537–11546.
19. Hardeland R, Madrid JA, Tan DX, Reiter RJ (2012) Melatonin, the circadian multioscillator system and health: The need for detailed analyses of peripheral melatonin signaling. *J. Pineal Res.* **52** (2):139–166.

20. Venegas C, et al. (2012) Extrapineal melatonin: Analysis of its subcellular distribution and daily fluctuations. *J. Pineal Res.* **52** (2): 217–227.
21. Bubenik GA (2002) Gastrointestinal melatonin: Localization, function, and clinical relevance. *Dig. Dis. Sci.* **47** (10): 2336–2348.
22. Balzer I, Hardeland R (1991) Photoperiodism and effects of indoleamines in a unicellular alga, *Gonyaulax polyedra*. *Science* **253** (5021): 795–797.
23. Tan DX, Chen L-D, Poeggeler B, Manchester LC, Reiter RJ (1993) Melatonin: a potent, endogenous hydroxyl radical scavenger. *Endocr. J.* **1**:57–60.
24. Reiter RJ, et al. (2003) Melatonin: detoxification of oxygen and nitrogen-based toxic reactants. *Adv. Exp. Med. Biol.* **527**: 539–348.
25. Galano A, Tan DX, Reiter RJ (2011) Melatonin as a natural ally against oxidative stress: A physicochemical examination. *J. Pineal Res.* **51** (1):1–16.
26. Manchester LC, et al. (2015) Melatonin: An ancient molecule that makes oxygen metabolically tolerable. *J. Pineal Res.* **59** (4):403–419.
27. Sainz RM, et al. (2000) Changes in lipid peroxidation during pregnancy and after delivery in rats: Effect of pinealectomy. *J. Reprod. Fertil.* **119** (1): 143-149.
28. García JJ, et al. (2014) Protective effects of melatonin in reducing oxidative stress and in preserving the fluidity of biological membranes: A review. *J. Pineal Res.* **56** (3): 225–237.
29. Mayo JC, Tan D-X, Sainz RM, Lopez-Burillo S, Reiter RJ (2003) Oxidative damage to catalase induced by peroxy radicals: functional protection by melatonin and other antioxidants. *Free Radic. Res.* **37** (5): 543–553.
30. Tan DX, et al. (1993) The pineal hormone melatonin inhibits DNA-adduct formation induced by the chemical carcinogen safrole in vivo. *Cancer Lett.* **70** (1–2): 65–71.
31. Tan DX, et al. (1994) Both physiological and pharmacological levels of melatonin reduce DNA adduct formation induced by the carcinogen safrole. *Carcinogenesis* **15** (2): 215–218.
32. Pappolla MA, et al. (1999) Alzheimer β protein mediated oxidative damage of mitochondrial DNA: Prevention by melatonin. *J. Pineal Res.* **27** (4): 226–229.
33. Tan DX, Manchester LC, Terron MP, Flores LJ, Reiter RJ (2007) One molecule, many derivatives: A never-ending interaction of melatonin with reactive oxygen and nitrogen species? *J. Pineal Res.* **42** (1): 28–42.
34. Abe M, Reiter RJ, Orhii PB, Hara M, Poeggeler B (1994) Inhibitory effect of melatonin on cataract formation in newborn rats: Evidence for an antioxidative role for melatonin. *J. Pineal Res.* **17** (2): 94–100.
35. Mayo JC, et al. (2002) Melatonin regulation of antioxidant enzyme gene expression. *Cell Mol. Life Sci.* **59** (10): 1706–1713.
36. Chen Y, et al. (2015) Melatonin protects hepatocytes against bile acid-induced mitochondrial oxidative stress via the AMPK-SIRT3-SOD2 pathway. *Free Radic. Res.* **49** (10): 1275–1284.
37. Choi S Il, Dadakhujaev S, Ryu H, Im Kim T, Kim EK (2011) Melatonin protects against oxidative stress in granular corneal dystrophy type 2 corneal fibroblasts by mechanisms that involve membrane melatonin receptors. *J. Pineal Res.* **51** (1):94–103.
38. Wang J, et al. (2015) Clock-controlled StAR's expression and corticosterone production contribute to the endotoxemia immune response. *Chronobiol. Int.* **32** (3):358-367. doi: 10.3109/07420528.
39. Hevia D, et al. (2008) Melatonin uptake in prostate cancer cells: Intracellular transport versus simple passive diffusion. *J. Pineal Res.* **45** (3):247–257.

40. Hevia D, Mayo JC, Quiros I, Gomez-Cordoves C, Sainz RM (2010) Monitoring intracellular melatonin levels in human prostate normal and cancer cells by HPLC. *Anal. Bioanal. Chem.* **397** (3):1235–1244.
41. Nguyen J, Wright KP (2010) Influence of weeks of circadian misalignment on leptin levels. *Nat. Sci. Sleep* **2**: 9–18.
42. Nduhirabandi F, Du Toit EF, Blackhurst D, Marais D, Lochner A (2011) Chronic melatonin consumption prevents obesity-related metabolic abnormalities and protects the heart against myocardial ischemia and reperfusion injury in a prediabetic model of diet-induced obesity. *J. Pineal Res.* **50** (2):171–182.
43. Agil A, *et al.* (2012) Melatonin improves glucose homeostasis in young Zucker diabetic fatty rats. *J. Pineal Res.* **52** (2): 203–210.
44. Karamitri A, Jockers R (2019) Melatonin in type 2 diabetes mellitus and obesity. *Nat. Rev. Endocrinol.* **15** (2):105-125. doi: 10.1038/s41574-018-0130-1.
45. Goyal A, *et al.* (2014) Melatonin supplementation to treat the metabolic syndrome: A randomized controlled trial. *Diabetol. Metab. Syndr.* **6** (1):124.
46. Amstrup AK, *et al.* (2016) Reduced fat mass and increased lean mass in response to 1 year of melatonin treatment in postmenopausal women: A randomized placebo-controlled trial. *Clin. Endocrinol. (Oxf)* **84** (3):342–347.
47. Buonfiglio D, *et al.* (2019) Removing melatonin receptor type 1 signaling leads to selective leptin resistance in the arcuate nucleus. *J. Pineal Res.* e: 12580.
48. Nogueira TC, *et al.* (2011) Absence of melatonin induces night-time hepatic insulin resistance and increased gluconeogenesis due to stimulation of nocturnal unfolded protein response. *Endocrinology* **152** (4): 1253–1263.
49. Sartori C, *et al.* (2009) Melatonin improves glucose homeostasis and endothelial vascular function in high-fat diet-fed insulin-resistant mice. *Endocrinology* **150** (12): 5311–5317.
50. Kadhim HM, *et al.* (2006) Effects of melatonin and zinc on lipid profile and renal function in type 2 diabetic patients poorly controlled with metformin. *J. Pineal Res.* **41** (2):189–193.
51. Zisapel N, *et al.* (2011) Efficacy and safety of prolonged-release melatonin in insomnia patients with diabetes: a randomized, double-blind, crossover study. *Diabetes Metab. Syndr. Obes. Targets Ther.* **4**: 307.
52. Contreras-Alcantara S, Baba K, Tosini G (2010) Removal of melatonin receptor type 1 induces insulin resistance in the mouse. *Obesity (Silver Spring)* **18** (9): 1861–1863.
53. Lyssenko V, *et al.* (2009) Common variant in MTNR1B associated with increased risk of type 2 diabetes and impaired early insulin secretion. *Nat. Genet.* **41** (1):82–88.
54. Bartsch C, *et al.* (1997) Nocturnal urinary 6-sulphatoxymelatonin excretion is decreased in primary breast cancer patients compared to age-matched controls and shows negative correlation with tumor-size. *J. Pineal Res.* **23** (2): 53–58.
55. Grin W, Grünberger W (1998) A significant correlation between melatonin deficiency and endometrial cancer. *Gynecol. Obstet. Invest.* **45** (1): 62–65.
56. Viswanathan AN, Schernhammer ES (2009) Circulating melatonin and the risk of breast and endometrial cancer in women. *Cancer Lett.* **281** (1): 1–7.
57. Bartsch C, *et al.* (2000) Serial transplants of DMBA-induced mammary tumors in Fischer rats as model system for human breast cancer: V. Myoepithelial-mesenchymal conversion during passaging as possible cause for modulation of pineal-tumor interaction. *Exp. Toxicol. Pathol.* **52** (2): 93–101.
58. Karasek M, Kowalski AJ, Suzin J, Zylinska K, Swietoslowski J (2005) Serum melatonin

- circadian profiles in women suffering from cervical cancer. *J. Pineal Res.* **39** (1): 73–76.
59. Schernhammer ES, Hankinson SE (2005) Urinary melatonin levels and breast cancer risk. *J. Natl. Cancer Inst.* **97** (14): 1084–1087.
 60. Reiter RJ, *et al.* (2007) Light at night, chronodisruption, melatonin suppression, and cancer risk: a review. *Crit. Rev. TM Oncog.* **13** (4): 303–328.
 61. Blask DE, Sauer L, Dauchy RT (2002) Melatonin as a chronobiotic/anticancer agent: cellular, biochemical, and molecular mechanisms of action and their implications for circadian-based cancer therapy. *Curr. Top. Med. Chem.* **2** (2):113–132.
 62. Mediavilla D, Sanchez-Barcelo MJ E, Tan DX, Manchester L, Reiter RJ (2011) Basic mechanisms involved in the anti-cancer effects of melatonin. *Curr. Med. Chem.* **17** (36): 4462–4481.
 63. Tan DX, *et al.* (2003) Melatonin: a hormone, a tissue factor, an autocoid, a paracoid, and an antioxidant vitamin. *J. Pineal Res.* **34** (1):75–78.
 64. Tan DX, *et al.* (1999) High physiological levels of melatonin in the bile of mammals. *Life Sci.* **65** (23): 2523–2529.
 65. Skinner DC, Malpoux B (1999) High melatonin concentrations in third ventricular cerebrospinal fluid are not due to Galen vein blood recirculating through the choroid plexus. *Endocrinology* **140** (10): 4399–4405.
 66. Tan DX, Manchester LC, Reiter RJ (2016) CSF generation by pineal gland results in a robust melatonin circadian rhythm in the third ventricle as an unique light/dark signal. *Med. Hypotheses* **86**: 3–9.
 67. Acuña-Castroviejo D, *et al.* (2014) Extrapineal melatonin: Sources, regulation, and potential functions. *Cell Mol. Life Sci.* **71** (16):2997–3025.
 68. Danielczyk K, Dziegiel P (2009) The expression of MT1 melatonin receptor and Ki-67 antigen in melanoma malignum. *Anticancer Res.* **29** (10): 3887–3895.
 69. Jablonska K, *et al.* (2013) Expression of melatonin receptor MT1 in cells of human invasive ductal breast carcinoma. *J. Pineal Res.* **54** (3): 334–345.
 70. Ying SW, Niles LP, Crocker C (1993) Human malignant melanoma cells express high-affinity receptors for melatonin: antiproliferative effects of melatonin and 6-chloromelatonin. *Eur. J. Pharmacol.* **246** (2): 89–96.
 71. Blask DE, *et al.* (1999) Melatonin inhibition of cancer growth in vivo involves suppression of tumor fatty acid metabolism via melatonin receptor-mediated signal transduction events. *Cancer Res.* **59** (18): 4693–4701.
 72. Blask DE, Hill SM (1986) Effects of melatonin on cancer: studies on MCF-7 human breast cancer cells in culture. *J. Neural. Transm. Suppl.* **21**: 433–449.
 73. Tam CW, *et al.* (2008) Melatonin as a negative mitogenic hormonal regulator of human prostate epithelial cell growth: Potential mechanisms and clinical significance. *J. Pineal Res.* **45** (4): 403–412.
 74. Xi SC, Siu SWF, Fong SW, Shiu SYW (2001) Inhibition of androgen-sensitive LNCaP prostate cancer growth in vivo by melatonin: Association of antiproliferative action of the pineal hormone with MT1 receptor protein expression. *Prostate* **46** (1): 52–61.
 75. Leja-Szpak A, *et al.* (2015) Kynuramines induce overexpression of heat shock proteins in pancreatic cancer cells via 5-hydroxytryptamine and MT1/MT2 receptors. *J. Physiol. Pharmacol.* **66** (5): 711–718.
 76. Pan Y, Niles LP (2015) Epigenetic mechanisms of melatonin action in human SH-SY5Y neuroblastoma cells. *Mol. Cell Endocrinol.* **402**: 57–63.
 77. Yuan L, Collins AR, Dai J, Dubocovich ML, Hill SM (2002) MT1 melatonin receptor

- overexpression enhances the growth suppressive effect of melatonin in human breast cancer cells. *Mol. Cell Endocrinol.* **192** (1–2): 147–156.
78. Mao L, *et al.* (2010) Inhibition of breast cancer cell invasion by melatonin is mediated through regulation of the p38 mitogen-activated protein kinase signaling pathway. *Breast Cancer Res.* **12** (6): R107.
 79. Treeck O, Haldar C, Ortmann O (2006) Antiestrogens modulate MT1 melatonin receptor expression in breast and ovarian cancer cell lines. *Oncol. Rep.* **15** (1): 231–235.
 80. Zonta YR, *et al.* (2017) Melatonin reduces angiogenesis in serous papillary ovarian carcinoma of ethanol-preferring rats. *Int. J. Mol. Sci.* **18** (4): 763.
 81. Chuffa LG de A, Reiter RJ, Lupi LA (2017) Melatonin as a promising agent to treat ovarian cancer: Molecular mechanisms. *Carcinogenesis* **38** (10):945–952.
 82. Akbarzadeh M, *et al.* (2017) The potential therapeutic effect of melatonin on human ovarian cancer by inhibition of invasion and migration of cancer stem cells. *Sci, Rep*, **7** (1):17062.
 83. Santoro R, Marani M, Blandino G, Muti P, Strano S (2012) Melatonin triggers p53Ser phosphorylation and prevents DNA damage accumulation. *Oncogene* **31** (24): 2931–2942.
 84. Santoro R, *et al.* (2013) Blockage of melatonin receptors impairs p53-mediated prevention of DNA damage accumulation. *Carcinogenesis* **34** (5):1051–1061.
 85. Marengo B, *et al.* (2016) Redox homeostasis and cellular antioxidant systems: Crucial players in cancer growth and therapy. *Oxid. Med. Cell Longev.* **2016**: 1–16.
 86. Holmström KM, Finkel T (2014) Cellular mechanisms and physiological consequences of redox-dependent signalling. *Nat. Rev. Mol. Cell Biol.* **15** (6): 411–421.
 87. Vijayalaxmi, Reiter RJ, Herman TS, Meltz ML (1998) Melatonin reduces gamma radiation-induced primary DNA damage in human blood lymphocytes. *Mutat. Res. Fundam. Mol. Mech. Mutagen* **397** (2):203–208.
 88. Cadenas S, Barja G (1999) Resveratrol, melatonin, vitamin E, and PBN protect against renal oxidative DNA damage induced by the kidney carcinogen KBrO₃. *Free Radic. Biol. Med.* **26** (11–12): 1531–1537.
 89. Sainz RM, *et al.* (2003) Antioxidant activity of melatonin in Chinese hamster ovarian cells: changes in cellular proliferation and differentiation. *Biochem. Biophys. Res. Commun.* **302** (3): 625–634.
 90. Sainz RM, *et al.* (2005) Melatonin reduces prostate cancer cell growth leading to neuroendocrine differentiation via a receptor and PKA independent mechanism. *Prostate* **63** (1): 29–43.
 91. Hevia D, *et al.* (2015) Melatonin uptake through glucose transporters: A new target for melatonin inhibition of cancer. *J. Pineal Res.* **58** (2): 234–250.
 92. Wang J, *et al.* (2012) Melatonin suppresses migration and invasion via inhibition of oxidative stress pathway in glioma cells. *J. Pineal Res.* **53** (2): 180–187.
 93. Ordoñez R, *et al.* (2014) Inhibition of matrix metalloproteinase-9 and nuclear factor kappa B contribute to melatonin prevention of motility and invasiveness in HepG2 liver cancer cells. *J. Pineal Res.* **56** (1): 20–30.
 94. Yeh CM, *et al.* (2016) Melatonin inhibits TPA-induced oral cancer cell migration by suppressing matrix metalloproteinase-9 activation through the histone acetylation. *Oncotarget* **7** (16): 21952–21967.
 95. Rudra DS, Pal U, Maiti NC, Reiter RJ, Swarnakar S (2013) Melatonin inhibits matrix metalloproteinase-9 activity by binding to its active site. *J. Pineal Res.* **54** (4): 398–405.
 96. Trivedi PP, Jena GB, Tikoo KB, Kumar V (2016) Melatonin modulated autophagy and

- Nrf2 signaling pathways in mice with colitis-associated colon carcinogenesis. *Mol. Carcinog.* **55** (3):255–267.
97. Reiter RJ, Tan D-X, Sainz RM, Mayo JC, Lopez-Burillo S (2002) Melatonin: reducing the toxicity and increasing the efficacy of drugs. *J. Pharm. Pharmacol.* **54** (10): 1299–321.
 98. Kelland L (2007) The resurgence of platinum-based cancer chemotherapy. *Nat. Rev. Cancer* **7** (8): 573–584.
 99. Jang H, *et al.* (2016) Melatonin prevents cisplatin-induced primordial follicle loss via suppression of PTEN/AKT/FOXO3a pathway activation in the mouse ovary. *J. Pineal Res.* **60** (3): 336–347.
 100. Rapozzi V, *et al.* (1998) Melatonin decreases bone marrow and lymphatic toxicity of adriamycin in mice bearing TLX5 lymphoma. *Life Sci.* **63** (19): 1701–1713.
 101. Kim C, *et al.* (2005) Modulation by melatonin of the cardiotoxic and antitumor activities of adriamycin. *J. Cardiovasc. Pharmacol.* **46** (2): 200–210.
 102. Öz E, Erbaş D, Sürücü HS, Düzgün E (2006) Prevention of doxorubicin-induced cardiotoxicity by melatonin. *Mol. Cell Biochem.* **282** (1–2): 31–37.
 103. Govender J, Loos B, Marais E, Engelbrecht AM (2014) Mitochondrial catastrophe during doxorubicin-induced cardiotoxicity: A review of the protective role of melatonin. *J. Pineal Res.* **57** (4): 367–380.
 104. Pariente R, Pariente JA, Rodríguez AB, Espino J (2016) Melatonin sensitizes human cervical cancer HeLa cells to cisplatin-induced cytotoxicity and apoptosis: Effects on oxidative stress and DNA fragmentation. *J. Pineal Res.* **60** (1): 55–64.
 105. Uguz AC, *et al.* (2012) Melatonin potentiates chemotherapy-induced cytotoxicity and apoptosis in rat pancreatic tumor cells. *J. Pineal Res.* **53** (1): 91–98.
 106. Hevia D, Mayo JC, Tan DX, Rodriguez-Garcia A, Sainz RM (2014) Melatonin enhances photo-oxidation of 2',7'-dichlorodihydrofluorescein by an antioxidant reaction that renders N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK). *PLoS One* **9** (10): e109257.
 107. Rasola A, Bernardi P (2014) The mitochondrial permeability transition pore and its adaptive responses in tumor cells. *Cell Calcium.* **56** (6):437–445.
 108. Li W, *et al.* (2015) Melatonin induces cell apoptosis in AGS cells through the activation of JNK and P38 MAPK and the suppression of nuclear Factor-Kappa B: A novel therapeutic implication for gastric cancer. *Cell Physiol. Biochem.* **37** (6): 2323–2338.
 109. Sainz RM, *et al.* (2008) Critical role of glutathione in melatonin enhancement of tumor necrosis factor and ionizing radiation-induced apoptosis in prostate cancer cells in vitro. *J. Pineal Res.* **45** (3): 258–270.
 110. Shen HM, Tergaonkar V (2009) NFκB signaling in carcinogenesis and as a potential molecular target for cancer therapy. *Apoptosis* **14** (4): 348–363.
 111. Ben-Neriah Y, Karin M (2011) Inflammation meets cancer, with NF-κB as the matchmaker. *Nat. Immunol.* **12** (8):715–723.
 112. Surcel CI, *et al.* (2015) Prognostic effect of neuroendocrine differentiation in prostate cancer: A critical review. *Urol. Oncol. Semin. Orig. Investig.* **33** (6): 265.e1-265.e7.
 113. Rodriguez-Garcia A, *et al.* (2013) Phenotypic changes caused by melatonin increased sensitivity of prostate cancer cells to cytokine-induced apoptosis. *J. Pineal Res.* **54** (1): 33–45.
 114. Hardeland R (2018) Melatonin and retinoid orphan receptors: Demand for new interpretations after their exclusion as nuclear melatonin receptors. *Melatonin Res.* **1** (1): 78–93.

115. Danforth DN, Tamarkin L, Lippman ME (1983) Melatonin increases oestrogen receptor binding activity of human breast cancer cells. *Nature* **305** (5932): 323–325.
116. Hill SM, Blask DE (1988) Effects of the pineal hormone melatonin on the proliferation and morphological characteristics of human breast cancer cells (MCF-7) in culture. *Cancer Res.* **48** (21):6121–6126.
117. Wilson ST, Blask DE, Lemus-Wilson AM (1992) Melatonin augments the sensitivity of MCF-7 human breast cancer cells to tamoxifen in vitro. *J. Clin. Endocrinol. Metab.* **75** (2): 669–670.
118. Cos S1, Fernández R, Güézmés A, Sánchez-Barceló EJ (1998) Influence of melatonin on invasive and metastatic properties of MCF-7 human breast cancer cells. *Cancer Res.* **58** (19):4383–4390.
119. Cos S, Mediavilla MD, Fernández R, González-Lamuño D, Sánchez-Barceló EJ (2002) Does melatonin induce apoptosis in MCF-7 human breast cancer cells in vitro? *J. Pineal Res.* **32** (2): 90–96.
120. Alvarez-García V, González A, Alonso-González C, Martínez-Campa C, Cos S (2013) Regulation of vascular endothelial growth factor by melatonin in human breast cancer cells. *J. Pineal Res.* **54** (4): 373–380.
121. Cos S, Martínez-Campa C, Mediavilla MD, Sánchez-Barceló EJ (2005) Melatonin modulates aromatase activity in MCF-7 human breast cancer cells. *J. Pineal Res.* **38** (2): 136–142.
122. Proietti S, *et al.* (2014) Melatonin down-regulates MDM2 gene expression and enhances p53 acetylation in MCF-7 cells. *J. Pineal Res.* **57** (1): 120–129.
123. El-Sokkary GH, Ismail IA, Saber SH (2019) Melatonin inhibits breast cancer cell invasion through modulating DJ-1/KLF17/ID-1 signaling pathway. *J. Cell Biochem.* **120** (3):3945–3957.
124. Czczuga-Semeniuk E, *et al.* (2002) Effect of melatonin and all-trans retinoic acid on the proliferation and induction of the apoptotic pathway in the culture of human breast cancer cell line MCF-7. *Pol. J. Pathol.* **53** (2): 59–65.
125. Margheri M, *et al.* (2012) Combined effects of melatonin and all-trans retinoic acid and somatostatin on breast cancer cell proliferation and death: molecular basis for the anticancer effect of these molecules. *Eur. J. Pharmacol.* **681** (1–3): 34–43.
126. Soto-Vega E, Meza I, Ramírez-Rodríguez G, Benitez-King G (2004) Melatonin stimulates calmodulin phosphorylation by protein kinase C. *J. Pineal Res.* **37** (2): 98–106.
127. Benítez-King G, Soto-Vega E, Ramírez-Rodríguez G (2009) Melatonin modulates microfilament phenotypes in epithelial cells: implications for adhesion and inhibition of cancer cell migration. *Histol. Histopathol.* **24** (6): 789–799.
128. Koşar PA, Nazıroğlu M, Övey İS, Çiğ B (2016) Synergic Effects of Doxorubicin and Melatonin on Apoptosis and Mitochondrial Oxidative Stress in MCF-7 Breast Cancer Cells: Involvement of TRPV1 Channels. *J. Membr. Biol.* **249** (1–2): 129–140.
129. Nooshinfar E, *et al.* (2016) Melatonin promotes ATO-induced apoptosis in MCF-7 cells: Proposing novel therapeutic potential for breast cancer. *Biomed. Pharmacother.* **83**: 456–465.
130. Alonso-González C, *et al.* (2018) Melatonin enhances the apoptotic effects and modulates the changes in gene expression induced by docetaxel in MCF-7 human breast cancer cells. *Int. J. Oncol.* **52** (2): 560–570.
131. Wenzel U, Nickel A, Daniel H (2005) Melatonin potentiates flavone-induced apoptosis in human colon cancer cells by increasing the level of glycolytic end products. *Int. J.*

- Cancer* **116** (2): 236–242.
132. González-Puga C, *et al.* (2005) Selective CCK-A but not CCK-B receptor antagonists inhibit HT-29 cell proliferation: Synergism with pharmacological levels of melatonin. *J. Pineal Res.* **39** (3): 243–250.
 133. García-Navarro A, *et al.* (2007) Cellular mechanisms involved in the melatonin inhibition of HT-29 human colon cancer cell proliferation in culture. *J. Pineal Res.* **43** (2): 195–205.
 134. Pariente R, Bejarano I, Espino J, Rodríguez AB, Pariente JA (2017) Participation of MT3 melatonin receptors in the synergistic effect of melatonin on cytotoxic and apoptotic actions evoked by chemotherapeutics. *Cancer Chemother. Pharmacol.* **80** (5):985–998.
 135. Espino J, *et al.* (2018) Melatonin increases the effect of 5-fluorouracil-based chemotherapy in human colorectal adenocarcinoma cells in vitro. *Mol. Cell Biochem.* **440** (1–2): 43–51.
 136. Kontek R, Jakubczak M, Matlawska-Wasowska K (2014) The antioxidants, vitamin A and E but not vitamin C and melatonin enhance the proapoptotic effects of irinotecan in cancer cells in vitro. *Toxicol. Vitro.* **28** (2): 282–291.
 137. Wang H, *et al.* (2013) Sodium arsenite induces cyclooxygenase-2 expression in human uroepithelial cells through MAPK pathway activation and reactive oxygen species induction. *Toxicol. Vitro.* **27** (3): 1043–1048.
 138. Hong Y, *et al.* (2014) Melatonin treatment induces interplay of apoptosis, autophagy, and senescence in human colorectal cancer cells. *J. Pineal Res.* **56** (3): 264–274.
 139. Batista APC, *et al.* (2014) Ultrastructural aspects of melatonin cytotoxicity on Caco-2 cells in vitro. *Micron.* **59**: 17–23.
 140. Zou D-B, *et al.* (2015) Melatonin inhibits the Migration of Colon Cancer RKO cells by Down-regulating Myosin Light Chain Kinase Expression through Cross-talk with p38 MAPK. *Asian Pac. J. Cancer Prev.* **16** (14): 5835–5842.
 141. Yun CW, Kim S, Lee JH, Lee SH (2018) Melatonin promotes apoptosis of colorectal cancer cells via superoxide-mediated or stress by inhibiting cellular prion protein expression. *Anticancer Res.* **38** (7): 3951–3960.
 142. Tam CHT, *et al.* (2010) Common polymorphisms in MTNR1B, G6PC2 and GCK are associated with increased fasting plasma glucose and impaired beta-cell function in Chinese subjects. *PLoS One* **5** (7): e11428.
 143. Granzotto M, Rapozzi V, Decorti G, Giraldi T (2001) Effects of melatonin on doxorubicin cytotoxicity in sensitive and pleiotropically resistant tumor cells. *J. Pineal Res.* **31** (3):206–213.
 144. Rubio S, *et al.* (2007) Inhibition of proliferation and induction of apoptosis by melatonin in human myeloid HL-60 cells. *J. Pineal Res.* **42** (2): 131–138.
 145. Bejarano I, *et al.* (2011) Pro-oxidant effect of melatonin in tumour leucocytes: Relation with its cytotoxic and pro-apoptotic effects. *Basic. Clin. Pharmacol. Toxicol.* **108** (1): 14–20.
 146. Krestinina O, *et al.* (2018) Melatonin can strengthen the effect of retinoic acid in HL-60 cells. *Int. J. Mol. Sci.* **19** (10): 2873.
 147. Jang SS, Kim WD, Park WY (2009) Melatonin exerts differential actions on X-ray radiation-induced apoptosis in normal mice splenocytes and Jurkat leukemia cells. *J. Pineal Res.* **47** (2): 147–155.
 148. Sánchez-Hidalgo M, Lee M, de la Lastra CA, Guerrero JM, Packham G (2012) Melatonin inhibits cell proliferation and induces caspase activation and apoptosis in

- human malignant lymphoid cell lines. *J. Pineal Res.* **53** (4): 366–373.
149. Zhelev Z, Ivanova D, Bakalova R, Aoki I, Higashi T (2017) Synergistic cytotoxicity of melatonin and new-generation anticancer drugs against leukemia lymphocytes but not normal lymphocytes. *Anticancer Res.* **37** (1): 149–159.
 150. Büyükcavci M, Özdemir Ö, Buck S, Ravindranath Y, Savaşan S (2011) Effect of melatonin on the cytotoxicity of chemotherapeutic drugs in human leukemia cells. *In Vivo (Brooklyn)* **25** (3): 405–409.
 151. Perdomo J, et al. (2013) Melatonin induces apoptosis through a caspase-dependent but reactive oxygen species-independent mechanism in human leukemia Molt-3 cells. *J. Pineal. Res.* **55** (2): 195–206.
 152. Quintana C, et al. (2016) Melatonin enhances hyperthermia-induced apoptotic cell death in human leukemia cells. *J. Pineal Res.* **61** (3): 381–395.
 153. Kikuchi Y, Kita T, Miyauchi M, Iwano I, Kato K (1989) Inhibition of human ovarian cancer cell proliferation in vitro by neuroendocrine hormones. *Gynecol. Oncol.* **32** (1): 60–64.
 154. Shellard SA, Whelan R, Hill BT (1989) Growth inhibitory and cytotoxic effects of melatonin and its metabolites on human tumour cell lines in vitro. *Br. J. Cancer* **60** (3): 288–290.
 155. Futagami M, Sato S, Sakamoto T, Yokoyama Y, Saito Y (2001) Effects of melatonin on the proliferation and cis-diamminedichloroplatinum (CDDP) sensitivity of cultured human ovarian cancer cells. *Gynecol. Oncol.* **82**(3): 544–549.
 156. Kim J-H, et al. (2012) Melatonin synergistically enhances cisplatin-induced apoptosis via the dephosphorylation of ERK/p90 ribosomal S6 kinase/heat shock protein 27 in SK-OV-3 cells. *J. Pineal Res.* **52** (2): 244–252.
 157. Akbarzadeh M, et al. (2016) Effects of combination of melatonin and laser irradiation on ovarian cancer cells and endothelial lineage viability. *Lasers Med. Sci.* **31** (8): 1565–1572.
 158. Shen CJ, Chang CC, Chen YT, Lai CS, Hsu YC (2016) Melatonin suppresses the growth of ovarian cancer cell lines (OVCAR-429 and PA-1) and potentiates the effect of G1 arrest by targeting CDKs. *Int. J. Mol. Sci.* **17** (2):176.
 159. Zemła A, Grzegorek I, Dzięgiel P, Jabłońska K (2017) Melatonin Synergizes the Chemotherapeutic Effect of Cisplatin in Ovarian Cancer Cells Independently of MT1 Melatonin Receptors. *In Vivo* **31** (5): 801–809.
 160. Ataei N, Aghaei M, Panjehpour M (2018) The protective role of melatonin in cadmium-induced proliferation of ovarian cancer cells. *Res. Pharm. Sci.* **13** (2): 159–167.
 161. Fic M, et al. (2007) Effect of melatonin on cytotoxicity of doxorubicin toward selected cell lines (human keratinocytes, lung cancer cell line A-549, laryngeal cancer cell line HEp-2). *In Vivo (Brooklyn)* **21** (3): 513–518.
 162. Kim W, Jeong JW, Kim JE (2014) CCAR2 deficiency augments genotoxic stress-induced apoptosis in the presence of melatonin in non-small cell lung cancer cells. *Tumor. Biol.* **35** (11): 10919–10929.
 163. Fan C, et al. (2015) HDAC1 inhibition by melatonin leads to suppression of lung adenocarcinoma cells via induction of oxidative stress and activation of apoptotic pathways. *J. Pineal Res.* **59** (3): 321–333.
 164. Lu JJ, et al. (2016) Melatonin inhibits AP-2 β /hTERT, NF- κ B/COX-2 and Akt/ERK and activates caspase/Cyto C signaling to enhance the antitumor activity of berberine in lung cancer cells. *Oncotarget* **7** (3): 2985–3001.
 165. Yun M, et al. (2014) Melatonin Sensitizes H1975 Non-Small-Cell Lung Cancer Cells

- Harboring a T790M-Targeted Epidermal Growth Factor Receptor Mutation to the Tyrosine Kinase Inhibitor Gefitinib. *Cell Physiol. Biochem.* **34** (3): 865–872.
166. Plaimee P, Khamphio M, Weerapreeyakul N, Barusrux S, Johns NP (2014) Immunomodulatory effect of melatonin in SK-LU-1 human lung adenocarcinoma cells co-cultured with peripheral blood mononuclear cells. *Cell Prolif.* **47** (5): 406–415.
 167. Plaimee P, Weerapreeyakul N, Barusrux S, Johns NP (2015) Melatonin potentiates cisplatin-induced apoptosis and cell cycle arrest in human lung adenocarcinoma cells. *Cell Prolif.* **48** (1): 67–77.
 168. Joo SS, Yoo YM (2009) Melatonin induces apoptotic death in LNCaP cells via p38 and JNK pathways: Therapeutic implications for prostate cancer. *J. Pineal Res.* **47** (1): 8–14.
 169. Franco DG, Moretti IF, Marie SKN (2018) Mitochondria transcription factor a: A putative target for the effect of melatonin on U87MG malignant glioma cell line. *Molecules* **23** (5): 1129.
 170. Kocyigit A, Guler EM, Karatas E, Caglar H, Bulut H (2018) Dose-dependent proliferative and cytotoxic effects of melatonin on human epidermoid carcinoma and normal skin fibroblast cells. *Mutat, Res. Genet. Toxicol. Environ. Mutagen* **829–830**: 50–60.
 171. Zou ZW, *et al.* (2018) Melatonin suppresses thyroid cancer growth and overcomes radioresistance via inhibition of p65 phosphorylation and induction of ROS. *Redox. Biol.* **16**: 226–236.
 172. Song J, *et al.* (2018) Melatonin induces the apoptosis and inhibits the proliferation of human gastric cancer cells via blockade of the AKT/MDM2 pathway. *Oncol. Rep.* **39** (4):1975–1983.
 173. Zhu C, Huang Q, Zhu H (2018) Melatonin Inhibits the Proliferation of Gastric Cancer Cells Through Regulating the miR-16-5p-Smad3 Pathway. *DNA Cell Biol.* **37** (3): 244–252.
 174. Shen Y-QQ, *et al.* (2018) Combination of melatonin and rapamycin for head and neck cancer therapy: Suppression of AKT/mTOR pathway activation, and activation of mitophagy and apoptosis via mitochondrial function regulation. *J. Pineal Res.* **64** (3): e12461.
 175. Halliwell B (2006) Reactive species and antioxidants. Redox biology is a fundamental theme of aerobic life. *Plant Physiol.* **141** (2): 312–322.
 176. Murphy MP (2009) How mitochondria produce reactive oxygen species. *Biochem. J.* **417** (1): 1–13.
 177. Lin MT, Beal MF (2006) Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature* **443** (7113): 787–795.
 178. Nunnari J, Suomalainen A (2012) Mitochondria: In sickness and in health. *Cell* **148** (6): 1145–1159.
 179. Tan DX, Reiter RJ (2019) Mitochondria: the birth place, battle ground and the site of melatonin metabolism in cells. *Melatonin Res.* **2** (1):44–66.
 180. Reiter RJ, *et al.* (2017) Melatonin as a mitochondria-targeted antioxidant: one of evolution’s best ideas. *Cell Mol. Life Sci.* **74** (21): 3863–3881.
 181. Suofu Y, *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** (38): E7997–E8006.
 182. Wang L, *et al.* (2017) Plant mitochondria synthesize melatonin and enhance the tolerance of plants to drought stress. *J. Pineal Res.* **63** (3): e12429.

183. He C, *et al.* (2016) Mitochondria synthesize melatonin to ameliorate its function and improve mice oocyte's quality under in vitro conditions. *Int. J. Mol. Sci.* **17** (6):939.
184. Yang M, *et al.* (2019) AANAT knockdown and melatonin supplementation in embryo development: involvement of mitochondrial function and dna methylation. *Antioxidants Redox. Signal.* **30** (18): 2050–2065.
185. Zheng X, *et al.* (2017) Chloroplastic biosynthesis of melatonin and its involvement in protection of plants from salt stress. *Sci. Rep.* **7** (1): 41236.
186. Sainz RM, *et al.* (2003) Melatonin and cell death: Differential actions on apoptosis in normal and cancer cells. *Cell Mol. Life Sci.* **60** (7): 1407–1426.
187. Lee CS, Park SY, Ko HH, Han ES (2004) Effect of change in cellular GSH levels on mitochondrial damage and cell viability loss due to mitomycin c in small cell lung cancer cells. *Biochem. Pharmacol.* **68** (9): 1857–1867.
188. Song N, *et al.* (2012) Melatonin suppresses doxorubicin-induced premature senescence of A549 lung cancer cells by ameliorating mitochondrial dysfunction. *J. Pineal Res.* **53** (4): 335–343.
189. Delbridge ARD, Strasser A (2015) The BCL-2 protein family, BH3-mimetics and cancer therapy. *Cell Death Differ.* **22** (7): 1071–1080.
190. Kong H, Chandel NS (2018) Regulation of redox balance in cancer and T cells. *J. Biol. Chem.* **293** (20): 7499–7507.
191. Proietti S, Cucina A, Minini M, Bizzarri M (2017) Melatonin, mitochondria, and the cancer cell. *Cell Mol. Life Sci.* **74** (21): 4015–4025.
192. de Almeida Chuffa LG, *et al.* (2019) Mitochondrial functions and melatonin: a tour of the reproductive cancers. *Cell Mol. Life Sci.* **76** (5): 837–863.
193. Hevia D, *et al.* (2017) Melatonin decreases glucose metabolism in prostate cancer cells: A ¹³C stable isotope-resolved metabolomic study. *Int. J. Mol. Sci.* **18** (8): 1620.
194. Mao L, *et al.* (2016) Melatonin suppression of aerobic glycolysis (Warburg effect), survival signalling and metastasis in human leiomyosarcoma. *J. Pineal Res.* **60** (2): 167–177.
195. Yu Z, *et al.* (2018) Mitochondrial cytochrome P450 (CYP) 1B1 is responsible for melatonin-induced apoptosis in neural cancer cells. *J. Pineal Res.* **65** (1): e12478.
196. Waseem M, *et al.* (2017) Melatonin pre-treatment mitigates SHSY-5Y cells against oxaliplatin induced mitochondrial stress and apoptotic cell death. *PLoS One* **12** (7): e0180953.
197. Huo X, *et al.* (2017) Human transporters, PEPT1/2, facilitate melatonin transportation into mitochondria of cancer cells: An implication of the therapeutic potential. *J. Pineal Res.* **62** (4): e12390.
198. Mayo JC, *et al.* (2017) IGFBP3 and MAPK/ERK signaling mediates melatonin-induced antitumor activity in prostate cancer. *J. Pineal Res.* **62** (1): 1–17.
199. Yang CY, *et al.* (2017) Melatonin exerts anti-oral cancer effect via suppressing LSD1 in patient-derived tumor xenograft models. *Oncotarget* **8** (20): 33756–33769.
200. Cavallo F, De Giovanni C, Nanni P, Forni G, Lollini PL (2011) 2011: The immune hallmarks of cancer. *Cancer Immunol. Immunother.* **60** (3): 319–326.
201. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: The next generation. *Cell* **144** (5): 646–674.
202. Weinhouse S, Warburg O, Burk D, Schade AL (1956) On respiratory impairment in cancer cells. *Science* **124** (3215): 267–272.
203. Warburg O (1964) Prefatory Chapter. *Annu. Rev. Biochem.* **33** (1): 1–15.
204. Pavlova NN, Thompson CB (2016) The Emerging Hallmarks of Cancer Metabolism.

- Cell Metab.* **23** (1): 27–47.
205. Thompson CB (2011) Rethinking the regulation of cellular metabolism. *Cold Spring Harb Symp. Quant. Biol.* **76**: 23–29.
 206. Barthel A, *et al.* (1999) Regulation of GLUT1 gene transcription by the serine/threonine kinase AKT1. *J. Biol. Chem.* **274** (29): 20281–20286.
 207. Murakami T, *et al.* (1992) Identification of two enhancer elements in the gene encoding the type 1 glucose transporter from the mouse which are responsive to serum, growth factor, and oncogenes. *J. Biol. Chem.* **267** (13): 9300–9306.
 208. Wang R, *et al.* (2011) The Transcription Factor Myc Controls Metabolic Reprogramming upon T Lymphocyte Activation. *Immunity* **35** (6): 871–882.
 209. Reynolds MR, *et al.* (2014) Control of glutamine metabolism by the tumor suppressor Rb. *Oncogene* **33** (5): 556–566.
 210. Koppenol WH, Bounds PL, Dang C V. (2011) Otto Warburg’s contributions to current concepts of cancer metabolism. *Nat. Rev. Cancer* **11** (5): 325–337.
 211. Warburg O (1956) On the origin of cancer cells. *Science* **123** (3191): 309–314.
 212. Heiden MG Vander, Cantley LC, Thompson CB (2009) Understanding the warburg effect: The metabolic requirements of cell proliferation. *Science* **324** (5930):1029–1033.
 213. DeBerardinis RJ, Lum JJ, Hatzivassiliou G, Thompson CB (2008) The Biology of cancer: metabolic reprogramming fuels cell growth and proliferation. *Cell Metab.* **7** (1): 11–20.
 214. Ward PS, Thompson CB (2012) Metabolic reprogramming: a cancer hallmark even Warburg did not anticipate. *Cancer Cell* **21** (3): 297–308.
 215. Wellen KE, Thompson CB (2012) A two-way street: Reciprocal regulation of metabolism and signalling. *Nat. Rev. Mol. Cell Biol.* **13** (4): 270–276.
 216. Dauchy RT, *et al.* (2014) Circadian and melatonin disruption by exposure to light at night drives intrinsic resistance to tamoxifen therapy in breast cancer. *Cancer Res.* **74** (15): 4099–4110.
 217. Xiang S, *et al.* (2015) Doxorubicin resistance in breast cancer is driven by light at night-induced disruption of the circadian melatonin signal. *J. Pineal Res.* **59** (1): 60–69.
 218. Sanchez-Sanchez AM, *et al.* (2015) Melatonin cytotoxicity is associated to Warburg effect inhibition in Ewing sarcoma cells. *PLoS One* **10** (8): e0135420.
 219. Gobbo MG, *et al.* (2015) Influence of melatonin on the proliferative and apoptotic responses of the prostate under normal and hyperglycemic conditions. *J. Diabetes Res.* **2015**: 538529.



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