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,

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 N^1-acetyl-N^2-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 inconsistence 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 a 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 ^{125}iodomelatonin 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 inconsistence 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 calls. However, the combination of cisplatin and melatonin did not modulate any signaling pathway related to the toxicity of cisplantin 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 *per se*/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 promyeolocytic leukemia cells	1mM	Induces apoptosis	↓BCL2↑BAX; MT1-independent	(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, ROS-independent	(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/ ERα expression	(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 O_2 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 bellow. 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 seemly 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/TNFα, 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 O_2 uptake were increased in the mid-dark phase in vehicle-treated dLEN rats compared with vehicle-treated rats. Similarly, tumor glucose and O_2 uptake increased more than 3 times in dLEN rats. Interestingly melatonin alone reduced both glucose and O_2 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 ± 0.5 µg/min/g vs 1.6 ± 0.1 µg/min/g). Likewise, and maybe consequently, melatonin reduced the production of lactate (27.3 ± 1.1 vs 10.40.4 nmol/min/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 reprograming 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 O_2 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 O_2 uptake up to 66% compared with vehicle or doxorubicin-treated rats. This data confirmed previous work and shows how melatonin, by reducing glucose and O_2 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 O_2 by tumor cells and the production of lactate and CO_2. 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 ^{13}C 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 ^{13}C-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).

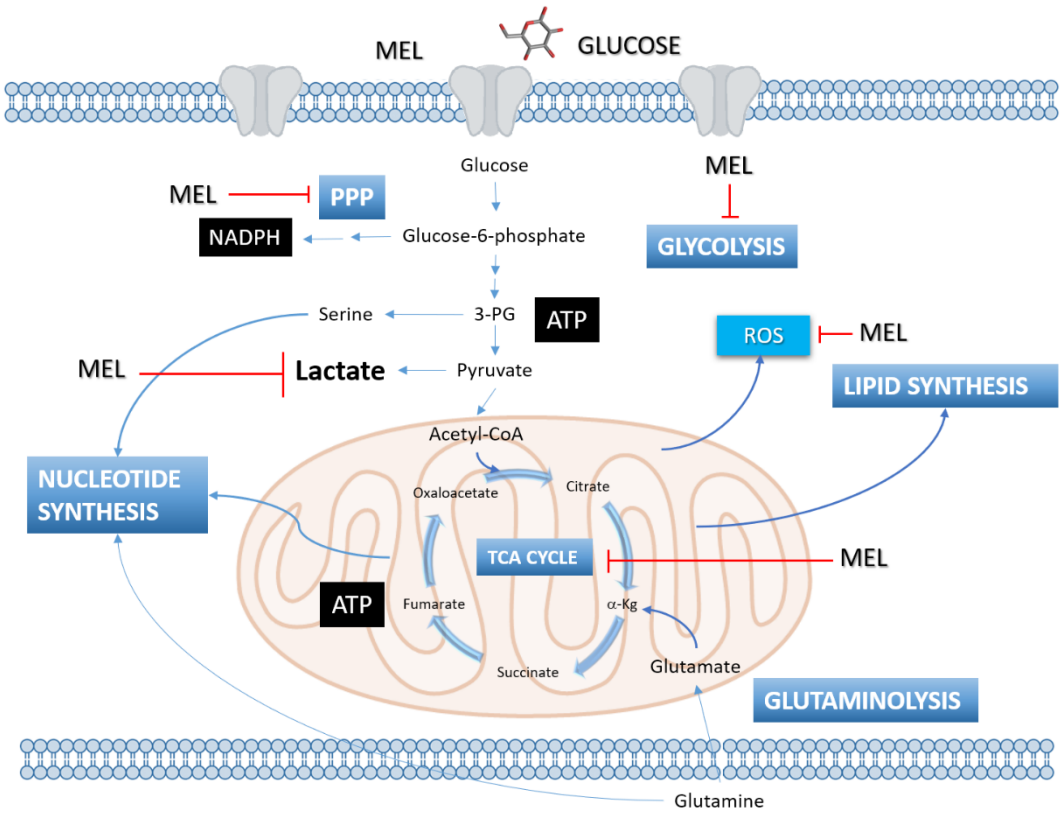

Fig. 1: The potential mechanisms that melatonin blocks the uptake of glucose in prostate cancer cells.

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 13C-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

crosstalk 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.

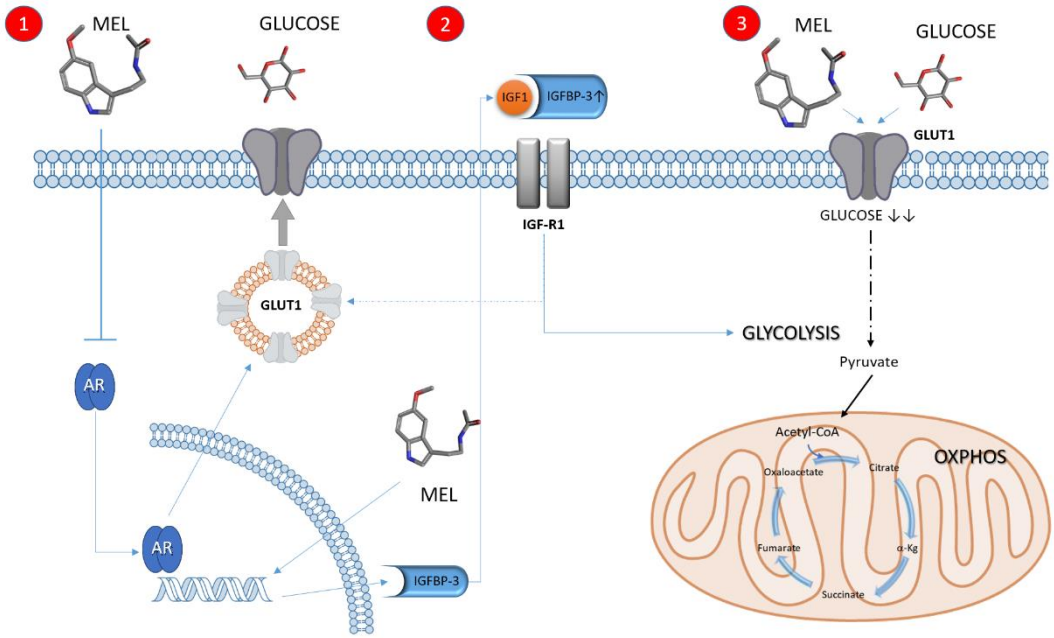

Fig. 2: Three different glucose-dependent mechanisms that likely meditate melatonin antiproliferative activity.

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

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