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Circadian and non-circadian melatonin: influences on glucose metabolism in cancer cells

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Abstract

This review considers the role of melatonin as an oncostatic agent and particularly as to how it relates to the mechanisms by which melatonin regulates glucose metabolism in cancer cells. Many tumor cells adopt a means of glucose utilization that is different from that of healthy cells. Thus, these cancer cells rapidly take up and metabolize glucose and after it is converted to pyruvate, they accelerate the production of lactate which is abundantly released into the circulation. The change in metabolism that cancer cells makes is referred to as aerobic glycolysis. The switch to aerobic glycolysis affords cancer cells major advantages in terms of an accelerated rate of ATP production and the synthesis of abundant molecular building blocks required for rapid proliferation, invasion, and metastasis. In normal cells, the bulk of the pyruvate formed is shunted into the mitochondria for conversion to acetyl-CoA. Melatonin is both produced and released in a circadian manner from the pineal gland and likely by the mitochondria of all normal cells in a non-circadian manner. In cancer cells, melatonin forces them to abandon aerobic glycolysis and function phenotypically as a normal cell by upregulating the enzyme, pyruvate dehydrogenase complex, that catalyzes pyruvate to acetyl-CoA; this is presumably achieved by the direct or indirect inhibition of pyruvate dehydrogenase kinase, which normally downregulates pyruvate dehydrogenase complex. By depriving cancer cells of aerobic glycolysis, melatonin reverts them to a normal cell phenotype thereby reducing the rapid cell proliferation and aggressive nature of cancer cells.

Keywords: *aerobic glycolysis, angiogenesis, cancer metastasis, glucose metabolism, Hypoxia inducible factor-1α, pyruvate dehydrogenase kinase*

Introduction

The unusually wide distribution and vast functional diversity of melatonin likely greatly exceeds what was envisaged by those working in the field just two decades ago. Melatonin is a highly conserved molecule that is present in ancient prokaryotes and possibly in all eukaryotic plant and animal cells. While its initial function is presumed to have been that as an antioxidant (Tan et al., 2013; Zhao et al., 2019) it broadened its physiological repertoire during evolution to the point where it is difficult to identify cellular functions in which it is not somehow involved (Reiter et al., 2010, 2020a; Tordjman et al., 2017; Majidinia et al., 2018; Prado et al., 2018; Cardinali 2019; Mortezaee et al., 2019). In the current review, we only address the role of melatonin in solid tumors that manifest the Warburg effect in which the cancer cells favor cytosolic glycolysis instead of mitochondrial oxidative phosphorylation (Schwartz et al., 2017). Glucose, the major macronutrient of all cells, is utilized for energy production in the form of ATP when it is oxidized. One common cytosolic end product of glucose oxidation is pyruvate, which in normal cells, enters the mitochondria where during respiration it is converted to CO_2. Rapidly growing and proliferating tumor cells hijack those processes by preventing pyruvate metabolism in mitochondria; rather they convert pyruvate to lactate in the cytosol (Liberti & Locasale 2016; Xu et al., 2015). The rate of glucose uptake and the production of lactate are strikingly elevated in cancer cells. Reducing the impact of mitochondrial glucose oxidation affords cancer cells advantages which they use to enhance their ability to overgrow or proliferate and to become invasive and metastatic.

Two pools of melatonin: releasable (circadian) and non-releasable (non-circadian)

For decades it was assumed that melatonin was exclusively a biosynthetic product of the vertebrate pineal gland. However, after its discovery in unicells (Poeggeler & Hardeland 1994) and in plants (Dubbels et al., 1995; Hattori et al., 1995), organisms that do not have a pineal, it was apparent that relegating melatonin synthesis only to this gland was clearly an error. Even in vertebrates, melatonin was eventually identified in organs other than the pineal, and the blood levels were not diminished when the pineal gland was removed (Bubenik 1980; Acuna-Castroviejo et al., 2014). Subsequently, melatonin was identified in the mitochondria of rodent brain and liver cells where, as in the gut, its levels are not depressed by surgical removal of the pineal (Venegas et al., 2012).

Because of these findings, in 2013 we proposed that mitochondria and chloroplasts are subcellular sites of melatonin production and, therefore, it occurs in every animal and plant cell (Tan et al., 2013). That mitochondria and chloroplasts are the factories for melatonin synthesis was also based on the observation that a primitive prokaryote, i.e., a bacterium, was identified as containing immunoreactive melatonin (Manchester et al., 1995).

The endosymbiotic theory surmises that mitochondria and chloroplasts originated bacteria that already produced melatonin that were phagocytized by early eukaryotes (Gabaldon, 2018). During the subsequent evolution of more complex eukaryotes, the synthetic melatonin activity of these organelles was retained such that animals and plants that currently exist as well as those that have become extinct all do/had synthesized melatonin (Figure 1). In this scheme, alphaproteobacteria would have been the precursors of mitochondria while photosynthetic cyanobacteria developed into chloroplasts. Verification of melatonin synthesis in both mitochondria (He et al., 2016; Suofu et al., 2017); and chloroplasts (Back et al., 2016; Choi et al., 2017; Lee et al., 2017; Zheng et al., 2017) has been forthcoming in the last several years.

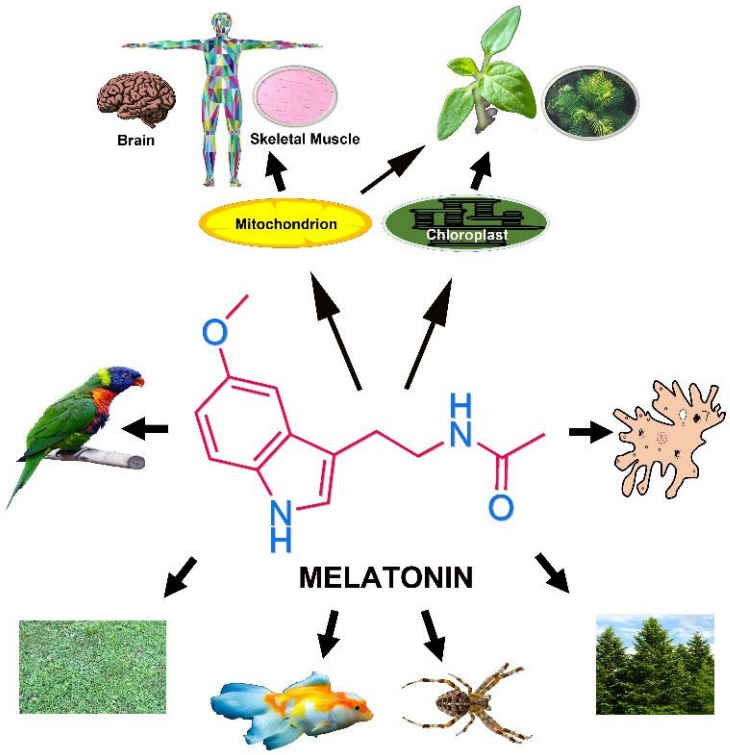

Figure 1 This figure illustrates the presumed universal presence of melatonin in the animal and plant kingdoms. Given that melatonin is believed to have evolved in prokaryotic bacteria which, after their engulfment by early eukaryotes, eventually became mitochondria and chloroplasts, all extinct and currently-surviving organisms had/do generate melatonin in every mitochondria/chloroplast-containing cell.

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Even though melatonin is manufactured in every cell, only the pineal gland is capable of discharging this product into the cerebrospinal fluid (CSF) and blood with the primary route of secretion probably being into the third ventricular CSF at least for its regulation of the biological clock (Tricoire et al., 2002; Reiter et al., 2014). In every species tested, pinealectomy lowers blood melatonin levels to near zero. Why only pinealocytes are capable of releasing melatonin into body fluids while other cells are not has yet to be determined.

These differences allow for the classification of two pools of melatonin, i.e., a releasable (circadian) pool and a non-releasable (non-circadian) pool (Figure 2). The light:dark dependent circadian variations in CSF/blood melatonin levels are derived from the pineal gland and impact all circadian genes in every cell in vertebrates. Conversely, the non-releasable pool is concerned with the metabolism of the cell in which it is produced and, possibly via a paracrine means, of adjacent cells. For example, melatonin released from the mucosal cells of the duodenum induces the liberation of bicarbonate ions from adjacent mucosal cells (Sjoblom & Flemstrom, 2001). Likewise, in the retina, locally-generated melatonin influences dopamine metabolism and, even though retinal melatonin exhibits a rhythm similar to that in the pineal, it never escapes into the systemic circulation (Dubocovich 1984; Zawilska 1994). The non-releasable melatonin pool does not enter the CSF or blood and is not circadian in its production.

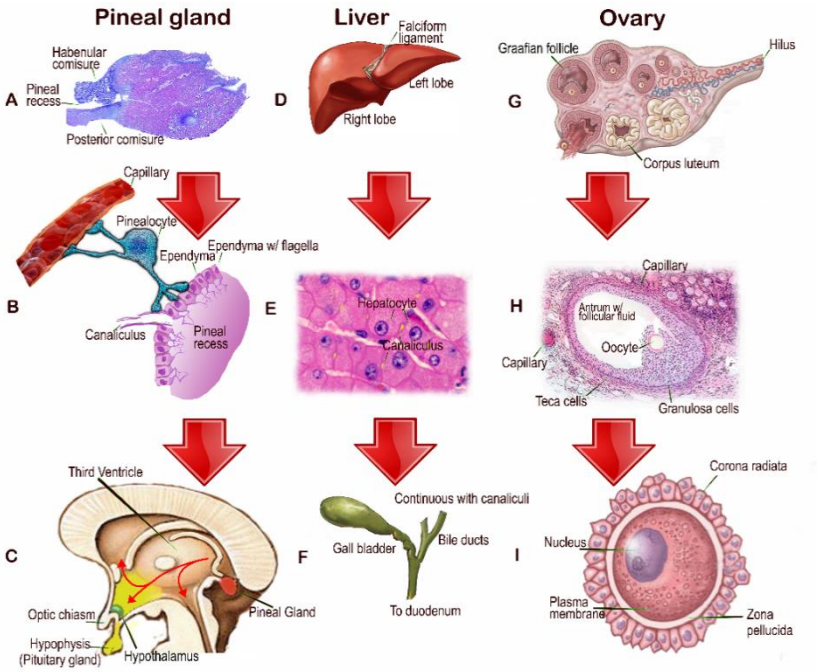

Figure 2 Examples of the releasable and non-releasable pools of melatonin are represented in this figure. The pineal gland (A) of mammals is the only tissue that liberates melatonin into the cerebrospinal fluid (CSF) and blood; this is the only releasable melatonin. This may be assisted by the presence of canaliculi, non-endothelial lined spaces between adjacent pinealocytes, which eventually connect to the third ventricle (B) (Reiter et al., 2014). Via the CSF, melatonin influences the seasonal reproductive responses of photosensitive animals and mediates its effects on circadian biology (C). The non-releasable pool is represented here by the liver and ovary, but also includes every cell in the organism, all of which synthesize melatonin intracellularly as well as possibly discharging it into the local cellular microenvironment where it has autocrine and paracrine actions without ever entering the general circulation (Reiter et al., 2020a). Canaliculi also exist between adjacent hepatocytes (E) by which melatonin may eventually drain into the bile in the biliary tree (F); the bile concentration of melatonin is exceptionally high (Tan et al., 1999). All ovarian cells, including the granulosa cells and the oocyte itself synthesize melatonin, from which it may leak (or be released) into the ovarian follicular fluid (H); again, however, melatonin produced in the ovarian or any tissue other than the pineal gland does not enter the blood. The non-releasable pool of melatonin has many regulatory actions in the cell in which it is produced as illustrated in this review.

The light:dark cycle and cancer cell mitochondrial dysregulation

Many solid tumors (Courtnay et al., 2015; Abdel-Wahab et al., 2019) and some other pathological tissues (Atlante et al., 2017; Burns & Manda 2017) abandon mitochondrial glucose metabolism and ATP production in favor of cytosolic aerobic glycolysis, a phenomenon known as the Warburg effect. This change enhances the growth and invasive potential of these cancers and aids in tumor growth (Liberti & Locasale 2016; Vaupel et al., 2019). As a result of this switch, glucose uptake is markedly accelerated due to stimulation of the glucose transporter, GLUT1, in the cell membrane (Mayo et al., 2019) and its associated conversion to pyruvate. Additionally, the pentose phosphate pathway is highly activated which contributes to the production of the necessary nucleotides, etc., required for the expedited cellular proliferation (Yamamoto et al., 2018; Jin & Zhou, 2019). These and other changes are depicted in Figure 3.

Recent studies indicate that melatonin from both the releasable and non-releasable pool may negate the Warburg effect (Reiter & Rosales-Corral 2019; Reiter et al., 2019; Puente-Moncada et al., 2020). In the studies in question, numerous endpoints indicative of cancer cell metabolism, i.e., rapid glucose uptake and lactic acid secretion, linoleic acid entrance into the cells and its conversion to the mitogenic molecule, 13-hydroxyoctadecanoic acid (13-HODE), 3H-thymidine incorporation into DNA, etc., all exhibited marked day:night differences (Blask et al., 2014). These reports included investigation of three different types of cancer xenotypes that were grown subcutaneously in immune-compromised rodents (Blask et al., 2014; Mao et al., 2016; Dauchy et al., 2018). During the day, the tumors were clearly metabolically highly active and underwent Warburg-type metabolism. Conversely, at night, they deserted aerobic glycolysis and adopted a conventional normal cell activity. Thus, in the day, these tumors functioned with a cancer phenotype while at night they displayed a normal metabolic phenotype (Reiter et al., 2019). To the best of our knowledge, no such circadian rhythm had been reported for any solid tumor type, possibly related to the fact that rarely is experimental cancer metabolism investigated at night and, moreover, cultured cancer cells would not display such fluctuations (Reiter et al., 2020b).

In these studies, the tumor-bearing animals had been kept under a strict light:dark cycle and when their blood melatonin levels were measured over the 24-hour period, daytime levels were uniformly low (associated with intensified cancer metabolism) while the dark period was accompanied by the usual large surge in blood melatonin concentrations (when the cancer cells exhibited a more normal-type metabolism) (Blask et al., 2014; Mao et al., 2016). The authors then anticipated that the shift in metabolic type may be related to the differential day:night melatonin concentrations given that melatonin already had a long history as an oncostatic agent (Hill et al., 2015; Li et al., 2017).

When the nocturnally-elevated blood melatonin levels were subdued by contaminating the dark period with a low light intensity where the melatonin rhythm persisted but at a greatly attenuated level, the cancer cell metabolic endpoints remained highly elevated throughout the 24-hour period and tumor growth was advanced (Blask et al., 2014). Thus, extinguishing the large day:night difference in circulating melatonin clearly related to a more active tumor metabolism and provided a likely explanation for the view that light pollution exaggerates the frequency or growth of human cancers, especially breast cancer (Sanchez-Barcelo et al., 2012; Hill et al., 2015).

While the findings that melatonin suppression caused an enhancement of the metabolic features, as predicted from the disturbed uptake and secretion of several metabolites by the tumors (Blask et al., 2014), little evidence was provided concerning the changed intracellular mechanisms that would account for the exaggerated metabolism. It was obvious, however, that the presence or absence of melatonin impacted aerobic glycolysis of the tumors (high uptake of glucose and elevated lactate secretion).

Melatonin reverses aerobic glycolysis in cancer cells

Based on the findings of Blask et al. (2014), Mao and colleagues (2016), and Dauchy and coworkers (2018), we proposed that melatonin functions like some other drugs (Sutendra & Michelakis 2013; Reiter & Rosales-Corral 2019; Reiter et al., 2019, 2020b), the so-called glycolytics, that are known to influence aerobic glycolysis in cancer cells. As envisioned, melatonin either directly or indirectly interferes

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with the ability of pyruvate dehydrogenase kinase (PDK) to suppress pyruvate dehydrogenase complex (PDC) which interrupts the conversion of pyruvate to acetyl-CoA in the mitochondria. The activation of PDK is well known to downregulate PDC, thereby causing cells to adopt cytosolic aerobic glycolysis as a means of ATP and metabolite production required to meet the energy demands of the rapidly proliferating tumor cells (Chen et al., 2009; Dang, 2012) (Figure 3).

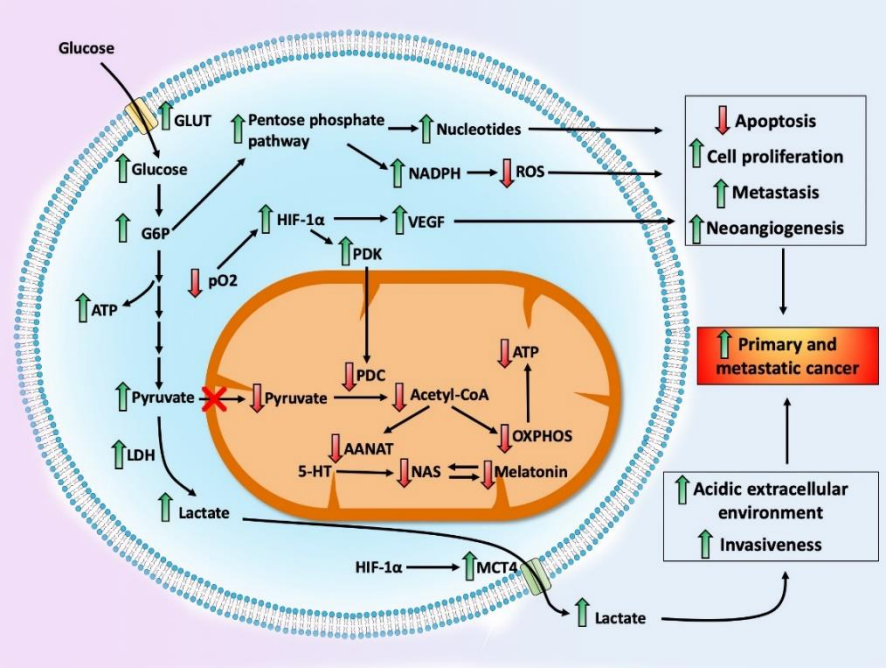

Figure 3 This figure illustrates the disrupted metabolism that occurs in the mitochondria of solid tumor cells. The changes involve a shift to glucose oxidation from the mitochondria to the cytosol, a process referred to as aerobic glycolysis or the Warburg effect. When rapidly dividing tumor cells are deprived of an ample oxygen supply (pO_2), hypoxia inducible factor (HIF-1α) is activated which promotes a number of changes including upregulation of inwardly-directed glucose transporter (GLUT) and the outwardly-directed monocarboxylate transporter (MCT4). This allows the rapid influx of glucose and its metabolism to pyruvate. In normal cells, much of the pyruvate formed enters the mitochondria to be converted to acetyl-CoA. In cancer cells, however, this process is stalemated (red X) because the enzyme that metabolizes pyruvate to acetyl-CoA, i.e., pyruvate dehydrogenase complex (PDC), is downregulated. As a result, cytosolic pyruvate undergoes conversion to lactic acid with the lactate, which is abundantly released via the MCT4, leading to the acidification of the local extracellular microenvironment (Balkwill et al., 2012). The activated HIF-1α also upregulates the gatekeeper enzyme, pyruvate dehydrogenase kinase (PDK), which downregulates pyruvate dehydrogenase complex (PDC) accounting for the interruption of the mitochondrial pyruvate to acetyl-CoA conversion. Moreover, HIF-1α promotes vascular endothelial growth factor (VEGF) which hastens blood vessel growth into the tumor ensuring an improved O_2 and nutrient supply and a route for cancer cell metastasis. To ensure adequate molecular building blocks for the rapid cell proliferation, the pentose phosphate pathway enhances nucleotide production and the generation of the reducing agent, nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), which neutralizes reactive oxygen species (ROS) that could kill cancer cells. In the mitochondria, the reduced production of acetyl-CoA diminishes the citric acid cycle and eventually oxidative phosphorylation (OXPHOS) with a lowered mitochondrial energy (ATP) production. Rather ATP is derived from its production in the cytosol and although the yield of ATP is reduced when this occurs, its synthesis is very rapid thus compensating for the loss of mitochondrial ATP. Finally, inadequate mitochondrial acetyl-CoA limits intramitochondrial melatonin production since acetyl-CoA is a necessary co-factor for the rate limiting enzyme in melatonin synthesis, arylalkylamine N-acetyltransferase (AANAT) which metabolizes serotonin (5-HT) to N-acetylserotonin (NAS), the immediate precursor of melatonin (Reiter et al., 2019). The loss of mitochondrial melatonin compromises other metabolic processes in this organelle, e.g., optimal function of SIRT3 (not shown). The boxed items on the right identify some of the consequences of the altered metabolism experienced by cancer cells along with the resulting elevation in primary and secondary cancer. In normal cells the blockade of the transfer of pyruvate into the mitochondria is lifted and PDC is not downregulated, so the metabolism of pyruvate to acetyl-CoA is ensured. Thus, all PDC downstream events in the mitochondria function differently in normal cells compared to cancer cells.

The scheme we proposed would require the suppression of PDK which would alleviate the inactivation of PDC permitting pyruvate to be enzymatically transformed into acetyl-CoA in mitochondria thereby reversing the Warburg effect (Reiter et al., 2019, 2020b). PDK is under control of several transcription factors which support its upregulation (Park et al., 2018). The most noteworthy of these is hypoxia-inducible factor 1α (HIF-1α) which not only exaggerates the activity of PDK but also stimulates the glucose membrane transporters (GLUTs), the activity of lactate dehydrogenase (LDH) and the excretion of lactate via the monocarboxylate transporter (MCT4) (Bensiger & Christofk 2012; Zhang et al., 2013). Melatonin, in a number of experimental situations, is a proven HIF-1α modulator. Melatonin treatment of ethanol-preferring rats that suffered with serous papillary carcinoma reduced HIF-1α level in the tumors (Zonta et al., 2017). Also, HIF-1α is known to be stabilized in an oxidizing environment and melatonin, as a potent scavenger of reactive oxygen species (ROS) (Reiter et al., 2016; Tan & Reiter 2019), would destabilize this factor limiting its ability to deactivate PDC (Park et al., 2010). Under other experimental conditions as well, melatonin has been repeatedly proven to be an inhibitor of HIF-1α (Dai et al., 2008; Cho et al., 2011; Lai et al., 2017; Lima Mota 2016). Based on the evidence thus far accumulated, HIF-1α suppression by melatonin is a means by which it could regulate PDK/PDC interactions and influence glycose metabolism in cancer cells as proposed (Reiter et al., 2019, 2020b).

Other regulators that influence cancer cell metabolism which melatonin sways also have been identified. MYC oncogene over expression leads to cellular changes compatible with supporting aerobic glycolysis; thus, like HIF-1α, it regulates PDK, the glucose membrane transporters and, additionally, LDH which augments the enzymatic conversion of pyruvate to lactate (Dang et al., 2008) (Figure. 3). MYC and LDH are known melatonin targets under some experimental conditions (Sanchez-Sanchez et al., 2015).

Anderson (2019) and Anderson and Reiter (2019) have speculated as to additional processes by which melatonin may regulate the PDK/PDC axis and mitochondrial metabolism. In this expanded scheme, which would fit with the currently-available information, this idea suggests the potential involvement of the aryl hydrocarbon receptor, the chaperone protein 14-3-3, microRNAs and the reversed metabolism of melatonin to N-acetylserotonin (NAS) by P4501B1. Accordingly, NAS and/or the NAS/melatonin ratio may determine mitochondrial metabolism.

Beyond the ability of melatonin to correct cancer cell mitochondrial metabolism via HIF-1α inhibition, several reports have shown that the regulatory actions of melatonin extend to other processes that interfere with cancer cell growth (Prieto-Dominguez et al., 2016; Chuffa et al., 2019; Oliveiro et al., 2016). Using hepatocellular carcinoma cells (114G2), they examined the impact of melatonin on HIF-1α and VEGF proteins, both of which advance angiogenesis in growing tumors. Under conditions of hypoxia, melatonin curtailed the expression of both proangiogenic factors. These findings are particularly important in that blood vessel growth into growing cancers helps in their nutrient support and provides an avenue for metastasis. Two other groups also found that melatonin interferes with the activation of HIF-1α under hypoxic conditions to curb endothelial growth and blood vessel formation (Park et al., 2010; Carbajo-Pescador et al., 2013). Other processes that may bypass HIF-1α inhibition by melatonin that also block cancer growth metastasis have been described (Su et al., 2017; Goncalvas Ndo et al., 2016; Marques et al., 2018).

Releasable versus non-releasable melatonin pool in regulating cancer cell glucose metabolism

As summarized above, there are two pools (circadian and non-circadian) of melatonin both of which may influence glucose metabolism in cancer cell mitochondria by mechanisms involving PDK inhibitions and upregulation of PDC. Mitochondrial melatonin synthesis uses the same enzymes as in the pineal gland. Thus, tryptophan is metabolized to serotonin (5-HT) which, via a two-step process is converted to melatonin utilizing two enzymes, aryl alkyl N-acetyltransferase (AANAT) and acetylserotonin methyltransferase (ASMT) (Ganguly et al., 2002).

Acetyl-CoA, however, also is a necessary co-factor/substrate for the rate limiting enzyme, AANAT, in melatonin synthesis. Since cancer cells have a limited transfer of pyruvate into mitochondria and its conversion to acetyl-CoA,

this organelle is deprived of the required co-factor to support the acetylation of 5-HT thereby preventing melatonin synthesis (Reiter et al., 2019, 2020b). Thus, since cancer cell mitochondria lack the melatonin-producing capacity, the circadian regulation of Warburg metabolism as reported by Blask and coworkers (2014) is likely a consequence releasable melatonin derived from the pineal gland (Reiter et al., 2019) and taken up by the cancer cells (Mocayar-Maron et al., 2019). In contrast, in normal cells where mitochondrial acetyl-CoA is abundant, local melatonin synthesis occurs unabated as indicated by the uniformly high mitochondrial melatonin concentrations throughout a light:dark cycle (Venegas et al., 2012; Suofu et al., 2017). A final implication of this is that while normal cell mitochondria have an ample supply of melatonin, mitochondria of cancer cells may be deficient in this important molecule (Reiter et al., 2019, 2020b) (Figure. 3). Given melatonin's substantial oncostatic activity, its reduction in cancer cells could be a major contribution to cell proliferation and metastasis (Huo et al., 2017).

Conclusions

Melatonin is a documented oncostatic agent against a wide variety of experimental cancer types, e.g., breast, prostate, pancreatic, colorectal, oral, lung, gastric, cervical, etc. (Courtnay et al., 2015). The recent demonstration of melatonin synthesis in mitochondria may have a direct bearing on its ability to modulate both the progression and metastasis of cancer. The means by which melatonin reduces cancer involves, as with some other agents, its ability to overcome aerobic glycolysis (the Warburg effect) as considered herein and elsewhere (Reiter et al., 2019; 2020b). Reversing the Warburg effect redirects pyruvate, the product of glycolysis, to the mitochondria for its conversion to acetyl-CoA. In doing so, exogenously administered melatonin not only negates cancer cell growth and chemoresistance, but also assures acetyl-CoA production which feeds into the citric acid cycle which, in turn, enhances oxidative phosphorylation and ATP synthesis. Thus, melatonin transforms cancer cells into a more normal cell phenotype.

By improving acetyl-CoA synthesis in mitochondria, when blood melatonin (either pineal-derived or exogenously administered) enters mitochondria, it also supports intramitochondrial melatonin production since acetyl-CoA is a required co-factor for the rate limiting enzyme in melatonin synthesis. A necessary corollary of this is that while healthy cell mitochondria produce melatonin, these organelles of cancer cells presumably are incapable of doing so at least during the day (Reiter et al., 2019). This loss of mitochondrial melatonin in cancer cells may well contribute to their ability to rapidly proliferate, invade and metastasize. Similarly, during aging when melatonin levels typically drop (presumably including melatonin levels in both the releasable and non-releasable pool, an elevated propensity for cancer initiation, progression and metastasis would be anticipated (Almohammed et al., 2020; Lee et al., 2020).

The means by which melatonin enhance the conversion of pyruvate to acetyl-CoA likely stems from its direct or indirect inhibition of HIF-1α. HIF-1α, which is upregulated in cancer cells due to hypoxia, normally stimulates the gatekeeper enzyme, PDK, which downregulates PDC causing the failure of acetyl-CoA production. These mechanisms deserve careful investigation to identify how it relates to the oncostatic functions of melatonin.

Finally, increased age is often associated with a significant reduction in endogenous melatonin production; conversely, many cancer types increase in frequency in the elderly. That these two events are functionally linked is not an absolute imperative but, based on currently available data, it is worthy of consideration. Moreover, thought should be given to the idea that vitamin D, a molecule produced during the day, and melatonin, the chemical expression of darkness, functionally interact to maintain healthy mitochondria and reduce the risk of cancer (and other age-related diseases) (Mocayar-Maron et al., 2020).

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