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Signalling Pathways Targeted by Melatonin in Cancer. A Short Review

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Introduction

Melatonin is a small indolamine principally produced in vertebrates by the pineal gland and released in the bloodstream. Melatonin shows a sharp peak of secretion at night, delivering the circadian message to the organism. In humans, it has several mechanisms of action, through its binding to G protein coupled melatonin receptors including circadian rhythm control, sleep cycle and many aspects of cancer inhibition. Melatonin also exerts receptor-independent functions, such as detoxification of free radicals, protecting key molecules from oxidative stress under conditions of ischemia, drug toxicity or ionizing radiation [1].

Melatonin interferes with cancer at all the phases of the illness: initiation, progression and spreading from the primary focus. Surprisingly, many molecular mechanisms have been proposed to explain its inhibitory actions [2]. Initially, most of the studies addressing the oncostatic actions of melatonin were performed in animal models undergoing chemically-induced mammary tumors and also in estrogen responsive human breast cancer cell lines. In this particular case, the anti-proliferative effect of the pineal hormone can be explained in terms of estrogen synthesis inhibition and interference with the estrogen-signaling pathways since melatonin has both SERM (selective estrogen receptor modulator) and SEEM (selective estrogen enzyme modulator) properties [3].

The value of melatonin as an adjuvant molecule to be combined with either chemotherapy or radiotherapy has been tested in cancer patients dealing with solid tumors at advanced stages of disease. The main conclusion was that this indoleamine restrains tumor development and growth, shows significant improvements in tumor remission, 1 and 5 years survival and importantly, ameliorates the undesirable side effects consequence of chemotherapy and radiotherapy [4,5]. In the past few years, the number of published articles supporting the oncostatic role of melatonin on experimental models of a variety of cancers is growing exponentially [6]. Many hormone-independent cancer types, such as leukemia, glioblastoma, ovarian, prostate, gastric, esophageal, colon, pancreas, hepatic and lung cancers have been shown to be susceptible to inhibition by melatonin when the pineal hormone is administered either alone or combined with either radiotherapy or chemotherapy. Practically all the results reported have been positive, and melatonin has been described as an inhibitor of tumor growth under both *in vitro* and *in vivo* experimental conditions. Melatonin has anti-proliferative actions in ovarian [7], prostate [8], gastric [9], colon [10], pancreatic [11], hepatic [12], lung [13], leukemia [14] and glioblastoma cancers [15]. Several mechanisms of action of melatonin have been proposed to explain how the pineal hormone achieves its anti-cancer effects. Among them, the most important are: modulation of signaling transduction pathways triggered by melatonin binding to the MT-1 and MT-2 cell membrane receptors, expressed in many normal tissues and cancer cells [16]. Melatonin also exerts anti-oxidant effects, controlling the production of reactive oxygen species modulating the intracellular free radical stress and therefore determining the progression of the tumor. For example, it has been described that melatonin, through its role as a direct scavenger of radical oxygen and nitrogen species (ROS and RNS) and also through activation of antioxidant enzymes, can effectively protect the pancreatic tissue against oxidative stress and inflammatory damage [11]. The protective role of melatonin as an anti-oxidant agent has been characterized in detail in other cancer types. Thus, in H4IIE hepatoma cells, H_2O_2-induced activation of the extracellular signal-regulated protein kinases ERK1/2 and p38 MAPK, and some of their downstream protein effectors, were strongly weakened by melatonin, as well as H_2O_2-induced phosphorylation of Akt and the Akt substrate mTOR,

and eIF4E-binding protein 1 (4E-BP1), mainly via preventing Ras activation. The main conclusion was that melatonin is able to triggered different protective mechanisms against ROS induced damage in hepatoma cells, preventing many of the H_2O_2-induced alterations in the MAPK and mTOR signaling pathways through inhibition of Ras [17].

Tumor angiogenesis, the formation of new vessels from preexisting vasculature in conditions of hypoxia, supports expansion of the tumor mass and is an event essential during progression of cancer. The value of melatonin as an antiagiogenic molecule has been demonstrated in several models. In hepatocarcinoma HepG2 cells, melatonin at pharmacological concentrations induced a decrease in the secreted levels of VEGF, and also prevented HUVEC (endothelial cells) tube formation under hypoxia. Prevention of tube formation seems to be associated with a down-regulation of the hypoxia inducible factor HIF-1α [18]. The inhibition of angiogenesis by melatonin has also been described in animal models. In nude mice bearing gastric tumors, melatonin treatment reduced the expression of the melatonin nuclear receptor RZR/RORγ, SUMO-specific protease 1, HIF-1α and VEGF at transcriptional and translational levels [9].

Escape from apoptosis plays a crucial role in cancer progression. The anti apoptotic properties of melatonin have been reported in all the cancer types mentioned above [6]. The molecular changes triggered by the pineal hormone are similar; thus, melatonin positively regulates the expression of p53 and p21, Bax, Bad, caspases 3, 7 and 9, cyclin D1, and down-regulates the expression of anti-apoptotic proteins such as Bcl-2 or surviving and XIAP. For example, in human hepatocarcinoma HepG2 and SMMC-7721 cells, cIAP-1, survivin and XIAP, were related to the co-expression of COX-2. Melatonin decreased COX-2 expression and prevented Akt activation. These results indicate that melatonin overcomes apoptosis resistance via the COX-2/PI3K/AKT pathway [12,19]. Melatonin can also potentiate the apoptotic properties of diverse chemotherapeutic compounds. A study in hepato carcinoma cells demonstrated that melatonin synergistically augmented sorafenib-induced apoptosis, and this result is dependent on the activation of caspase-3 and the JNK/c-jun pathway [20].

Local invasion, the first stage prior to the development of secondary tumors or metastases is another aspect of cancer progression that can be regulated by melatonin. The pineal hormone exhibits anti-invasive and anti-metastatic properties in a variety of tumors by suppressing the enzymatic activity of MMP-9. In HepG2 cells, pharmacological concentrations of melatonin impaired MMP-9 gelatinase activity and effectively blocked cell invasion and motility through a simultaneous down regulation of MMP-9 gene expression and up regulation of the MMP-9-specific inhibitor metalloproteinase (TIMP)-1 [21].

A part from all the effects in cancer cell proliferation, apoptosis, angiogenesis, invasion, it is becoming clear that melatonin co-administration improves the sensitivity of cancers to inhibition by conventional chemotherapeutic agents. One of the most striking recent findings described, concerning melatonin´s anti-cancer activity is its ability to transform cancers that are totally resistant to chemotherapeutic drugs to a sensitive to chemotherapy state. Thus, it has been recently reported that incubation with melatonin resulted in a marked increase in the cytotoxicity of clofarabine in leukemic resistant cells. Melatonin treatment induced higher levels of acetylation, which suggest that melatonin alters DNA accessibility via histone acetylation and relaxation of the chromatin structure, which could allow clofarabine to target the DNA more efficiently. The molecular mechanisms of clofarabine resistance probably include an ABCG2 over expression simultaneous to a decreased expression of dCKgene with methylated promoter regions. No changes in ABCG2 expression or any changes in methylation status in clofarabine-resistant cells where identified. However, acetylation of histone increases gene expression, which is known to be an epigenetic mechanism. This is the first report to find that histone deacetylation of the dCK promoter is responsible for the decreased expression of dCK in clofarabine-resistant leukemic cells [22]. As mentioned above, melatonin overcomes apoptosis resistance in hepatocarcinoma cells via the COX-2/PI3K/AKT pathway [12]. In several pancreatic tumor cell lines (AsPc-1, MiaPaCa-2 and Panc-28) and nude mice with pancreatic tumors bearing xenografts, melatonin enhanced the effects of gemcitabine on cell proliferation and invasion, action that was independent of melatonin membrane receptors. Mice treated simultaneously with both agents have greater reductions in tumor size compared to animals treated only with gemcitabine. The effect of melatonin seems to take account through a suppression of IKB-phosphorylation, which in turn results in an inhibition of NF-kB. Genes that respond to NF-kB show lover levels of expression and these molecular changes seem to reverse gemcitabine resistance in pancreatic tumors [23].

Conclusion

In summary, melatonin, through a variety of MT1 and MT2 dependent mechanisms, and melatonin receptor independent mechanisms, impairs cancer development and growth. It has become clear that melatonin exerts anti-proliferative actions, not only in hormone-dependent tumors, but also in practically all the tumors that have been tested. The anti-proliferative actions are accompanied by an apoptotic effect of the pineal hormone. Melatonin causes a delay in the cell cycle progression, restrains cancer invasion and inhibits signaling pathways leading to metastases. In agreement with this, it has been demonstrated for many kind of cancers that melatonin has anti-angiogenic effects. Finally, melatonin renders cancers resistant to chemotherapeutic agents to treatment sensitive, and enhances the cytotoxicity of most of the chemo drugs tested. The molecular targets up or down-regulated by melatonin participate in a variety or mechanisms and are similar in most of the tumor studied. Among them, there are cell cycle controllers, such as p21, p53 and cyclins; apoptosis regulators (Bcl2, Bax, Bad, surviving) and effectors (caspases 3, 7 and 9); kinases such as AKT or ERK; transcription

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factors (NF-kB) metalloproteinase (MMP9); cytokines (IL6, TNF α) and proteins implicated in angiogenesis such as VEGF. For all the reasons pointed above, melatonin is a molecule with a great potential to be considered in cancer therapy.

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