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, H₂O₂ 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 H₂O₂-induced phosphorylation of Akt and the Akt substrate mTOR,
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 dCK gene 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 IκB-phosphorylation, which in turn results in an inhibition of NF-kB. Genes that respond to NF-kB show lower 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 of 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 as AKT or ERK; transcription...
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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