

## Melatonin: Antiproliferative Actions, Protection of Normal Tissue and Enhancement of Radiosensitivity of Breast Cancer Cells

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### Opinion

Melatonin is a small indolamine produced in mammals by the pineal gland, which regulates the sleep-wake cycle in humans, transducing the changes of environmental lighting into a darkness production of melatonin. This hormone has several mechanisms of action involving receptor-dependent and receptor-independent functions. Among these last actions, we can cite melatonin's ability to protect the cells from oxidative stress under ischemia, drug toxicity and ionizing radiation [1].

It is well known that melatonin reduces tumor progression in animal models undergoing chemically-induced mammary tumors [2]. Also in human breast cancer cell lines (*in vitro* models), melatonin shows an oncostatic role on hormone-dependent tumors. Experimental evidence suggest that the antiproliferative action of melatonin on hormone-dependent breast cancer cells is based on its interaction with the synthesis of estrogens or interfering with the estrogen-signaling pathways [3,4]. The mechanisms involved in the inhibition of the tumoral growth are: i) down-regulation of the circulating levels of gonadal estrogens. ii) direct actions at the tumoral cell interfering with the activation of the estrogen receptor, therefore behaving as a SERM (selective estrogen receptor modulator) and iii) by regulating the enzymes involved in the biosynthesis of estrogens in peritumoral tissues thus behaving as a SEEM (Selective Estrogen Enzyme Modulator) [5]. Moreover, melatonin also exerts an important effect not only over the tumoral cells, but also in the tumor microenvironment by decreasing the secretion of cytokines by breast cancer cells, which regulates the differentiation and the aromatase expression and activity of fibroblasts and endothelial cells surrounding malignant cells [6]. Aromatase, Steroid sulfotransferase (STS) and 17 $\beta$ -Hydroxysteroid dehydrogenase type 1 (17 $\beta$ -HSD1) are key enzymes involved in estradiol formation in both normal and breast cancer cells. Therefore, aromatase inhibitors are in many cases administered in breast cancer treatment together with radiation. As pointed above, melatonin shows an anti-aromatase action comparable to that of antiestrogens currently used in breast cancer therapy and might be an interesting option to be considered as treatment for patients with hormone-dependent tumors.

Since some investigations demonstrated an altered melatonin secretion in cancer patients [7], clinical trials have been conducted to evaluate the effects of melatonin in human neoplasms. Thus, melatonin in combination with chemotherapy did not worsen survival and adverse effects of advanced patients with non-small cell lung cancer but there was a trend for better health-related quality of life [8,9]. A systematic review about the effect of melatonin in conjunction with chemotherapy and radiotherapy in cancer patients, which dealt with solid tumors concludes that melatonin showed substantial improvements in tumor remission, 1-year survival and was able to ameliorate the side effects of chemotherapy and radiotherapy [10].

To enhance the radiosensitivity of cancer cells whilst preserving as much as possible the health of the non-tumoral cells is one of the most important goals in clinical radiology. In patients diagnosed with locally advanced, positive estrogen receptor breast cancer, endocrine and radiotherapy treatments are commonly applied together. Several experimental and clinical studies that have investigated the protective effects of melatonin against radiation *in vivo* have been recently published. All of them have focused on the protective actions of the pineal hormone against injury in healthy tissues from gamma or X-ray when the indolamine is administered prior to exposure to ionizing radiation. The main conclusion is that melatonin can counteract, acting as a direct free radical scavenger and an indirect antioxidant, the production of free radicals induced by radiation. In animal models, melatonin shows a great potential to prevent side effects of radiation therapy and protects against the damage inflicted to the normal tissue [11,12]. Studies carried out in Swiss ND4 mice showed that exposure to 950 cGy of whole body radiation caused the death of all the animals of the control group 12 days later; however, when mice were pretreated with melatonin, almost half of the animals survived at least 30 days after treatment [13]. Therefore, if similar results are obtained in human patients in clinical trials, the pineal hormone could have a great potential to palliate the side effects of radiotherapy in cancer patients.

Apart from the protective effects on normal tissues, it is very interesting that antiestrogen treatments had as synergistic effect on tumor cells when combined with radiotherapy. Aromatase inhibitors such as letrozole, sensitize breast cancer cells to ionizing radiation [14]. Recently, fulvestrant, a member of the newest endocrine therapy, has also been described as a sensitizing agent to the ionizing effects of radiation [15].

As melatonin has both anti-estrogen and anti-aromatase properties [4], we have recently investigated its effects on human breast cancer cells exposed to radiation. Our group has recently described how melatonin, *in vitro*, acts as a radiosensitizer; we have addressed the effects of combining ionizing radiation and melatonin on the hormone-dependent breast cancer cell line MCF-7. Pretreatment of the cells with melatonin one week before radiation resulted in a greater inhibition of RAD51 and DNA-protein kinase (PKcs) expression, proteins that are

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involved in double-strand DNA break repair compared with radiation alone. Pretreatment with melatonin also led to a significantly greater inhibition of cell proliferation compared with the cells only radiated. These results point to a role of melatonin sensitizing breast cancer cells to the ionizing effects of radiation, by diminishing the rate of proliferation, inducing a cell cycle arrest and causing a downregulation of proteins involved in double-strand break repair [16]. Melatonin pretreatment results in an enhancement of p53 expression in breast cancer cells; this fact might represent a link between melatonin and its regulatory effect sensitizing the hormone-dependent breast cancer cells to ionizing radiation [17]. Melatonin sensitizes breast cancer cells to the ionizing effects of radiation by inducing cell cycle arrest by decreasing cell proliferation, downregulating proteins involved in double-strand DNA break repair and also by downregulating aromatase. Considering that p53 promotes cell cycle arrest, we believe that the modulatory action of melatonin through p53 could be the link between the pineal hormone and its actions as an enhancer of the radiosensitivity of human breast cancer cells.

Moreover, since melatonin shows the ability of modulate the expression and activity of the enzymes involved in estrogen synthesis, behaving as a selective estrogen enzyme modulator, the effects of combining ionizing radiation and melatonin on the enzymes necessary for estrogen biosynthesis in hormone-dependent breast cancer cells was next evaluated. Melatonin sensitizes the tumor cells to radiation by decreasing the activity and expression of proteins involved in the synthesis of estrogens, reducing the amount of active estrogens at the tumoral cell level. Therefore, in addition to the p53 and downregulation of the proteins involved in double-strand DNA repair, a second explanation to the enhanced radiosensitivity of cancer cells pretreated with melatonin could be the downregulation of aromatase, sulfotransferase and 17 $\beta$ -HSD1, which might reduce active estrogen levels.

In summary, we think that melatonin is a molecule with high expectations to be considered as an interesting anticancer drug both in prevention and treatment of, not only estrogen-dependent tumors, but also, other kinds of cancer. The pineal hormone seems to lower the damage inflicted to non-tumoral tissues and sensitizes the tumoral cells to ionizing radiation; if these promising results can be confirmed in human clinical studies, our opinion is that melatonin has the potential to be considered as a protective agent in radiation oncology treatments.

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