The Association of Melatonin and Childhood Cancer with Particular Emphasis on Metastasis

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Melatonin, which normally exhibits a robust circadian rhythm in the circulation of children, is derived from the pineal gland in the central nervous system. The high nocturnal blood levels of melatonin are inhibited by light exposure at night, with blue wavelengths (peaking at about 480 nanometers) being especially suppressive. The blue light wavelengths that modulate pineal melatonin production and synthesis are detected by specific cells in the retinas that contain a photopigment, melanopsin, which is located in the intrinsically photosensitive retinal ganglion cells (*ip*RGC). Unfortunately, light pollution is the most rapidly growing environmental pollutant. The suppression of the melatonin rhythm is also always accompanied by a disturbance in the biological clock in the suprachiasmatic nuclei in the hypothalamus. The suppression of melatonin and perturbations of circadian rhythms are both known to be linked to cancer initiation, progression and metastasis. Melatonin is well documented for having multiple tumor-suppressive properties in a myriad of cancers, but rather little has been done in reference to childhood cancers. Osteosarcoma, which has a very high metastatic potential, is a highly prevalent malignant bone tumor in children and adolescents. In tests of the role of melatonin on osteosarcoma cell invasion, we used human osteosarcoma cells, U2OS and HOS, In this in vitro study, we found that melatonin inhibited osteosarcoma cell motility, migration and invasion.

These findings are consistent with the anti-metastatic actions of melatonin on other cancers (Reiter et al, 2017; Su et al., 2017). RNA sequencing technology revealed that melatonin suppressed C-C motif chemokine ligand 24 (CCL24) gene expression. Manipulation of CCL24 levels influenced the motility of osteosarcoma cells since cell migration and invasion were enhanced by the addition of recombinant human CCL24 and attenuated when CCL24 was silenced. Melatonin suppressed CCL24 and migration of osteosarcoma cells. The results reveal that melatonin attenuates chemokine CCL24 levels through inhibition of the c-Jun N-terminal kinase (JNK) pathway to interfere with osteosarcoma cell invasion; the findings highlight the therapeutic potential of melatonin in osteosarcoma metastasis. Reducing cancer metastasis has important therapeutic potential since the secondary cancer sites are often responsible for the high mortality in cancer patients.

Reiter RJ, Rosales-Corral SA, Tan DX, Acuna-Castroviejo D, Qin L, Yang SF, Xu K. (2017) Melatonin, a full service anti-cancer agent: Inhibition of initiation, progression and metastasis. Int J Mol Sci 18: E843

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