Extended Abstract

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Melatonin, Circadian Clock and Cancer

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Abstract:
Melatonin (N-acetyl-5 methoxytryptamine) is an omnipresent naturally occurring compound widely distributed in nature, both in plants as well as animals. Dietary sources of melatonin are cereals, nuts, yeast, eggs, breast milk and fish etc. Melatonin is primarily synthesized by pineal gland and several peripheral organs such as retina, gut, skin, bone marrow and lymphocytes. The synthesis and secretion of both pineal and retinal melatonin exhibits a 'circadian rhythm' with higher level at night time and low levels during day hours. Circadian clocks drive such rhythms. The mammalian clocks consist of a central light-sensitive clock (central circadian pacemaker) located in the hypothalamic suprachiasmatic nucleus (SCN) and peripheral (cell-intrinsic) molecular clock found virtually in all nucleated cells. Molecular design of the clock is a circuit of transcription factors like CLOCK-BMAL1 which stimulates the circadian expression and PER & CRY, which suppresses CLOCK-BMAL1.

The circadian clock or the circadian oscillator plays a pivotal role in regulating cellular metabolism, including mitochondrial respiration, proteostasis, autophagy, biogenesis of ribosome and DNA repair [1].Previous studies elucidated that alteration of clock components (BMAL1 & PER2) in human cancer and chronic circadian disruption through night shift/ rotating night work or trans meridian flight, may play a role in carcinogenesis, tumor growth and progression[2] .Expression of clock components BMAL1 & PER2 appears to decreased in human cancer. BMAL1 could directly activate the tumor suppressor protein p53 which suppresses the tumorigenesis[3].

Melatonin is often called 'Sleep hormone'. It works closely with body circadian rhythm and induces good sleep and helps to reduce jet lag. Sleep disturbances is common and a multifactorial problem in patients with advanced cancer .It has been reported in anticancer chemotherapy and radiation therapy of which produce sleep disturbances. Immune pathways deregulation by cancer, is the potential mechanism underlying cancer-associated sleep disruption.Tumor associated immune response can enhance the growth and propagation of cancer. Tumor cell can secrete leukocyte attracting chemokines, leading to an infiltration of tumor associated macrophages, neutrophils and T cells. In turn, these leukocytes secrete various growth factors (eg.Platelet-derived growth factor(PDGF), insulin like growth factor(IGF), fibroblast growth factor(FGF), epidermal growth factor (EGF) and transforming growth factor beta(TGF-β) etc.) and cytokines(eg.interleukin-1(IL-1),interleukin-1(IL-2),interleukin-1(IL-6), interleukin-1(IL-10) etc.) and tumor necrosis factor alpha (TNF-α) etc.). Tumor secreted cytokines can enter to the brain via humoral and neural route. IL-1β effect cancer progression and sleep (i.e.,acts as somnogen).In the brain IL-1β enhances both delta power during NERM sleep as well as duration of NERM sleep and suppress REM sleep[4,5].
The disruption of the circadian rhythm and abnormal levels of circulating melatonin influences the sleep-wake cycle and cellular metabolism with negative impacts such as epigenetic abnormalities and increased chances of metabolic and neoplastic disorders[6,7].

The melatonin is a pleiotropic molecule with many bioactivities, including but not limited to, antioxidative, anti-inflammatory, anticancer activities, immunomodulation, haematopoiesisand regulation of circadian cycle. Its anticancer mechanism includes inhibition of tumor cell growth and proliferation, modulation of tumor cell metabolism, enhancing apoptosis, exerting anti-angiogenic and anti-metastatic effects[8, 9.The]oncostatic effect of melatonin is through receptor-dependent and receptor-independent mechanisms. The melatonin receptors belong to the G-protein-coupled receptor (GPCR) group. Ant-proliferative effect of melatonin is due to receptor dependent inhibition of linoleic acid uptake through inhibition of adenylcyclase and cyclic AMP (cAMP) [10.]

Exogenous melatonin supplementation in life-threatening malignancies, may prevent oxidative damage to host cells, as it has been proven that melatonin in high concentration may act as a potent endogenous scavenger of free radical, reactive oxygen species (ROS) and reactive nitrogen species[11].Melatonin exerts its indirect protective effects, at all concentrations, by activating membrane-bound melatonin receptors MT1 & MT2 which stimulate production of several antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidise,and glutathione reductase through multiple signaling pathways[12]. Besides melatonin enhances the efficacy of the electron transport chain in mitochondria, thereby reducing free radical

generation[13].Reiter and colleague reported that melatonin regulates the metabolism of glucose in tumor cells, by causing cancer cells to overcome cytosolic glycolysis, thereby reducing tumor biomass and reversing the insensitivity of cancer cells to anticancer chemotherapy [14]. Other possible mechanism ofoncostatic effect of melatonin may linkedto autophagy and mitophagy,a prominent feature of programmed cell death[15]. Wei et al demonstrated that melatonin at pharmacological concentrations; significantly induce apoptosis of colorectal cancer in dose-dependent manner by reducing Bcl-2 expression which is mediated by inactivating Ca++ /calmodulin-dependent protein kinase IIα (CaMK IIα) **[16]**.

Melatonin further inhibited cancer metastasis by limiting cancer cell migration into the vascular channel and preventing secondary tumor growth at a distant site.
Borin et al described an oncostatic, antimetastatic and anti-angiogenic effects of melatonin in breast cancer[17].Melatonin exerts inhibitory influence on vascular endothelial growth factors (VEGF) and matrix metalloproteinase required for tumor invasiveness and neoangiogenesis. Melatonin causes up-regulation of tissue inhibitor of metalloproteinase-1(TIMR1).It has also been demonstrated that melatonin administration, prior to radiotherapy, enhances the sensitivity of human breast cancer possibly through inhibiting proliferation, promoting cell cycle arrest and inhibiting repair of double-strand DNA break and increase of p53 expression[18].In vivo study showed that melatonin (25mg/kg) could synergize response of chemotherapy in colon cancer[19].The exogenousadministration of melatonin has been used in treatment of cancer.The low dose (1-5mg per night) melatonin is recommended for treating insomnia or jet lag and high dose (20 mg or more per day) melatonin for treating malignant tumors[20].

Therefore, it can be argued that high dose of melatonin may be an adjuvant therapy for advanced staged critical cancer patients .The parental administration of melatonin may enhance the therapeutic effects and reducing the side effects of systemic chemotherapeutic agents or radiotherapy. Melatonin might help in improving the sleep and life quality of cancer patients. Previous studies support the potential use of melatonin in the prevention and treatment of both hormone dependent and hormone independent cancers.

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