Journal of Gerontology & Geriatric Research

Gubareva, et al., J Gerontol Geriatr Res 2016, 5:6
DOI: 10.4172/2167-7182.1000363

Short Communication Open Access

# Cancer and Aging: Why Bother about Light at Night?

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**Rec date:** Oct 15, 2016; **Acc date:** Nov 11, 2016; **Pub date:** Nov 14, 2016



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Shift work which causes circadian disruption is an established cancer risk factor. A large body of experimental and epidemiological data proves that exposure to light at night promotes carcinogenesis in various tissues and accelerates aging [1-3]. Artificial or natural light through master clock located in suprachiasmatic nuclei of hypothalamus suppresses night peak of melatonin synthesis in the pineal gland. Melatonin is known to exert antioxidant, antigonadotropic, immunostimulating and anticancer effects [4-6]. Except direct antioxidant action through free radicals scavenging melatonin works as a chronobiotic which tunes cellular clock. Exact molecular pathway by which melatonin regulates cellular clock is still not established. Melatonin is a ligand for two membrane-bound G-protein coupled receptors, MT1 and MT2 [7]; in nucleus it interacts with members of retinoid-related orphan nuclear receptor family (RORalpha/RZRalpha) [8]. One of the latter, RORa, is a part of cellular clock machinery.

Clock genes Bmal1, Clock, Per1-3, Cry1-2, RevErba, Rora and Rorb are expressed almost in every cell [9]. Their protein products comprise several transcriptional-translational feedback loops which regulate circadian rhythm of approximately 10% to 15% of cellular transcriptome. Clock-Bmal1 complex binds special sequence (E-box) in genes promoters (including other clock genes) while Per and Cry are their negative regulators. The whole cycle takes 24 hours though its length may vary because of environmental cues or some drugs. Clock-controlled genes regulate proliferation, apoptosis, metabolism and other cellular functions, many of which are involved in cancer initiation, promotion and progression.

Changes in clock genes expression or protein level in human tumors have been extensively studied [10,11]. In most cases Per1 or Per2 expression was downregulated while Clock and Bmal1 had elevated transcription level as compared to normal tissue. Nevertheless, we should admit circadian phase of studied tissues was not assessed. It has been shown that both phase and amplitude in clock and clock-controlled genes expression changed in murine colorectal tumors as compared to normal colon [12]. Per2 expression is reduced in mammary gland tumors of HER2/neu transgenic mice compared to liver in the same animal [13]. Some structural polymorphism in clock genes (Per3) associated with cancer susceptibility were found [14].

We have studied the effect of exposure to light at night and melatonin on chemically induced carcinogenesis in lung and skin in mice. Half of animals were maintained at standard light regimen (12L: 12D), others were subjected to constant illumination (LL). Part of mice in each group were treated with melatonin dissolved in drinking water over night (20:00 to 08:00, 20 mg/L). Light at night exposure was followed by promotion of both skin and lung tumor development, whereas nocturnal melatonin treatment inhibited carcinogenesis, mainly in LL condition. Lung samples immunohistochemical staining with antibodies against Clock and Bmal1 revealed higher content of Bmal1 in lung adenomas against normal alveolar epithelium and in adenocarcinomas against adenomas. LL exposure significantly increased Bmal1 expression in adenomas but not adenocarcinomas. Clock staining in alveolocytes was weak though in malignant tumors it was relatively high and significantly exceeded one in benign tumors [15]. Increased level of Clock and Bmal1 was observed in skin tumors and hyperplastic epidermis as compared with normal skin while Cry1 was downregulated. In skin and skin tumors Bmal1 expression was higher in LL group as compared to LD, but in LL+melatonin group this protein was not upregulated. Clock expression was significantly enhanced by both light and melatonin in skin tumors, whereas Cry1 expression changed in response to light and melatonin only in hyperplastic epidermis [16].

It is still unclear whether clock genes in fact control tumor growth *in vivo* (though Per genes are claimed as antitumor genes). Some drugs including melatonin, metformin and others were shown to influence circadian rhythm *in vivo* and *in vitro*, and some of them have antitumor properties [17,18]. *In vitro* melatonin was shown to influence Per1 expression amplitude in young and aged rat fibroblasts [19]. In prostate cancer cells, it reduced Bmal1 and increased Clock and Per2 expression [20]. Taken together highlighted data suggests that melatonin may inhibit tumor growth in part due to its influence on cellular clock. We assume that pharmacological adjustment of cellular clock may be beneficial for cancer and premature aging prevention.

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