Cancer and Aging: Why Bother about Light at Night?
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Short Communication

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, antitumoral, anti-inflammatory, 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, RORalpha, is a part of cellular clock machinery.

Clock genes Bmal1, Clock, Per1-3, Cry1-2, RevErba, Rora and Rorb expression are 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 breast and mammary gland tumors of HER2/neu transgenic mice compared to normal colon [13]. In prostate cancer cells, it reduced Bmal1 and increased Clock expression [14]. 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 [15]. In vitro melatonin was shown to influence Per1 expression amplitude in young and aged rat fibroblasts [16]. 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.

References