The Circadian Rhythm, A Continuous Transcription-Translation Feedback Loop, Contributes to Low-Dose Radiation-Induced Radioadaptive Response

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The initiation of the circadian rhythm field occurred when the Takahashi group defined a mutation in the mouse gene "Clock" and cloned the circadian locomotor output cycles kaput (Clock) in the mid-1990's (1-3). Currently more than a dozen clock genes have been identified (3-4). Disruptions in the circadian rhythm via changes in environmental conditions, such as, diet, temperature, and night/day hours lead to the pathogenesis of a multitude of diseases, such as, cancer, diabetes mellitus, neurological diseases, and sleep disorders. A disruption in the circadian rhythm was found to be more prevalent in shift work i.e. nurses, air flight attendants, and pilots. Shift work was shown to increase individuals' risk for breast cancer via disruption of their circadian rhythm. Male and female flight attendants undergoing frequent transmeridian flights have an increased risk of non-hormone and hormone-dependent cancers (5-7). A decrease of nocturnal melatonin secretion from exposure to light at night and subsequently a resulting stimulation of estrogen production potentially cause an increased risk of breast cancer (5).

According to recent studies, normal "healthy" epithelial cells exhibit high expression levels of the clock gene Per2. We hypothesize this Per2 will act as a survival gene and therefore have a protective effect induced by low-dose radiation (LDR; i.e. 10 cGy). Mammalian cells with altered expression level of Per2 gene will have deleterious effects, such as, DNA damage induced by UV, stress activated reactive oxygen species, stress induced cortisol, and depletion of melatonin and serotonin. Our current studies focus on elucidating the contribution of low-dose (10 cGy) IR on Per2 protein expression levels in different normal and cancer cell lines. Our initial data show that human breast epithelial MCF-10A cells treated with high-dose gamma radiation (10 Gy) attenuate Per2 protein expression levels. In contrast, we expect that LDR is able to enhance Per2 expression levels in MCF-10A cells and thus contribute to the radiation-induced radioadaptive response. Low-dose ionizing radiation effect on Per2 expression will be shown via Western Blot analysis in MCF-7, HCT116, MDA-MB-231, JB6, and HK-18 cell lines with a time course containing 4-hour intervals (0, 4, 8, 12, 16, 20, 24).

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