Preface: Circadian Rhythm and Oncogenesis Part 1

The focused topic on *Circadian Rhythm* is published in two consecutive issues, issues 3 and 4, in *Critical Reviews™ in Oncogenesis* (CRO), 2021. They cover various aspects of the inter-relationship between the regulation of oncogenesis in various cancers and the circadian clock genes. Several chapters have been reviewed by established investigators in the field. The major highlights by the contributors to the first issue are briefly discussed below.

In Chapter 1: “Circadian Rhythm and Melatonin in Liver Carcinogenesis: Updates on Current Findings,” Han et al. review two liver cancer types, hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA), and the various risk factors including the disruption of melatonin levels. The authors describe the general properties and characteristics of both HCC and CCA and the risk factors associated with the hepatitis C virus and/or non-alcoholic fatty liver disease (NAFLD). Both HCC and CCA develop from several processes involving genetic and epigenetic manifestations. Interestingly, a large subset (60–80%) of patients with chronic liver diseases suffer from fatigue, poor quality of sleep, and insomnia. It was reported that fatigued patients with chronic liver diseases have increased levels of melatonin, an altered circadian rhythm, and liver enzymes showing a circadian rhythm. The circadian rhythm is regulated by melatonin, which shows a peak in the dark phase and 24-hour oscillation in the blood, and is also involved in the regulation of clock genes. The authors describe in detail the relationship between circadian rhythm and chronic liver diseases, the connection between circadian rhythm and liver cancer, and the inter-relationships of melatonin, circadian rhythm, and chronic liver diseases and liver cancer. They also discuss the various treatments related to circadian rhythm and melatonin and project future perspectives.

In Chapter 2: “The Potential Oncostatic Effects of Melatonin against Prostate Cancer,” Samanta reviews the potential oncogenic effect of melatonin on the prostate leading to prostate cancer. Melatonin synthesis and levels are affected by many factors

such as circadian rhythm, indoor and outdoor light, night work, jet lag, etc. Melatonin differentially regulates the cell cycle, cell survival, and the metabolism of malignant cells, including prostate cancer. The various functions mediated by melatonin are described at length, along with their relationships to prostate cancer. For instance, the author describes the cytostatic and cytotoxic effects of melatonin, the response of prostate cancer to anti-androgenic agents, how melatonin affects the metabolism of prostate cancer, the role of melatonin in angiogenesis and the anti-metastatic effects of melatonin. The author describes the relationship between the circadian clock genes’ expression and prostate cancer, and addresses the therapeutic potential of melatonin in prostate cancer and the need for additional clinical trials on the use of melatonin for prostate cancer therapy.

In Chapter 3: “Association between the Circadian Clock and the Tumor Microenvironment in Breast Cancer,” Malla et al. review the regulation of breast cancer progression and its immunosuppressive tumor microenvironment (TME). It has been reported that the circadian rhythm is involved in the remodeling of the TME. In this chapter, the authors review the circadian clock genes and their molecular functions, the various circadian rhythm signaling pathways in cancer, the association of the circadian rhythm genes and the biology of breast cancer, and how to manage the circadian rhythm for the potential treatment of breast cancer. Breast cancer is a very aggressive cancer with high mortality and morbidity. These are the result of the TME heterogeneity and immunosuppression. Hence, the circadian rhythm sleep disorder is manifested by increasing tumor progression through the remodeling of the TME. The authors postulate that the development of small molecules that can manage disturbances of the circadian rhythm via their interactions with the clock gene products may be exploited to treat breast cancer.

In Chapter 4: “A Profound Relationship between Circadian Rhythm Dysfunction and Cancer

Progression: An Approach to Exploration,” Samanta reviews the influence of disruptions of the circadian rhythm clock functions and the development of cancer. In this chapter, he reviews the structural organization and neural connections of the suprachiasmatic nucleus (SCN), the molecular signaling pathways upon exposure of the SCN to light, the synthesis and regulation of melatonin via the SCN–pineal loop, features of the melatonin receptors, the clock genes’ functions, and the impact of circadian dysfunction in the progression of cancer. Of interest, Dr. Samanta reviews the circadian dysfunction in various cancers including breast cancer, ovarian cancer, prostate cancer, colorectal cancer, hematologic cancers, liver cancer, and other cancers. He also presents various approaches and future

perspectives to target the circadian rhythm for therapeutic applications.

Clearly, these extensive reviews offer different perspectives in the complex arena of the tight relationship between the circadian clock genes and their direct involvement in cancer development and progression with the potential of developing new therapeutic strategies targeting the circadian clock.

These reviews also are up-to-date references for both new investigators and established scientists. The Editor-in-Chief expresses his sincere thanks to the contributors who spent considerable effort to generate their excellent reviews.

Benjamin Bonavida, PhD
Editor-in-Chief