Preface: Circadian Rhythm and Oncogenesis Part 2

This issue, issue 4, 2021, is a continuation of the reviews published in Critical Reviews™ in Oncogenesis (CRO) issue 3, extending the reported investigations on the relationship between the circadian clock genes and their effects on the regulation of the oncogenic process. Established investigators in the field have focused on various topics and also provided new features and analyses of cross talks as well as bioinformatic analyses that support these postulated cross talks. Four chapters are reported in this issue as well as a commentary on the relationship between photodynamic therapy and oncogenesis.

In Chapter 1: “Insights into Oncogenesis from Circadian Timing in Cancer Stem Cells,” Geusz et al. review evidence that challenges the simplicity of carcinogenesis models and the circadian clock. In this report, the authors review the published data on circadian rhythms in cancer cells and particularly on cancer stem cells, the underlying mechanisms by which the circadian rhythms are generated via transcription factors and genes products translated and feedback loops, by what means the disruption of the circadian rhythms can initiate the oncogenic process via cancer stem cells, the various features that initiate and regulate cancer stem cells, the current evidence that there exist molecular interactions between circadian rhythm and cancer, which clock genes have been identified that control oncogenesis, and means to target the modified clock genes in cancer. Also, the authors present data on the circadian clocks of the liver and their role in oncogenesis. The authors discuss their prospective views on the future directions of research investigations to manipulate clock genes that will result in the interference of the oncogenic process and cancer progression.

In Chapter 2: “Cross-Talks between the Circadian Clock Proteins in Cancer and Therapeutic Significance and TP53,” Valafar et al. review how several clock genes are involved in the regulation of the tumor suppressor TP53 and the inhibition of oncogenesis and the significance of these findings in therapeutic interventions in the treatment of resistant cancers. In this chapter, the authors review the general characteristics, development, and origin of the circadian rhythm; the circadian rhythm gene products; the transcription factors that regulate these gene products and feedback loops; and its post-transcriptional and translational regulations. The authors describe TP53’s tumor suppressor properties and activities, its molecular regulation and expression, and its role in homeostasis and inhibition of cancer development via its mediated mechanisms of apoptosis and the regulation of metabolic pathways in normal cells. Various analyses are made regarding the role of each clock gene product in the regulation of TP53 and how the disruption of certain clock genes results in the inhibition of TP53-mediated tumor suppressor activity. The findings reported in the literature as well as the extrapolated cross-talks between clock gene products and TP53 in cancer are validated and extended by bioinformatic analyses. Then, the authors present their own perspectives on the current findings and future challenges to resolve for the ultimate means to target disrupted clock gene products in cancer for the reversal of the oncogenic process and cancer progression.

In Chapter 3: “The Rhythmic of Life: A Review of the Circadian Clocks,” Ackgoz et al. review the molecular aspects of the circadian physiology and underlying mechanisms of circadian disruptions at multiple levels that lead to various diseases and the induction of oncogenes and cancer. This extensive review covers several aspects of the circadian rhythms including the biological clocks and their gene products, the genetic and epigenetic bases of the circadian rhythms and the cross-talks between the circadian rhythm and carcinogenesis. Hence, circadian rhythms are driven by sophisticated networks of biological events that maintain normal homeostasis. The hypothalamus is the master organizer via clock proteins, which are essential for a well-established physiological system, and is also under the regulation of rhythmic oscillations. Thus, disruptions of normal circadian rhythms, manifested by genetic and epigenetic alterations, will affect the daily normal functions and will also lead to the
induction of oncogenic processes, including cancer metabolism, proliferation, apoptosis, etc., that are observed in pathological conditions. The authors warned that more research is warranted to establish a direct link between disruption of the circadian rhythms and oncogenesis.

In Chapter 4: “The Regulation of the c-Myc Oncogene by the Circadian Clock and Oncogenesis,” Ung et al. discuss the relationship between the disruption of the circadian clock and the induction of the proto-oncogene c-Myc and the oncogenic process. Herein, the authors review the role of each of the circadian clock genes in the regulation of c-Myc expression. A general overview of the circadian clock genes and their molecular and both the genetic and epigenetic regulations is discussed. Further, an overview of the close relationship between disruptions of the circadian clock and carcinogenesis. Emphasis is on the exploration of the role of the tumor suppressor TP53 pathway and the circadian clock and specifically the role of the c-Myc pathway. The authors describe in detail the underlying mechanisms by which each of the disrupted circadian genes, namely, PER1, PER2, CRY1, CRY2, BMAL1, are involved in the regulation of c-Myc expression. Clearly, these various manifestations are not all universally observed in all cancers but vary in different cancers. Also, c-Myc has been reported to have dual and contrasting effects such as promoting cell proliferation and induction of apoptosis and better interpretations of the findings must not be overlooked. The authors speculate that the disruption of the circadian clock is an independent risk factor for cancer. Also, further investigations must be pursued to investigate other proto-oncogenes and tumor suppressor genes that are regulated by disrupted clock genes. Clearly, future approaches may be feasible to specifically target certain disrupted clock genes to inhibit c-Myc induction and the inhibition of the oncogenic process as therapeutic modalities.

These extensive and updated 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.

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Editor-in-Chief