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Commentary

Significance of Circardian Rhythms in Colorectal Cancer

Nicholas Kenyatta*

Department of Experimental and Clinical Pharmacology, University of Nairobi, Nairobi, Kenya

ABOUT THE STUDY

Colorectal Cancer (CRC) is the third most common type of cancer in people. Colorectal cancer is also the most lethal of the gastrointestinal tumors. Most patients' specific CRC development pathways are yet unknown. Numerous genetic, environmental and epigenetic risk factors have so far been found to contribute the development of CRC. The 24-hour circadian rhythm regulates numerous biological activities. The Supra-Chiasmatic Nucleus (SCN) in the hypothalamus, a central pacemaker that controls the circadian system. Circadian clock genes, cytokines, and hormones like melatonin control circadian rhythm.

It is well recognized that certain diseases, including cancer, have substantial correlations with disturbances in biological cycles. The involvement of several circadian genes in various malignancies has been established; however, less research has been done on the routes by which these circadian genes contribute to CRC development. Researchers can investigate new treatments for the cancer by identifying the specific pathways in CRC.

The third most frequently diagnosed cancer worldwide; Colorectal Cancer (CRC) is responsible for 10% of all cancer-related deaths in developed nations. Hereditary or family variables are typically not present in CRCs. The risk of developing CRC is raised by the lifestyles practiced in developed nations, which frequently involve the eating of red meat, fat, alcohol, and tobacco. Additionally, the risk of CRC is rising due to bacterial infection, heart disease, type 2 diabetes, high blood pressure, and obesity. The CRC is a diverse disease. The primary mechanism behind the onset and progression of CRC is the accumulation of many genetic and epigenetic alterations in the colon epithelial cells. The inactivation of Adenomatous Polyposis Coli (APC) is the initial event in the adenoma-carcinoma cascade that transforms the colon's normal epithelium to Colorectal Cancer (CRC) is the third CRC is a heterogeneous disease. Adenoma develops into cancer as a result of KRAS and TP53 gene mutations. Based on the three main pathophysiological pathways of Chromosomal Instability (CIN), Micro-Satellite Instability (MSI), and CpG Island Methylator Phenotype (CIMP), CRCs are divided into subgroups. About 80%-85% of CRC cases are caused by the CIN pathway. As a result of the inactivation of the APC gene, adenomatous polyps evolve into neoplasia in this pathway, which then progresses to adenocarcinomas as a result of additional activating mutations in the KRAS gene and the inactivation of the *SMAD4* and *Tp53* genes. When MMR genes like *MLH1, MSH2, MSH6,* and *PMS2* are defective in DNA mismatch repair, MSI results from alterations in microsatellites. Based on CpG island hyper methylation at the promoters of certain tumor suppressor genes, the CIMP subgroup is defined. This form of CRC frequently exhibits hyper methylation of the *MLH1* promoter. A mix of surgery, radiation therapy, chemotherapy, and targeted therapy made up the CRC treatment approach. Surgery can effectively treat tumors that have spread only to the colon's wall, but palliative treatment is recommended for metastatic malignancies since it can enhance quality of life and lessen symptoms. Due to its greater effectiveness and fewer side effects when compared to conventional medications, targeted therapy for cancer is now highly regarded.

Most living things have circadian rhythms as their fundamental biological processes, which are controlled by a circadian clock located in the suprachiasmatic nucleus of the hypothalamus. The circadian system regulates biological processes like metabolism, DNA damage response, and cell cycle that are involved in tumor development. Numerous studies have shown that disruption of circadian rhythms causes a wide range of health issues, such as metabolic syndrome, cardiovascular dysfunction, immunological dysregulation, reproductive issues, sleep disorders, exhaustion, learning challenges, and cancer growth and carcinogenesis. Circadian Locomotors Output Cycles Kaput Protein (CLOCK), Neuronal PAS Domain Protein 2 (NPAS2), Ary1 Hydrocarbon Receptor Nuclear Translocator-Like (ARNTL), Period 1 (PER1), Period 2 (PER2), and Period 3 (PER3) are the genes that make up the circadian principal clock pathway. Other genes in the pathway include brain and muscle ARNT-like protein 1 (Bmal1), cryptochrome 1 (*CRY1*), cryptochrome 2 (*CRY2*).

The relationship between circadian genes and the emergence of cancer has been the subject of substantial development over the past few decades. For instance, a study found that the circadian

Correspondence to: Nicholas Kenyatta, Department of Experimental and Clinical Pharmacology, University of Nairobi, Nairobi, Kenya, E-mail: kenyattanicholas@gmail.com

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rhythm regulator melatonin is linked to an increased risk of developing cancer. In mouse and human studies, circadian rhythm disruption has been shown in a variety of cancers, including colorectal, lung, breast, ovarian, and hematologic malignancies in humans.

Changes in the expression of the *CLOCK, PER, CRY,* and *TIMELESS* genes have also been linked to related gene methylation, the development, and progression of cancer. Circadian genes are a very significant and critical collection of genes that establish an internal clock in various organisms and influence behaviour.

The majority of organisms organise their behaviour, such as mood, cognition, attention, metabolism, and physiology, such as fluctuations in circulating hormone levels and body temperature, into the 24 hour solar cycle by using the association between circadian genes dys-regulation and various diseases, such as cancer. Numerous diseases, including cancer, Alzheimer's, metabolic disorders, and sleep problems, are impacted by the aberrant expression of circadian genes. The replacement of one amino acid (471 Leu/Ser) in neuronal PAS domain protein 2 (Npas2) causes the development of the seasonal affective disorder (SAD). Bipolar disorder is linked to a single nucleotide polymorphism (SNP) in the clock gene's 3′ flanking region (3111 T to C).

The expression of many genes, including cell-cycle regulators, oncogenes, and tumor suppressor genes, is regulated by clock genes in a time-dependent way. The timing of fundamental cellular processes like metabolism, DNA damage repair, and autophagy is controlled by clock-controlled genes. The circadian system also controls DNA replication-related proteins' transcription and post-translational modifications, which controls cell growth and death. The replacement of one amino acid (471 Leu/Ser) in Neuronal PAS domain protein 2 (Npas2) causes the development of Seasonal Affective Disorder (SAD) Bipolar disorder is linked to A Single Nucleotide Polymorphism (SNP) in the clock gene's 3' flanking region (3111 T to C).

The circadian system is important for digestive physiology, and alterations in the molecular clock may contribute to the tumorigenesis of colorectal cancer. The circadian genes and proteins are frequently altered in colorectal cancers and have an impact on the phenotypic of colon cancer cells, the development of the disease, patient survival, and chemotherapy responses.