Journal of Cell and Tissue Research Vol. 25(1): 7569-7571 (2025)
(Available online at www.tcrjournals.com)
ISSN: 0973-0028; E-ISSN: 0974-0910

Review Article

COLORECTAL CANCER: REGULATED BY GUT'S CLOCK

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Received: December 25, 2024: Accepted: January 5, 2025

AAbstract: ***Biological clock is composed of proteins encoded by thousands of genes that switch on and off in a specific order. A master clock coordinates all the cellular biological clocks in an organism. It regulates an organism's sense of time and controls many bodily functions. When particular group of cellular clocks go disarray, normal body functions go stray and can even produce cancer. In in vitro experiments scientists showed that intestinal barrier/ permeability functions are clock-dependent. A circadian rhythm disorder can be long-term and caused by aging, genes, or a medical condition. circadian rhythm disorder for huger can influence the progression of many diseases such as colorectal cancer***

Keywords: Colorectal cancer, Gut's clock

INTRODUCTION

The circadian rhythm cycles about every 24 hours plays an important role in a wide range of human physiology and pathology [1]. Circadian rhythm disorders are problems that occur when body's internal clock is out of sync with the environment. Our body tries to align our hunger and sleep-wake cycle to cues from the environment, such as when it gets light or dark outside [2], when to eat, and when we are physically active [3]. A circadian rhythm disorder can be long-term and caused by aging, genes, or a medical condition.

People with fasting/feeding cycles, the circadian clock also influences homeostasis across a broad range of behavioural and physiological processes, including glucose and lipid metabolism, body temperature, endocrine hormone secretion [4]. Previous research has shown that circadian rhythm disorder for huger can influence the progression of many diseases such as colorectal cancer (CRC). In a new study in mice, researchers from the University of California, Irvine (UCI), demonstrated how disruption of the circadian clock may accelerate the progression of colorectal cancer by affecting the gut microbiome and intestinal barrier function. The new study may lead to new prevention and treatment strategies [5]. There is an alarming rise in early-onset colorectal cancer in adults under the age of 50 [6]. Circadian misalignment through extended light exposure, late-night meals, and other environmental factors could [be] driving these cases. Many studies suggest that clock disruption, particularly through lifestyle choices, may play a significant role in gut health and subsequently cancer risk [7].

The study used a mouse model with genetic

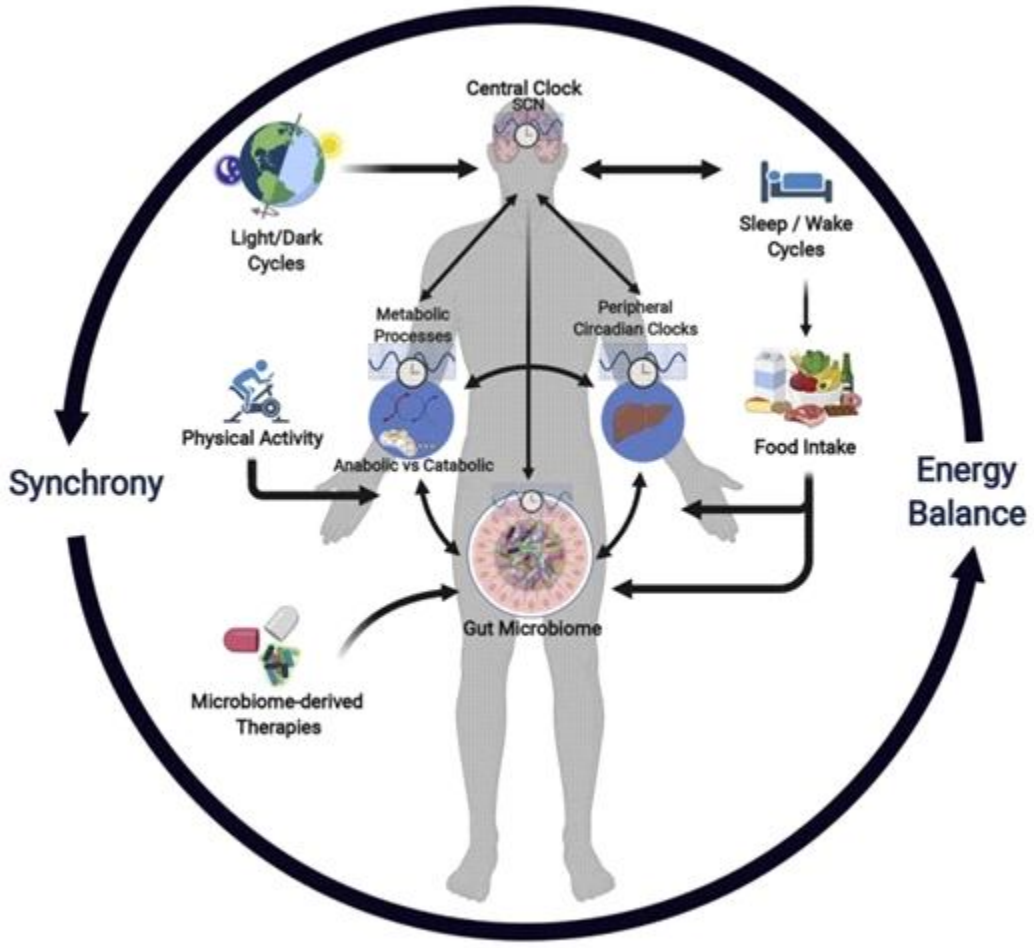

Fig.1 Circadian rhythms and the gut microbiota synchronize the host's metabolic response to diet

The study used a mouse model with genetic mutations. These mutations were designed to disrupt the normal circadian rhythm in the gut and to predispose the mice to developing CRC. The researchers then analyzed the gut microbiome and gene expression in these mice compared to healthy controls [8].

Diet is a robust entrainment cue that regulates diurnal rhythms of the gut microbiome. We and others have shown that disruption of the circadian clock drives the progression of colorectal cancer (CRC). While certain bacterial species have been suggested to play driver roles in CRC, it is unknown whether the intestinal clock impinges on the microbiome to accelerate CRC pathogenesis [9].

To address this, genetic disruption of the circadian clock, in an Apc-driven mouse model of CRC, was used to define the impact on the gut microbiota. When clock disruption is combined with CRC, metagenomic sequencing identified dysregulation of many bacterial genera including *Bacteroides, Helicobacter,* and *Megasphaera* [10-12]. By identifying these bacterial species, the study highlights potential targets for future therapeutic interventions. The researchers also identified alterations in the microbial pathways involved in the metabolism of nucleic acids, amino acids, and carbohydrates. These functional changes were linked to reduced levels of intestinal mucus, which normally protects the gut lining from harmful bacteria, suggesting that the circadian clock is crucial for maintaining barrier integrity [13]. While these findings are important, more work needs to be done. In particular, if changes in the timing and abundance of certain gut bacteria

could directly lead to colorectal cancer development over time. Long-term studies will be critical in determining whether circadian misalignment drives cancer and how we might prevent it in the future. Deeper insights into how the body's internal clock shapes the gut's ecosystem could pave the way for treatments that not only address cancer but also improve overall health (Fig. 1).

Clock-dependent control of intestinal barrier function: It has been reported that intestinal permeability oscillates over the day-night cycle [14]. However, the contribution of clock disruption on intestinal permeability during tumour progression remains unknown. To test this, an *in vitro* intestinal epithelial model using human Caco-2 cells was used to establish differentiated monolayers for permeability assays [15]. Scientists chose 12-hour intervals (Fig. 1) so that they could capture the entire 24-hour circadian cycle with two time points and thus be able to compare gene expression to permeability.

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