

DISRUPTION OF THE CIRCADIAN CLOCK ACCELERATES COLORECTAL CANCER AND PROMOTES IMMUNOSUPPRESSION

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Background Colorectal cancer (CRC) is the third leading cause of cancer-related deaths and the third most diagnosed cancer in the United States. The circadian clock is the primary biological pacemaker of the body, which controls several physiological, endocrine and metabolic processes that operate to maintain organismal homeostasis. Disruption of this endogenous rhythm and function has been linked to several cancers, yet the precise molecular mechanisms and detailed signaling pathways by which disruption of circadian rhythm is linked to cancer progression have not yet been elucidated. In colorectal cancer specifically, epidemiological evidence links night-shift work with elevated incidence of colorectal cancer (CRC), suggesting that light-at-night exposure could potentially have adverse effects on human physiology. In fact, CRC clinical data reports the downregulation of key clock genes, in addition to metabolic dysregulation.

Methods To address this gap in knowledge, we developed a new genetically engineered mouse model that allows us to look at clinically relevant mutations of colorectal cancer with and without genetic disruption of the clock. From these mice we make organoids that allow us to study the complete intestinal epithelium in an *ex vivo* setting.

Results Circadian clock disruption was found to accelerate colorectal cancer progression in a novel genetically-engineered mouse model. Both genetic and environmental disruption of the circadian clock promotes the abundance of myeloid cells and suppressed the proportion of cytotoxic T cells in the intestine. Importantly, circadian clock disruption also promotes an inflammatory response in both *ex vivo* intestinal organoids derived from humans and mice.

Conclusions The circadian clock regulates immunity through suppressing inflammation. It is expected that circadian clock disruption leads to an inflammatory response that, if it persists, can alter the immune landscape in an immunosuppressive manner.

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