Time Will Tell: The Involvement of the Circadian Clock in Colorectal Cancer

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A circadian rhythm is a 24 hour recurring biological process. A group of core genes and transcription factors (CLK, BMAL1, PER, CRY) called the circadian clock regulates these 24 hour rhythms through a transcription/translation feedback loop. Over 40% of the genome is transcribed rhythmically implicating the clock in many cellular processes. Recently, it has been shown that WNT, a mediator of intestinal stem cell proliferation is transcribed rhythmically. Uncontrolled cell proliferation can lead to cancer, which is seen with the mutation of APC, a regulator of Wnt mutated in 80% of all colorectal cancer cases. Colorectal cancer incidence has been steadily increasing due to chronic photoperiod disruptions such as shift work. My project will examine how the disruption of the circadian clock in the intestine affects cancer incidence. I hypothesize that a dysfunctional clock will lead to enhanced tumorigenesis. Due to the implication of APC in colorectal cancer, we will use a mouse that is heterozygous for the APC gene, \( \text{APC}^{\text{min}+/-} \) to model colorectal cancer in a mouse. I will compare \( \text{APC}^{\text{min}+/-}; \text{BMAL1}^{+/-} \) intestines, which have a normal circadian clock, to \( \text{APC}^{\text{min}+/-}; \text{BMAL1}^{-/-} \) intestines, where the clock is dysfunctional. I will count polyps, and use H&E stained tissue sections to quantify the size of each tumour. The Wnt pathway, cell cycle activity and the circadian clock will be examined using immunofluorescence to study the potential relationship between cancer development and the clock. PER2, a core clock protein as well as cMYC, a Wnt target will be investigated. I predict that the \( \text{APC}^{\text{min}+/-}; \text{BMAL1}^{+/-} \) mice, will have fewer tumors than the \( \text{APC}^{\text{min}+/-}; \text{BMAL1}^{-/-} \). My preliminary data shows that the \( \text{APC}^{\text{min}+/-}; \text{BMAL1}^{+/-} \) tissue has more tumours than \( \text{APC}^{+/-}; \text{BMAL1}^{+/-} \) suggesting this colorectal mouse model works. Implicating the circadian clock in colorectal cancer may allow for greater understanding in how to treat or avoid it.