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Clock Work: The Role of the Circadian Clock in Colorectal Cancer

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Circadian rhythms are free-running biological processes that repeat every 24-hours in many cells. In the mouse genome, 43% of protein-encoding genes were found to have circadian rhythms. These rhythms are controlled by biological clocks and may regulate many processes including the cell cycle. In the mouse clock the transcription factors CLOCK and BMAL1 transcribe PER and CRY, which then inactivate CLOCK/BMAL1 in a negative transcription feedback loop. Previous research has demonstrated that the disruption of an organism's circadian clock may contribute to the increased propensity for colorectal cancer. In most colorectal cancers, the tumour suppressor gene *APC* is mutated. *APC* is an important negative regulator of B-catenin, which is a transcription factor of cell proliferation in the Wnt pathway. Previous research has shown that the Wnt pathway may have circadian rhythms and that overexpression may lead to tumour progression in colorectal cancer. Focusing on the circadian clock and its connection to cancer and Wnt signalling could lead to novel cancer therapies and treatments.

I hypothesize that tumours lack circadian rhythms. To investigate the clock's potential role in tumorigenesis, I am dissecting individual polyps/tumours from $APC^{min/+}$ mice with a functional clock (*BMAL1 +/+)*. I will collect non-tumour marginal areas to be used as a non-cancerous tissue control. Using qPCR analysis, I am detecting for clock related genes including *PER2, BMAL1, and REV-ERB* and for downstream Wnt targets including *c-Myc, CCND1,* and *Axin2*. Preliminary results have shown that there is a slight variation in gene targets between polyps and their corresponding margins. Future work will include qPCR analysis of the above genes on $APC^{min/+}$ mice with dysfunctional clocks (BMAL -/-).