Correlation of Circadian Rhythm Disruption and Cancer Progression in Mammalian Cells
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Circadian rhythms are innate biological time tracking systems that regulate protein expression to help organisms adapt to the time of day. These time-dependent systems control multiple functions in the body, including sleep and wakefulness, body temperature, blood pressure, hormone production, digestive secretion, and immune activity. Alterations in circadian rhythms can have profound impacts on human health. Both epidemiological analyses and studies in animal models have revealed that disruptions of circadian rhythms are important factors that contribute to cancer development in mammals. This association can be rationalized by the critical roles of circadian genes in the cell cycle, cell proliferation, DNA damage response, and angiogenesis. However, prior molecular studies have only approximated this relationship: overexpression or deletion of circadian genes are often used, and the majority have only assessed single, average points. No studies have modulated the rhythm and directly analyzed the association between cancer and altered circadian rhythms at the cellular level in real time.

In the presented work, chemical and biological methods will be used to elucidate the connection between circadian rhythms and cancer. Luciferase reporter constructs will be used to track the expression patterns of circadian proteins associated with the core clock and cancer and metastasis in real time. These reporter constructs will be introduced into breast cancer cell lines that represent different stages associated with the disease. We will analyze the endogenous circadian expression patterns for core-clock and cancer-associated proteins, providing a direct correlation between cancer severity and increasingly altered circadian rhythms. Then, we will perturb the circadian rhythms of these cell lines by treating them with small molecules that modify circadian rhythms, and test for changes in metastatic markers and characteristics. To confirm that changes in circadian rhythms lead to altered cellular traits, we will perform the converse experiment by treating cells with agents that can promote or suppress metastasis, and monitor accompanying changes to circadian rhythms. By correlating circadian rhythm with cancer severity, we will be able to offer significant insight to this devastating disease, leading to improved means for prevention, and the development of new drugs and targets.