Graduate School of Science and Technology Master's Thesis Abstract

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Thesis title	Elucidating the interactions between circadian transcription factors and circadian clock-controlled genes E2F8 and NNMT through gene network inference 遺伝子ネットワーク推論による概日転写因子と概日時計制御遺伝子E2F8およびNNMTの相互作用の解明		

Abstract

The circadian clock is the biological mechanism that controls the sleep-wake cycle, as well as various changes in the human body throughout the day. Many genes in the human body are regulated by the circadian clock, and these clock-controlled genes exhibit daily rhythmic oscillations in their expression profiles.

Recent research indicates that cancer and the circadian clock are connected. For example, some genes that are associated with tumor growth, such as E2F8 and NNMT, are circadian clock-controlled, and breast cancer in mice causes changes in the temporal expression profiles of core clock genes and clock-controlled genes in the liver. However, the physiological mechanisms underlying this connection between the circadian clock and cancer are not yet well-understood. One way of understanding these physiological mechanisms is by constructing gene regulatory networks, which show the regulatory relationships between the circadian clock genes and the clock-controlled genes. Currently, it is possible to infer gene regulatory networks using machine learning, due to the availability of large amounts of omics data as well as the development of many algorithms for inferring gene regulatory networks using such data.

In this research, we used two gene regulatory network inference algorithms, dynGENIE3 and GRENITS, to infer the regulatory interactions from the core clock genes to two cancer-related clock-controlled genes, E2F8 and NNMT, using gene expression data of the livers of mice with and without 4T1 breast cancer. The results show significant rewiring of the gene regulatory networks in the livers of mice with 4T1 breast cancer. The results also indicate that the GRENITS nonlinear model outperforms dynGENIE3 and the GRENITS linear model with default parameters in terms of true positive rate, provided that the number of knot points used by each B-spline function is much lower than the number of time points. Based on the inferred rewiring of the gene regulatory network in mice with 4T1 breast cancer, we also proposed a hypothetical explanation for the change in the temporal expression profiles of E2F8 and NNMT in the livers of mice with 4T1 breast cancer observed by a previous study. We also produced a list of predicted regulatory interactions from the core clock genes to E2F8 and NNMT, which can serve as candidates for future experimental verification.